THE CANCER LETTER

Nov. 20, 2015 • www.cancerletter.com • Vol. 41 No. 43

Congressman Questions Whether J&J, Brigham Reported Morcellation Adverse Events to FDA

By Matthew Bin Han Ong

The House Committee on Energy & Commerce has stepped into a key role in the controversy over power morcellation.

At a hearing earlier this week, Rep. Tim Murphy (R-Pa.), chairman of the Subcommittee on Oversight and Investigations questioned whether Johnson & Johnson and Brigham & Women's Hospital violated federal law by not reporting adverse outcomes resulting from power morcellation.

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CBER's All-Day Voyage into Slippery Science Ends in 18-6 Vote against Bladder Therapy

By Paul Goldberg and Conor Hale

One might surmise that by the time FDA asks an advisory committee to vet an application, the questions would deal primarily with clinical utility.

By that stage in the game, advisors would be asked to discuss the outcomes, as opposed to the biological mechanisms for achieving them.

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NCI Announces First Class of Outstanding Investigators

NCI named the inaugural 43 recipients of its Outstanding Investigator Awards.

Developed last year, the grant program provides funding to investigators with outstanding records of productivity in cancer research to support projects of unusual potential in cancer research.

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The Cancer Letter will take a publication break for Thanksgiving and will return Dec. 4

Congressman Asks If Morcellation Adverse Events were Reported

(Continued from page 1)

At the Nov. 17 hearing by the Subcommittee on Health, Murphy quizzed Jeffrey Shuren, director of the FDA Center for Devices and Radiological Health, in an apparent effort to determine whether manufacturers of power morcellators as well as hospitals that used these devices had failed to notify FDA that patients were being harmed.

"Are you aware of this problem?" Murphy asked Shuren. "[Johnson & Johnson] was apparently aware of the dangers of this device as early as 2006, based upon a report from Dr. [Robert] Lamparter, a pathologist from central Pennsylvania, who cited about one out of 300 samples of morcellated tissue from his hospital had evidence of a hidden cancer, which is morcellated."

At the hearing, Murphy pressed FDA's Shuren on how much the agency knew about these incidents.

"Let me ask another question: Brigham & Women's Hospital was aware of the dangers in 2012," Murphy said. "A patient by the name of Mrs. Erica Kaitz was seriously injured in 2012 by the device and then died in 2013, according to reports.

"I wonder, do you know if the hospital reported that to the FDA? Would you know?"

Shuren: "I'm not aware of that."

Contacted by The Cancer Letter after the hearing, Brigham declined to comment. The J&J subsidiary Ethicon said the company wasn't aware of any reportable adverse events prior to December 2013.

"Dr. Lamparter did contact the company in 2006 seeking advice on ways to collect and evaluate endometrial specimens following morcellation," an Ethicon spokesperson acknowledged to The Cancer Letter.

However, the company spokesman said the communication didn't constitute a reportable event. "Because Dr. Lamparter did not report an actual experience with a patient, his communication was handled as a complaint, and was not reportable as an MDR," the spokesman said.

A story about Lamparter's report to J&J appears here.

In an earlier statement to The Cancer Letter, FDA said it received no reports of adverse outcomes before December 2013. Since then, the agency was informed of about two dozen cases of upstaging of cancer via power morcellation at a variety of health care institutions.

FDA's answers to questions from The Cancer Letter are posted here.

The congressional hearing this week was part of a string of investigations of the controversy stemming from widespread use of power morcellators, gynecological devices now known to spread undetected cancers during hysterectomies and myomectomies.

The questions also stem from correspondence between FDA and Rep. Mike Fitzpatrick (R-Pa.), who is not a member of Energy & Commerce. Fitzpatrick became involved in response to advocacy by his constituents Amy Reed and Hooman Noorchashm (The Cancer Letter, Nov. 13).

Reed's uterine sarcoma was upstaged as a result of a power morcellation surgery performed at Brigham.

"Under section 519 of the [Federal Food, Drug, and Cosmetic] Act (see also 21 CFR part 803), manufacturers must report to FDA information that suggests that a device they market may have caused or contributed to a death or serious injury," the agency said in a Nov. 12 letter to Fitzpatrick. "Moreover, user facilities must report device-related serious injuries to the manufacturer and device-related deaths to the manufacturer and FDA.

"FDA has taken enforcement action in the past against user facilities and manufacturers who fail to comply with FDA's reporting requirements. We have generally focused our enforcement resources on manufacturers—who are required under law to investigate any MDR-reportable complaint they receive—and not on user facilities. We have found that encouraging more reporting—and more complete reporting—by user facilities is a good use of our limited resources in this area," FDA wrote in response to Fitzpatrick's questions.

Fitzpatrick's letter and the agency's response are posted here.

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General Information: www.cancerletter.com

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

"You will note that it is an incomplete response," a spokesperson for Rep. Fitzpatrick said to The Cancer Letter. "We will be sending out a full release when we get a complete response."

Separately, the Federal Bureau of Investigation is reportedly looking into the issue, and the Government Accountability Office is investigating the controversy at the behest of 12 members of Congress (The Cancer Letter, May 29, Sept. 11).

In November 2014, The Cancer Letter first reported on Brigham's role in upstaging Erica Kaitz's leiomyosarcoma via power morcellation. Kaitz died on Dec. 7, 2013, nearly two months after Reed received her cancer diagnosis at Brigham (The Cancer Letter, Nov. 26, 2014).

Her widower Richard Kaitz, a Boston real estate lawyer, said that Brigham doctors mischaracterized the risk his wife was facing when she underwent power morcellation.

"They gave us numbers—one out of 10,000—that they knew to be wrong," Kaitz said to The Cancer Letter last year. "The Seidman, Muto article was published in November 2012. It says right in that article that multiple parties at Brigham said that the number they are quoting for the risk are nine times lower than the real risk."

A transcript of the exchange between Murphy and Shuren follows:

Rep. Tim Murphy: Doctors, doctors, good to have you here. I appreciate this. I want to pivot a little here to talk about and piece together postmarket and premarket analysis and to look at this. In particular, a couple of devices used in women's health care.

One is called a morcellator. Are you familiar with the morcellator? A device that is supposed to shred tumors etc. but has been associated with complications in women in terms of actually spreading cancer for them. It's been on the market for 20-plus years, and FDA admitted for the first time it became aware of the safety issue with power morcellators after December 2013—correspondence from a physician citing a case of a family member.

This is someone who just recently had another surgery to remove another recurrence of cancer that was spread by the morcellator. The manufacturer [Johnson & Johnson] was apparently aware of the dangers of this device as early as 2006, based upon a report from Dr. [Robert] Lamparter, a pathologist from central Pennsylvania, who cited about one out of 300 samples of morcellated tissue from his hospital had evidence of a hidden cancer, which is morcellated.

My question is, did the FDA have any evidence of these dangers in 2006 or prior to that? Are you aware of this problem?

Jeffrey Shuren: In the past, the thought was that the risk—what risk of cancer there may be for a fibroma, for a fibroid—was significantly less, and one of the things that we looked into more recently, we came to a different conclusion that the likelihood of cancer is higher.

There's still disagreement in the community, because, as you know, the [gynecology] health care professional societies disagree. They think we have overestimated the risk of the cancer, we said we have a different perspective, and that's why we went out and we put contraindications and warnings on the use of that device, that it should only be used in a more limited set—or offered as an option—of women, and think about primarily women who, in the absence of using the device, would no longer be able to bear children, but want to bear children, and we felt in those cases the risk of a cancer is very low. They share the opportunity to weigh in, but we scaled back dramatically how that should be used.

TM: So there's a case where the science available at the premarket analysis has changed, and once being used in the data, you have a mechanism to go forward on this and make some changes.

Let me ask another question: Brigham & Women's Hospital was aware of the dangers in 2012. A patient by the name of Mrs. Erica Kaitz was seriously injured in 2012 by the device and then died in 2013, according to reports.

I wonder, do you know if the hospital reported that to the FDA? Would you know?

JS: I'm not aware of that.

TM: Is there a mechanism where the hospital is supposed to report that, or the manufacturer is supposed to report that so you can do an analysis?

JS: So, user facilities have certain requirements for reporting, so do manufacturers, if they become aware of certain events. And what I can tell you is we've been looking into those concerns that have been raised regarding reporting.

TM: OK. In a response to Congressional inquiries about this, the FDA admitted that the one out of 350 risk does not address other types of malignancies, which, you would add to that risk, you said. They went on to say the FDA also identified studies showing that morcellated patients had worse outcomes than patients who had not undergone morcellation.

So, this is more than just the issue with just a

fibroid or if it's cancerous. It is also a question of outcomes. Is this something that the FDA is reviewing, also with regard to their stamp of approval on these things, in terms of the outcome measures?

JS: So in terms of the tests we've looked at, we think where we have constrained it right now, is for use—is where the benefits outweigh the risks, but we are continuing to look at new data as it arises, and if so, we will act accordingly.

TM: Thank you. There is another issue in women's health as brought to my attention. It's a product called Essure. It's a permanent birth control device that went through FDA's rigorous premarket approval process.

Yet, despite getting the agency's approval, it's been linked to at least four deaths and deaths of five unborn children. Apparently, a total of 24,000 women have come forward, claiming that they have been harmed by this device.

And so the question is, how it remains on the market with potential for problems, and because this has the FDA stamp of approval, these women feel disappointed—they cannot take their cases forward, and feel they don't have any recourse.

Is the FDA also reviewing this issue as well?

JS: In fact, we held an advisory committee meeting a few weeks ago at our behest to give an opportunity to put what new evidence is on the table to assure that people who wanted to raise concerns about it had an opportunity to provide those concerns.

And we are now currently reviewing the feedback received from the advisory committee, as well as what we have heard from other people as well as the state of the evidence, and we will come out with our conclusions on that to the public.

TM: Thank you. And as this goes through, since this hearing is a lot about premarket analysis, what this comes down to is, I just want to make sure that we are aware of what mechanism you have, because I understand the science of 1996 is different from the science of 2015 and our knowledge base, but to have an ongoing mechanism for review and changes of devices and getting information there and looking at those things.

I'm glad you had some hearings on this, but I'd certainly like to know that that's part of the system. I'm out of time, but I look forward to hearing your comments on that in the future. Thank you.

FDA: Federal Law Requires Reporting of Morcellation Adverse Events, But None Reached Agency's Attention For Eight Years

FDA officials said the agency didn't receive any reports of adverse outcomes resulting from power morcellation prior to December 2013.

"Of note, prior to December, the FDA had received no MDRs specifically on cancer and upstaging/dissemination," the agency said in response to questions from The Cancer Letter. "Since then, the agency has become aware of about two dozen that have discussed 'cancer' and 'upstaging or dissemination' as of November 2014. All of these reports pertained to procedures that took place prior to December 2013."

Robert Lamparter, a retired pathologist, alerted Ethicon, a Johnson & Johnson subsidiary, about potential problems with morcellators in 2006. The Pittsburgh Business Times reported on the whistleblower case in May 2014.

A full account of Lamparter's 2006 complaint is published here.

According to an FDA advisory in April 2014, one in 350 women with undergoing hysterectomy for the treatment of is found to have an unsuspected uterine sarcoma, a type of uterine cancer that includes leiomyosarcoma.

Two women—Erica Kaitz and Amy Reed—underwent power morcellation performed at Brigham & Women's Hospital in 2012 and 2013, respectively. Kaitz died on Dec. 7, 2013 from metastatic leiomyosarcoma, and Reed recently underwent surgery for a third recurrence (The Cancer Letter, Nov. 26, 2014, Nov. 3, 2015).

Responding to similar questions from Rep. Mike Fitzpatrick (R-Pa.), FDA said it disagrees with the 2011recommendations from the Institute of Medicine, which called for an overhaul of the agency's 510(k) process for clearing devices (The Cancer Letter, July 4, 2014).

"The Institute of Medicine made eight recommendations to FDA, one of which was that FDA should design a new system for the review of Class II devices," FDA wrote to Fitzpatrick. "While FDA does not agree with IOM's recommendation to create a new system, we do believe that we can make improvements to the current system and we have worked to do so over the past four years."

FDA responded to questions from Matthew Ong, a reporter with The Cancer Letter.

Matthew Ong: *Knowing what we know now, should the power morcellator have gone through more rigorous testing before it was cleared for the market?*

FDA: Having more rigorous testing of morcellators before clearance likely would not have addressed the issue of spreading unsuspected cancer through morcellation, because uterine sarcomas are a rare type of cancer; the rate of unsuspected uterine sarcoma in women undergoing hysterectomy or myomectomy for the treatment of uterine fibroids is about 1 in 350.

Even a large clinical trial involving hundreds of patients would have been unlikely to detect these events. After the risks of power morcellators spreading unsuspected cancer became known, the FDA took several steps to reduce the risk of spreading unsuspected cancer by laparoscopic power morcellation during fibroid surgery, including asking manufacturers to add a boxed warning to product labels specifying:

1) Laparoscopic power morcellators are contraindicated for removal of uterine tissue containing suspected fibroids in patients who are: peri- or post-menopausal, or are candidates for *en bloc* tissue removal, e.g. through the vagina or mini-laparotomy incision. (These groups of women represent the majority of women with fibroids who undergo hysterectomy and myomectomy.)

2) Laparoscopic power morcellators are contraindicated in gynecologic surgery in which the tissue to be morcellated is known or suspected to contain malignancy.

The contraindications cover a majority of women who would undergo morcellation during myomectomy or hysterectomy. This should help to reduce the use of the device in patients at greatest risk.

The FDA has also asked manufacturers to include the following boxed warning in their product labeling: Uterine tissue may contain unsuspected cancer. The use of laparoscopic power morcellators during fibroid surgery may spread cancer, and decrease the long-term survival of patients. This information should be shared with patients when considering surgery with the use of these devices.

MO: *Are there any lessons to be learned at FDA from the power morcellation case?*

FDA: Any device cleared or approved for marketing carries a certain element of risk that must be weighed against potential benefits offered to patients. FDA believes there is an opportunity for manufacturers to develop products that may further reduce this risk of spreading existing cancer.

Better diagnostics aimed at detecting uterine cancer as well as containment systems designed specifically for gynecological surgery could be helpful. Experts from our July 2014 panel meeting agreed that innovation in these areas may further address this risk.

The FDA continues to actively work to strengthen its medical device post market surveillance system.

MO: *Does FDA have any plans to tighten the medical device clearance process i.e. the 510(k) or to seek additional authority from Congress to do so?*

FDA: The 510(k) program works well to determine whether new devices are substantially equivalent to a previously cleared device, meaning that the new device is as safe and effective as its predicate.

We've had tens of thousands of good products come on the market through that pathway, and it encourages manufacturers of lower risk devices to make important upgrades to enhance the performance of their device without having to go through the expense of a premarket approval.

FDA does acknowledge that the clearance process can be improved, and we remain open to opportunities to enhance the programs we have whether through a program reform, or if there are appropriate changes that can be made to the law, to new legislation.

MO: *How would the 21st Century Cures Act—if passed in its current form—change regulation of medical devices at FDA?*

FDA: FDA cannot predict how this legislation will affect device regulation in the future since it is still in transitory stage and has not yet been passed by both houses of Congress or signed into law.

MO: *Is it true that manufacturers and user facilities—Johnson & Johnson/Ethicon and Brigham & Women's Hospital—did not report adverse events resulting from power morcellation as per the Section 803 Title 21 mandate? Does FDA see a need to ensure that user facilities report in a more robust fashion?*

FDA: Manufacturers, such as J&J/Ethicon, are required to report to the FDA when they learn that any of their devices may have caused or contributed to a death or serious injury.

Manufacturers must also report to the FDA when they become aware that their device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

A "device user facility" is a hospital, ambulatory surgical facility, nursing home, outpatient diagnostic facility, or outpatient treatment facility, which is not a

physician's office.

User facilities are required to report a suspected medical device-related death to the FDA and the manufacturer within 10 workdays of becoming aware of the event. They must report serious device-related injuries to the manufacturer and to the FDA if the manufacturer is unknown.

With regard to the spread of unsuspected cancer when using laparoscopic power morcellation for hysterectomy or myomectomy in women with symptomatic uterine fibroids, the FDA has clarified that it considers such an event to be reportable as a serious injury.

The FDA has generally focused its enforcement resources on manufacturers—who are required under law to investigate any MDR-reportable complaint they receive—and not on hospitals.

The FDA has found that encouraging more reporting—and more complete reporting—by hospitals/user facilities and physicians, is a good use of the limited resources in this area.

Of note, prior to December, the FDA had received no MDRs specifically on cancer and upstaging/dissemination. Since then, the agency has become aware of about two dozen that have discussed 'cancer' and 'upstaging or dissemination' as of November 2014. All of these reports pertained to procedures that took place prior to December 2013.

The timing of these reports may be due to the heightened sensitivity and media attention given to the subject in late 2013. The FDA is still analyzing the adverse event data it has received on morcellation.

MO: *Is it true that some PMA-approved devices (and/or 510k-cleared devices) are exempt/excluded from civil/product liability litigation because FDA has approved them?*

FDA: The FDA does not "exempt" devices from lawsuits. Rather, certain state requirements that apply to medical devices are preempted under section 521 of the Federal Food, Drug, and Cosmetic Act.

Interpreting this provision, the Supreme Court has said that state common law claims relating to approved class III devices generally are preempted. In other words, people injured from a class III, PMA-approved device typically cannot recover damages from device manufacturers for their injuries under state common law theories.

In contrast, the Court has said that such claims are generally *not* preempted under section 521 when they relate to class I devices.

J&J Says There were No Reportable Morcellation Events; Whistleblower Disagrees—And Produces Letters

By Matthew Bin Han Ong

Johnson & Johnson officials said the company was unaware of any reportable adverse events resulting from the use of power morcellators prior to 2013.

"[J&J subsidiary] Ethicon was not aware of any reportable events related to morcellators and the possibility of upstaged cancer prior to December 2013," a company spokesman said to The Cancer Letter. "Since that time, we have filed reports with the FDA for all reportable events that have come to our attention."

Ethicon responded to The Cancer Letter's questions after the Nov. 17 hearing by the Subcommittee on Health, where Rep. Tim Murphy (R-Pa.) noted that the company had received a report about the dangers of power morcellators.

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

J&J requested withdrawal of morcellators in July 2014, after an FDA panel expressed low confidence in the devices for use in hysterectomies and myomectomies (The Cancer Letter, July 25, 2014).

At the congressional hearing, Murphy said J&J was informed of similar estimates as early as 2006, when Robert Lamparter, a pathologist from central Pennsylvania, alerted J&J officials to the risk of the device spreading undetected uterine sarcoma.

"Dr. Lamparter did contact the company in 2006 seeking advice on ways to collect and evaluate endometrial specimens following morcellation," Ethicon said in a statement to The Cancer Letter. "Because Dr. Lamparter did not report an actual experience with a patient, his communication was handled as a complaint, and was not reportable as an MDR."

FDA officials said the agency didn't receive any reports of adverse outcomes resulting from power morcellation prior to December 2013.

Lamparter, 64, a retired pathologist who practiced at Evangelical Community Hospital in Lewisburg, Pa., for 28 years, said that J&J is not telling the whole truth.

"Technically, they're saying that I didn't report it as a patient whose cancer was spread, so technically, they didn't lie," Lamparter said to The Cancer Letter.

"But they're implying that I didn't tell them, and

that's not the truth.

"I'm sort of an accidental whistleblower. I didn't go out with an ax to grind, but I do feel strongly that the company has tried to hide this from people, and I'm glad to see that somebody like Dr. Hooman Noorchashm is bringing this to the forefront.

"I think what they're going to try to do in laying out a legal strategy is, 'This didn't meet the standards for a reportable event, so we're clear,'" Lamparter said. "That's how they are going to try to defend themselves."

Lamparter's 2006 correspondence with Ethicon is posted here.

"I Hope You Reconsider"

Lamparter said he first reported the issue as a "near-miss" case—a patient who was scheduled for power morcellation, but ultimately wasn't subjected to the procedure.

"We had a patient who was saved by her guardian angel," Lamparter said. "It was a situation where an operation was started as a morcellation. The doctor couldn't do it as a laparoscopic surgery because of adhesions, so they elected to do it open. When they took the uterus out, there was a cancer there, and had they morcellated it, that cancer would've been spread.

"Now, we knew theoretically this was a possibility prior to this index case, but as we had this near-miss case, we felt that we had enough information that we could mention this to the company. It's no longer a hypothetical—we had a near miss."

Lamparter initially brought his concerns to David Robinson, the medical director of Ethicon Women's Health and Urology at the time.

"My conversations with Ethicon started as, 'How do we solve this problem? The way our gynecologists were using the device, we couldn't find the endometrium to document the status of the inner lining of the uterus,' Lamparter said. "That's how the conversation began, and during that conversation, we had our near-miss case, and that gave me the opportunity to tell Dr. Robinson about it."

Lamparter said he sent several emails to Robinson "until [Robinson] understood the significance of what I was telling."

"We recently had a patient with an unexpected malignancy who almost had a morcellization [sic], save that she was saved from inappropriate morcellization by adhesions," Lamparter wrote in a February 2006 email to Robinson. "We have had a good endometrial biopsy six months prior to the procedure. After we found a carcinoma in the endometrium after hysterectomy, we reviewed the endometrial biopsy and found no malignancy.

"If this woman had had a morcellization, her tumor would have been seeded into the peritoneum. We pathologists might not have even found it, until it had metastasized if she had a morcellization. Or, we might have documented benign endometrium, because that what's was covering the majority of the endometrial cavity.

"At least one missed malignancy after morcellization has been reported in the literature: 1997 American Journal of Obstetrics and Gynecology, 'Recurrence of unclassifiable uterine cancer after modified laparoscopic hysterectomy with morcellation' by A. Schneider."

Lamparter said Robinson forwarded his report to Ethicon's World Wide Customer Quality Department. Ethicon classified Lamparter's concerns as pertaining to an "off-label use."

"I got a nonsensical letter back from Lori Pasternack, who was the representative of that committee," Lamparter said. "That wasn't my inquiry, about how to use it off label.

"They never really responded to why we couldn't find the endometrium. By trial and error, we eventually did figure out what happened, and why that was—it was the technique our surgeons were using, which they apparently weren't well taught at the training center on how to use this thing. Once we changed the technique, we began to find the endometrium."

Ethicon reviewed the correspondence between Lamparter and Robinson and informed Lamparter that the company was ending the investigation.

"You reported to our Medical Director that you have experienced difficulty of examining the endometrium of uteri that have undergone morcellation by our morcellator device," Ethicon's Pasternack wrote in a May 2006 email to Lamparter. "Your concern is that you fear missing an endometrial cancer.

"The morcellator device is indicated to remove tissue, and it is not indicted [sic] for sample gathering or preparation. Therefore, your concern is in regards to an off-label use."

Enclosed with Pasternack's letter was a copy of Ethicon's power morcellator user manual.

Lamparter replied, asking Ethicon to "reconsider" his report and inform the gynecology community of the risks.

"In about 1/300 hysterectomies at our hospital, we discover an endometrial carcinoma that was unexpected at the time of surgery," Lamparter wrote. "To recommend to the gynecologist users that it important to evaluate the endometrium for cancer prior to performing

morcellation is such a simple solution that I find it difficult to understand why Ethicon-Gynecare hasn't made the recommendation.

"It doesn't cost the company anything to make the recommendation, and it's cheap insurance for all the involved parties. Trying to put myself in your shoes, the only reason I can see for the company's stance is that others haven't reported the problem yet.

"My speculation in that regard is that the literature hasn't yet been written on this topic, so nobody knows to knock on your door at this time. Time will tell.

"If your letter to me was written in haste, I hope you reconsider."

Lamparter said he did not receive a response.

Lamparter: I Don't Think J&J Looked

Lamparter said J&J's statement that the company was not "aware of…the possibility of upstaged cancer prior to December 2013" ignores his past correspondence with Ethicon.

"In that letter to Lori Pasternack, I pointed out this thing would seed tumor on the peritoneum and upstage the cancer," Lamparter said. "They've had two opportunities to act—I told Dr. Robinson, and I told the person who is the representative of J&J's World Wide Customer Quality counsel that they have a problem.

"If you have a cancer that is hidden in the uterus and it's at a much lower stage and you seed that, it metastasizes and is considered to be a much higher stage. So they did know that this procedure could upstage the cancer. They knew that in 2006.

"I can understand that they would be skeptical of some local yokel in a community hospital telling this, but they could at least investigate and look over their shoulder and see that the statistics show risk way too high compared to what we think it is.

"I can understand their inclination to just give me a polite letter and blow me off, but you know, when somebody is telling you something like that, you should at least look. And I don't think they looked, because if they had, they would've found it.

"In the beginning, I thought it was just a matter of educating the doctors to be more careful in patient selection. As time went on, it became apparent that it wouldn't make any difference. They would still accidentally morcellate cancers in about one in 300 times.

"I'm not the only person who had a patient that had morcellated cancer. Over time, we had between four and seven patients with morcellated malignancies at our hospital.

"We were a 95-bed hospital, now, you multiply the number of hospitals with many more hospital beds—and more active gynecology services than we had—around the country.

"J&J had to have known, because there were other patients having problems."

The full text of Ethicon's statement follows:

First, we sympathize with the women and their families who may have suffered the spread of a malignancy following surgical treatment for gynecologic conditions, and continue to collaborate with the medical community in efforts to potentially reduce the risk in the future and to better enable physicians and patients to understand the risks and limitations ahead of their surgery.

As the medical community's understanding of the risk of undiagnosed malignancies prior to uterine surgery evolved in 2014, we elected to suspend sales and then to voluntarily withdraw our powered morcellation devices from the marketplace. We remain the only manufacturer to have taken these steps.

Ethicon files Medical Device Reports (MDRs) on our products with the FDA in a timely manner once information is received or noticed by the company indicating that reporting is appropriate under FDA guidelines.

Ethicon was not aware of any reportable events related to morcellators and the possibility of upstaged cancer prior to December 2013. Since that time, we have filed reports with the FDA for all reportable events that have come to our attention, even when it was unclear whether one of our devices was involved.

We take our reporting responsibilities seriously, and have filed reports related to morcellation devices even when we were unable to confirm that the device used was manufactured by Ethicon.

Nearly all of the reports we have filed were not the result of reports made directly to Ethicon, but based on information from news articles and lawsuits following increased public attention to this issue beginning in the fall of 2013. Ethicon morcellation devices have always included cautions in their instructions for use (IFU) about the potential spread of cancerous tissue.

We highly value the feedback we receive from physicians and we are continually assessing the totality of the available data and information related to our products, including peer-reviewed studies and scientific literature, as well as physician feedback.

Dr. Lamparter did contact the company in 2006 seeking advice on ways to collect and evaluate endometrial specimens following morcellation. Because

Dr. Lamparter did not report an actual experience with a patient, his communication was handled as a complaint, and was not reportable as an MDR.

His questions, along with other medical consultation at that time, prompted Ethicon to revise the precautions contained in the device's IFU to address the issue of the preoperative pathologic evaluation of the endometrium to minimize the risk of inadvertent morcellation of an occult malignancy.

Capitol Hill

FDA Lists Potentially Avoidable Harms in 20 LDT Case Studies, Including Tests from Duke, Caris and Genomic Health

By Conor Hale

Ahead of a Capitol Hill hearing this week on the role of the FDA in the regulation of laboratory-developed tests, the federal agency published a report of 20 case studies that illustrated the possible harms presented to patients when laboratories do not comply with FDA requirements.

The case studies included LDTs such as the Target Now cancer biomarker test, developed by Caris Life Sciences Inc.; the Oncotype DX HER2 RT-PCR breast cancer test; and the Duke University Chemotherapy Assessment genetic tumor assay.

The report also examined tests used to screen women for ovarian cancer, to identify breast cancer patients that have HER2 receptors, HPV genetic exams, a leukemia therapy companion diagnostic, and a genetic mutation test to guide melanoma treatment—as well as tests for whooping cough, Lyme disease, prenatal tests, and others.

"The costs of this lack of oversight are staggering," said Peter Lurie, associate commissioner for public health strategy and analysis, in an FDA blog post about the report and why the agency should oversee LDTs.

"We were able to derive an estimate of the public health cost for five of the 20 cited tests," Lurie wrote Nov. 16. "For the CARE Clinical Autism Biomarkers Test alone (one of those cited in the report), FDA economists estimated a total public health cost of $66.1 million."

FDA issued a draft guidance last year, proposing to step up oversight of LDTs. "FDA oversight would help ensure that tests are supported by rigorous evidence, that patients and health care providers can have confidence in the test results, and that LDTs have more scientifically accurate product labeling," Lurie wrote.

The report listed situations where the tests may have caused actual harm: "In some cases, due to false-positive tests, patients were told they have conditions they do not really have, causing unnecessary distress and resulting in unneeded treatment."

"In other cases, the LDTs were prone to false-negative results, in which patients' life-threatening diseases went undetected. As a result, patients failed to receive effective treatments," according to the report.

In the case of the Duke genetic tests, the report cited errors in data management and analysis, and a lack of clinical validation. The makers of the tests claimed they were able to predict response in ovarian, lung and breast cancers. The FDA, in their report, described them as tests that undermined drug approval or drug treatment selection.

"The data suggested that results from gene expression panels, implemented as LDTs, could predict individuals' responses to specific chemotherapy regimens," the report said. "Without further validation of predictive validity for the laboratory's LDTs, three clinical trials were conducted, using LDT results to allocate patients to chemotherapy treatments."

"Scientific rigor dictates that a test should be developed with one set of data, and validated on an entirely separate set of data in order to avoid over-estimation of performance. The Duke investigators, however, allowed overlap of the data sets, which produced overestimates of test accuracy."

The case of the three Duke clinical trials led to an investigation conducted by the Institute of Medicine, and the retraction of scientific papers in Nature Medicine, the Journal of Clinical Oncology, and the New England Journal of Medicine, among many others—totaling 27 complete or partial retractions, according to the report. The Cancer Letter's coverage of the Duke scandal is available here.

"In the IOM's assessment, greater FDA oversight and involvement may have uncovered errors and validation issues before the test was used in clinical trials," the report said. "At a minimum, said the IOM, researchers should discuss LDTs with FDA prior to initiating validation studies, particularly when the test is intended for future clinical use." The cost impact of the tests' inaccuracy was not estimated.

The Oncotype DX HER2 breast cancer RT-PCR test had poor sensitivity, and that many tests reported as normal HER2 levels actually had high HER2 levels, according the report.

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

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

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

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

"We estimated the social cost when patients fail to receive appropriate trastuzumab therapy by multiplying the number of years a patient could gain from appropriate cancer treatment by the value of a statistical life-year," the report said.

"Standard estimates for the VSLY are $129,213, $258,426, and $387,639. Research has shown that the projected life expectancy is three years longer for HER2-positive patients who receive trastuzumab in addition to chemotherapy, compared to those receiving chemotherapy alone. Multiplying the three life-years gained from therapy by the middle VSLY value of $258,426 allows us to estimate the cost to society for each patient who fails to receive trastuzumab as $775,278."

The Target Now test, first offered in 2008, was described as a molecular test to detect 20 cancer biomarkers for a range of tumor types, and to profile a cancer and suggest appropriate chemotherapy.

The FDA said the clinical trial design behind the test was improperly designed to validate it, and that the list of suggested treatments generated by the test have have not necessarily been shown to have an impact for a patient's particular cancer, nor have they been studied in combination.

The FDA said that patients may forego standard cancer therapy for unproven alternative therapy, with a related risk of serious adverse events.

"By the end of December 2010, more than 12,550 tests had been sold," the report said.

"That year, in a single uncontrolled study of 86 patients with recurrence of various metastatic cancers, 66 patients had tumors that generated biomarker targets detected by the test and received treatment according to the list of suggested drugs generated by the test.

"At four months, 14 patients had not experienced progression, and 18 experienced a longer time to progression than they had on the regimens in use when they enrolled in the study. This study was small and had no control arm, and so provides little evidence of clinical validity."

In another example, the report examined both the OvaSure Screening Test and the PreOvar KRAS-Variant Test for ovarian cancer screening. OvaSure is a blood test on four biomarkers based on initial research in the published literature reporting an association with ovarian cancer, and PreOvar uses blood or saliva to test for KRAS-variant genetic mutation.

Both were listed to have the potential clinical consequence of false-positives leading to unnecessary surgery to remove healthy ovaries. The FDA estimated the cost impact of $12,578 per ovary removal after false-positive for each test.

"In September 2010, the Society of Gynecologic Oncology released a statement that the test was developed and marketed to the public with insufficient clinical validation," the report said, referring to the case of the PreOvar test.

"Concerned that the initial study was too small to generate a definitive assessment of ovarian cancer risk, researchers from the Ovarian Cancer Association Consortium performed an independent evaluation of over 21,000 subjects, finding no evidence of an association between the KRAS-variant and ovarian cancer."

The report continues: "The authors suggested that earlier associations may have been due to small sample size or associations between the KRAS variant and other factors. Despite these actions from the scientific community, this test remains on the market, and the company's website states that the test 'results are >99.9% accurate,' placing women at risk of being incorrectly told that they have a high risk of ovarian cancer or a better chance of responding to therapies."

On Capitol Hill

The hearing, held Nov. 17 by the House Energy and Commerce Subcommittee on Health, heard testimony from Jeffrey Shuren, director of the FDA Center for Devices and Radiological Health, and Patrick Conway, deputy administrator for innovation and quality, and chief medical officer of CMS.

"Currently, FDA exercises enforcement discretion concerning premarket evaluation and other requirements for LDTs," according to Shuren's testimony. "As such, the agency generally does not review such tests for clinical validity prior to such tests being marketed, nor does the Centers for Medicare & Medicaid Services."

The law granting FDA that authority is nearly 40 years old, and Shuren says that since then, the science has changed:

"Today, many companion diagnostics and other high-risk tests are developed by laboratories. Modern LDTs are often complex, have a nationwide reach, and have high-risk uses, and without oversight could present risks for patients and health care providers who rely on the results of LDTs to make medical decisions."

"In these respects, LDTs today differ from the relatively simple LDTs in use at the time of the Medical Device Amendments of 1976. In many cases, the only difference between many modern LDTs and other IVDs is where they are manufactured, and the accuracy and reliability are every bit as important for modern LDTs as for any other IVD," according to Shuren's testimony.

Committee Ranking Member Rep. Frank Pallone (D-N.J.), in his opening remarks, said: "Patients deserve to know that the test results they are relying on to diagnose or treat a condition is accurate, a comfort that they do not always have today. As we have heard from many organizations, patients and their physicians should be able to trust the results of their tests regardless of how or where a test is developed or performed. It does not make sense to regulate tests differently based on who develops them."

Rep. Joseph Pitts (R-Pa.), chair of the subcommittee, said: "Such tests are increasingly important, not only for diagnosing the onset of a specific disease or condition, but in determining the right course of treatment or procedure. It goes without saying that tests providing information to a doctor or consumer are fundamentally different products than traditional medical devices which actually deliver therapy to or are implanted in a patient," according to his opening statement.

"Today, I am far less interested in litigating the boundaries of current FDA or CMS legal authority than in hearing from our witnesses about how such authority could be clarified or improved, understanding the unique and evolving nature of what it is being regulated and each agency's areas of expertise."

Pitts continued: "I do not believe imposing a new regulatory reality on an increasingly important component of our health care system via guidance is the best way to address these issues. These products warrant a regulatory system designed with them in mind. They should not be shoehorned into a system that was drafted in the 1970s."

The American Cancer Society Cancer Action Network, in a statement issued before the hearing, said: "The FDA report provides examples of how a lack of oversight of laboratory developed tests can result in misdiagnoses that can have life-threatening consequences. False results, or missed or incorrect diagnoses, could mean that patients either will not receive the therapy they need, or will be subject to adverse effects and costs of therapy that will not work for them. It is paramount that patients and their physicians know that regardless of how or where a test is manufactured or performed, they can trust the information produced by that test.

"The FDA is the most appropriate agency to evaluate the analytical and clinical validity of diagnostic tests, along with their safety, to help ensure that patients and their doctors are able to make appropriate treatment decisions based on accurate information."

FDA Advisory Committees Vote Against Recommending MCNA

(Continued from page 1)

This was even before the agency's reorganization of its oncology units more than a decade ago. In those days, small-molecule compounds went to one bureaucratic unit of the FDA Center for Drugs Evaluation and Research—while biologics, including monoclonal antibodies and growth factors, went to the Center for Biologics Evaluation and Research.

Nonetheless, small-molecule drugs and biologics both went to the same advisory group: the Oncologic Drugs Advisory Committee, which offered clinical guidance.

After the reorganization, cellular, tissue and gene therapies for cancer remained in the FDA Center for Biologics Evaluation and Research, and, as the Nov. 18 meeting of the advisory committee summoned by

that unit of FDA illustrated, things at CBER are done differently.

First, it's unlikely that the therapy in question, a biologic immunotherapy for bladder cancer sponsored by Telesta Therapeutics Inc., would have made it to an advisory committee at CDER—certainly not in that form.

The company's single-arm trial missed its primary endpoint and was stopped prematurely. Worse, it was unclear what kind of patients benefited and what the characteristics of their disease were.

"The evidence of effectiveness comes from a study that failed to meet its primary endpoint, and there are issues in interpreting the study results. Nonetheless, given the unmet medical need of patients with non-muscle invasive bladder cancer, the question of potential benefit to patients still warrants discussion," said Celia Witten, director of the CBER Office of Cellular, Tissue and Gene Therapies, during the FDA's opening statement at a joint meeting of two of the agency's advisory committees.

The composition of the advisory body was worthy of note: it included the entire ODAC and the entire Cellular, Tissue, and Gene Therapies Advisory Committee. That's 25 voting members altogether—roughly double the size of ODAC. Fittingly, the meeting went twice as long as ODAC.

While some of these advisors were experts in oncology, others weren't.

With the committee taking a vote, people who don't know cancer could have easily drowned out those who understand the disease.

Oddly, the number of people on the committee exceeded the number of patients who, according to the application, might have benefited from the treatment in question.

"At the end of the day, I thought there was a handful of patients, maybe even less than the number of committee members [here], that we could say had clear and durable benefit from the drug," said ODAC member Brian Rini, an associate professor of medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University.

The drug went down in flames, with an 18-6 vote against—but with urologists and non-oncologists on the panel forming a united front, the application appeared to be very much in play to the end.

After all the votes were cast, the chair of the joint committee, Timothy Cripe, professor of Hematology, Oncology and Bone Marrow Transplantation at Nationwide Children's Hospital at Ohio State University, expressed disappointment with the outcome.

"We're still losing the war on cancer in general, and we need all the help we can get," Cripe said. "And with immunotherapies on the rise, if this were approved, I'm sure there would be a lot more trials and combinations that would augment its activity."

Telstra was seeking approval of Mycobacterium phlei Cell Wall-Nucleic Acid Complex, or MCNA, for intravesical use in the treatment of non-muscle-invasive bladder cancer at high risk of recurrence or progression in adult patients who failed prior bacillus Calmette-Guérin immunotherapy—e.g., in patients who are BCG refractory or BCG relapsing.

MCNA is a microbiologically derived, antineoplastic agent with immune-stimulant and direct anti-cancer activity.

The patient population in the pivotal trial included 129 adult subjects with NMIBC at high risk of recurrence or progression who had failed prior BCG treatment. These subjects had different histologies at baseline: high-grade Ta and/or T1 papillary lesions, as well as carcinoma in situ either alone or with papillary lesions of any grades.

Through most of the all-day meeting, Telesta officials and their outside clinical advisors were asked to respond to questions, and, in a novel procedural twist, the company's two clinical advisors were allowed to deliver what one of them called a "closing statement."

Cripe also floated a proposal to take an informal straw poll before the binding vote, presumably to determine how many committee members were opposed to the application. And when a voting patient representative noted that approval is important because it would lead to reimbursement, neither Cripe nor FDA staff members stepped in to point out that FDA has no authority to consider the cost of therapies.

Ultimately, even with oncology expertise diluted, the data presented to the committee was confusing. The two biostatisticians on the committee described the application's weaknesses with devastating brevity:

"As a statistician, in a one-armed trial, with no control, I need to see convincing evidence of benefit," said temporary voting member Janet Wittes, president of Statistics Collaborative Inc.

"I expect to see large benefit compared to historical controls. There are comparisons to historical controls, the ones that they did show, [and they] show me that progression-free survival is likely worse, at least in the first 18 months.

"There is too little data beyond that to say anything," Wittes said. "I can't interpret safety without a control and without information on longitudinal data."

ODAC member Bernard Cole, a professor in the Department of Mathematics and Statistics at the University of Vermont, agreed.

"The single-arm design is a major limitation, in light of the empirical data which failed to demonstrate a clear advantage in comparison with benchmarks and historical controls which were unfortunately only vaguely described," Cole said.

"In particular, it's not possible to statistically rule out minimal response rates. I was heartened seeing the response rates in the CIS-containing group, and that was more promising.

"But that suffers from a triple of statistical limitations: namely, it's a non-prespecified analysis, it's conducted in a subgroup, and it's a single-arm study. Given that, I think that a confirmatory study of some sort would be necessary.

"Looking at the CIS-containing group, I do think that's promising. And I'd also like to finish by saying that I appreciate the sponsor's interest in addressing such a difficult disease area."

The latest meeting represents a continuation of a long-running drama at FDA: the push to reorganize the agency.

The consolidation of drugs and biologics wasn't entirely voluntary on the agency's part. It was mandated by a congressional oversight committee after its investigation of the ImClone controversy showed that drugs weren't evaluated in the same manner as biologics.

Over the past decade, the agency has been pushed by oncology groups to consolidate its cancer operations, this making it possible to place cancer drugs, biologics, vaccines, diagnostics and devices under the same regulatory roof (The Cancer Letter, July 9, 2004, July 23, 2004, Feb. 18, 2005, March 4, 2005, April 22, 2005).

This drive is visibly intensifying as the agency's Office of Hematology and Oncology Products is changing the structure of drug development—and approving more drugs than any other part of FDA (The Cancer Letter, Feb. 14, 2014).

This is happening in part because, likely more so than at any other time in the history of oncology, all participants understand the approval criteria.

By way of comparison, the CBER oncology outpost is a small operation that appears to be operating based on its own rules.

"Advances in science and technology have led to treatment protocols that involve different types of medical products over the course of treating patients," Ellen Sigal, chair of Friends of Cancer Research, wrote in a recent opinion piece published in The Hill.

"In addition, many of these products are now being developed concurrently, such as drugs that require a diagnostic test to identify patients who are most likely to benefit. Having these products regulated within isolated portions of the FDA can lead to incongruent timelines that may result in development delays.

"Previous efforts to develop a more disease-oriented approach to product regulation have demonstrated the positive effect of this type of organizational structure. In 2004, several therapeutic biologic products were relocated into the current organization for oncology drugs at FDA. This was an important change that has helped usher in a new era of anti-cancer products that in some instances are now having a profound impact on previously untreatable diseases. But this was just a first step to build on. The science in major disease areas such as cancer, neurologic disorders, cardiovascular disease and infectious disease is advancing at a rapid pace and relies on diverse technologies to treat patients. This presents immediate opportunities where disease-oriented coordination across FDA could catalyze the development of new treatments to address serious public health needs.

"By forming teams of FDA staff with cutting-edge expertise in the treatment and prevention of specific disease areas, the agency can improve coordination within and between FDA medical product centers and ensure that the regulation of products is more reflective of how they are used in medical practice. This approach will break down decades' old silos within the agency."

The most spectacular snag in its operations involved the drug Provenge, which was approved by the advisory committee in 2007, only to encounter a backlash from cancer experts who had been outvoted by non-oncologists on the committee (The Cancer Letter, April 13, 2007, April 27, 2007, May 4, 2007).

Despair and validation of the field are not an accepted criterion for drug approval. However, these themes were sounded by Cripe at the Nov. 18 meeting and by members of the committee that voted to approve Provenge.

"Let's put it this way: If I had prostate cancer, I would try this before chemotherapy," announced

Francesco Marincola, director of the Immunogenetics Laboratory at the NIH Clinical Center.

Being "harsh" on Provenge would be tantamount to "missing the point," he said at the 2007 meeting.

"We are opening a new field," he said. "Even if we make a mistake, even if the [therapy] is not this effective, there is so much to learn by starting to see patients being treated with this and see what else can be added. We should not underestimate the importance of this decision. I don't think it's just about the drug and what the drug does, but it's about opening a field, and the investigation on that field."

What Committee Members Said:

After casting their votes during the Nov. 18 joint meeting, the committee members expressed their frustration with the disease—and with the data:

HAROLD BURSTEIN, *associate professor of medicine at Harvard Medical School:*

I thought it was a great discussion. I came away from today's session a little angry that we don't have better therapies for bladder cancer.

There's a compelling argument that this is a disease that needs attention. It is not an orphan disease; it has the same number of cases as gastrointestinal stromal tumors or mantle cell lymphoma—oncologic conditions where we are seeing successful clinical trials and innovative drugs coming forward.

But it is clearly a disease where we have dismal outcomes and unacceptable choices for way too many people.

I also came away really struck that FDA needs to address the problem of drug supply. It's ridiculous that our clinics are telling us that they do not have access to drugs that have been around for decades.

There's clearly an education, and to some degree an advocacy gap, in this disease. So I'm sure there are factors that play into that, but those were the eye-opening pieces of the discussion for me today.

Having said that, I voted no. I did not see the measurable benefit for this product in terms of what one would tell a patient it really did to affect the endpoint of interest to them: be it cystectomy, be it quality of life, be it symptom control, or be it survival.

And the actual data from the study fell short of the somewhat arbitrary consensus endpoint to find by the investigator community, which, by itself, I think, is an unknown prognostic of surrogate significance.

My final concern was that there are many other imperfect but existing alternatives, and I wasn't convinced that this was even as good as the literature suggests some of those might be for patients, and so, to enshrine it as an FDA-approved choice struck me as a situation that might keep people from getting other effective therapies.

BRIAN RINI, *associate professor of medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University:*

I voted no. I think the compound clearly has some potential antitumor activity in places you might have heard were desperate for more therapies. To me, the robustness of the data fell short of either what's been published, or what we heard, which has been sort of modified guidelines or requirements for activity in a single-arm trial, which are necessary going to be higher to show that it's clinically meaningful.

At the end of the day, I thought there was a handful of patients, maybe even less than the number of committee members, that we could say had clear and durable benefit from the drug.

There were too many questions on the data—I think on the data that the sponsor was unprepared to provide in terms of characteristics of the patients who develop metastatic disease, for instance, which was a primary concern of the committee. I would absolutely encourage them to study it further.

I think we heard a lot of good ideas from around the table about either BCG-naïve or other appropriately defined populations or combinations, and I think we are a lot smarter immunologically from a tissue standpoint, with the emergence of checkpoint inhibitors, to understand biomarkers—or at least have the tools to measure things that could be potential biomarkers.

Lastly, I know we were asked to comment on this, I would not have changed my vote if the cause of cystectomy was added; I actually had a primary concern that, as we heard in the beginning, there's probably 30,000 patients a year who are not getting cystectomies who should, at least pathologically.

And I would worry that, especially in a community setting, not in all academic settings, from the urologists on the panel, but in a community setting, this would be yet another reason not to do cystectomy for patients who need it as an important therapeutic option for their disease.

I realize that cystectomy is not fun for the doctor or patient, but metastatic disease is not fun either. And I think cystectomy is underutilized in this setting.

BRUCE ROTH, *professor of medicine in the Division of Oncology at Washington University in St. Louis:*

I voted no. I think for all the reasons that we talked about the data problems with the trial, the single-arm study—we're looking at a subset of a single-arm study to try to find benefit. The statistical considerations were called into question.

The lack of long-term follow-up to give us information on the secondary endpoints—this just didn't rise to the level of proving benefit for me. There are those, philosophically, who will say, well if you don't prove lack of benefit, then approve the drug.

That's not my philosophy. I still believe in the null hypothesis.

I think I would love to see this drug again in other trials; trials that prove the benefit may be there. Whether that's a first-line trial with BCG with crossover; whether it's a refractory CIS population randomized valrubicin or this compound with a mandatory biopsy at whatever follow-up time point is the primary endpoint. There just wasn't sufficient information at this time for me to vote yes.

BERNARD COLE, *professor in the Department of Mathematics and Statistics at the University of Vermont:*

I voted no, mainly because of the statistical evidence of effectiveness, which I viewed as being quite weak.

The single-arm design is a major limitation, in light of the empirical data, which failed to demonstrate a clear advantage in comparison with benchmarks and historical controls, which were unfortunately only vaguely described.

In particular, it's not possible to statistically rule out minimal response rates as shown, for example, in slide 38 of the FDA presentation. I was heartened seeing the response rates in the CIS-containing group, and that was more promising.

But, as Dr. Roth just mentioned, that suffers from a triple of statistical limitations: namely, it's a non-prespecified analysis, it's conducted in a subgroup, and it's a single-arm study. Given that, I think that a confirmatory study of some sort would be necessary.

Looking at the CIS-containing group, I do think that's promising. And I'd also like to finish by saying that I appreciate the sponsor's interest in addressing such a difficult disease area.

PATRICK WALSH, professor and director of the Brady Urological Institute at the Johns Hopkins Medical Institutions:

I voted yes, because I came to this meeting believing that if the activity was limited, at least the toxicity of the drug seemed acceptable.

My concern was delaying cystectomy. And I've been convinced at this meeting that if you delayed cystectomy for six months, and the drug didn't work, the patient wouldn't be harmed. We don't have a drug that a doctor to order exactly for this setting.

I think Dr. [Michael] O'Donnell's [presenter for Telesta and director of Urologic Oncology at the University of Iowa Hospitals and Clinics] comments were right on in terms of how I feel as a physician facing a patient who fails, and what do you have to give them?

If you give them a drug for six months and it worked that's fine, but if not, they could have a cystectomy. That's why I voted yes.

CHRISTIAN PAVLOVICH, *director of Urologic Oncology at the Johns Hopkins Medical Institutions:*

I voted no. I think that most of my thoughts were said better, and I agree with Dr. Roth with pretty much all of his comments.

I also think that, like Dr. Walsh, on the other hand, that it sure would be nice to have something to offer the patient who is not ready for the cystectomy and BCG is not working.

But when the patient asks me what they can expect other than it not causing a lot of side effects, I don't think I could really answer the question well as to percentage chances this will work—based on the data presented, the single-arm nature of the design, the heterogeneity of the disease going into the study, and the wide confidence intervals based on just numbers.

I said no, although I would like to see this kind of agent, or this specific agent, come back in the form of another trial in another population.

PHIL HANNO, *professor of urology in surgery at the University of Pennsylvania:*

I voted yes. I agree that the trial left a lot to be desired. I thought the drug had low toxicity and seemed to be very safe. I thought the benefits outweighed the risks. The response to CIS seemed to be there, as Dr. O'Donnell said, it's another arrow in the quiver.

More studies would be encouraged if the drug were approved. I didn't really see a downside. If it turned out not to be effective over the long run, I don't

think it would be misused or driven by advertising. So I thought there was little to lose and a lot to potentially gain by approval.

PIYUSH AGARWAL, *head of the Bladder Cancer Section in the NIH Urologic Oncology Branch:*

I voted yes. I echo the comments of Dr. Hanno and Dr. Walsh; I can't argue with some of the cogent remarks by Dr. Rini and others who voted no, but I do think that in this disease we have limited options.

And I think a very informed patient with a close follow-up of six months, and the decision to continue or go with cystectomy—I agree with Dr. O'Donnell that often these patients need one more attempt at a different drug before they cross that line where they accept a cystectomy. Perhaps if this drug came back with an indication to only be offered to patients who are not cystectomy candidates who refuse cystectomy. And maybe after six months of no response, maybe that might be a little bit more palatable.

But this is a difficult disease base in which to conduct trials because they're very heterogeneous and we're going to find a mixture of different types of tumors.

Hopefully we'll get some guidance from this on how to better conduct future trials. I think it's a step in the right direction. Hopefully with some repurposed indication it might see the light of day.

THOMAS GRIFFITH, *associate professor in the Department of Urology at the University of Minnesota:*

I voted yes. I think a lot of the deficiencies that were raised were clearly there. These weaknesses were outweighed by a number of strengths, especially the fact that there are not a lot of options for this population of patients that need something that is not so much of a radical procedure.

The tolerability was also something that I felt was a positive. That needs to be considered.

TITO FOJO, *professor of medicine at Columbia University:*

I voted no. At times I was really feeling uncomfortable when we were talking almost about anecdotes or small groups of patients, and I'm not quite sure that's where we should be making the decision.

I think Dr. Rini made the point that we want solid data on more people than there are committee members and maybe that ought to be the bar that we set going forward.

But to your concerns, which were addressed, I think we all wanted to vote yes. We want it to be so. I think that what you're sensing is that everybody's saying we think there's something here, please, FDA, work something going forward to see that this doesn't disappear, and one hopes that that's the case.

And I suspect the sponsors had very little to do with the design of this study and are now stuck with a study that they themselves would not have designed.

For those reasons I voted no, but know that we're not opposed to it.

VASSILIKI PAPADIMITRAKOPOULOU, *professor of medicine at MD Anderson Cancer Center:*

I would also agree that there is a need for agents in this particular area, and therefore it's very hard to say no, but there are many good scientific reasons to say no: study design; small population; subsets that benefited that are too small and undefined; lack of anything to really assign the activity to—biomarkers were cited—other things; clinical pathology characteristics. Nothing that is really clear.

I think the drug is safe, and I don't think there is harm as long as the patients are monitored. They do need their opportunity to get the right therapy, but I do not believe that we should approve drugs on the basis of no harm—I think we should approve them on the basis of benefit.

I would also like to say that I was completely disheartened by the fact that there has been no other approval in this setting. And I think trials are feasible even if you think that your population is diverse. That happened in every other disease; every other disease is a subset.

So I think trials need to be brought to the community and patients can participate in them, and get to the endpoints.

TIMOTHY CRIPE, *chair of the Cellular, Tissue and Gene Therapies Advisory Committee, and professor of Hematology, Oncology and Bone Marrow Transplantation at Nationwide Children's Hospital at The Ohio State University:*

I voted yes. We were asked about benefit-risk ratios—there's clearly some benefit in my view, and very little risk, so that ratio is very favorable. We're still losing the war on cancer in general, and we need all the help we can get.

And with immunotherapies on the rise, if this were approved, I'm sure there would be a lot more trials and combinations that would augment its activity.

So that's why I voted yes.

NCI Names Outstanding Investigator Award Winners

The award provides funding of up to $600,000 in direct costs each year for seven years. One goal of the award is to provide investigators with substantial time to break new ground or extend previous discoveries to advance biomedical, behavioral or clinical cancer research.

Award recipients are cancer researchers, nominated by their institutions, who have served as a principal investigator on an NCI grant for the last five years.

"The NCI Outstanding Investigator Award addresses a problem that many cancer researchers experience: finding a balance between focusing on their science while ensuring that they will have funds to continue their research in the future," said Dinah Singer, director of NCI's Division of Cancer Biology.

"With seven years of uninterrupted funding, NCI is providing investigators the opportunity to fully develop exceptional and ambitious cancer research programs."

The full list of all 43 individual recipients and details of their research are below:

Steven Artandi, professor of medicine (hematology) and of biochemistry at Stanford University, for addressing the target cell populations from which cancers emerge and determining how these early beginnings are linked to one of the most fundamental properties of cancer cells, the acquisition of immortal proliferative properties.

Laura Attardi, professor in the Departments of Radiation Oncology and Genetics at Stanford University, for deconstructing the transcriptional programs through which wild-type p53 suppresses cancer and through which missense mutant p53 exerts GOF effects to promote cancer; and using integrated genetic, genomic, cell biological and biochemical approaches to define the p53 transcriptional programs critical for p53-mediated suppression of pancreatic cancer.

Darell Bigner, director of The Preston Robert Tisch Brain Tumor Center at Duke University, for focusing on oncolytic polovirus, immunotoxin, and checkpoint inhibitor therapy of gliomas. Intended outcome will represent paradigm shifts in glioblastoma multiforme cells treatment resulting in significant increases in high quality of life and overall survival.

John Byrd, professor of medicine and D. Warren Brown Chair of Leukemia Research at The Ohio State University, for focusing on basic and translational biologic questions to develop novel immunologic and targeted therapies for acute myeloid leukemia and chronic lymphocytic leukemia.

Andrea Califano, Clyde and Helen Wu Professor of Chemical Systems Biology at Columbia University Medical Center, for developing a novel methodological framework integrating both experimental and computational approaches to systematically elucidate the mechanisms by which tumor heterogeneity drives tumor progression and emergence of drug resistance.

Simon Cherry, Distinguished Professor, Departments of Biomedical Engineering and Radiology at University of California, Davis, for focusing on discovering new opportunities for cancer imaging and cancer therapy based on radiation and photonics science.

Craig Crews, Lewis B. Cullman Professor of Molecular, Cellular, and Developmental Biology at Yale University, for contributing toward developing the new field of `Controlled Proteostasis' and help develop the Proteolysis Targeting Chimerae technology further to target truly undruggable proteins that are key oncogenic drivers.

Carlo Croce, chair of the Department of Molecular Virology, Immunology and Medical Genetics at Ohio State University Medical Center, for focusing on the identification of genetic and genomic alterations that cause human cancer in order to develop novel targeted treatments for different human tumors.

Michael Fiore, professor of medicine at University of Wisconsin-Madison, for focusing on electronic health records and using groundbreaking research methods to re-engineer healthcare delivery systems to efficiently organize and deliver state-of-the-art treatment to smokers visiting primary care settings.

Levi Garraway, associate professor of medicine at Harvard Medical School, for the hypothesis that the spectrum of resistance mechanisms for any given cancer therapeutic modality could coalesce onto a much smaller set of critical downstream effect or nodes, and for focusing on discerning the mechanisms operating within these "points of coalescence" to yield new insights into oncogenic dependencies and illuminate guiding principles for the design of novel therapeutic combinations.

Jean Gautier, professor of genetics and development at Columbia University Medical Center, for building a map of protein-protein interactions for repair factors common to multiple repair pathways and identify protein-protein interactions that are specifically enhanced or reduced following treatment.

These differentially regulated modules will identify potential vulnerabilities in the DNA repair networks of cancer cells and will open the possibility for precise, targeted therapies.

Amato Giaccia, professor of radiation oncology at Stanford University, for exploring the molecular mechanisms governing lipid homeostasis in cancer, characterize their contribution to tumorigenesis and identify ways that they can be therapeutically targeted in solid tumors and determine how to best exploit them therapeutically.

Kun-Liang Guan, distinguished professor in the Department of Pharmacology at University of California, San Diego, for obtaining a comprehensive molecular understanding of the mTORC1 and Hippo pathways under normal physiological conditions and elucidate how dysregulation of these pathways contributes to tumorigenesis.

Stephen Hursting, professor in the Department of Nutrition and Nutrition Research Institute; director of the Division of Nutritional Biochemistry; and member of the UNC Lineberger Comprehensive Cancer Center at University of North Carolina at Chapel Hill, for utilizing a transdisciplinary approach combining well-characterized preclinical models with expertise in nutrition, metabolism and molecular biology in partnership with strong translational collaborations to identify new biomarkers, develop effective interventions to break obesity-cancer links, and reduce the burden of obesity-associated cancer.

Rakesh Jain, A.W. Cook Professor of Tumor Biology (Radiation Oncology) and director of the Edwin L. Steele Laboratory for Tumor Biology at Massachusetts General Hospital and Harvard Medical School, for dissecting the microenvironment of pediatric brain tumors with the goal of improving existing therapies and developing new ones using non-invasive, high-resolution imaging.

Thomas Kensler, professor in the Department of Pharmacology and Chemical Biology at University of Pittsburgh, for focusing on chemoprevention, which may offer practical opportunities to reduce risks associated with "unavoidable" or largely intractable exposures, using natural products that target the Nrf2 cytoprotective pathway.

Mary-Claire King, professor of genome sciences and of medicine at University of Washington, for discovering new mutational mechanisms and new genes in extended kindreds severely affected by breast or ovarian cancer with normal sequences of all known breast and ovarian cancer genes.

Hartmut Land, chairman of the Department of Biomedical Genetics, director of research and co-director of the Wilmot Cancer Institute at University of Rochester Medical Center, for exploring the hypothesis that cooperation response genes are critical to sustaining core features of a malignant phenotype shared between diverse cancers. Land will use genetically tractable in vivo and in vitro models in combination with genomic RNA expression and bioinformatics analyses to identify key regulatory pathways to identify key regulatory pathways and circuits related to CRG activity that control cancer cell homeostasis.

Caryn Lerman, Mary Calkins Professor of Psychiatry, and deputy director of the Abramson Cancer Center at the University of Pennsylvania, for merging concepts and tools from the fields of cognitive neuroscience and behavioral science to develop and evaluate novel neuroscience-based interventions to promote sustainable behavior change for cancer prevention.

Maciej Lesniak, professor and chair of the Department of Neurological Surgery at Northwestern University Feinberg School of Medicine, for focusing on therapeutic targeting of malignant glioma stem cells, guided by the hypothesis that novel non-viral gene therapies can be designed to arrest GSC fate in gliomas by suppressing the master neurodevelopmental transcriptional factors that control GSC phenotypes.

Timothy Ley, Lewis T. and Rosalind B. Apple Professor of Oncology at Washington University in St. Louis, for exploring the hypothesis that a complete understanding of the consequences of initiating mutations is required to fully understand acute myeloid leukemia pathogenesis, and for focusing on the therapeutic approaches against initiating mutations with the potential of providing long-term benefits for AML patients.

Xihong Lin, chair, Henry Pickering Walcott Professor of Biostatistics, and professor of statistics at Harvard T.H. Chan School of Public Health, for developing and applying statistical and computational methods for analysis of whole genome sequencing

association studies, investigation of gene-environment interactions, integrative analysis, risk prediction using genetic, genomic and environmental data, and analysis of large administrative databases, to advance genetic and genomic epidemiology, precision prevention, and precision medicine for cancer.

Ian Macara, chair of the Cell & Developmental Biology Department at Vanderbilt University, for focusing on understanding how cell context determines phenotype, and determine the roles of mitotic spindle mis-orientation in cancer initiation, tumor suppression by myoepithelial cells, and the subversion of mechanical tension signaling by breast cancer cells.

Jeanne Mandelblatt, associate director for population sciences at the Lombardi Comprehensive Cancer Center at Georgetown University, for using a bio-behavioral framework to conduct population sciences research at the intersection of cancer and aging, and for focusing on shifting the paradigms of research and care for the growing older population; determine whether biological age markers can identify survivors at greatest risk for functional declines; inform future intervention trials; and expand the limited number of cancer and aging researchers.

Brendan Manning, professor of genetics and complex diseases at Harvard School of Public Health, for defining the wiring and functions of the PI3K-mTOR network that is aberrantly regulated at a high frequency across a wide spectrum of human cancers. Projects focus on the critical role of this network in influencing the sensitivity and resistance of tumors to targeted cancer therapies and in tumor cell metabolism.

Joshua Mendell, professor in the Molecular Biology Department at University of Texas Southwestern Medical Center, for focusing on the analysis of miRNA functions in normal physiology and cancer in vivo, investigation of the regulation of miRNA processing in normal development and tumorigenesis, elucidation of lncRNA functions in normal physiology and cancer and application of CRISPR-based genomic editing to illuminate noncoding RNA functions in cells and animals and to discover and validate novel regulators of malignancy-associated phenotypes.

Matthew Meyerson, professor of pathology at Dana-Farber Cancer Institute, for aiming to understand the mechanism of how significant alterations in the DNA of lung cancers, such as loss or gain of chromosomes, genetic mutations, and genomic amplification cause the disease. Insights are aimed at uncovering new therapeutic approaches to combat lung cancer.

Jeffrey Miller, deputy director of Masonic Cancer Center at the University of Minnesota, for developing strategies to enhance the anti-tumor activity of endogenous natural killer cells in patients with solid tumor malignancies; and develop "off the shelf" reagents to activate NK cells, overcome inhibitory receptor signaling, and target them to specific tumor antigens.

Shuji Ogino, professor of pathology, and professor in the Department of Epidemiology at Dana-Farber Cancer Institute, for conducting molecular pathological epidemiology research on colorectal cancer omics, intratumor heterogeneity and immunity, to gain insights on roles of environmental, diet, lifestyle and genetic factors; and accelerate transdisciplinary integration to develop new research frameworks, analysis designs and statistical methods; grow the International MPE Meeting Series with a goal of making "the STROBE-MPE guideline;" and build new integrative interdisciplinary models including causal inference-MPE, immuno-MPE, social-MPE, and MPE-health communication research.

Paolo Pier Pandolfi, director of the cancer center and Cancer Research Institute at Beth Israel Deaconess Medical Center, for contributing toward the study of critical cancer genes as paradigms for tumor suppression, through the development of a second generation of models and tools in order to explore how they function in leukemia and other cancers, and, importantly, to develop and test new cancer therapies.

Marcus Peter, professor of medicine-hematology/oncology at Northwestern University Feinberg School of Medicine, for focusing on death induced by CD95R/L elimination mechanisms, related mechanisms, and the development of a novel form of cancer therapy that is based on targeting tumor suppressors rather than oncogenes.

Kornelia Polyak, professor of medicine and medical oncology at Dana-Farber Cancer Institute, for exploring the hypothesis that clonal heterogeneity within tumors drives metastatic progression and therapeutic resistance and that understanding the molecular and cellular mechanisms underlying clonal interactions within tumors will improve the clinical management of breast cancer patients; and test these hypotheses using a multidisciplinary approach applied to clinical samples and experimental models.

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Holly Prigerson, Irving Sherwood Wright Professor of Medicine at Weill Cornell Medicine, for translating the foundational observational research findings from her previous research into interventional trials to improve end-of-life cancer care; and develop the necessary research tools and build the capacity to develop psychosocial interventions to improve end-of-life cancer care.

Tannishtha Reya, professor in the Departments of Pharmacology and Medicine at University of California, San Diego, for combining strategies for the design of early detection tools with an understanding of cancer progression from benign lesions to a malignant state. The overall goal is to enable development of new therapies that can be delivered early in disease, providing a more balanced and effective approach to cancer control.

Antoni Ribas, professor of medicine and hematology-oncology at University of California, Los Angeles, for tumor immunotherapy for melanoma using checkpoint blockade alone or in combination with BRAF inhibitors, and gene engineered adoptive cell transfer therapy.

Jeremy Rich, chairman in the Department of Stem Cell Biology and Regenerative Medicine at Cleveland Clinic Lerner Research Institute, for investigating the role of mitochondrial dynamics and metabolic control in the maintenance of brain tumor stem cells, regulation of the epigenetic stem cell state, and as a therapeutic modality; and provide an enhanced model of glioma hierarchy and inform the development of novel clinical trials.

Ali Shilatifard, chair of the Department of Biochemistry and Molecular Genetics at Northwestern University Feinberg School of Medicine, for full molecular and biochemical characterization of the COMPASS family of histone H3K4 methylases in the regulation of gene expression and during development, and determination of how their mutations contribute to the pathogenesis of a large number of human cancers including solid tumors and hematological malignancies.

Paul Sondel, Reed and Carolee Walker Professor of Pediatrics, Human Oncology and Genetics at University of Wisconsin-Madison, for developing preclinical and clinical regimens that combine tumor reactive monoclonal antibody based therapeutics and other "off the shelf" agents along with genetic evaluation of innate immune function in order to decrease the morbidity and mortality of cancer worldwide.

Daniel Tenen, professor of medicine at Harvard Medical School, for focusing on exploring novel areas of RNA biology and investigating their role in cancer, as well as potential development of more specific therapeutic modalities, using acute myeloid leukemia as a model disease.

Geoffrey Wahl, professor at the Salk Institute for Biological Studies, for determining the molecular programs that drive embryonic mammary cells into the stem cell state, and use gene editing technologies to generate a new mouse model that will enable the lab to identify fMaSCs in real time based on the cytokeratins they express.

Loren Walensky, associate professor of pediatrics and pediatric hematology/oncology at Dana-Farber Cancer Institute, Boston Children's Hospital, and Harvard Medical School, for elucidating the fundamental interaction mechanisms of BCL-2 family apoptotic proteins to advance new therapeutic strategies for reactivating cell death in human cancer: apply multidisciplinary approaches to define the conformational activation and homo-oligomerization mechanism(s) of BAX and BAK, characterize a novel mechanism for BAX and BAK suppression by the BH4 domains of anti-apoptotic BCL-2 proteins, and investigate a new allosteric mechanism that controls the apoptotic functionalities of BCL-2 proteins.

Michael White, professor in the Department of Cell Biology at the University of Texas Southwestern Medical Center, for a focused investigation of conditional vulnerabilities that arise as a consequence of oncogene expression and tumor evolution. A broad-scale functional annotation of the diverse intervention targets present within tumorigenic regulatory systems, collection of features that allow these targets to be identified in patients, and assignment of chemicals that strike these targets will be conducted.

Jin Zhang, professor in the Department of Pharmacology at the University of California, San Diego, for developing enabling technologies to probe the active molecules in their native environment and characterizing how these active molecules change in cancer, to lead to new ways of studying dysregulated molecular machinery in cancer, thereby better guiding therapeutic interventions that target the dysregulation.

In Brief

Kantoff Named Chair of MSKCC Department of Medicine

PHILIP KANTOFF was named chair of the Department of Medicine at **Memorial Sloan Kettering Cancer Center**.

Kantoff served the Dana-Farber Cancer Institute and Harvard Medical School since 1987 in a variety of capacities. He formally assumes his new position as George Bosl steps down from his role after 18 years. Kantoff will continue to see patients in addition to heading a program of laboratory-based research.

Kantoff was previously director of the Lank Center for Genitourinary Oncology, chief of the Division of Solid Tumor Oncology, vice chair of the Department of Medical Oncology, and chair of the Executive Committee on Clinical Research at Dana-Farber, as well as a professor of medicine at HMS. He was the Jerome and Nancy Kohlberg Endowed Chair at HMS, leader of the Dana-Farber/Harvard Cancer Center Prostate Cancer Program, and director of its Prostate Cancer Specialized Program of Research Excellence (SPORE) grant.

As director of the Lank Center, Kantoff oversaw programs of clinical care and research as well as laboratory research. His lab focused on the genetics and genetic epidemiology of prostate cancer, mechanisms of resistance to therapies, and the role of noncoding RNAs in prostate cancer as well as the discovery of biomarkers that may be useful prognostic tools and/or therapeutic targets. He served as a clinical researcher and principal investigator in significant trials devoted to the development of new therapeutic targets for men with advanced prostate cancer.

As professor of medicine at HMS since 2004, Kantoff's research program focused on the molecular basis of genitourinary cancers and improved treatment for patients with prostate, kidney, bladder and testicular cancers.

Kantoff also currently serves as the chairman of the Global Treatment Science Network of the Prostate Cancer Foundation. He was honored with the Baruj Benacerraf Clinical Investigator Award from 1994 to 1997 and the HMS Kantoff-Sang Lectureship Award since 2011. He was also recognized with the first Prostate Cancer Foundation Mentor of Excellence Award.

Bosl has served as Chairman of MSK's Department of Medicine since 1997. He has helped to identify more-effective and less-toxic treatments for testicular cancer as well as a marker chromosome for germ-cell tumors that allows more specific treatment for this disease.

MICHAEL LANG was named chief product development officer for the **Cancer Prevention and Research Institute of Texas**. Lang will lead CPRIT's product development research program.

Prior to joining CPRIT, Lang was the founder and CEO of NanoVision, a cancer diagnostics company. He headed business development at the venture capital-funded wound healing company Gilatech, where he led its novel biomaterial therapy. Lang oversaw a company restructuring as president of Dallas-based Galt Medical, served as a product manager at Johnson & Johnson, and was vice president of business development at BioEnterprise, where he led the startup and growth of early stage firms.

ALEXANDRA LEVINE was awarded the Hospital Physician Leadership Award by the **Los Angeles County Medical Association**. Levine is the chief medical officer of City of Hope.

Levine is also a professor at the institution's Hematologic Malignancies and Stem Cell Transplantation Institute. She served as chief of USC School of Medicine's Division of Hematology from 1991 to 2006, where she was a distinguished professor of medicine, medical director of the USC/Norris Cancer Hospital and past executive associate dean of the medical school.

Levine was among the first to recognize the epidemic of lymphoma and other cancers among HIV infected persons in the United States, and has been an advocate for HIV-infected patients over the years. Internationally, she served as a consultant on HIV/AIDS programs for the health departments of Chile, Russia, India and China.

In 1995, former President Bill Clinton appointed Levine to the Presidential Advisory Council on HIV/AIDS, where she served as the chair of the Research Committee. She was appointed to the NCI Board of Scientific Counselors from 1996 to 1999 and again from 2010 to 2015. Levine was elected a master of the American College of Physicians in 2009.

STEVEN ROSEN, provost and chief scientific officer for City of Hope, will receive a Lifetime Achievement Award from the **Israel Cancer Research Fund**, the largest organization in North America devoted solely to supporting cancer research in Israel.

"This Lifetime Achievement Award is a remarkable honor, especially coming from the ICRF, an organization that advances scientific understanding of cancer and supports innovations that are transforming lives," said Rosen, who serves as director of City of Hope's comprehensive cancer center, Beckman Research Institute and Irell & Manella Graduate School of Biological Sciences. He also holds the Irell & Manella Cancer Center Director's Distinguished Chair. "I am extremely proud, and humbled, to be the recipient of such an honor."

Prior to joining City of Hope in 2014 at its first provost and chief scientific officer, Rosen served for 24 years as director of Northwestern University's Robert H. Lurie Comprehensive Cancer Center. It received continuous NCI funding beginning in 1993 and built nationally recognized programs in laboratory sciences, clinical investigations, translational research and cancer prevention and control. Rosen also was Northwestern's Genevieve Teuton Professor of Medicine at the Feinberg School of Medicine.

Rosen is a recipient of the Martin Luther King Humanitarian Award from Northwestern Memorial Hospital and the Man of Distinction Award from the ICRF.

THE INTERNATIONAL CANCER GENOME CONSORTIUM made 1,200 encrypted cancer whole genome sequences available on the Amazon Web Services Cloud for access by cancer researchers worldwide.

The Ontario Institute for Cancer Research, which houses the ICGC's Data Coordination Center, copied genome data onto the cloud and is providing authorized researchers with credentials to access and analyze the data. The ICGC Data Access Compliance Office has established a framework that protects the confidentiality of research participants.

Researchers can work and run experiments in the cloud without needing to download the data. The set of 1,200 genomes now available on AWS is the first installment of ICGC data to be posted and is expected to grow over the next 12 months with the addition of data from more cancer patients.

The Pan-Cancer Analysis of Whole Genomes project of the ICGC and The Cancer Genome Atlas is coordinating analysis of more than 2,800 cancer genomes, and is making extensive use of AWS and the genomes stored on Amazon Simple Storage Service. Each genome is being characterized through a suite of standardized algorithms, including alignment to the reference genome, uniform quality assessment, and the calling of multiple classes of somatic mutations. Scientists participating in the research projects of PCAWG are addressing a series of fundamental questions about cancer biology and evolution based on these data.

There are currently 89 ICGC projects underway at research institutes in Asia, Australia, Europe, North America, and South America.

AARP published a report detailing how retail prices for over one hundred widely used specialty prescription drugs surged skyward by nearly 11 percent in 2013, surpassing the median income of an American family.

The average annual cost of a specialty medication used on a chronic basis exceeded $53,000 in 2013. This cost was greater than the median U.S. household income of $52,250, more than twice the median income of $23,500 for people on Medicare, and almost three-and-a-half times higher than the average Social Security retirement benefit of $15,526 over the same time period, the report said.

The report, produced by the AARP Public Policy Institute, also found that specialty drug prices are considerably higher than other drug prices. In 2013, the average annual cost for specialty prescription drugs was 18 times higher than the cost of brand name prescription drugs and 189 times higher than the cost of generic prescription drugs. The average annual price increase was more than seven times higher than inflation: 10.6 vs. 1.5 percent.

The report, the third in a series of reports on prescription drug prices, examined the retail prices of 115 specialty prescription drugs most widely used by older Americans. The analysis included 47 different drug manufacturers and covered 30 different therapeutic categories; 85 percent of the 115 specialty drugs studied are used to treat chronic health conditions.

THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY published 11 principles and detailed guidance to the Centers for Medicare & Medicaid Services as it implements the Merit-based Incentive Payment System and Alternative Payment Models under the Medicare Access and CHIP Reauthorization on Act of 2015, which replaced the Sustainable Growth Rate formula.

In a letter responding to the CMS request for information from stakeholders on implementation, ASCO outlined the society's principles and provided

responses to many of agency's specific questions on MIPS and APMs.

"MACRA is an important opportunity for CMS and ASCO to work together to create a fair and sustainable reimbursement system for clinical oncology that serves the best interests of Medicare beneficiaries and the Medicare program," said ASCO President Julie Vose. "As CMS works to transform the Medicare physician reimbursement system, we provided—and will continue to provide—the agency with robust feedback based on what we've learned over many years from ASCO's payment reform efforts."

ASCO's guiding principles for the development of a sustainable Medicare payment system for clinical oncology include:

- Ensuring that there are multiple Alternative Payment Models focused on clinical oncology to permit oncologists to select a model that is patient-centered and that meets the challenges facing their patients, practice, and community.
- Creating multiple mechanisms to facilitate transitions for physicians who initially participate in MIPS to subsequently move to an APM in future years.
- Improving quality reporting and minimizing disparities in access to high-quality, high-value oncology care by promoting meaningful quality measures and promoting quality improvement in cancer care through the use of qualified clinical data registries, such as ASCO's Qualified Oncology Practice Initiative.
- Facilitating group reporting of quality data in APMs and MIPS, since it is essential to improving clinical cancer care.
- Partnering with ASCO to create a risk adjustment methodology that is specific to cancer treatment to ensure that financial incentives do not exacerbate disparities in patient access to high-quality, high-value cancer care and hold oncologists accountable under resource use measurements primarily for expenditures that are under their direct control.
- Ensuring that oncologists are not penalized on the basis of resource consumption for providing high-quality, high-value cancer care.
- Permitting oncologists to select concordance with nationally recognized evidence-based, value-based clinical pathways in lieu of tracking resource use due to drug utilization under Medicare Part B or Part D.
- Promoting the use of existing audit tools for oncology under both MIPS and APMs to facilitate meaningful improvements in quality and value in cancer care.
- Taking active steps to ensure that the implementation of MIPS and APMs does not hinder access to clinical trials.
- Working with the Office of the National Coordinator for Health IT and Congress to ensure that achieving interoperability and preventing information blocking are national priorities.
- Avoiding the creation of additional administrative burdens and unfunded mandates that could undermine the ability of oncology practices to provide high-quality cancer care.

MD ANDERSON CANCER CENTER and **Codiak BioSciences** formed license and sponsored research agreements. Codiak also recently completed the first portion of $80+ million Series A and B financing.

Codiak is founded in part on technology developed in the laboratories of Raghu Kalluri, professor and chairman of the MD Anderson Department of Cancer Biology. Kalluri and his colleagues have demonstrated that exosomes derived from normal cells can act as a potent and safe delivery system for multiple therapeutic payloads.

Kalluri's work with exosomes involves discoveries related to identification of double stranded genomic DNA, exosome microRNAs and their biogenesis, exosome proteins, identification of cancer-specific exosomes and exosome-mediated therapies.

THE PAN-MASS CHALLENGE announced a gift of $45 million to support adult and pediatric patient care and cancer research at **Dana-Farber Cancer Institute**, bringing the PMC's 36-year fundraising total to a half-billion dollars raised since the organization's inception in 1980.

The PMC is Dana-Farber's largest single contributor, raising more than 50 percent of the Jimmy Fund's annual revenue and the $500 million fundraising total is the largest sum ever raised by a single athletic fundraising event.

The record gift was raised by 6,000 cyclists, including Massachusetts Governor Charlie Baker and Boston Mayor Marty Walsh, who participated in one of the PMC's twelve routes Aug. 1 and 2, ranging from Sturbridge to Provincetown, Babson to Bourne and Babson to Patriot Place, among others.

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Drugs and Targets

Approvals Granted to Darzalex And Ninlaro in Multiple Myeloma

FDA granted accelerated approval for Darzalex (daratumumab) to treat patients with multiple myeloma who have received at least three prior treatments. Darzalex is the first monoclonal antibody approved for treating multiple myeloma.

"Targeting proteins that are found on the surface of cancer cells has led to the development of important oncology treatments," said Richard Pazdur, director of the Office of Hematology and Oncology Products in FDA's Center for Drug Evaluation and Research. "Darzalex provides another treatment option for patients with multiple myeloma who have become resistant to other therapies."

Darzalex, marketed by Janssen Biotech, is a monoclonal antibody that works by helping certain cells in the immune system attack cancer cells. The safety and efficacy of Darzalex were demonstrated in two open-label studies.

In one study of 106 participants receiving Darzalex, 29 percent of patients experienced a complete or partial reduction in their tumor burden, which lasted for an average of 7.4 months. In the second study of 42 participants receiving Darzalex, 36 percent had a complete or partial reduction in their tumor burden.

The most common side effects of Darzalex were infusion-related reactions, fatigue, nausea, back pain, fever and cough. Darzalex may also result in lymphopenia, neutropenia, leukopenia or anemia and low levels of blood platelets.

The FDA granted breakthrough designation for this application based on preliminary clinical evidence suggesting that if approved, Darzalex may offer a substantial improvement over available therapies. Darzalex also received priority review and orphan drug designations.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

FDA approved Ninlaro (ixazomib), developed by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy. Ixazomib is the first approved oral proteasome inhibitor.

The approval was based on an improvement in progression- free survival in a multicenter, randomized, double-blind, placebo-controlled trial enrolling 722 patients with multiple myeloma who had received one to three prior lines of therapy. Patients were randomized in a 1:1 ratio to either the combination of ixazomib, lenalidomide and dexamethasone (n=360) or the combination of placebo, lenalidomide and dexamethasone (n=362). Patients continued treatment until disease progression or unacceptable toxicity.

The trial showed a statistically significant improvement in PFS. The median PFS on the combination arm of ixazomib, lenalidomide and dexamethasone was 20.6 months (95% CI: 17.0, NE) compared to a median PFS of 14.7 months (95% CI: 12.9, 17.6) on the combination arm of placebo, lenalidomide and dexamethasone (PFS HR 0.74, 95% CI: 0.59, 0.94; p=0.012).

The more common adverse reactions associated with an increased rate on the ixazomib combination arm compared to the placebo combination arm were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain.

This application was approved before its Prescription Drug User Fee Act date of March 10, 2016 and was previously granted Priority Review.

Eli Lilly and Company and Merck extended an existing collaboration to evaluate the safety and efficacy of the combination of Lilly's Alimta (pemetrexed for injection) and Merck's Keytruda (pembrolizumab) in a phase III study in first-line nonsquamous non-small cell lung cancer.

The study will be sponsored by Merck and will be open to patients with NSCLC in the first-line setting, regardless of PD-L1 status. Financial details of the collaboration were not disclosed.

The expansion of this trial collaboration comes following the release of data from a phase I study, presented earlier this year at the World Congress on Lung Cancer, which evaluated pemetrexed, carboplatin and pembrolizumab in first-line nonsquamous NSCLC.