THE CANCER LETTER

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As FDA Weighs its Options on Morcellation, Debate Erupts Over Harvard Device Study

By Matthew Bin Han Ong

Here is what we know: A surgical device used to perform about 100,000 hysterectomies and myomectomies every year in the U.S. has been shown to spread cells from undetected or missed uterine cancers—rapidly upstaging the disease.

And here is what we don't know: What will FDA do about it?

The agency is under pressure to respond to the growing outcry from patient advocates, who want a ban on the device.

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Conversation with The Cancer Letter

Demetri: Morcellation Worsens Outcomes In Patients with Undiagnosed Cancers

As an oncologist who treats sarcoma, George Demetri has seen the adverse consequences of power morcellation, the surgical technique widely used to perform laparoscopic hysterectomies and remove putative fibroids.

In a small minority of cases, these fibroids instead represent unsuspected malignancies—including rare and aggressive leiomyosarcomas—which were impossible to detect prior to the morcellation procedure.

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In Brief

Gilliland Named President and Director Of Fred Hutchinson Cancer Research Center

D. GARY GILLILAND was named president and director of the **Fred Hutchinson Cancer Research Center**, effective Jan. 2, 2015.

Gilliland comes from the University of Pennsylvania's Perelman School of Medicine, where he served as vice president of precision medicine.

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FDA Likely to Not Ban Power Morcellators, Observers Say

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On the other side of the morcellation debate, major gynecologic organizations generally favor continued use of the minimally invasive device for hysterectomies and fibroid removal. And of course, some manufacturers want to keep selling power morcellators.

As FDA develops a strategy for balancing its legal authorities and moral imperatives, it has the following options:

• Ban, recall, or issue a warning on the risks of using the power morcellators for hysterectomies and myomectomies;

• Order device manufacturers to resubmit the power morcellator through the Class III high-risk device approval protocol;

• Put a black box label on the devices—FDA's sternest warning for significant risk of serious or life-threatening adverse effects;

• Request more data via post-market surveillance studies, which can include registries and controlled trials.

Patient advocates, who propelled the controversy to the top of FDA's must-do list, have the highest imaginable expectations from the regulatory agency. They are demanding fundamental change in the levels of evidence required for market clearance of a class of devices that include power morcellators.

Ultimately, they are looking to FDA to give meaning to the catastrophes that struck them by preventing harm from coming to others.

"It goes back to the Hippocratic Oath, 'Do no harm.' You're dealing with entrenched economic interests that shouldn't have gotten to where they are today," said Rick Kaitz, a Boston real-estate attorney and a donor to Dana-Farber Cancer Institute, a Harvard-affiliated institution.

Kaitz's wife, Erica, died Dec. 7, 2013, after she underwent power morcellation at Brigham & Women's Hospital, a member institution of Partners HealthCare, a Harvard hospital network. It contributed to the upstaging of her fatal leiomyosarcoma.

After her cancer diagnosis, the Kaitzes assembled a group of friends and supporters who have raised about $4 million for leiomyosarcoma research at Dana-Farber.

For almost a year after his wife's death, Kaitz worked behind the scenes to convince Harvard-affiliated institutions to ban power morcellation altogether. He has not spoken publicly with reporters on power morcellation before. A television news story by Boston's ABC affiliate about Erica's cancer, her post-diagnosis experience, and the couple's efforts to fundraise for leiomyosarcoma is posted here.

Today, Kaitz is disappointed by Brigham's launch of a prospective study focused on using power morcellators inside containment bags.

"I've given Brigham, privately, the opportunity to do the right thing about 10 different times and 10 different ways," Kaitz said to The Cancer Letter. "I told them last June in a written exchange—including to the associate general counsel and chairman at Partners HealthCare, amongst others—that I would not go public, and I would not sue if Partners instituted a permanent ban on power morcellation."

Kaitz said the health care system considered his request "for a while" and declined to institute a permanent ban.

A total of 400 patients will be enrolled in Brigham's study across several Partners institutions.

"This is a prospective study to evaluate the feasibility and safety of electromechanical morcellation within a containment system (bag) during laparoscopic myomectomy or hysterectomy," Brigham officials said in a statement to The Cancer Letter. "There are no study sponsors. The study coordination is done internally at BWH, and there is no industrial support for this study." The study's investigators declined to speak with this reporter.

Cover Photo: Rick and Erica Kaitz in summer 2011, a year before Erica's leiomyosarcoma diagnosis. Power morcellation at Brigham & Women's Hospital contributed to the upstaging of the disease. Erica died on Dec. 7, 2013.

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By going public, Kaitz joins Amy Reed and Hooman Noorchashm, two former Harvard physicians, who led an international campaign that put power morcellation on FDA's must-do list.

There is no deadline for FDA to act.

Reed and Noorchashm demand nothing less than a ban, and a complete overhaul of 510(k) regulations, the FDA process that put power morcellators on the market. Together, these two couples lend human faces to a 2011 Institute of Medicine committee report that recommended a revamp of the clearance process (The Cancer Letter, July 4).

"I hope you can bring yourself and the FDA to do justice," Noorchashm wrote in an email to Peter Lurie, acting associate commissioner for policy and planning at FDA. "Leaving these devices in gynecological operating rooms will leave open the door to defiant or under-informed gynecologists morcellating other trusting women with occult or missed cancer somewhere in the U.S. and abroad.

"Recall these devices, Dr. Lurie."

Brigham's study is approved through a separate Institutional Review Board from Dana-Farber's, said George Demetri, director of the Center for Sarcoma and Bone Oncology at Dana-Farber and a professor of medicine at Harvard Medical School.

"I'm a fan of regulatory science. I'm not a negative person, so I would have to say that our gynecology colleagues at the Brigham and Women's Hospital hopefully have a good rationale for what they're doing," said Demetri, who was involved in treating Erica Kaitz, and whose research is partially financed by the couple's fundraising. "I think that the patients who would conceivably be study participants in this—it would be an interesting consent process. It would be interesting to know what doctors tell patients in such a consent process.

"As we all know, a consent form is a form; consenting patients to a clinical investigation is a process. I've served on our IRB for about 24 years and I love it, and I take informed consent extremely seriously.

"I'm not going to shirk from saying it's terrible when we get one of these patients who had morcellation. And then, the question is, 'Well, gee whiz, did she understand the risks prior to the procedure? Would she have possibly died from an open procedure? And so, although it was an undiagnosed disease, it may be less difficult if she doesn't look back with any regret?'

"I think this is where I do trust our regulators to look out for the safety of our patients."

A May 2014 version of the patient consent form for the Brigham study can be downloaded from The Cancer Letter website.

A conversation with Demetri appears on p. 1.

The Debate and the Data

FDA's pending decision on power morcellators follows this timeline of events:

• Oct. 17, 2013: Amy Reed, formerly an anesthesiologist at Beth Israel Deaconness Medical Center, underwent power morcellation performed at Brigham & Women's Hospital. Reed and her husband, Hooman Noorchashm, linked her disseminated leiomyosarcoma to the device's spinning blades, and launched a high-profile campaign (The Cancer Letter, July 4). Erica Kaitz died nearly two months after Reed received her diagnosis.

• April 17, 2014: FDA issued an advisory discouraging the use of power morcellation, stating that one in 350 women who undergo hysterectomy or myomectomy for fibroids have an unsuspected uterine sarcoma.

• July 10-11: Several members of an FDA advisory panel expressed low confidence in power morcellation as a treatment for uterine fibroids. No vote was taken, and no formal consensus was reached on either an outright ban or issuance of warning labels (The Cancer Letter, July 25).

• July 22: JAMA published a retrospective study of 36,470 women who underwent power morcellation from 2006 to 2012. The study found that one in 368 women undergoing hysterectomies have an undetected uterine cancer that could be spread by a power morcellator.

• July 31: Johnson & Johnson subsidiary Ethicon withdrew its power morcellators from the market, a few months after it suspended global sales of the devices. J&J's morcellators accounted for about 75 percent of the market (The Cancer Letter, Aug. 1).

As the controversy developed, Brigham banned all open, unbagged morcellation procedures for gynecologic surgery (The Cancer Letter, July 4). Several hospitals and health systems stopped using power morcellators altogether, and some insurance companies—including Harvard Pilgrim, AmeriHealth, UPMC Health Plan, and Blue Cross Blue Shield in Massachusetts and Pennsylvania (Highmark)—have ended payments for the procedure.

Reed's and Noorchashm's advocacy has drawn the attention of several lawmakers, including Sens. Kirsten Gillibrand (D-N.Y.), Elizabeth Warren (D-Mass.), Bob Casey (D-Penn.), Charles Schumer (D-N.Y.), and Rand Paul (R-Ky.) who issued statements on power morcellation and wrote letters to FDA Commissioner Margaret

Hamburg. Their statements can be downloaded here.

The power morcellator is categorized as a Class II moderate-risk device, which is cleared—not approved—through the 510(k) process, which applies to new devices that are based on comparability to predicate devices already in use. Only Class III high-risk devices require an FDA premarket approval application.

Risk estimates for the dissemination of undetected sarcomas via power morcellation range from one in 350, according to the April 17 FDA advisory, to one in 7,450, according to gynecology researchers.

The American Congress of Obstetricians and Gynecologists and the American Association of Gynecologic Laparoscopists argue that the risk is minimal, because the incidence of uterine cancers—especially leiomyosarcoma, one of the most aggressive forms—is very low.

Using this logic, power morcellation benefits the majority of women. Unlike open abdominal procedures that generally remove uterine tissue intact, it can be used to preserve fertility, prevent large scars, and avoid or shorten hospital stays.

However, for patients with undiagnosed cancers who underwent morcellation, the data tell a sad story, Dana-Farber's Demetri said.

"[Patients] who had morcellation did worse," Demetri said to The Cancer Letter. "Their disease came back faster. I think the data are quite remarkably consistent. The last few years of publications—now several different independent publications—are honing in on what I would consider to be a believable truth.

"But, you know, at some point, you have to use common sense, and I'm comfortable with the data saying, 'It does worsen outcomes.' That's a key point.

"If there is a cogent argument about why this is such an important procedure and tool for this group of doctors and some specifiable type of patients, I would like to understand that.

"And I think the public would want to understand that—in words that we can all understand. If there is a rational, understandable argument for why the risk-benefit would tilt in certain patients, let's define who those patients are."

FDA's Tool Chest

Few FDA-watchers expect to see the agency ban the power morcellator.

The agency has the capacity to accomplish the same practical results via other strategies, they say.

"There is a regulatory tool that FDA has called 'a banned device,' which they have only used once in the history of FDA—for synthetic hair implantation," said Bill Vodra, a former FDA associate chief counsel for drugs.

Vodra helped draft many agency regulations still in use, including those implementing the Controlled Substances Act and FDA's rules for Good Manufacturing Practices, Good Laboratory Practices, Good Clinical Practices, bioequivalency and the Orange Book.

"The authority to ban devices basically turns out to be a very cumbersome tool. It was one of those things that was written into the statute in 1976, and Congress said, 'What a great thing!'" Vodra said to The Cancer Letter. "But the process for imposing a ban is fairly elaborate, and FDA has learned that the resources to do that are expensive, compared to simply putting out a warning from the commissioner to tell America not to use this.

"Every product liability and malpractice lawyer in the United States picks this warning up in a minute, and any doctor that uses it after that is exposing himself to all kinds of risks." Vodra is a retired partner of the Washington, D.C., law firm Arnold and Porter.

"So for FDA, a warning is one of those tools they can use that's not in the statute, but it can modify behavior dramatically fast in that regard. There are other courses of action besides the law to get things done."

In the past, FDA's press releases have demonstrated the capacity to destroy markets for products overnight, Vodra said.

"FDA has demanded a recall that pulled a product from the market," he said. "The recall did not legally prohibit reentry, but it left no customers who would touch the product.

"They have also ordered a product to go through the PMA Class III process, and never had the product do so, thereby preventing it from being marketed.

"In short, the ultimate effect is whether physicians, hospitals with internal risk committees, and liability insurers elect to abandon a product or practice, rather than run risks of financial exposure to handle the product or perform the practice.

"The effect can be produced by a product ban, a recall, a requirement for preclearance, or a press release."

In addition to a black box warning, some panel members at the FDA devices advisory hearing recommended the withdrawal of the power morcellator's Class II status, and for any future iterations of the device to be submitted through the Class III process, which requires pre-market testing (The Cancer Letter, July 25).

FDA may also elect to put a black box label on the power morcellator, as well as require post-market surveillance.

"FDA can say, 'based on the best available information, it is very risky to use this device in this way…' and also say, 'We want better data to quantify the risk,'" Vodra said. "Don't underestimate the potency of a black box. They intensify the duty of care that a doctor must exhibit in order to avoid malpractice exposure.

"Many oncologic agents carry black boxes—which may explain why most GPs and internists don't use them in their practices, but refer patients to oncologists."

Post-Market Surveillance Possible

If FDA chooses to allow the power morcellator to remain as-is on the market, it would need to conduct post-market surveillance, said David Challoner, emeritus vice president for health affairs at the University of Florida.

Challoner chaired the Institute of Medicine committee tasked by FDA and Congress in 2009 to review the 510(k) process that clears Class II devices such as the power morcellator based on predicate devices.

"FDA does have the capacity, which they have not used very often with 510(k) devices, to add that they want some kind of post-market surveillance or monitoring to take place," Challoner said to The Cancer Letter. "They could be considering allowing the morcellator to stay on the market, but under the condition that the manufacturer set in place a post-market surveillance monitoring system.

"That exists for a lot of other devices—some 510(k), some with other kinds of clearances to the market."

Creating a registry is one post-market strategy to collect data.

"Now who would do it?" Challoner said. "FDA can require the manufacturer to establish and maintain a registry through the physicians that use that product.

"In other cases, the establishment of a registry has come through specialty providers, in many cases. So exactly how [Johnson & Johnson]—assuming they would even want to get back into the business—and Karl Storz [a German-based company that continues to make power morcellators] would establish and require a physician who purchases and uses their morcellator to report all cases to them, I don't know exactly what the details of that would be."

Establishing a registry would mean encompassing 100 percent of the patients in whom the device is used, Vodra said.

"Registries are useful when you may wish to contact every patient after an extended period of time, such as implant wearers," Vodra said. "They seem less useful for a surgical or diagnostic tool that is not implanted, and where long-term follow-up or notification is foreseen."

"It is expensive to create and to maintain; and it may not yield any better data than a focused post-market surveillance study on 2,000 to 5,000 patients at a select number of hospitals. FDA can get a group of institutions to enroll in a registry, or go to Boston, New York or California where there are major hospitals and say, 'We want to follow the next 2,000 patients that are treated, put them in a study, and follow those patients for a period of time.'"

A registry may work for power morcellation patients, if the adverse effects surface rapidly, Vodra said.

"If the gestation period for cancers disseminated by the power morcellator is a couple of weeks, it's very quick and easy to do that study," he said. "What FDA would need, if it decides to do this, is a large enough denominator that an incidence rate can be obtained.

"If there is a conflict among the data that has been developed since FDA issued its advisory, FDA might well say, 'Gee, we are now stepping back. We're not sure that we got the right numbers here.'

What would FDA need to say to justify asking for a post-market study focused on assessing the risk of disseminating malignant tissue?

"If the decision is to collect more data, then what FDA would require is to say, 'Yes, we know a qualitative risk of injury, but we don't know if it's one in 10,000 or one in 500. And we need the data to answer that question,'" Vodra said.

Registries or studies would expose large numbers of patients to potential harm, said Challoner.

"Given what we've discovered so far about the incidence of the tumor dissemination, it's going to put a lot of people at risk," Challoner said. "There are ways to take care of fibroids without this risk, that we discovered is being introduced by morcellation, and that Hooman Noorchashm has widely disseminated.

"With the Hippocratic Oath in mind, until we have a means of preoperatively determining the presence or absence of a sarcoma vs. a fibroid, the morcellator has no place in clinical use for this purpose.

"So what we probably ought to do, in my point of view, is put it off until our geniuses—as they are doing with other kinds of tumors—find a way of preoperatively detecting the genetic abnormalities in a uterine sarcoma, and with a simple blood test.

"We're not there yet, and if companies who are currently manufacturing morcellators are going to be impatient about it, I think we ought to sit on this technology until such time as we actually have that kind of preoperative determination of the risk vs. no risk."

Debate Over Brigham's Containment Bag Study

FDA's other option is to mandate creation of a post-market surveillance study combining power morcellators with a containment system or bag, which would be used to prevent the dissemination of any tissue, benign or malignant.

One such independent prospective study is underway at Brigham.

Titled "A Partners prospective study assessing the safety, feasibility and efficiency of morcellation in a containment system," the study tests whether the bags would break or leak when used with a power morcellator.

"Indigo carmine dye will be used in a portion of the study population to assess leakage during the contained morcellation procedure, and is approved by the FDA to be used in laparascopic procedures," according to a patient consent form for the trial obtained by The Cancer Letter.

About 400 women will take part in this research study, which is conducted at Brigham, Faulkner Hospital, Massachusetts General Hospital, and Newton-Wellesley Hospital.

"We expect to enroll approximately 100 women from each hospital," the consent form reads.

The principal investigator of the study is Jon Einarsson, a minimally invasive gynecologic surgeon at Brigham. Site principal investigators include: Stephanie Morris, associate medical director at the Center for Minimally Invasive Gynecologic Surgery at Newton-Wellesley; Douglas Brown, director of the Center for Minimally Invasive Gynecology Surgery at MGH; and James Greenberg, chief of the division of gynecology at Faulkner.

Containment bags are cleared by FDA under the 510(k) for oncologic surgery—which removes malignant tissue intact—but not for specific use with power morcellators.

Brigham officials said that the study did not require applying for an Investigational Device Exemption with FDA for the express use of the bag with power morcellation of uterine tissue. The IDE is a process that allows potentially high-risk devices to be tested in patients. By inference, this would mean that the Partners HealthCare IRB had concluded the study to be of "minimal risk," and therefore did not see the need for an IDE application.

Brigham officials said the study does not have industrial support or sponsors, and is conducted internally at Brigham. However, "sponsors" of the study are mentioned in the patient consent form numerous times, but are not identified.

The Storz Rotocut G1, a power morcellator manufactured by Karl Storz, is used in the study.

The German company had previously threatened Noorchashm with legal action if he did not end his campaign to ban power morcellation (The Cancer Letter, Aug. 27).

"Should we get to know further public statements from you that our device and/or management would be responsible for your wife's or any other women's uterine cancer, and/or any aggravation of their cancerous situations, we would not hesitate to take appropriate legal actions to protect our good name and our rights," Storz wrote at the time in a letter to Noorchashm.

"We trust that you understand our position and conclude by wishing you and your wife that you win the battle against the shocking illness which, nevertheless, cannot be attributed to any of our devices or acts."

Storz's threats stem from its concern that possible FDA decisions would negatively impact their sales, now that Johnson & Johnson, their largest competitor, has withdrawn its devices from the market, Challoner said.

"Karl Storz's issue is not with Hooman," said Challoner. "Their issue is what the FDA is going to do, and their issue is that they simply want to continue to market their product.

"If you want to paraphrase it, it's almost as if they said, 'Your wife almost died when someone used our machine the same way everybody uses it. Machines don't kill people, but doctors do.'

"I mean, what a great line that is, for God's sake. So if doctors want to kill people with our machine, fine, keep your nose out of our business. It was really a bad line in that letter. I am simply appalled."

At the FDA hearing in July, several experts said that training surgeons to morcellate uterine tissue within the confines of a bag would be an intensive process.

Visibility can be an issue, and surgical gynecologists would need to avoid perforating the bag with the morcellator's spinning blades while removing strips of the patient's tissue, which may contain undiagnosed malignancies.

In the committee's summary focused on containment bags, panel chair Michael Diamond, professor and chair of the Department of Obstetrics and Gynecology and associate dean for research at Georgia Regents University, said:

"First of all, there are some techniques, such as vaginal surgery, when it's possible, for the removal of an intact uterus—that would be a mitigation strategy that could be utilized. There is also concern with supracervical hysterectomy, and potentially cutting across a tumor. Multiple individuals mentioned the desire to avoid any kind of morcellation of tissues, and

to remove the specimens intact.

"There was a lot of discussion about the use of bags, and while it was thought that, intuitively, that may have advantages in reducing dissemination of an unrecognized malignancy, the data to support that appears to be totally lacking at this point in time.

"Therefore, the conclusion is that we don't know, through the use of the bags, to what extent, if any, we're able to reduce the risk at this point."

Challoner: Dye is not Cancer

According to Brigham officials, the study will enroll 400 patients to evaluate "a number of commercially available morcellators and bags."

Challoner said he is skeptical about the investigators' use of dye leakage as a measure for the dissemination of fibroid or sarcoma cells.

"My guess is that they are going to try and determine whether the dye leaks out of the bag in any way during the course of the procedure, as a clue to whether the bag could prevent any dissemination of morcellated fibroid, or sarcoma, in the worst case," Challoner said. "It seems to me a pretty weak study.

"The carmine dye and bag are new to this usage. Under what kind of evidence that the combination of a morcellator and a containment bag gives you a 100 percent retrieval of morcellated tissue, I don't know.

"To me, that is not an adequate study to see whether the bag captures the dye as a stalking horse for a fibroid or a sarcoma."

The study will not change the risk that individual patients face with the power morcellator, Challoner said.

"Given that there are other alternatives to deal with the fundamental disease, which are not really any more traumatic or difficult than the use of the morcellator, and given the historic experience with the device—the risk in the use of the power morcellator at this moment, it seems to me, is not ethical to take.

"We should have every expectation—from what science is going to bring to this clinical equation over the next years—that we will be able to preoperatively make that diagnosis, and therefore make the use of morcellation and its marginal improvement in ease for the patient, a safe thing to do.

"We'll know ahead of time who we can use it on and who we can't. But right now, that's not what we've got."

In a statement to The Cancer Letter, Reed and Noorchashm wrote:

"In the end, this is very simple. A massive error in judgment, practice, design and ethics has killed a lot of women prematurely or unnecessarily for over two decades.

"What is tremendously and historically tragic is that almost the entire specialty of gynecology and its associated industry are defending this clear wrong and attempting to recover. Instead of humbly admitting a grave wrong and abandoning a hazardous practice, they are creating a controversy out of the incontrovertible.

"In medicine, we do not expose our patients to avoidable deadly harm. Morcellation is, indeed, an avoidable and potentially deadly harm that was adopted by gynecological surgeons for ease and vanity—patient safety and ethics seem to have been entirely abandoned.

"Nor is morcellation to be equated with minimally invasive surgery—morcellation is 'maximally invasive' surgery through small incisions. No other surgical subspecialty, except gynecology, accepts this practice as correct or safe.

"The only question that remains now is if, in the face of deadly peril and many victims, FDA and the United States Congress have the resolve, ethics and courage to act decisively to protect the minority subset of unsuspecting women whose cancers would be spread by morcellators.

"But perhaps our government will remain party to this travesty, choosing to adopt the 'benefit of the majority argument'—after all, in politics and government, there are more dollars and more votes in that kind of argument."

Study Investigators Applied for Patents on Bags

Jon Einarsson and James Greenberg, two principal investigators of the Brigham study, have applied for or own patents on containment bags that are intended for use with power morcellators.

Einarsson is listed as an inventor on a patent application filed March 5. The patent application is for a morcellating device comprising of a "containment mechanism including an aperture; the containment mechanism having an interior space."

Einarsson and Greenberg do not have conflicts of interest that are specifically relevant to the study, and are not testing their own inventions in the study, Brigham officials said in a statement to The Cancer Letter.

"Dr. Einarsson's patent is for a system and method for a laparoscopic morcellator," officials said. "At the time this study was reviewed by the Institutional Review Board which governs research at BWH, Dr. Greenberg was listed as an inventor for a tissue extraction bag.

"While both of these technologies are generally relevant to the area of morcellation, neither of these patent/technologies are relevant to the specific study in question.

"The study does not involve, use, test or evaluate

technologies under either the patent or invention. We are not aware that any of the other investigators have patents or financial interests that are relevant to the study."

Einarsson was Erica Kaitz's surgeon.

"There was unequivocally never a mention of morcellation until three days after Erica's diagnosis," Rick Kaitz said to The Cancer Letter. "In my meetings with the Brigham leadership, there was an acknowledgment of multiple things.

"One, that morcellation significantly harmed Erica. Two, that morcellation was not discussed or disclosed in any way, shape or form pre-surgery. And three, that the one in 10,000 risk number was used."

Kaitz questions the ethical underpinnings of Brigham's study.

"Einarsson has a patent," Kaitz said. "He has a vested economic interest. They are trying to protect their turf, rather than asking front-end questions: 'What type of harm are we causing,' or 'What's the cost-benefit analysis of this device?' That's part one. Obviously, Erica's story is instrumental to the whole thing.

"And part two is, unfortunately, the Harvard/Brigham position is in large part colored by institutional arrogance, because Hooman Noorchashm attacked them so publicly and so vociferously, that to continue their ban on power morcellation would be an admission of wrong-doing, which they would never do in the face of an insider attacking them like Hooman attacked them.

"That's probably the biggest reason that the Brigham won't do and hasn't done the right thing."

Brigham officials said that there was no need to disclose Einarsson's patent or Greenberg's invention in the patient consent form.

"The study was reviewed and approved by the Institutional Review Board which governs research at BWH," officials said. "At the time of review, the IRB and the Partners Office for Interactions with Industry, which reviews researchers' financial and other interests in connection with research studies and grants, were aware of the patent held by Drs. Einarsson and the invention of a containment bag by Dr. Greenberg.

"The Einarsson patent and the Greenberg invention were reviewed in connection with this study.

"It was determined that because neither Dr. Greenberg's containment bag nor Dr. Einarsson's morcellator is used, tested or evaluated in this study, neither the Einarsson patent nor the Greenberg invention are directly relevant to this study.

"Therefore, there was no requirement to disclose these technologies to the participants enrolling in this study."

Conversation with The Cancer Letter

Demetri: "I'm Comfortable With the Data Saying, 'It Does Worsen Outcomes'"

(Continued from page 1)

In those cases, power morcellators end up spreading the disease and, according to recent data, worsen patient outcomes.

Some proponents of the procedure have said that patients with sarcomas would have a poor prognosis with or without morcellation. Demetri, director of the Center for Sarcoma and Bone Oncology at Dana-Farber Cancer Institute and a professor of medicine at Harvard Medical School, disagrees.

"There's a nihilism that I want to counteract in those who might say, 'Well, these patients have a sarcoma, they're destined to do badly anyway.'" Demetri said to The Cancer Letter.

"That's an unfair assessment. That is a negative assessment of people who may do well. I have several patients who have had a uterine leiomyosarcoma that was treated optimally, and who are alive and well for 14 years.

"I think nihilism is not warranted, and that, to me, is the most important thing a sarcoma medical oncologist can add. I think we need to look out for the best interests of our patients."

Demetri discussed this cross-disciplinary controversy in a conversation with Matthew Bin Han Ong, a reporter with The Cancer Letter.

Like repeated lightning strikes, two tragic events placed Harvard-affiliated institutions in the center of this controversy.

• Power morcellation performed at Brigham & Women's Hospital was a part of the diagnostic step that was associated with the upstaged leiomyosarcoma of Erica Kaitz, who died Dec. 7, 2013. Kaitz, of Boston, had been active in raising money for research at Dana-Farber Cancer Institute.

• The morcellation procedure also upstaged the undetected tumor of former Beth Israel Deaconess Medical Center anesthesiologist Amy Reed (The Cancer Letter, July 4, 2014).

The debate over morcellation is especially divisive at Harvard, because gynecology-based investigators at Brigham and Women's Hospital are conducting a clinical study aimed at gauging whether power morcellation performed in a containment bag might be able to limit the spread of cells (The Cancer Letter, July 4, 2014).

Critics say that power morcellation in routine gynecological surgery is not worth the risk, and alternative surgical procedures should be performed instead. Erica's widower, Richard Kaitz, as well as Amy Reed and her husband, Hooman Noorchashm, formerly a cardiothoracic surgeon at Brigham, have been urging the Harvard institutions to abandon power morcellation altogether.

Demetri and his team had treated Erica Kaitz.

The Kaitzes were prominent donors to Dana-Farber. They started riding in the Pan-Mass Challenge charity biking event in 1993. It is the largest athletic fundraiser in the U.S., and raised $41 million for research at Dana-Farber this year.

Demetri oversees leiomyosarcoma research funded in part through the Erica Kaitz LMS NOW Research Fund at Dana-Farber. This fund raised about $2.9 million in 2012 and 2013. This year, Erica's Entourage, a team riding with the Pan-Mass Challenge, raised over $1 million for the Erica's Entourage Sarcoma Epigenomic Research Project at Dana-Farber and Harvard Medical School.

Matthew Ong: *How do you know Richard Kaitz?*

George Demetri: Erica, Rick's wife, was a patient in our program, and Rick has given me permission to speak publicly about this. Our team knew her well.

Rick and I have biked together in Dana-Farber's signature fundraising bike ride event. Our clinical director, Dr. Suzanne George, has led research and publications on this—so we know a good deal about power morcellation. However, I know that we're on the medical oncology side of this equation—we see the patients after a diagnosis of sarcoma has been made—and the morcellation debate concerns arise before any such patients would be referred to us.

My expertise is in the disease biology and management of patients with a sarcoma diagnosis. Once the diagnosis has been made, there is no debate: if a patient has a diagnosed malignancy, morcellation is contraindicated.

I think we've missed the fundamental issue: there's no reproducible, reliable, dependable way to know if a patient has a malignancy, so I don't know how a doctor would know not to use this.

That's where we are—but I am the first to say that I am not a surgeon—I am on the other side of the "therapy system" in this matter, after diagnosis.

MO: *Do you think power morcellation should continue to be an option? If I'm not mistaken, the FDA Obstetrics and Gynecology Devices Advisory Committee had previously highlighted that there isn't a surefire way of detecting these uterine malignancies pre-surgery.*

GD: Imaging studies with CTs or MRIs show masses, but "masses" aren't a diagnosis, so I'll leave it at that.

Here's the issue for our surgical colleagues:

What is a cogent, understandable argument for why morcellation is needed, and in which patients, given the risks of this procedure, in context with the risks of alternatives? That's it.

The arguments are, of course, as we've all read and as we've all heard is, "Well, it's easier to recover from this [morcellation] surgery, there may be frail patients who could not tolerate alternatives etc."

If that is the case, I would like to think that the gynecological community can define and decide which patients are appropriate for this procedure that they view as medically necessary. That community needs to state this in no uncertain terms to patients, to themselves, to other physicians, to the FDA, and then that's the way medical practice moves forward.

It's no different than any other issue in medicine—or surgeries, for that matter.

Again, I want to emphasize that I am not a surgeon, and I have great respect for my surgical colleagues. I think very few surgeons talk to me about my drug development, and I don't want to be on the other side of the fence talking about their surgery, since I respect their expertise.

MO: *What would you say to a patient who may come to you and ask for your advice as to whether she should have her hysterectomy or myomectomy done via power morcellation?*

GD: I doubt I would recommend it. But, again, maybe there are other details which would drive decisions in a specific case. Maybe there's some issue that makes alternatives to a morcellation procedure more uniquely dangerous to some specific patient. Any decision in medicine and surgery is all about the details—and risks are inherent in any such decision as well.

Talk to the gynecologists. Even within that community, as I understand it, there are radical divisions of opinion. It's their specialty. I can only talk about the people I've seen who have had the disease diagnosed.

There's a nihilism that I want to counteract in those who might say, "Well, these patients have a sarcoma, they're destined to do badly anyway." That's something that I can speak to.

That's an unfair assessment. That is a negative assessment of people who may do well. I have several patients who have had a uterine leiomyosarcoma that was treated optimally, and who are alive and well enough for 14 years.

A subset of these patients are fine, God bless them. So I think not all of these patients do badly. I think nihilism is not warranted, and that, to me, is the most important thing a sarcoma medical oncologist can add. I think we need to look out for the best interests of our patients.

If there is a rational, understandable argument for why the risk-benefit would tilt in certain patients, let's define who those patients are. Let's explain the risk to our patients, as we do with everything else in medicine, and move forward as a community.

I don't want to throw incendiary opinions or my bias as to what I might do, because none of us ever know what we would do if it were our wife, or our sister, or our daughter, until we're in that position, and until we're faced with real facts.

But that's down to the fact that we have facts. And now, I think the data are quite remarkably consistent. The last few years of publications—now several different independent publications—are honing in on what I would consider to be a believable truth.

There is a certain number of patients who had a previously undiagnosed sarcoma or endometrial cancer or whatever, that underwent morcellation. That's a fact.

So then the argument is, "How do you identify who they are?" Are there some patients for whom that procedure still represents—for whatever reason—a more favorable risk-benefit than any alternative procedure?

I know there are open procedures; there are other ways of doing things. I can't comment on those, since that is the expertise of the gynecologic surgery community, and it is their responsibility to be held to that light of scientific inquiry, where patients and regulatory authorities can help them come to a wise decision. That's probably the most responsible thing any of us can say.

I'm not going to shirk from saying it's terrible when we get one of these patients who had morcellation. And then, the question is, "Well, gee whiz, did she understand the risks prior to the procedure? Would she have possibly died from an open procedure? And so, although it was an undiagnosed disease, it may be less difficult if she doesn't look back with any regret?"

That's what I'd like to hear. And that's a rational, dispassionate discussion that serves the best interests of patients, and I think that should be our focus.

MO: *If a patient has an undetected sarcoma or leiomyosarcoma, and it's disseminated by a power morcellator, how fast does it propagate throughout the peritoneal cavity?*

GD: I think it varies for different people. The biology of any individual's sarcoma varies from one to another, and the argument is always that none of this is controlled data.

There is one example of a patient who had morcellation and is rendered free of disease, but within three weeks, has massive, bulky disease in multiple places. Well, do I think it's because the morcellator spread things around, and during the healing process, growth factors were released and that accelerated the process?

In my heart of hearts, probably yes. Can I prove it? Absolutely not.

And the argument would be, "Well, you don't know what would've happened to her had she just had an open procedure. Maybe all of this would've happened anyway."

And to be rigorous, you have to say, "Yes, that is possible." But that's why you do studies and when you look at all the studies where there are people who had undiagnosed leiomyosarcomas and got sarcoma-type open procedures vs. those who were undiagnosed and had a "surprise" diagnosis with morcellation.

The ones who had morcellation did worse. Their disease came back faster.

So I think the data are quite consistent in multiple independent, retrospective analyses—again, retrospective, not controlled.

But, you know, at some point, you have to use common sense, and I'm comfortable with the data saying, "It does worsen outcomes."

That's a key point. It worsens outcomes. That's a qualitative statement—how much worse vs. how much would whatever outcome would have been worse with an alternative surgical procedure.

I don't know: Were all of those women adequately informed? Did they really understand? Were the numbers quoted as correctly as we now know them, I think, to be?

These are the questions. And I think, also, I don't want doctors to be graded or judged based on current information that really wasn't available even five years ago. Our whole view of the epidemiology of the undiagnosed leiomyosarcomas is very different now because we have independent sources from Korea, from the recent Columbia University study, as well as from studies at Harvard.[1234]

These papers were published in the last three to four years. So I think it's not fair to say, "Well, doctors seven years ago should've known that." How could

they have known that? They didn't know that.

But now that we know that, can we move on and start talking from data? And I think that's the discussion to have.

MO: *Have you heard of the registry study that Brigham is conducting?*

GD: Believe it or not, that goes through a separate IRB. That's through the Partners IRB, not our cancer center IRB.

I'm not a device developer. I actually don't really know how the device researchers design their clinical studies.

I'm a fan of regulatory science. I'm not a negative person, so I would have to say that our gynecology colleagues at the Brigham and Women's Hospital hopefully have a good rationale for what they're doing. I think that the patients who would conceivably be study participants in this—it would be an interesting consent process. It would be interesting to know what doctors tell patients in such a consent process.

As we all know, a consent form is a form; consenting patients to a clinical investigation is a process. I've served on our IRB for about 24 years and I love it, and I take informed consent extremely seriously.

There are so many interesting elements to this that—what can I say—this is a different kind of research from what I do. This is surgery, and I would have to say, on some level, it would be interesting to have the FDA speak for themselves.

It's a very difficult situation; isn't it? And again, I think this is where I do trust our regulators to look out for the safety of our patients.

I have to trust them, and that's where, if there is a cogent argument about why this is such an important procedure and tool for this group of doctors and some specifiable type of patients, I would like to understand that. And I think the public would want to understand that—in words that we can all understand.

MO: *Did I miss anything that you'd like to address?*

GD: I would like to see this come to some conclusion. I would have everybody be able to move on with some peace around this. It's painful for all of us to watch.

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CPRIT Awards 32 New Grants

The Cancer Prevention and Research Institute of Texas awarded 20 grants through its product development program, five grants through its prevention program and seven recruitment grants through its research program, totaling more than $65 million.

With a total requested amount of approximately $33.9 million, these early translational research grants awarded to Texas institutions include projects developing therapeutics, devices and new drugs.

The awarded research grants total approximately $24 million. The awarded prevention grants, totaling approximately $7.3 million, support prevention services for underserved populations in Texas.

The projects receiving grants focus on increasing HPV vaccination rates and providing access to colorectal and cervical cancer screening. The project receiving a competitive continuation grant provides screening, training and educational services related to colon cancer.

The awarded product development grants for early translational research are:

• **Baylor College of Medicine**—three grants totaling $5,927,789: Novel Separase Inhibitors to Treat Refractory Breast Cancer, $2,000,000; Oral Stat3 Inhibitor as Targeted Treatment for Triple-negative Breast Cancer, $1,999,569; and NKT Cell Platform for Cancer Immunotherapy, $1,928,220.

• **MD Anderson Cancer Center**—three grants totaling $5,045,493: Genetic Engineering of T Cells as an "Off-the-shelf" Therapy for Leukemias and Lymphomas, $1,992,245; Blood-based Markers for Screening and Early Detection of Colorectal Neoplasia, $1,693,599; and High-throughput Flow-proteometric System in Screening Functional Complexes as Cancer Biomarkers, $1,359,649.

• **The University of Texas at Austin**—three grants totaling $4,949,450: Preclinical Development of a Therapeutic Enzyme for Immune Checkpoint Inhibition in Cancer, $1,790,486; Image-guided Smart Laser Knife for Cancer Surgery, $1,694,460; and Pre-IND Development of OxaliTex, $1,464,504.

• **The University of Texas Southwestern Medical Center**—three grants totaling $4,521,535: New Antibody Therapy for Treating Leukemia, $2,000,000; Targeting the SWI/SNF Chromatin-remodeling Complex in Liver Cirrhosis and Hepatocellular Carcinoma, $1,357,880; and Targeting the DC-HIL Receptor for Anti-cancer Immunotherapy, $1,163,655.

• **The University of Texas Health Science Center at San Antonio**—two grants totaling $3,990,904: Druggable Targets that Regulate the Antitumor Activity of ER-beta, $1,998,444; and ESR1 Coregulator Binding Site Inhibitors (ECBIs) as Novel Therapeutics to Target Hormone Therapy Resistant Metastatic Breast Cancer, $1,992,460.

• **The University of Texas Health Science Center at Houston**—two grants totaling $3,481,666: Targeting an Elusive Foe: Development of K-ras Inhibitors, $1,969,826; and Development of a Novel K-ras Therapeutic, $1,511,840.

• **Texas A&M University System Health Science Center**—Therapeutic Targeting of Skp2/Ck1 to Restore Nuclear p27, $1,999,979.

• **The University of Texas Medical Branch at Galveston**— Inhibitors of Hydrogen Sulfide Biosynthesis: Preclinical Development of Novel Colorectal Cancer Therapies, $1,605,119.

• **Methodist Hospital Research Institute**—Immunotherapy Targeting Triple Negative Breast Cancer Using NY-ESO-1-Specific TCRs and Blockade of Immune, $1,592,992.

• **University of North Texas Health Science Center at Fort Worth**—Selective Tumor Delivery of Anti-cancer Agents in Ovarian Cancer Therapy, $742,048.

The awarded prevention grants include funding for evidence-based cancer prevention services:

• **Texas Tech University Health Sciences Center**: ACCION for Rural West Texas, $1,467,820.

• **Texas Tech University Health Sciences Center**: Get FIT to Stay Fit. Stepping Up to Fight Colorectal Cancer in the Panhandle, $1,455,409.

• **MD Anderson Cancer Center**: Improving Cervical Cancer Screening and Prevention in the Lower Rio Grande Valley Through Public Outreach, Patient Navigation and Telementoring, $1,441,085.

• **The University of Texas Medical Branch at Galveston**: A Multi-pronged Approach to Increase HPV Vaccination Rates among Adolescents 9-17 years of Age from Galveston and Brazoria Counties, $1,406,919

• And a competitive continuation/expansion grant for **Texas A&M University System Health Science Center**: Continuation and Expansion of Texas A&M's Colon Cancer Screening, Training, Education and Prevention Program, $1,500,000.

Recruitment grants awarded indicate only approval to negotiate offers; at this time the candidates have not accepted offers. The research grants for recruitment were awarded to:

• **Robert Mattrey**, for recruitment to The University of Texas Southwestern Medical Center from the University of California, San Diego, $6,000,000.

• **Samara Reck-Peterson**, for recruitment to The University of Texas Southwestern Medical Center Department of Cell Biology from Harvard Medical School, $4,000,000.

• **Andres Leschziner**, for recruitment to The University of Texas Southwestern Medical Center from Harvard University, $4,000,000.

• **Issam El Naqa**, for recruitment to The University of Texas Southwestern Medical Center from McGill University Health Center, $4,000,000.

• **Xi Chen**, for recruitment to Baylor College of Medicine from Weill Cornell Medical College, $2,000,000.

• **Marcin Imielinski**, for recruitment to MD Anderson Cancer Center from Broad Institute of Harvard, $2,000,000.

• **Melanie Samuel**, for recruitment to Baylor College of Medicine from Harvard University, $2,000,000.

ASCO Proposes Principles For Future Debate on Medicaid

The American Society of Clinical Oncology has proposed a set of principles for shaping future debate of the role of Medicaid.

The principles set forth in a paper published in the Nov. 17 issue of the Journal of Clinical Oncology are:

• No individual diagnosed with cancer should be without health insurance that guarantees access to high-quality cancer care delivered by a cancer specialist.

• Patients with cancer who have Medicaid should receive the same timely and high-quality cancer care as patients with private insurance.

• Medicaid payments should be sufficient to ensure that Medicaid patients can have access to quality cancer care.

• Patients with cancer who have Medicaid should not face insurance barriers to clinical trial participation.

ASCO said it regards Medicaid reform as one of its top priorities.

"Every patient should be able to receive high-quality cancer care, regardless of his or her financial circumstances," ASCO President Peter Paul Yu said in a statement. "Millions of Americans who rely on Medicaid won't be able to take advantage of advances in cancer prevention and treatment unless meaningful reform occurs."

Altogether, 67.9 million Americans—about one in five—are enrolled in Medicaid. Cancer patients and cancer survivors account for about 2.1 million Medicaid recipients, according to ASCO.

Studies show that Medicaid patients often do not receive the same quality of cancer care as patients with private insurance, and they are up to three times more likely to be diagnosed with cancer at a late stage, when treatment is less likely to be effective, the society said.

ASCO's policy recommendations follow:

1. Expand insurance coverage for individuals below the federal poverty level.

2. Ensure oral parity for patients with Medicaid coverage and include oral and intravenous cancer therapies, as well as supportive care medications, as exempt services for cost-sharing purposes (similar to preventative services, services provided to hospice patients, and so on).

3. Extend clinical trial protections included in the ACA to patients with Medicaid coverage, and allow patients with Medicaid coverage to cross state lines to participate in those trials.

4. Eliminate artificial barriers between current Medicaid beneficiaries and newly eligible beneficiaries, and apply ACA final-rule mandates for cancer screening and diagnostic follow-up without copay for all Medicaid beneficiaries.

5. Require coverage for genetic testing, without deductibles or copays, in any patient deemed at high risk for an inheritable cancer risk syndrome as defined by published guidelines.

6. Improve the 340B Drug Pricing Program so that it is used for its original intent: to incentivize care for the uninsured and underinsured and patients with Medicaid coverage, regardless of care setting.

7. Eliminate variation between Medicare and Medicaid physician payment rates for cancer diagnosis and treatment by raising Medicaid payments to Medicare rates.

8. Tie state flexibility in running Medicaid programs to the requirement to meet predefined cancer quality metrics.

9. Allow oncology practices to be designated as medical homes, and develop expanded reimbursement for care coordination and patient education for oncology practices.

FDA News

FDA Taking Comments on "First Generic" ANDA Process

FDA has opened a public docket and is requesting comments on proposed criteria for "first generic" abbreviated new drug application submissions.

The purpose is to facilitate FDA's establishment of review prioritization under the Generic Drug User Fee Amendments of 2012.

Establishing clear criteria for this review prioritization category will allow the agency to appropriately prioritize and track ANDA submissions.

Clear criteria for this category will also lead to less industry confusion and more consistent identification of first generic submissions, the agency said.

FDA is requesting comments and supporting information on the following criteria—a first generic application is any received ANDA:

(1) That is a first-to-file ANDA eligible for 180-day exclusivity, or for which there are no blocking patents or exclusivities; and

(2) for which there is no previously-approved ANDA for the drug product.

FDA believes that these proposed criteria appropriately focus FDA's resources on approving as quickly as possible, new safe and effective generic drug products for patient use.

The agency said these criteria enable it to prioritize review of a pending ANDA when the date on which the ANDA can be approved alters due to changes in the patent or exclusivity landscape.

Under these proposed criteria, first generic status is predicated largely on circumstances outside agency control, and ones that may change while the ANDA is pending, for example, developments related to the disposition of related patent litigation.

FDA also is seeking comments and supporting information on mechanisms the agency could put in place to facilitate ANDA sponsor submission of such relevant information in a timely manner, in addition to that already required under the regulations.

As a result of such developments, ANDA submissions that originally met the criteria for a first generic submission may no longer meet those criteria, the agency said. For example, the validity of a patent may be upheld in litigation, thereby blocking approval until patent expiration.

The agency is therefore seeking comment on whether it should change the review prioritization for an ANDA that no longer meets the first generic criteria during its review.

Comments must be submitted by Dec. 19. Electronic comments can be submitted to the federal eRulemaking Portal: http://www.regulations.gov.

FDA granted a Fast Track designation to MM-398 (nanoliposomal irinotecan injection) for the treatment of patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy.

Fast Track is designed by the FDA to facilitate and expedite the development and review of drugs that treat serious conditions and fill an unmet medical need.

Merrimack is currently preparing a New Drug Application for the indication. Fast Track designation allows sections of the NDA to be submitted to the FDA as they are completed.

According to Merrimack, the company expects to initiate the NDA submission in 2014 with the goal of completing the NDA submission late in the first quarter or early in the second quarter of 2015.

FDA and the European Medicines Agency have granted MM-398 orphan drug designation in metastatic pancreatic cancer.

MM-398 is a nanoliposomal encapsulation of the chemotherapeutic irinotecan. MM-398 has demonstrated extended circulation in comparison to free irinotecan in the clinical setting. The activated form of irinotecan is SN-38, which functions by inhibiting topoisomerase I and promoting cell death.

FDA granted Orphan Drug Designation to the JCAR015 chimeric antigen receptor product candidate, developed by Juno Therapeutics Inc., for the treatment of acute lymphoblastic leukemia. Phase I trials are currently underway at Memorial Sloan Kettering Cancer Center, Juno's collaboration partner.

All three of Juno's CAR T cell product candidates currently in trial, including JCAR015, are based on chimeric antigen receptor technology that employs the body's immune system to attack cancer cells.

JCAR017, in phase I/II trials at Seattle Children's Hospital, is being tested for pediatric and young adult relapsed/refractory CD19 positive leukemia.

JCAR014, currently in phase I/II trials at the Fred Hutchison Cancer Research Center, is being tested for relapsed or refractory chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and acute lymphoblastic leukemia.

In Brief

Gilliland Named Director of Fred Hutch Research Center

(Continued from page 1)

Previously, he was an executive at Merck Research Laboratories, a professor of medicine for more than 20 years at Harvard Medical School, and a Howard Hughes Medical Institute investigator.

He directed the leukemia program at Dana-Farber/Harvard Cancer Center, and was also a professor of stem cell and regenerative biology. His research has focused on the genetic basis of blood cancers.

He will become the fifth president and director of Fred Hutch, taking over for **Mark Groudine**, the acting president and director. He is preceded by Lawrence Corey, Nobel laureate Lee Hartwell, Robert Day, and founder William Hutchinson.

According to the center, Gilliland is hopeful that immunotherapy can be successfully applied against a host of diseases that are caused by viruses, from hepatitis C to Burkitt lymphoma and other infectious disease-related cancers, which account for about a quarter of all malignancies worldwide. He also wants to focus on the development of targeted cancer therapies, working with the University of Washington.

Gilliland has received the William Dameshek Prize from the American Society of Hematology, the Emil J. Freireich Award from the MD Anderson Cancer Center, and the Stanley J. Korsmeyer Award from the American Society for Clinical Investigation, of which he is an elected member. He is also an elected member of the American Association of Physicians.

MARK GILBERT was named chief of the **Neuro-Oncology Branch at the NIH**, within the Center for Cancer Research of NCI.

Gilbert was previously deputy chairman of the Department of Neuro-Oncology at MD Anderson Cancer Center.

The Neuro-Oncology Branch is a cooperative program between the NCI and the National Institute for Neurological Disorders and Stroke. Established in 2000, the NOB became one of the first trans-institutional initiatives at the NIH.

Gilbert has served as co-chair of the Brain Tumor Committee for the Radiation Therapy Oncology Group since 2010, and has been the primary investigator on a number of pivotal studies in the field of neuro-oncology. He is expected to begin his new role in late November.

BERT VOGELSTEIN was awarded 2014 Warren Triennial Prize by **Massachusetts General Hospital**.

Vogelstein is the Clayton Professor of Oncology and Pathology and director of the Ludwig Center for Cancer Genetics and Therapeutics at Johns Hopkins University School of Medicine. The award will be presented at the Warren Triennial Prize Symposium, "The Genetics of Cancer," on Nov. 24 at MGH.

Vogelstein and his colleagues demonstrated that colorectal tumors result from the gradual accumulation of alterations in specific oncogenes and tumor suppressor genes, with major implications for improved diagnostic and therapeutic strategies.

He and his colleagues were also the first to map cancer genomes and to use genome-wide sequencing to identify the basis of a hereditary disease. His team has determined the genetic landscapes of more than a dozen tumor types.

The Warren Prize is the top scientific award presented by MGH, and includes a cash award of $50,000. Created in 1871, the prize was named for John Collins Warren, a co-founder of the MGH who played a leading role in establishing what became the New England Journal of Medicine, and also performed the first public surgical operation utilizing ether anesthesia in 1846.

Twenty-three Warren recipients have also received the Nobel Prize–including 2011 recipient Shinya Yamanaka, a 2012 Nobel laureate; and 2004 recipients Craig Mello and Andrew Fire, who received the 2006 Nobel.

SUSAN MAYNE was appointed director of the **FDA Center for Food Safety and Applied Nutrition**.

Mayne is the Winslow Professor of Epidemiology; associate director for population sciences at Yale Cancer Center; and chair of the Department of Chronic Disease Epidemiology at the Yale School of Public Health.

Mayne joined Yale University in 1987 as a post-doctoral fellow, and directed Yale Cancer Center's Cancer Prevention and Control Research Program from 1993-2010. She also served as associate director for population sciences from 1995. She is the recipient of several national awards in mentoring and training and for her service to many organizations including the National Academy of Sciences. She has also served on the NCI Board of Scientific Counselors.

The center regulates $417 billion worth of domestic food, $49 billion worth of imported foods, and over $60 billion worth of cosmetics sold across state lines, and is supported by a staff of over 800 employees, with a budget of nearly $300 million.

MERCK KGAA and **Pfizer Inc**. will co-develop and co-commercialize MSB0010718C, an investigational anti-PD-L1 antibody currently in development by Merck KGaA as a potential treatment for multiple tumor types.

The asset will be developed as a single agent as well as in various combinations with the two companies' portfolios of drug candidates. The two companies will also advance Pfizer's anti-PD-1 antibody into phase I trials. As part of the agreement, Merck KGaA will co-promote Pfizer's Xalkori for the treatment of non-small cell lung cancer.

"Up to 20 high priority immuno-oncology clinical development programs are expected to commence in 2015, including pivotal registration studies," said Belén Garijo, president and CEO of the biopharmaceutical division of Merck KGaA. There are currently two clinical development programs underway evaluating MSB0010718C.

In a phase I trial, more than 550 patients have been treated with the drug across multiple types of cancers, with interim data demonstrating a complete response and partial responses in patients with non-small cell lung cancer and ovarian cancer. Additional data are expected to be presented at medical congresses in 2015.

There is also an ongoing phase II trial evaluating this antibody in patients with m-Merkel cell carcinoma.

Under the terms of the agreement, Merck KGaA will receive an upfront payment of $850 million and is eligible to receive regulatory and commercial milestone payments up to $2 billion. Both companies will jointly fund all development and commercialization costs, and all revenues obtained from selling any anti-PD-L1 or anti-PD-1 products generated from this collaboration will be shared.

NYU LANGONE Medical Center and **Lutheran Medical Center** will create a clinically integrated health care provider network for the New York metropolitan area.

This agreement creates a formal health system between the two organizations that extends NYU Langone's presence in Brooklyn, while bolstering Lutheran's access to NYU Langone's vast offering of medical and surgical specialties. Regulatory approval for the combination and new health system entity are expected to be completed in 2015.

NYU Langone has multiple ambulatory sites throughout the region, in addition to its main Manhattan hospital campuses, and Lutheran, in collaboration with its affiliated health center, Lutheran Family Health Centers, operates an expansive network of ambulatory practices in four boroughs of New York.

"We have been working closely with Lutheran over the last several months to assess whether a partnership would benefit each of our institutions, the Brooklyn community and, most importantly, the patients and families who turn to us for help," said Robert Grossman, dean and CEO of NYU Langone.

This affiliation agreement allows both institutions to respond to this changing landscape and stabilize health care delivery in Brooklyn. This will be accomplished by:

The affiliation will create a fully integrated delivery system in Brooklyn using Lutheran's existing primary care network, develop a system-wide IT infrastructure, and will focus on key initiatives including maternal and child health, cancer services, cardiac and vascular services, and physician network development.

DANA-FARBER CANCER INSTITUTE and **Astellas Pharma Inc**. announced a three-year collaboration to research and develop small molecule inhibitors of oncogenic K-Ras for the treatment of cancer.

Astellas will provide research support and retain the option to obtain from Dana-Farber an exclusive, worldwide license to novel K-Ras inhibitors obtained from the collaboration. Astellas would then conduct further research, development and commercialization.

Nathanael Gray, of the Cancer Biology Department at Dana-Farber and professor at Harvard Medical School, will lead this collaborative research. His laboratory and the Dana-Farber Medicinal Chemistry Core will be joined by the laboratories of Pasi Jänne, and Kwok-Kin Wong, of the Thoracic Oncology Program and co-directors of the Belfer Institute for Applied Cancer Science at Dana-Farber and Professors at Harvard Medical School.

TAPIMMUNE Inc. and the **Vaccine & Gene Therapy Institute of Florida** formed a partnership to advance TapImmune's cancer vaccines into phase II clinical trials for the treatment of breast and ovarian cancers.

These cancer vaccine candidates were developed by the institute's director of cancer vaccines and immune therapies program, Keith Knutson. VGTI Florida will work with TapImmune to design and execute the clinical programs, including the design of the clinical protocols, and selection of clinical trial sites and external manufacturing and clinical resources.

TapImmune had previously announced the licensing of these vaccines technologies for the treatment of HER2/neu breast cancer and ovarian and breast cancer developed in the laboratory of Knutson while he was at the Mayo Clinic.

ST. JUDE CHILDREN'S RESEARCH HOSPITAL dedicated and opened **The Marlo Thomas Center for Global Education & Collaboration** on the St. Jude campus in Memphis, Tenn., Nov. 20. The center will focus on childhood cancer.

The center will also become the hub for the St. Jude International Outreach Program, which has 25 official partner sites in 17 countries. The center also will support the training of St. Jude's postdoctoral and graduate fellows.

The center is named for St. Jude National Outreach Director Marlo Thomas. Both she and Hillary Clinton were scheduled to attend the dedication, with Clinton as honored guest and featured speaker. Clinton also attended the 1994 dedication of the St. Jude Patient Care Center when she served as first lady.

THE BARBARA ANN KARMANOS CANCER INSTITUTE was honored by the **Michigan Cancer Consortium** with the 2014 Spirit of Collaboration Award for its Jewish Women's Health Project; and also received an Honorable Mention for its Harley Men's Health Event.

The Spirit of Collaboration Award is the highest honor the Michigan Cancer Consortium presents to member organizations, recognizing outstanding collaborative work that significantly moves cancer prevention and control activities forward in Michigan. The award presentation took place this month during the Michigan Cancer Consortium's annual meeting in Lansing.

Karmanos Cancer Institute's Jewish Women's Health Project is a collaboration of the Council of Orthodox Rabbis, the Women's Orthodox League, The Jewish Fund, Jewish Family Service, The Jewish Community Center of Oak Park, and Kids Kicking Cancer. The purpose of the program is to better understand and help prevent the genetic risk factor of the BRCA I and II genes among Orthodox Jews.

Genetic research documents a high prevalence of the BRCA I and II and anedomatous polyposis coli genes among Ashkenazi (i.e. European) Jewish women. Mutations in these genes place carriers at a significantly greater risk for breast, ovarian, pancreatic, colorectal, and other cancers.

The Harley Men's Health Event is a collaborative project with Wolverine Harley Davidson that has for the past three years helped to increase awareness and access to recommended cancer screenings for an underserved population in Michigan. In the past three years, the event has reached 530 community members.

Obituary

Connie Curran, 67, C-Change Executive Director

Connie Curran, 67, the first executive director of C-Change, died Nov. 10.

C-Change brings together leaders in cancer from the public, private, and not-for-profit sectors.

Curran was born in Berlin, Wis. She held degrees from the University of Wisconsin, DePaul University, and Northern Illinois University. She also is a graduate of Harvard University Business School's Owner/President Management program.

One of her first appointments was at the University of San Francisco School of Nursing, where she served as a dean and faculty member from 1977-1981.

At the time of her death, Curran was chairman of the board of DeVry Education Group, the parent corporation for DeVry University, Chamberlain School of Nursing, and others. She also served on the board of Hospira Inc., and was previously on the boards of Volcano, Pyxis, Allegiance, Cardiodynamics, and IDX.

She was also a board member at DePaul University; Lurie Children's Hospital of Chicago; and the University of Wisconsin Foundation. She also is a past chair of Silver Cross Hospital and formerly was a board member of the National Student Nurses Association.

She also was vice president of the American Hospital Association; the founding dean of the former Medical College of Wisconsin School of Nursing; chair of nursing at Montefiore Medical Center; and vice chair of APM Inc.

In 1995, Curran founded CurranCare in 1995, a national health care consulting and management company, which was acquired in 2000 by Cardinal Health. Curran authored more than 200 scholarly articles and research projects. She is the first editor emeritus of Nursing Economics, which she led editorially for more than 18 years.

She is survived by daughter Melissa Curran, son-in-law Adam Oberweiser, and grandson Oliver Oberweiser. She also is survived by her father Pat Curran; siblings Colleen Raterman; Tom Curran; Ann Curran Gleichert; Mary Curran; and Patty Curran; and former husband and friend, Donovan Riley.

A memorial gathering sponsored by DePaul University, is planned for December 6, 2014, 10 a.m., at St. Vincent de Paul Parish in Chicago.

Memorials can be made in Curran's name to the Breast Cancer Research Foundation, or the University of Wisconsin Foundation/School of Nursing.