THE CANCER LETTER

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NEJM Says Henschke Conflicts Irrelevant; Propriety Of Granting CME Questioned

By Paul Goldberg

The study claiming dramatic benefits of computed tomography screening for lung cancer had the look of a landmark in medicine. The conclusion that a regimen of low-dose spiral CT scans could make lung cancer a curable disease was its most astounding feature.

More than a year after publication, the paper reporting the results of a single-arm trial by the International Early Lung Cancer Action Program is becoming a landmark of a different sort as its publisher, The New England Journal of Medicine, stands confronted with reports that the study's principal authors were named as inventors on one issued U.S. patent and 26 patent applications worldwide, and that the first of these inventions was licensed by the leading manufacturer of CT scanners in 2001 (The Cancer Letter, Jan. 18).

Yet, the disclosure statement on the paper published in the Oct. 26, 2006, issue of the journal reads: "No potential conflict of interest relevant to this article was reported."

The I-ELCAP paper endorsed changing medical practice to include

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ESA Controversy:

ODAC Advice: Avoid ESAs In Curative Settings, Require Patients To Sign Informed Consent

By Paul Goldberg

The FDA Oncologic Drugs Advisory Committee said erythropoiesis stimulating agents shouldn't be given to patients receiving potentially curative treatments.

At the meeting March 13, the committee that provides clinical advice to the agency voted 11-2 with one abstention not to expose patients to ESAs in the adjuvant and neo-adjuvant settings.

The meeting was convened in response to a neo-adjuvant breast cancer study and a cervical cancer study that found inferior results in patients receiving ESAs (The Cancer Letter, Dec. 7, 2007).

In other highlights:

—The committee voted 9-5 to exclude breast and head-and-neck cancers from the label.

—Voting 8-5 with one abstention, the committee recommended requiring administering informed consent procedures to every patient placed

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Grassley: Patents, Royalties Need Congressional Scrutiny

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screening based on the group's protocol, which, in turn, relies on technologies that are similar if not the same as those protected by the patents. Some of these inventions have tangible commercial value: GE Healthcare licensed a technology for interpreting scans, and PneumRx Inc., a California start-up company, licensed a biopsy needle.

Did the authors fail to disclose relevant conflicts to the New England Journal? Did the journal make a mistake?

After sifting through the files, the NEJM editors issued a statement: "The editors and authors followed standard editorial procedures on disclosure. The authors disclosed all potentially relevant information, including patents pending to the editors, and the editors reviewed this information in the light of the content of the article. Because it was not considered to be directly relevant to the point of the article, it was not published."

Asked to elaborate on the journal's criteria for determining relevance of conflicts, Karen Pedersen, a spokesman for NEJM, said that the editors "felt that the disclosures were not relevant to the outcomes of the paper, as the technology wasn't being tested or required to be used."

Disclosure rules vary from journal to journal. However, in the case of the I-ELCAP article, NEJM granted continuing medical education credit to any physician who read it and answered three questions. By acknowledging that they had known about the authors' intellectual property, the NEJM editors in effect invited scrutiny of their criteria for determining relevance in the context of CME.

The purpose of CME is to improve the practice of medicine, and disclosure is the central element in the system of safeguards designed to prevent business interests from influencing information presented to physicians. Formulated by an organization that accredits CME providers, these standards are explicit and close to uniformity.

Cancer experts and advocates of better disclosure in medical research said they disagreed with the journal's decision. "More disclosure is always better when it comes to accountability," said Sen. Chuck Grassley (R-Iowa), ranking member of the Senate Committee on Finance, whose investigations of pharmaceutical companies frequently focus on abuses of CME. "It's becoming clear that patents and royalty payments to doctors deserve a lot more scrutiny from Congress, the FDA, professional journals, and other watchdogs. I intend to do my part of this oversight."

Merrill Goozner, director of the Integrity in Science Project of the Center for Science in the Public Interest, said his group may file a complaint against NEJM with the CME accreditation authorities. "The New England Journal of Medicine appears to have adopted a standard of relevance that makes mockery of the disclosure requirement," Goozner said. "Because this was a CME activity, this appears to clearly violate the Accreditation Council for Continuing Medical Education guidelines on conflict of interest disclosure for approved CME activities. We are investigating the possibility of filing a complaint with ACCME."

The journal's editors stand by the decision to provide CME credit for the paper "because the questions were about the paper, not the screening field," Pedersen said.

The NEJM CME program is run by the Massachusetts Medical Society, which also publishes the journal.

Inconsistent Disclosure

The Cancer Letter reviewed the disclosures the I-ELCAP principal investigator and Weill Cornell Medical College radiologist Claudia Henschke made at lectures and in publications that award CME credit. A table summarizing these disclosures from Oct. 26, 2006, through Feb. 12, 2008, appears on p. 3.

Unlike the NEJM editors, scientists who organize CME events where Henschke delivered lectures or

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Date	CME Lecture or Publication	Disclosure	Title of Paper or Event	CME Accreditation
Oct. 26, 2006	New England Journal of Medicine	**No conflicts**	Survival of Patients With Lung Cancer Detected on CT Screening	ACCME, Mass Med Society
Nov. 29, 2006	Radiological Society of North America and American Association of Women Radiologists	**Eastman Kodak Co. consultant**	Lung Cancer Screening and Coronary Artery Disease Screening: The Present and the Future	ACCME
April 16, 2007	American Association for Cancer Research	**No conflicts**	Forum: Controversies in Lung Cancer Screening	ACCME credit awarded jointly with Vanderbilt University
June 1, 2007	Center for Biomedical Continuing Education/National Lung Cancer Partnership Annual Meeting	**General Electric royalty**	CT Screening for Lung Cancer-- What More Do We Need to Know?	ACCME
Aug. 16, 2007	Centers for Disease Control 2007 Cancer Conference	**No conflicts**	CT Screening for Lung Cancer: Update 2007	ACCME
Sept. 3, 2007	International Association for the Study of Lung Cancer	**No conflicts**	Meet the Professor; International Early Lung Cancer Action Program	ACCME
Oct. 26, 2007	5th Annual Atlanta Lung Cancer Symposium	**No conflicts**	Low Dose Spiral CT-Scan in Early Diagnosis of Lung Cancer	ACCME
Feb. 1, 2008	The Oncologist	**No conflicts**	CT Screening for Lung Cancer: Update 2007	ACCME, provided through University of North Carolina
Feb. 12, 2008	Brigham and Women's Hospital Sosman Lecture	**General Electric royalty**	CT Screening for Lung Cancer: Update 2008	ACCME

Henschke's conflict of interest disclosures at CME events varied. Her most commonly used declaration was "no conflicts."

engaged in debates said they weren't aware of her conflicts until reading about them in the Jan. 18 issue of The Cancer Letter.

Had these business interests been brought to their attention, they would have been deemed highly relevant. "I think the NEJM article and what Dr. Henschke has been presenting is clearly related to her patents and royalties," said Paul Bunn, executive director of the International Association for the Study of Lung Cancer, which invited Henschke to speak at a conference in Seoul, Korea, last year.

According to the ISLAC conference documents, Henschke disclosed that she had no conflicts.

Disclosure alone isn't sufficient at CME events. To resolve or manage conflicts, presenters can be steered to areas where their business interests aren't relevant. For example, a physician who holds patents for a lung cancer diagnostic might be asked to speak about the natural history of lung cancer rather than the technologies she invented. However, conflicts can be managed only when proper disclosure is made.

NEJM appears to be the only CME provider to dismiss Henschke's conflicts. A month after the NEJM publication, Henschke spoke at a CME event sponsored by the Radiological Society of North America, where her disclosure didn't mention GE, but did mention a consulting arrangement with Eastman Kodak.

"The Eastman Kodak disclosure was the only one provided to RSNA by Dr. Henschke," said Linda Brooks, a spokesman for the society. "RSNA never withholds relevant disclosure information, i.e., any disclosure involving a commercial entity. GE would fall into this category." RSNA doesn't accept commercial sponsorship for its CME activities, Brooks said.

Bruce Chabner, editor-in-chief of The Oncologist, a journal that published a paper by Henschke and collaborator David Yankelevitz, also of Weill Cornell, said the patents were relevant to the papers published by NEJM and his journal.

"If you believe the content of these articles, it's clear that both the biopsy needle and the software would be positively affected as commercial items," said Chabner, clinical director of the Massachusetts General Hospital Cancer Center. "If I stand to profit as a result of my article, that ought to be disclosed. This article would greatly broaden the use of CT scanning for screening. They are advocating an intervention, and they own a stake in it."

In CME disclosure forms submitted in conjunction with the paper published in the February issue of The Oncologist, Yankelevitz and Henschke reported that they had no conflicts of interest. However, a month earlier, in the January issue of the journal Radiology, Yankelevitz disclosed that he was "a consultant for PneumRx (Mountain View, Calif.) and receives royalties from Cornell University from a licensing arrangement for patented technology with General Electric."

Henschke isn't a party to the licensing agreement with PneumRx. Her disclosures were similarly inconsistent: she disclosed the GE licensing agreement

at a June 1 CME event, declared that she had no conflicts at three subsequent events in 2007, then once again declared GE at a CME lecture last month. A copy of her disclosure slide from that presentation, at the Feb. 12 lecture at Brigham & Women's Hospital in Boston, appears on p. 5.

Henschke, Yankelevitz, Weill Cornell officials, and GE declined to discuss the details of their licensing agreement. However, The Cancer Letter has learned that the agreement with GE was made in 2001.

The patent licensed by the company describes three-dimensional image rendering of nodules and is used in its VCAR products, The Cancer Letter learned. A description of VCAR is posted at http://www.gehealthcare.com/usen/ct/clin_app/products/lunganalysis.html. It's not publicly known whether the company has licensed any of the group's other pending patents, some of which appear to be related to the VCAR technology.

Henschke's and Yankelevitz's presentations and publications don't recommend CT screening in general. They recommend a specific regimen based on their protocol. I-ELCAP leaders and their critics would agree on one point: the group's 3-D analysis of nodules—as opposed to two-dimensional technology—is the fundamental feature of the I-ELCAP protocol.

"CT screening according to the I-ELCAP regimen can detect clinical stage I lung cancer in a high proportion of persons when it is curable by surgery," the group writes in the NEJM paper. This reference to the protocol is followed by the paper's most prominent claim: "In a population at risk for lung cancer, such screening could prevent some 80 percent of deaths from lung cancer."

"The product wasn't expressly identified in the articles—no one talked about the software and the biopsy needle—but their work, if correct, would lead to an expanded need for biopsies and for analysis of nodules," Chabner said, referring to the papers in NEJM and in his journal. "So it's in the field of interest, if not specifically mentioned. It's relevant."

After learning about the conflicts, Chabner wrote to Henschke and Yankelevitz, who acknowledged that they held patents, but argued that since their technologies weren't specifically mentioned in the paper published in The Oncologist, they had no obligation to disclose.

John Minna, a lung cancer expert who moderated a CME session at the 2007 annual meeting of the American Association for Cancer Research, said the audience at that event would have benefited from knowing that Henschke was listed as an inventor on a patent licensed to produce a GE scanning system.

"That's the whole reason for disclosing a conflict, to allow people to make an interpretation of what's presented with that fact in mind," said Minna, a professor at the University of Texas Southwestern Medical School. "I didn't review the forms to see what she declared or didn't declare, but the presumption is that if there is a chance of a conflict of interest, it would be disclosed in written format, or, if necessary, verbal format. In any event, if there is a potential conflict of interest, one wants to err on the conservative side of disclosing things."

Jerome Kassirer, a professor at the Tufts University School of Medicine and former editor of NEJM, wrote in a Feb. 8 OpEd piece in the Boston Globe that Henschke's and Yankelevitz's conflicts were relevant to the I-ELCAP paper.

Though he stopped short of criticizing or even naming NEJM, Kassirer pointedly described I-ELCAP as a "self-selected consortium of radiologists" who "published an uncontrolled study of early detection in which they claimed to cure more than 90 percent of lung cancers; an astonishing rate."

Why would these people push to change the standard of care to include CT screening?

"Perhaps they were true believers, convinced that their interpretation of the evidence would provide a great benefit for humanity, and impatient with the sluggishness of the big professional societies as well as the snail's pace by which physicians often change their practices," Kassirer wrote. "Perhaps.

"But given the expansion of privately owned CT scanners in the country, and the possibility of a reimbursement bonanza for such procedures, another… explanation is possible, namely a profit motive. Such a motive became more credible when [The Cancer Letter] found that the two lead investigators of the lung cancer study held 27 patents on procedures for CT screening and lung biopsy procedures."

The article is posted at www.boston.com/news/health/articles/2008/02/08/stemming_the_craze_on_ct_scans/.

Henschke, Yankelevitz and Weill Cornell officials didn't respond to questions The Cancer Letter submitted to them repeatedly since Jan. 15, and similarly didn't respond to a request for an explanation of discrepancies in Henschke's disclosures at CME events.

CME Programs Require Patent Disclosure

Lecturers at CME events and authors of journal papers that offer CME credit are expected to disclose

any relationship with commercial interests that has produced a benefit "in any financial amount" over 12 months preceding to the educational event.

"Intellectual property rights" are specifically included in the definition of financial relationships. A summary of the CME conflict of interest requirements is posted at http://www.accme.org/dir_docs/doc_upload/dc0e76c4-16bd-4b78-819b-912ff57ca936_uploaddocument.pdf.

Murray Kopelow, ACCME chief executive, said that disclosure of intellectual property has been required since 2005. "Ownership of the patent and the potential for royalties establishes a financial relationship with a commercial interest," Kopelow said in an e-mail explaining the council's policies, but not addressing the specifics of the I-ELCAP case.

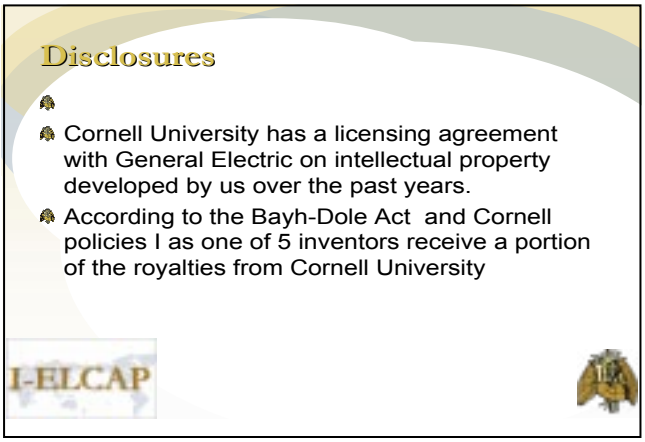
"The relationship is relevant in CME only if the content of the CME being developed is about the product or service from which royalties are generated," Kopelow wrote. "If the CME is about the product, then the CME provider needs to know about the financial relationship, and the provider needs to take steps to resolve, or manage, the conflict of interest that ensues. Also, learners need to be informed about this relevant financial relationship prior to the education being delivered to the learners."

In the case of I-ELCAP leadership, all but one of the inventions—the biopsy needle—have been assigned to Cornell Research Foundation, which has the licensing agreement with GE. Kopelow said that in the context of CME, arrangements where a patent is assigned to the inventor's institution should be disclosed.

"Royalties by themselves establish the financial relationship of the person with a commercial interest and create the potential for conflict of interest," he said. "Therefore, the relationship is relevant in CME. The name of the firm that licenses the invention needs to be disclosed."

Even in cases where a patent is pending, a disclosure should be made. "Having applied for a patent would still be relevant to conflict of interest and disclosure in CME," Kopelow said. This standard, too, has been in place since 2005.

ACCME's goal is to bring providers into compliance rather than to impose penalties. However, the group has the capacity to mandate costly audits and "self-studies," and, in extreme cases, it can revoke accreditation. Providers are responsible for managing the conflicts on the part of presenters, who can be barred from future appearances for failure to disclose conflicts or presenting biased information.



Henschke's disclosure slide at a CME lecture at Brigham and Women's Hospital Feb. 12. She declared that she had no conflicts of interest in four previous CME settings.

"Do You Want to Change This Form?"

The issues of The Oncologist were printed when Chabner read in The Cancer Letter that Henschke and Yankelevitz held patents for screening technologies. Immediately, he placed an editor's note on the journal's web site and stopped availability of CME credits.

"CME is about education of students and oncologists," Chabner said, describing his concern about introducing commercially biased information into medical practice. "Screening in that paper is being promoted as a standard."

Bunn said IASLC is contemplating corrective actions. "This will be brought to the attention of the board at the next meeting in April, and they will have to decide what to do," said Bunn, director of the University of Colorado Cancer Center.

Most likely, the group will start by contacting Henschke. "I would probably send Claudia the disclosure policy and say, 'Do you want to change this form?'" Bunn said. "If she changes it, we would send it to all the attendees at the meeting. If she doesn't change it, we would have to send all the attendees some information.

"We have never had a situation where we policed disclosure—until now," Bunn said. "This is the first instance when anything has been brought to our attention. Clearly, this should have been disclosed."

Fadlo Khuri, co-chairman of the Atlanta Lung Cancer Symposium, where Henschke declared that she had no conflicts, said he is evaluating the proper course of action.

"We would do what's appropriate, but we need guidance here, and it's not clear where to turn for that guidance," said Khuri, chairman of the Department of

Hematology and Medical Oncology at Emory University School of Medicine and the Roberto C. Goizueta professor of cancer research. "I've run meetings on four continents, and I don't know what the right corrective actions are."

Khuri agrees that the patents and licensing agreements should have been disclosed.

"This is the standard I expect: Thought leaders drive practice, they are disproportionally influential, and it's incumbent upon them to act as leaders and be as open as they possibly can," he said. "The most important thing for us to have as physicians and thought leaders is our credibility. Declaration of the conflicts is a bare minimum. If we don't have open declaration of the conflicts, we don't know where to go."

Tracy Miller, executive director of the Center for Health and Pharmaceutical Law at Seton Hall Law School, said disclosure of potential conflicts should be made both to the CME providers and to the audiences.

"I am not familiar with the particular facts of this case, but in general ACCME requires presenters to disclose relevant financial relationships to the audience and to the organization that is running the CME program," Miller said. "ACCME defines financial relationship broadly, including a financial benefit in any amount in the prior 12 months that creates a conflict of interest for the presenter."

Michael Clark, a former federal prosecutor and a healthcare attorney with the firm of Hamel, Bowers & Clark in Houston, said he is surprised by NEJM's criteria for determining relevance.

"I simply cannot fathom how the NEJM can take the position that disclosing a potential conflict of interest isn't necessary," Clark said. "Lawyers are cautioned as part of the ethics rules to avoid even the appearance of impropriety. The familiar and long-standing principle of informed consent means what it says despite whatever gloss the NEJM's current cognoscenti want to put on their troubling decision.

"Even learned intermediaries, such as physicians, cannot fully evaluate the merits of such matters unless they are provided with the facts to independently evaluate whether the otherwise hidden relationships—direct or indirect—may affect the facts being represented," Clark said. "I am, frankly, amazed that this issue is being presented in light of the reputation of this venerable journal, particularly in this age of transparency and heightened awareness of the importance of ethics and developing strong cultural values within organizations."

Patented Inventions Embedded In Protocol

Patients decide to get screened for many reasons.

Some worried smokers might have been intrigued by an ad on the side of a New York bus or a roadside billboard south of Baltimore. Others may have been swayed by publicity that followed the NEJM publication or convinced by a doctor who might have heard Henschke speak at Brigham & Women's Hospital.

Whatever the path, these patients aren't merely choosing to get a scan. They opt into a healthcare system where the I-ELCAP protocol either dictates or merely points to reliance on technologies patented by Henschke, Yankelevitz and several of their collaborators.

The protocol, as described in the NEJM paper, pegs medical decisions to changes in sizes of nodules detected through scans. While early monitoring is performed at centers that enroll patients, when the rate of growth of a nodule starts to suggest malignancy, the scan can be transmitted electronically to the I-ELCAP Coordinating Center at Weill Cornell, where it can be analyzed based on the group's in-house, three-dimensional "volumetric" technology.

Is this the same technology as the VCAR system for which Henschke, Yankelevitz and Cornell receive royalties from GE? Is it compatible with other volumetric analysis software on the market? Is volumetric analysis superior to 2-D analysis? Has this in-house system been used consistently through the history of I-ELCAP?

The protocol, posted at http://www.ielcap.org/professionals/protocols.html, doesn't answer these questions, and neither does the NEJM paper. This absence of information is remarkable, considering that protocols usually offer considerable detail about interpretation of radiographic evidence.

I-ELCAP requires that participating centers "deploy the ELCAP web-based management system for CT screening for lung cancer, and in this framework… submit the research data [including] images." These centers "register" further information on the screened patients, the outcome of screening, the workup pursued, and the outcome of diagnosed patients.

These functions appear to be tied in with three pending U.S. patents: 20060026040 (System and Method for Providing Remote Analysis of Medical Data); 20060026034 (System and Method for Conducting a Clinical Trial Study); and 20060059145 (System and Method for Analyzing Medical Data to Determine Diagnosis and Treatment).

If a center encounters a nodule measured 5 to 14 mm in diameter, the authors state in the NEJM paper

that "the preferred option was to perform another CT at 3 months [to assess growth rates]."

The key to assessing growth rates is to determine the change in size of the nodule. This corresponds with methods covered in patents and detailed in the I-ELCAP protocol itself. For example, the patent licensed by GE (US7274810) describes "a method of estimating volumetric doubling time of an object which changes size."

Similarly, pending patent 2070100226 covers "an automated method for… estimating a change in size by comparing the first and second apparent lesion sizes," and pending patent 20040184647 covers "a method for analyzing a computed tomography scan of a whole lung for nodules."

When it comes to the assessment of growth, the I-ELCAP protocol notes:

"Short-term assessment of growth, based on CT images, includes consideration of whether the rate of growth is consistent with malignancy. In this assessment, [a participating screening site] has access to collaboration with the Coordinating Center [at Weill Cornell], upon electronic image transmission provided by the web-based management system of the I-ELCAP."

The protocol emphasizes the primacy of the I-ELCAP software for three-dimensional nodule growth rate assessment:

"With careful technical and clinical quality review, as outlined below, the results of computer analysis [of volume changes in nodules] are useful in guiding the workup. The following guidelines have been developed as a result of the evaluation of our in-house software…."

The patent licensed by GE echoes this point, referring to the I-ELCAP protocol: "The cornerstone of the I-ELCAP study is the use of computed tomography (CT) for the detection of small pulmonary nodules and the use of early-repeat CT (ERCT) for evaluation of these nodules, by high-resolution computed tomography (HRCT).

The value of exclusive reliance on 3-D nodule assessment isn't necessarily clear to lung cancer experts.

"I'm not sure how much this would necessarily add to the evaluation, compared to another modality, e.g. PET scan, for further assessing the nodule, or whether or not it would give you that much more additional growth information compared to routine comparison of CT scans," said Andrew Yee, an oncologist who specializes in lung cancer at Massachusetts General Hospital. "On the other hand, perhaps this 3-D visualization approach may be able to spare the patient the inconvenience of undergoing a PET scan. Ultimately, could these screening follow-up CTs be adapted to conventional patient care and done without 3-D nodule assessment and without requiring patented technology? Probably yes."

When abnormalities persist, the I-ELCAP protocol promotes one specific approach to obtaining a tissue diagnosis: "As the biopsy procedure, CT-guided percutaneous transthoracic fine-needle aspiration should be used, as this is a 1-hour minimally invasive outpatient procedure. If this is not feasible, video-assisted thoracoscopic biopsy can be used," the protocol states.

Yankelevitz is an inventor on US patent application 20060167416, which covers a "Steerable Device for Accessing a Target Site and Methods." This invention has been licensed by a company, which, according to some of Yankelevitz's disclosures, gave him stock and employed him as a consultant. A joystick-operated biopsy needle is described on the company's website: http://www.pneumrx.com/prod_anim.html.

"Inevitably, because of the nature of screening, there will be many more workups of detected pulmonary nodules of uncertain significance," said Barnett Kramer, NIH associate director for disease prevention and member of the executive committee of the National Lung Screening Trial, a $200 million randomized trial comparing CT with chest x-ray. "Dr. Henschke has reported an algorithm to work up those nodules that she states enabled her group to avoid unnecessary workup.

"However, that approach has not been compared head-to-head with other approaches," Kramer said. "Since current evidence does not establish superiority of one published algorithm over another, each radiologist and treating physician must use his or her best judgment."

Peter Bach, a pulmonary and critical care physician and a member of the Health Outcomes Research Group in the Department of Epidemiology and Biostatistics at Memorial Sloan-Kettering Cancer Center, agrees.

"The concern here is not whether the protocol deviates from the standard of care," Bach said. "The real issue is that screening begets nodule detection, and so a reasonable person might conclude that an expansion in screening would lead to opportunities for their nodule finding and measuring software, as well as their biopsy needle."

The I-ELCAP leaders appear to be aware of commercial applications of their inventions, particularly

if CT screening using their protocol is adopted worldwide.

"As a result of the inventors having the perspicacity to think and analyze based on three-dimensional vision, new methods and corresponding systems are now available for use in various applications," they state in the patent licensed by GE. "As the expected widespread acceptance of CT screening for early detection of lung cancer increases, computer-aided tools should play a prominent role in the early detection, characterization, and cure of lung cancer in many thousands of patients around the world."

Unapproved Uses: "Not Applicable"

Before delivering the Sosman Lecture at Brigham & Women's Hospital on Feb. 12, Henschke filled out a standard Harvard Medical School form that asked her to respond to the following statement:

"If I am discussing any drug/product use that is off label, I will disclose that the use or indication in question is not currently approved by FDA."

Henschke was asked to check off one of three boxes: "Agree," "Disagree," and "Not Applicable." She checked off "Not Applicable."

FDA officials would disagree with her choice. "No data have been presented to the FDA to demonstrate that these devices are effective for screening, i.e., testing individuals without symptoms," the agency states on its website. "Before FDA would allow such a claim or indication for use by the manufacturer, the manufacturer would have to provide valid scientific data for such a new use by submitting a pre-market approval application for this new indication. This means that manufacturers of CT imaging systems cannot make claims that the products are intended to be used for screening non-symptomatic individuals. Nevertheless, individual physicians may decide that a patient without symptoms can benefit from screening with CT, even though data supporting such a use has not been submitted to the agency. Such use of a medical device is referred to as 'off-label' use and is a judgment left to physicians."

Ironically, physicians who are skeptical about the value of CT screening for lung cancer have been making disclosures about the procedure's regulatory status.

At the 2007 CDC Cancer Conference, Bach and H. Lee Moffitt Cancer Center researcher Gerold Bepler disclosed that they would be discussing an "unlabeled use of a product or a product under investigational use."

Henschke, who appeared at that CME event to argue for screening, made no such declaration.

This is more than a fight over an obscure regulatory fine point. While, doctors are free to gather at hospital canteens and CME lectures to discuss unapproved uses of drugs, companies are more limited.

To prevent even the appearance of doctors speaking of unapproved uses on behalf of business interests, many CME providers including Harvard and the Massachusetts Medical Society, ask speakers to disclose whether they would be describing unapproved uses. Though this information isn't always included in disclosure alongside financial interests, it helps providers manage disclosed conflicts.

The I-ELCAP protocol refers to CT screening as "an experimental regimen of early diagnosis." The Cancer Letter obtained a copy of an informed consent form used at one I-ELCAP site. That document states that "the CT examination as such, is not an experimental procedure." However, the consent form continues, "in your particular case, this albeit standard examination is performed for the purposes of research only [and] it is not part of standard care."

FDA rules on dissemination of information on off-label use allow company reps to hand out unaltered reprints from peer-reviewed journals. However, these materials have to contain disclosure of conflicts of interest and biases on the part of everyone involved in their publication. A summary of the agency's recent proposed guidance on the subject is posted at http://www.fda.gov/bbs/topics/NEWS/2008/NEW01798.html

Nonetheless, GE has been distributing a marketing brochure that contains a case study of a 57-year-old man who took part in Depiscan, a randomized French lung cancer screening trial for heavy smokers. According to the brochure, the man's pulmonary adenocarcinoma was diagnosed with the help of VCAR technology.

The brochure is not a reprint from a journal. It fails to state that the case study involves an unapproved use of the device, cites no published materials, and contains no disclosure. The copyright on the document belongs to GE Healthcare and is dated 2005.

After a reporter raised questions about the case study, GE said it would withdraw the brochure. "We need to scrutinize the language in this piece further and are having it pulled off our website while we do," Corey Miller, a spokesman for the company, said in an e-mail. "Please know that we take these matters very seriously and do not engage in off-label promotion. Thank you for bringing this to our attention. Please let us know if you find any other questionable material on our website." Within 24 hours, the brochure disappeared from the

company's website.

Sidney Wolfe, director of the Public Citizen Health Research Group, said GE's assessment of the marketing document shouldn't require much effort. "If they handed out the New England Journal article, it would be something else," Wolfe said. "But here the company is handing out a brochure that constitutes illegal off-label promotion, and FDA should stop it."

Former prosecutor Clark said that overall, Henschke's inconsistent disclosures and the company's case study create a "disconcerting appearance."

"When researchers appear at CME meetings to push an off-label use of a technology without disclosing that they receive royalties from the manufacturer of that technology, some very important boundaries are crossed," Clark said. "When the company in question fails to comply with FDA rules to promote that same unapproved use, it crosses a boundary as well.

"I'd hate to think the company and the researchers are collaborating in their promotional efforts."

ESA Controversy:

Studies Don't Justify Dropping Oncology Indication For ESAs, ODAC Advises In 13-1 Vote

(Continued from page 1)
on ESAs.

However, the committee voted 13-1 against withholding the agents' cancer indication altogether, and, in a 10-2 vote with one abstention, recommended against placing the drug in a restricted distribution system. The group split 8-6, voting against limiting the agents' use to just one indication, small-cell lung cancer.

On March 7, FDA and the ESA sponsors Johnson & Johnson and Amgen Inc. announced that additional warnings would be placed in the agents' label. "ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers when dosed to target a hemoglobin of greater than or equal to 12 g/dL," the new warning reads.

Companies say utilization of ESAs has dropped by more than half over the past year.

FDA has no deadline for making additional changes based on ODAC advice.

A detailed story about the committee discussion will appear in next week's issue of The Cancer Letter.

NIH Advocacy:

Flat Budget Threatens Future Of Research, Universities Say

Five consecutive years of flat funding for NIH is deterring promising young researchers and threatening the future of Americans' health, a group of seven academic research institutions warned this week.

In a report, the six research universities and a major teaching hospital described the toll that cumulative stagnant NIH funding is taking on the American medical research enterprise. The institutions warned that if NIH does not get consistent and robust support in the future, the nation will lose a generation of young investigators to other careers and other countries and, with them, a generation of promising research.

At a March 11 hearing of the Senate Committee on Health, Education, Labor and Pensions, Harvard University President Drew Gilpin Faust said the flat NIH budget is taking a "significant toll" on biomedical research, particularly for young investigators.

"This is a real problem, discussed at almost every meeting one attends on campus, that can't be simply dismissed," Faust said. "This is about the investment that America is—or is not—making in the health of its citizens and its economy. Right now, the nation's brightest, young researchers, upon whom the future of American medicine rests, are getting the message that biomedical research may be a dead end and they should explore other career options—and in too many cases, they're taking that message to heart. The President's latest budget proposal that calls for another year without an increase will only make the problem worse."

The biomedical research advocates urged Congress to support a 6.7 percent increase for the NIH budget for fiscal 2009.

The report, "A Broken Pipeline? Flat Funding of the NIH Puts a Generation of Science at Risk," was co-authored by Brown University, Duke University, Harvard University, Ohio State University, Partners Healthcare, the University of California Los Angeles, and Vanderbilt University.

The report profiles 12 junior researchers who, despite their qualifications and noteworthy research, attest to the funding difficulties that they and their professional peers are experiencing. These researchers are devising new ways to manipulate stem cells to repair the heart, revealing critical pathways involved in cancer and brain diseases, and using new technologies to diagnose and treat kidney disease.

The 20-page report follows up on a related report

released by a group of academic institutions last year, "Within Our Grasp—Or Slipping Away? Assuring a New Era of Scientific and Medical Progress." That report, issued by a similar group of nine institutions, showed how stagnant NIH funding was slowing discovery and squandering significant opportunities.

The new report focuses on the effect that recurring flat funding is having on young researchers in particular. Junior researchers—typically assistant and associate professors who are trying to establish their own research laboratories—are getting a much smaller piece of the NIH funding pie to conduct their medical investigations, the report says. However, competition for limited resources is affecting scientists at every point of the academic research pipeline.

Between 1998 and 2003, the Clinton and Bush Administrations and Congress doubled the budget of the NIH. In 2003, the budget increases stopped and, since then, the NIH has experienced a 13 percent drop in real purchasing power. As a result, researchers' ideas are stuck at a toll-gate that allows one in 10 grants to be funded upon first submission. Rejected grants that must be revised and resubmitted are clogging the system, creating a queue in which young researchers feel they are at the back of the pack, the report said.

"There's been a lot of discussion in the last year about the negative impact of the tight NIH budget on senior researchers and their labs," said Robert Golden, dean of the University of Wisconsin School of Medicine and Public Health. "But it appears that junior investigators may be having the toughest time in this fiscal climate. They are competing for funding with established researchers, who are their mentors, and finding that the financial support just isn't there, or that they can't afford to support themselves while writing and rewriting grant proposals."

"The feedback I received from one reviewer was that my ideas were 'very innovative and had the potential to make a big impact, but they were too risky,'" said Tricia Serio, assistant professor, Department of Molecular, Cellular Biology, and Biochemistry, Brown University. "To succeed in reaching our goals, we need the freedom to try risky things, to develop new approaches and techniques." Serio's research is focused on progressive brain diseases, including Alzheimer's, Huntington's, Parkinson's, and Creutzfeldt-Jakob. She was named one of America's top biomedical researchers by the Pew Charitable Trusts in 2003.

Fewer resources means that NIH is experiencing a backlog in high-quality research proposals, and too few are getting funded. The overall success rate for NIH research project grants dropped from 32 percent in 1999 to 24 percent in 2007. Only about one in four original research applications to the NIH is being funded, and many of those are only partially funded, and only after lengthy delays and cumbersome reapplications.

"Reviewers told us we have good data, a strong team, and well-thought-out experiments. We didn't get funded just because there were others going for their second and third round who were waiting in line," said Jill Rafael-Fortney, associate professor in the Department of Molecular and Cellular Biochemistry at Ohio State University, who is working on a new treatment for heart failure.

The report offered some statistics on the effect of flat funding on research:

• In 1990, young researchers received 29 percent of R01 grants. By 2007, that dropped to 25 percent.

• While the success rate has dropped for all R01 applicants, it is only 18 percent for first-time applicants.

• First-time R01 recipients also are older. The average age is now 43, up from 39 years in 1990.

Scientists who review NIH proposals have become more conservative when judging the merits of funding research projects. They are demanding more evidence of eventual success of proposed theories prior to approving funding and inadvertently changing the way science is being conducted, discouraging innovative, big ideas in favor of safer approaches for incremental progress to scientific discovery.

"With this tight funding situation, I've stepped away from the riskier stuff," says Pampee Young, assistant professor of Pathology, Vanderbilt University. "My salary and that of everyone in the lab is dependent on my getting grants. You become very savvy to what is fundable." Toung's research is focused on using adult bone marrow stem cells to block the growth of tumors and to also repair damaged heart muscle.

Anil Potti, an assistant professor of Medicine at Duke University who works on lung cancer diagnosis and treatment, said the funding situation is hurting patients who are looking to research to help with their conditions. "I don't worry about the difficulty of getting funding from NIH for myself. I worry more about what it means in terms of patient care. The whole [grant] cycle can take 12-18 months, and that's if you're successful on the first or second try. In the meantime, I'm seeing patients every day who could benefit from this research."

The report is available at www.brokenpipeline.org.

In the cancer Centers:

Fox Chase Awards Funding To Four Research Teams

FOX CHASE CANCER CENTER announced the first four awards in a new research program designed to bring the power of team-based science to bear on significant questions in cancer research.

Selected after a competitive external peer-review process, each of the new Keystone Programs for Collaborative Discovery will receive at least $5 million in support over five years. The funding will come primarily from new sources, including Fox Chase's Board of Directors and private philanthropy. Additional Keystone Programs are in development and will be added to the portfolio as soon as is feasible.

"The Keystone Programs for Collaborative Discovery represent an unprecedented reimagining of Fox Chase's research enterprise to seize the opportunities for progress against cancer unique to this moment in scientific history," said Michael Seiden, president and CEO of Fox Chase.

"In launching the Keystone Programs, Fox Chase Cancer Center is making a remarkable institutional commitment to promoting team-based research to accelerate discovery in cancer medicine," Seiden said. "The scope of our investment in this program is unusual and may well be unique among academic research centers."

In recent years, federal agencies funding biomedical research have recognized the importance of multidisciplinary team-based strategies for solving disease problems. Funding mechanisms intended to support this kind of research include the Program Project Grants (P01) sponsored by NIH and the Specialized Programs of Research Excellence (SPORE) supported by NCI.

Twelve proposals for Keystone Programs funding were submitted by teams of Fox Chase researchers. An external scientific advisory panel of 16 cancer scientists and clinicians reviewed the proposals. The panel also traveled to Fox Chase to listen to presentations by the proposal teams. The first four Keystone Programs for Collaborative Discovery are:

—The Keystone Program in Personalized Risk and Prevention, to discover molecular markers that predict cancer risk and to develop risk reduction strategies tailored to the profile and personal values of the individual. Leader: **Mary Daly**. Co-Leader: **Margie Clapper**.

—The Keystone Program in Epigenetics and Progenitor Cells, to investigate two new views of the origins and maintenance of tumor cells with the aim of creating novel approaches to diagnosis, treatment, and prevention. Leader: **Kenneth Zaret**. Co-Leaders: **Maureen Murphy** and **Alfonso Bellacosa**.

—The Keystone Program in Blood Cell Development and Cancer, to identify the genes essential for blood precursor cells to give rise to the many distinct blood cell types, a critical step towards understanding blood cell cancers and improving the treatment of patients with leukemias and lymphomas. Leader: **David Wiest**. Co-Leader: **Richard Hardy**.

—The Keystone Program in Personalized Kidney Cancer Therapy, to investigate the mechanisms of kidney cancer metastasis and to uncover the molecular signals that anticipate how a kidney tumor will respond to therapies in order to optimize therapy for individual patients. Lader: **Robert Uzzo**. Co-Leaders: **Elizabeth Petri Henske** and **Gary Hudes**.

Funding Opportunities:

PA-08-097: Functional Links between the Immune System, Brain Function and Behavior. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-097.html. Inquiries: Paige McDonald, 301-435-5037; mcdonalp@mail.nih.gov.

PA-08-098: Functional Links between the Immune System, Brain Function and Behavior. R21. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-098.html.

RFP S08-119: Cancer Biomarker Assays for Evaluation of In Vitro Nanoscale Diagnostic Devices. Response Due date: March 14. Full text: http://www.fbodaily.com/archive/2008/02-February/21-Feb-2008/FBO-01511461.htm. Inquiries: Matt Desantis, 301-228-4002, mdesantis@ncifcrf.gov. or Gene Anderson, 301-228-4008, eanderson@ncifcrf.gov.

RFP S07-103: caBIG Knowledge Centers. Response Due date: March 19. Full text: http://www.fbodaily.com/archive/2008/02-February/21-Feb-2008/FBO-01511466.htm. Inquiries: Jennifer Thomas, 301-228-4004, thomasj@ncifcrf-gov. or Shannon Jackson, 301-228-4022, sjackson@mail.ncifcrf.gov.

RFP N02-CP-81015-49: Multi-disciplinary Investigations of Environmental Causes of Cancer. Full text: http://www.fbodaily.com/archive/2008/02-February/16-Feb-2008/FBO-01508819.htm. Inquiries: Sharon Miller, 301-435-3783, sm103r@nih.gov or George Kennedy, 301-435-3779. kennedyg@mail.nih.gov.

NOT-CA-08-011: Administrative Supplements for Gene Identification Efforts: Replication and Fine-Mapping Studies for The Genes, Environment, and Health Initiative. Full text: http://www.grants.nih.gov/grants/guide/notice-files/NOT-CA-08-011.html. Inquiries: Elizabeth Gillanders, 301-594-5868; gilland@mail.nih.gov.

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