

# THE CANCER LETTER

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## Harvard Physician Whose Cancer Was Spread Through Morcellation Seeks to Revamp FDA Regulation of Medical Devices

*By Matthew Bin Han Ong*

On Oct. 17, 2013, a surgical instrument called a power morcellator tore into the uterus of Amy Reed, an anesthesiologist at Beth Israel Deaconess Medical Center, pulverizing what were believed to be benign fibroids.

Reed's "minimally invasive" hysterectomy, a routine procedure, was performed at the Brigham and Women's Hospital, a teaching hospital of Harvard Medical School.

Alas, Reed's uterus contained an occult sarcoma, which the morcellator proceeded to spread through her abdominal pelvic cavity. Over ensuing months, as Reed battled to stay alive, her husband, Hooman Noorchashm, a cardiothoracic surgeon and, at the time, a lecturer at Harvard, waged a national campaign to put an end to the practice of power morcellation.

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## BSA Approves Trial of Carbon Ion Therapy, Extends EDRN and Provocative Questions

*By Tessa Vellek and Will Craft*

Question: What's more expensive than proton beam radiation therapy?

Answer: Carbon ion radiation therapy.

With CIRT centers costing about \$300 million to construct—about twice as much as proton beam centers—the potential adoption of this technology threatens to further inflate health spending worldwide.

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## Ma and Tyner Receive Award from AAAS

LI MA and JEFFREY TYNER were named the recipients of the American Association for the Advancement of Science's Martin and Rose Wachtel Cancer Research Award.

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## FDA Advisory Group to Consider Power Morcellation July 10-11

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The couple hasn't pursued legal remedies.

At least in the beginning, there was no obvious target for legal action. Medical malpractice claims usually involve deviation from standard practice. Power morcellation, by contrast, *is* the standard of care, and it works just fine, except for the unlucky few, Reed among them.

Laparoscopic power morcellation is performed on about 100,000 women a year in the U.S. The procedure is popular because patients end up with smaller scars, and since they recover faster, hospital stays are shorter or avoided altogether.

After receiving the devastating news, Reed and Noorchashm, both 41, rallied their friends and peers, and Noorchashm single-handedly launched a social media campaign, contacting the press, and dumping hundreds of pages of documents on [a Change.org petition](#). On some days, folks on his list receive three or more emails in which he urges immediate action.

Noorchashm is taking on the entire establishment—starting with his own institution, moving on to the gynecology specialty organizations, and then the FDA.

He wants to change the way medical devices are regulated. If new legislation is required to pull power morcellators off the market, so be it, Noorchashm reasons.

And—amazingly—in *Hooman vs. the World*, Hooman is ending up on top.

In recent months, Brigham & Women's Hospital

and other medical institutions have either suspended power morcellation or mandated the use of a containment system.

On April 17, FDA [issued an advisory](#) discouraging the use of power morcellation, stating that one in 350 women who undergo hysterectomy or myomectomy for fibroids have an unsuspected uterine sarcoma.

On July 10 and 11, an FDA panel—the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee—will meet to discuss power morcellation.

Ethicon Inc., a Johnson & Johnson unit that manufactures power morcellators, announced recently that it would suspend sales of three of its devices pending the FDA hearing. The devices in question are Gynecare Morcellex, Morcellex Sigma Tissue Morcellator System, and Gynecare X-Tract Tissue Morcellator.

And lawyers are casting nets for plaintiffs in class action suits. “The firm is now offering free morcellator lawsuit reviews to women who may have experienced the spread of undiagnosed uterine sarcoma and other cancers due to uterine morcellation,” said one firm in a press release earlier this week. Brigham & Women's has since stopped power morcellation.

“In the early use of power morcellators, I don't think we—we being the medical profession—properly understood the risk,” said Monica Bertagnolli, chief of the Division of Surgical Oncology at BWH and professor of surgery at Harvard. Bertagnolli was designated by the hospital to discuss clinical issues involving morcellation with *The Cancer Letter*.

“Based upon data from our hospital, we believe that open power morcellation in the setting of a malignancy significantly increases the risk of tumor recurrence and overall death from the disease. These data were recently published in the journal *Cancer* (George, et al, EPub June 12, 2014).”

The hospital is conducting an IRB-approved registry study focused on morcellation with a closed containment system.

### Tilting at FDA

“All this would not have occurred without Hooman,” said David Challoner, emeritus vice president for health affairs at the University of Florida.

“That's part of the problem here, with the morcellator,” Challoner said to *The Cancer Letter*. “Not only was the technology put to a new use without any real evaluation, but the signal from the clinical environment back to the regulatory environment that ‘there's a problem,’ is a very low level signal in this

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particular case—until a wise doctor had it used on his unfortunate wife, and figured out what the hell was going on and blew the whistle.”

Noorchashm’s actions have served the public interest well, Bertagnolli said.

“Hooman is a really fine individual and a fine surgeon,” she said. “Raising awareness of the risk of the morcellation procedure is an important and valuable contribution. His work, unfortunately resulting from personal tragedy, has galvanized all of us to be very aggressive in developing better policies so that we can avoid this horrible result in the future.”

Noorchashm and Reed said they took their case to the public, the press, and Congress, because BWH officials and gynecology organizations had ignored them.

“I pretty much knew immediately, as a general and cardiothoracic surgeon, that we were looking at a systemic error and that this was a very serious women’s health hazard that was being caused by gynecologists,” Noorchashm said to *The Cancer Letter*. “We initially went to BWH, and I subsequently went to the American Congress of Obstetricians and Gynecologists—I got absolutely no cooperation from them.

“So we decided we’re going to launch this campaign and let people know, and let government regulators decide.”

Noorchashm, Reed, and an increasing number of critics say the prevalence of morcellation is the result of a dysfunctional medical device approval mechanism at FDA. The agency’s 510(k) process needs to be revamped, they say.

“I have learned a lot about 510(k) and the device industry since 2009,” said Challoner, who chaired an Institute of Medicine committee tasked by FDA and Congress to review the legislation in 2009. “At the end of two years, the [IOM] committee unanimously recommended that the 510(k) process was—we didn’t use the word irrational, but we certainly could have—defective and should be replaced.

“There is no mechanism by which the health of the public could be protected when moderate risk devices were only cleared to the market place, not approved, under 510(k). They are cleared to the market based on, in some cases, a multi-year multi-device, daisy chain of predicate devices.”

The absolute number of women at risk of being harmed by morcellation in the U.S. is uncertain, but experts estimate the range at one in 350 to one in 1,000.

“One in 350 is a death knell; it’s pretty devastating,” said Paul Sugarbaker, director of the Center for Gastrointestinal Malignancies and chief of the Program

in Peritoneal Surface Oncology at MedStar Washington Hospital Center. “If that data is indeed true, Hooman has put us onto a much larger problem, and that is the dangers of these large fibroids.”

Sugarbaker treated Reed’s leiomyosarcoma in an emergency procedure. She is one of at least seven patients he has seen in the past two years for cancer spread through morcellation.

“There seem to be more patients coming in, since it has been written up in the papers,” Sugarbaker said to *The Cancer Letter*. “Disseminating cancer while you’re removing it can’t be a good thing, because these sarcomas grow, and they grow like crazy.”

“But the larger picture is, there needs to be more attention focused on large and symptomatic fibroids. It’s much more dangerous than gynecologists have been aware of. And I think that comes about as a result of this investigation.”

Since the recent FDA advisory, many hospitals have put a stop to using power morcellation.

“It’s happening all over the country,” Sugarbaker said. “Hospitals and doctors don’t want to be associated with something that’s dangerous for patients, and medically and legally disastrous.”

Some institutions have mandated the use of “containment bags” with the procedure. Such bags are commonly used in oncologic surgery, though FDA hasn’t approved them for use with power morcellation.

“From the administrative standpoint, I think the best move is, don’t do it,” said Larry Kaiser, chief executive officer, dean and a thoracic surgeon at Temple University Medical Center. “I don’t think there is a tremendous downside there. It really shouldn’t be done.

“If you are going to do it, and you want to do it in a containment bag, there is a chance the bags can break,” Kaiser said to *The Cancer Letter*. “Overall, yes, there is a very small chance of spreading malignant cells, but you can’t make that diagnosis until the tissue is removed.”

Unfortunately, it’s not easy to determine when power morcellation should be avoided.

“If we know *a priori* that a woman has a malignancy, then every effort is made to avoid fragmenting it in ways that can spill tumor cells into the abdomen,” Bertagnolli said to *The Cancer Letter*. “Surgery for benign leiomyomas is very common, and beneficial to many women. Many women benefit from morcellation of their tumor, because this allows much smaller incisions, quicker recovery, and also allows tumors to be removed in ways that can preserve fertility.

“The big issue, therefore, lies in detecting which women have malignant disease prior to operation.

Unfortunately, we don't have a reliable method to determine whether or not a uterine tumor is malignant before it has been removed and fully examined.

"That's our main concern: we never want to see this happen to another woman. By the same token, we also don't want to see this over-applied so that young women lose their fertility unnecessarily, because of some global policy that can't assess risk-benefit.

"Even with a containment device, we can't be certain that the procedure is safe if the tumor turns out to be a sarcoma," Bertagnolli said. "We aren't even happy with the modified technique yet. The only way you assess risk-benefit is by getting the data, which is what we are doing."

Gynecology organizations agree, calling for more data and research, and cautioning against sweeping, definitive policies to end the use of power morcellation.

"I am someone that specializes in rare tumors, and I can share with you that it is very frustrating to not have great data about rare tumors, so we are stuck with not having extensive databases or research to draw conclusions from," said Jubilee Brown, director of gynecologic oncology at The Woman's Hospital of Texas, and associate professor in the Department of Gynecology Oncology and Reproductive Medicine at MD Anderson Cancer Center. "The thing that has been lost in much of the discussion is the benefit that minimally invasive surgery brings to the vast majority of women.

"We are not just talking about small incisions; we are talking about substantial improvements in morbidity and mortality, compared with open surgery," said Brown, a member on the board of trustees of the American Association of Gynecologic Laparoscopists. "That's why this becomes a really important issue for women who are looking at this procedure."

Noorchashm disagrees.

"It is not a tenable ethical position to sacrifice the lives of a minority subset of women with missed or occult uterine cancers for the 'benefit of the majority,'" he counters. "That's unethical. If morcellators stay on the market, the standard of care won't change.

"What an FDA ban would do is, when someone's cancer gets spread through morcellation, the surgeon who spread the cancer, can be taken to court. So it's going to put pressure on gynecological surgeons to be careful not to cut things up inside someone's body."

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### **The 510(k) Process and Adverse Outcomes**

Power morcellators entered the market via the 510(k) process, which clears devices for use based on predicate devices that had already been in the market prior to the establishment of the 510(k).

"It's designed as a transition," said Challoner, chair of the IOM committee that issued a report on 510(k) three years ago. "The reason this whole thing was put in place the way it was in 1975 was that when devices were, for the first time, coming to the public attention, and there were some moderate-risk devices, like for instance, the Dalkon Shield IUD, which were creating tremendous pelvic damage.

"Congress asked the FDA and HHS to put together a study to devise some way to regulate moderate risk devices. Nobody is worried about a tongue depressor, which is a low risk device. Everybody is worried about an implantable pacemaker, which gets treated like drugs and requires pre-market evaluation analogous to drugs.

"The device industry is very different from big pharma in terms of how they design and how they modify serially, and how they need, from their point of view, to get to market as quickly as possible after a device is designed and manufactured. There is a very strong pressure from the device industry to get into the market quickly.

"The device companies have been able to make [the 510(k)] survive politically over the ensuing 40 years."

Challoner's IOM panel—the Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process—was formed because of a series of failures of several devices prior to 2009.

"We recommended that FDA go back to the drawing board and get all the players around a table and devise a safer way to get into the market than just a clearance process," Challoner said. "The pre-market evaluation would have a rationale for use and careful review of engineering and manufacture. And, more rapid means for adverse affects to be reported from the marketplace back to the FDA so we get an early warning signal when a device was doing something unexpected.

"And now the morcellator thing is just one more example of the clearance of a device for a use, not approval, based on predicates already in the market, that is, prior morcellators for other uses."

Noorchashm says an adverse events reporting process should be included in the 510(k) legislation. "They dropped the ball, they sided with industry over patient safety," he said. "That is not right.

"Fundamentally, 510(k) has no mandate or requirement for the practitioner or hospital to report

adverse outcomes back to the FDA or the manufacturers. In 2011, the Institute of Medicine did an analysis and testified before the Senate [Health, Education, Labor and Pensions] Committee, concluding that 510(k) provides no legal basis to ensure patient safety, because it is lacking in post-market surveillance and because it does not require demonstrating safety at the time of approval.”

A beefed up adverse events reporting process would be helpful, gynecologists and surgeons agree.

“I am a clinical trials researcher, and so I am strongly in favor of collecting accurate data for any device that could potentially alter a patient’s outcome,” said BWH’s Bertagnolli, chair of Alliance for Clinical Trials in Oncology. “Devices with this potential should have to, at a minimum, be studied for a certain period of time under a design that allows examination of adverse outcomes.

“If you don’t have reporting, you can’t gather the data in a timely matter, potentially saving lives,” Bertagnolli said. “Would these cases have come to light more quickly if we had a reporting system from when the power morcellator was first placed in use? It seems likely.

“It is hard to believe we haven’t done this yet.”

More information is better, MD Anderson’s Brown agrees.

“Any way that we can obtain more data surrounding this issue is a benefit,” she said. “Whether that is reporting of adverse events, or forming a database, or more research funding, or more technology—I think all of those are ways that patients potentially stand to benefit.”

However, Noorchashm sees no reason to set up a prospective data collection mechanism for morcellation.

“What’s the use of that?” he said. “It’ll be a prospective registry of death from iatrogenic cancer upstaging. We already know what happens to women whose cancers are spread by morcellation. This suggestion is not an ethical one, and is designed to buy time for the industry to do damage control. We stop entire clinical trials for one death.

“I’m not sure what the gynecological leadership is really thinking.”

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### On The Principles of Surgery

Noorchashm attributes his wife’s complication in part to deficits in the gynecologists’ surgical training.

“Gynecologists as a whole are not trained in general surgery at all, and they thought that it’s okay to morcellate,” Noorchashm said. “Really, no other surgical specialty does this. Some urologists here and there morcellate things, but as a systemic practice, it’s nowhere practiced like gynecologists do it.

“In fact, general surgeons and oncologic surgeons never do it for this reason—because there’s concern that cancer would spread. But these guys have systematized it as a routine, and they think it’s okay.

“And the reason for that is because they don’t get any training in the fundamental principles of general surgery. During their residency, they take no time to do general surgical training, which is different from all other surgeons, who spend, at least, a minimum of a year doing general surgery training.

“The next thing is I think they are not looking at it correctly, meaning, they were looking at it as a one in 10,000 to 20,000 event, and they were saying, ‘Oh, that’s acceptable, I guess.’ I don’t think that’s acceptable anyway.

“Who’s going to pick who that one in 10,000 is going to be? And that is why oncologic surgeons and thoracic surgeons never do that.

“They were looking at the wrong denominator—it should be the subset of women with symptomatic fibroids, not the general population.”

MD Anderson’s Brown said risk cannot be eliminated, regardless of surgical procedure.

“I think that every area of surgery and every area of patient care is unique,” Brown said. “There are, however, lower-risk procedures than others. The issue centers around comparative risk in the population of women who are candidates for surgery that could include morcellation.”

It’s unfair to compare gynecologists with oncologists and other surgeons, BWH’s Bertagnolli said.

“It is very unfortunate to label a field in a negative way over an issue such as this,” she said. “Instead, we should emphasize more inter-disciplinary education. In a case such as this one, close communication between the oncology and general gynecology communities is a key requirement for reducing morbidity and deaths due to uterine sarcomas.”

Sugarbaker, from MedStar Washington Hospital Center said oncologists generally do not deal with specimens as large as fibroids.

“Some of these things are as big as a woman’s head—they’re gigantic,” Sugarbaker said. “I’ve

removed fibroids that weigh 10 pounds. But I'm seeing this woman who had power morcellation a year ago. They didn't even make the diagnosis of sarcoma.

"The pathologist looked at the morcellated specimens that were removed and no sarcoma was detected, until she got a recurrency. There's no doubt that it was spread by power morcellation—100 percent. She's now got a 12 cm mass in the right lower quadrant. This thing has grown quite rapidly over the course of a year and a half.

"Then and only then did they make a diagnosis, and that's because the fibroid was 99 percent benign, but they cut through the small focus of malignancy. And even though the pathologist didn't see it when he examined the specimen, the sarcoma grew out 18 months later. Now I'm going to have a big surgery to try and get rid of it, and there'll be large nodules and a lot of small nodules.

"From my perspective, if indeed there is a disaster—a fibroid gets morcellated and it has a sarcoma in it—that patient needs immediate referral to a peritoneal surface oncology treatment center, and there are 20 or so of them around the country. That doesn't mean they're not going to develop disease in their lungs, but I think we can prevent a small volume of the disease from growing out on their peritoneal surfaces."

Morcellation is not an option in general surgery, said Kaiser, a thoracic surgeon at Temple University.

"The safest thing is not to do it; again, I am not a gynecologist, I don't do this," Kaiser said. "But I can tell you, in general surgery and in chest surgery, we would never morcellate. We do everything we can to remove specimens intact. It goes against surgical principles to chop something up inside a body cavity.

"I think that if a surgeon is going to do it, there needs to be fully informed consent. The woman needs to know there is a small chance they could be spreading cancer. And if they agree to that, they can go ahead and do it, recognizing what the risks are. But I think, from a policy standpoint, the safest thing is, don't do it. Surgical principles are surgical principles, no matter what the specialty is."

"On the other hand, there clearly are some differences. We also, in the non-GYN world, there are not a whole lot of indications to do debulking type procedures, which they have been very successful at in ovarian cancer. There are very few other procedures where we do any sort of debulking procedure."

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### **The Risk-Benefit Debate**

Nearly half of minimally invasive hysterectomies, and over 80 percent of myomectomies are performed robotically and laparoscopically.

"This is a very lucrative practice," Noorchashm said. "The procedure itself bills \$30,000 to \$50,000, depending on the center. I can tell you that when a patient gets discharged on the same day, she doesn't have all the liability risks that they incur by keeping a patient in the hospital for a day or two because of an open operation.

"That's probably in terms of both liability as well as costs that are probably left as a margin for the hospital and the doctor."

Gynecologists say the procedure shouldn't be eliminated.

"I think the AAGL has taken a very careful stance on this issue, making sure that we put together all of the appropriate information and very meticulously analyze this for the benefit of our patients," Brown said. "We convened a 12-member task force of people who got together, face to face, reviewed every piece of literature and data that we have regarding tissue extraction and uterine morcellation, specifically with regard to power morcellation in order to synthesize all of those data, and really review risks and benefits for patients in various circumstances.

"And at this point, based on those data, the AAGL has not recommended elimination of power morcellation as a procedure, but instead suggest that it be individually considered.

"The procedure itself—hysterectomy—is of course very common. The issue with large fibroids is also very common. When we are looking at risks and benefits of different procedures, it is a very difficult set of risks and benefits to balance.

"We are looking at the possible rare, very adverse event of an undetected leiomyosarcoma, compared with the potential adverse events compared to minimally invasive surgery. That's why this isn't an easy answer.

"What you may recognize is that what we are talking about here is a huge number of women that need to undergo a hysterectomy for uterine fibroids and essentially about 77 percent of women that undergo a hysterectomy have some evidence of fibroids in their specimen. The numbers we are talking about, 600,000 women a year, and 77 percent of those have some fibroids. It's a large denominator of women we are looking at."

BWH's Bertagnolli concurs that the data are insufficient for a risk-benefit assessment.

"Unfortunately, an accurate understanding of the

risk is just not possible with the data we have,” she said. “I agree with those figures, anywhere from 1 in 350 to 1 in 1,000; we just don’t know. In my mind, even one woman is too many; of course, we never want to see this happen.”

Gynecologists should instead focus on the fact that power morcellation can be avoided, Noorchashm said.

“Morcellation is totally avoidable, and its victims unidentifiable pre-operatively,” he said. “Therefore, the death it imposes is not accidental. It is systematic and victimizes the minority subset of women with occult or missed uterine cancers.”

There are safe alternatives that do not involve morcellation of potentially malignant tissue, Kaiser said.

“I think [the argument that power morcellation lowers risk and has more benefits than open surgery] is a specious argument,” Kaiser said. “We did open surgery for an awful lot of years, and if you do a laparoscopic approach and the last thing you have to do is make a little larger incision in order to do this thing, you haven’t put any kind of spreader in there, it’s highly likely that the patient isn’t going to have that much additional pain.

“It can be removed through the vagina as well, if you have done a total hysterectomy, because you have got to close the vaginal cuff so, now if the specimen is too big, then it’s difficult to remove it that way, you can make a larger incision.

“It comes down to fully informed consent. If a woman is told, ‘Look, we are going to chop this thing up to save any sort of incision, there is a chance we could be chopping up a tumor, in which case it would put you at very high risk of spreading your cancer through the peritoneal cavity.’

“I don’t think all that many women would say, ‘Yeah go ahead and do that.’”

Informed consent does not protect the patient, Noorchashm said.

“How does informed consent about the mortality risk protect the patient from the spread of an occult or missed uterine cancers via morcellation? It doesn’t!” he said. “It’s at best a feeble attempt at medically and legally protecting an industry and, at worst, ethical negligence on the part of doctors who should know better.”

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### **Reed: Change Will Happen**

Several senators have been responsive to Noorchashm’s cause.

“All the U.S. senators are aware of this issue,” he said. “Congress can put pressure on FDA to ban the devices.

“The Senate has a responsibility to set a hearing. The 510(k) deficit is one of the main reasons why my family has fallen to morcellation. The 510k process needs to be revised, and that’s something I’m working on with Sen. Elizabeth Warren’s [D-Mass.] office. And I think the morcellator is only one prominent example of a systemic problem with what the FDA classifies as type 2 devices.”

The FDA hearing July 10 and 11 is an opportunity to discuss potential legislation, Challoner said. A statement he submitted to the agency reads:

“After nearly four decades, at a time of rapidly changing science and technology questions persist about whether the 510(k) process is protecting the public’s health. Unfortunately, the sad saga of the evolution and modification of morcellation devices for gynecologic use under 510(k) clearance adds yet another example to the need to reconsider the safety and public health protection of this process.

“There is great difficulty in detecting many device failures because of our inability to detect, suspect, and report ‘weak’ or rare signals from the clinical environment. That also appears to have contributed to the current issue of morcellation of malignant gynecologic tumors. These incidents should give us pause and urge the FDA once again to begin the conversations the committee recommended in our report.

“The passage of time and the appearance of new information technologies give the opportunity to shorten evaluation times premarket with appropriate engineering and product planning which industry should support.”

Noorchashm and Reed said their goal from the outset was to ban the medical practice and the specific set of devices used to perform it.

“This campaign is not a personal attack,” Noorchashm said. “I believe that this is an industry-wide act of ignorance and a major error in medical judgment. They weren’t aware that there was such a risk, because of how they train. They hadn’t thought about it critically enough and unfortunately an industry evolved around it. But now that they are aware, continuing it in any form constitutes deliberate and prosecutable negligence.”

Common sense will prevail, Reed said to The Cancer Letter.

“I’m optimistic,” she said. “I think it’s human nature to resist change, and I think that’s sort of what

we're encountering.

"As physicians, we do want what's best for our patients, and I believe that even the gynecologists who are morcellating think that's best for their patients.

"And it will take time to push them in a direction of change, and maybe not even them, but the generations to come so you can be sure that GYNs in training right now, this is on their plate.

"I think change will happen," she said.

Noorchashm and Reed will be leaving Harvard Medical School and Boston with their six children, ages one to 12, to be near their extended family in Philadelphia.

Noorchashm will serve as a cardiac surgeon at Thomas Jefferson University Hospital, and Reed is negotiating with another academic medical center.

### Conversation with The Cancer Letter **Challoner: We Recommended FDA Replace 510(k) Clearance**

The Cancer Letter asked David Challoner, emeritus vice president for health affairs at the University of Florida, to discuss FDA's 510(k) medical device clearance process.

The process has come under scrutiny after laparoscopic power morcellation procedures were found to spread previously undetected sarcomas inside benign fibroids.

Challoner chaired an Institute of Medicine committee tasked by FDA and Congress in 2009 to [review the 510\(k\) approval process](#).

"Not only was the technology put to a new use without any real evaluation, but the signal from the clinical environment back to the regulatory environment that 'there's a problem,' is a very low level signal in this particular case—until a wise doctor had it used on his unfortunate wife, and figured out what the hell was going on and blew the whistle," said Challoner.

"At the end of two years, the [IOM] committee unanimously recommended that the 510(k) process was—we didn't use the word irrational, but we certainly could have—defective and should be replaced.

"We recommended that FDA go back to the drawing board and get all the players around a table and devise a safer way to get into the market than just a clearance process."

Challoner spoke with The Cancer Letter reporter Matthew Bin Han Ong.

**Matthew Ong:** *How did you get involved in the debate on the 510(k) process?*

**David Challoner:** I began as a full-time clinical researcher in endocrinology and found that science, health and health care policy was a nice avocation. I became involved in academic medical administration fairly early and went finally to the University of Florida as vice president for health affairs in 1982, which is, in our system, the chief executive officer for a large multi-college and hospital academic medical center.

I was fortunate enough to be elected as a member of the Institute of Medicine early in my career and was actively involved since the 1970s serving on or chairing study committees. I served as foreign secretary and I also on the National Research Council governing board.

So I have policy experience in Washington, D.C., and racked up a lot of miles on Delta between Florida and D.C. over 35 years.

In 2009, Harvey Feinberg, then the president of the IOM, asked if I would be willing to chair the study on recommendations for improving the 510(k) that had been requested of the IOM. It was a well-balanced committee—we had members who had been in the FDA, we had members who had been inventors, we had members who were lawyers for device companies and who were now retired. We had the full spectrum of points of view as members of the committee.

My only experience with the device industry had been during my time in Gainesville in the late 80's to mid 90's. I had been on the board of a device company in Miami, Fla., called Cordis Corporation, which was then purchased and is now a part of Johnson & Johnson. Thus I had some past experience in some of the issues with devices. That's why they asked me to chair the committee.

I have learned a lot about 510(k) and the device industry since 2009. At the end of two years, the committee unanimously recommended that the 510(k) process was—we didn't use the word irrational, but we certainly could have—defective and should be replaced. There is no mechanism by which the health of the public could be protected when moderate risk devices were only cleared to the market place, not approved, under 510(k). They are cleared to the market based on, in some cases, a multi-year, multi-device daisy chain of predicate devices.

The reason this whole thing was put in place the way it was in 1975 was because that was when devices were, for the first time, coming to the public attention, and there were some moderate-risk devices. Like for



instance, the Dalkon Shield IUD in women, which were creating tremendous pelvic damage. Congress asked the FDA and the Department of Health and Human Services to put together a study to devise some way to regulate moderate-risk devices. Nobody is worried about a tongue depressor, which is a low-risk device. Everybody is worried about an implantable pacemaker, which gets treated like and requires pre-market evaluation analogous to drugs.

The device industry is very different from big pharma in terms of how they design and how they modify serially—and how they need, from their point of view, to get to market as quickly as possible after a device is designed and manufactured. There is a very strong pressure from the device industry to get into the market quickly.

That, in some way, led to the 510(k) process in 1975, which was designed originally only to last for two or three years to allow new designs and new devices to get into the post-1975 marketplace by comparison with predicate devices that had already been in the market prior to the new law. It's designed as a transition.

The device companies loved it because it got their devices into the marketplace by a clearance process not by an approval process. They have been able to make it survive politically over the ensuing 40 years.

**MO:** *Until today, essentially.*

**DC:** Yes. Our committee was put in place because there had been a series of failures of individual devices prior to 2009, and that's where the political attention to the 510(k) process was coming from. And now the morcellator thing is just one more example of the clearance of a device for a use, not approval, based on predicates already in the market, that is, prior morcellators for other uses.

We recommended that FDA go back to the drawing board and get all the players around a table and devise a safer way to get into the market than just a clearance process. The pre-market evaluation would have a rationale for use and careful review of engineering and manufacture. And, more rapid means for adverse affects to be reported from the marketplace back to the FDA so we get an early warning signal when a device was doing something unexpected.

That's part of the problem here, with the morcellator. Not only was the technology put to a new use without any real evaluation, but the signal from the clinical environment back to the regulatory environment that there's a problem is a very low level signal in this particular case, and was hard to detect.

Until a wise doctor had it used on his unfortunate wife, figured out what the hell was going on and blew the whistle.

That is a sort of quick summary of our report. We said 510(k) going into the marketplace makes no sense. That needs to be revised. We also said to the FDA, you really have to make your signals from the marketplace back to the regulatory system more sensitive. We said this on the basis of the studies of the devices that had failed before 2010.

The FDA, on its own, has been active in trying to make its surveillance system better. There are some particular medical societies with special interests like the orthopods with hips that are also undertaking improved surveillance.

The problem on the surveillance side is that everybody has got a reason not to report an unexpected or weak finding. The nurse in the operating room may have been told, 'We don't know exactly why this device did this, but it probably doesn't mean anything. We have never seen this before.'

The doctor's going to say, 'God, I am busy, I don't want to talk to the clinic administrator about this.' The clinic administrator is going to ask his or her lawyer, and the lawyer is going to say, 'Maybe you don't have to report it, it doesn't look like it does.'

And the device company sure as hell doesn't want to report something unless they are sure—and their lawyers are damn sure—and they'd get in trouble if they didn't report it. So you have a whole set of negative incentives before a report gets to the FDA about a problem.

That's not to say that everyone is weaseling out, it's just the way the system works. It's not a system that magnifies or speeds signals on the way to the FDA, it's a system that at every level would diminish the message getting to the FDA.

**MO:** *So in the specific case of the morcellator, you are saying that there are two main points that are not addressed by 510(k) that would obviously lead to something like this, because of a non-reporting of any kind of adverse outcomes. You are saying that the first point is that they need to change the way they evaluate pre-market clearance for devices such as the morcellator, and the second part is to require—within the process—reporting of adverse outcomes and patient follow-up. Would that be accurate?*

**DC:** Yes. Improve the systems. Basically, the requirements are there, the systems are faulty. You want my hypothesis about the best of all possible worlds, how things might work five to 10 years from now?

Three things:

Number one: We have going in to place a uniform electronic medical record. We have early examples of large systems like Kaiser and the [Veterans Affairs] medical system in which universal electronic medical records already exist. And slowly, especially with the help of the new legislation, we'll be trying to put in place universal electronic medical records for everybody over the course of the next decade.

Number two: The FDA has already begun to put a unique device identifier on every device that is made and to require that it be done by the manufacturer. So that, just like you scan a box of macaroni when you leave the grocery store at the clerk's desk, every device is going to have a unique identifier on it that will tell the device, the date, the manufacturer—every detail. It will be tracked in every detail as only computers can. When something is put in you, or an X-ray machine is used on you, that unique device identifier will be in your electronic medical record.

Number three: We've got the new science and technology of big data that has been developed in particular by our intelligence agencies such as the CIA and the NSA as they scan communications data for clues in ways that I don't understand. It's amazing what quantities of data can be scanned and clues sought. We have seen a little bit of this in medicine, where Google flu has scanned and looked at symptom searches. They have been able to pick up early-on flu epidemics simply by questions that are being asked on Google. That's a primitive example of the use of big data analyses to solve medical questions.

So you put those things together—electronic medical records, unique device identifier, and big data analyses—and you have a means by which the public's health can be protected and the industries' interest in getting a device into the marketplace early could both be dealt with.

You could make sure a device was engineered properly on the approval side, and FDA could let devices into the market that made sense early because the understanding would be that something like the morcellator complication would be picked up as an early-warning signal out of the big data analyses of the electronic medical record.

The device industry would be happy, and the public health could be protected—but that's not where we are right now.

**MO:** *How would things have been different if the 510(k) process had been done right?*

**DC:** First of all, I am not a surgeon. Certainly,

I am not in that ballgame. I am also not fully aware of what the earlier uses were of the morcellator devices. There were some other previous uses, but what happened in this case, I think, was it was fairly easily adapted to gynecologic use. It was, through the predicate process, it was micro-sized to a smaller and smaller blender. One instrument was the predicate for another was the predicate for another and then with the use of robotic microsurgery, it sort of—exploded is too strong a word—but widespread use appeared fairly quickly.

The FDA, at some point, might have asked the questions that they are now being forced to ask, but given the 510(k) process as it is currently in law, it's a clearance.

Get it into the marketplace. It's similar enough to this predicate device which is already in the marketplace which is similar enough to the predicate device which was in the marketplace four years before that. It just sweeps into the marketplace without the adverse effects being thought through and certainly without a system by which the adverse effects, especially a low signal effect, is going to feed back into the currently existing adverse reporting system.

This situation we find ourselves in now is a combination of both things, the failure of the 510(k) and the failure of the reporting systems.

**MO:** *Why do you think the process was not changed earlier? Do you think it's because there was no real catalyst?*

**DC:** Let me give you my assessment of the political environment in which this has occurred. We know how big pharma does things. We also know that big pharma is wealthy and because of that wealth, has political power. But it's primarily on the east coast and the west coast. So they maybe have 10 senators who look after their welfare, even though they contribute to a bunch of others, obviously.

The device industry is structurally extraordinarily different. The device industry has a shop in the district of almost every representative in the House of Representatives—I'm exaggerating a little bit now—even in rural Oklahoma.

The head of orthopedic surgery at his community hospital has designed an orthopedic screw for a broken elbow, and is manufacturing it in his garage, there in rural Oklahoma. The device industry has a widespread, hometown, know-each-other-by name, contributed-to-his-or-her-campaign constituency in the House. Their lobbying is personal, active, vocal and nationally organized in a couple of different national

device organizations.

They can kill any piece of legislation in the House that they don't like. In a way that big pharma can't even. There are big players in the device industry in Minneapolis such as Medtronic, and St. Jude in Memphis, but it is primarily a small-company, national enterprise with widespread geographic influence. It will be interesting to see if Medtronic will still have the same influence as a foreign company, which they are trying to pull off.

That's simply to say that our report given to the FDA in 2011 fell not only on deaf ears, but fell on a very noisy counter power play by the device industry to keep the 510(k) process in play. So that's the politics.

**MO:** *The next natural question in that case would be, do you think there is sufficient traction on the issue we have at hand, open power morcellation, to compel the relevant authorities to change the 510(k) process? Do you think this has what it takes, and what else needs to happen before that can happen?*

**DC:** A whole series of incidents from 1975 to 2009 were what created the political momentum for the study that I chaired to be requested of the IOM in the first place. And there have been failures of joints and cardiac leads, since then.

But the morcellation story has got an interesting set of public relations legs that some of these others did not. This is simply yet again another story of a public health failure of a device clearance process that may attract enough interest back to the issue—to

our recommendations in 2011—so that the FDA will sit down and rethink this process with all the players around the table.

**MO:** *Do you think that the FDA hearing will in any way address the 510(k) process?*

**DC:** I think the 510(k) process will clearly be part of the process at that hearing. I have submitted a brief statement about our study, and our assessment of the weaknesses of the 510(k) process.

I think that, given the momentum that appears to be building, and the understanding that the primary provocateur has both a medical side to this issue and has developed the understanding of the importance of the regulatory side of the cautions here. He seems to be set on making sure the 510(k) process is part of the discussion. I think it will be.

**MO:** *Does that advisory committee have any authority whatsoever to speak on the 510(k) process, and if they do, would the FDA listen to them?*

**DC:** I don't know. My understanding is the committee is comprised of an OBGYN advisory group. Will that committee itself do that? That is hard for me to predict. But there is no other than what Hooman is doing himself to make sure it's part of the discussion. And there may or may not be on that roster someone who really understands 510(k). I just don't know. But it's certainly going to be part of the public discussion now.

What kind of political legs it'll have after that, I don't know.

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## Conversation with The Cancer Letter **Bertagnolli: Why Brigham Stopped Making Morcellation Available Outside of a Registry Trial**

Current controversy over power morcellation points to the importance of multidisciplinary education and consultation, said Monica Bertagnolli, chief of the Division of Surgical Oncology at Brigham and Women's Hospital, and professor of surgery at Harvard Medical School.

"We know that this improves patient care," Bertagnolli said in an interview with Matthew Bin Han Ong, a reporter with The Cancer Letter. "In a case such as this one, close communication between the oncology and general gynecology communities is a key requirement for reducing morbidity and deaths due to uterine sarcomas."

Bertagnolli was designated by Brigham & Women's to discuss the clinical issues involved in morcellation.

**Matthew Ong:** *Hi Monica, thanks so much for discussing your thoughts on the use of morcellation for management of uterine tumors.*

**Monica Bertagnolli:** This is an interesting and important issue, and I appreciate the opportunity to weigh in. One of my clinical roles is that of a sarcoma surgeon, so unfortunately I see patients who have recurrent uterine sarcomas. Because the Dana-Farber/Brigham & Women's Cancer Center is a referral center, we see quite a few of these patients each year.

Based upon data from our hospital, we believe that open power morcellation in the setting of a malignancy significantly increases the risk of tumor recurrence and overall death from the disease. These data were recently published in the journal *Cancer* (George, et al, EPub June 12, 2014).

The retrospective data from 58 patients treated at our center show that intraperitoneal morcellation, that is, cutting a tumor into small bits within the peritoneal cavity, of a leiomyosarcoma increases risk of disease recurrence and significantly shortens median recurrence-free survival. These data support what we already suspected clinically—that morcellation can lead to implantation of tumor cells, and that these tumor cells are able to establish colonies of metastatic disease.

If we know *a priori* that a woman has a malignancy, then every effort is made to avoid fragmenting it in ways that can spill tumor cells into the abdomen. Surgery for benign leiomyomas is very

common, and beneficial to many women.

Many women benefit from morcellation of their tumor because this allows much smaller incisions, quicker recovery, and also allows tumors to be removed in ways that can preserve fertility. The big issue, therefore, lies in detecting which women have malignant disease prior to operation. Unfortunately, we don't have a reliable method to determine whether or not a uterine tumor is malignant before it has been removed and fully examined.

**MO:** *You're saying it boils down to a basic risk-benefit debate.*

**MB:** Right. Benign uterine leiomyomas are very common, and (fortunately) uterine sarcomas are fairly rare. In general, very large tumors or ones that grow quickly are more likely to be malignant, but PET scans, CAT scans, and biopsies are not accurate enough to be sure beyond a doubt that a malignancy is not present. We need better diagnosis methods to help us better assign risk.

When morcellation is done in a way that allows cells to be spilled into the peritoneal cavity, there is a small but real risk that harm can be done. Although we don't have conclusive data, it stands to reason that the use of power morcellators, which generate the most widespread spillage of cells, have the highest risk.

In the early use of [power morcellators], I don't think we—we being the medical profession—properly understood the risk. I would say over the last two years roughly, we have been increasingly convinced that we need to change our approach to patient management based on this risk.

**MO:** *One of the biggest points of contention right now—at least in the public debate—is about the number of women at risk. The FDA issued a warning that 1 out of 350 women are at risk for the spread of an undetected malignancy with the use of power morcellation. Other sources say it is as low as 1 in 1,000.*

*You have people on one side saying it's a death knell for many undergoing the procedure. If you extrapolate the FDA estimate, it's 285 a year; if I am not mistaken. Then you have others saying the benefit of the procedure for the majority of the women who undergo this procedure cannot be dismissed.*

*What's important for you to address, if you can, is, what is the truth here?*

**MB:** Unfortunately, an accurate understanding of the risk is just not possible with the data we have. I agree with those figures, anywhere from 1 in 350 to 1 in 1,000, we just don't know.

In my mind, even one woman is too many; of

course we never want to see this happen.

**MO:** *That sounds consistent with what ACOG and AAGL are saying in their reports, which were recently issued over the past two months.*

*They're saying: We can't make a global policy on this right now, and we need a lot of research because we can't properly assess the risk, but we shouldn't demand that morcellation stop right away. Would you say that is consistent across the board?*

**MB:** Yes, I would. But I think we can do something immediately. At least for the power morcellator, it is my opinion that we know enough to say that it should not be used without a containment device to limit spillage of cells within the abdomen.

Even with a containment device, we can't be certain that the procedure is safe if the tumor turns out to be a sarcoma. At our center, we require use of a containment device for cases where power morcellation of tumors is to be performed, and we are studying the issue prospectively through an IRB-approved protocol to be sure that we see the desired reduction in risk of tumor spread.

There are also a number of safe alternatives to power morcellation, and these should be used for all but the lowest risk situations.

**MO:** *Speaking of the containment bags, is there a standard containment bag that has been approved by the FDA?*

**MB:** No, not that I know of. We have a lot of different containment bags, because we have used them in oncology for a long time. This is because of the concern that, even without morcellation, taking out a tumor through a very small incision has a potential to seed tumor cells within the incision.

We have some level of comfort with containment devices, because their use has been applied to other diseases, particularly colon cancer, and the same risk of tumor spread does not seem to be a problem in this setting.

**MO:** *And there is no data on that so far?*

**MB:** No data on that. The group at Dana Farber/Brigham & Women's has a registry trial underway, so hopefully we will have data in the future. Brigham and Women's Hospital patients are not being treated with power morcellation unless they participate in

an IRB-approved study that mandates the use of a containment device.

**MO:** *Do you know of any other hospitals taking steps to generate data on this?*

**MB:** Not that I know of, although now that this issue has been recognized we should see better reporting of negative outcomes, which will lead to more information.

**MO:** *Speaking of collecting data, what do you know about the 510(k) legislation? Morcellators are 510(k) approved devices, and 510(k) doesn't require practitioners to report adverse outcomes.*

*Could you tell me if a change to this legislation, requiring practitioners to report adverse outcomes, would help the cause of collecting data?*

**MB:** I am a clinical trials researcher, and so I am strongly in favor of collecting accurate data for any device that could potentially alter a patient's outcome.

I think that devices with this potential should have to, at a minimum, be studied for a certain period of time under a design that allows examination of adverse outcomes.

It is hard to believe we haven't done this yet. The time has certainly come.

**MO:** *So you are saying it is time for 510(k) to actually include this provision that requires practitioners to report adverse outcomes?*

**MB:** Absolutely.

**MO:** *That appears to be the thrust of the efforts on the issue right now. The IOM did a good bit back then on 510(k), but there was no catalyst for a push to change the legislation until now, right?*

**MB:** Right. And that's the only appropriate response. I acknowledge that this is not simple, particularly in this case. A great many women are safely treated for benign tumors with power morcellators, and a small number are harmed. As a result, we need a lot of data to understand the risk and how it might be modified. And if you don't have reporting you can't gather the data in a timely matter, potentially saving lives.

Would these cases have come to light more quickly if we had a reporting system from when the power morcellator was first placed in use? It seems likely.

**MO:** *Maybe then we would have 20 years of data?*

**MB:** Power morcellation is certainly used more often lately because minimally invasive techniques 20 years ago were not nearly as uniformly as applied as they are now, so its use has been in a significant upswing.

We do think this is a rare event. We don't want to scare women everywhere out there who might have

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had a fibroid removed, and we don't want to introduce panic that is unwarranted.

**MO:** *There is, in the public debate, a comparison of gynecologic surgery with surgical oncology, and how gynecology is the only specialty that accepts systematic morcellation of tissues as a standard of practice.*

*The questions revolve around: Why do gynecologists do this when oncologists are against it?*

*However, I do understand that it makes sense for oncologists to not morcellate anything because you are primarily dealing with known malignancies.*

**MB:** I think that it is very unfortunate to label a field in a negative way over an issue such as this. Instead we should emphasize more interdisciplinary education. I am very fortunate as a surgical oncologist that I was trained in an era where it was routine for general surgeons to rotate on general gynecology services, and where surgical oncology fellows worked together with gynecologic oncologists. In fact, I learned many minimally invasive surgery skills from gynecologists, who were experts in these techniques long before surgical oncologists were involved.

It is very important and worthwhile to have a call, throughout all oncology, for multidisciplinary education and consultation. We know that this improves patient care. In a case such as this one, close communication between the oncology and general gynecology communities is a key requirement for reducing morbidity and deaths due to uterine sarcomas.

**MO:** *Finally, what do you think is Hooman's contribution to this whole issue?*

**MB:** Hooman is a really fine individual and a fine surgeon. Raising awareness of the risk of the morcellation procedure is an important and valuable contribution. His work, unfortunately resulting from personal tragedy, has galvanized all of us to be very aggressive in developing better policies so that we can avoid this horrible result in the future.

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## NCI News

### Provocative Questions Budget Cut by \$2 Million to \$20 Million

(Continued from page 1)

NCI's strategy is to conduct a randomized controlled trial to determine the safety and efficacy of carbon ion therapy in Japan, where the new technology is available. Thus, ideally, CIRT would be thoroughly assessed before adoption in the U.S.

The concept was approved by the NCI Board of Scientific Advisors at a meeting June 22-23.

Data coming from single-arm studies of CIRT in unresectable pancreatic cancer show a potential two-year survival rate of 54 percent. With standard therapies, the two-year survival rate is less than 10 percent. There are no randomized controlled trials of CIRT underway.

The carbon ion trial was one of six concepts approved by the BSA. The other five are:

- The Early Detection Research Network,
- Breast Cancer and the Environment Research Program,
- The Provocative Questions initiative,
- Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer,
- The International Agency for Research on Cancer.

By conducting the trial outside the U.S., where no CIRT centers are in operation, NCI also seeks to head off the problem now observed with proton beam, a technology being rapidly adopted throughout the U.S. ahead of conclusive evidence from randomized trials (The Cancer Letter, [June 20, 2014](#), [Oct. 25, 2013](#)).

The proposal approved by BSA sought to conduct a five-year randomized trial in Japan—a country heavily invested in carbon ion radiation therapy but with no previous or planned randomized trials—at a cost of \$2 million per year.

Bhadrasain Vikram, chief of the NCI Clinical Radiation Oncology Branch, presented the concept.

Though the board supported the study and unanimously approved it, comparative data are needed for all radiation modalities, several BSA members said.

“Should we consider doing this with photons, protons, and carbon?” said Kevin Cullen, director of the Marlene and Stewart Greenebaum Cancer Center at the University of Maryland.

“Because if you don't, if the trial is positive, people are going to say, ‘Aha! We should build carbon

facilities on every corner of the block.’ And if it’s negative, then people will still say, ‘Maybe protons are better.’ So you leave big questions that are going to have seismic implications in terms of how we’re spending our resources building facilities.”

“My concern would be that the results from this single study might be used to fill machines with patients with breast cancer or prostate cancer, where, in fact, there may be harms associated with the treatment, let alone lack of benefit,” said Ethan Basch, director of the Cancer Outcomes Research Program at the University of North Carolina Lineberger Comprehensive Cancer Center.

William Sellers, global head of oncology at the Novartis Institute for BioMedical Research, said it would make sense to conduct the study in several countries.

“I’m concerned if you do one site only, especially in Japan,” Sellers said. “If Japan has already reported a 54 percent response rate, what incentive do they have to randomize patients? So I want more than one site, especially Germany.”

### **BSA Approves Continuation of EDRN**

BSA approved funding the Early Detection Research Network at its current level of \$25 million, but balked at a proposed budget increase of \$5 million per year. The EDRN brings together institutions to support both the discovery of new biomarkers and the creation of a standardized set of criteria for biomarker validation.

Faced with several years of declining budget—from \$32 million to \$25 million—the EDRN proposal sought an annual \$5 million increase to a total of \$30 million per year over the next five years.

The boost would help cover costs of the increased complexity of mid- to late-phase marker validation, and for the addition of laboratories focused on recalcitrant cancers, said Barnett Kramer, director of the NCI Division of Cancer Prevention,

Though the EDRN reissuance was passed unanimously, the board voted 16-7, with one abstention, to withhold the proposed increase.

The board supported the EDRN validation mechanisms, but one board member questioned whether the EDRN should be both discovering and validating biomarkers.

“I’m very supportive of this program with respect to the portion that has to do with validation,” said Andrea Califano, chair of the Department of Systems Biology at Columbia University. “The problem is that

there is a fundamental conflict of interest.

“If you had an independent board, maybe people would not be so discouraged about submitting their biomarkers for review. Because right now people will choose the one internal to the network anyway.”

Others questioned the returns on the proposed increase in investment.

“One concern was that the biomarkers that have come all the way through the pipeline so far didn’t seem like the most impactful yet,” said Sangeeta Bhatia, director of the Laboratory for Multiscale Regenerative Technologies at MIT, raising the concern that the five EDRN biomarker assays approved by FDA are not medically transformative.

“If your return of investment is 1,000 biomarkers, and now five biomarkers are FDA approved, this is even worse than normal drug development, so I think [the discovery arm] may not be the most appropriate way to invest the money,” Califano concurred.

EDRN also validates markers discovered outside of the network. “Anyone inside or outside the EDRN can look at the specific criteria [to see] what kind of cut points we’re looking at,” Kramer said.

“There is an objective measure that they all must meet, that’s number one. Number two, whatever their level of enthusiasm, even if they’re within the EDRN, they have to face the other biomarkers and researchers, including the reference labs and validation centers. There is this correction mechanism to make sure that any interest is warranted.”

Speaking to the strengths of the network, Larry Norton, deputy physician-in-chief for Breast Cancer Programs at Memorial Sloan Kettering Cancer Center, delivering the report of the EDRN consulting team, said that that EDRN sets the standards for validation of biomarkers.

“The most important thing, and this appeared in many of our reports, is the validation step,” Norton said. “This is what is usually missing before you go to application. Without validation, if you just go from discovery to application, which can happen, you have the potential for disasters, which can cost lives.

“To emphasize something that’s already been mentioned by Barry Kramer, this is very cost-effective. It would probably be impossible to duplicate this for anywhere near this level of expenditure, if only because the organization and the infrastructure already exist.”

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## Provocative Questions Get a Haircut

Funding for the Provocative Questions initiative, a grant-awarding program spearheaded by NCI Director Harold Varmus, was approved by the BSA for three RFA issuances at \$20 million per year.

The four-year-old grant program was started to encourage research in understudied areas. Rather than identifying projects, the initiative invites applicants to submit project proposals aimed at answering “provocative questions.”

The proposal presented to BSA included several changes. The level of funding set aside was \$20 million per year, a little less than 2011’s \$22 million, and substantially less than the \$39.2 million granted in 2012.

The number of questions was reduced as well, from 20 to 24 in the first few years of the initiative, to between eight and a dozen.

Edward Harlow, head of biological chemistry and molecular pharmacology at Harvard Medical School, who presented the initiative, said the budget was cut in part due to funding constraints.

“Twenty million is less than what we have been spending in the past,” Harlow said. “We are being responsive, I think, to the budgetary constraints that are going on, so that number has been coming down a little bit. But because we have gone down to fewer questions, and doing two years, that will increase the number of funded applications in any one area.”

The number of questions is being reduced both to allow for a concentration of efforts. Also, several questions generated no funded applications, Harlow said.

“One of the things we are proposing for next round is to shrink the number of questions we do in any one RFA,” Harlow said. “Rather than doing 24 or 20, we are suggesting doing eight to 12, depending on what questions we have available to try and concentrate our efforts.

“There are other examples, however, where we’ve had questions that we had no funded applications. In general, they have been quite difficult to fund in the next year as well. There are lots of possible reasons for that. The field isn’t ready to consider it, we are missing key reagents and resources, the right people aren’t applying, or, in fact, the question is just poorly written.”

The five questions that have generated no funded applications in previous years are:

- Why do second, independent cancers occur at higher rates in patients who have survived a primary cancer than in a cancer-naïve population?
- How do we determine the clinical significance

of finding cells from a primary tumor at another site?

- Why are some disseminated cancers cured by chemotherapy alone?
- Can we determine why some tumors evolve to aggressive malignancy after years of indolence?
- How does susceptibility of exposure to cancer risk factors change during development?

In addition to shrinking the number of questions, the renewal RFA proposes formation of a “question team.” The team will be in charge of monitoring research progress as well as evaluating the relevancy and usefulness of each question.

“At the end of the cycle they recommend what happens with the question and they begin to figure out how one can follow the question and begin to build a better, more cohesive activity in the question areas,” Harlow said.

The PQ concept was approved unanimously.

## In Other Actions:

- The International Agency for Research on Cancer sought a new avenue of funding for the **IARC Monograph** program, which provides scientific evaluations of possible carcinogenic hazards.

NCI has provided support for the IARC Monograph program through an U01 award since 1982, but a new cooperative agreement would allow for the submission of a renewal application.

The proposal provides \$859,000 per year for five years.

The Monograph Advisory Group prioritizes the types of agents, which are then evaluated via a comprehensive literature review by working groups with 60 to 70 high priority agents evaluated per year.

Planned evaluations for the next cycle include bisphenol A, aspartame, indium tin oxide, and nicotine/e-cigarettes.

- The second renewal RFA, the **Breast Cancer and the Environment Research Program**, a joint effort by the National Institute of Environmental Health Sciences and the NCI, aims to identify environmental factors and exposures that occur throughout a woman’s life that could predispose her to breast cancer.

The proposal sought 40 percent funding from the NCI, with 60 percent already guaranteed by the NIEHS, for a total budget of \$48.4 million.

- **The Consortium of the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer**, the fourth renewal proposal, is a consortium proposing to address the connection between different types of diabetes and chronic pancreatitis and the risk of later



development of pancreatic cancer.

The goal is to identify patients at high risk for developing pancreatic cancer, develop methods for detecting early-stage pancreatic cancer, and determine the relationship between type 3c diabetes and pancreatic cancer.

The NCI approved the funding request for \$2 million per year for five years. This will be in addition to funding from the NIDDK (\$3.5 million per year) and from the NIAAA (\$500,000 to \$1 million per year).

### *In Brief*

## **Ma and Tyner Receive AAAS Wachtel Award for Research**

(Continued from page 1)

The award honors investigators who have performed outstanding work in the field of cancer research, and have received their Ph.D. or M.D. within the last 10 years.

Tyner and Ma's award entry essays were published in the July 2 edition of *Science Translational Medicine*. Both will deliver public lectures on their research July 7 at an event co-hosted by the NCI Center for Cancer Research at the NIH Lipsett Amphitheater in Bethesda, Md. They will split the award of \$25,000.

Ma is an assistant professor of experimental radiation oncology at MD Anderson Cancer Center. Tyner is an assistant professor of cell, developmental and cancer biology at the Oregon Health and Science University.

Ma's research focuses on regulating breast cancer metastasis, breast tumor radioresistance, and key breast cancer proteins and pathways. Tyner helped develop a research program that more rapidly identifies the mutations driving a patient's cancer and accelerates development of precision treatments.

**JOHN CLEVELAND** was named associate center director of basic science at **Moffitt Cancer Center**.

Cleveland comes to Moffitt from the Scripps Florida campus of The Scripps Research Institute, where he served nearly eight years as a professor and chair of the Department of Cancer Biology. Prior to that, he spent more than 17 years at St. Jude Children's Research Hospital. He also completed a fellowship and senior fellowship at NCI.

He currently serves as a member of the Extramural Scientific Advisory Board for the Gastrointestinal

SPORE programs at the University of Arizona and the Blood Research Institute of Wisconsin. He has served as editor for numerous scientific journals and has been a long-serving member and ad-hoc reviewer for NIH R01 Grant Program and Project Grant Review Committees.

**THE COMMUNITY ONCOLOGY ALLIANCE** appointed new officers. **Bruce Gould**, of Northwest Georgia Oncology Centers in Marietta, Ga., was named president of COA.

**Jeff Vacirca**, of North Shore Hematology Oncology Associates in East Setauket, N.Y., was named vice-president; **Michael Diaz**, of Florida Cancer Specialists and Research Institute in Tampa, Fla., was named secretary; and **Ricky Newton**, of Cancer Specialists of Tidewater in Chesapeake, Va., was named treasurer.

The COA's immediate past president is **Mark Thompson**, of The Zangmeister Center in Columbus, Ohio, who will continue to serve as chairman of the COA Payment Reform Task Force and legislative liaison on congressional matters. Past President **David Eagle**, of Lake Norman Hematology Oncology in Charlotte, N.C., will assume the position of chairman of the Oncology Medical Home Steering Committee.

**ROSWELL PARK CANCER INSTITUTE** received an "outstanding" distinction from NCI, which renewed its Cancer Center Support Grant and extended its **Comprehensive Cancer Center designation**, following an in-depth peer review. Roswell Park will receive \$19 million with the core grant covering a five-year period.

"With this renewal comes recognition from our peers from cancer centers around the nation of Roswell Park's excellence in conducting innovative research, distinguished education programs and exemplary patient care," said RPCI President and CEO Donald Trump.

The panel of peer reviewers from other NCI-designated centers wrote: "Under the exemplary leadership of the Center Director and with the continued involvement of the outstanding and productive Senior Leaders and commitment of the Institution... this established Cancer Center is well positioned to continue its contributions to the national mission to understand and eliminate cancer."

New York State Governor Andrew Cuomo and Congressman Brian Higgins, along with other state and local leaders, joined Trump for Tuesday's announcement at the 116-year-old cancer center.

**THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY** has named 30 society members to receive the Fellow of ASTRO designation. The 2014 class will receive the recognition during an awards ceremony Sept. 16 at the society's annual meeting in San Francisco.

The Fellows Program honors radiation oncology leaders who have been an ASTRO member for at least 15 years, who have contributed the equivalent of 10 years of service to ASTRO and who have made substantial contributions to the field of radiation oncology in the areas of research, education, patient care or service, and leadership. Including this year's class, 242 of more than 10,000 members worldwide have received the FASTRO designation.

*The members of the 2014 Fellows class are:*

• **John Buatti**, chair of and professor in the Department of Radiation Oncology of the University of Iowa

• **Thomas Delaney**, medical director of the Francis H. Burr Proton Therapy Center, co-director of the Center for Sarcoma and Connective Tissue Oncology and a radiation oncologist at Massachusetts General Hospital

• **Adam Dicker**, chair of the Department of Radiation Oncology at Thomas Jefferson University

• **Avraham Eisbruch**, the Newman Family Professor of Radiation Oncology, at the University of Michigan

• **Eduardo Fernandez**, senior vice-president of medical affairs and medical director for Latin America at 21st Century Oncology

• **David Gaffney**, medical director of the Radiation Oncology Clinic and vice-chair of and professor in the Department of Radiation Oncology at the Huntsman Cancer Institute and University of Utah

• **Adam Garden**, associate medical director of the Head and Neck Center and professor of radiation oncology at MD Anderson Cancer Center

• **Katherine Griem**, professor of radiation oncology at Rush University Medical Center

• **William Hartsell**, medical director of the CDH Proton Center

• **James Alan Hayman**, associate chair for clinical activities and professor of radiation oncology at the University of Michigan

• **I-Chow Hsu**, vice-chair of and professor in the Department of Radiation Oncology, at the University of California, San Francisco

• **Lisa Kachnic**, chair of the Department of Radiation Oncology at Boston Medical Center

• **Brian Kavanagh**, vice-chair and clinical practice director of and professor in the Department

of Radiation Oncology at the University of Colorado

• **Timothy Kinsella**, research scholar professor in the Department of Radiation Oncology at Warren Alpert Medical School

• **Andre Konski**, clinical professor in the Department of Radiation Oncology at the University of Pennsylvania

• **Patrick Kupelian**, vice-chair of clinical operations and clinical research and professor of radiation oncology at University of California, Los Angeles

• **Quynh-Thu Le**, chair of the Department of Radiation Oncology and the Katherine Dexter McCormick and Stanley McCormick Memorial Professor at Stanford University

• **W. Robert Lee**, professor of radiation oncology at Duke University School of Medicine

• **Stephen Lutz**, attending radiation oncologist at Blanchard Valley Regional Cancer Center

• **C.M. Charlie Ma**, vice-chair of the Department of Radiation Oncology and director and professor of medical physics at Fox Chase Cancer Center

• **Bruce Minsky**, deputy division head, director of clinical research, Frank T. McGraw Memorial Chair in the Study of Cancer and professor in the Division of Radiation Oncology at MD Anderson Cancer Center

• **Najeeb Mohideen**, attending radiation oncologist at Northwest Community Hospital

• **Simon Powell**, chair of the Department of Radiation Oncology and the Enid A. Haupt Chair in Radiation Oncology at Memorial Sloan Kettering Cancer Center

• **Mack Roach III**, chair of and professor in the Department of Radiation Oncology, at the University of California, San Francisco

• **Kenneth Rosenzweig**, chair of and professor in the Department of Radiation Oncology at the Icahn School of Medicine at Mount Sinai

• **Christopher Schultz**, professor of radiation oncology at the Medical College of Wisconsin

• **Dennis Shrieve**, chair of the Department of Radiation Oncology and the Rudolph P. and Edna S. Reese Research Professor in Radiation Oncology at the University of Utah

• **Paul Sperduto**, co-director of the Gamma Knife Center, University of Minnesota, Minneapolis, and radiation oncologist, at Minneapolis Radiation Oncology

• **Maria Werner-Wasik**, director of clinical research and professor in the Department of Radiation Oncology, at Thomas Jefferson University

• **Jeffrey Williamson**, professor of medical physics, Virginia Commonwealth University Medical Center