A Bumper Crop of Conflicts

A clash between clinical researchers over whether former smokers and others at high risk for lung cancer should be screened using computed tomography (CT) scans (see main text) has turned bitterly personal. Some of the most contentious questions have been about intellectual and financial conflicts.

The Lung Cancer Alliance (LCA), a patient advocacy group in Washington, D.C., cast the first allegation. LCA's president, Laurie Fenton Ambrose, is irate that the U.S. government has refused to endorse CT imaging for lung-cancer screening while it awaits results from a $200 million trial to evaluate the procedure, the National Lung Screening Trial (NLST). She has charged that some leaders of the trial revealed their bias against CT screening when they agreed in past years to testify for tobacco companies about how screening might do more harm than good. Ambrose and an ally at another advocacy group leveled these charges in a blitz of correspondence to federal agencies, targeting two distinguished NLST leaders—radiologists William Black of Dartmouth Medical School and Denise Aberle of the University of California, Los Angeles.

The letters prompted several inquiries, including one in the U.S. House of Representatives last fall led by Michigan Democrat John Dingell.* Dingell's probe, which made headlines and then faded from view, is "active and ongoing," committee staff claim.

Black and Aberle have acknowledged that they agreed to testify for tobacco companies but said they did nothing improper. Aberle, who coordinates a large network of NLST clinical centers, provided testimony in 2003 in a class-action trial in Louisiana. As Aberle explained in a letter to the National Cancer Institute, she "violated no conflict of interest disclosure requirements," and the checks she received—reportedly totaling about $30,000—went to her university. In the letter, she said she wanted to "articulate the uncertainties of CT screening and the potential risk" to people in Louisiana who might sign up for it. Black similarly agreed to provide testimony in 2006 for attorneys defending Philip Morris in a New York class-action suit by smokers who wanted the company to pay for their annual CT scans. As Dartmouth's general counsel explained in a letter to Ambrose, Black believes that widespread screening may "cause more harm than benefit" and prepared testimony about why it would be a mistake for the court to set a precedent for screening. But he changed his mind, withdrew, and returned a $700 payment because he realized his participation "might be misconstrued as support for the tobacco industry." A review by the National Institutes of Health found that neither grantee had violated rules on disclosing conflicts of interest.

As the dust settled on this controversy, *The Cancer Letter*, a Washington, D.C., weekly, published an exposé of potential conflicts on the other side of the debate. It revealed that two well-known researchers who claim unprecedented success with CT screening for lung cancer—Claudia Henschke and David Yankelevitz, both of the Weill Cornell Medical College in New York City—have a financial stake in an invention that could be used in connection with CT screening. They have applied for 27 patents related to lung screening and have accepted royalty income from one license, but, *The Cancer Letter*

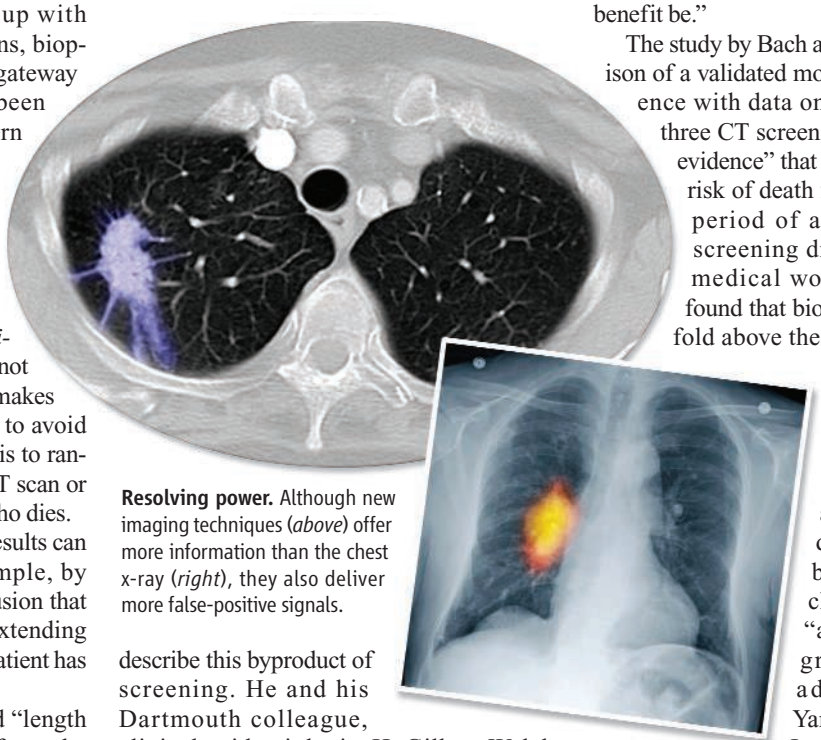
* energycommerce.house.gov/Investigations/NIH.101907.NIH.NCI.ltr.pdf

initial CT scan may be modest—about $200 to $300—but that's just the first installment. An anomaly "gins up all kinds of business," says Bach, as clinicians follow up with positron emission tomography scans, biopsies, and other tests. Imaging is a gateway into high-cost medicine and has been flagged as a growing budget concern by the U.S. Medicare program.

The glaring weakness of I-ELCAP, according to Bach, who with epidemiologist Colin Begg of Sloan-Kettering and others published a study on lung screening last year in *The Journal of the American Medical Association*, is that it is not a randomized controlled trial. This makes it susceptible to bias. The best way to avoid bias in a screening trial, they argue, is to randomly assign patients to receive a CT scan or no CT scan and then keep track of who dies.

Without random selection, trial results can be dramatically skewed, for example, by "lead-time bias." It produces the illusion that early diagnosis is responsible for extending the life of a patient when in fact the patient has just received a diagnosis earlier.

Other common problems, called "length bias" and "overdiagnosis," arise from the imprecision of cancer biology. Too little is known about early stage tumors to predict which will become malignant; intensive screening can flag many that are benign or slow-growing as dangerous when they really are not. "Pseudodisease" is the term used by William Black, a radiologist and lung-cancer specialist at Dartmouth Medical School, to describe this byproduct of screening. He and his Dartmouth colleague, clinical epidemiologist H. Gilbert Welch, argue that this is a big medical risk that clinicians need to guard against. In addition to causing harm, overdiagnosis can boost the number of people who are diagnosed with cancer and appear to overcome it. "Everyone should know that when you go down this road [of cancer screening]," says Welch, "there is going to be harm; the question is, what will the benefit be."



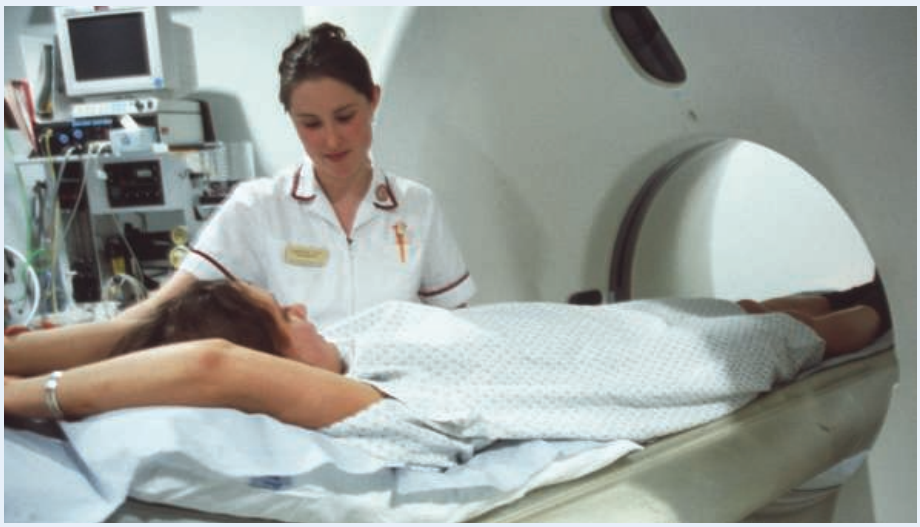
Resolving power. Although new imaging techniques (*above*) offer more information than the chest x-ray (*right*), they also deliver more false-positive signals.

The study by Bach and others—a comparison of a validated model of clinical experience with data on 3246 patients from three CT screening trials—found "no evidence" that screening reduced the risk of death from lung cancer in a period of almost 5 years. But screening dramatically boosted medical workups. The authors found that biopsies increased threefold above the expected level; lung surgeries, 10-fold.

Henschke and Yankelevitz claim that the extreme vigilance built into their approach keeps overdiagnosis and other biases to a minimum; clinicians intervene if "a malignant rate" of growth is evident. In addition, she and Yankelevitz write in the January 2008 issue of *The Oncologist*, a panel of pathology experts has examined all specimens removed by surgery and "confirmed that they are all genuine lung cancers and that 95% of them are already invasive."

CREDITS (TOP TO BOTTOM): LIVING ART ENTERPRISES LLC/PHOTO RESEARCHERS INC.; SCOTT CAMAZINE/GETTY IMAGES

Published by AAAS



Tobacco's dividend? CT screening to catch lung cancer early is being considered for all smokers—and there are 45 million of them in the United States.

charged, they did not properly disclose these interests in medical journal articles. In addition, *The New York Times* and *The Cancer Letter* reported in coordinated articles that most of the funds supporting the Weill project came from a tobacco company gift of $3.6 million.

Henschke and Yankelevitz have since acknowledged that their widely cited 2006 article in *The New England Journal of Medicine*, for one, should have disclosed that they received royalties from their patented "methods to assess tumor growth and regression in imaging tests"—inventions that have been licensed to General Electric (GE), a maker of CT machines. In addition, they acknowledged that "virtually all" of the money from a foundation listed as a sponsor of their research actually came from an "unrestricted gift by the Vector Group, the parent company of Liggett Tobacco, which manufactures cigarettes." In a separate statement, Weill says that Vector's original pledge was disclosed and reported in the national press 5 years ago and should be viewed in the same light as funding that "peer institutions and medical schools" received from antitobacco lawsuits.

Even the group that first raised these questions may have a conflict of its own. Ambrose acknowledges that LCA, a tireless advocate for government action to expand CT imaging, has received funding from GE. Ambrose says the alliance always made known that it receives 40% of its funding from "corporate interests," including the unrestricted GE grant and a larger one from a biotech company involved in lung-cancer research. **–E.M.**

None of this satisfies the skeptics. Bach's doubts have grown so that he now says: "We worry that the basic principle [of CT screening] is wrong. … Most of the lung cancers that are claiming lives, we think, are coming like a meteor. They come out of nowhere and are everywhere." Screening can't catch them. Yet others argue that Bach has gone overboard. Says James Mulshine, a leader of the Lung Cancer Alliance and associate provost for research at the Rush University Medical Center in Chicago, Illinois: "I haven't seen evidence in the literature that supports" Bach's view of meteorlike cancers.

Bruce Chabner, editor-in-chief of *The Oncologist* and clinical director of the Massachusetts General Hospital Cancer Center in Boston, says he's planning to air new concerns that go beyond study design in an editorial about the I-ELCAP results. For example, he claims that, unlike all clinical trials sponsored by drug companies and NCI, this privately funded project has not submitted its data to an outside audit. The Weill researchers did not respond to a request for comment.

CREDIT: MICHAEL DONNE/PHOTO RESEARCHERS INC.

A hard endpoint

NCI's proposed answer to the confusion is to look for help from a $200 million project it is now funding, the National Lung Screening Trial (NLST), a randomized controlled study. From 2002 to 2004, it enrolled and screened more than 50,000 individuals through a network of more than 30 study sites in the United States. The volunteers, all with an elevated risk for lung cancer, were randomly assigned to receive a chest x-ray or CT scan. Individual centers have been following up with standard monitoring and therapy. From 2008 on, researchers will be adding up deaths until they detect a statistically valid result showing that more people died in the x-ray group or the CT group—or neither.

By 2010, the first results should be available from NLST. But CT screening advocates have already been taking shots at it. For example, some suggest that it was a mistake—perhaps unethical—to recruit people with the promise of high-quality diagnosis and then give chest x-rays, long viewed as a poor diagnostic tool. Henschke and Yankelevitz stopped using chest x-rays early in their study because, as they wrote in *The Oncologist*, it "missed" 76% of the screening-diagnosed cancers found by CT.

The Lung Cancer Alliance also questioned whether patient follow-up was aggressive enough throughout the NLST network, because a slow response could make the diagnostic method look poor. NCI Director John Niederhuber responded in a letter last year that treatment "is not standardized in the NLST." But he argued that this should not compromise the trial because "variations in treatment should occur equally in both arms." According to Laurie Fenton Ambrose, president of the Lung Cancer Alliance, the emphasis on counting deaths rather than aggressively screening and treating patients is akin to "doing nothing" and is "just not acceptable."

Last year, Ambrose and other leaders of the pro-screening movement appealed to NCI for an interim view of CT screening, before NLST is done. They proposed combining data from I-ELCAP with data from NCI-funded trials, including NLST and another known as PLCO, in an attempt to get an early sense of the potential value of CT screening. Niederhuber met with the petitioners but decided it would not be "appropriate or fiscally responsible" for NCI to hold a review, he wrote to Ambrose.

Otis Brawley, chief medical officer of the American Cancer Society (ACS), has agreed to serve as a broker. He is not an advocate of trying to get an early view of CT screening's benefits. (The idea was proposed by an epidemiologist at ACS, Robert Smith.) But Brawley says that he intends to host a meeting of experts on the topic; NCI and major international cancer institutions will be invited to participate. Brawley aims to bring investigators together in May or early June from four randomized trials, including three from Europe, and "perhaps" someone to represent the I-ELCAP study. It will be a kind of "grand jury," he says, to review the trials and see whether it would be possible to use existing data to conduct a meta-analysis of CT screening.

This grand jury may not lead to a new course of action, but it could help bring some calm to a hotly contested field of clinical research. **–ELIOT MARSHALL**

Published by AAAS