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Mammography Screening For Ages 40-49 Not Supported By Data, NIH Panel Says

Women in their 40s should weigh the risks and benefits as they decide whether to undergo mammographic screening, an NIH panel said in a consensus statement last week.

"At the present time, the available data do not warrant a single recommendation for mammography for all women in their forties," the panel of non-federal advisors said Jan. 23. "Each woman should decide for herself whether to undergo mammography."

The panel said health insurers should cover screening mammograms for women in their 40s.

The conclusions, reached after a day and a half of scientific presentations, stunned and angered the proponents of screening. The American Cancer Society, a vocal supporter of breast cancer screening,

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In Brief

Resolution Seeks Two-Fold Increase For NIH; Hartwell Named President At Fred Hutchinson

SEN. CONNIE MACK (R-FL) last week introduced a "sense of the Senate" resolution calling for doubling the federal commitment to biomedical research over the next five years. The measure, which is not binding, is co-sponsored by Phil Gramm (R-TX), Bill Frist (R-TN), Arlen Specter (R-PA), Alfonse D'Amato (R-NY) and Mike DeWine (R-OH). "This resolution will help to ensure that researchers throughout our nation will have the necessary resources to build upon the discoveries of the past, and to continue making innovations in the future," Mack said in a statement. "Turning those discoveries into new methods for treating disease will make every American the beneficiary of these monumental achievements." . . . **LELAND HARTWELL** was appointed president and director of the Fred Hutchinson Cancer Research Center, effective July 1. Hartwell, 57, a geneticist and the center's senior scientific advisor since April 1996, will succeed **Robert Day**, who has served as president and director for 16 years. Day announced a year ago that he would retire effective June 30. Day, 66, became president and director in 1981, succeeding William Hutchinson, who founded the center in 1975 in memory of his brother. Day will retain a faculty position within the Center's Public Health Sciences Division following his retirement. Hartwell has held a professorship in genetics at the University of Washington since 1968.

Panel Supports Coverage For Mammographic Screening

(Continued from page 1)

said it was "disappointed" by the consensus statement. The society also reaffirmed its recommendation that women 40-49 have a mammogram every one to two years.

The consensus conference was convened at the request of NCI Director Richard Klausner. Last spring, following a review of new data from randomized trials in Sweden, Klausner decided the Institute needed to re-examine its 1993 decision to cease recommending routine screening for women in their 40s (**The Cancer Letter**, April 19, 1996).

In his initial reaction to the panel's recommendations, Klausner said he was disappointed by what he described as the panel's failure to present a balanced discussion of the evidence in favor of screening. While reasonable people looking at the data could reach divergent conclusions, failure to discuss all evidence could diminish the credibility of the recommendations, he said.

"I agree with the sentiment of the panel that women should make decisions based on the best available evidence," Klausner said at a press conference. "I am concerned that women are not being given, in the report, all the evidence they need.

"My evaluation, from the best population-based evidence, is that these studies have reached statistical significance, and there is now evidence that fulfills the standard norms," Klausner said. "My evaluation is, the data supports screening in women in their 40s. It does look significant, and women need to know that.

"It is reasonable to agree to disagree," Klausner said following the briefing by the consensus panel. "I'm giving my own opinion. I am disagreeing with the balance of the evidence."

Klausner said he would ask the National Cancer Advisory Board to discuss the consensus statement at its next meeting, Feb. 25. "We will proceed with our own evaluation of the benefit and risks," he said.

Later, in an interview with **The Cancer Letter**, Klausner said he hoped the NCAB would help the Institute prepare materials that would communicate the risks and benefits of screening mammography for women in their 40s. He said he did not expect the NCAB or the Institute to develop its own guidelines (Story on page 6).

It is rare for an Institute director to take issue with the results of an NIH consensus conference. Klausner said he happened to be in the audience during the press conference following the meeting when a reporter asked for his opinion. "I was not looking to speak," Klausner said to **The Cancer Letter**. "The question was asked and [panel chairman] Dr. [Leon] Gordis invited me up."

Mixed Reactions

Reactions to the consensus statement—as well as reactions to Klausner's comments—were mixed (Story on page 8).

Some experts and advocates who have taken a conservative view of screening women in their 40s said the panel's statement could have provided more specific information about the latest data from screening trials.

"I was disappointed that if the panel disagreed with the new data, they did not refute those data," said Barbara Rimer, chairman of the National Cancer Advisory Board. "The conference report did not provide relative risks, confidence intervals or data, and did not refute the data presented."

Fran Visco, president of the National Breast Cancer Coalition, said the consensus statement was reasonable and advised NCI to move on to other issues. "We are supportive of the statement and we want to put the issue behind us and spend money on answering the research questions posed by the

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panel," Visco said to **The Cancer Letter**. "We all wish that mammography was the answer because it is a tool that exists. But the data are simply not there."

Those who advocated screening mammography for women in their 40s applauded Klausner's remarks.

"I am extremely proud of Rick Klausner and his leadership," said Ellen Sigal, a member of the NCAB. "He took a moral stand and a courageous stand. He cares about the health of American women."

Other observers, who asked not to be quoted by name, said they feared that by taking a public stand on the issue, Klausner had heightened the controversy, drawing NCI deeper into the debate over practice guidelines.

The American Cancer Society and the American College of Radiology issued statements criticizing the panel's conclusions. Both organizations said they continue to strongly recommend screening beginning at age 40.

ACS plans to convene its own expert panel in March to review the data, a spokesman said. The society will consider whether to recommend annual screening for women 40-49, instead of the current recommendation of screening every one to two years.

In another development, Sen. Arlen Specter (R-PA), chairman of the Labor, HHS and Education appropriations subcommittee, called a hearing on the consensus statement. The hearing was scheduled for Feb. 5.

Swedish Trialists Present Updates

The latest debate over mammography screening turns on the interpretation of long term follow-up data from Swedish trials.

Two of the Swedish trials presented to the consensus panel demonstrated statistically significant reductions in breast cancer mortality for women ages 40-49 who were invited for screening mammography.

Follow-up data from a trial in the city of Gothenburg demonstrated a 44 percent mortality reduction (95 percent confidence interval 0.32-0.98). Women in the trial were screened every two years, and some of the women in the control group received mammograms over the 12 years they were followed.

"The mortality reduction occurred in spite of mammographic activity in the control group," said Nils Bjurstam, principal investigator of the Gothenburg trial.

Most of the breast cancer deaths in the women who were screened occurred as a result of cancers found during the two-year interval, not at screening, Bjurstam said.

"If we shortened the interval to one year, we might have still better results than 44 percent," Bjurstam said. "Our study suggests the benefit of enrollment in an organized screening program with high-quality mammography and strict adherence to a short screening interval."

A trial in Malmö found a 36 percent reduction in mortality for women in their 40s who were invited for screening. However, principal investigator Ingvar Andersson, of the University Hospital of Malmö, calculated that 625 women would have to be screened repeatedly to extend the life of one woman.

"One can reduce breast cancer mortality in women under age 50 with repeated screening," Andersson said. "But I think the balance between the cost and the benefit is unfavorable. It is a matter of personal preference."

An overview that combined the data from five Swedish trials showed a 23 percent statistically significant mortality reduction (95 percent confidence interval 0.59-1.01).

Another meta-analysis that combined the most current data on women who were 40-49 at entry to the five Swedish trials, a trial in Edinburgh, UK, and the Health Insurance Plan of New York, found a 24 percent statistically significant mortality reduction (95 percent confidence interval 0.62-0.95).

Former NCI scientist Charles Smart, the author of the meta-analysis, said the actual benefit of mammography for a woman who wants to be screened is likely to exceed the benefit shown in the randomized trials. This occurs because 10 to 40 percent of the women offered screening in the trials declined to get mammograms, yet they were counted as being in the screened group.

In addition, mammographic technology has improved. "Women receiving regular, high-quality mammography today are more likely to have their cancers detected at smaller sizes and at earlier stages than women who participated in the randomized, controlled trials," Smart said to the panel.

Last-Minute Revisions

The consensus panel's 12-page draft consensus

statement, with hand-written revisions, was released following a contentious and emotional discussion period on the last day of the conference.

The panel took suggestions of the audience on changes to the wording of the document, but those changes did not significantly alter either the tone of the report or the conclusions.

In its discussion of the data from clinical trials on the benefits of screening, the panel wrote:

"There is no difference in breast cancer deaths within seven years between the women randomized to receive or not to receive screening. Some studies show a decrease in breast cancer mortality after 10 years, but this may be due to other factors, including [clinical breast exams] given to women in the screening group and mammograms after age 49 in the screening group."

The Swedish trialists who were present at the conference said the statement indicated that the panel had dismissed the Swedish data.

"As someone who is skeptical about screening, I do not think the two sentences... properly reflect the state of knowledge and what has come out of this meeting," said Andersson.

"Why did you completely ignore the Swedish trial results?" asked Laszlo Tabar, associate professor and director at the Department of Mammography at Falun Central Hospital.

Donald Berry, a panel member and professor of statistics at Duke University, said the panel was familiar with the Swedish data. "We did not completely ignore the Swedish results," he said. "We admire the Swedish trials."

Instead of citing specific trials, the consensus statement used meta-analyses. "Based on meta-analyses of the [randomized controlled trials], 0 to 10 women would have their lives extended per 10,000 women ages 40-49 who were regularly screened. About 2,500 women should be screened regularly in order to extend one life," the statement said.

According to the statement, other benefits of screening may include earlier detection, giving patients greater choice of treatment options.

The risks include "false-negative mammograms, additional diagnostic testing induced by false-positive examinations, psychosocial consequences of abnormal examinations, the potential risk of overtreatment of low-risk or in situ cancers, and radiation exposure risk," the statement said.

"Up to one-fourth of all invasive breast cancers are not detected by mammography 40- to 49-year-olds, compared with one-tenth of cancers in 50- to 59-year-olds," the statement said. "Approximately 10 percent of all screening mammograms are read as abnormal and two additional diagnostic tests are performed."

Abnormal mammograms cause "psychosocial sequelae, including inconvenience, anxiety and fear," the statement said.

The statement's discussion of radiation exposure from mammography was criticized several times during the conference.

"Radiation can cause breast cancer in women, and the risk is proportional to dose," the statement said. "The younger the woman at the time of exposure, the greater her lifetime risk for breast cancer. Radiation-related breast cancers occur at least 10 years after exposure. Radiation from yearly mammograms during ages 40-49 has been estimated to cause one additional breast cancer death per 10,000 women. Because this estimate is based on statistical models of limited high dose epidemiologic studies, the actual value may be much higher or nonexistent."

Stephen Feig, professor of radiology at Thomas Jefferson University Hospital, said the panel's statement overstated the risk of radiation exposure. In his presentation to the panel, Feig said no women have ever been shown to have developed breast cancer as a result of mammography, even at much higher radiation doses than those used today.

"For the general population of women, the theoretical risk from screening mammography is negligible compare to the known benefit," Feig said.

Panelists Defend Statement

The consensus panel read hundreds of documents in preparation for the conference Jan. 21-23, panelists said. The panel listened to 32 presentations over a day and a half, and was writing the statement up until 3 a.m. on Jan. 23, the day it was presented.

"We believe there are a great number of potential benefits of mammography screening for women in their 40s, but a number of potential risks," panel chairman Leon Gordis, professor of epidemiology at Johns Hopkins School of Medicine, said in presenting the consensus statement.

"We cannot at this point make an across-the-board recommendation for screening women in their

40s, but we are dealing with a changing situation," Gordis said. "We believe the best recommendation is to provide women with the best information about mammography screening so they can, with their physician, consider the risks and benefits."

"We are not saying there is no benefit to screening women in their 40s, but the benefit might be small and might be late," said panelist Leslie Laufman, an oncologist in Worthington, OH, and principal investigator of the NCI-supported Columbus Community Clinical Oncology Program.

"We needed a little more convincing data," said panelist Susan Chu, associate director of Group Health Cooperative of Seattle.

Making a recommendation for screening a healthy population requires a greater amount of confidence in the data, said panelist Constance Rufenbarger, an official of the Catherine Peachey Fund of Warsaw, IN. "We would have to say that the data irrefutably support screening and if you have a screening mammogram, we can guarantee you will find an early cancer and you will be cured," Rufenbarger said. "That is the message we would have to give."

Two physicians on the panel said they would recommend that women in their 40s receive screening mammograms.

"I see the benefits of mammography every day," said panelist Daniel Sullivan, professor of geriatrics at Dartmouth Medical School. "If women ask me my personal opinion, my recommendation for most women in their 40s is that an annual mammogram is likely to be beneficial to them."

"Women in their 40s should have an annual mammogram," said panelist Jeanne Petrek, a breast cancer surgeon at Memorial Sloan-Kettering Cancer Center.

Statement Posted On NIH Web Site

A final version of the statement will be published in about a year, NIH staff said.

Copies of the draft NIH Consensus Development Conference Statement, "Breast Cancer Screening for Women Ages 40-49," are available from the NIH Consensus Program, PO Box 2577, Kensington, MD 20891, tel: 888/644-2667, fax: 301/816-2494.

The statement was expected to be posted on the NIH Web site at the following URL: http://consensus.nih.gov.

Members of the consensus panel were: Chairman, Leon Gordis, professor of epidemiology, associate dean for admissions and academic affairs, Johns Hopkins University School of Medicine; Donald Berry, professor, Institute of Statistics and Decision Sciences and Cancer Center Biostatistics, Duke University; Susan Chu, associate director, Center for Health Studies, Group Health Cooperative of Puget Sound; Laurie Fajardo, professor of radiology and vice chair for research, University of Virginia; David Hoel, professor and chairman, Department of Biometry and Epidemiology, Medical University of South Carolina; Leslie Laufman, Hematology Oncology Consultants, Columbus, OH; Jeanne Petrek, associate professor of surgery, Memorial Sloan-Kettering Cancer Center; Constance Rufenbarger, The Catherine Peachey Fund Inc., Warsaw, IN; Julia Scott, president and CEO, National Black Women's Health Project Inc., Washington, DC; Daniel Sullivan, associate professor of radiology, University of Pennsylvania Medical Center; John Wasson, professor of geriatrics, Dartmouth Medical School; Carolyn Westhoff, associate professor, obstetrics, gynecology and public health, Columbia University College of Physicians and Surgeons; Ruthann Zern, obstetrician/gynecologist, Towson, MD.

More Discord Than Consensus At Statement's Presentation

The panel's draft statement was completed at 3:15 a.m. on Jan. 23. At 9 a.m., panel chairman Leon Gordis read the document to the assembled conference.

Before Gordis had finished reading, conference participants were lined up about 10 persons deep for the microphones. The audience grilled the panel for one-and-a-half hours.

Several questioners asked why the document made scant reference to the recent data from the Swedish trials.

"We ignored none of the information presented at this meeting," replied Donald Berry, panel member and professor of statistics, Duke University. "We find the data presented at this meeting do not change very much the meta-analysis."

On the pro-screening side, the debate was dominated by Daniel Kopans, director of breast imaging at Massachusetts General Hospital, as well as by the Swedish clinical trialists who produced the

studies that prompted the consensus conference.

"Nowhere in the document do you say that two randomized controlled trials show a statistically significant benefit for women 40-49," Kopans said to the panel.

"This is the same level of evidence that is accepted as proof of efficacy for older women. There are only two trials in women 50-59 that show a statistically significant benefit. Where is it written that seven years is the goal? This document sounds like it was written before this meeting. It should not be released to the public until it is corrected. Otherwise it is fraudulent."

GORDIS: I'm not going to respond to accusational remarks.

EDWARD HENDRICK, associate professor and chief, Division of Radiological Sciences, University of Colorado Health Sciences Center: The statement alludes to data from a meta-analysis that was not presented at the meeting. Do you have data not presented here?

BERRY: I have no data not presented here. I conducted a meta-analysis to assure that the meta-analysis data had not changed substantially.

LASZLO TABAR, associate professor and director, Department of Mammography, Falun Central Hospital, Sweden: Did the panel have access to the most recent publication of the Falun meeting?

GORDIS: Yes.

TABAR: We, the Swedish trialists, were kind enough to come here and present our updated results. I cannot accept Dr. Berry's answer to Dr. Hendrick. Was there any other statistician on the panel?

GORDIS: No.

TABAR: You owe it to us and the public and American women to say more about our 20-year results than "some studies." I would ask Dr. Berry, why did you completely ignore the Swedish trial results?

BERRY: We did not completely ignore the Swedish results. We did not use seven years as a cut-off. It is a descriptive. We will most definitely make it clear that 10 years refers to the follow-up. We admire the Swedish trials.

TABAR: I don't see a trace of that admiration in your statement.

[Applause from the audience.]

Later, Kopans raised the issue of the panel's selection. "Certainly radiologists are accused of having a vested interest in this, so I would ask how many members of the panel receive funding from NCI?" he asked.

GORDIS: That's public information. It's available on the Internet.

KOPANS: Could we just have a show of hands? How many people on the panel receive NCI funding?

[A shout from the audience: "Give us a show of hands!"]

GORDIS: [Consults with NIH staff.] No, we do not believe there is a conflict of interest.

"Tone" Of Panel's Statement Lacks Balance, Klausner Says

NCI Director Richard Klausner said news reports have overemphasized his disagreement with the NIH consensus panel on breast cancer screening and misquoted his passing remark to a reporter that he was "shocked" by the conference.

In an interview with **The Cancer Letter,** Klausner said he, in fact, agreed with the panel's conclusions, but disagreed with the "tone" of the report.

"When I spoke, I said I basically agreed with [the panel], but I continue to feel it is important if we are going to say to a woman that deciding to receive screening mammograms beginning in the 40s is O.K., then we have to be clear it is O.K. because there is some evidence that supports that decision," Klausner said in an interview Jan. 26. "Even if there are conflicting data, there is a justification for a woman choosing screening.

"I wanted to make sure that the support for choosing mammography can be buttressed by evidence that supports a benefit," Klausner said. "As I said, as far as I can see, the benefit is small."

Women should be given more information on breast cancer and screening, Klausner said. "It is important that we learn to provide women and their physicians with a whole variety of ways to look at the data and numbers," he said. "What is my risk of getting breast cancer? What is my risk of dying of breast cancer? What is my risk of dying of breast cancer if I do regular screening mammography, and what's the range of that from the evidence that is available?

"The reality is, the benefit is small," Klausner said. "But who, then, places a value on that quantity? My belief is, that should be the woman."

The panel's report overemphasized the risks of

screening, Klausner said. "I felt the balance was overly skeptical about benefit, and overly accepting about a type of fixed risk, including the risk of radiation-induced cancer, which is extremely hypothetical," he said. "I am concerned that this was presented with much more strength than the data of possible benefit.

"For example, the risk of false positives: the woman has to make her own decision about whether that's a significant risk or not. I worry about assigning a number to it, because we saw at the conference that there was a tremendous disparity from different parts of the world, different approaches to the follow-up to mammograms, the number of invasive procedures, versus the number of cancers diagnosed.

"I wouldn't assume that the number of 10 or 20 procedures in young women for any cancer diagnosed is a fixed number," Klausner said.

"I think much in the panel's report was really excellent," Klausner said. "I was uncomfortable with the tone.

"My disagreement, to the extent that there was a disagreement—and I was asked to describe it in terms of agreement/disagreement—was that I agreed with their conclusion, but I think we need to do a much better and much clearer job of communicating that there are studies that support a benefit of mammography versus no mammography."

"It sounds much more dramatic when you see it written as, 'Dr. Klausner disagreed with his own advisors.' They were not my advisors. I do not feel I was in opposition."

Was "Shocked" At Level of Anger

In a Jan. 24 front-page article, The New York *Times quoted Klausner* saying he was "shocked" by the panel's conclusions.

In a follow-up story on the consensus conference Jan. 28, the Times repeated the quote. According to the article, Klausner "rushed to the hallway to use a public telephone" after the consensus statement was read. "In an interview there, he said he was 'shocked' by the conclusions, adding that he disliked their negative tone," the Times reported.

Klausner said he was asked what he thought about the conference.

"I am very concerned and upset about the level of anger and the level of personalization of positions that I saw at the conference," Klausner said to **The Cancer Letter**. "I was 'shocked' about that, not the statement. I was shocked at the level of vitriol and personal animus."

Some of the conference participants questioned the impartiality of the panel and the members of the conference planning committee. "The presumption of bias is the most extraordinary attack on science that I have seen," Klausner said. "The idea that looking at data and coming to different conclusions carries moral and ethical consequences is as fundamental a threat to science as I've seen.

"No one at NCI chose the panel members," Klausner said. "I don't feel there is any reason to presume bias on the part of the panel members.

"I can say without any question that my approach to this conference, and the reason we didn't hold it at NCI, but turned to [the NIH] Office of Medical Applications of Research, was to avoid any appearance of bias," he said. "Throughout this whole process, I felt confident that people from NCI who did a lot of work on the planning committee were people of extraordinary integrity and I will vouch for them absolutely. I feel they were incredibly sensitized, not by me, but from the whole experience, and based upon their own integrity, to make sure there was no bias to the extent possible."

Wants Discussion, Not Guidelines, From NCAB

NCI should not issue its own guidelines, Klausner said. "I do not expect or feel comfortable with NCI making a practice recommendation," he said. "NCI's role needs to be more pro-active about providing high-quality and understandable information about risk and benefit in ways people can understand, and to do more research in risk communication and risk understanding."

Klausner said he hoped the NCAB would hold a balanced discussion of the conference. "My hope is that out of that will come a commitment to provide for the NCI exactly the type of useful information about risk of cancer, risk of dying of cancer, and benefit in ways that are much more understandable than the types of numbers that are generally thrown around," he said.

"I am not looking for the NCAB to push us back into the guidelines business," Klausner said. "There are many organizations that are very competent at describing guidelines for all sorts of things. I want to see the NCI do its job of helping to create data, helping to gather evidence, and doing a much better

job at communicating."

Was Timing Right For A Consensus?

Was it too soon for a scientific "consensus" on screening mammography for women in their 40s? Were the latest data just too new?

"I've thought about that," Klausner said to **The Cancer Letter**. "Before we thought about this conference, I asked people from NCI to evaluate data as we were able to see it from the Falun conference. I asked [former NCI official] Ed Sondik to go to the Falun conference.

"It was based upon those recommendations that I discussed with [NIH Director] Dr. [Harold] Varmus the idea that it seemed we were ready for a consensus conference," Klausner said. "In retrospect, were we? Maybe not.

"It was certainly my choice, based upon my discussions with many individuals, including individuals who were quite skeptical about whether screening mammography starting in the 40s was advisable," Klausner said. "All of those individuals reported to me that as far as they could see, there really is new data that changes things.

"Not necessarily changes the conclusion, but changes the amount of data that was available."

NIH Statement Doesn't Resolve Mammography Controversy

"Consensus" would be the wrong word to describe the aftermath of the statement produced by the NIH panel of experts at last week's conference on mammography screening for younger women.

While opponents of screening for younger women applauded the panel's conservative statement, the proponents have not changed their minds. In fact, many of the proponents are raising questions about the process used by NIH to arrive at the consensus.

Instead of resolving the controversy in light of new data, the statement may have exacerbated it. In fact, the statement will be re-examined by the National Cancer Advisory Board and the American Cancer Society. Capitol Hill, too, is joining the re-examination, with a hearing by Sen. Arlen Specter (R-PA).

The following is an overview of positions taken by several key players as well as prominent cancer groups:

Rimer: NCAB Needs to Consider New Data

"One of real dilemmas for anyone in the audience who came in with an open mind was the fact that there were 32 speakers who presented new information, but no papers were provided to those in attendance who were not panel members," said NCAB Chairman Barbara Rimer, who participated in the conference as a member of the planning committee and a speaker.

"Beyond the knowledge and preconceptions anyone brought to the conference, it was difficult to integrate the new information," Rimer said to **The Cancer Letter**. "All might have come to the conclusion of the trialists if we had a chance to review the data.

"I need time to look at the new data, along with the NCAB, to help guide the board through the process of understanding what happened at the consensus conference, and how the new data presented at the meeting might change the interpretation that the consensus panel came to about the data.

"I was disappointed that if the panel disagreed with the new data, they did not refute those data. The conference report did not provide relative risks, confidence intervals or data, and did not refute the data presented.

"It left everybody hanging and wondering why they didn't. And it left people wondering if they had adequately considered the data. The onus was on the panel to reflect back what they heard from a day and a half of carefully presented papers.

"We now have a huge gulf between a consensus statement and the larger community's sense that there is at least a modest benefit of screening women in their 40s with mammography.

"Even the most conservative people are inching toward an acceptance that there is some benefit, although maybe a small benefit. What we are going to have to do as a board is grapple with that gulf and come to some conclusion of our own about where we think things stand.

"We will work closely with Dr. Klausner on this and I am certain it will be quite different from the discordant process that occurred in 1993.

"It should not be lost that there were a number of valuable points made in the report. Informed decision-making should be the goal for women of all ages. And the report identified a number of

important areas for future study.

"I think its time for [the NIH] Office of Medical Applications of Research to look at how it conducts a consensus conference on a topic as emotionally charged and as complex as this one. To digest so much new data and write a report overnight is perhaps beyond the intellectual capacity of any human being, and when the group process is added to the mixture, that makes the task even more daunting."

ACS To Hold Conference

"New data provide further support that women in their 40s benefit from participation in routine mammography screening programs," the American Cancer Society said in a statement.

"Indeed, the latest data presented at this meeting meet the criteria for scientific evidence that the NCI claimed was absent when they rescinded their guidelines for women in their 40s in 1993.

"The panel seemed to place undue emphasis on hypothetical issues such as radiation risk, anxiety caused by positive findings, and the fact that mammography will not detect 100 percent of cancers. We find it especially troubling that the panel would issue a pessimistic statement, and conclude once again that the burden of decision for a women in her 40s is hers alone."

ACS recommended that women begin a regular program of mammography screening at age 40. In the past, the society recommended that women 40-49 received mammography screening every one to two years.

ACS plans to convene a panel in March to review all of its guidelines for breast cancer screening, particularly the screening interval, a spokesman said.

The panel will meet March 7-9 in Chicago to make guideline recommendations to the society's Board of Directors.

Brown: NCI Should Not Set Guidelines

"NCI should not be in the guidelines business. NCI should be developing knowledge, doing research, including translational research, but as far as guidelines on the practice of medicine, NCI should leave that to other organizations," said Helene Brown, a long-time ACS activist and director of community applications of research, at the UCLA Jonsson Comprehensive Cancer Center.

ACR: Panel Ignored New Data

The American College of Radiology reaffirmed its strong support for mammography screening for women in their 40s.

The radiologists' society said the NIH panel "failed to recognize and incorporate important new follow-up data from clinical trials that confirms the benefits" of mammography

"Not only is the evidence compelling that this age group should be screened, but a growing number of studies clearly indicate the screening interval for women 40-49 should be shortened from the present recommendation of every one to two years to every year. More than 30,000 women in the US aged 40-49 are diagnosed with breast cancer each year and to discourage women in their 40s from having life-saving mammography is a tragic mistake."

Kopans: "Clear Proof" of Benefit

"There is now clear proof that screening women aged 40-49, using mammography, can reduce the death rate from breast cancer," said Daniel Kopans, associate professor of radiology, Harvard Medical School, and director of breast imaging, Massachusetts General Hospital.

"At the consensus conference, trialists from Sweden presented their most recent data and revealed a statistically significant mortality reduction of 44 percent in Gothenburg, and a 36 percent statistically significant reduction in Malmö," Kopans said to **The Cancer Letter**. "These are actually greater reductions than the two trials that show statistically significant benefit for women ages 50 and over.

"The overview of the Swedish trials revealed a 24 percent mortality reduction when all five trials are combined, which is also statistically significant. Adding the Edinburgh and HIP trials provides a 23 percent reduction that is also statistically significant. These results are all the more compelling in that the randomized, controlled trials were not designed to be split into subgroups, and there were not enough women in the trials, under the age of 50, to have any statistical power in the early years of follow-up.

"Furthermore, since women who refused the invitation to be screened and died of breast cancer are still counted as having been screened, and women in the control groups, who may have been saved by mammograms that they obtained on their own outside the trials, are still counted as unscreened controls, the benefit is likely even higher.

"The consensus panel chose to virtually ignore the recent data and focus on the results from the trials at only seven years of follow-up. These were the same data that were analyzed in 1993, and had been used to withdraw support for screening at that time. The purpose of the consensus conference was to analyze the new data. The panel trivialized the new data.

"The panel's statement repeatedly provides information out of context and in several instances, contains factual errors:

—The panel states that the studies may show a benefit as great as 30 percent, when the data from Gothenburg show a 44 percent decrease in deaths for these women.

—The panel suggests the benefit may have been due to clinical breast examination among the screened women. The Swedish trials did not include CBE.

—The panel suggests the benefit may be due to women reaching the age of 50 during the trials and having a benefit suddenly appear. The panel ignored the warning that analyzing trials by the age at diagnosis introduces significant bias against detection of cancers in women under age 50. Even omitting this fact, the panel was provided data showing that, in the three trials that provided such analysis, the majority of the benefit was from cancers detected before women reached age 50. In the HIP trial, the benefit was greatest for women ages 40-44 who never reached age 50 during the four years of screening. These facts were ignored.

—The panel suggests that only two women out of 1,000 would have their lives extended if screened in their forties. They neglect point out that screening programs, such as those for cervical cancer, only benefit a small number of the screened women. Using their same analysis, 'only' three to four women per 1,000 benefit from screening ages 50-59, and 'only' four to six women per 1,000 benefit from screening women in their sixties.

—The most recent radiation risk assessments show that, if there is any risk from radiation, it is extremely low, and greatly outweighed by the benefit, and there is likely no risk from radiation for women ages 40 and over. The panel provided its own radiation risk assessments that were at least an order of magnitude greater than the most pessimistic estimates in the literature.

"The panel abdicated its responsibility to provide guidance to women and their physicians in making the decision whether to receive screening mammography. It is a given that an individual must decide for herself. Guidelines are not requirements. The panel neglected to provide women and their physicians with the most recent information and a balanced presentation of the facts. The panel has done little more than provide fallacious information that should never have been released to the public."

Glick: Statement Not Helpful to Physicians

"The statement doesn't help physicians in the field. I had hoped the panel would have taken a more positive view," said John Glick, director of the University of Pennsylvania Cancer Center.

"While it is important that all women have the range of benefits and risks described to them to participate in making their own decisions, I would have interpreted the data as demonstrating a significant benefit in terms of reduced death from breast cancer for women in their 40s," Glick said to **The Cancer Letter**.

"There are some false positives with mammography, but when you do detect breast cancer in women in their 40s, there is a better chance of detecting a smaller cancer, so a woman has the choice of conservative surgery. It's important to have that choice."

Sigal: Convene Panel of Clinicians

"As one member of the NCAB, I could not let this recommendation go without further action," said Ellen Sigal, a member of the NCAB.

"I am very unhappy. I would like to have another group—perhaps clinicians who deal with this all the time—look at the recommendation," Sigal said to **The Cancer Letter**.

"As one who has been deeply affected by breast cancer, on a personal basis, I would rather have many more false positive findings from mammography than miss a diagnosis of cancer," Sigal said.

"I am extremely proud of Rick Klausner and his leadership. He took a moral stand and a courageous stand. He cares about the health of American women."

NBCC: Women Should Make Own Decisions

National Breast Cancer Coalition has for several years taken a position similar to that of the consensus statement, said Fran Visco, NBCC president. "We see nothing that has occurred recently to change that

position," Visco said to **The Cancer Letter**.

"We are supportive of the statement and we want to put the issue behind us and spend money on answering the research questions posed by the panel," Visco said. "We all wish that mammography was the answer because it is a tool that exists. But the data are simply not there.

"The experts came together and looked at the data, and made their statement," Visco said. "It is perfectly acceptable to say that, given all this, women should make a decision with their physicians."

PA Breast Cancer Coalition: "Deadly Message"

The panel's report "sends a confusing and deadly message to women in their 40s," said Pat Halpin-Murphy, president of the Pennsylvania Breast Cancer Coalition.

"The panel side-stepped the issue and left the decision up to the individual," the coalition said in a statement. "This lack of commitment places the burden of understanding this complex medical data on the woman."

NABCO: Mammogram Risk Overstated

"The panel's draft statement did not give sufficient weight to the mortality benefit past 10 years of follow up," the National Alliance of Breast Cancer Organizations said in a statement.

"In addition, the draft statement overemphasized the risks of screening, including concerns about radiation exposure and 'anxiety' produced by false positive results confirmed by biopsy," the statement said.

NABCO said it continued to support the ACS recommendations for breast cancer screening. The group's executive director, Amy Langer, served on the planning committee for the consensus conference.

In a discussion period after the statement was presented, Langer suggested the document could have provided more perspective on the data.

"Since the document seems to place the burden or the opportunity on American women, I would ask that the panel, when referring to data for women 40-49 also provide the data for women 50-59, to put it into context, since screening for women in their 50s is recognized," Langer said.

NCCS: Panel Took Easy Way Out

"My understanding it that consensus panels are convened for the purpose of making a recommendation, and in my view they made no recommendation," said Ellen Stovall, executive director of the National Coalition for Cancer Survivorship and a member of NCAB. "The panel took an easy way out of a difficult dilemma, which does not help women considering mammography."

NCCS has not made a policy statement on mammography.

Rep. Nadler: Provide Access

A day after the conference, Rep. Jerrold Nadler (D-NY) introduced legislation in the House that would require insurance companies and Medicaid to pay for screening mammograms for women 40 and older.

"There remains controversy as to the degree to which mammograms for women in their 40s can save lives, but the experts are now unanimous that all women should have access to this potentially life-saving diagnostic procedure," Nadler said in a statement.

Funding Opportunities:

RFAs Available

RFA DK-97-003

Title: **Helicobacter Pylori and its Relationship to Digestive Disease and Cancer**

Letter of Intent Receipt Date: March 21

Application Receipt Date: April 22

The National Institute of Diabetes and Digestive and Kidney Diseases, the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the Office of Research on Minority Health in partnership with the American Digestive Health Foundation invite applications for basic and clinical research focusing on the role of Helicobacter pylori infection in peptic ulcer disease, nonulcer dyspepsia, and gastric cancer, particularly in minority populations.

Studies on the epidemiology of Helicobacter pylori in minority populations, genetic susceptibility to and the acquisition of Helicobacter infection, the role of Helicobacter in development and the regulation of the inflammatory response are encouraged. Support will be through NIH research project grant (R01) award, the FIRST (R29) award,

and the small grants (R03) award.

Inquiries: Frank Hamilton, Division of Digestive Diseases and Nutrition, NIDDK, Natcher Bldg Rm 6AN-12B, Bethesda, MD 20892-6600, tel: 301/594-8877, fax: 301/480-8300, email: hamiltonf@ep.niddk.nih.gov

RFA CA-97-010

Title: **Prevention and Cessation of Tobacco Use by Children and Youth in the U.S.**

Letter of Intent Receipt Date: March 15

Application Receipt Date: May 8

The NCI Division of Cancer Prevention and Control, the National Institute of Child Health and Human Development and the National Institute of Nursing Research seek grant applications for innovative research that has clear implications for the immediate and significant reduction of tobacco use by children and youth in the U.S. This RFA will use the NIH research project grant (R01). Approximately $4.6 million, per year, in total costs for four years will be committed to fund applications submitted in response to each of the two solicitations of this RFA. It is anticipated that eight to 12 new awards will be made through this solicitation.

Inquiries: Thomas Glynn, DCPC, NCI, 6130 Executive Blvd Rm 243, Bethesda, MD 20892-7330, tel: 301/496-8520, fax: 301/496-8675, email: glynnt@dcpcepn.nci.nih.gov

Norman Krasnegor, Human Learning and Behavior Branch, NICHD, 6100 Executive Blvd Rm 4B05, Rockville, MD 20852, tel: 301/496-6591, fax: 301/480-7773, email: Krasnegn@hd01.nichd.nih.gov

June Lunney, Division of Extramural Activities, NINR, Bldg 45 Rm 3AN-12, Bethesda, MD 20892-6300, tel: 301/594-6908, fax: 301/480-8260, email: Jlunney@ep.ninr.nih.gov

RFA CA-97-011

Title: **Novel Technologies for Evaluation of Molecular Alterations in Tissue**

Letter of Intent Receipt Date: Feb. 15, Aug. 15

Application Receipt Date: May 8, Nov. 13

The NCI Technology Development Branch of the Cancer Diagnosis Program, Division of Cancer Treatment, Diagnosis and Centers and the Division of Human Communication of the National Institute on Deafness and Other Communication Disorders invite applications proposing the development of novel technologies to facilitate generation of a comprehensive molecular profile of human tissues.

Development of these innovative technologies is intended to impact the discovery process in research on the biology of human disease at the level of both gene discovery and molecular cellular biology.

This initiative supports development of efficient, cost effective, sensitive technologies to permit the simultaneous, rapid evaluation of the spectrum of molecular alterations in tissue specimens and, ultimately, in single cells.

These technologies can be designed to detect genome-wide molecular alterations at the level of DNA, RNA or protein. Investigators may propose technologies to scan the entire genome of a cell or tissue for constellations of cytogenetic changes or other DNA alterations.

They may also propose development of technologies to identify changes in gene expression at the level of both RNA and protein. Technologies to evaluate the function status of proteins including proteins of cellular regulatory pathways are also appropriate.

As a secondary goal, this initiative is intended to encourage the development of all components of integrated analytical systems including preparation of samples, sample analysis and appropriate informatics systems for data collection and analysis.

Applications may be submitted *as either* research project grants (R01s) or exploratory/developmental grants (R21s). Investigators with sufficient preliminary data are encouraged to apply for funding using the R01 grant mechanism.

Use of the R21 mechanism is designed to support applications where insufficient preliminary data has been generated to support a full R01 application.

Approximately $1.5 million from NCI and $150,000 from NIDCD will be available to support six to eight grants.

Inquiries: James Jacobson, DCTDC, NCI, 6130 Executive Blvd Rm 513-MSC 7388, Bethesda, MD 20892-7388, tel: 301/496-1591, fax: 301/402-1037, email: JJ37D@NIH.GOV

Kenneth Gruber, Division of Human Communication, National Institute on Deafness and Other Communication Disorders, 6120 Executive Blvd Rm 400-C, MSC 7180, Bethesda, MD 20892-7180, tel: 301/402-3458, fax: 301/402-6251, email: kenneth_gruber@nih.gov