THE CANCER LETTER

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Groups Have No Budgets

As NCTN Begins Work March 1

By Paul Goldberg

Two years ago, NCI officials made a promise to increase the budget of the cooperative groups program by $25.6 million.

The boost, which was approved by the NCI Board of Scientific Advisors, was part of an effort to revamp the groups inspired by a report from the Institute of Medicine.

On March 1, as the cooperative group program officially becomes the NCI National Clinical Trials Network, new money will not be a part of the transformation.

(Continued to page 2)

Intramural Research

NCI National Lab's Budget to Grow Over Its $299.2 Million FY2013 Level

By Matthew Bin Han Ong

The contractor running the Frederick National Laboratory for Cancer Research received nearly $300 million from NCI in the 2013 fiscal year, and is slated for an increase, officials said at a recent advisory committee meeting.

(Continued to page 7)

In Brief

Van Andel Institute to Build Epigenetics Hub

THE VAN ANDEL INSTITUTE announced the establishment of a global epigenetics research hub.

Leading this effort is **Peter Jones**, director of research and chief scientific officer of the institute. Jones's recent research has focused on epigenetics and epigenetic therapies.

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Added Scrutiny for Large Trials Hits Phase III Adjuvant Studies

(Continued from page 1)

Leaders of the network groups say they haven't been told what their budgets will be for the rest of the year. However, they have been told that total enrollment in the four adult groups will drop to about 17,500—of whom 14,000 will be adults. In recent years, enrollment has been between 20,000 and 23,000 (The Cancer Letter, Feb. 21).

"We don't have a budget, as of today," Robert Comis, co-chair of ECOG-ACRIN Cancer Research Group, said to The Cancer Letter in an interview Feb. 26. "The old grant is over as of March 1. We were told that we would receive some notification before March 1 as to what our level of funding might be, but we haven't received it yet. We are continuing to do our work, for now."

Walter Curran, co-chair of NRG Oncology, said his group hasn't received a notice of award either.

"When a group like NRG is making decisions on how to prioritize our trials, it's very difficult to do this without knowing the scope of our budget," Curran said in an interview Feb. 25. "One of the frustrating things—and it's not the fault of CTEP [the NCI Cancer Therapy Evaluation Program]—is that due to delays in the federal budgeting process, we are literally four days from starting this network, and none of us know our budgets.

"This system begins this Saturday, and we only have a general idea on what funding will run this operation. And these are all new awards to reorganized entities. While we are going to be able to use some carryover funds from our legacy groups, it's a very difficult process to be going through without knowing what kind of support we have."

Charles Blanke, chair of SWOG, said he is assuming that the budget, when there is one, will be flat, which would amount to a bit more than $150 million for the entire program. "But we are all a little bit scared, and we would like to know," Blanke said to The Cancer Letter.

Jeff Abrams, director for clinical research of the NCI Division of Cancer Treatment and Diagnosis, said NCI is in no position to award the money to the network groups.

"Unfortunately, NIH/NCI has not yet received the actual monetary funds, so we are not able to make group awards yet," Abrams said to The Cancer Letter. "We hope to do it soon, but it may take till the end of March or even longer."

Promised $25.6 Million

Two years ago, NCI had solid rationale for promising the $25.6 million boost to the groups.

The new funds were intended to help double the per-case payments to high-performing clinical sites for putting patients on studies. This is needed, because institutions have been complaining that per-case payments have been so low that they lose money when they put patients on cooperative group trials.

With the money failing to materialize, the only thing NCI can do is drop accrual targets for fiscal 2014.

"I think Dr. Varmus was committed to that, and that was the budget that was approved by the BSA," said Comis, who is also the president and chairman of the Coalition of Cancer Cooperative Groups and professor of medicine at Drexel University. "The additional $25 million was going to primarily cover increased capitation for high-performing sites, raising the level of funding from $2,000 to $4,000.

"With a flat budget, that $25 million is going to come out of the existing dollars, which is a huge cut, compounded by the fact that we were all—NIH, NCI and us—working on about a negative 20 percent buying power to start with. It's a big hit. We all worked in good faith with the NCI to establish the NCTN, but it has come to pass at a time that couldn't be worse with regard to availability of dollars."

NCI's Abrams said there is a chance that funds may be reprogrammed to NCTN.

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National Cancer Institute

5-Year Annual Funding Request for NCI Clinical Trials Network

Category for Base Division Set-Aside for Network Program	Annual Total Cost for FY14 to FY18 Based on 20% Reduction in Accrual Compared to Average Accrual Over Last 6 Years (Approx. 20,000 Treatment Trial Enrollments)
Funding Based on FY2011 Levels:	
Group Operations & Statistical Centers (includes Capitation), Lead Academic Participating Sites, and Core Services	$ 152,644,335
Funding Request Based on New Funding Model & BIQSFP:	
Increase Capitation to "High-Performance" DCTD-funded Sites	$ 11,520,000
Increase Capitation to "High-Performance" DCP-funded CCOPs & MB-CCOPs	$ 10,080,000
Increase Funding for Integral and Integrated Markers (BIQSPF)	$ 4,000,000
Subtotal:	$ 25,600,000
Grand Total:	$ 178,244,335 *

* The 5-Year Total Cost Funding Request for FY2014 to FY2018 for the NCTN is $891,221,675

The Money That Never Came: NCI promised a $25.6 million increase (circled) to enable an increase in payments for patient accrual at high-performing sites.
The slides from the presentation made two years ago are posted on our website.

"It is true that we were approved to have an increase of $25 million when we presented the RFA," Abrams said to The Cancer Letter. "However, due to sequester and an overall flat budget, NCI is not able to provide this $25 million at this time. Later in this fiscal year, if we have additional funds after existing commitments are paid, we may be able to increase the NCTN line but this is uncertain at present."

Group leaders cooperated in NCI-mandated consolidation of cooperative groups to create NCTN, and most describe the new structure as promising.

"The NCTN represents a dramatic change from the former cooperative groups," said Monica Bertagnolli, chair of the Alliance for Clinical Trials in Oncology.

"On the positive side, there is an unprecedented level of collaboration and advances in study design in the activation of exciting new trials for patients with molecularly-defined tumors. On the negative side, budgetary constraints are severely limiting the scope of research, and many important questions will go unanswered.

"We already know that far fewer patients have the opportunity to participate in publicly-funded trials, and we are also concerned that lack of opportunity for scientific progress will reduce the number of U.S. researchers committed to clinical trials."

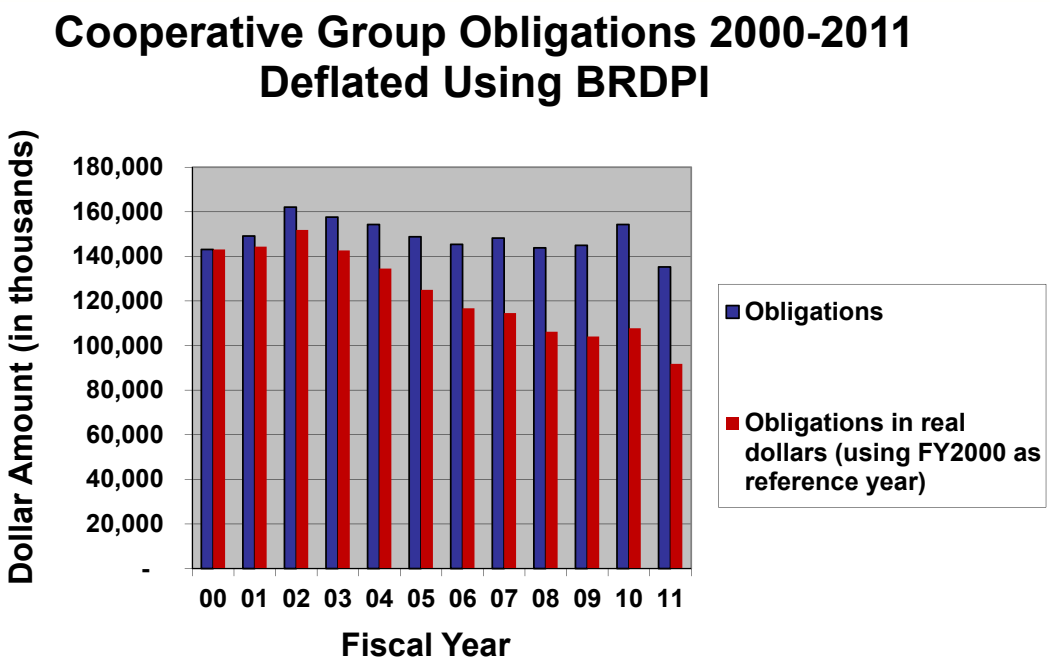
Bertagnolli is also chief of the Division of Surgical Oncology at Brigham and Women's Hospital and a professor of surgery at Harvard Medical School.

Curran sees promise in integrating cancer centers and cooperative groups.

"A lot of positive things can come out of this reorganization," said Curran, executive director of Winship Cancer Institute of Emory University. "I believe that the decision to give many cancer centers Lead Academic Participating Site (LAPS) U10 awards is actually an excellent way to align the cancer centers with the network groups. I think it incentivized the centers to

National Cancer Institute

Trials Program Funding 2000 to 2011: Real $



In the same talk, NCI officials illustrated the erosion in the groups' purchasing power over the past decade.

be active across all four of the new adult network groups.

"It's incentivized some centers to be more conscious of enrolling their patients on these trials and to look at how their leaders can provide scientific leadership to the groups. As GOG, RTOG and NSABP came together, this integration has enabled us to learn from one another and bring many scientific efforts together .We believe this should translate into higher quality clinical trials for our members and patients.

"All the groups underwent peer review. They were all favorably reviewed, and all have important as well as complementary visions of what we can do. We of course need sufficient resources to execute this."

Additional Scrutiny for Large Trials

To stay within budgetary targets, NCI will scrutinize trials that enroll 1,000 or more patients, officials said. Though these trials will be subjected to a secondary level of review, it's unclear what this additional scrutiny will entail.

"The rationale is simply that we are paying higher reimbursement per case—$4,000/case compared to $2,000/case—for about 50 percent of the patients we enroll overall," Abrams said to The Cancer Letter. "To do this, we have to live more strictly within our budget and thus not overshoot our total enrollment, estimated at about 17,000 interventional patient and 2,500 screened patients. To ensure that we don't overshoot as we transition into this new system, NCI is holding up approval of large, costly trials as we are uncertain whether our budget will permit us to support all of them. If only some can be supported, we will have a second level review to compare these trials across diseases and make prioritization decisions.

"The process for this second level review is currently under discussion."

Comis described the overall accrual target as "meager."

"The primary emphasis at the NCI is now on phase II trials, as opposed to large phase III trials, which reflects current thinking relative to the new age of targeted treatments, but there is no question in my mind that large, definitive studies sponsored by the public side of the system are still required to work out, for instance, the PD-1 and immune checkpoint inhibitors." Comis said. "I think we should still be in that game, and it is not clear to me how this will play out given the financial realities."

Limits on enrollment will be particularly constricting to adjuvant trials, group leaders say.

SWOG, for example, is unable to go forward with an adjuvant trial in melanoma.

"There is a lot of discussion among all the groups in terms of what publicly funded research should look like," Blanke said. "We are moving toward targeted therapy, where we expect the bang per drug to be much higher in a smaller population. That said, a drug like imatinib has happened four times in the history of oncology. I think we've made huge gains incrementally through these large trials. In colon cancer, the median survival used to be six months. Now it's well over two years, and it was not achieved with any single drug being a blockbuster. It was three-month gains, and a lot of it was through benefit in the adjuvant setting."

The industry is unlikely to ask many of the questions cooperative groups can address.

For example, industry would be unwilling to conduct a trial aimed to show that a smaller dose or shorter duration of treatment can produce equivalent results. Blanke said that one of the most interesting trials now conducted in colorectal cancer is a non-inferiority study comparing three months of FOLFOX with six months of the regimen.

"I would argue that if that's a positive trial and if the people who get FOLFOX don't get neuropathy, that will be the biggest gain in colon cancer ever, bigger than any single drug is going to achieve in terms of patient benefit," Blanke said. "You can imagine that the company that makes the drug isn't going to be particularly interested in selling three months less of the drug. There is no other mechanism for doing that kind of trial but the cooperative groups."

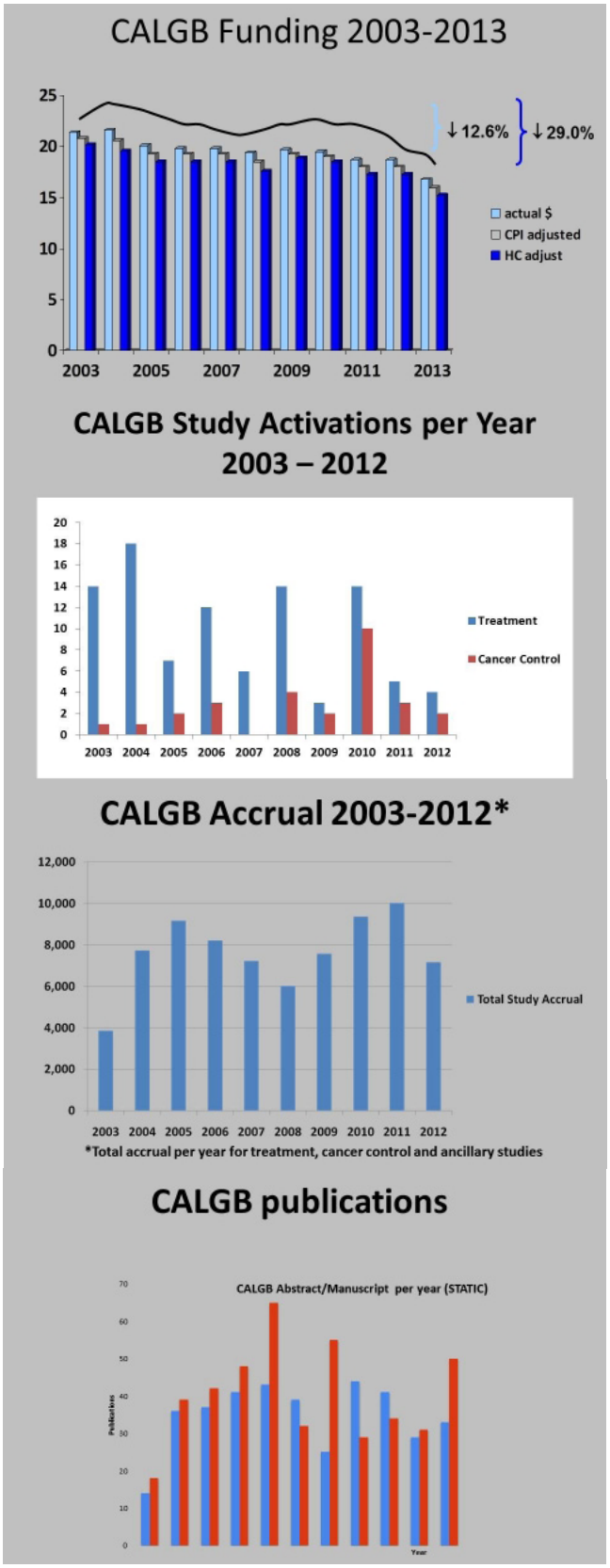
Over 10,000 patients to show non-inferiority, and roughly 2,500 are being accrued in the U.S. trial.

"It's going on now, but it wouldn't have a chance if it were proposed today," Blanke said. "If this trial were proposed today, even if it were approved, the activation would be suspended. Whether or not there is an appetite to do this type of trial is questionable."

Adjuvant trials aren't getting started, group chairs say. "While there are currently active breast cancer adjuvant trials, to the best of our knowledge, no new breast adjuvant concept has been approved in the last six months," Blanke said.

Comis said NCI's new-generation trials of targeted agents are focused on small populations.

"If you look at the targeted agents, you see that, aside from Herceptin, very few of them have been shown to cure people or have a huge impact in the adjuvant



How the cuts affected CALGB.
Source: CALGB

setting." Comis said. "A few upcoming trials will be more directed, like ALCHEMIST, where we are going to assess lung cancer patients with regional disease for enrollment onto one of two adjuvant trials based on specific mutations, but there are tens of thousands of other lung cancer patients who are still being treated with therapies from the 1980's and 1990's. Who will perform the large trials necessary to define new treatments for these patients?"

Altogether, 30 academic centers were chosen to receive increased per-patient reimbursement. According to critics, this will have a negative impact on many important academic groups that are not well supported.

"It's unfortunate that funds did not permit to fund more than 30," Abrams said. "For sites that don't have Lead Academic Participating Sites awards, they will have their participation funded via subcontract by the NCTN Operations Centers. They will be funded at the $2,000 per case rate instead of the higher $4,000 rate that the LAPS will get. If more funds become available, we would be able to have another round of competition and potentially increase the number of LAPS awards."

Changes Affect Reference Labs

NCI is also changing the way tissue banks are funded. Reference labs will no longer be supported through funds received for group operations.

"This is a major concern for the groups because our reference laboratories generate the science that forms the basis for our trial designs. For example, our characterization of leukemic cells led us to generate the innovative study designs that you see in our current leukemia trials, so the NCI decision really doesn't make a lot of sense to me." Comis said. "In addition, the NCI seems determined to control the use of our resources at exactly the wrong time. The biorepositories are our lifeblood, in the sense that we have the best annotated tissue banks in the country, if not the world. At a time when budgets are tight at the NCI, both philanthropy and industry are interested in working with us on innovative research efforts that require the scientific resources produced by our labs. With NCI dollars becoming less and less a component of our overall portfolio, we ought to be free to use our laboratory resources directly with industry and foundations and not have them controlled by a system that has made the decision not to support them financially."

Abrams said that in the past, NCI funded banks partially out of a U24 infrastructure mechanism and partially out of some funds that were given to the Operations Centers of the Groups.

"Going forward, the banks will be supported entirely out of the U24 mechanism," Abrams said. "I guess this has led to some unhappiness among some group members as some may miss the funds they received to support banking via the Group Ops. However, the overall funding for banks is not going down—it will just be given via the U24. What is changing is 'reference labs.'

"Support for standing reference labs will no longer be possible in the group operations awards as we need all the funds to support the actual trials. If biomarkers or other lab tests are needed to conduct a trial, the groups will have to seek support for this on a trial-by-trial basis.

"Possible sources of such support are an NCI mechanism called BISQFP which sets aside about $10 million per year for this purpose. Groups also seek industry and philanthropic support for this sort of thing to supplement the NCI funds."

Another unknown is the role the new NCI Community Oncology Research Program will play in the new clinical trials infrastructure. NCORP is created through a merger of the Clinical Cancer Oncology Program, which was run through the Division of Cancer Prevention and the Community Cancer Centers Program, which was administered as a subcontract with what was then called SAIC-Frederick Inc., now called Leidos-Frederick Inc.

Historically, CCOPs contributed substantially to accrual to group trials. Though the funding level for the new NCORP isn't publically known, it's expected that it will be lower than the sum of the two programs. Also, NCORP has another major mandate: to engage in health services research.

"In the recent RFA for the NCORP Research Base that we just responded to in January, there wasn't much money allotted for cancer care delivery research, yet the application criteria required us to put a lot of effort into this area of research." Comis said. "We are going to have to wait and see how it all plays out."

All of this is frustrating, group chairs say.

"The cooperative groups still continue to conduct transformational research," Curran said. "Our budgets have been, in actual dollars, stable for a dozen years, even during the periods when the overall NIH and the NCI budgets have gone up. Despite the fact that we have had no real increases in our funding, we've continued to execute remarkable work.

"It's tough to go initiate a new system with such budgetary uncertainty."

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Lower Support Leads to Lower Output

Recently, Bertagnolli examined the effect of funding cuts on Cancer and Leukemia Group B, one of the groups that merged to form Alliance, which she chairs.

"Even before the funding cuts brought on by sequestration, funding deficits have significantly limited our ability to conduct potentially transformative clinical research," Bertagnolli said in a talk at the 2013 ASCO annual meeting. The talk is summarized on the ASCO website.

The groups' NCI funding fell by 12 percent from 2003 to 2011. Adjusted for inflation, the decrease resulted in a 29 percent loss of purchasing power. Over that same period, the group's rate of new clinical trials fell. "The shape of the curve precisely matches what we've had in terms of dollar fluctuation," Bertagnolli said.

The number of patients enrolled in trials dropped also. "The current 33 percent reduction in patients treated on NCTN trials is one tangible example of the loss in research productivity experienced due to lack of research funding over the past four years," Bertagnolli said.

The number of scientific publications of research results has fallen as well.

"Publications always lag in timing, because it takes a while to begin the study, get the patients on, and then analyze the data, but you see a three-year lag in these curves tracking exactly the same," Bertagnolli said.

"So in every measure of our productivity, the number of studies we can get going, the number of patients we can study, and the numbers of publications and results—all of these important variables are directly and dramatically affected by the 29 percent reduction in our public support. These reductions also lead to fewer numbers of qualified researchers to conduct trials, as young people entering the field are discouraged from pursuing a career without opportunities to advance their ideas.

"As a result, the effects of budget cuts can persist for many years."

Intramural Research

Varmus: People Didn't Know What Frederick Lab Was

(Continued from page 1)

The lab, located on the 68-acre research and development campus in Frederick, Md., is one of 39 Federally Funded Research and Development Centers. FFRDCs are programs that receive 70 percent or more of their financial support from the federal government.

The FFRDC includes the Advanced Technology Research Facility, a 330,000-square-foot complex with a biopharmaceutical development wing.

"People just didn't know what Frederick was," said NCI Director Harold Varmus at an NCI-Frederick Advisory Committee meeting Feb. 4. "And part of this is—I hate the word—'transparency,' and of course, transparency requires first, some understanding of what we're dealing with."

Varmus's changes in the Frederick program include reshaping this little-understood outpost of the institute into a national lab in February 2012, and creating the advisory committee to guide its programs.

"We aren't creating resources here, we are trying to reuse resources in a sort of very sensible way to foster the best use of NCI's money," he said.

The institute's revamping of Frederick comes at a time when many of the institute's programs are facing financial difficulties, and many have sustained budget cuts. For example, the NCI National Clinical Trials Network has lowered patient enrollment to 17,500 patients, and groups that make up the new network were told trials that enroll 1,000 patients or more will require additional scrutiny (See story on p. 1).

The Frederick lab is operated by Leidos Biomedical Research Inc.—formerly named SAIC-Frederick—the same contractor that has run the Frederick operation since 1995.

"The national lab will have somewhat more money than it had last year to work with," Varmus said at the advisory committee meeting. "There will be money embedded in the system and in reserves that we, who control that money, can allocate."

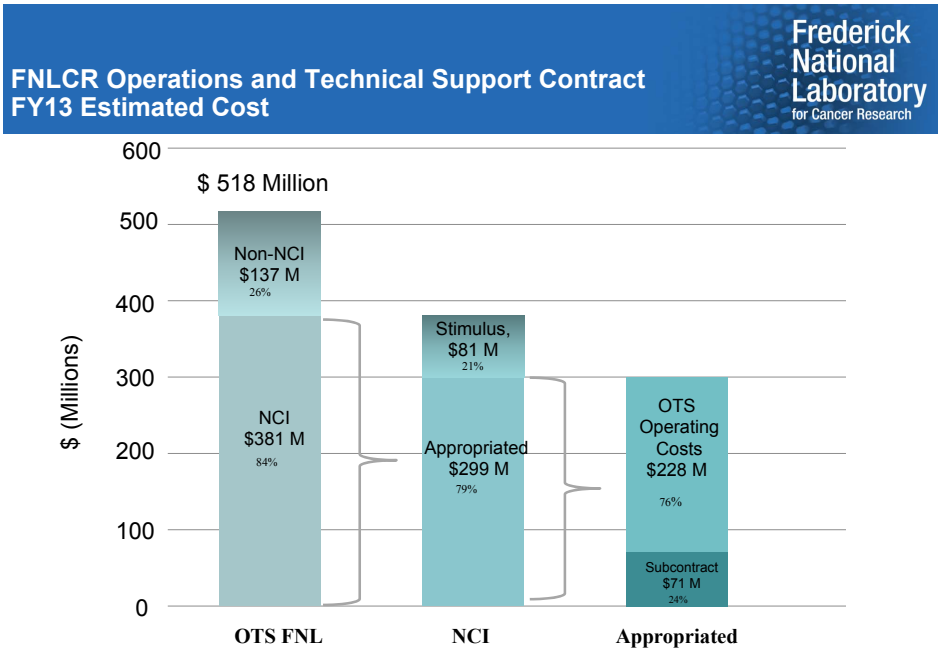
The 2014 budget figures have not been released.

Using a contractor to operate the national laboratory allows flexibility to fund programs and hire staff without having to use government mechanisms—giving NCI officials the ability to shift projects and move dollars with greater ease.

The Frederick lab is the only federally funded research center dedicated to biomedical research.

"As we understand the Frederick National Lab—as it is now happily called—a little better, and we realize that it is closely integrated within many of the divisions and operating entities like the intramural program of the NCI," Varmus said at the meeting.

"As we understand those relationships, some of them are extremely beneficial, services are provided by the extramural community. A lot of interesting projects are carried out in a, perhaps unheralded, but nevertheless highly significant fashion."



The NFAC meeting featured presentations by administrators of Department of Energy national laboratories.

An excerpt from Varmus's remarks follows:

I think we have a lot to learn from how the other [national] labs work. We don't need to replicate them, we can't replicate them, but I think you'll be interested to hear about who operates those labs, how the ideas get generated, how the projects get done, what the planning process is like, what the execution process is like.

They are often on a much longer time scale, because many of these energy projects are very infrastructure-dependent, and require very long setup time, and very long performance time, and many of the things that we contemplate at the NCI are just on a shorter time scale, and that works to our advantage. But I still think we're going to find the general governance and execution processes that are used by the other labs will be helpful.

We don't care so much about the details. What we want is, "Is there a big idea here that is commanding in its articulation and seems to show real promise of making headway against cancer?" and represent something that the national lab is uniquely qualified to do and of course, how we actually do it, whether it means bringing talented people, like Frank [McCormick, director of the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco, and associate dean of the UCSF School of Medicine] to Frederick or whether it means farming some of those things up through subcontracts or using staff that are now at the Frederick National Lab.

My goal here is to do more things that generate the kind of excitement and intense new research activity that the RAS project is illustrating. But not everything needs to be done at the national lab.

Some things are more suited to the typical RFP and RFA or just a program announcement, and we don't want to put all the burden of dealing more effectively with cancer on the Frederick National Lab. That would simply not be appropriate. So that's my general sense of where we're headed.

The goal here is to establish the virtue of an idea, and a task that's appropriate to the national lab.

The FFRDC Advantage

The FFRDC provides NCI with resources for acquisition and rapid response, said David Heimbrook, laboratory director and president of Leidos Biomedical Research.

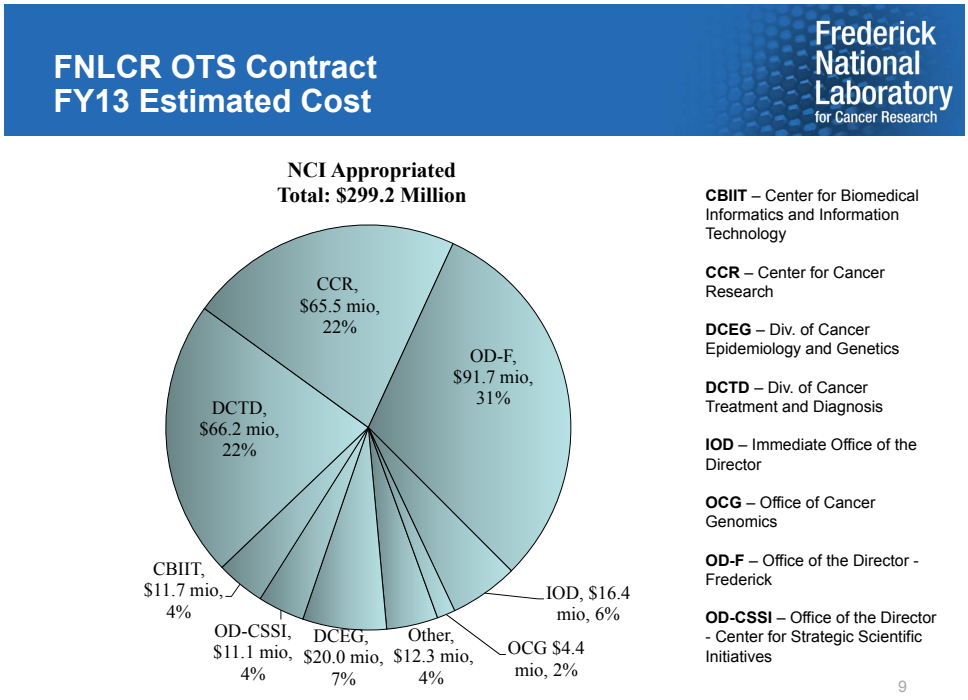
"The idea is that because it's using contractor staff and has a fairly broad charter, we can be much more flexible in terms of adjusting to rapidly changing biomedical priorities within the NCI," Heimbrook said at the committee meeting.

In the past, NCI directors have sheltered their pet projects from peer review by funding them as subcontracts of the SAIC contract. Under previous directors, the institute has been known to use Frederick as a depository for funds left over from the fiscal year, which can be reinvested in the following year's budget, sources said.

"The key thing, or the boundaries, if you

will, is that the FFRDC designation requires the national labs to meet the needs that cannot be achieved as effectively by other NCI components or through other government mechanisms," Heimbrook said at the advisory committee meeting. "So this is obviously a bit of a grayscale. There are some things, which you could envision, could go in one area or another—I think that's a constant discussion.

"And I think that's one example of recent evidence for that is the pivot to accomplish the RAS program, so this rapid response element is a key driver of the value."



Running Frederick: The Numbers

Heimbrook's remarks on Frederick's budget to the advisory committee follow:

In this kind of environment, then, the sort of tight financial environment, I think it's important to recognize how much money is actually being spent on the operational and technical support contract, or OTS contract, within FNL.

Within the operational and technical support contract overall, that value was $518 million. About $137 million of it came from other government agencies beside NCI, the biggest of those being NIAID, which provides us with support on the order of about $100 million, as well as work for CDC and other government agencies. So the totals portion of that which came from the NCI was about $381 million.

Of that $381 million, about $81 million of it was stimulus or [American Recovery and Reinvestment Act] funding—that's obviously going to be trending down and going away over the next couple of years, but it's still supporting some pretty important programs within Frederick, such as [The Cancer Genome Atlas].

The core money, the sustainable money, is about $299 million in appropriated money. Harold mentioned before about some of the financial pressures and I do want to say this number has dropped about 10 percent since 2010 when you exclude one-time efforts such as construction of the ATRF facility and excluding the stimulus money. So we have seen a significant fall-off in that number in the last couple of years.

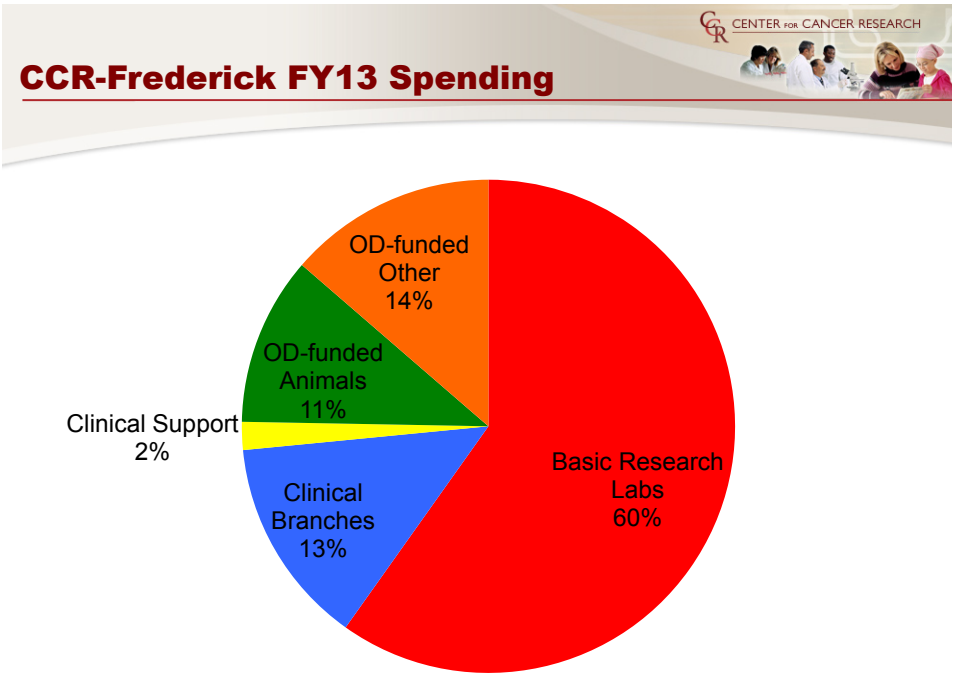
The appropriated money, the OTS actual operating costs of $228 million, and I'll go into more detail about what that represents, and then about $70 million of that $300 million is actually subcontracted out to other organizations—subcontracts supporting NExT (NCI Experimental Therapeutics) and a variety of other different areas. So, only about $228 million of that is actually supporting the sort of intramural FNL projects.

This seems like a fairly simple thing, and it seems as you're talking about priorities, well then, you could just shift some of that $299 million around. Unfortunately, it's not quite that simple, and I think it's important to recognize how work actually comes in to FNL and how it's funded.

So there is that total of $300 million, but it doesn't come as one big tranche where Harold cuts us a check. That's sort of the indirect way that might be the way it happens because obviously Harold distributes the money to all the divisions, offices and centers, but the individual offices and centers decide how much of their budgets they want to spend on FNL science and services. So for instance, [Robert] Wiltrout [director of NCI's Center for Cancer Research] will get a budget and he'll decide how much he wants to spend at Frederick versus other things that might be happening in his portfolio, and he'll be going over that a little

bit later.

The infrastructural management and oversight-insured services are all funded by the office of the director—what's called the OD Frederick—and those shared resources are a portion of what we do. But virtually all the other staff that we have are dedicated to the division, office or center that actually funds them. And this is a fairly important element of how Frederick works because not everybody is one big pot that can just be moved around.



In fact, people tend to work for CCR, or people tend to work for DCTD. That has some very big advantages in terms of building a sustainable long-term relationship between them, but it is important to recognize that that's a pragmatic element of the way things work on the ground at Frederick.

So changes in how work comes in or is eliminated at FNL are performed through an electronic approval system called the Yellow Task System. The way this works is that a government customer or scientist will decide that they want to do some work at Frederick, this request will be vetted for the suitability for FNL.

That's actually appropriate for this to be done at FNL by a project officer or a contract officer, both of those are NCI government employees, and then the appropriate FNL program that can respond to this will develop a budget and a work plan with the customer, and that's usually a highly iterative process.

That plan and the budget would then be approved by the customer and then it goes to the administrative officer for approval and ultimately the OTS contract is modified to reflect the change in funding because every one of these work plans obviously has to have a budget associated with it.

I'm sure there are many similar discussions on the government side as to how that's all going to happen, and how this is sort of the way it looks from the contractor's perspective.

Last year, we did about 195 yellow tasks that were submitted by 23 individual divisions, institutes and other government agencies. Each one of these, almost all of these had changes in funding either pro or con, increases or decreases associated with it. For this one, the total value of all those costs was about $240 million, which spanned a period of about 5 years.

One of the very important things that we try and monitor, that measures how well we're doing, is how quickly we can turn these around. The average Yellow Task turnaround time last year was about 38 days, with a range of about 4 to 160.

Actually the last startup initiative started as a Yellow Task that was submitted—and obviously when something has the prominence of that—we turned around the initial proposal quite quickly in 13 days, that was approved in April, then we developed a work plan during the summer and the implementation became a reality in the fall.

The Office of the Director at Frederick, which I mentioned, covers infrastructure as well as some significant scientific programs has about, in FY13, had about $91 million. CCL and DCTD are next at about $65 million apiece, and then you can see a variety of small but still quite significant organizations that contribute funding or do work and are funding it, such as DCEG, CBIIT and the Office of the Director-Center for Strategic Scientific Initiatives.

The CCR Perspective

An excerpt follows of the remarks made by the director of NCI's Center for Cancer Research, Robert Wiltrout, on the center's interactions with Frederick. Both his and Heimbrook's presentations can be downloaded on The Cancer Letter website.

This is always the question: How did you guys get into Frederick? What's the history of the intramural program?

There were two components back then—what now is 15 years ago—there was a small component, which was characterized as part of the Division of Basic Sciences, which is intramural.

There also was this Frederick [Advanced Bioscience Laboratories] basic research program, a very successful contract program that had been headed by George Vande Woude, and that was in the context of there also being part of the Division of Basic Sciences in Bethesda, as well as a Division of Clinical Sciences on the Bethesda campus.

As a result of some reviews and Richard Klausner's decisions—he was the NCI director at the time—there was a fusion of the Frederick contractor program with the intramural component in Frederick.

That subsequently resulted in a program that was more robust in Frederick along with the basic science program in Bethesda—then still the clinical program.

And then in 2001, when Rick Klausner recruited Carl Barrett, the Center for Cancer Research was formed, combining all of the basic sciences programs that were intramural—on both the Bethesda and Frederick campus—with the Division of Clinical Sciences to form what we now have as the Center for Cancer Research.

So if we look at the appropriated dollars that CCR, or if we look first at the distribution of the labs by campus, about 70 percent is on the Bethesda campus, both clinical and basic, about 30 percent is on the Frederick campus, and we have a small component out at the Advanced Technology Center, which we're currently in the process of trying to draw down to zero, so that in fact was can actually save some money by getting out of that facility.

So if one looks in at the total appropriated funds that are spent by the CCR on the Frederick campus, this comes again, as Dave [Heimbrook] said, as part of the appropriations that we get from Harold to run the CCR.

Best way I can frame this for you is like: we get $100 and we take some percentage of those dollars, convert them to a different currency and spend them in a different place, kind of like going to Europe.

We don't get extra dollars, it all comes out of the CCR appropriated budget. About three-quarters are spent directly by basic research or clinical laboratories, either for staffing or positions on the Frederick or Bethesda campuses.

There is a small amount, which is spent on clinical infrastructure such as our protocol group recruitment of some nurses, recruitment of positions that are difficult for us to sometimes get through the government mechanisms.

These types of positions for us are good in the sense that many of them are contract—they are flexible with regard to as we expand and contract in different areas, allowing us to either recruit or in fact, to offload staff if in fact we want to go in different directions.

Another significant portion of our budget that is provided to Frederick is on behalf of our animal program, which is a very important and vital component of research across the CCR for both Bethesda and Frederick, and then there are a number of other OD-funded activities which are largely infrastructured to allow us to fully use the contract that we pay to Leidos to administer the staff that are hired within the basic research or the clinical laboratories.

So that's the breakdown of how the CCR dollars are spent on the Frederick campus. And again, there's benefit not only to scientists on the Frederick campus, but also to many labs and branches in Bethesda, in terms of services that are provided through those components.

What are the historical benefits or intersections between the intramural labs in Frederick and FNL? Clearly, the interest in HIV chemistry, structural biology—this intersects with a number of programs that Leidos has been funding, and I think, to some extent, to the advanced technology activities, although with the pivot to the RAS program, I think this intersection is probably is going to be a bit less.

We benefit a lot from the flexibility and expertise and staffing, and the ability to recruit staff without having to recruit them through the government mechanisms, which, frankly, is a nightmare, particularly at the higher-level positions.

We have done things like creating a protocol review office, used Leidos quite a bit for our reengineering initiatives in our clinical program, and also have a number of our clinical monitoring labs are in Frederick, particularly those that do immune monitoring, which are very important for a lot of the clinical trials that were actually performed in the hospital on this campus.

Corporate Structure

Leidos Biomedical Research is a wholly owned subsidiary of Leidos Holdings, Inc., which split from the Science Applications International Corporation in September 2013. SAIC will remain entirely devoted to government IT services.

With revenues of about $6 billion a year and about 23,000 employees, Leidos Holdings is focused on three areas: national security, engineering and commercial health.

"National security is by far the largest component of what Leidos does," Heimbrook said. "We sometimes refer to it as Leidos Corporate, if you will, or Corporate Leidos, and the national security element includes maritime and aerial surveillance supporting U.S. troops in Afghanistan and other areas. They also do extensive work in cybersecurity and military logistics.

"The engineering area is primarily focused on energy. So for instance, Smart Grid is a big part of the components of what they support as well as design and engineering of facilities. For instance, they just opened a new biomass energy facility up in Connecticut.

"The third area, health, obviously sort of a peripheral component, is primarily focused on electronic health records implementation and IT and helping hospitals get their EHR systems up and running.

"So this is our corporate parent, if you will.

"Now, because we're operating the national lab in the public interest, we're a wholly-owned subsidiary," Heimbrook said. "There has to be a very bright line between Leidos Biomedical Research and Corporate Leidos.

"We're owned by Leidos, but there is that very big distinction and separation between what we do and what Leidos is. And that's to insure that public interest element behind it."

However, some interactions between the parent company and Leidos Biomedical do cross that bright line.

"First of all, the award fee, which is essentially paid out of the performance basis as a result of how well Leidos does for the NCI, flows into Corporate Leidos as revenue," Heimbrook said. "They, in turn, reinvest a significant portion of that award fee back into Leidos Biomedical Research or FNL in terms of paying down liable costs.

"This can allow some additional discretion in terms of being able to recruit and retain employees so they can supplement the government cap, if you will, on employee salaries, and they can also cover other things, which are not allowable under the contract.

"And this turned out to be a fairly big event for us following the government shutdown, that they were able to help with some of the costs and impact on our employees when we were shutdown in October.

"In a bit more softer area, some of the true value that Leidos Biomedical Research provides to Leidos is that, because we operate this large contract for the government, they can use us as a reference qualification in terms of bidding on other government work.

"So we're not directly contributing or participating in that, but based on how well we execute this contract, that serves as a standard that they can use for how well the government might expect to execute on other similar, sizable contracts.

"In addition, through some fairly restricted consulting opportunities, we can provide biomedical R&D expertise, but again, that's all done on a consulting basis after hours, not a part of our normal work stream.

In return, corporate Leidos provides Leidos Biomedical with legal and financial oversight, besides coverage of non-allowable costs.

"We're a company, and obviously we have our own financial and legal staff, but some more complicated issues, Corporate can provide us additional resources, and that becomes a very important element for us," Heimbrook said. "Then the other thing is because the other business that they do, especially on the national security and the cyber side, they have a lot of experience in terms of IT and big data expertise. The company just spun off last fall, but this is becoming an area of increasing interest for us to see if we can tap into this expertise."

The parent company's surveillance technology and expertise can be applied to cancer research programs at Frederick, Heimbrook said.

"To be honest, to be able to analyze gigabytes or terabytes of visual data that's coming from airborne surveillance or something along those lines and be able to pick out those little elements of what's changing and what you're interested in, it's not that dissimilar from the same types of things that you might want to do in terms of imaging tumors or other models. So the same types of principles can apply.

"So this is now actually a fairly significant corporate imperative—to be able to figure out how we can integrate across the entire structure to utilize the IT and big data expertise for the benefit of Leidos Biomedical Research, but also the other business components of Corporate Leidos."

In Brief

Van Andel Institute to Build Epigenetics Research Hub

(Continued from page 1)

Jones' plan includes developing a consortium of five academic institutions, four in the U.S. and one abroad, and is currently recruiting researchers and developing a clinical program.

JENNIFER DOUDNA was named the winner of the **Lurie Prize in the Biomedical Sciences** by the **Foundation for the NIH**.

Doudna is a professor of biochemistry, biophysics and structural biology at the University of California, Berkeley, and is a Howard Hughes Investigator. She will be presented the medal and a $100,000 honorarium on May 20 in Washington, D.C. Doudna's work centers on the molecular structure of RNA.

Doudna, who is also a grantee of the National Institutes of Health and the National Science Foundation, was selected for the award by a jury of six distinguished biomedical researchers, working under the auspices of FNIH, and chaired by Solomon H. Snyder, M.D., Director-Emeritus of The Solomon H. Snyder Department of Neuroscience at Johns Hopkins University.

Doudna and her colleagues discovered a gene-editing technique called CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats. The technology "gives researchers the equivalent of a molecular surgery kit for routinely disabling, activating or changing genes," wrote Science magazine in a Dec. 2013 article naming CRISPR one of its runners-up for breakthrough of the year.

GRU CANCER CENTER received a commitment of $6 million from the Masters Tournament and Augusta National Golf Club through the Community Foundation for the Central Savannah River Area.

Two-thirds of that commitment will help fund the construction of a new cancer center facility. The remaining $2 million was committed to Camp Lakeside, a collaborative effort by the cancer center, Children's Hospital of Georgia, and the Family Y, for children with significant medical issues.

The first phase of the construction project will be a 115,000-square-foot research facility. When complete, the complex will include approximately 400,000 square feet of research, clinical and community spaces.

Twenty-six public health and medical organizations called on drug stores and other retailers to follow the example of CVS Caremark and end the sale of cigarettes and other tobacco products.

CVS announced earlier this month that by October 1, it would stop selling tobacco products at its more than 7,600 stores throughout the U.S.

"CVS Caremark is absolutely right: The sale of tobacco products—the number one cause of preventable death and disease—is fundamentally inconsistent with a commitment to improving health," the open letter stated. "No corporation truly devoted to saving lives—like the nation's pharmacies are—can continue to simultaneously reap billions in profits from products that kill nearly half of the people who use them."

The letter was signed by: American Association for Respiratory Care, American Association for Cancer Research, American Academy of Otolaryngology - Head and Neck Surgery, American Academy of Pediatrics, American College of Cardiology, American Congress of Obstetricians and Gynecologists, American Lung Association, American Public Health Association, American Society of Clinical Oncology, American Thoracic Society, Americans for Nonsmokers' Rights, Campaign for Tobacco-Free Kids, Cancer Prevention and Treatment Fund, CASA Columbia, Legacy, LIVESTRONG, Lung Cancer Alliance, National Consumers League, National Association of City and County Health Officials, National Latino Alliance for Health Equity, National Physicians Alliance, North American Quitline Consortium, Oncology Nursing Society, Partnership for Prevention, Smoking Cessation Leadership Center, and the Trust for American's Health.

ION SOLUTIONS selected **Foundation Medicine** as its preferred partner for comprehensive cancer genomic profiling services.

Foundation Medicine developed the first

commercially available targeted sequencing assays using comprehensive, clinical next-generation sequencing to assess routine cancer specimens for all genes that are currently known to be somatically altered and unambiguous drivers of oncogenesis in solid tumors and hematologic malignancies, as well as many sarcomas and pediatric cancers.

Genomic profile results are reported to the oncologist and matched with targeted therapies and clinical trials that may be relevant to each individual patient based on the most recent scientific and medical research.

MYLAN INC. and its subsidiary, Mylan Pharmaceuticals Private Limited, launched the world's first **Herceptin biosimilar** in India.

The product, which will be marketed by Mylan under the brand name Hertraz, is a biosimilar to Roche's Herceptin (trastuzumab). Hertraz is indicated for the treatment of HER2-positive metastatic breast cancer and is available in, 440 mg and 150 mg.

Hertraz was approved by the Drug Controller General of India. In support of this approval, Mylan conducted a series of physicochemical and functional assays to demonstrate similarity to the reference brand Herceptin. These analytical methodologies confirmed the high degree of molecular similarity as well as biological activity of Hertraz. In addition, Mylan conducted a multi-center clinical trial to demonstrate comparable safety and efficacy to the reference product.

Mylan has exclusive commercialization rights for biosimilar trastuzumab in the U.S., Canada, Japan, Australia, New Zealand and in the European Union and European Free Trade Association countries.

NEOGENOMICS INC. launched a series of NeoTYPE cancer profiling tests covering 22 different categories of cancer.

The 22 categories of tumors covered in this series of tests are: brain, lung, breast, cervix, colorectal, endometrium, esophagus, stomach, ovary, soft tissue, thyroid, GIST, melanoma, acute myeloid leukemia, myelodysplastic syndrome, AML favorable-risk, chronic lymphocytic leukemia, lymphoma, juvenile myelomonocytic leukemia, myeloproliferative neoplasms, cancer not-otherwise specified, and spliceosomal abnormalities.

The genetic abnormalities are investigated using sequencing, fluorescent in-situ hybridization, methylation analysis, fragment length analysis, and SNP-cytogenetic array technology. Although more than 60 different genes are investigated in all these tumors, only 8-18 genes are investigated per patient or tumor type.

CLARIENT added the THxID-BRAF molecular diagnostic test, developed by **BioMerieux Inc**., to its service offerings.

Clarient, a GE Healthcare Company, will use the test to aid oncologists in selecting metastatic melanoma patients whose tumors carry the BRAF V600E mutation for possible treatment with GlaxoSmithKline's Tafinlar (dabrafenib) as well as in selecting melanoma patients whose tumors carry the BRAF V600E or V600K mutation for possible treatment with Mekinist (trametinib).

The companion diagnostic assay received PMA approval from the FDA in May 2013.