THE CANCER LETTER

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*Lung Cancer Screening:*

## Henschke, Supporters Call For Urgent Action Based on Results of NCI Randomized Trial

*By Conor Hale*

In her first public appearance following a blast of controversy surrounding her clinical studies, radiologist Claudia Henschke said that low-dose helical computed tomography screening for lung cancer should become the standard of care for current and former smokers.

At a panel discussion May 9, Henschke and her key supporters said that screening for early signs of lung cancer—as developed in Henschke's International Early Lung Cancer Action Program—should be given an "A" recommendation from the U.S. Preventive Services Task Force.

Cheryl Healton, president and CEO of the American Legacy Foundaton and one of the panel members, said there is no time to waste.

"We have to get ourselves ready to save what will something on the order of potentially 70,000 lives every year, just by beginning to implement this screening, post-haste," said Healton.

"There's never been any single breakthrough that has the overnight, not

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*Appropriations 2011:*

## NIH Grant Success Rate Drops Under 20 Percent After 2011 Compromise Budget Cuts Take Effect

*By Conor Hale*

Facing Senate appropriators, NIH Director Francis Collins said he was thankful that the budget cuts didn't go much deeper.

"Many of the proposals were vastly worse than this, and I know that many people really went to bat for NIH," said Collins, testifying on Capitol Hill May 11, after the 2011 compromise budget bill cut NIH funding by $322 million. "And we appreciate that enormously."

Collins and a group of institute directors came to Capitol Hill to make their case for the institutes' 2012 budget.

In his testimony, Collins listed the benefits NIH has contributed to the country in terms of public health, advances in clinical and translational research, and—in the most important measure of the day—impact on the economy.

Though the president's budget request for the next fiscal year calls for an increase in NIH funding, the prevailing mood is not wondering whether there will be cuts, but wondering how large these cuts will be.

The budget cut this year has forced the NIH to only approve one out of every six grant applications—a success rate of 17-18 percent and the

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## Legacy's Healton Demands Quick Action by USPSTF

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literally, but the overnight potential to save as many as half the people who in any given year are destined to die of lung cancer in this country," she said.

"And I actually am quite startled that, at least by all external measures, it looks like the U.S. Preventive Services Task Force and those who lead its decision making are treating this as a business as usual situation," said Healton.

"And if I asked everyone here who ever smoked to put their hands up and how many of you have gotten a CT scan, I could probably do a back-of-the-envelope estimate of how many of you are walking around potentially dying because of the inaction that we may actually proceed with."

The discussion was sponsored by Henschke's most loyal supporters: the Lung Cancer Alliance and Legacy.

CT screening of former and current smokers may indeed become the standard of care, but this would happen as a result of the NCI-sponsored National Lung Screening Trial, a randomized study that measured cause-specific mortality in a high-risk population of current and former smokers monitored via CT screening or standard chest x-ray.

If USPSTF gives CT screening a high mark, it would almost certainly do so for a well-defined population, and as a result of review process that takes years to complete.

Meanwhile, I-ELCAP, its investigators and host institutions are under scrutiny by medical journals, following revelations that the consent forms could be missing for as many as 90 percent of participants and that the group's principal study was designed without a sample size calculation. With 53,000 patients scanned, it's essentially a registry that has no stopping point and can go on forever without producing a result.

This criticism emerged in a confidential document produced by a committee of four experts who reviewed I-ELCAP for its former host institution, Weill-Cornell Medical College (The Cancer Letter, April 29; The New York Times, April 30). The operations center has since moved to the Arizona State University's Biodesign Institute.

Since then, at least three journal editors have mailed letters to Henschke and Weill Cornell, requesting additional information and copies of the report. The letters were sent by the New England Journal of Medicine, the journals of the American Cancer Society, and The Oncologist.

One editor said that without an absolute response from the group, they would publish a retraction of the group's work (The Cancer Letter, May 6).

However, this was not mentioned directly by the panel members, who largely agreed that the work done in I-ELCAP and NLST was ready for a leap from clinical research into public policy—and that the federal government should give it its highest rating, and do so quickly.

Healton alluded to the controversy while describing her decision to become Henschke's patient:

"I did the math…and I concluded that I had a one in six chance of developing lung cancer…so the minute I heard about Claudia, I became one of Claudia's patients.

"And I hasten to add that I signed the fully executed consent," she said, drawing laughs from the crowd.

Legacy funds an I-ELCAP study, called the Legacy Project, where smokers over the age of 50 receive CT scans and smoking cessation materials.

The main premise behind advancing the practice of early CT lung cancer screening would be based on the results of the NLST, which concluded in November 2010 (The Cancer Letter, Nov. 5, 2010).

The trial was stopped after demonstrating a 20.3 percent mortality benefit in current and former smokers between ages 55 and 74, with at least a 30 pack-year smoking history.

A manuscript based on the study is in preparation,

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and its publication is weeks away.

Computer models would be required to assess the impact of different frequencies of screening, ages at starting, and risk levels. It's not at all clear what the risks are for 20-pack-year smokers or 40-pack-year smokers.

And it's not clear that rounds of annual screening would improve the outcome, modelers say (The Cancer Letter, Nov. 26, 2010).

Henschke has argued that NLST amounts to vindication of her own results.

"I would say that the NLST showing a 20 percent mortality reduction after three years of screening and five years of follow-up is tremendous," Henschke, now a professor at Mt. Sinai School of Medicine and Arizona State University, said at the May 9 meeting.

But Henschke said true results of the intervention could be even better than they appear:

"It's comparing it with chest X-ray, and chest X-ray does have a benefit. So it would be even more if it had compared CT with no screening—and it would have been even more if there were more rounds of screening. So every year, an additional round of screening for 10 years would probably show higher reduction."

This would more than double the drop in mortality rates, she said.

"What people have to understand is that that mortality reduction of 20 percent is a population figure," she said. "So if you only focus—and I looked at some theoretical curves, what I think those curves will look like when they're published—that if you looked on an annual basis it would have been as much as almost 50 percent reduction, even after three rounds of screening.

"While I always say I'm a researcher, not a public policy person…I think that it will get an 'A' recommendation. Whether it will is another question," said Henschke.

James Mulshine, associate provost for research and vice president of Rush University Translational Sciences Consortium, also said that the NLST finding of 20 percent mortality reduction may understate the true benefit.

"It may be that the 20 percent benefit may be the floor and not the ceiling of what can be obtained through spiral CT screening," said Mulshine, a panel member.

He described the outcome of these studies as a "teachable moment" and a challenge for the U.S. health care system, which he said would have difficulty providing CT screening for such a large population.

"Anybody who looks at this fact set understands that there are challenges," Mulshine said. "But those challenges are systematic ones that if we take on lung cancer screening as a demonstration project for the nation on how we approach population-based medicine in a thoughtful quality outcomes kind of way, it could be an extraordinarily important pivot point for medicine in our society."

The panel members didn't define a target population that would be subjected to low-dose spiral CT scanning, even as they called for an "A" rating from USPSTF.

Mulshine said the benefits of CT screening extend beyond finding early-stage tumors in current and former smokers, the populations in I-ELCAP and NLST, and may be applied anyone at risk for cardiovascular disease or chronic obstructive pulmonary disease.

"And so, predictably, if this goes forward with a B or with an A from the U.S. Preventive Services Task Force, we will have a challenge of this screening being disseminated nationally, if that's in fact their declaration, across a very heterogeneous healthcare system," said Mulshine.

"Claudia and others have shown that spiral CT, looking at calcification of the vascular tree of the heart is a very powerful risk marker. More powerful than cholesterol," he said. "Three major smoking-related diseases—lung disease, heart disease, and COPD, which account for every other premature death in our society—are all detected by early spiral CT."

**Changing the Standard of Care**

"For years, a line of resistance that you ran into was, yes, you might identify nodules early, and some of those nodules it was argued are not going to be lung cancer, but were going to subject patients to surgery and other treatment unnecessarily," panel moderator Susan Dentzer, editor-in-chief of Health Affairs, asked Henschke. "Talk about what progress you've made on refuting that argument, and how specifically a continuum of very careful scrutiny of the nodules can lead to effective care and not to inappropriate care."

"As CT scans get better all of us will have a nodule," replied Henschke. "So what distinguishes lung cancer from those other nodules? Well lung cancer has certain growth rates, it's fairly well known what those growth rates are and everyone's in the process of developing technology that will allow very careful assessment of that growth.

"Today, we have a low-dose CT scan, and if taken in the same way and taken at the same place—that's why the process and where you get it done is so important—you can differentiate very well in a relatively short time what is a cancer and what is not.

"There will be unnecessary harms related to

spiral CT screening," Mulshine said. "And this is very problematic because we have scarce resources and we're talking about people's lives, and we do not want to intervene in such a way that we undermine people's health, but we improve it."

How would national CT screening be paid for?

"It's probably not premature to start a dialogue of whether or not there shouldn't be any sort of user fee on the product that would underwrite a national system of screening centers," said Healton. "That type of a system could be built on around 20 cents per pack."

Panel members said screening protocols could be tested in a demonstration project within the Veterans Administration.

Dentzer asked Barbara Campling, of Thomas Jefferson University Hospital, to talk about the VA's electronic health records system, which Dentzer described as "light years ahead of our health care non-system," and could provide "marvelous opportunities for identifying a portion of the population that could benefit from CT screening."

"Anybody that goes to the VA is required to have a smoking history taken," said Campling. "You can't go on in the record without recording that information, So you could immediately identify everybody at the VA who would be eligible for screening. And my guess is that that's going to be a majority of people that go to the VA that will be eligible."

But whether this pilot project had a definite future at the VA, Campling did not know.

"I can't get a definite answer on that, but I can tell you what I think is going on. I have no access to any inside information, so I'm going to tell you what I think is probably going on in the VA," she said.

"I think that they are probably planning to implement it. I think they will probably wait until the results of the [National Lung Screening Trial] are published, or available for all to see before they actually make an announcement about how they're going to do it. But I think they will do it. And I think that they will do a much better job of it than in the private sector," Campling said. "And this is because they have got a really outstanding record for cancer prevention and cancer screening.

"I predict that when they do this, veterans will benefit more than any other group. Because it has been shown that veterans have a higher incidence of smoking, they have a higher incidence of lung cancer, the people who do smoke tend to smoke more. These are the exact kind of people you want to target for screening programs," she said.

"**Shame on Us**"

While under a spotlight of professional criticisms and questions, both the panel and moderator appeared defiant.

"You have suffered the slings and arrows of amazing criticism and opposition to get there, but now we see it finally scientifically validated to the satisfaction of even some of the lung cancer experts who challenged you along your way," said Dentzer to Henschke.

And if the program fails to go national, "shame on us as a country for not taking the steps to put together a system that all of these folks have said might work," said Dentzer.

Healton said political action would be required to change the standard of care.

"I continue to be one of Claudia's patients in her trial, because I know that the odds that I will develop cancer are high and I would prefer to continue to live," said Healton. "So we are at a turning point, we should be watching very carefully what happens. And if something untoward happens, we should rise up, and in the name of all of those who are dying of, and will die in the future of lung cancer…we have to make sure that does not happen."

"**Screening is a Process**"

Responding to criticism that could lead to retraction of her papers, Henschke said her registry approach is valid.

"People should set up screening programs as a study and pool the data, that way we continuously improve the process," she said. "We've developed a collaboration of 60 institutions around the world who contribute their data prospectively, they've all signed consent forms.

"And that has enabled us to keep up with the state of the art. When you go to a program for CT screening, or any screening, you want to go to a program that is the state of the art, that uses the latest equipment, the latest surgery, the latest biopsies—and also looks at the ancillary things.

"We've found that, for example, that low-dose CT scan gives us a lot of information about the risk of cardiovascular disease, which is also associated with smoking and emphysema.

"And as we learn more and more we will be able to individualize the risk of those different diseases.

"Screening is a process that will continue forever. It's going to be a continuously evolving process that gets better and better. And we will be better able to define those risks. Who should get those CT scans as well, and

we will be able to integrate biomarkers or any genetic information we have."

In her remarks, Henschke said the true benefit of screening far exceeds the NLST results.

"Screening is something that even as a smoker or a former smoker you continue for a long time. We don't have any good idea yet on when that endpoint is, but you remain vulnerable for the rest of your life," said Henschke. "So we say that if you have a life expectancy of 10 years, consider getting screened. But we don't have the data on that. We say screening finds it five years earlier, and then you should have another five years that you'll enjoy because of the fact that you had your lung cancer taken out earlier.

"That's really a lot of data still needs to be generated on that count, but at the moment you have to do it every year. And perhaps we'll get better. For some people we only do it every two years or every three years. That's research that still needs to be done."

*Appropriations 2011:*

## Collins, Varmus Emphasize Returns on Investment in NIH

(Continued from page 1)

institutes' lowest rate ever.

"In FY '10, we funded approximately 9,300 research grants," said Collins. "The success rate in FY '10 came out at just about 20 percent. With the FY '11 budget now in front of us, now that it's been decided, we won't do that well."

"But for every one grant that you can fund, how many are unfunded?" asked Sen. Barbara Mikulski (D-Md.).

"It would be five out of the six," responded Collins. "If you have six grants in front of you, you're going to fund one of them and five are going to go begging."

Collins was joined by NCI Director Harold Varmus, National Institute of Allergy and Infectious Diseases Director Anthony Fauci, National Institute of Diabetes, Digestive and Kidney Diseases Director Griffin Rodgers, and National Heart, Lung and Blood Institute Acting Director Susan Shurin.

They were asked several questions about the how the U.S. competes with foreign countries in biomedical research, and senators requested an update on plans for the new National Center for Advancing Translational Sciences.

Collins described four major points, accentuating all of the positives—and all of the money—that investment in the NIH can offer, through accelerating discovery through technology, applying science to prevention, enhancing the U.S. economy and global competitiveness, and advancing translational science.

For his first example, he showed that NIH research, over the past 10 years, has dramatically lowered the cost of sequencing a single human genome—from $100 million in 2001, to about $10,000 today, and possibly to as little as $1,000 in the next few years.

That will open the feasibility of providing personalized therapies to many more patients, he said. It has greatly lowered the cost of doing science, specifically making The Cancer Genome Atlas possible.

"My colleague Harold Varmus and others are analyzing the DNA of tumors of hundreds of patients to identify comprehensively the genetic mutations associated with specific cancers," said Collins. "This approach will lead to a new generation of targeted therapies."

Sen. Tom Harkin (D-Iowa), chairman of the Senate Appropriations Subcommittee on Labor, HHS, and Education, noted that the NIH Human Genome Project was an example of some of the best investments the government can make.

"The federal government spent $3.8 billion on this historic initiative," Harkin said. "That's a lot of money. But the return on investment is staggering. That research translated into an economic output of $796 billion between 1988 and 2010. And we'll be seeing benefits from the Human Genome Project for many more decades to come."

According to a report from United for Medical Research, an umbrella group pf health organizations, NIH funding supported 488,000 jobs in 2010 alone, producing $68 billion in new economic activity. NIH funding supported over 71,000 jobs in California, over 34,000 in Massachusetts, over 33,000 in New York, and 31,000 in Texas.

Also, over the past 15 years, cancer mortality rates dropped 13.5 percent for women and 21.2 percent for men, saving an estimated 750,000 lives, Collins wrote in his testimony.

"Let me just cite a couple of figures," Collins said. "If you look, for instance, at heart disease…we've seen a 60 percent drop in mortality from heart attack [in the past] 40 years. The cost of that, in terms of the research that led to those advances is about $3.70 per American, per year. It's the cost of a latte—and not even a grande latte."

"And if you add up the economic benefits that have resulted from increased longevity, that have occurred between 1970 and 2000, I am told credible economists believe that adds up to $91 trillion," he said.

"Each time the frequency of cancer goes down by one percent, economists say that saves our country $500 billion," he said. "And that's actually happening each year. The return is enormous."

"I'm not surprised by that," said Sen. Jerry Moran (R-Kan.). "It would be very helpful to have that—I don't like the word soundbite, but that phrase that says, 'For every dollar spent, here's what we're able to save,' in otherwise spending on healthcare."

"This is such an example of public service and why government matters," said Sen. Sherrod Brown (D-Ohio). "And when I hear some of the know-nothings, that hold jobs like we hold, say that the government is broke, and that government can't function, and that government doesn't contribute anything, and that government doesn't create jobs. I think primarily of what NIH does and what you contribute to public health and to the wealth of our country."

**An update on NCATS**

The subcommittee asked for an update on the progress of NIH's plan to shift its centers to make room for the new translational research center that NIH hopes to open at the beginning of the next fiscal year.

"We've not received a budget amendment of specific structure details on NCATS, a program you want to implement by October 1. How can the committee support a program that does not yet exist in budget documents?" asked Sen. Richard Shelby (R-Ala.), the subcommittee's ranking member. "When will we receive some more details… do you have a timeline?

"I had certainly hoped that by the time of this hearing, we would have been able to provide the details about the budgetary consequences of setting up this exciting new center," said Collins.

"Rather than putting this off until FY '13—which I thought would really have wasted an opportunity—we decided we would try to move as quickly as possible. Although some people said, 'Hey this is the government! You can't possibly do that by October!' Well, they used to say that about the genome project. So I decided that we could, and we should, because this is the best way to move the science forward.

"We needed, of course, to communicate with our communities and constituencies, and as we figured out how to do this shifting right down to every employee, we had to be sure we had that right. We are at the point now where we believe we have that together. It needs to be reviewed by the HHS and OMB experts. We hope to get that to you, Senator, in the fairly near future, certainly within the next few weeks, and hopefully very few weeks," said Collins.

**Why are there no more Gleevecs?**

"In 2001, Gleevec was on the cover of all our national news magazines," said Harkin. "They talked about it being the magic bullet, heralding in a new age in the war against cancer. For the first time we had a drug that specifically targeted a lung cancer gene. It took this deadly blood disease, turned it into a chronic but survivable condition. We were told that Gleevec was the future. We talked about it in our committee hearings at that time. But that was 10 years ago. We haven't had any other Gleevecs. What happened? How come no more Gleevecs?"

"I wouldn't characterize it quite that way. Gleevec remains the poster child for targeted therapy," said Varmus. "Just to give you a brief update, it's used not only for the treatment of chronic myeloid leukemia, but it's used for the treatment of several other diseases in which potential targets for the drug are mutated, and that includes gastro-intestinal stromal tumors, a number of other blood diseases, and indeed a few other cases in which certain genes are known to be mutated, as the result of the sequenced genomes of those cancers.

"Moreover it's recently been challenged that we can deal with drug resistance, a common problem in cancer therapy, by using drugs closely related to Gleevec, but not identical to it, and to treat patients that become resistant to Gleevec.

"Secondly, it's been shown recently that a person in their 40's or 50's that developed that leukemia now have normal life expectancy, which was previously five years. That's a dramatic change. That shows the efficacy of Gleevec has been sustained over the past ten years nationally. There are a number of other targeted therapies. They tend to work quite well initially, but then their tumors become resistant to therapy.

"Let me give you a couple of examples. One happens to involve my own work on lung cancer, in which a significant percentage, perhaps 10 percent of

cancers, have mutations in specific genes against which we have effective inhibitors. But generally speaking, within a year or so, on average, patients become resistant to those drugs. We don't have good therapies to counter the tumors that are resistant.

"Recently, in the case of a disease called metastatic melanoma, it's been found as recently as seven or eight years ago that about 60 percent of those cancers have a mutation in a specific gene in which we have an inhibitor that has been developed.

"It's extremely effective in inducing remissions in a fairly non-toxic way. There are two drugs that do this, and they are likely to soon be approved by the FDA. They don't cause persistent regressions, but there's every reason to hope that, with additional drugs to help counter the drug resistance.

"I will say that we've had a number of other targeted therapies, they've not in general been quite as dramatic as Gleevec, but most of us who are working in this area are quite optimistic about a number of new drugs, some of which I haven't mentioned that are in the pipeline."

"This is about as important as Gleevec. This attacks metastatic melanoma in later stages," said Harkin.

"Correct," said Varmus. "We are quite optimistic that after many years of trying to manipulate the immune system that we have some various handles on how the immune system works that we can use in cancer therapies."

**The Government Shutdown and NIH Morale**

"With all the talk of a shutdown, and during H.R. 1—which had a cut to the NCI, which was stunning to me—what is the morale at NIH?" asked Mikulski. "Now that they've thought they might be sent home, and told that they were non-essential and that the cuts might be coming…and I must say that both the chairman and the ranking member were enormously supportive to minimize the disaster, but it was not a victory."

"I would say this was a difficult period to go through," said Collins.

"We were required, of course, in preparation for what appeared to be a very high likelihood of shutdown, to define how we would manage that. And that meant defining which particular employees were considered essential—which were accepted, was the term that was used—and which were non-accepted. And, of course, those that were involved in patient care or management of animals couldn't very well just not come to work.

"But others were told, 'I'm sorry. If there's a shutdown, you can't come to work.' Think about how that feels if you're a post-doctoral fellow in the middle of an experiment that you've been working on for two to three weeks, and has a couple of weeks to go, and you're being told, 'I'm sorry, you're not allowed to come to work tomorrow if the government shuts down.'

"It did have a very significant effect. People were quite shaken up by that. I think people are, in the aftermath of that, feeling a little uncertain about what it's like to work in this environment. And we're hoping that we won't face that again. But, again, I think everybody understands these are terribly, terribly difficult times for our country."

**Varmus's Testimony**

Varmus's testimony focused on the budget request for the next fiscal year, an update on scientific work being done at NCI, information on the reorganization of the adult clinical trials cooperative groups, and another look at NCI's Provocative Questions initiative.

*The text of Varmus's testimony follows:*

Mr. Chairman and Members of the Committee:

I am pleased to present the President's Fiscal Year (FY) 2012 Budget request for the National Cancer Institute (NCI) of the National Institutes of Health (NIH). The FY 2012 request includes $5,196,136,000 for NCI, which reflects an increase of $141,899,000 over the comparable FY 2011 level of $5,054,237,000.

We now know that cancer is a collection of diseases reflecting changes in a cell's genetic makeup and thus its programmed behavior. Sometimes the genetic changes occur spontaneously or are inherited; sometimes they are caused by environmental triggers, such as chemicals in tobacco smoke, ultraviolet radiation from sunlight, or viruses. While cancers constitute an incredibly diverse and bewilderingly complex set of diseases, we have at hand the methods to identify essentially all of the genetic changes in a cell and to use that knowledge to rework the landscape of cancer research and cancer care, from basic science to prevention, diagnosis, and treatment. The funds in the President's budget for NCI represent a bold investment strategy critical for realizing that goal.

The emerging scientific landscape offers the promise of significant advances for current and future cancer patients, and for preventing cancer so that many never become cancer patients. And it offers scientists at the National Cancer Institute—and in the thousands of laboratories across the United States that receive NCI support—the opportunity to increase the pace of lifesaving discoveries dramatically.

In the past year alone, we have seen powerful

examples of how research dollars have translated into concrete advances against cancer through basic science, prevention and early detection, and treatment.

**Basic Science**

In collaboration with NHGRI, the NCI is leading The Cancer Genome Atlas (TCGA), the largest and most comprehensive analysis of the molecular basis of cancer ever undertaken. TCGA aims to identify and catalog all of the relevant genetic alterations in many types of cancer. For instance, building on their recent reclassification of glioblastoma multiforme (GBM), an aggressive form of brain cancer, this year TCGA investigators discovered that about 10 percent of patients with one of the four subtypes of GBM are younger at diagnosis and live longer than patients with other subtypes of the disease, but their tumors are unresponsive to current intensive therapies. The molecular profile of this subtype offers new targets for developing drugs to treat this form of the disease more effectively. TCGA scientists are also preparing to publish similarly important findings about the major form of ovarian cancer in mid-2011 and are in the midst of analyzing nearly 20 other types of cancer.

**Prevention and Early Detection**

NCI's intensive efforts to study and reduce the use of tobacco products have contributed to a sustained annual reduction in age-adjusted cancer mortality rates over the past decade and more. But current and former heavy smokers remain at high risk of developing lethal lung cancers, which are the leading cause of cancer mortality. In late 2010, NCI announced initial results from the National Lung Screening Trial, a large, multi-year randomized trial that enrolled more than 53,000 subjects. Because early detection provides the potential to intervene at the earliest, most treatable stages of disease, thus reducing potentially difficult to treat outcomes seen in more advanced disease, current and former smokers who were screened with low-dose helical computed tomography were 20 percent less likely to die of lung cancer than were peers who received standard chest x-rays**.** These results provide the first clear demonstration that a screening procedure can be effective in reducing mortality from lung cancer—a finding that could save many lives among those at greatest risk. Over the course of the $240-million study, NLST investigators collected samples of early and advanced lung cancers from enrolled subjects, and these specimens will be invaluable for determining genetic alterations that may be used to predict which tumors are likely to progress to an advanced stage.

**Cancer Treatment**

The potential therapeutic impact of basic discoveries made by TCGA and other efforts in cancer genomics has been dramatically illustrated this year by the development of effective drugs against the most deadly form of skin cancer, melanoma**.** Almost a decade ago, studies of cancer genomes first uncovered a common mutation in a gene that encodes an enzyme called BRAF. Last year, early stage clinical trials at NCI-designated Cancer Centers of drugs targeted against the mutant BRAF enzyme showed that most melanomas with the relevant mutation regressed dramatically. Although tumor regression generally lasted less than a year, NCI-supported investigators have already pinpointed some causes of resistance to BRAF inhibitors, outlining a pathway to more sustained control of this lethal disease.

Another benefit of a prolonged and broad-based investment in cancer research has also been realized in the context of malignant melanoma this year, with the recent approval by the FDA of an antibody, ipilimumab, which extends the lives of patients with metastatic melanoma. Ipilimumab stimulates the immune system to act against cancer by blocking natural inhibitors of the immune response, an approach that would not be possible without a profound understanding of the immune system and one that promises to harness immunological tools against other cancers.

These examples of NCI's progress in understanding, treating, and detecting different forms of cancer illustrate what can be achieved at an accelerated pace with sustained investments across the cancer research spectrum, such as proposed under the President's budget. While those perspectives are only beginning to inform the American public's perception about cancer and its treatment, the downward trajectory of cancer deaths – reported by NCI and its partners in March -- reflects real and sustained reductions over more than a decade for numerous cancers, including the four most common: breast, colorectal, lung, and prostate. We have identified proteins and pathways that different cancers may have in common and represent targets for new drugs for these and many other cancers—since so often research in one cancer creates potential benefits across others.

Additional progress against cancer also will require building these research advances into clinical treatments and diagnostic tools for better patient care and by our many connections with public and private sector partners. The Institute's investments in translational research are broad and deep, and will receive NCI's full energies, recognizing that the publicly

announced proposal for reorganizing services that support translational science in general could give NIH additional focus in this important area.

**Revitalizing the Cancer Clinical Trials System**

For today's new understandings of cancer biology to benefit cancer patients on a broad scale, they must be coupled with a modernized system for conducting cancer clinical trials. This system must enable clinical researchers across the nation to acquire tumor specimens and conduct genetic tests on each patient, to efficiently analyze molecular changes in those samples, to manage and secure vast quantities of genetic and clinical data, and to identify subsets of patients with tumors that demonstrate changes in specific molecular pathways—pathways that can be targeted by a new generation of cancer therapies.

As part of its effort to transform the cancer clinical trials system, NCI asked the Institute of Medicine (IOM) in 2009 to review the Clinical Trials Cooperative Group Program. This program involves a national network of 14,000 investigators currently organized into nine U.S. adult Cooperative Groups and one pediatric cooperative group that conduct large-scale cancer clinical trials at 3,100 sites across the U.S. The IOM report, issued in April 2010, noted that the current trials system—established a half-century ago—is inefficient, cumbersome, under-funded, and overly complex. Among a series of recommendations, the report urged that the existing adult cooperative groups be consolidated into a smaller number of groups, each with greater individual capabilities and with new means to function with the others in a more integrated manner.

In December 2010, NCI announced its intent to begin consolidating the current nine adult cooperative groups into four state-of-the-art entities that will design and perform improved trials of cancer treatments, as well as explore methods of cancer prevention and early detection, enhance the ability of the cooperative groups to assess the molecular characteristics of individual patients' tumors, and study quality-of-life issues and rehabilitation during and after treatment. The sole pediatric cooperative group was created by consolidating four pediatric cooperative groups almost a decade ago, and that group will not be affected by the current consolidation effort.

**Provocative Questions**

This has been a challenging and hopeful time for NCI to lead the nation's cancer research program. Over the past two decades researchers have unraveled some of the damage that occurs in the genome of a cancer cell and how a cancer cell behaves in its local environment as a result of those changes.

With this better understanding of cancer and recent technological advances in many fields, such as genomics, molecular biology, biochemistry, and computational sciences, progress has been made on many fronts, and a portrait has emerged for several cancers.

With sustained and accelerated funding, and NCI's strong leadership in defining cancer research priorities, we can build upon today's cancer advances with provocative thinking by asking better questions.

To that end, NCI is asking researchers in various disciplines to pose and articulate "provocative questions" that can help guide the nation's investment in cancer. Provocative questions may be built on older, neglected observations that have never been adequately explored, or on recent findings that are perplexing, or on problems that were traditionally thought to be intractable but now might be vulnerable to attack with new methods.

Many of these provocative questions are being asked–and answered – by young scientists who are early in their careers. The 2012 budget will support NCI's commitment to ensuring that an equitable share of our research grants will go to the young men and women, who are at the forefront of understanding cancer.

We are now reaping the rewards of investments in cancer research made over the past 40 years or more, even as we stake out an investment strategy to realize the potential we see so clearly for the future. The public has benefitted from past generous Congressional stewardship of biomedical research funding; cancer research over the past four decades has provided the evidence required to lower the incidence and mortality of many kinds of cancer, to improve the care of cancer patients, and to establish the new understanding of cancer that is now beginning to revolutionize control of cancer throughout the world.

No matter what the fiscal climate, NCI will strive to commit the resources necessary to bring about a new era of cancer research, diagnosis, prevention, treatment, and survivorship.

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*NCI News:*

## Varmus to be Keynote Speaker At Lung Cancer Partnership Meeting

**NCI DIRECTOR Harold Varmus** will be the keynote speaker at the **National Lung Cancer Partnership**'s annual meeting in Chicago, June 3.

Varmus will discuss the promise of the Scientific Revolution, and how lung cancer researchers can contribute.

Panel discussions include: The National Lung Screening Trial: Ramifications and Challenges Moving Forward, debating screening guidelines, minimally invasive surgical procedures, and advances in biomarker development; and State of the Art in Lung Cancer Treatment, discussing adaptive clinical trial designs, the MET signaling pathway, EGFR inhibitors and palliative care.

The full agenda for the meeting can be found here: http://www.nationallungcancerpartnership.org/downloads/Events/annual_meeting/2011_annual_meeting_agenda.pdf

**NCI** has elected new members to the steering committee of the **Public Affairs and Marketing Network**, a professional network of public affairs, marketing and communications officers at the nation's leading cancer centers. The following members were elected to two-year terms:

• **Theresa DiNardo Brown**, chief communications officer, The Ohio State University Comprehensive Cancer Center–James Cancer Hospital and Solove Research Institute

• **Lynn Clark**, communications manager, University of Colorado Cancer Center

• **Alicia Jansen**, associate vice president for marketing, MD Anderson Cancer Center

• **Bill Schaller**, director of media relations, Dana-Farber Cancer Institute

Members of the network represent NCI-designated comprehensive, clinical, basic and consortium cancer centers or academically based centers that are members of the Association of American Cancer Institutes.

The network meets each year in collaboration with a sister organization of cancer center fundraising officers, the National Association of Cancer Center Development Officers.

*In the Cancer Centers:*

## Columbia Recieves $1.35 Million From Komen and Conquer Cancer

**COLUMBIA UNIVERSITY** will receive a $1.35 million grant from the **Conquer Cancer Foundation** and funded by **Susan G. Komen for the Cure**, to lead a randomized trial of women receiving adjuvant hormone therapy for breast cancer, as part of the foundation's Improving Cancer Care Grant program.

To improve adherence to prescribed therapies, the women will receive text messages versus traditional follow-up care. The trial will also help establish a methodology for testing other intervention techniques to improve adherence in other cancers. The project is led by **Alfred Neugut**.

"The Improving Cancer Care Grant provides researchers with an opportunity to test real and practical solutions that ultimately improve patient care," said Martin Murphy, chair of the foundation's board of directors.

The foundation gave out two awards as part of its Diversity in Oncology Initiative. The initiative consists of the Loan Repayment Program and the Medical Student Rotation, offering funding to physicians who commit to practicing oncology in a medically underserved region of the United States for at least two years and to medical students with an interest in oncology who self-identify as minorities.

The Loan Repayment Program awardees include: **Jason Brown,** Yolanda G. Barco Oncology Institute; **Waina Cheng,** Lincoln Medical and Mental Health Center; **Sharyn Nan Lewin,** Columbia University Medical Center; and **Sarah Temkin,** University of Maryland.

The Medical Student Rotation awardees participate in 8- to 10-week rotations in oncology with a mentor oncologist who provides ongoing academic and career support.

This year's recipients are: **Marcela Augusta Azevedo,** The Ohio State University; **Mark Edmund Bernard,** University of Pittsburgh; **Christina Hunter Chapman,** University of Pennsylvania; **Kristina Lauren Demas,** George Washington University; **Tiffany George,** Meharry Medical College; **Sheri Jones,** University of Medicine and Dentistry of New Jersey; **Nicole Ashley Sample,** The City College of New York; and **Kimberly Michelle Thomas,** The University of Texas.