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→PAGE 3

In this issue

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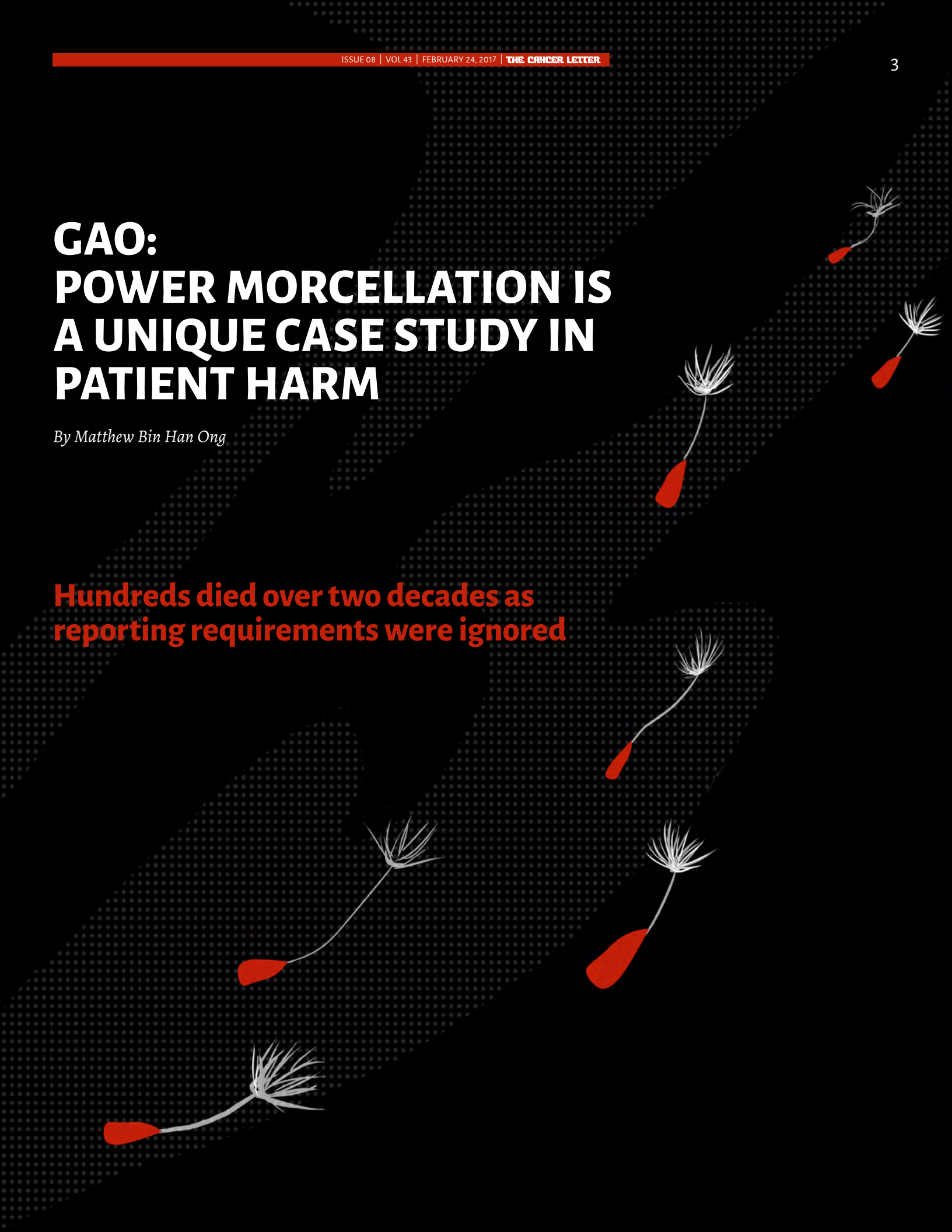
GAO: POWER MORCELLATION IS A UNIQUE CASE STUDY IN PATIENT HARM

By Matthew Bin Han Ong

Hundreds died over two decades as reporting requirements were ignored



FDA's passive reliance on self-reporting by hospitals and device manufacturers allowed harm caused by power morcellators to go unnoticed for over two decades—likely contributing to injury and deaths of hundreds of women, the U.S. Government Accountability Office said.

The power morcellator presents a unique case study in patient harm, said Marcia Crosse, director of the health care team at GAO.

The power morcellators worked as they were intended to work: they did not fail at their intended use of morcellating large uterine tumors. As a result, some hospitals interpreted the language of the statutory requirement to report adverse events as not applicable to the dissemination of malignant tissue. FDA has debunked this contention, saying that such cases should, in fact, have been reported.

Physicians need to start thinking of adverse events in the context of a device that functions as intended, GAO's Crosse said in a conversation with The Cancer Letter, in which she elaborated on the findings of a GAO investigation.

GAO recently released a 49-page report that sums up the three-year controversy over the once-common minimally invasive surgical procedure, now believed to have disseminated unsuspected uterine cancer in about one in 350 women.

"If the device had broken in the middle of a surgery, if the device had left a piece behind, the tip had fallen off or something like that, I think that the medical establishment is used to thinking of those kinds of device-related events as adverse events to be reported," Crosse said. "They may not be accustomed to thinking—and they need to think more broadly—that the device can work as it was intended to work and still cause harm.

"I think that was not, perhaps, being recognized sufficiently. There are folks in large medical centers charged with responsibility for this reporting, and so I'm hoping this was a wake-up call."

The conversation with Crosse appears on page 11.

The GAO report evaluated FDA's clearance process for power morcellators as well as the agency's handling of the hazards these devices posed to public health. The watchdog agency prepared the report in response to a request by 12 members of Congress to investigate why "hundreds, if not thousands, of women in America are dead." The House members requested the investigation in August 2015.

"Certainly, the hundreds seem reasonable, I cannot say thousands," Crosse said to The Cancer Letter. "While we're aware of 285 adverse event reports that were filed with the FDA [since December 2013], we are not making any independent estimate of the number of women harmed."

The hazards of power morcellation made national headlines after one patient, Amy Reed, an anesthesiologist and mother of six, underwent the procedure at Brigham & Women's Hospital in October 2013. The device's spinning blades had spread her undetected leiomyosarcoma, an aggressive uterine cancer, during the surgery. Reed is being treated for stage IV disease.

There are no authoritative estimates for the number of women who have died as a result of power morcellation. Over 80 percent of black women and nearly 70 percent of white women develop fibroids in their lifetime. According to studies, between 50,000 to 100,000 women a year in the U.S. underwent the procedure before FDA severely limited the use of power morcellators for hysterectomies and myomectomies in November 2014.

GAO notes that FDA cleared 25 versions or submissions for power morcellators between 1991 and 2014 to be marketed in the U.S. Critics of power morcellation say this is evidence that hundreds or thousands of patients have been harmed or have died from upstaged metastatic disease in that period.

Despite evidence that device manufacturers and physicians at prominent hospitals knew that patients were being harmed by power morcellation, nobody reported these adverse events to FDA—an action required of user facilities and manufacturers by federal law—until Reed reported her case in December 2013 (The Cancer Letter, Nov. 20, 2015).

Source: FDA | GAO-17-231

Summary of Adverse Event Reporting Requirements for Medical Device Importers, Manufacturers, and User Facilities

What to report	To whom	When
Importers		
Deaths and serious injuries[a]	FDA and the manufacturer	Within 30 calendar days of becoming aware of an event
Malfunctions[b]	Manufacturer	Within 30 calendar days of becoming aware of an event
Manufacturers		
Deaths, serious injuries, and malfunctions	FDA	Within 30 calendar days of becoming aware of an event (or within 5 work days upon FDA's request)
Deaths, serious injuries, and malfunctions requiring remedial action	FDA	Within 5 work days of becoming aware of an event
Supplemental reports to provide new, changed, or corrected information for a previously submitted report	FDA	Within 30 calendar days of receipt of the information
User facility[c]		
Death	FDA and manufacturer, if manufacturer is known	Within 10 work days
Serious injury	Manufacturer, or FDA if manufacturer unknown	Within 10 work days
Annual summary of death and serious injury[d]	FDA	January 1 for the preceding year

[a]Serious injuries are injuries or illnesses that are life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, or that necessitate medical or surgical intervention to preclude permanent impairment of a body function or damage to a body structure.

[b]Malfunctions are defined as the failure of a device to meet its performance specifications or otherwise perform as intended.

[c]A user facility is a hospital, ambulatory surgical facility, nursing home, or outpatient treatment or diagnostic facility that is not a physician's office.

[d]User facilities are required to file annual reports that summarize their adverse event reports.

"I do think it was a failure of the adverse event reporting system, yes," Crosse said. "I think it's a failure because reports were not being filed."

In an investigative series, "How Medical Devices Do Harm," The Cancer Letter broke stories in 2014 and 2015 examining FDA's system for reporting adverse events, and found that physicians at Brigham & Women's Hospital and Johnson & Johnson officials had direct knowledge of patient death and harm years before Reed's highly publicized account.

In December 2015, FDA initiated inspections at 17 hospitals to review their compliance with medical device reporting requirements. The vast majority of those hospitals did not file timely reports of injuries and deaths caused by medical devices. However, the agency decided against taking punitive action. (The Cancer Letter, Dec. 16, 2016).

"These inspections included five hospitals that, according to FDA officials, were chosen because there were reports of adverse events at these facilities related to the spread of uterine cancer from the use of power morcellators," the GAO report states.

The GAO investigation found that FDA's system for reporting adverse events has the following limitations:

- **Incomplete or erroneous reporting.** Adverse event reports can include incomplete reporting, where key data are not reported, or erroneous reporting, where the information provided is not accurate.

- **Reports that are not timely.** Adverse event reporting does not always reflect real time reporting, as some reports document events that occurred years earlier.

- **Underreporting.** Adverse events may not always be reported.

Members of Congress are planning on taking the issue to the White House. Rep. Brian Fitzpatrick (R-PA), who succeeded his brother Mike Fitzpatrick in the recent election, is leading the charge, his office confirmed.

Fitzpatrick plans to reintroduce the Medical Device Guardians Act, which would require individual physicians and practitioners—instead of only at the hospital administration level—to report adverse events.

"There are serious gaps in the FDA's device reporting system and immediate Congressional action is needed to reform the process and save lives," Fitzpatrick and Rep. Louise Slaughter (D-NY) said in a statement. "Armed with this information, we will move forward to find bipartisan legislative solutions to address these shortcomings and ensure a system is in place that provides real, accurate information to patients, professionals and regulators."

FDA knew of the risk of dissemination since 1991

The GAO report notes that FDA officials were aware of the potential for spreading tissue—cancerous or noncancerous—during procedures that involved the use of power morcellators since the agency cleared the first device in 1991.

"We found that this awareness was reflected in the labeling for 12 of the 25 devices cleared by FDA," the report states. "Agency officials, however, noted that [prior to December 2013], there was no consensus within the clinical community regarding the risk of this occurring, particularly for cancerous tissue.

"FDA officials stated that prior to December 2013, the general understanding was that the risk of a woman undergoing treatment for fibroids having unsuspected cancer—specifically, a difficult to diagnose cancer called uterine sarcoma—was low. FDA officials were not aware of any definitive scientific publications regarding the actual risk of cancer in uterine fibroids."

After Reed and her husband Hooman Noorchashm, a cardiothoracic surgeon, launched an aggressive campaign to stop the use of the procedure, FDA conducted a review of published and unpublished literature, including patients operated on from 1980 to 2011, to determine the risk of spreading unsuspected cancerous tissue.

"This report makes it an indisputable fact that a professional and corporate failure in gynecology left the severe oncological hazard of power morcellators unreported to the FDA," Noorchashm said to The Cancer Letter. "The GAO clearly documents that federal reporting requirements directed at hospitals and manufacturers were violated, leading to a sustained level of harm for two decades.

"But the report also highlights that, with adequate expert reporting, FDA can and does act to protect the public. It is a fact confirmed by the GAO, that our [adverse event] report in December 2013 triggered the FDA into action. So adequate expert reporting could very clearly serve to curtail dangers in the medical device space."

According to Columbia University researchers, the use of morcellators has dropped by nearly 80 percent after FDA's guidance document in November 2014 contraindicated the device for hysterectomies or fibroid removal in the vast majority of women getting these procedures.

Gynecology is now in a "post-morcellator era," Amanda Nickles Fader, associate professor and director of the Kelly Gynecologic Oncology Service at Johns Hopkins, wrote in an email to Noorchashm, who routinely makes his correspondence dealing with the scientific and policy issues on morcellation available to reporters and regulators.

"The medical community must find a solution to the morcellation issue so that more women do not suffer in the same way Amy [Reed] has, while aiming to strike a balance and maximize MIS in the hundreds of thousands of women who will benefit from it," Fader wrote in the email to Noorchashm. "We know that a large shift away from MIS will lead to great morbidity, and even mortality, in women.

"But we also recognize that we are in a post-morcellator era, and I (and many other investigators) are committed to developing better and safer technology so that we can avoid dissemination of occult malignancies."- Fader did not respond to this reporter's request to discuss her comments further.

"Dr. Fader's position that we are currently in a 'post-morcellator era' is an indication that many leading gynecologists see the serious problem with this practice, and are moving courageously in the direction of taking 'universal oncological precautions' to protect all women from cancer upstaging," Reed and Noorchashm said. "But unfortunately, so long as this device stays on the market, more women will be harmed by gynecologists who do not share Dr. Fader's sentiment."

Crosse cites failure to produce risk estimates of cancer

FDA concluded in April 2014—two decades after power morcellators started to be used for gynecologic laparoscopic procedures—that approximately one in 350 women undergoing hysterectomy or myomectomy for the treatment of fibroids is found to have an unsuspected uterine sarcoma.

"I think the problem here was a failure to have an accurate estimate of the frequency with which there is an undiagnosed leiomyosarcoma in what is believed to be a uterine fibroid, a benign fibroid," Crosse said.

Some FDA insiders say that input from cancer experts within the agency into the review process for medical devices might have prompted FDA to prioritize studying the risk sooner, potentially saving lives. While the agency's centers do collaborate, products are largely reviewed and regulated separately according to category: drugs, devices, and biologics.

An intercenter institute, the FDA Oncology Center of Excellence was established in June 2016 as a part of then-Vice President Joe Biden's National Cancer Moonshot Initiative to streamline and consolidate regulation of cancer-related products. Richard Pazdur, director of the FDA Office of Hematology and Oncology Products, was recently named director of the OCE (The Cancer Letter, Jan. 20).

"It is a significant analytical error on the part of the GAO to state that the problem was a 'failure to have an accurate estimate' of occult sarcoma," Noorchashm said. "How would knowing the 'one-in-however many' incidence address the fact that no one reported this danger to FDA?

"The only relevant failures that led to the sustained level of harm caused by power morcellators for over 20 years were: 1) a professional and corporate non-compliance with federal public health law by failing to report specific cases of cancer upstaging to FDA, of which there were many, and 2) the failure of leading gynecologists to think critically and ethically about this practice and its deadly but avoidable hazard to their specific patients."

FDA officials said they agreed with GAO's findings, and that FDA has noted the limitations of the existing system for reporting adverse events.

"The FDA has reviewed the GAO report on laparoscopic power morcellators and agrees with its findings," agency officials said in a statement to The Cancer Letter. "To reduce the risk of spreading unsuspected cancer, the FDA continues to warn against the use of laparoscopic power morcellation for the vast majority of women undergoing the removal of the uterus or removal of uterine fibroids.

"A boxed warning for laparoscopic power morcellators states that uterine tissue may contain unsuspected cancer and that patients should be informed of the risk of spreading cancer from the use of these devices during fibroid surgery. The FDA continues to review information on laparoscopic power morcellation, including the latest data and evolving scientific literature, and will communicate publically if the agency's recommendations change.

"In addition, the FDA has noted the shortcomings of the current passive postmarket surveillance system and has been taking steps to establish a better system to evaluate device performance in clinical practice. For example, the agency has awarded a grant to the Medical Device Innovation Consortium to establish a coordinating center for the National Evaluation System for health Technology (NEST). NEST is intended to improve the quality of real-world evidence that health care providers and patients can use to make better informed treatment decisions."

GAO did not include recommendations for further action, because investigators believe FDA adequately addressed the crisis.

"We felt that FDA had taken and was taking appropriate steps. They had put out information about this," Crosse said. "They had requested labeling changes from manufacturers and manufacturers had made those labeling changes. And they had undertaken a review to develop a better estimate of the underlying risk. They had taken the kinds of steps that we potentially could have recommended, had they not already been done."

> "Certainly, the hundreds seem reasonable, I cannot say thousands. I do think it was a failure of the adverse event reporting system, yes. I think it's a failure because reports were not being filed. There are folks in large medical centers charged with responsibility for this reporting, and so I'm hoping this was a wake-up call."

FDA enforcement of reporting requirements

Will FDA's new surveillance system—which will require at least five years of development before it is fully functional—improve the agency's ability to track and quickly address significant adverse events?

"I think it's too soon to know how much more effective it will be," Crosse said.

In the meantime, Rep. Fitzpatrick's Medical Device Guardians Act, which requires individual physicians to report adverse events, would be effective for catching signals of harm, Noorchashm said.

"In an ideal world, one would design robust active surveillance frameworks for devices to detect dangers," Noorchashm said. "But such a surveillance system will require several years of labor and cost intensive work for FDA to design and implement—not to mention the need for even more regulations to impose such as system. And even then outcomes surveillance systems would require active data mining to identify significant problems.

"So it stands to reason that enhancing reporting requirements, directed specifically at expert practitioners (as is missing from current regulation), would be a powerful stop-gap measure to provide FDA with the high fidelity 'intel' it needs from the ground to contain and curtail hazards to public health in the medical device arena. Such a system would be relatively cost-neutral, as a reporting framework and database already exists at the FDA and was the pathway through which the power morcellator disaster came to light."

It's unclear whether requiring individual practitioners to report adverse events would have prevented harm from power morcellators, Crosse said. She declined to comment on the Medical Device Guardians Act.

"That's speculation, I don't know. I think if FDA had been aware of it sooner, it could have taken action sooner," Crosse said. "I don't know if the entire problem could have been avoided by that."

FDA does not have the resources to conduct regular inspections to ensure hospitals are compliant with reporting requirements, Crosse said.

"[The agency has] been reliant upon the good faith and execution of those requirements by the medical establishment," she said. "I think FDA's investigation and the warning letters that they issued showed that there was more room for enforcement of those requirements, because, clearly, there was a failure to comply at many institutions."

“FDA's investigation and the warning letters that they issued showed that there was more room for enforcement of those [reporting] requirements, because, clearly, there was a failure to comply at many institutions.”

Following the December 2015 inspection of 17 institutions, FDA imposed no penalties against the hospitals that failed to comply with the reporting requirements, because "these hospitals indicated their willingness to work with us and address the violations," officials said at the time (The Cancer Letter, Dec. 16, 2016).

For reporting requirements to be effective, adequate law enforcement by FDA is an "absolute necessity," Noorchashm said.

"If hospitals and manufacturers are found to be in definitive violation of federal reporting requirements, as is the case here, a letter of warning from FDA is fully insufficient, especially when unsuspecting patients have been harmed or died as a result," Noorchashm said. "The FDA's law enforcement unit ought to impose significant fines or recommend prosecutions by the U.S. attorney general or inspector general of HHS for wrongful deaths in such cases."

Patients with leiomyosarcoma have a 5-year relative survival rate of 63 percent when diagnosed at stage I, according to the American Cancer Society. At stage IV, the survival rate drops to 14 percent.

A retrospective cohort study of 58 patients, published in the journal Cancer, found that patients who underwent morcellation were almost four times more likely to have a recurrence of malignant disease. The median recurrence-free survival for these patients was significantly shorter compared to those who underwent total abdominal hysterectomies (10.8 vs. 39.6 months).

Patients who underwent morcellation were twice as likely to die from metastatic disease—the median overall survival was 48 months—than patients who had total abdominal hysterectomies.

Since Reed's report in December 2013, a number of patients who underwent power morcellation and their family members shared their stories with the press. Following is a partial list of women who have died in recent years from metastatic uterine cancer upstaged by the procedure:

- Martha Ariri, Riverside, Calif. Chicago Tribune
- Nancy Curtis, Missoula, Mont. KPAX.com
- Bonnie Davis, Pittsburgh Pittsburgh Post-Gazette
- Linda Interlichia, Brighton, N.Y. The Wall Street Journal
- Elizabeth Jacobson, Sacramento, Calif. The Washington Post
- Erica Kaitz, Boston The Cancer Letter
- Barbara Leary, Greece, N.Y. Democrat & Chronicle
- Brenda Leuzzi, Perinton, N.Y. Democrat & Chronicle
- Viviana Ruscitto, Nyack, N.Y. The Record/NorthJersey.com
- Danusia Taber, Newbury Park, Calif. CBS Los Angeles

ACOG: All medical procedures carry risk

Risk can never be completely eliminated, and power morcellation remains an important option for women, said Hal Lawrence, executive vice president and CEO of the American College of Obstetricians and Gynecologists.

"ACOG applauds the U.S. Government Accountability Office on its recent report regarding the use of power morcellators in minimally invasive gynecologic surgery," Lawrence said in a statement. "The report presents a thorough investigation of the issue, and ACOG shares in the federal government's commitment to provide the best evidence to patients regarding the safety of using power morcellators to treat uterine fibroids.

"While the device has faced scrutiny in recent years, as the leading organization representing health care providers for women, ACOG maintains that power morcellation is an important option for women undergoing surgery for uterine fibroids. Morcellation is a minimally invasive technique that spares women from increased morbidity and mortality associated with abdominal surgery.

"Of course, when considering any procedure, ACOG recommends that ob-gyns conduct a thorough patient evaluation, engage in shared decision making, and follow the informed consent process with each patient. In the case of morcellation, this also includes reviewing appropriate measures to evaluate risk factors for potential malignant uterine sarcoma before moving forward with this treatment option.

"All medical procedures carry risk and that risk can never be completely eliminated. Moving forward, ACOG welcomes the collection of meaningful data that will help provide for the safe and effective use of power morcellation."

The GAO report is thorough and reflective of the history surrounding power morcellators, according to the American Association of Gynecologic Laparoscopists.

"The AAGL has reviewed with interest the Bipartisan Group Release GAO Report on Medical Device Safety," AAGL officials said in a statement. "The GAO has evaluated in detail the process by which the FDA reviewed 510(k) submissions for power morcellators, the FDA's understanding of any concerns surrounding the use of power morcellators, and the professional standards and guidance for physicians using these devices.

"We believe that the FDA fulfilled its responsibility in reviewing the devices, investigating reports of adverse events, providing education surrounding its findings, incorporating information into required product labeling, and following up with organizations and hospitals to ascertain uptake of their recommendations.

"The AAGL remains supportive of products and techniques that improve the outcomes of women undergoing minimally invasive surgery for gynecologic care and appreciates the FDA's commitment to ensure the safety of approved devices."

Timeline of Key Events Related to Laparoscopic Power Morcellators	
Date	**Key event**
March 1988	The Food and Drug Administration (FDA) clears the PacesetterTM 3500 Arthroscopic Surgical System—a predicate device for the first power morcellator—for the U.S. market.
June 1991	FDA clears the Cook Tissue Morcellator—the first power morcellator—for the U.S. market.
May 1995	FDA clears the KSEA Steiner Electromechanic Morcellator—the first power morcellator with indications for use for gynecologic laparoscopic procedu res—for the U.S. market. The indications for use specifically identified the removal or morcellation of uterine fibroids.
February 2000	FDA clears the Ethicon Gynecare Laparoscopic Morcellator—the first power morcellator with indications for use that identified hysterectomies (among other procedures)—for the U.S. market.
November 2013	FDA receives the first notification of an event where the use of a power morcellator during surgery to treat uterine fibroids may have spread an unsuspected uterine cancer.
December 2013	The Wall Street Journal publishes an article on the same event. FDA receives the first adverse event reports of the spread of unsuspected uterine cancer following the use of a power morcellator. In response, the agency convenes a signal review team to coordinate and lead FDA's evaluation and response to the potential power morcellator safety issue.
April 2014	FDA publishes the results of a review of scientific literature published since 1980, and finds that the risk of having an unsuspected and difficult to diagnose type of cancer, uterine sarcoma, is about 1 in 350 for women undergoing the surgical procedures of hysterectomy or myomectomy to treat uterine fibroids. FDA also estimated that the risk for having a specific type of sarcoma called leiomyosarcoma was about 1 in 500 among such women. FDA issues a safety communication that (1) reports the higher rate of unsuspected uterine cancer in women who undergo treatment for uterine fibroids (about 1 in 350), and (2) discourages the use of power morcellators in surgical procedures (hysterectomy or myomectomy) to treat uterine fibroids. FDA also sends letters to power morcellator manufacturers strongly recommending the review of product labeling and coordination with the agency to ensure that such labeling addresses the estimated risk.
July 2014	FDA convenes a meeting of the Obstetrics and Gynecology Devices Panel of FDA's Medical Devices Advisory Committee to solicit stakeholder input and available data related to the potential power morcellator safety issue. One manufacturer of power morcellators initiates a voluntary withdrawal of its power morcellators from the U.S. market.
November 2014	FDA issues an updated safety communication and an "immediately in effect" guidance recommending manufacturers include a boxed warning and additional contraindications in their product labeling. FDA's guidance states that manufacturers should implement these labeling recommendations and that within 120 days, a manufacturer with an existing 510(k) clearance should (1) add the contraindications and boxed warning to their labeling; (2) submit revised labeling to FDA; and (3) provide updated labeling to purchasers for power morcellators that have already been distributed. The safety communication also states that FDA considers the spread of an unsuspected cancer following the use of a power morcellator to treat uterine fibroids as a serious injury reportable under adverse event reporting regulations.
December 2015	FDA initiates inspections at selected hospitals to review their compliance with medical device reporting requirements. These inspections included five hospitals that, according to FDA, were chosen because there were reports of adverse events at these facilities related to the spread of uterine cancer from the use of power morcellators. Enrollment begins in the COMPARE-UF registry phase, which is expected to enroll about 10,000 women and evaluate the effects of treatments for uterine fibroids.
April 2016	FDA permits the marketing of a new type of device, a tissue containment system that could be used with certain power morcellators during morcellation of noncancerous uterine tissue for certain patients. FDA required the manufacturer of the new tissue containment system to warn patients and health care providers that the system has not been clinically proven to reduce the risk of spreading an unsuspected uterine cancer.

Source: GAO | GAO-17-231

Marcia Crosse: This "failure of the adverse event reporting system" should serve as a "wake up call"

CONVERSATION WITH THE CANCER LETTER

Marcia Crosse
Director of the health care team at the GAO

> "It points to the weaknesses in the passive surveillance system, that so many years went by before any reports were submitted to FDA. There are folks in large medical centers charged with responsibility for this reporting, and so I'm hoping this was a wake up call."

Q & A

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

Hundreds of women were injured or have died from upstaging of unsuspected uterine cancer by power morcellation because FDA didn't know the actual risk of cancer in fibroids, and hospitals failed to report harm, according to the U.S. Government Accountability Office.

Between 1991 and 2014, FDA cleared 25 submissions for power morcellators to be marketed in the U.S. The GAO report notes that FDA had been aware of the device's potential for spreading tissue since 1991.

The agency didn't receive reports of adverse events—which the federal government requires of hospitals and device manufacturers—resulting from power morcellators until December 2013. An FDA inspection of 17 hospitals in December 2015 found that the vast majority of these institutions did not file timely reports of injuries and deaths caused by medical devices.

"I do think it was a failure of the adverse event reporting system, yes. I think it's a failure because reports were not being filed," said Marcia Crosse, director of the health care team at the GAO. "The problem here was a failure to have an accurate estimate of the frequency with which there is an undiagnosed leiomyosarcoma in what is believed to be a uterine fibroid, a benign fibroid."

In your opinion, what is the most significant finding of the GAO report on power morcellators?

Marcia Crosse:
Well, I would say that I think it points to the weaknesses in the passive surveillance system, that so many years went by before any reports were submitted to FDA.

According to congressional critics of power morcellators, "hundreds, if not thousands of women in America" have been harmed or have died over the past 20 years because of this device. Based on your investigation, is this an accurate statement?

MC:
While we're aware of 285 adverse event reports that were filed with the FDA, we are not making any independent estimate of the number of women harmed.

Certainly, the hundreds seem reasonable, I cannot say thousands. I don't have data about the frequency of the procedure, and we did not make any estimates of how many women may have been harmed. I'm not extrapolating. That's a question for FDA.

Are you concerned about other devices doing similar grave harm?

MC:
I don't know about the same kind of harm. Certainly, we have seen several examples of devices where it has been some time before problems are identified.

There's the duodenoscopes, and so the extent to which they might not have been properly cleaned, I think, was not well recognized and it took some time for that to be identified.

And again, that's another area where reports were not being filed, that the passive surveillance systems seems not to have worked as quickly as one would hope. And then the metal on metal hips.

So there certainly are several examples where large numbers of patients have been treated and certainly have been potentially exposed to harm. We have not studied the full range; there are so many medical devices.

Obviously the fact that there are so many medical devices and you don't see more of these, I think, means that things are not in complete breakdown, but we see more examples than we'd hope to.

Does this regulatory issue have implications for other devices and other patient cohorts?

MC:
I don't want to speculate on what other devices might have similar kinds of problems. I think, certainly, the issue of a passive surveillance system is true for virtually all devices. And so, to the extent that there are unrecognized problems, then this kind of issue could recur.

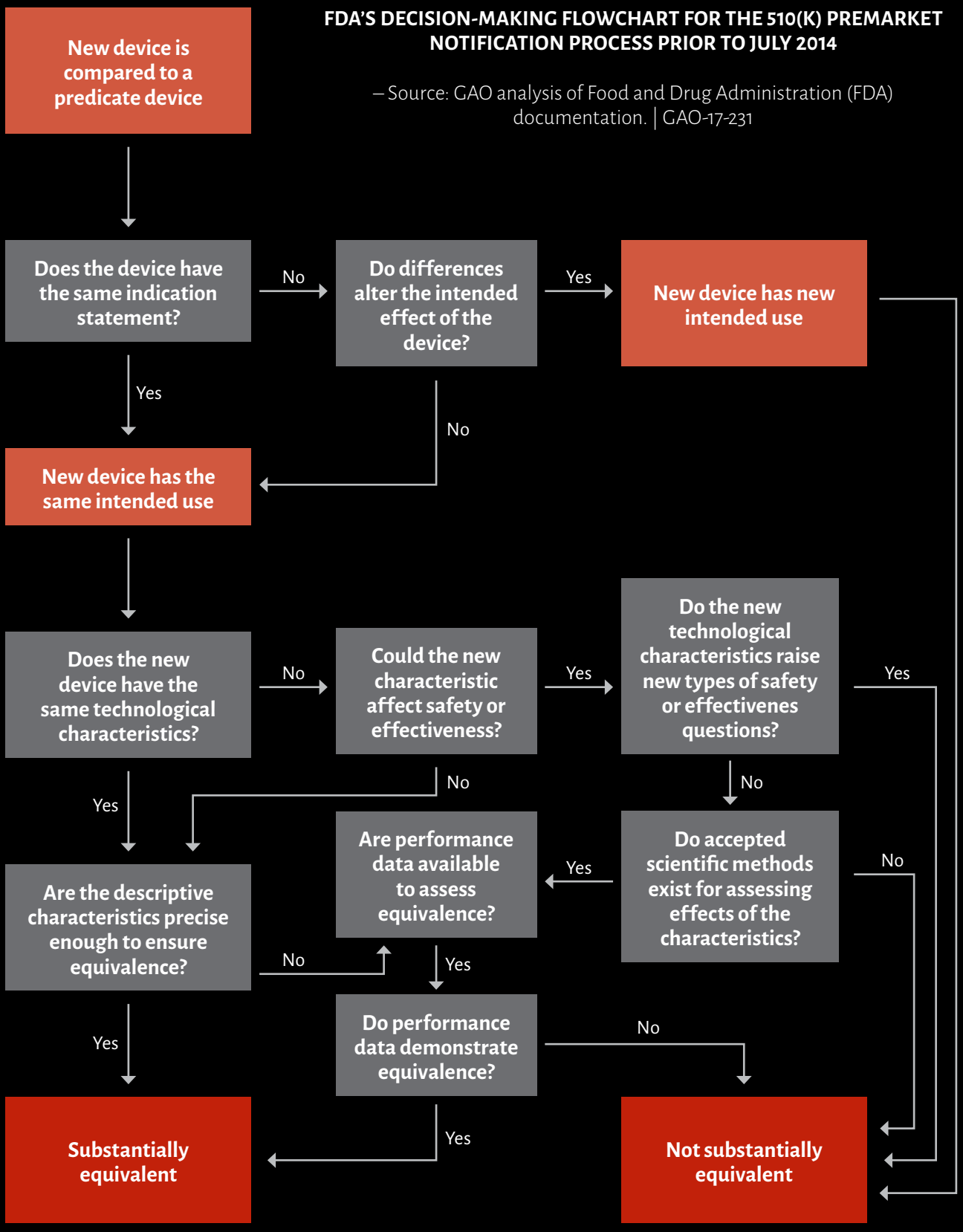
They are taking some additional steps now. For example, the Unique Device Identifiers that might allow for better tracing of patients and then for case identification. If some reports are filed, then that might facilitate the ability to go back and look and see if there were additional cases.

So I would say that there is some movement in the right direction, and they are trying to take some steps towards building better data systems to be able to do some case finding. But they're not there yet.

What is the root cause of this problem, and why do you think the harm caused by these devices had gone unnoticed and unreported for so long? Is this a failure in reporting?

FDA'S DECISION-MAKING FLOWCHART FOR THE 510(K) PREMARKET NOTIFICATION PROCESS PRIOR TO JULY 2014

– Source: GAO analysis of Food and Drug Administration (FDA) documentation. | GAO-17-231



Note: Figure depicts FDA's decision-making flowchart in effect when FDA cleared the 510(k) submissions for laparoscopic power morcellators included in our analysis.

MC:
I do think it was a failure of the adverse event reporting system, yes. I think it's a failure because reports were not being filed.

The law requires hospitals/user facilities and device manufacturers to report adverse events caused by medical devices. Are these reporting requirements adequate and sufficient?

MC:
I think FDA's investigation and the warning letters that they issued showed that there was more room for enforcement of those requirements, because, clearly, there was a failure to comply at many institutions.

Right, the agency inspected 17 institutions in December 2015.

MC:
And they haven't looked at the full range of institutions. It's not as though they are going out every year and doing these kinds of reviews at hospitals, nor do they have the resources to be able to do that.

And so they have been reliant upon the good faith and execution of those requirements by the medical establishment. I think this points to a breakdown at some very prominent hospitals in their compliance with these requirements.

This issue came to light because two affected physicians reported the problem to the FDA. Could this problem have been avoided if individual physicians had a specific responsibility to report adverse outcomes associated with medical devices?

MC:
I don't know. That's speculation. I don't know. I think if FDA had been aware of it sooner, it could have taken action sooner.

I don't know if the entire problem could have been avoided by that, because clearly there was some recognition of this risk when the devices were first approved. Just the magnitude of the risk was not well understood.

As you know, FDA is in the process of creating an intensive surveillance system to protect patients from high-risk medical devices.

MC:
Right, that's what I was describing before.

Critics say this will take several years to implement, potentially leaving patients at risk. Last year, there was a bill in the House called the Medical Device Guardians Act that would require individual practitioners to report adverse events without fear of liability. Would this be an effective strategy to give FDA access to high quality signals from physicians?

MC:
It's not appropriate for me to comment on proposed legislation. We are a support agency for the Congress and we were not asked to review that legislation and the likely impact of it. So I would just be speculating. I don't really have a position on that.

Power morcellators are still on the market. Are you concerned about them being used?

MC:
I think, as with any medical procedure, there are risks, and it's appropriate for patients to have conversations with their physicians about what's the best approach for their individual treatment.

There certainly are concerns that we heard about from not using power morcellators, from doing an open procedure, which can carry different kinds of risks.

And so, we are not saying that these devices should never be used. That is not our call to make. That's a call to be made between the practitioner and the patient.

The 510(k) clearance process for Class II medical devices did not account for the potential for power morcellators to cause harm, and was not sensitive to signals of harm for over 20 years. What is the problem here? Is this device an anomaly? Would classifying the power morcellator as a class III device have brought the oncological hazard to light earlier? Is this a classification issue? Or is the 510(k) a flawed process that should be revisited?

MC:
I would pick none of the above. I think the problem here was a failure to have an accurate estimate of the frequency with which there is an undiagnosed leiomyosarcoma in what is believed to be a uterine fibroid, a benign fibroid.

So it is not that the device didn't work as it was intended to work, it is not that the device broke, or failed in carrying out the surgery as it was intended to be used.

There's no evidence that it was not an appropriate choice to use a 510(k) pathway, that this device posed any more risk that the predicate devices upon which it was based, or that other devices used in laparoscopic surgery shouldn't be going through a 510(k) process.

I think the failure here was a lack of information and understanding of the underlying risk posed by use of the device when a cancerous tissue was present. And that's more of an epidemiological issue than a 510(k) process issue.

Critics have said that if this device, instead of being cleared through the 510(k) pathway, was reviewed through the Class III premarket approval process—which assesses for risk—the PMA might have caught the signal earlier. Is this pertinent?

MC:
I don't know that I fully agree with that. I think that you would have to have the data, and I'm not sure that … I don't know if it would have been identified.

The House members who requested the report did not ask for recommendations from your team. Imagine a hypothetical situation where you are asked to present recommendations: what would your recommendations be?

MC:
We would have made recommendations if we felt recommendations were warranted. We don't have to be asked to make recommendations.

We felt that FDA had taken and was taking appropriate steps. They had put out information about this. They had requested labeling changes from manufacturers and manufacturers had made those labeling changes.

And they had undertaken a review to develop a better estimate of the underlying risk. They had taken the kinds of steps that we potentially could have recommended, had they not already been done.

But we make recommendations to the government. We would not make recommendations to hospitals, for example, for what they should be doing. That's not an appropriate function for us.

So I think that the gaps that we see as remaining are gaps in reporting by the medical establishment. And that's not something that we have. Our recommendations are to federal agencies.

We felt that FDA had, now, taken appropriate steps and we had no further steps we thought they needed to be undertaking that they were not on the pathway to do.

Going forward, will FDA's action on this issue—with the new surveillance system and the Unique Device Identifiers—create an improved signaling system for adverse events caused by medical devices?

MC:
I think that they are taking steps that are certainly in the right direction. I think it's too soon to know how much more effective it will be.

Did I miss anything, and do you have any closing comments?

MC:
I don't think so, no. I think this certainly points to, as I said at the outset, this larger concern about the reliance of the system upon the medical establishment to report instances of problems to FDA when they're identified. In this situation, I think that the medical establishment has not been thinking of adverse events, perhaps, in a broad enough way.

If the device had broken in the middle of a surgery, if the device had left a piece behind, the tip had fallen off or something like that, I think that the medical establishment is used to thinking of those kinds of device-related events as adverse events to be reported. They may not be accustomed to thinking—and they need to think more broadly—that the device can work as it was intended to work and still cause harm.

I think that was not, perhaps, being recognized sufficiently. There are folks in large medical centers charged with responsibility for this reporting, and so I'm hoping this was a wake-up call.

Moonshot funds are not a substitute for sustained NCI funding, Lowy warns as prospect of year-long continuing resolution looms

Moonshot appropriations are not a substitute for sustained increases in appropriations, NCI Acting Director Doug Lowy said at the meeting of the National Cancer Advisory Board Feb. 15.

"It's critically important for us to be able to continue to meet our obligations in terms of inflation, but far more important to meet our obligations to the cancer research community," Lowy said at the virtual meeting.

"For example, the regular appropriation covers investigator-initiated research and, as I discussed at the joint board meeting back in December, we need to add tens of millions of dollars from that appropriation in order to sustain the out years for the RPG thanks to the substantial increases that we have given to the Type 1 and Type 2 awards over the last few years.

"Also, our important increases for training, which we hope will lead to having better trainees and more successful outcomes in training the best and the brightest of young scientists.

"We have our commitment to the cancer centers to increase the appropriations there and we have ongoing initiatives such as the RAS Initiative and other initiatives that are ripe and ready for expansion and the potential for new initiatives.

"Therefore, if we are in a full year continuing resolution, it will be a substantial challenge to meet all of our goals because the Cancer Moonshot is not a substitute for the regular appropriation."

A transcript of the director's report follows:

Doug Lowy: I want to make sure that everyone understands that, currently, for the regular appropriation, we have a continuing resolution that goes through April 28. It is unclear what will happen at that time. There are really two main possibilities. One is that there would end up being a full year continuing resolution and the other is that there will be an appropriation.

If there is a full year continuing resolution, while we would have the benefit of the moonshot appropriation, the moonshot appropriation is not a substitute for the sustained increases in our regular appropriation that we need in order to be able to maximize the progress that we make in cancer research.

And so, from the point of view of NIH and NCI, and I think from the point of view of the cancer research community, having a continuing resolution would be nowhere near as positive as having an appropriation. Part of the reason for that is that last year, the House Appropriations Subcommittee marked an increase of $1.25 billion for the NIH, with the NCI getting around $100 million. And the Senate subcommittee on appropriations marked up a bill to increase NIH appropriations by $2 billion with NCI getting around $200 million.

The advantages of increased sustained funding—I've gone over them in the past. But it's critically important for us to be able to continue to meet our obligations in terms of inflation, but far more important to meet our obligations to the cancer research community.

For example, the regular appropriation covers investigator-initiated research and, as I discussed at the joint board meeting back in December, we need to add tens of millions of dollars from that appropriation in order to sustain the out

years for the RPG thanks to the substantial increases that we have given to the Type 1 and Type 2 awards over the last few years.

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We have our commitment to the cancer centers to increase the appropriations there and we have ongoing initiatives such as the RAS Initiative and other initiatives that are ripe and ready for expansion and the potential for new initiatives.

Therefore, if we are in a full year continuing resolution, it will be a substantial challenge to meet all of our goals because the Cancer Moonshot is not a substitute for the regular appropriation.

I just do want to reiterate what I have said in the past about the broad bipartisan support for NIH in general, including the NCI. Last week, the House Appropriations Subcommittee came to NIH. There were both Republicans as well as Democrats who came and they spent a good part of the afternoon visiting the NIH.

There was one segment where they heard about activities, cancer research activities at NCI. Peter Pinto [an investigator and faculty member in the NCI Urologic Oncology Branch, Peter Choyke [senior investigator and head of the Molecular Imaging Program at the NCI Center for Cancer Research], and Bill Dahut [clinical director and scientific director for clinical research at the NCI Center for Cancer Research] from the Intramural Research Program presented imaging modalities that were pioneered in the Intramural Research Program in the Center for Cancer Research and now have been commercialized.

I will tell you that all of the members of Congress were very engaged—the female members of Congress at least as engaged as the male members of Congress--with issues related to prostate cancer. And there was a presentation of a patient who with random biopsies had not had a definitive diagnosis, but with a directed biopsy was able to get a definitive diagnosis of prostate cancer, get treated appropriately and is doing very well.

Perhaps the highlight from the visit from the House subcommittee, however, was meeting the trainees from the Intramural Research Program, clearly just a subset of them. But I think that the members of the House Subcommittee came away impressed by the passion, the commitment, and the quality of people who want to go into research. Just before turning the microphone over to Dr. Doroshow, I just want to reiterate, on the one hand there's tremendous bipartisan support, but on the other hand I do get concerned that if the regular appropriation stays the way it is, that we will have challenges meeting all of our goals.

One aspect that I didn't mention is that we also need to make compelling arguments, all of us, about the importance of the regular appropriation for cancer research, because there could be some people who might see some of the Cancer Moonshot funds be considered an offset instead of getting a full appropriate increase for the NCI regular appropriation.

Doroshow on Virtual Formulary and NCI-MATCH

Jim Doroshow [director of the Division of Cancer Treatment and Diagnosis and NCI deputy director for clinical and translational research]: You've all heard me talk a little bit about the concept of a Virtual Formulary before, and I just wanted to update you very briefly, because that activity launched a couple weeks ago.

This was principally an issue and an idea that many of you and your colleagues at cancer centers came forward with. That is the issue of trying to rapidly obtain investigational agents from multiple different companies for combination trials. And so we began working on this about a year, year and a half ago. Tried to understand whether this might be possible to facilitate these activities.

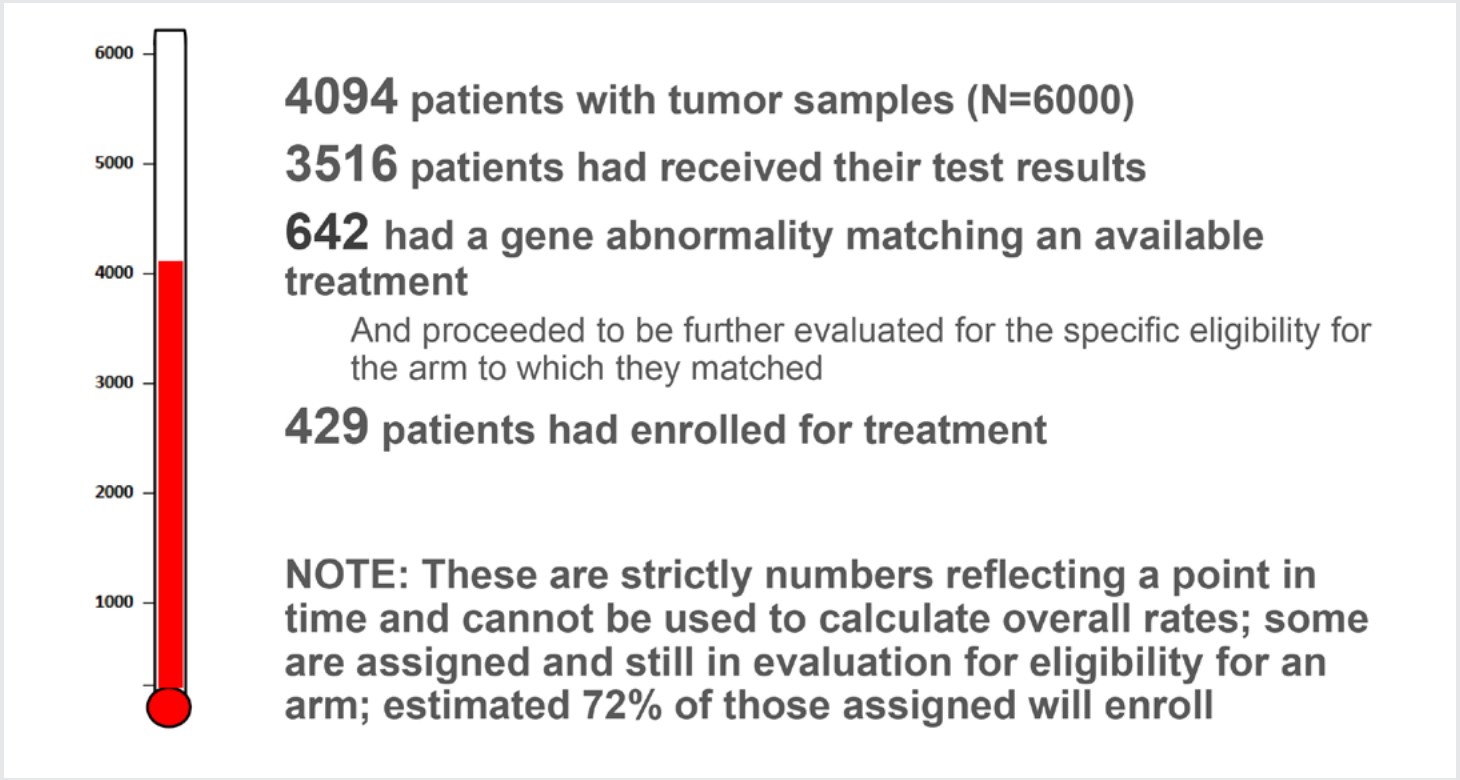
And what we have now, and I'll show you the website, is an activity that launched. We have 16 drugs from six companies. We are in active negotiation with several others. I think it's a near certainty that that number of drugs and number of companies will expand.

For a process, it really involves you as PIs or your colleagues as PIs and whether or not they're interested in doing a combination or single agent trial at your cancer center or obtaining clinical grade drug for combination or single agent pre-clinical investigations. It involves filling out a relatively modest form.

We serve, the NCI serves, really, only as a middleman. We facilitate this by taking the forms, getting them to our pharmaceutical partners. They have signed agreements that will allow rapid evaluation of those requests. We hope that within six to eight weeks from each of those companies, you or your colleagues would get an up or down reading on whether or not drug will be supplied either for a laboratory set of experiments or for a clinical trial that will be supported at your cancer center.

This is an activity for the time being is focused exclusively on NCI-designated cancer centers, which have the resourc-

NCI-MATCH TESTING AND ENROLLMENT AS OF 1/29/17 – Source: NCI



es to do and support investigator initiated INDs for this process. Let me just, in the interest of time, see if you can, I hope you have a copy of this slide. This is just a screenshot of the website for the formulary. It gives all the details, where you can get additional information, the drugs, the form to request the drugs. I strongly urge you, especially the pre-clinical investigators that need clinical grade drug for in-vivo experiments, where the quantities are much harder to obtain, that are required than for in-vitro or cell culture experiments, to avail yourself of this activity because we will work very hard to get as large a group of drugs from as many companies as possible.

The last thing I would like to say about this is that as you will see if you go to the website, all of the IP issues related to the use of these drugs follow pre-negotiated IP arrangements that we already have with these companies, which essentially all of your cancer centers have signed on to. So that this should be relatively easy in terms of getting the MTAs to allow these drugs to be used for the experiments that are of interest to you.

So I would just ask you please, if your colleagues don't already know about this, to please make them known and to call us or email us so we can facilitate their access to these compounds.

Let me move on to the MATCH Trial because there are some significant updates for you.

You all know about this study that was opened about a year and a half ago now. We are up to a thousand approved sites. If you see on right of your screens, one of the most heartening things about this issue of this trial is that essentially about 80 percent and 90 percent all of our clinical trial sites have this study open, which is really something of a record and something we're very thankful. And thankful to all of you and all of your colleagues. We originally estimated that we would have something like 40 or 50 patients screened per week. For now quite steadily for a year and a half we have been at 110, 120 patients per week that have been entered.

Here's the data of just two weeks ago. So, two-thirds of the accrual has been completed. About 20 percent of the patients who undergo screening are actually eligible and enter a study. This is a dynamic business because it really depends on the nature of the mutations that are found and the nature of the trial arms that are open in any one particular point in time.

So, as I said, we're averaging about 115 registrations per week. And we have continued again with great thanks to the four laboratories that are doing the screenings to maintain a turn around time of just over two weeks to getting the information back to the investigators and physicians who are enrolling their patients in the study.

This is a question Doug asked me to address, and I think it's a very important one. This is as of October, but the data are pretty similar now in terms of distribution of patients that have been screened. So one of the concerns when this was started a year and a half ago, is that well all of the patients screened will be in the big four: in breast, colon, lung, and prostate cancer.

You can see that there have been many patients with breast cancer and colorectal cancer screened, but in fact a very few patients with prostate cancer. Probably an underrepresentation, and I can't tell you why, in the area of lung cancer. But many diseases like uterine cancer, ovarian cancer et cetera and certainly pretty reasonable spread of underrepresented cancers, patients have been entered on this trial. We're very appreciative because we worried it would be dominated by one set of diseases and that does not seem to be the case.

This is also data as of October, but not substantially different now in terms of distribution based on gender and ethnicity. See that about 80 percent of the patients entered are Caucasian. I think 8 percent are African American, 5 percent are Hispanic. That has held up as the trial has progressed. I hope you can read this if you have copy of the slides because it's pretty small.

But this is a distribution of accrual by state, which I find very interesting. Because it doesn't strictly correspond to population. It might be expected that California, and Pennsylvania, Michigan would have high numbers. But it wouldn't necessarily be expected that Minnesota would be number two. On the flip side, it probably wouldn't be expected several other states to remain unremarked upon are much lower down on the list of accrual. I think particularly noteworthy is that there've been 100 patients from Oklahoma entered on this study. Pretty remarkable event I think.

NCI-MATCH EXPANDED TO 24 ARMS MAY 31, 2016 – Source: NCI

Arm	Target	Drugs(s)
A	EGFR mut	Afatinib
B	HER2 mut	Afatinib
C1	MET amp	Crizotinib
C2	MET ex 14 sk	Crizotinib
E	EGFR T790M	AZD9291
F	ALK transloc	Crizotinib
G	ROS1 transloc	Crizotinib
H	BRAF V600	Dabrafenib+trametinib
I	PIK3CA mut	Taselisib
N	PTEN mut	GSK2636771
P	PTEN loss	GSK2636771
Q	HER 2 amp	Ado-trastuzumab emtansine
R	BRAF nonV600	Trametinib
S1	NF1 mut	Trametinib
S2	GNAQ/GNA11	Trametinib
T	SMO/PTCH1	Vismodegib
U	NF2 loss	Defactinib
V	cKIT mut	Sunitinib
W	FGFR1/2/3	AZD 4547
X	DDR2 mut	Dasatinib
Y	AKT1 mut	AZD 5363
Z1A	NRAS mut	Binimetinib
Z1B	CCND1,2,3 amp	Palbociclib
Z1D	dMMR	Nivolumab

Red = accrued 35 patients
Gray = nearing 35 patients

Here are the first 24 arms that were reopened as of May 31, 2016. And what you can see in red are the patients who accrued their 35 patients. So those trials may accrue a few more patients but by in large they are now undergoing initial evaluation as to efficacy which will take several months. There's several more in green that are near their 35 patient accrual cut off and so we're making good progress in completing trials. And these are the additional seven arms that will be opened this month. This is really a large signal seeking trial with something over 30 patient arms that will, we hope, be completed by the time the study is over.

But I'd like to talk to you about how we're trying to deal with the issue of those diseases, I should say those mutations that are quite rare and for which even with 6,000 patients accrued what is our intention? How do we plan to deal with the fact that it's unlikely that even after the 6,000th patient screened how do we deal with that? Because we very much want to complete appropriate accrual for all of the arms. And so after a significant amount negotiation over the past many months, an amendment that is winding its way through various regulatory processes has been agreed to.

So that we will be working after the 6,000th patient is biopsied and screed, we will be working with Foundation Medicine and Caris [Life Sciences] as well as with Memorial [Sloan Kettering Cancer Center] and MD Anderson [Cancer Center] to try to make available and specifically focus on these specific patients' mutations that are hard to find. So that these patients from those companies and from those two institutions can specifically be recommended for accrual. And we hope actually the ability to enhance the accrual and completion of the rare, so called rare mutations process can utilize patients who are being screened in their normal process either of clinical care or as a process that is ongoing at several of our large cancer centers to facilitate the completion of the trial. So I think we are very much working on how to fund this at the present time.

One of the optimal things we will learn if this is completed in an expeditious way is really, the next phase of doing these kinds of experiments. How do we take advantage of all the many institutions that are already screening their patients or in a variety of mutational panels? One thing I will say is that its already been apparent that patients who are screened by these other organizations and who are felt to be eligible and go on study will have their panels and their mutational analysis be confirmed at one of our MATCH assay sites so that data will be homogenous and analyzable across all of the trials that we conduct.

Kibbe on GDC

Warren Kibbe [director of the NCI Center for Biomedical Informatics and Information Technology]: I'd like to keep this fairly brief and its just really an opportunity to give you an update on what's been going on with the Genomic Data Commons, and also talk a bit about the NIH Data Commons, the NCI Data Commons and how that flows into the recommendations from the Blue Ribbon Panel around national data ecosystem for cancer.

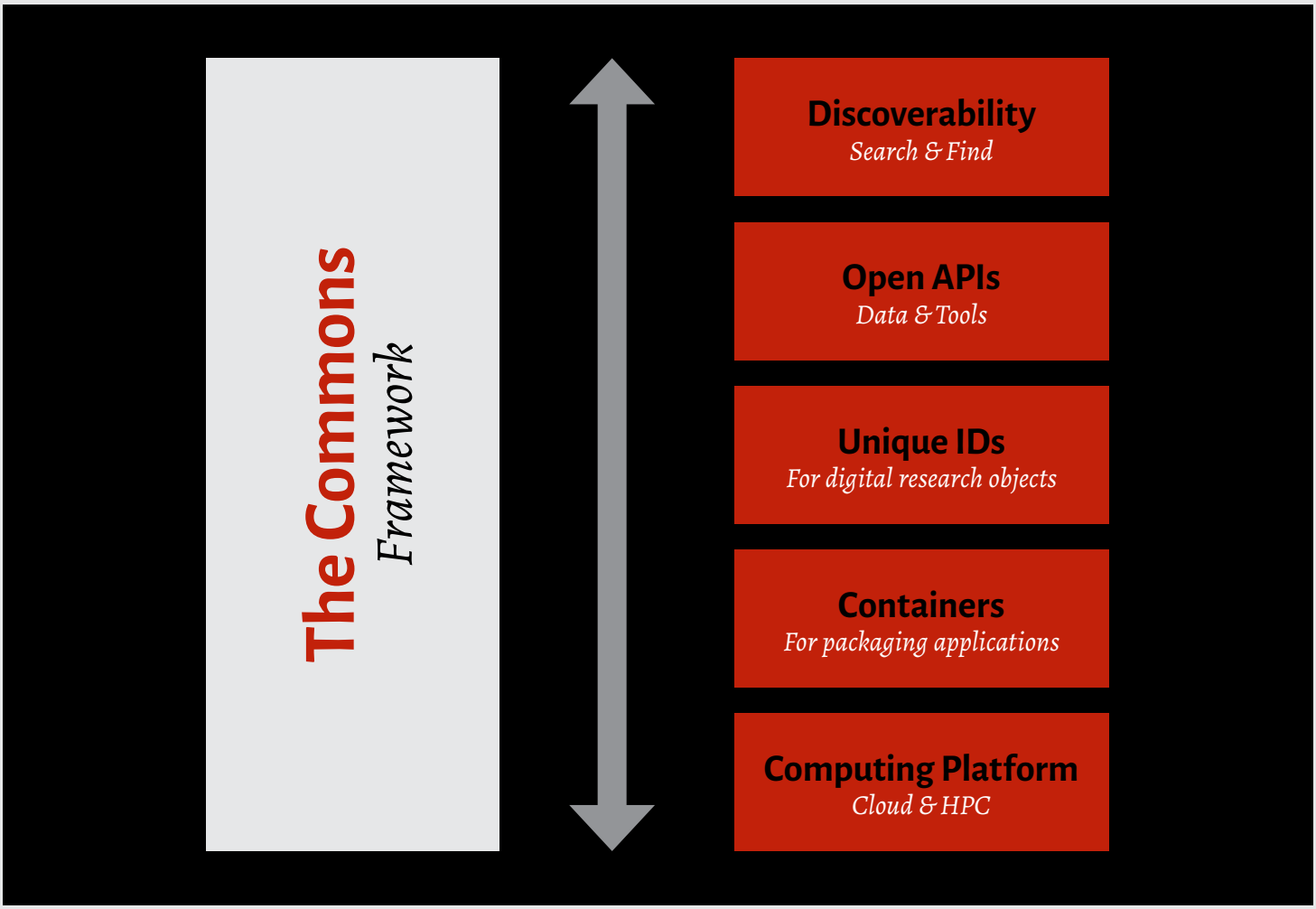
The graphic up there is actually describing, if you will, a generic Data Commons framework. It's, how do we make data discoverable? How do we support open APIs so that different kinds of data and tooling can connect to a Data Commons? How do we support unique IDs? And that's an incredibly important part of making things searchable and findable and reproducible, so that when we couple a specific dataset, we can find exactly those datasets again. More from a computation standpoint, supporting different kinds of containers and having everything be able to run in either commercial clouds or in high performance computing environments. So that's kind of, if you will, schematic of how a Data Commons can be constructed.

I've shown this graphic before. This is really the Cancer Data Research Ecosystem, and it's one way depicting part of what came out of the Blue Ribbon Panel. Its focused very much on the NCI view of the ecosystem, not necessarily the national piece. And on the left hand side is really thinking about discovery and discovery data. So where genomics, proteomics, imaging data, clinical trial data, and in data that I would characterize as coming from well characterized research datasets can be combined.

We have one example of a system like that and that the Genomic Data Commons which I'll come back to in a second. The middle tier, the middle pillar is really around patient engagement. That's another side of the Blue Ribbon Panel recommendations, thinking about how do we engage patients more effectively in research. And how do we make that a two way conversation? So what is it that would patient most benefit from, from research, as well as, how to get patients engaged in that research? And then in the third pillar is really looking at it from a population standpoint. So what is it that is happening throughout the world, throughout the U.S. in care and incidents? And the SEER Registry in particular is an example of an existing repository that NCI's been supporting since 1974.

So then to transition, just to talk about the GDC a bit. And again, this is a slide that I think you've all seen before. There are some principles behind the Genomic Data Commons and it's really about making data findable, accessible, attributable, interoperable, reusable and provide recognition to the folks that contribute data, contribute tools, contribute annotations to

DATA COMMONS FRAMEWORK – Source: NCI



the Genomic Data Commons. And we think that those fair principles are really important for any kind of Data Commons, any kind of repository that has cancer research data in it. And there's a number of groups that have been really laying out some of those principles very effectively: Global Alliance for Genomics and Health, Force11. And again, it's keeping in mind and keeping aligned with the activities of those groups as well.

Just to show you the GDC, if you go to gdc.cancer.gov you get this view of the current data in the Genomic Data Commons. And I won't go through the graph except for to say that data is both live and it's very graphically pleasing. I'm going to just, again this is a slide that all of you have seen with perhaps the exception of the last two lines. And that's that Genomic Data Commons went live back in June with rough four petabytes of data and a little bit more than 1.5 petabytes of highly harmonized data for the whole community to use.

Foundation Medicine announced back in June that they would release 18,000 genomic profiles and I'll give you an update on that submission in a minute. And then also in September, the Multiple Myeloma Research Foundation announced that it would be releasing its CoMMpass Study of more than a thousand cases of multiple myeloma patients back in September. So those have all been very exciting contributions that the community's been making for the Genomic Data Commons.

I want to highlight GDC's monthly usage in December. I apologize, I would've rather had January, cause as we all know, in December some of us do take break and may not be working quite as hard as in other months. But these are the monthly usage stats from GDC. So folks visiting the front page: there were more than 16,000 visits that month and more than 29 gigabytes of data were delivered to users across the world.

Hitting the APIs, that's how investigators can access the datasets behind

the front end of the GDC—roughly three terabytes, three and a half terabytes were downloaded that way. And then the other websites that are really around how to use it and how to think about getting training on using GDC and those were all very active as well. So multiple thousands of users even in the month of December. And the bottom table is just showing the capacity, the current capacity of the GDC for storing data and it's in the safe zone, which is good.

The next page is just looking at specific disease areas and seeing where most of the traffic has been. And you can see that breast cancer and glioblastoma in particular, have been a major source of traffic for the GDC as well as kidney clear cell carcinoma.

Last two things I want to talk about are just where we are with the Foundation Medicine dataset. So 18,000 cases were sent to the GDC and they have been working for the last six months or so realigning all the data, moving it to the most recent human genome build and making it all compatible with the existing GDC data. There's a last QA process that's in place, cause of the number of things as it was moved to the new build are different than the old genome build and it's going back to Foundation Medicine and making sure that, in fact, we've interpreted all those data appropriately. So, we're hoping that by April all that data will be available to the community.

And the last thing that I'm going to talk about is the Multiple Myeloma Research Foundation that I mentioned. They agree to submit all their data through the GDC for public release back in September. And that work is ongoing as well. The GDC folks are mapping all the data from the CoMMpass Study into the GDC and the data is being uploaded as we speak. So we're hoping that by summer those data will also be available through the GDC.

Singer on moonshot implementation

Dinah Singer [director of the NCI Division of Cancer Biology]: As all of you are undoubtedly aware, the Cancer Moonshot identified three major goals, with the acceleration in the progress in cancer including across the entire cancer research continuum, from basic research to clinical to population sciences being a major focus.

While we are actively looking at all three to achieve those goals, our major focus right now is on accelerating the progress in cancer research. To identify those opportunities that were as we called them, poised for acceleration, the NCAB actually established the Blue Ribbon Panel that was charged with identifying major scientific opportunities and developing a set of recommendations of opportunities that we would or should pursue through the Cancer Moonshot through the support and the funding that that provided. The Blue Ribbon Panel worked through the spring and summer looking very broadly at what those opportunities were and by the fall established a set of recommendations that were summarized in the report that you've all seen.

I've highlighted or summarized all of them here. Again, to remind you of the breadth and scope of those recommendations across the entire cancer continuum. There are 10 of them. In addition to those 10 specific recommendations, we also identified cross cutting themes that emerged in all of the discussions. They include importantly health disparities, prevention, technology development, data sharing [and other aspects] of the moonshot and partnerships, which I'll come back to.

Even though the Blue Ribbon Panel finished its work by the end of September, or the beginning of September, we didn't have an allocation until the end of December, and so we couldn't do much until we got that allocation, which came at the very end of September through the funding in the 21st Century Cures Act.

That act actually provided funding to the Cancer Moonshot, which is now called the Beau Biden Cancer Moonshot Initiative, and it provided $1.8 billion over seven years for cancer research in support of the moonshot recommendations with $300 million already allocated in FY17 with the broad guidance to support cancer research. So with that in hand we're now in a position to begin to implement the recommendations of the moonshot.

The funds in FY17, as welcome as they were, came in the middle of the year which limited our ability to go out to the broader community to get input on their implementation. But we did have sufficient ... so let me backup, that our goal for FY17 really is to establish the foundation to lay the groundwork for implementing the broader initiatives through the Blue Ribbon Panel report.

We were in a position to accelerate the progress on some areas of research, which could be funded in FY18 and those are summarized here. In six recommendation areas, we're going to be able to support a number of new initiatives that will lay the foundation for the implementation in FY18 and FY19 of the broader initiatives that were recommended. And they're summarized here and you'll see all of these are already out on the street and will be funded with FY17 funds. So for FY18 and FY19 we're now putting into place a much more structured process to allow us to have broader input, both from the NCI community and the broader cancer research community. And I'm going to summarize that process for you, again, very briefly.

Clearly, with so many different and disparate recommendations, with so much to achieve, we need to have a very structured process and that's what's outlined here. I'll take you through it.

A number of people have responded to this by saying, "Oh my God, it's so bureaucratic and cumbersome." I hope to convince you that that's not the case, but if it is, we are prepared to revise it.

So let's start from the bottom. Each of the recommendations has an implementation team assigned to it. Two of the recommendations actually have two teams which is why we have a total of 12 teams. Immunology has both a adult and a pediatric immunotherapy team and prevention has both a cancer screening and prevention team. There are a total of 12 teams. In total, we have representatives from Intramural NCI, Extramural NCI, and representatives from other institutes. And at the last count we had over 250 people participating in these teams, helping to formulate the initiatives that are going to be started to support the goals of each of those Cancer Moonshot recommendations. The teams are specifically charged with discussing and developing initiatives for FY18 and FY19. And they are asked to identify the gaps and opportunities in the current landscape of existing initiatives, even though the recommendations were quite explicit on what is to be achieved. It's going to be important to understand what we're already doing that can be leveraged, what gaps are there, and what opportunities there are to build on.

Importantly, we're going to have the teams seek input from others including the broader cancer community, including the boards like the NCAB, advocates, and the professional associations. An important component of what we want to achieve is to identify partners. I've said in the past, and I think it's worth repeating, that NCI cannot, on its own, achieve all of the goals of the moonshot. Nor would we want to. We really want to do this in partnership with academia, with industry, with pharma, and with other government agencies. And I'll tell you in a minute about the partnership committee that we've organized with the explicit task of identifying the appropriate partners for the different initiatives and the different recommendations.

"NCI cannot, on its own, achieve all of the goals of the moonshot. Nor would we want to. We really want to do this in partnership with academia, with industry, with pharma, and with other government agencies."

Once the initiatives have been funded, the teams will continue to work by providing oversight and coordination to those initiatives making sure they're progressing appropriately, making linkages across the different initiatives as appropriate, organizing meetings, and providing general program management.

In addition to the teams, and because there's so many of them, it's very clear that communication across all those teams and throughout the NCI is going to be critical to the success of the implementation. While we want the teams to function independently, we don't want them to function in isolation. An so the idea of the coordinating team, that big blue box on the slide is really to be a point of communication.

Each team has a coordinator assigned to it who will represent that team on the coordination committee which will meet every other week to share ideas, information, discuss concepts that are being developed. Because we fully expect that there's going to be a lot of crosstalk, a lot of areas where groups can work together on a common initiative.

For example, the immunotherapy group, the human tumor atlas group, and the prevention group, all had components of their recommendations, the development of a human tumor atlas. So we anticipate that they will at some point work together to collaborate on developing initiatives of common interest.

That coordinating committee really serves as a communication vehicle but also to provide feedback to the teams in ways that their initiatives might be refined, and finally to forward to the steering committee initiatives or concepts that they think have high priority.

In addition, and this is where the partnership committee comes in, this will be the venue it will be clear where we need partners. And the partnership committee will be able to, then go out and identify appropriate partners for the initiatives as they are being developed.

Once the concepts are approved, they go to the implementation steering committee, which Doug chairs. That's also the place where we're going to merge the science with the budget and prioritize all of the initiatives that will finally go to the SPL for approval.

The teams were first launched a week ago. Nine of the 12 teams have met at least once. Some of them have met twice. As I said, there are over 250 people involved and there's a huge amount of enthusiasm within the NCI and the NIH to begin to implement these recommendations.

IN BRIEF

Cleveland Clinic opens new cancer center

The new Cleveland Clinic Taussig Cancer Center will begin welcoming patients March 6.

The 377,000-square-foot facility, estimated at $276 million, will house all outpatient cancer treatment services in one location. The seven-story cancer building is located on the north side of Carnegie Avenue between East 102nd and 105th Streets.

The building, designed by William Rawn Associates, Architects, Inc. and Stantec Architecture, is organized by cancer type, allowing patients to now have all of their appointments in one area where clinical caregivers come to the patient.

"As one of the nation's most progressive cancer centers, the new Taussig Cancer Center will provide a seamless, personalized experience," said Brian Bolwell, chairman of the Cleveland Clinic Taussig Cancer Institute. "Our design priorities of reduced wait times, improved patient flow, multidisciplinary clinics and a healing environment, combined with a commitment to cancer research, will deliver the best possible care and support for our patients."

The new building includes an open first level featuring a large laboratory to help avoid long waits for blood testing; an outpatient pharmacy; a retail store stocked with items to meet cancer patients' needs; and a café that accommodates special diets. Clinical features of the Cleveland Clinic Taussig Cancer Center include:

- 126 exams rooms and 98 treatment rooms in close proximity
- Private chemotherapy infusion suites along the north side of the building with floor-to-ceiling windows that overlook the tree-lined lawn
- Genetics and genomics testing
- A centralized home for existing high-level treatment technology, including six linear accelerators and a Gamma Knife suite
- On-site diagnostic imaging
- Dedicated area for phase I, II and III clinical trials, with a special emphasis on supporting phase I trials

Jeffrey Patrick new director of Ohio State Drug Development Institute

Jeffrey Patrick was named director of the Drug Development Institute at The Ohio State University Comprehensive Cancer Center–Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

Created by the OSUCCC–James and, with the help of seven Ohio State colleges and the university's technology commercialization office, the DDI helps accelerate cancer drug development through strategic partnerships within the global pharmaceutical and research/development industries. DDI has cataloged 30 novel anticancer agents developed at Ohio State and is currently working to advance the most promising toward phase I testing by seeking investigational new drug applications by 2020.

Patrick joins the OSUCCC–James from New Haven Pharmaceuticals in Connecticut, where he served as chief scientific officer. The DDI exists to advance early stage cancer research

developed at Ohio State and serve as a bridge between faculty researchers and pharmaceutical industry.

Using an external, peer-reviewed evaluation process, the DDI has identified six core projects that will receive Pelotonia funding as well as drug development technical support, provided by a team of dedicated scientists and advisors with deep experience in creating high-value new drug candidates.

The projects represent a $1 million investment and include:

- **B cells as Personalized Cancer Immunotherapy Investigators:** Thomas Cherpes and Rodolfo Vicetti Miguel. This multidisciplinary team is developing a novel B cell-based cancer immunotherapy. The therapy deploys a patient's own B cells as "warheads" that activate the immune system to aggressively attack tumors. This approach has potential to treat a wide variety of cancer types, and may even be personalized to attack targets that are unique to an individual's tumor.

- **Tumor-Targeted Payload Delivery Investigators:** Michael Tweedle and Joshua Goldberger. One of the hallmarks of cancer is the continuous replication and high metabolic activity of cells in the tumor. This activity leads to the production of an acidic environment in the tumor. A team at Ohio State has designed molecules that can home in on this acidity and accumulate in the tumor. These specialized molecules could be used to deliver chemo- or radio-therapeutic agents to kill tumor cells or imaging agents to enhance visualization of tumors. DDI investment will support the production and testing of these molecules as a cross-functional delivery platform.

- **Reprogramming the Immune System to Fight Cancer Investigators:** Mikhail Dikov, Thomas Magliery, Ming Poi, and David Carbone. The immune system is an important defense mechanism for recognizing and destroying abnormal cells in the body. Cancer cells often have the unique ability to escape the watchdog effects of the immune system, allowing the cells to grow and to metastasize to other locations. A team of Ohio State researchers have demonstrated that by modulating a signaling pathway in immune cells, they can reprogram the immune system to once again recognize and fight evasive tumor cells. The DDI is investing in research to develop and test a new class of molecules that impact this pathway.

- **A Vaccine Against a Cancer-causing Virus Investigator:** Robert Baiocchi. Epstein-Barr Virus (EBV) is a virus that infects 90 to 95 percent of adults and is associated with the development of several cancers, including lymphomas, in patients receiving organ or bone marrow transplants. The DDI is supporting the research team to develop a vaccine against the virus, which could be used to improve the body's immune response to EBV and prevent cancers.

- **A Novel Target for Cancer Treatment Investigators:** Steven Sizemore and Steffen Lindert. The Ral A protein has been shown to be critical for the growth of several types of cancer. Inhibitors of this target have yet to be clinically explored. A team of Ohio State researchers including Steven Sizemore, PhD, of radiation oncology and Steffen Lindert, PhD, of chemistry and biochemistry, are working with the DDI to design and test inhibitors of Ral A for the treatment of cancer.

- **A New Approach to Targeting a Cancer Driver Investigator:** Werner Tjarks. Estrogen receptors are established targets implicated in both cancer and metabolic disorders. Werner Tjarks in the College of Pharmacy has teamed up with colleagues in the Czech Republic to develop a novel series of selective estrogen receptor beta agonists. Tjarks and the DDI are now collaborating to advance these promising molecules for treating cancer.

DRUGS & TARGETS

FDA approves Revlimid as maintenance in multiple myeloma following transplant

FDA approved lenalidomide (Revlimid) as maintenance therapy for patients with multiple myeloma following autologous stem cell transplant.

The drug is sponsored by Celgene Corp.

In 2006, lenalidomide, an orally administered thalidomide analogue, received FDA approval for use with dexamethasone in patients with multiple myeloma who received at least one prior therapy. In 2015, the indication was expanded for use in combination with dexamethasone for the treatment of patients with multiple myeloma, to include newly diagnosed multiple myeloma patients who are not eligible for autologous stem cell transplant. Lenalidomide is also approved in myelodysplastic syndromes and mantle cell lymphoma.

The current approval was based on two randomized, controlled trials evaluating the efficacy and safety of lenalidomide maintenance therapy for the treatment of multiple myeloma patients after autologous stem cell transplant (CALGB 100104 and IFM 2005-02 trials).

These trials demonstrated approximately a 15-month (CALGB) and 18-month (IFM) progression-free survival advantage, at the time of the primary analysis, in patients treated with lenalidomide compared with patients receiving placebo (hazard ratio (HR) in CALGB=0.38; 95% CI: 0.27, 0.54; p<0.001 and HR in IFM=0.50; 95% CI: 0.39, 0.64; p<0.001). The median overall survival was 111 and 106 months for patients treated with lenalidomide compared with 84 and 88 months for patients receiving placebo in the CALGB and IFM trials, respectively. The types, frequency, and severity of adverse events (AEs) observed in the two trials were similar to those previously described in the product label.

Neutropenia, affecting 56% of the 517 patients treated with lenalidomide in both trials, was the most frequently reported grade 3/4 AE. An increased incidence of second primary malignancies was reported among patients treated with lenalidomide compared with those receiving placebo. The lenalidomide product label notes an increase in second primary malignancies in patients with multiple myeloma treated with lenalidomide. The recommended dose and schedule for lenalidomide is 10mg once daily continuously on days 1-28 of repeated 28-day cycles.

Full prescribing information is available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021880s049lbl.pdf

Zykadia receives a Priority Review for frontline use in ALK+ metastatic NSCLC

Novartis said FDA has accepted the company's supplemental New Drug Application for filing, and granted Priority Review for the expanded use of Zykadia (ceritinib) as a first-line treatment for patients with metastatic non-small cell lung cancer whose tumors are anaplastic lymphoma kinase-positive as detected by an FDA-approved test.

FDA also granted Breakthrough Therapy designation to Zykadia for the first-line treatment of patients with ALK+ metastatic NSCLC with metastases to the brain.

The sNDA submission for first-line use of Zykadia is based on the primary analysis of ASCEND-4, a global phase III, randomized, open-label, multicenter clinical trial which evaluated safety and efficacy of Zykadia compared to platinum-based chemotherapy, including maintenance, in adult patients with Stage IIIB or IV ALK+ NSCLC.

The study was conducted at 134 clinical trial sites across 28 countries, and randomized across 376 patients.

The study found:

- Patients treated with first-line Zykadia had a median progression-free survival (PFS) of 16.6 months (95% confidence interval [CI]: 12.6, 27.2), compared to 8.1 months (95% CI: 5.8, 11.1) for patients treated with standard first-line pemetrexed-platinum chemotherapy with pemetrexed maintenance. A 45% risk reduction in PFS was obtained in the Zykadia arm compared to the chemotherapy arm (hazard ratio [HR] = 0.55, [95% CI: 0.42, 0.73; one-sided p value <0.001])1.
- In a pre-specified analysis of patients receiving Zykadia without brain metastases at screening, patients experienced a median PFS of 26.3 months (95% CI: 15.4, 27.7), compared with 8.3 months (95% CI: 6.0, 13.7) among patients treated

with chemotherapy (HR = 0.48 [95% CI: 0.33, 0.69])1.

- In a pre-specified analysis of patients receiving Zykadia with brain metastases at baseline, the median PFS was 10.7 months (95% CI: 8.1, 16.4) in the Zykadia group versus 6.7 months (95% CI: 4.1, 10.6) in the chemotherapy group (HR = 0.70 [95% CI: 0.44, 1.12])1. Intracranial overall response rate (ORR) (72.7%, [95% CI: 49.8, 89.3]) is consistent with whole body ORR (72.5% [95% CI: 65.5, 78.7]). The most common adverse events (AEs) occurring in more than 25% of Zykadia patients were diarrhea (85% vs. 11% with chemotherapy), nausea (69% vs. 55% with chemotherapy), vomiting (66% vs. 36% with chemotherapy), ALT increase (60% vs. 22% with chemotherapy), AST increase (53% vs. 19% with chemotherapy), gamma-glutamyltransferase increase (37% vs. 10% in chemotherapy), decreased appetite (34% vs. 31% with chemotherapy), blood alkaline phosphate increase (29% vs. 5% with chemotherapy) and fatigue (29% vs. 30% with chemotherapy).

FDA accepts Mylan's BLA for biosimilar pegfilgrastim

Mylan N.V. and Biocon Ltd. said the FDA has accepted Mylan's Biologics License Application for MYL-1401H, a proposed biosimilar to Neulasta (pegfilgrastim), for filing through the 351(k) pathway.

The proposed biosimilar to Neulasta is used to reduce the duration of neutropenia (low count of neutrophils, a type of white blood cells) and the incidence of fever associated with neutropenia in adult patients treated with chemotherapy in certain types of cancer. The FDA goal date set under the Biosimilar User Fee Act is Oct. 9.

The proposed biosimilar pegfilgrastim is one of the six biologic products co-developed by Mylan and Biocon for the global marketplace.

MIODx licenses immunotherapy technologies from UCSF

MIODx said it has signed an exclusive license for two key immunotherapy technologies from the University of California, San Francisco.

The first technology provides a method to monitor a patient for response to immune checkpoint inhibitor therapy such as PD-L1 and CTLA-4. The second license extends the technology with a method to detect if a patient is likely to have an immune-related adverse event from their immunotherapy regimen.

MIODx also announced that they have entered into an agreement with UCSF to provide immunosequencing services as part of the validation and commercialization of the technology.

MIODx is a privately held company focused on discovery of early detection and prognostic cancer biomarkers through the company's proprietary platforms. The company's VerifyDx™ platform utilizes a highly sensitive, multiplex PCR assay and advanced bioinformatics to interrogate multiple DNA and RNA pathways that are implicated in highly metastatic cancer.

In addition to the VerifyDx platform, MIODx utilizes high throughput immune sequencing to generate information on T and B cell diversity that is being applied to monitoring a patient's response to immunotherapy.

FUNDING OPPORTUNITIES

DOD Lung Cancer Research Program publishes anticipated funding opportunities

Due to the current Continuing Resolution, the Fiscal Year 2017 Defense Appropriations bill has not been passed.

Although funds have not been appropriated for the Department of Defense Lung Cancer Research Program (LCRP), the LCRP is providing the information in this pre-announcement to allow investigators time to plan and develop ideas for submission to the anticipated FY17 funding opportunities.

FY17 LCRP Program Announcements and General Application Instructions for the following award mechanisms are anticipated to be posted on Grants.gov in April 2017. Pre-application and application deadlines will be available when the Program Announcements are released.

The pre-announcement should not be construed as an obligation by the Government, and funding of research projects received in response to these Program Announcements is contingent on the availability of Federal funds appropriated for the LCRP. As directed by the Office of the Assistant Secretary

of Defense for Health Affairs, the Defense Health Agency, J9 Research and Development Directorate manages the Defense Health Program Research, Development, Test, and Evaluation appropriation.

The managing agent for the anticipated Program Announcements/Funding Opportunities is the Congressionally Directed Medical Research Programs. Applications submitted to the FY17 LCRP must address at least one of the seven Areas of Emphasis listed below:

- Identify, develop, or optimize noninvasive or minimally invasive tools to improve the detection of the initial stages of lung cancer, such as, but not limited to, optimizing strategies for management of indeterminate nodules.
- Identify, develop, and/or build upon already existing tools for screening or early detection of lung cancer. Screening may include, but is not limited to, imaging modalities, biomarkers, genetics/genomics/proteomics/metabolomics/transcriptomics, and assessment of risk factors.
- Understand the molecular mechanisms of initiation and progression to clinically significant lung cancer.
- Identify innovative strategies for prevention and treatment of early and/or localized lung cancer.
- Understand predictive and prognostic markers to identify responders and nonresponders.
- Understand susceptibility or resistance to treatment.
- Understand contributors to lung cancer development other than tobacco.

Military Relevance: The FY17 LCRP seeks to support research that is relevant to the healthcare needs of military Service members, Veterans, and their families. Military relevance will be considered in determining relevance to the mission of the DHP and FY17 LCRP during programmatic review. Investigators are strongly encouraged to consider the following characteristics as examples of how a project may demonstrate military relevance:

- Use of military or Veteran populations, biospecimens, data/databases, or programs in the proposed research.
- Collaboration with Department of Defense or Department of Veterans Affairs investigators.
- Involvement of military consultants (Army, Air Force) or specialty leaders (Navy, Marine Corps) to the Surgeons General in a relevant specialty area.
- Description of how the knowledge, information, products, or technologies gained from the proposed research could be implemented in a dual-use capacity to address a military need that also benefits the civilian population.
- Explanation of how the project addresses an aspect of lung cancer that has direct relevance to military Service members, Veterans, or other military health system beneficiaries, including environmental exposures other than tobacco.

Concept Award

- Investigators at all academic levels
- Supports highly innovative, untested, potentially groundbreaking concepts in lung cancer
- Emphasis on innovation
- Clinical trials not allowed
- Preliminary data discouraged
- Military relevance strongly encouraged
- Maximum funding of $100,000 in direct costs (plus indirect costs)
- Period of performance should not exceed 1 year.

Career Development Award

- Principal Investigator: Independent investigators at the level of Assistant Professor, Instructor, or equivalent
- Must be within 5 years of first faculty appointment Mentor: At or above the level of Associate Professor (or equivalent)
- Have a proven publication and funding record in lung cancer research
- Supports early-career, independent researchers to conduct research under mentorship of an experienced lung cancer researcher
- Clinical trials not allowed
- Preliminary data not required
- Military relevance strongly encouraged
- Maximum funding of $250,000 in direct costs (plus indirect costs)
- Period of performance should not exceed 2 years

Idea Development Award

- Established Investigators: Independent investigators at or above

the level of Assistant Professor (or equivalent); or New Investigators:

- Investigators that meet the following criteria at the application submission deadline date:
- Have not previously received a LCRP Idea Development Award or Early Investigator Synergistic Idea Award
- Are within 10 years of first faculty appointment (or equivalent)
- Supports new ideas in the early stages of development representing innovative, high-risk/high-gain research
- Emphasis on innovation and impact
- New Investigator category supports applicants early in their faculty appointments or in the process of developing independent research careers
- Clinical trials not allowed
- Preliminary data required, but may be from outside of lung cancer
- Military relevance strongly encouraged
- Maximum funding of $350,000 in direct costs (plus indirect costs)
- Period of performance should not exceed 2 years

Investigator-Initiated Translational Research Award

- Independent investigators at or above the level of Assistant Professor (or equivalent)
- Supports translational research that will develop promising ideas in lung cancer into clinical applications. Translational research may be defined as an integration of basic science and clinical observations
- This mechanism is intended to fund a broad range of translational studies, including, but not limited to, the following:
- Studies advancing/translating in vitro and/or animal studies to applications with human samples/cohorts
- Late-stage preclinical work leading to/preparing for a clinical trial, e.g., Investigational New Drug submission
- Correlative studies that are associated with an ongoing or completed clinical trial and projects that develop endpoints for clinical trials
- Preliminary data required, but may be from outside of lung cancer
- Military relevance strongly encouraged
- Maximum funding of $400,000 in direct costs (plus indirect costs) Period of performance should not exceed 2 years

Translational Research Partnership Award

- Investigators at or above the level of Assistant Professor (or equivalent)
- Supports partnerships between clinicians and laboratory scientists that accelerate ideas in lung cancer into clinical applications
- One partner must be from either a Military Treatment Facility or a VA medical center Non-Traditional Partnerships are encouraged
- Small-scale clinical trials allowed Preliminary data required, but may be from outside of lung cancer
- Military relevance strongly encouraged
- Maximum combined funding of $900,000 for direct costs (plus indirect costs)
- Maximum period of performance is 3 years

A pre-application is required and must be submitted through the electronic Biomedical Research Application Portal (eBRAP) at https://eBRAP.org prior to the pre-application deadline.

All applications must conform to the final Program Announcements and General Application Instructions that will be available for electronic downloading from the Grants.gov website.

The application package containing the required forms for each award mechanism will also be found on Grants.gov.

A listing of all CDMRP funding opportunities can be obtained on the Grants.gov website by performing a basic search using CFDA Number 12.420.

Applications must be submitted through the federal government's single-entry portal, Grants.gov.

Submission deadlines are not available until the Program Announcements are released.

For email notification when Program Announcements are released, subscribe to program-specific news and updates under "email subscriptions" on the eBRAP homepage at https://eBRAP.org.