THE CANCER LETTER

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As Sequestration Hits

Varmus on Living in "Pretty Awful Times"

Sequestration and the low success rate in funding grants have introduced reticence in the conduct of scientific research, NCI Director Harold Varmus said to the joint meeting of two NCI advisory boards June 24.

"I've been out at a number of institutions, talking to trainees and senior investigators alike, who are saying that people are simply economizing in ways that I believe are detrimental to the ways that we do science: doing experiments more slowly, not using the full range of technologies, and not working at the pace that could be achieved in this incredibly productive time in cancer research," Varmus said to the National Cancer Advisory Board and the Board of Scientific Advisors.

NCI has been precluded from reducing its staff or resorting to furloughs, which has led it to make cuts that "share the pain until we can either see our way to a rosier future, or think about ways we can reconstruct our community in a way that is less difficult," Varmus said.

Some of the new restrictions HHS has imposed on the institute undermine its ability act as a catalyst for research, Varmus said. Institute scientists and administrators are restricted in their ability to convene and attend meetings.

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A video of Varmus's remarks is on The Cancer Letter website

Paying For Cancer Drugs

UK's NICE Set to Deny Payments For Zaltrap In Second-Line Metastatic Colorectal Cancer

By Paul Goldberg

Great Britain's National Institute for Health and Care Excellence said it would decline to pay for the Sanofi drug Zaltrap (aflibercept) for metastatic colorectal cancer after progression on an oxaliplatin-containing regimen.

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In Brief

Northwestern's Kibbe Named Director of CBIIT

WARREN KIBBE will lead the **NCI Center for Biomedical Informatics and Information Technology**, CBIIT.

Kibbe is the director of bioinformatics for the Center for Genetic Medicine, director of cancer informatics for the Robert H. Lurie Comprehensive Cancer Center, co-director of the Northwestern University Biomedical Informatics

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Money Woes Make Some Labs Set Lesser Goals, Varmus Says

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"There has also been strong pressure from the department for us to conserve on items that I consider to be an interference with the way that we do business—namely restrictions on travel to meetings and the development of meetings in our field," Varmus said.

"Some of this is working not only to undermine the way we spend money, because some people can't make airplane reservations until the fares go up three- or four-fold, or they're unable to plan for a trip to go to a meeting. We've even seen the absurdity of restricting a number of people in the NCI intramural program to go to a meeting, which was held in Washington!

"We know one of the most important functions of the NCI is to act as a convener, and as a place where people come together to discuss the future of our science. If we are restrained to the point of paralysis in putting together meetings, and getting people to go to meetings and exchange their views with their colleagues—and, indeed the NIH generally; the NCI isn't being picked out here, these restrictions apply to all of our fellow institutes and centers."

A transcript of Varmus's remarks follows:

This year, of course, is coming soon to an end at the end of September, and it's shocking that this is the first meeting at which I can tell you something you probably already know, but I couldn't say anything about, because I didn't know at our last meetings, and that's precisely what our budget was.

It took a long time to resolve it, thanks to uncertainty about our appropriations and the sequester and the role of other events, including taps from the department, that left us uncertain—until sometime in April—of how much money we'd actually have.

The final budget for this year is $4.788 billion. That was $293 million less than fiscal year 2012, down a total of 5.8 percent. Roughly 80 percent of that, at 5.1 percent of the reduction, is the due to sequestration, and then there were some taps, and importantly a fairly substantial use of the secretary's one-percent transfer authority to help her fund the state insurance exchanges. That led to yet further reductions.

We've tried to be as transparent as possible about how we are going to manage this kind of reduction. Even before we had the final numbers, I sent out a letter to all grantees about what we intended to do; and then, when the numbers came through, I described exactly what we are going to do and are doing. That information is on the NCI website.

I remind you just very briefly—it is inappropriate to go into too much detail here now—that what I tried to explain in this letter is that, if you look at the NCI budget, first of all, 20 percent is fixed costs, which can't be reduced. The department says no reduction in salaries and no layoffs, and that obviously reduces our flexibility.

One of our goals was to try to maintain at least close to the number of new grants and competing renewals, and to try to minimize the effect, at least in the first year, of the obligations to people we had to people who had been previously awarded their grants. We took reductions in our non-competing renewals, the Type 5s, by 6 percent.

The cancer centers were each reduced by about 6.5 percent; research and development contracts, 8.5 percent; and then we took similar reductions in the discretionary parts of the budget, for the intramural program and for research management and support.

Everybody felt the pain and I don't minimize that—but, how we are doing, with respect to making grant awards and success rates for competing grants? It's too early to give a definitive account. Those numbers are not going to be all in until the end of fiscal year—but so far, it looks like we are on a very similar track to last year.

I think we'll be awarding more or less the normal number of grants. The number of applications may be slightly down in the area of new investigators—mind you, new investigators are not necessarily young investigators, that just means not having received an

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NIH award before—but we'll have a clearer idea at the end of the year.

Now. that shouldn't be taken as evidence that we absorbed this cut without difficulty, because we kept the number of grants and the success rate more or less at the normal level. A lot of loss of spending power by highly productive grantees has occurred.

I've been out at a number of institutions, talking to trainees and senior investigators alike, who are saying that people are simply economizing in ways that I believe are detrimental to the ways that we do science: doing experiments more slowly, not using the full range of technologies, and not working at the pace that could be achieved in this incredibly productive time in cancer research.

So let's just be careful in the way we talk to our colleagues and say, "well, we kept the success rate up"—first off the success rate was terrible to begin with, with 13 to 14 percent. The size of grants is slightly smaller. Everyone is hurting.

We are simply trying to share the pain until we can either see our way to a rosier future, or think about ways we can reconstruct our community in a way that is less difficult. And I'll come back to that in a couple of moments.

I would add one point about the role of the department in this fiscal environment. I mentioned that the department has said no layoffs and no salary cuts, and that I think has been beneficial.

But there has also been strong pressure from the department for us to conserve on items that I consider to be an interference with the way that we do business—namely restrictions on travel to meetings and the development of meetings in our field.

Some of this is understandable political fallout from a few embarrassing episodes that have affected other agencies, that I will not name, and they ended up in the newspaper as embarrassments to the Obama administration. Some of it is an attempt to give us a false sense of security about how we are conserving funds and recognizing the depth of the fiscal restraints placed on us by the sequester.

Some of this is working not only to undermine the way we spend money, because some people can't make airplane reservations until the fares go up three- or four-fold, or they're unable to plan for a trip to go to a meeting. We've even seen the absurdity of restricting a number of people in the NCI intramural program to go to a meeting, which was held in Washington!

So the need to get clearance, either from what I sometimes—with a bit of inner anguish—call Building One, or having to go to the department to get clearance for meetings that would cost the NIH more than a certain level, whether $75,000 or $150,000.

We know one of the most important functions of the NCI is to act as a convener, and as a place where people come together to discuss the future of our science. If we are restrained to the point of paralysis in putting together meetings, and getting people to go to meetings and exchange their views with their colleagues—and, indeed the NIH generally; the NCI isn't being picked out here, these restrictions apply to all of our fellow institutes and centers.

One thing that your groups as a whole might want to consider is a dispassionate, but levelheaded letter describing the effect of these restrictions, and the elaborate approval process in which the NIH works.

It affects the way everyone works extramurally as well, because you get involved in meetings and you want to see your intramural colleagues at the meetings, and you want to see your research management staff at meetings. So all of these things have a direct influence on the way you and the rest of the scientific community operate. I think some representation from these groups to the department on this topic would be beneficial.

Outlook for FY 2014

The president's budget request came extraordinarily late this year.

Those of us who have been in government for a while expect the president's budget at the end of January or late February.

April 12 was the day, and part of this had to do with what appropriations would look like this year and the whole series of battles over sequestration.

When the budget was released, the president, wisely in our view, proposed a 1.5 percent increase over FY12—not FY13, but FY12. This would cancel sequestration and give us a modest increase of $470 million over FY12. Now, that is good news, but is it predictable that it is going to happen? It's very unlikely.

At the moment the House and the Senate have starkly different plans for what they are going to do for FY14. For example, the House—which I remind you is controlled by Republicans; the senate has a Democratic majority, but not 60 votes—is behaving quite differently with respect to FY14 appropriations.

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House allocations to the spending committees so far is about $90 billion less than the Senate allocations—and that includes about $35 billion less for our committee, the Labor-HHS committee.

Sen. Barbara Mikulski (D-Md.), a dear and constant friend of the NIH, is now the chair of the appropriations committee overall, she basically wants to reverse the sequester and restore funding for agencies like NIH, but there is opposition to that, obviously from the Republican side in the House.

If there is no resolution to this discrepancy, and there is no so-called grand bargain achieved, the sequester will be applied again across the whole U.S. government, maybe somewhat more severe than FY13 because of some complicated shenanigans during the end of 2013, which somewhat muted the effects of the sequester. It may be as much as 2 or 3 percent greater than it was this year.

With respect to the usual activities that surround appropriations, there hasn't been a whole lot of activity. There was one Senate hearing held May 5 by Sen. Tom Harkin's (D-Iowa) committee. You may know that Sen. Harkin has announced his intention not to run for reelection in 2014. That will be a very significant loss for us.

The hearing was very friendly. A number of our supporters on both sides to the aisle turned up and gave laudatory statements about the NIH. The four institute directors who were there and NIH Director Francis Collins were asked a series of friendly questions, and I think it was an informative hearing, but there were no difficult issues raised.

On the House side, there hasn't been an NIH-specific hearing. There was a hearing about the effect of sequestration on the department in early March, attended of course by the secretary, and Collins was there. There have, however, been a series of letters from the Republican leadership of the House appropriations subcommittee expressing some specific interest in NIH activities.

The topics that were addressed by these letters have required all the institutes to provide accounts to what they do on these topics, through the office of the director, have included the activities in the communications and education offices of various institutes, the way in which awards are made, and the way peer review is balanced with programmatic assessment.

There has been concern, particularly by Rep. Jack Kingston (R-Ga.), regarding the adherence to anti-lobbying provisions in appropriations law, and we of course at the NCI have provided all the necessary information.

We've assured our Congressional appropriators that we have re-educated our grantee institutions and grantees about the lobbying provisions, and we have found no evidence that any of our grantees are using federal funds for lobbying.

I would also mention, with respect to the leadership of that committee, that Mr. Kingston has made clear to several people his intention to run for the Senate in Georgia in 2014, and that could occasion yet another change—remember that our previous chair from Montana [Rep. Dennis Rehberg (R)] failed to achieve election to the Senate in 2012, and that led to his replacement by Mr. Kingston. We may be facing such another situation after the 2014 election.

One bright side of our Congressional relationships has been a number of Congressional visits—visits by members of Congress, especially appropriators and people who are on our authorizing committees.

Perhaps the most important of these visits was a recent one, which occurred last week when I was actually out of town, by Sen. Harry Reid (D-Nev.) the majority leader.

He came to the NIH and saw a lot of important folks over the course of an hour, and obviously was quite taken by what he saw.

He's always been quite a good supporter of the NIH and he returned to Congress and made a number of statements, including a substantial one on the floor about the value of NIH and the tremendous effects of sequestration—and there are a number of reports even in today's news accounts that say he seems to be working behind the scenes to try to reverse sequestration for the NIH.

Whether he can succeed in the face of all the opposition to that, I don't know—but it's great to have someone of his stature and experience talking in a very activist fashion in trying to do something to improve our budgetary situation.

There was another visit of consequence when Rep. Eric Cantor (R-Va.) and a number of other members of the House, both Republicans and Democrats, came to the campus May 9.

Among the visits they made were to Lou Staudt's

lab, and they were tremendously impressed with what Lou was doing to treat patients with lymphoma. Cantor remains a very outspoken supporter of the NIH and it was very useful to have him bring a number of colleagues with him on this trip.

We also had a visit a few months earlier from Sen. Ben Cardin (D) from Maryland, a longtime supporter of the NIH, who not only visited but also gave a town meeting, in which he alluded to his visit to Marston Linehan's lab and talked in appropriately extravagant terms about his support for the NIH.

Replication of Data

I would draw to your attention one other Congressional interest that we talked about in the winter, and that is the Congressional interest in the claims that replication of data that is generated in NIH funding doesn't always occur.

You will remember that we talked to, I think both to the BSA and then to the NCAB, about efforts that the NIH generally, and the NCI specifically, are making to try to address these concerns that data replication is not at the level that we might have expected.

The NCI held a workshop on this topic, which I have reported on here. There is now an NIH-wide committee, held by Story Landis, in which I also take an active role. The House science committee, actually a subcommittee on research in the science committee, held a hearing on science integrity and transparency March 5. Bruce Alberts represented biomedical science. Bruce, as you know, has been the editor of Science magazine for the last five years, and was previous head of the academy.

He has recently stepped down as head of Science magazine, and replaced by Marcia McNutt, but that's another story, but Bruce gave a very useful explanation of how science works, and what some of the things might be done to improve data sharing and improve the reliability of scientific products.

Many of those views, which are available online, are consummate with some of the things that are coming out of our committee. The committee on campus has had a chance to present its findings to all of the institute directors on one occasion—I also made a presentation about our own workshop and Lisa McShane from the NCI talked about role she's played in developing checklists for many of the clinical journals. Those checklists are widely regarded as having been quite successful.

A number of those journals are now using checklists, especially with clinical and preclinical papers, to be sure that adequate data scrutiny and physical methodology has been employed. Last week, the advisory committee to the NIH director heard from Story about some of the findings of our committee and the active level of interest of all the NIH in this problem.

There will be a follow-up at this week's institute directors meeting to talk about some recommendations that are coming forward about how we can use various kinds of training programs, especially the traditional ethics presentations, under the terms of our NIH training programs, in the methods of science that are required to enhance reproducibility.

But there are also other aspects of how we behave as a scientific community and how we behave as individual scientists in getting our work into publishable form—that ranges from checklists, to competition, to getting into certain journals, which are undermining some of the confidence that we might have in the results that we were all producing. I'll have a little more to say about that in about five minutes.

New Alliance Assembles Genomic and Clinical Data

A couple of short items that are of great importance that are not directly NIH-generated or NCI-generated, but are nonetheless things that I want to bring to your attention, if you are not aware of them already:

I suspect most of you read in the newspapers a couple of weeks ago about the formation of an alliance to put together, in digital form, the vast reams of both genomic and clinical data that are coming forward in a number of medical topics—and not just cancer, but cancer is in the forefront—both because it's entered the realm of the petabyte, and data is pouring forth at a tremendous rate.

I mentioned here before to both committees meeting separately in the winter that a meeting was held in January in New York to begin to think about how to form such an alliance; to make information that is generated accessible and interpretative, and conforming to certain standards through the development of a governance—and for an alliance that would be international in scope, and would cover the data coming forward from those studying many different diseases.

That meeting was guided by a white paper put together by a small executive group—to which Charles [Sawyers] belongs, so we might ask him for a comment later on about this.

Following that meeting, it was agreed that the executive group—and I should say that I and Francis Collins and David Lipman and Mark Guyer from NIH were also on hand—but following the meeting the white

paper was further revised, and a number of institutions were invited to provide letters of intent to say that they intended to, depending on the outcome of the final guidance, agree to the formation of the IT operating entities and the final rules of governance.

They intended to join this coalition, with the stipulations about openness and forming harmonious rules for consent and privacy—and agreed to work in accord with the IT standards that would be established.

Now, over 80 institutions from at least 14 countries, and some of these are actually multilateral organizations, so arguable over 40 or 50 countries are already engaged. On June 11, there was widespread coverage of an announcement that a number of important institutions, including the NIH and specifically the NCI, were intent on joining the alliance.

The coverage was very favorable and we are now waiting for the next steps on the model for governance. The actual standards that will be enforced include some ideas about how this enterprise will be funded, what name it will have—'global alliance' being inherently too generic for my taste—and we're now waiting to hear from the executive committee which is chaired by David Altshuler at the Broad Institute and his colleagues about next steps.

You will notice a relationship here between this activity and the cloud pilot competition that George is going to describe a little later, and we'll probably come back to this discussion of what relationship the investigators who will be building cloud pilot might have to the global alliance enterprise.

Myriad's Unwillingness to Share Data "Unfortunate"

I don't usually talk here about the third branch of government. We always talk a lot about the executive branch, which we belong to, and the legislative branch—but we don't usually talk much about the Supreme Court.

But today I'm happy to do so, because I have some good news I suspect you all know. Indeed the NIH was quite engaged in the case of Association for Molecular Pathology against Myriad Genetics.

Several of us attended a moot court that was run by the solicitor general, and we attended the Supreme Court hearing on the case April 15. And I'm sure everybody in this room has heard that June 13 verdict—which, was to me, somewhat surprisingly unanimous—delivered by Justice Clarence Thomas, with a comment by Justice Antonin Scalia, which basically opposed the patenting of naturally occurring genes.

I strongly urge you to read Clarence Thomas's well-reasoned opinion. The basic decision is to deny the claim from Myriad that naturally occurring DNA could be patented on the basis that nothing was invented; that this was a discovery, and a laudable discovery, but not an invention.

It didn't satisfy the composition matter standard for patent protection. cDNA is, in some sense, a fabrication and a laboratory product, and remains eligible for patent protection—however much protection one can get from a cDNA patent at this stage is arguable, but it is eligible.

There are a lot of implications here, very favorable it seems to me, with respect to the development of the diagnostic test and tests for risk assessment. The effect on Myriad will not be particularly favorable. Its stock did go up transiently, by about 10 percent, but since has fallen to well below earlier levels. The biotech industry in general is not going to experience much of a negative influence. We can discuss that later if you like.

There is one remaining issue that we all should be paying some attention to.

Under the terms of its previous patent protection, Myriad dominated the testing for mutations in BRCA1 and BRCA2 genes and collected an immense amount of genomic and clinical data which is of great interest to the scientific community. That information has not been shared and that's unfortunate.

We don't know as yet how much willingness they will have to share those very large datasets, but it is of interest to follow the activities of a former colleague of ours at the NIH, Bob Nussbaum, who's now on the faculty of UCSF, who has developed what is arguably a crowdsourcing approach to this question, by writing to physicians who ordered these tests from Myriad to patients who got them to see if they can begin to accumulate data provided by those who paid for the tests.

I think he has obtained responses from 15 or 20 percent of the people he has addressed, and I think that could be a way to do an end-run around the difficult problem—because there is a tremendous amount of useful information that will help us address the influence of the allegedly mutant alleles that, especially those that are not very frequent, the consequences of having a variation from the standard sequence can't be fully evaluated without accumulating data from multiple individuals.

Also, surprisingly enough, there were two cases decided by the Supreme Court within a single week that have a bearing on the NCI.

The other case known as the FTC v. Actavis, sometimes called the pay-for-delay case, in which the Supreme Court ruled five to three with one abstention—Justice Samuel Alito was recused in this case—which ruled that federal regulators like the Federal Trade Commission may challenge, in court, the arrangements made between a patent holder of a drug and a generic manufacturer at the time when the loss of patent protection is about to occur.

The case specifically involved a drug called AndroGel from Solvay Pharmaceuticals, which was testosterone present in a gel, but the general effect of this decision will be felt in many domains—especially in oncology, where a number of very expensive drugs are coming off patent will now be made by generic manufacturers.

The FTC will feel emboldened to question the terms on which negotiations occur between the patent-holding manufacturer of such drugs—imatinib may be one of them—and the many interested in making these as generics.

The estimate is that this could not only make many drugs accessible to consumers who might not otherwise be able to afford them, but might save the public as much as $3 billion to $4 billion a year.

Thinking Beyond Sequestration

Nearing the end, I want to mention the fact that we're going to have another of our semiannual NCI retreats. There will be members of boards who are invited to attend, if they wish.

This is going to occur July 23, I apologize that invitations have yet to go out but they will very soon. There will be two major topics discussed: one is basically a follow-up to a discussion we had at one of our last meetings about the way in which we manage information technology internally at the NCI—who runs it, what are the pathways for sharing information, and how we can insure that we can actually talk to each other.

That produced a lively discussion at the last retreat and we'll resume that conversation.

The other major topic will be one that is of greater widespread interest in the scientific community—that is, what are the essential ingredients of the current research climate? And how can the NCI, even in the short-run, try to improve it?

I and many of my colleagues—and I'm sure many of you—have been thinking about this, because I think the problems we have go well beyond whether one, two- or five-percent change may occur as a result of sequestration.

We had trouble before sequestration and we are in a little bit more trouble now, but there are many things that are ailing our community at a time of remarkable scientific progress.

And I think we need to think a little bit more deeply than we usually do about whether there are some practices, that are now deeply ingrained in how we and other NIH institutes operate, that may foster excessive growth of the enterprise; that may undermine the way in which we evaluate each other; that may affect the way scientists do their work, and in fact their very moods.

So I'd like to think about whether this, and not just imagine the ideal world, but think about whether NCI has, within its power, the potential to rearrange some of our grant mechanisms; redesign our training programs; think about the procedures used in the applicants of some of our grants; and consider the possibility that by making some of these changes, we can effect both short term and long term improvements in the way we do business.

That topic is not unlinked to the last point I want to raise, which has something to do with something you've heard me talk about here before, and that is the way in which we ask our investigators to describe themselves in their biosketch.

And you may know from past conversations that I am troubled that we are still providing a template for a biosketch in which the major ingredient is simply a listing of a certain number of published articles that allow evaluators to see whether someone's a first or last author in journals that someone's published in—without an ability to explain the nature of the work; the contribution made by the investigator, especially in an era of team science when it's not uncommon for people to make a tremendously important contributions to a very large effort that could not be discerned at either the place that the journal was published, or the position of that contributor within a list of a hundred authors.

So the biosketch revision that we have discussed at length internally, and proposed to NIH generally, would be very similar, but perhaps more explicit than what's done by perhaps a few academic institutions—including my former institution Memorial Sloan-Kettering or by Howard Hughes Medical Institute—and that is to ask people to describe, in a paragraph, up to five major contributions they've made to their scientific field.

Their biosketch should describe the problem they worked on, what their contribution was, and what they worked on specifically—and perhaps place less

emphasis on whether this appeared in Nature, and more emphasis on what the actual results were and what contribution was made by that individual.

In my efforts to make this an NIH-wide initiative, I have to say I encountered much reason to feel frustrated. We have decided to launch an NCI pilot.

It's, to my taste, somewhat limited, but there are on the street now some RFAs—and I thank [director of the Division of Extramural Activities] Paulette [Gray] for guiding me through this bureaucratic morass—but we will be seeing and assessing the consequences of what I think are a much more reasonable set of information points from our applicants.

And we'll see how the applicants and those reviewers of those applications feel this worked, and perhaps go back to NIH central and see if we can make some progress.

I've discussed this with numerous other institute directors. There is widespread enthusiasm for making this change, but I can just tell you that within the NIH bureaucracy—not influenced in part by the anticipation of further pushback from the department and the Office of Management and Budget—it's very difficult to get things done, even when everybody recognizes that we live in pretty awful times.

And that, to make some cultural changes that are advantageous to everybody, it's sometimes not as easy as it ought to be.

Paying for Cancer Drugs

Zaltrap's U.S. Price Has Dropped By Nearly Half Since Introduction

(Continued from page 1)

"We are disappointed not to be able to add aflibercept to the list of treatments for this stage of the disease," Andrew Dillon, the chief executive of NICE, said in a statement. "However, we have to be confident that the benefits that drugs offer patients really do justify what the NHS will have to pay for them."

A Sanofi study, called VELOUR, showed that aflibercept extended overall survival by a median of 1.44 months compared to a placebo. In the U.S., an OS advantage of about six weeks qualifies as a slam-dunk, enough for FDA to approve the drug without consulting the Oncologic Drugs Advisory Committee.

The FDA, which cannot consider the drug's price in its decision-making, approved the drug in August 2012, and the Centers for Medicare and Medicaid Services pay for it.

However, Zaltrap's price in the U.S. on introduction late last year—about $11,000, or roughly double the price of Avastin—caused an unexpected, unprecedented uproar. The controversy over its price marked the first time key opinion leaders in the U.S. have objected publicly to the price of any cancer drug—and, more importantly, the first time a drug company has yielded to public pressure over drug pricing.

At least one premier U.S. institution, Memorial Sloan-Kettering Cancer Center, declined to include Zaltrap in its formulary.

In an OpEd piece in The New York Times, three MSKCC physicians wrote that Zaltrap will not be used at their institution because of its high cost and the absence of data that could enable a comparison with Avastin (The Cancer Letter, Nov. 2, 2012).

In the pivotal trial, Zaltrap was added to the FOLFIRI regimen and compared with placebo as a second-line treatment for patients with metastatic colorectal cancer previously treated with oxaliplatin.

Sanofi's response to public criticism and exclusion from formularies was dramatic. The company agreed to discount the drug by about half (The Cancer Letter, Nov. 16, 2012).

The case emboldened other U.S. physicians to use formularies and public forums as a means to pressure pharmaceutical companies to reduce the prices of cancer drugs.

One such campaign was launched by Hagop Kantarjian, chair of the Department of Leukemia at MD Anderson Cancer Center, and lead author of a recent paper on drug pricing, published in the journal Blood.

"It was the first example ever where a cancer drug company responded to the advocacy of oncologists on behalf of their patients," Kantarjian said in a conversation with The Cancer Letter.

"The pressure led them to reduce the price of Zaltrap to the one equivalent to Avastin. They really didn't do any big favors to the community, except to say that if we want to sell our drug, we are going to price it the same as the drug that exists, which already has a very high price (The Cancer Letter, May 31)."

Indeed, Zaltrap's price in the U.S. has been dropping, according to figures compiled by Peter Bach, director of the MSKCC Center for Health Policy and Outcomes.

A month of treatment, calculated using the Medicare average sales price plus 6 percent—was $11,063 a month in September 2012.

It dipped to $9,444 in March, and then to $6,731

earlier this month. Meanwhile, Avastin in a commonly used schedule sells today for $4,901 a month. (Zaltrap's price is calculated using the 4 mg/kg every two weeks dose, and Avastin's dose is calculated as 5 mg/kg every two weeks.)

Notably, even without the discount Sanofi proposed to the UK National Health Service, the net price cited by NICE was far lower than the price at which the drug is reimbursed in the U.S. The magnitude of the discount is being held confidential

The British agency cited the net price of £295.65 ($450.30) for a 100 mg vial and £591.30 ($900.61) for a 200 mg vial of Zaltrap.

Using the same calculation as MSKCC researchers, this net price would result in the price of about $2,700 per month, about 60 percent less than the U.S. ASP plus 6 percent.

Even at a lower price, MSKCC hasn't included Zaltrap in its formulary.

NICE has previously declined to pay for the Hoffmann-La Roche drug Avastin (bevacizumab) for the indication. Both drugs inhibit angiogenesis.

The NICE decision represents the first step in the process of rendering a payment decision. The agency's draft guidance was posted on its website June 21.

Until final guidance is issued to the National Health Service, NHS bodies would make decisions locally. Once NICE issues a final guidance, it replaces local recommendations across the UK.

NICE has recommended irinotecan, oxaliplatin, capecitabine, tegafur with uracil and cetuximab for the treatment of colorectal cancer.

The committee considered the most plausible cost per Quality Adjusted Life Year—which ranged from £62,900 ($95,803) per QALY gained to £66,500 ($101,479) per QALY gained, depending on whether the treatment benefits of aflibercept plus FOLFIRI and FOLFIRI alone became the same after 30 or 36 months of starting treatment.

The committee agreed that these figures would be higher when accounting for an extra preparation cost for aflibercept of more than £15, and a cost for an additional hour of infusion time of £45.

Sanofi estimates that 4,028 patients in England and Wales would receive second line treatment for metastatic colorectal cancer. In February, Zaltrap received marketing authorization from the European Union. Zaltrap is marketed by Sanofi and Regeneron Pharmaceuticals.

Clinical Guidelines

Clinical Practice Guidelines Don't Meet IOM Standards

By Matthew Bin Han Ong

Clinical practice guidelines used to determine care for common cancers do not meet the standards set in 2011 by the Institute of Medicine, a study by University of Michigan Comprehensive Cancer Center researchers found.

Researchers reviewed 169 cancer clinical practice guidelines for lung, breast, prostate and colorectal cancers, and found that none fully met the standards.

Of the eight criteria proposed by IOM, the guidelines on average met fewer than three.

"None of the current guidelines we looked at

meet all of the standards, but some of these are really good guidelines," said lead study author Sandra Wong, associate professor of surgery at the University of Michigan Medical School. "It begs the question: how pragmatic are the IOM standards? In some ways, are these standards too strict?"

The IOM standards for clinical practice guidelines, published in 2011, were developed to ensure that guidelines reflect the best quality of care.

The study, published in the Journal of Clinical Oncology, found that guidelines, on average, met 2.75 of eight major criteria and 8.24 of 20 sub-criteria.

The eight major criteria listed by IOM are: establishing transparency; management of conflict of interest; guideline development group composition; clinical practice guideline-systematic review intersection; establishing evidence foundations for, and rating strength of, recommendations; articulation of recommendations; external review; and updating.

The most common gaps were in managing conflict of interest and including patients in the process.

"The IOM was trying to define what you need to have trustworthy guidelines," Wong said. "But if a group does not include a forum for public comment on the guidelines, does that make the guideline less trustworthy?

"Is that as important as whether they incorporate a systematic review of the literature?

"One consideration is that perhaps all standards should not be weighted the same across the board," Wong said.

Wong suggests creating a balance between ideal standards and what is practical to ensure guidelines can be put in place in a timely manner.

"Everybody is much more worried about quality standards and evidence-based care," she said. "Clinicians are inundated with a lot of information and must be able to rely on guidelines produced by major professional organizations.

"At the same time, standards must ensure a practical and pragmatic approach to creating guidelines," Wong said.

Screening Guidelines

USPSTF Recommends Hep-C Screening for Baby Boomers

The U.S. Preventive Services Task Force June 25 recommended hepatitis C screening for adults born between 1945 and 1965, as well as people who received a blood transfusion before 1992.

Task force members concluded that "the benefit of screening for HCV infection in persons in the birth cohort is likely similar to the benefit of screening in persons at higher risk for infection."

A similar screening was recommended by the Centers for Disease Control and Prevention in 2012.

"Hepatitis C infection is a leading cause of liver damage, liver cancer, and liver transplants in the United States," said task force member Kirsten Bibbins-Domingo. "Millions of people in the U.S. are infected with hepatitis C, and many are unaware of their condition, in large part because they may not have any symptoms.

"Screening for hepatitis C can help people who are infected live longer, healthier lives."

HCV is usually an asymptomatic disease, and three out of four of those afflicted are unaware of their infection until their liver disease is far advanced.

The task force also recommends that injection drug users should be screened regularly.

"Baby boomers account for three out of four people with hepatitis C," said task force Co-Chair Albert Siu. "Many people in this age group contracted hepatitis C from a blood transfusion or unknown or unreported high-risk behaviors."

The task force changed the rating from a "C" to a "B" for hepatitis screening for baby boomers—allowing for payment by Medicare and private insurers for testing with no copayment by patients.

In Brief

Warren Kibbe To Lead CBIIT

(Continued from page 1)

Center and director, Translational Informatics Group, Feinberg School of Medicine.

"[Kibbe] has had a lot of contact with the cooperative groups in helping them to design appropriate informatics platforms for clinical trials," NCI Director Harold Varmus said at the joint meeting of the National Cancer Advisory Board and the Board of Scientific Advisors June 24.

CBIIT's first director, Kenneth Buetow, left in

early 2012 in the midst of scrutiny of the massive enterprise, which relied on contractors, including Booz Allen Hamilton and SAIC, and used as much as $350 million in appropriated NCI money, augmented by funds from the American Recovery and Reinvestment Act to build the cancer Biomedical Informatics Grid, abbreviated as caBIG (The Cancer Letter, Dec. 16, 2011).

After Buetow's departure, the NCI bioinformatics activities were run by interim director George Komatsoulis, who will remain in his job until Kibbe arrives Oct. 1, Varmus said.

Kibbe will join NCI under an intergovernmental personnel agreement that will assigns him to NCI from Northwestern. He will be permanently appointed sometime next year, Varmus said.

LOUIS STAUDT was named permanent director of the **NCI Center for Cancer Genomics**.

Staudt, an NCI intramural investigator, has been serving with Stephen Chanock as an acting co-director of the center, which was established by Barbara Wold during her sabbatical from California Institute of Technology.

"You all know Lou from his extraordinary work in using molecular tools to reclassify lymphomas and discover new forms of B-cell lymphoma and beginning to figure out appropriate targets, and indeed target some of those targets with good effect. And for all this work he was, this year, elected to the National Academy of Sciences—and I'm really pleased to see that he's willing to oversee this difficult task," Varmus said at the NCAB-BSA meeting.

PATRICK McGAREY was named director of the **NCI Office of Budget and Finance**.

McGarey retired from his position as FDA assistant commissioner for budget. He replaces acting director Karen Colbert.

PELAYO CORREA received the Distinguished Achievement Award from the **American Gastroenterological Association**.

Correa is the Anne Potter Wilson Professor of Medicine in the Division of Gastroenterology, Hepatology and Nutrition and professor of Pathology, Microbiology and Immunology at Vanderbilt University Medical Center. He joined the Vanderbilt University faculty in 2005.

He is known for his research on the role of the Helicobacter pylori bacteria in gastric cancer and served as a member of the World Health Organization committee that designated Helicobacter pylori as a Class 1 carcinogen.

Correa received the inaugural American Cancer Society Award on Cancer Epidemiology and Prevention, and the Distinguished Achievement Award from the American Society of Preventive Oncology. He has received presidential appointments to the President's Cancer Panel and the National Cancer Advisory Board.

THE CONQUER CANCER FOUNDATION of the American Society of Clinical Oncology named the recipients of its 2013 **Long-term International Fellowship** and **International Development and Education Awards**.

The Long-term International Fellowship provides early-career oncologists in developing nations with support and resources to advance their training by connecting them with an American or Canadian colleague through a one-year medical fellowship.

The 2013 LIFe recipient is Siraji Obayo, of the Uganda Cancer Institute. Obayo will be training at Case Western Reserve University, under the mentorship of Matthew Cooney. His research project is studying the utility of a non-invasive prostate cancer biomarker to diagnose prostate cancer in resource-poor settings.

The International Development and Education Award provides support for early-career oncologists in low- and middle-income countries by helping them establish relationships with leading ASCO members who serve as scientific mentors to each recipient. Recipients of the award travelled to the ASCO annual meeting and will participate in a post-meeting visit to their mentor's institution.

This year's IDEA recipients are:

• Amit Bahl, of the Post Graduate Institute of Medical Education and Research in India

• Kesang Diki Bista, of Tribhuvan University Teaching Hospital in Nepal

• Maria Bourlon, Instituto Naciona de Nutricion Salvador Zubiran in Mexico

• Srinivas Chilukuri, Yashoda Hospital in India

• Ary Darwish, Hewa Cancer Hospital in Iraq

• Abdul Hannan, Shaukat Khanum Memorial Cancer Hospital and Research Center in Pakistan

• Luliana Ramona Giurgiu, Regional Oncologic Institute in Romania

• Houda Jamous, Cancer Care Center Benbadis Hospital in Algeria

• Natia Jokhadze, National Cancer Center of Georgia

• Herdee Gloriane Luna, National Kidney and

Transplant Institute of the Philippines

• Amira Mansour, Nasser Institute in Egypt

• Joy Mburu, Kenyatta National Hospital in Kenya

• Micheal Misauno, Jos University Teaching Hospital in Nigeria

• Tatiane Montella, Brazilian National Cancer Institute

• Sandra Ndarukwa, Parirenyatwa Group of Hospitals in Zimbabwe

• Ahn Tuan Pham, the National Cancer Institute of Vietnam

• Luis Leonardo Rojas Puentes, the National Cancer Institute of Mexico

• Salah Abdullaah Faraa Saif, South Egypt Cancer Institute; Egypt and Yemen

• Gevorg Tamamyan, Yerevan State Medical University in Armenia

• Shuhang Wang, Beijing Cancer Hospital

Four received the International Development and Education Award in Palliative Care:

• Ganesh Dangal, Kathmandu Model Hospital in Nepal

• Elia Hakim, Cairo Oncology Center in Egypt

• Andrew Olagunju, Lagos University Teaching Hospital/University of Lagos, Nigeria

• Do Thuy, Hanoi Medical University Hospital in Vietnam

Obituary

Michael Potter, NIH Researcher

Michael Potter, a prominent researcher at the NCI who won the Lasker Award for medical research, died June 18 at his home in Bethesda. He was 89 and had acute myeloid leukemia.

Potter worked for more than 50 years at NCI, and is most famous for his work on the induction of myeloma models in mice. His research led to greater understanding of tumors and the immune system.

"I myself developed my first serious interest in cancer etiology in a course that he gave 1969, when I was a yellow beret at the NIH," NCI Director Harold Varmus said at the meeting of the National Cancer Advisory Board and the Board of Scientific Advisors. "I owe him a lot."

An M.D. by training, Potter was known for his fundamental research in the genetics of immunoglobulin molecules and for paving the way for the development of hybridomas and monoclonal antibodies. The first of his seminal discoveries was made in 1956, when he found that adjuvants containing mineral oil could cause plasma cell malignancies in mice.

Potter used this experimental model of human disease to identify tumor susceptibility genes and fundamental processes of tumorigenesis, including chromosomal translocations. Many others throughout the world—immunologists and cancer biologists—benefited from his model.

Potter catalyzed the field of antibody research, holding a decade's worth of annual workshops from 1969 to 1979 on "Homogeneous Antibodies and Lymphocyte Hybridomas," followed by another two decades of annual workshops on the "Mechanisms of B Cell Neoplasia." He shared materials, cell lines, and information as freely as he shared his interest in B cell biology.

Starting in 1976, Potter pioneered graduate training at NIH, and he was appointed adjunct or research professor in three different departments at the University of Maryland. He was instrumental in launching the careers of many graduate students who conducted their pre-doctoral research in his laboratory, as well as a large number of postdoctoral fellows.

Potter was a graduate of Princeton University and received his M.D. from the University of Virginia. After service in the U.S. Army from 1950 to 1951, he became a research assistant in the Department of Microbiology at the University of Virginia.

In 1954, he joined the NCI Laboratory of Cell Biology, where he worked with Lloyd Law. He became head of the LCB Immunochemistry Section in 1970, and he served as chief of the Laboratory of Genetics from 1982 to 2003.

Potter received the status of scientist emeritus in 2009 and had been a frequent contributor to scientific endeavors until his death. In 2010, the NIH held a conference on the etiology of chromosomal translocations in his honor.

Potter received the Paul Ehrlich and Ludwig-Darmstaedter Prize, the Waldenstrom Award, the NIH Director›s Award, and the Albert Lasker Medical Research Award, which he shared with Georges Kohler and Cesar Milstein. He was elected to the National Academy of Sciences in 1981.

Potter was an avid fisherman and bird watcher, and had a special fondness for the Chesapeake Bay. He was well known for his expeditions to James Island in Maryland in pursuit of bluefish, herons, shark teeth, and chips of blue pottery from a bygone era.

Potter is survived by one daughter, Melissa Magrath, and three grandchildren. His wife, Jeanne Ann, and his son, Michael, died before him.