THE CANCER LETTER

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HHS Secretary Rebukes Task Force Guidelines On Breast Cancer Screening

By Paul Goldberg

"Confusion" is the last thing a cancer screening guideline should be expected to cause.

Yet, two days after the U.S. Preventive Services Task Force set off a blast of accusations and name-calling by issuing a breast cancer screening guideline, HHS Secretary Kathleen Sebelius put some distance between the Obama administration and the non-partisan group of public health experts who reviewed the data and came up with a new set of screening recommendations.

"There is no question that the U.S. Preventive Services Task Force recommendations have caused a great deal of confusion and worry among

(Continued to page 2)

Historical Perspective:

Clarity Was The First Casualty In 30-Year War Over Mammography For Younger Women

By Kirsten Boyd Goldberg

In the past three decades, attempts to develop rational, evidence-based screening guidelines for breast cancer in the U.S. have always generated intense controversy.

What happened this week with the new U.S. Preventive Services Task Force recommendation has happened many times before:

An independent panel of experts is assigned to rationally assess the data and evaluate the level of evidence for screening in order to minimize the role of commercial and political interests in promoting a test that might or might not reduce cancer mortality.

The moment the panel's document is released, political combat ensues. The result is a cacophony. The resulting cacophony angers politicians who don't understand why "the experts" can't agree on "one simple message."

The anger of politicians frightens federal health officials who want to protect their budgets and their ability to run programs without meddling from Congress.

The federal health officials bob and weave and distance from the expert panel's recommendations.

The expert panel becomes the focal point of the anger. Commercial and political interests make accusations about the panel's composition, experience, and potential conflicts of interest. The panel must have been politically

(Continued to page 8)

Guidelines Cause Firestorm As Congress Mulls Health Care

(Continued from page 1)

women and their families across this country," Sebelius said in a statement Nov. 18. "I want to address that confusion head on. The U.S. Preventive Services Task Force is an outside independent panel of doctors and scientists who make recommendations.

"They do not set federal policy, and they don't determine what services are covered by the federal government."

Reviewing pooled data from randomized trials and relying on modeling, the group of academic experts recommended against routine screening of women between the ages of 40 and 49, and said that for older women, mammograms should be performed every two years.

Professional societies involved in screening—radiologists among them—accused the administration of rationing healthcare. Critics of the Obama health plan similarly picked up on the "R" word, prompting administration spokesmen to point out that the task force started its work on the breast cancer guideline in 2006, during the Bush administration. Meanwhile, traditionally pro-screening groups—including the American Cancer Society and Susan G. Komen for the Cure—reaffirmed their support for starting mammography at 40 and performing it annually.

In retrospect, it seems that the administration was never committed to the task force guidelines, and that the timing—coinciding with Capitol Hill debates over healthcare reform legislation—was inopportune. The document didn't get an HHS "roll-out" when it was published in the Annals of Internal Medicine the afternoon of Nov. 16. There was no press conference, and no one even attempted to explain the intellectually challenging concept of over-treatment or show how the 2009 guidelines compared with the 2002 version.

The timing was inopportune for the administration, but there was no way to control it. Publication date for the guidelines was determined months in advance by the Annals, a journal of the American College of Physicians.

Over the ensuing two news cycles—on Monday and Tuesday—the voices of epidemiologists and patient groups that believe that mammography has been overemphasized and oversold were simply drowned out. At noon Wednesday, Sebelius publicly disowned the guideline.

"There has been debate in this country for years about the age at which routine screening mammograms should begin, and how often they should be given," Sebelius said. "The task force has presented some new evidence for consideration, but our policies remain unchanged. Indeed, I would be very surprised if any private insurance company changed its mammography coverage decisions as a result of this action."

The HHS secretary concluded this extraordinary message by stating that available data do not support any change, and—in essence—urged women to ignore everything they heard in the preceding two days.

"What is clear is that there is a great need for more evidence, more research and more scientific innovation to help women prevent, detect, and fight breast cancer, the second leading cause of cancer deaths among women," Sebelius said. "My message to women is simple. Mammograms have always been an important life-saving tool in the fight against breast cancer, and they still are today. Keep doing what you have been doing for years—talk to your doctor about your individual history, ask questions, and make the decision that is right for you."

Task Force: No Routine Mammograms Until 50

As governor of Kansas, Sebelius defended abortion rights and challenged the creationists who controlled the state's school board. But as health care reform hung in the balance on Capitol Hill, Sebelius chose not to stand by the work of the HHS guideline-making component.

An argument can be made that Sebelius's decision

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to cave is something of a political landmark: pragmatic recognition that over the past three decades, every effort to separate breast cancer outcomes data from belief has set off catastrophic political backlash.

Critics say that the action invalidates the entire reason for making guidelines and leaves patients unprotected from commercial interests even as the administration carries out a massive program of studies of comparative effectiveness in medicine.

"It's the triumph of faith over medicine," said Shannon Brownlee, a fellow at the New America Foundation and author of "Overtreated," a book about medical care in the U.S. "But in the end, patients need to understand that mammography is not a slam-dunk, and that there are tradeoffs."

Fran Visco, president of the National Breast Cancer Coalition, said Sebelius's action seems inconsistent with reliance on evidence-based medicine.

"The official HHS position should be based on science," Visco said. "They should not accept science only when they agree with the results and when it's politically expedient. That's not what science is about. I don't think they should be issuing any statements right now. The whole world needs to take a moment, take a step back, take a breath. Let's understand why this panel of independent, objective experts made these recommendations. These are the experts. Who should write guidelines on when we should be screening a healthy population? The American College of Radiology?"

Reliance on impartial, independently written guidelines is one of the pillars of modern medicine, said David Ransohoff, an epidemiologist and gastroenterologist at the University of North Carolina.

"It's discouraging if guidelines can be easily dismissed because of political motivations," Ransohoff said. "At their best, professional guidelines should lead to recommendations in the best interests of patients, not of companies, doctors or payers. If we aren't prepared to trust the guidelines-making process to do that, then we should fix it."

Radiologists were pleased with Sebelius's action and eager to consolidate the gains. In a statement praising the HHS Secretary, the American College of Radiology asked Sebelius to "officially ask the task force to rescind their mammography recommendations in order to avoid confusion as health care reform moves forward."

This is important because health reform legislation moving through Congress relies on USPSTF to determine which preventative services may be offered under the government "insurance exchanges."

Moreover, radiologists asked for a seat at the table in writing future guidelines.

"We urge HHS to include in the USPSTF experts from the areas on which they will be advising lawmakers and submit their recommendations for comment and review to outside stakeholders in similar fashion to rules enacted by the Centers for Medicare and Medicaid Services," the radiologists said. "A more inclusive process can only benefit Americans as we seek to improve our health care system."

Inclusion of special interests is precisely what the task force was created to avoid, said Russell Harris, professor of medicine and epidemiology at the University of North Carolina and past member of the task force who was involved in developing the 2002 and 2009 guidelines.

"The people most expert in developing guidelines are people who don't think that they already know the answer, and they go into it with an open mind, and they go into it with no conflict of interest, either intellectual or financial," Harris said. "The task force's sole purpose is to look at the evidence and try to do their best to make a judgment about the benefits and harms of this particular service and this particular set of people."

Harris said he was disappointed to hear critics characterize the guidelines as an effort to ration health care.

"Money is never mentioned at our meetings," said Harris, who has attended every one of the task force meetings for a decade. From 1997 to 2002, he performed systematic reviews of literature, and from 2002 through 2007, he was a member of the task force. "Government rationing, trying to decrease the cost of things, trying to worry about how much we are spending—that's just not part of the decision," Harris said. "Here is what we talk about: 'Is this randomized, controlled trial properly done? Did they randomize right? If we did this to 1,000 women, how many would be helped, and, by the way, how many would be hurt?' Those are the things that we lose sleep about."

Politics don't figure into the equation, either, Harris said.

When he was appointed to the task force in 2002, no one asked him about his party affiliation. "I have never voted for a Bush," Harris said. "If you asked me if I canvassed and went door to door for Obama, the answer is, 'Yes, I did.' Do I favor health care reform? Absolutely. Does this pierce me in the heart? Yes, it does.'"

Five Screening Modalities Examined

Donald Berry, head of the Division of Quantitative Sciences at M.D. Anderson Cancer Center, said the task force recommendation indeed give the administration the opportunity to save billions of dollars while benefiting public health.

"One issue of concern is that these recommendations will be perceived by some right-wing extremists as an Obama administration attempt to save money at the expense of women," said Berry, who took part in simulating outcomes under several screening schedules. "Indeed, it will save billions of health care dollars. But the money was buying nothing of value."

Though USPSTF examined five screening modalities, its most controversial stance was a recommendation against routine screening mammography for women between 40 and 49.

Women between 50 and 74 should get mammograms every two years, the task force recommended, adding that evidence to assess mammography after age 75 is insufficient.

Mammograms should be performed every other year, rather than annually, the task force said.

The task force recommended against clinicians teaching women to perform breast self-exams and said evidence is insufficient to assess benefits and harms of clinical breast exams, digital mammography and magnetic resonance imaging of the breast.

The recommendations are at odds with those of the American Cancer Society, the National Comprehensive Cancer Network, the radiology groups, and Komen. However, NBCC, Breast Cancer Action, and a number of epidemiologists described the new guideline as scientifically valid.

No federal organization is more familiar with the political hazards of breast cancer screening than NCI.

Over the years, the institute has repeatedly provided a platform for skeptics, often finding itself under attack and needing to cave under pressure. As a result of this pressure, NCI found itself in the guideline writing business, adopting only one guideline—for breast cancer screening.

This position is so anachronistic that the institute's initial reaction to the USPSTF recommendation was to hint that it may reconsider its own guideline (which recommends mammography starting at 40), and that it would prefer to focus on science rather than directives to patients.

"NCI's primary role as a biomedical research agency is to generate scientific knowledge that can be used by the task force and other organizations in their deliberations and recommendations," the institute said in an un-attributed, carefully crafted statement. "Today's report reflects the fact that more questions need to be answered, and that will be NCI's central focus going forward."

Two Additional RCTs Included In Meta-Analysis

The task force last examined breast cancer screening seven years ago. At that time, it recommended that mammography with or without clinical breast exam begin at 40 and continue through 69 at one to two-year intervals.

This broad recommendation carried the grade B, which means that clinicians should provide these services to eligible patients. At the time, the task force said it lacked evidence to determine the value of breast self-exams and clinical breast exams without mammography.

The new recommendations consider mammography in finer detail. The recommendation against routine delivery of the procedure in younger women is graded C, which indicates that the balance of risks and benefits is very close.

However, the task force is more certain—with a B recommendation—that screening should be biennial, and that it continue for five years beyond the 2002 recommendation.

The update was a routine review rather than a re-evaluation prompted by new evidence.

The 2002 guideline was based on meta-analysis of seven randomized trials. Two new randomized trials have been reported since. These are the U.K. Age trial, which randomized 160,921 women to screening vs. not screening at age 40, and an update of the Swedish Gothenburg trial.

In the UK trial, after 10.7 years of follow-up, the relative risk for all-cause mortality was 0.97 (95% CI 0.89 to 1.04) and the relative risk of breast cancer mortality was 0.83 (95% CI 0.66 to 1.04) in the screened group. In the Gothenburg trial, follow-up showed that women who entered the study at ages 39 to 49 had the relative risk of breast cancer mortality of 0.69 (95% CI 0.45 to 1.05 after 13 years of follow-up.

As the task force included these two new trials in a meta-analysis, it found about a 15 percent reduction in the relative risk of breast cancer mortality for both the 40 to 49 age group and the 50 to 59 age group. However, models show that 60 percent more false-positive results occur for every 1,000 patients if screening begins at 50.

Harris said the 2009 guideline is consistent with

the 2002 version.

Seven years ago, the task force noted that "the balance of benefits and potential harms… grows more favorable as women age" and the decision to screen should be based on risk factors, such as family history of breast cancer diagnosed before menopause.

"The task force did not intend at that time to say routinely—this is a rule—everybody start at 40 and be screened," Harris said. "That was not what they were saying. It was misinterpreted. That's what the task force is saying now. We are trying to say it in a different way, because the point didn't get across before. We actually quoted a part of the 2002 recommendation to point out that we still agree with what we said in 2002."

ACS Stands By Annual Screening After 40

"With its new recommendations, the USPSTF is essentially telling women that mammography at age 40 to 49 saves lives; just not enough of them," said Otis Brawley, chief medical officer of the American Cancer Society.

"The USPSTF says that screening 1,339 women in their 50s to save one life makes screening worthwhile in that age group. Yet USPSTF also says screening 1,904 women ages 40 to 49 in order to save one life is not worthwhile," Brawley said. "The American Cancer Society feels that in both cases, the lifesaving benefits of screening outweigh any potential harms. Surveys of women show that they are aware of these limitations, and also place high value on detecting breast cancer early.

"As someone who has long been a critic of those overstating the benefits of screening, I use these words advisedly: this is one screening test I recommend unequivocally, and would recommend to any woman 40 and over, be she a patient, a stranger, or a family member," Brawley said.

Berry disagrees with the rationale of Brawley's critique of the recommendation.

"Any number to save one life is misleading," Berry said. "It presupposes that screening saves lives, for which there is not one scintilla of evidence. Even if we grant a survival benefit for screening, this benefit may be due exclusively to delaying the disease and curing no one. Also, the 1,904 figure has much greater variability than does the 1,339 figure. The range might be something like 1,000 to infinity—no benefit—and that's the point."

Harris said the one in 1,904 figure points to potential for harm. "You have to understand what this means," he said. "It means is that if you were to screen 1,904 women in their 40s for up to 10 years, then within the next 11 to 20 years after you started screening, one woman would have her life extended," he said. "One out of 1,904 over 20 years. Is that small or large? It doesn't seem very large to me. Almost certainly, there will be more women who are treated unnecessarily. We don't know the exact number, but it's almost certainly more than one. Several of these 1,904 women would be treated, which means mastectomy, tamoxifen, and cytotoxic therapy."

The recommendation to perform mammography every two years starting at 50 is based on the results of randomized trials as well as modeling.

Annual screening was "consistent with the attitude in U.S. medicine that if some is good, then more is better," Berry said. "We've opted for more. With no evidence." To get the answers, the task force asked the NCI Cancer Intervention and Surveillance Modeling Network whether annual screening is better, and by how much.

"We said it's not much better at all," Berry said. "So little better as to make the harms of additional screening dominate in any decision-making process. The harms of halving the number of mammograms come close to being halved while the benefits are nearly unaffected. The decision is so clear as to enable a broad recommendation. Sometimes less is more."

Harris, who served as liaison between the task force and the CISNET group, agrees. "When we used the models from the CISNET group this time, it was clear that every two years works just about as well as every year, and—by the way—it cuts the false positives in half," he said. "Why wouldn't you reduce the harms by a lot and get almost the same benefit?

"It's not the matter of money, it's the matter of hurting people."

The guidelines and supporting documents are posted at http://www.ahrq.gov/clinic/uspstf/uspsbrca.htm

Reactions: Outrage From Believers Drowns Out Skeptics

The range of reactions to the U.S. Preventive Services Task Force demonstrates that proponents of screening are far more numerous than skeptics:

Tens of thousands of lives are being saved by mammography screening, and these idiots want to do away with it. It's crazy—unethical, really.

—Daniel Kopans, radiologist, Harvard Medical School, quoted by The Washington Post

We hope that policy makers, the public and the health care community will take the time to carefully analyze the basis of the revised recommendations. Women have been given different messages for years, but unfortunately those messages were not based on strong evidence. Women deserve the truth even when it is complicated. They can accept it.

—Fran Visco, president, National Breast Cancer Coalition

These unfounded USPSTF recommendations ignore the valid scientific data and place a great many women at risk of dying unnecessarily from a disease that we have made significant headway against over the past 20 years. Mammography is not a perfect test, but it has unquestionably been shown to save lives - including in women aged 40-49. These new recommendations seem to reflect a conscious decision to ration care. If Medicare and private insurers adopt these incredibly flawed USPSTF recommendations as a rationale for refusing women coverage of these life-saving exams, it could have deadly effects for American women.

The USPSTF claims that the "harms" of mammography, including discomfort of the exam, anxiety over positive results, and possibility of overtreatment because medical science cannot distinguish which cancers will become deadly most quickly - outweigh the greatly decreased number of deaths each year resulting from breast cancer screening. Without doubt, the possibility of having one's life saved through early detection far outweighs any of these concerns. Their premise is tragically incorrect and will result in many needless deaths if their recommendations are adopted by the American public," said Lee.

—Carol Lee, chair of the American College of Radiology Breast Imaging Commission

Breast Cancer Action has been saying for years that there is no evidence that routine screening of women at normal risk for breast cancer aged 40 to 49 saves lives. Now the Preventive Task Force has caught up with us (in Europe, mammograms are given to post-menopausal women every other year, with no worse outcome than the U.S.)

—Barbara Brenner, executive director, Breast Cancer Action

NCI appreciates the U.S. Preventive Services Task Force's careful review and analysis of the evidence regarding breast cancer screening for women at average risk. The take-away message is that each woman needs to consider her individual benefits and risks and discuss them with her health care provider before making a decision on when to start screening mammography and how often to get one. The task force report concludes that screening mammography remains an important, effective tool for early detection of breast cancer. It also indicates, however, that the evidence of benefit might vary, according to age and individual risk factors.

NCI has had screening mammography recommendations for many years, and we need to evaluate them in light of the task force's recommendations—for all women, not only for those of average risk. It's too early for us to make any decisions right now. NCI's primary role as a biomedical research agency is to generate scientific knowledge that can be used by the task force and other organizations in their deliberations and recommendations. Today's report reflects the fact that more questions need to be answered, and that will be NCI's central focus going forward.

—Statement by the National Cancer Institute

I am deeply concerned about the actions of the USPSTF in severely limiting screening for breast cancer. These recommendations, in combination with recent CMS imaging cuts, jeopardize access to both long proven and cutting-edge diagnostic imaging technologies. Government policy makers need to consider the consequences of such decisions. I can't help but think that we are moving toward a new health care rationing policy that will turn back the clock on medicine for decades and needlessly reverse advances in cancer detection that have saved countless lives.

—James Thrall, chair of the American College of Radiology Board of Chancellors

Annual clinical breast examinations and screening mammography, with breast awareness encouraged is stated in the NCCN Guidelines as a recommendation for women 40 years and older at normal risk.

Age should not be an absolute when determining who should receive mammography screening. It is imperative to consider the patient's individual risk factors when considering an appropriate screening routine."

—Therese Bevers, of M. D. Anderson Cancer Center and chair of the NCCN Guidelines Panel for Breast Cancer Screening and Diagnosis

Susan G. Komen for the Cure wants to eliminate any impediments to regular mammography screening for

women age 40 and older. While there is no question that mammograms save lives for women over 50 and women 40–49, there is enough uncertainty about the age at which mammography should begin and the frequency of screening that we would not want to see a change in policy for screening mammography at this time.

Our real focus, however, should be on the fact that one-third of the women who qualify for screening under today's guidelines are not being screened due to lack of access, education or awareness. That issue needs focus and attention: if we can make progress with screening in vulnerable populations, we could make more progress in the fight against breast cancer.

Mammography is not perfect, but is still our best tool for early detection and successful treatment of this disease. New screening approaches and more individualized recommendations for breast cancer screening are urgently needed. Susan G. Komen for the Cure is currently funding research initiatives designed to improve screening, and we believe that it is imperative that this research move forward rapidly. Komen also provides funding for more than 1,900 education, awareness and screening programs.

We encourage women to be aware of their breast health, understand their risks, and continue to follow existing recommendations for routine screenings including mammography beginning at age 40.

—Eric Winer, chief scientific advisor and chair of Komen's Scientific Advisory Board and director of the breast oncology center at Dana-Farber Cancer Institute

We used to think that all cancers were the same, that they all grew at the same pace, and that there was a window when all breast cancers could be caught before they spread. We now know that there are at least five different kinds of breast cancer based on their molecular biology. Some breast tumors are so slow growing and are so unlikely to spread that they will never do any harm. Others grow and spread very quickly. The idea that they all can be "caught early" is wishful thinking. In fact screening is best at finding the "good ones" that might even disappear if left alone. Remember the reduced the mortality from mammography is 30% not 100%! If early detection always worked, the number of aggressive cancers we see would have gone down as a result of screening.

The goal of breast cancer screening should be this: to find the cancers that have the potential to kill you, so that an intervention is necessary and can make a difference. We need to stop finding the cancers that will never do anything, and stop over-treating women who have them.

—Susan Love, Dr. Susan Love Research Foundation

Today's recommendations from the USPSTF recognize the value of mammography in reducing breast cancer deaths, affirm the importance of mammography among women aged 50 and older, and emphasize that mammography should be seriously considered in women 40-49 after assessment of the risks and benefits. It is therefore of concern that at present more than a third of women who are now recommended for screening are not getting regular mammograms.

While the optimal scheduling of regular mammograms is being discussed by experts in the field, ASCO would not want to see any impediments to mammography screening for any woman age 40 and above.

From ASCO's perspective, the critical message is that all women—beginning at age 40—should speak with their doctors about mammography to understand the benefits and potential risks, and determine what is best for them.

—The American Society of Clinical Oncology

The American Cancer Society continues to recommend annual screening using mammography and clinical breast examination for all women beginning at age 40.

Our experts make this recommendation having reviewed virtually all the same data reviewed by the USPSTF, but also additional data that the USPSTF did not consider. When recommendations are based on judgments about the balance of risks and benefits, reasonable experts can look at the same data and reach different conclusions.

In 2003, an expert panel convened by the American Cancer Society conducted an extensive review of the data available at the time, which was not substantially different from the data included in the current USPSTF review.

Like the USPSTF, the society's panel found convincing evidence that screening with mammography reduces breast cancer mortality in women ages 40-74, with age-specific benefits varying depending on the results of individual trials and which trials were combined in meta-analyses.

And like the USPSTF, the American Cancer Society panel also found that mammography has limitations—some women who are screened will

have false alarms; some cancers will be missed; and some women will undergo unnecessary treatment. These limitations are somewhat greater in women in their forties compared with women in their fifties, and somewhat greater in women in their fifties compared with women in their sixties.

We specifically noted that the overall effectiveness of mammography increases with increasing age. But the limitations do not change the fact that breast cancer screening using mammography starting at age 40 saves lives.

"As someone who has long been a critic of those overstating the benefits of screening, I use these words advisedly: this is one screening test I recommend unequivocally, and would recommend to any woman 40 and over, be she a patient, a stranger, or a family member.

The USPSTF says that screening 1,339 women in their 50s to save one life makes screening worthwhile in that age group. Yet USPSTF also says screening 1,904 women ages 40 to 49 in order to save one life is not worthwhile. The American Cancer Society feels that in both cases, the lifesaving benefits of screening outweigh any potential harms. Surveys of women show that they are aware of these limitations, and also place high value on detecting breast cancer early.

With its new recommendations, the USPSTF is essentially telling women that mammography at age 40 to 49 saves lives; just not enough of them.

The task force says screening women in their 40s would reduce their risk of death from breast cancer by 15 percent, just as it does for women in their 50s. But because women in their 40s are at lower risk of the disease than women 50 and above, the USPSTF says the actual number of lives saved is not enough to recommend widespread screening.

The most recent data show us that approximately 17 percent of breast cancer deaths occurred in women who were diagnosed in their 40s, and 22 percent occurred in women diagnosed in their 50s. Breast cancer is a serious health problem facing adult women, and mammography is part of our solution beginning at age 40 for average risk women."

—Otis Brawley, chief medical officer, the American Cancer Society

We believe there is sufficient data to support annual mammography screening for women age 40 and older.

We also believe the breast cancer survival rate of women between 40 and 50 will improve from the increased use of digital mammographic screening, which is superior to older plain film techniques in detecting breast cancer in that age group.

While we recognize that there will be a number of benign biopsies, we also recognize that mammography is the optimal screening tool for the early diagnosis of breast cancer in terms of cost-effectiveness, practical use, and accuracy.

To restrict its use will mean that breast cancers will go undiagnosed for an unacceptable period of time. This restriction of mammographic screening defeats the goals of early detection, which often allows for breast conserving surgery and avoidance of chemotherapy.

The USPSTF also does not make a recommendation for mammography screening for women age 75 and older. Women in this age group are at the greatest risk for breast cancer and at the point where mammography is most sensitive.

We believe these recommendations effectively turn back the clock to pre-mammography days by making the diagnosis of breast cancer occur only when the tumor is large enough to be felt on a physical exam. The society will continue to advocate for routine annual mammography screening for all women beginning at age 40. Mammography screening reduces breast cancer mortality and saves lives.

—The American Society of Breast Surgeons

Historical Perspective:

NCI Sought Simple Message As Science Grew Complicated

(Continued from page 1)

influenced, critics charge. The specter of "rationing" health care is raised.

The beleaguered panel members either defend their recommendation or say nothing.

Rational assessment has always had a tough road to travel in the U.S., starting with the dawn of randomized clinical trials, when doctors didn't accept trial results as being valid. But that's another story.

By the late 1970s, randomized trials were accepted as the "gold standard" to prove whether an intervention worked or whether its perceived effect was merely due to chance. But in the face of rising incidence of breast cancer and few effective therapies, clinicians were willing and eager to accept even a hint of benefit for screening mammography.

For women in their 40s, the trials didn't meet statistical significance, but were "trending to" significance, proponents said. One could "infer" that

women would benefit from screening, even if it wasn't proven.

From this inference, the message drummed into public consciousness throughout the 1980s was that "mammography saves lives."

NCI got into the business of breast cancer screening guidelines in 1977, and then had a messy time trying to get out of it in the 1990s. The U.S. Preventive Services Task Force, formed in 1984, never fully agreed with the NCI and American Cancer Society recommendations.

In part, the controversy of this past week is just another step in a long and painful withdrawal from the "one simple message" of the 1980s.

In May 1977, NCI first adopts guidelines for mammography for use in breast cancer screening (The Cancer Letter, May 13, 1977). This was not a guideline for all women, just those women under 50 who were participating in the NCI-American Cancer Society study called the Breast Cancer Detection Demonstration Project. Younger women in the study were to receive screening only if they had a previous history of breast cancer or a mother or sister with the disease.

Later that year, the very first NIH Consensus Development Conference examined the issue of screening mammography and whether to continue the BCDDP. The panel concluded, based on data from the study, that screening mammography should be available for women over 50. Women 40-49 with a personal history of breast cancer or whose mothers or sisters had breast cancer should continue to be screened within the study (The Cancer Letter, Sept. 23, 1977).

In 1987, the results of the BCDDP came in. Though it was not a randomized trial, the results seemed to infer that younger women would benefit from screening to the same degree as older women. About this time, NCI, ACS, and about 18 other organizations got together to establish a consensus on screening mammograms. The Health Insurance Plan of New York trial showed a 30 percent mortality reduction in women over 50, but could not demonstrate a benefit for women between 40 and 49.

Still, NCI, ACS and the other organizations recommended annual clinical breast exam beginning at age 40, with screening mammography at one- to two-year intervals; and beginning at age 50, annual CBE and mammography. The statement also advised all women to perform monthly breast self-exam, and suggested "special surveillance" for women with a history of breast cancer or breast cancer in her mother or sister.

In 1988, a new analysis of the HIP trial, by Kenneth Chu, was published in the Journal of the National Cancer Institute. Women screened at ages 40-49 and followed for at least 18 years after trial entry had 24 percent fewer breast cancer deaths than the controls. However, the benefit didn't show up until nine years later.

According to a 1988 Cancer Letter story on these results, "the researchers said they hope that this study will help settle the under-50 screening debate."

The results did strengthen what became known as the "consensus guideline," and though the guideline was not accepted by every health organization, it was publicized widely by NCI, ACS and the groups that signed onto it. Plastic shower cards with the mammography screening recommendations and pictures of how to perform breast self exam became ubiquitous.

In 1992, the results of the National Breast Screening Study of Canada were published in the Canadian Medical Association Journal. This was supposed to be the trial designed specifically to answer the question about screening mammography for women in their 40s. The study showed that women 40-49 who received mammograms did no better than women were weren't screened. In fact, the trial found that the women who were screened did *worse* than the control group. More advanced cancers were found in the screened group in the first round of screening than in the control group.

Radiologists claimed that this demonstrated that the Canadian trial was biased. Something must have gone wrong in the randomization, they said. Stephen Feig, of Thomas Jefferson University, and Daniel Kopans, of Massachusetts General Hospital and Harvard University, in a report for the American College of Radiology, identified all the things they found objectionable in the Canadian trial.

Letters and rebuttals between the Canadian investigators and Feig and Kopans, and others, filled various journals during 1992.

To deal with this imbroglio, NCI officials decided to hold a conference.

In February 1993, the NCI Workshop on Breast Cancer Screening developed a report that became known as the Fletcher report after the panel's chairman, Suzanne Fletcher of the American College of Physicians. This report didn't make any recommendation, but reviewed the available data. For the 40-49 age group, "there is no reduction in mortality from breast cancer that can be attributed to screening," the report said. "There is an uncertain, and, if present, marginal reduction in mortality at about 10 to 12 years. Only one study provides information on long-term effects beyond 12

years, and more information is needed." The report also called these 10-year age groupings "arbitrary and without biologic justification."

Radiologists attacked the report—and questioned Fletcher's qualifications. "Women and physicians should be aware of the fact that there are strong inferential data that screening can reduce mortality for women 40-49," Kopans wrote in a letter to The Cancer Letter.

"Inferential" benefit—rather than statistically significant benefit—was what NCI had based its original guideline on for women in their 40s. Many organizations, clinicians, and radiologists took the view that there was no need to change the guideline.

But maintaining the status quo didn't sit well with then NCI director, Samuel Broder. In his public remarks, he seemed to view it as a moral issue: How can you claim that screening mammography saves lives if you don't have statistically significant evidence that it save lives?

This represented a seismic shift at NCI. The institute was changing the rules of the game.

This change was alluded to when, in September 1993, the NCI Physician's Data Query database stopped referring to screening guidelines, instead issuing "summary of evidence statements" about cancer screening methods (The Cancer Letter, Sept. 17, 1993).

Having made that change, the institute had no choice but to back away from the 1988 guideline. The result was a brutal political battle.

In September 1993, Broder presented NCI's proposed revised statement on screening mammography to the National Cancer Advisory Board. The board was informed rather late in the game about the change of rules. PDQ had already made its changes.

The proposed guideline recommended that women 40-49 "discuss with a health professional the advisability of screening with mammography, taking into account family history of breast cancer and other risk factors. NCI also recommends annual clinical breast examination as a prudent practice for this age group" (The Cancer Letter, Sept. 24, 1993).

"Our job is only to convey scientific knowledge," Broder said. "The best course is to acknowledge where we are. We can't protect the public from the fact that science may change things."

But the NCAB wasn't ready to back the proposed new guideline, and instead passed a resolution on a 14-1 vote asking NCI to delay action on the guideline. The prevailing view was stated by then NCAB member Ellen Sigal. "If there is no agreement on the science, how can we change the policy?" she said. "I went to all of those meetings. I heard those scientists say, 'We don't know.' Then I heard the scientists and physicians say they will continue to get mammography for themselves and would have their family members get it. How can we possibly change the guidelines?"

Proponents of screening alleged that NCI had to toe the line because the Clinton health care reform plan didn't include a screening mammography benefit for women in their 40s. Some NCI officials were intimating behind closed doors to some participants that there was pressure from the administration to make the changes, perhaps as a way of trying to push the board to support the change.

In December 1993, NCI issued a "summary of scientific fact," not a guideline. The three-sentence statement: "There is a general consensus among experts that routine screening every one to two years with mammography and clinical breast examination can reduce breast cancer mortality by about one-third for women ages 50 and older. Experts do not agree on the role of routine screening mammography for women ages 40 to 49. To date, randomized clinical trials have not shown a statistically significant reduction in mortality for women under the age of 50."

In early 1994, NCI was called to answer for this at Congressional hearings. Several members of Congress believed NCI's actions confused women and took away hope, and they were eager to browbeat those Bethesda scientists. At one hearing, Rep. Edolphus Towns (D-N.Y.) called NCI racist, sexist, and callous. Rep. Bernie Saunders (I-Vt.) called for kicking the rascals out.

Broder stated at Congressional hearings that the change had nothing to do with the Clinton health reform plan, and that NCI's movement away from the 1988 guideline was set in motion the year before the Clinton plan emerged.

Meanwhile, ACS and the American College of Radiology and others acknowledged that the data aren't in. However, while waiting for conclusive data, it would be prudent health practice to screen, they said.

The pressure to reach a consensus, to speak in a single voice and "avoid confusion" continued.

In 1996, new data were coming out of trials in Sweden, claiming a mortality reduction for women 40-49. NCI's new director, Richard Klausner, said it was time to re-examine the 1993 statement. Time for another conference.

The Swedish data had not been published yet in scientific journals, but had been presented at an international meeting, just one step on the road to

validation. Was the institute under political pressure to quickly change the statement back to supporting mammograms for younger women? Certainly, the lashing by Congress was a recent memory.

This time, in an attempt to head off accusations of institutional bias, NCI decided against sponsoring the necessary conference. Instead, NIH would hold a Consensus Conference with a panel not selected by NCI.

In January 1997, the NIH Consensus Conference statement said that the evidence was insufficient to determine the benefits of mammography among women aged 40-49. The panel recommended that women aged 40-49 should be counseled about potential benefits and harms before making decisions about mammography

The statement didn't provide much further information. When the statement was released at the conference, even some scientists who had been neutral on the subject of screening for women in their 40s attacked it for not addressing the Swedish data in a more detailed fashion.

According to a story in The New York Times, Klausner came running out of the conference auditorium to use the telephone. Klausner said he was "shocked by the conclusions and disliked their negative tone." Klausner later claimed he was misquoted, and actually had been shocked by the level of anger that erupted at the end of the conference.

Be that as it may, the quote, as well as Klausner's comments at the press conference after the meeting, served to immediately trample the panel's conclusions.

At the press conference, Klausner said: "I am concerned that women are not being given, with the report, all the evidence that they actually need.... [M]y evaluation is that these studies have reached a statistical significance and that there is now evidence that we didn't have previously."

As NCI distanced from the panel's report, the NCAB began work on a separate statement.

In February 1997, the Senate passed a "sense of the Senate" resolution in a 98-0 vote, urging the NCAB to consider recommending screening for women 40-49 or to direct the public to consider guidelines issued by other organizations. NCI officials were brought to Congress again to explain why scientists can't agree.

Pennsylvania Senator Arlen Specter, then the Republican chairman of the Labor, HHS appropriations subcommittee, held four hearings in four months on this issue.

It seemed that members of Congress this time had determined that screening in younger women saves lives. According to Sen. Kay Bailey Hutchinson (R-Tex.), NCI's role should be to "help us get a clear message, tell us what the risks are, tell us what the advantages are. There is no question," she said at a hearing, "that the advantages outweigh the risks."

In March 1997, as Congress and the Clinton administration exerted pressure on the institute to act immediately, the NCAB endorsed screening mammograms for women 40-49 every one to two years if they are at "average risk" for breast cancer. In a demonstration of solidarity, NCI and ACS released a joint statement saying that the two groups agreed that screening women in their 40s is "beneficial and supportable with current scientific evidence."

In a White House press briefing, President Clinton praised the NCAB's recommendations for providing "consistent guidance to women" (The Cancer Letter, April 4 and April 11, 1997).

ESAs Increased Blood Clots, Didn't Reduce Transfusions

By Paul Goldberg

A retrospective population study of the use of erythropoiesis-stimulating agents in cancer patients found that these widely used drugs had no impact on lowering blood transfusions, but increased the risk of thromboembolism.

The study, published online by JNCI, focuses on the period between 1991 and 2002, the decade when ESAs came on the market and started to penetrate the oncology market.

The finding that these agents failed to decrease the use of blood transfusions is noteworthy because ESAs were approved based on their ability to decrease blood transfusions for patients with solid tumors. Harder endpoints, such as survival and time to progression, were not considered at the time of approval, but concerns about safety of these widely drugs emerged in recent years.

"This research answers important questions about outcomes of ESAs when used in long-term clinical practice with oncology patients," the study's senior author Dawn Hershman, the Florence Irving Assistant Professor of Medicine and Epidemiology at Columbia University Medical Center, said in a statement. "While ESAs were given to reduce the need for blood transfusions, a substantial reduction in the use of blood transfusions was not observed. However, an increase risk of deep vein thrombosis or pulmonary embolism was confirmed."

The study focuses an unusually large cohort, 56,210 patients over age 65, who were identified through the Surveillance, Epidemiology, and End Results-Medicare database. These patients had colon cancers, non-small cell lung cancer, breast cancer and diffuse large B-cell lymphoma. (ESAs are not approved for the treatment of lymphoma.).

The findings are also noteworthy because the study was designed to capture the results of standard care and reflects comparative effectiveness, as opposed to efficacy.

"This analysis confirms the association between ESAs and venous thromboembolism, which was observed in previous meta-analysis," Hershman said. "This new finding is significant because where the meta-analysis looked at pooled data from randomized clinical trials, this data is from community practice—real-life clinical settings—where you can often see things that wouldn't necessarily show-up in a short-term, 12-week study. Additionally, this analysis included data from more than 50,000 patients, including those with more advanced cancer or high-risk status, who therefore might not have been candidates for clinical trials."

During the decade, the proportion of patients receiving ESAs increased tenfold, from 4.8% in 1991 to 45.9% in 2002 ($p<.001$). Yet, the rate of blood transfusion remained unchanged: 22%.

Meanwhile, venous thromboembolism developed in 1,796 (14.3%) of the 12,522 patients who received ESAs vs. 3,400 (9.8%) of the 34,820 patients who didn't (HR 1.93, 95% CI 1.79-2.07). Overall survival was the same in both groups.

The label for ESAs currently carries a black box warning noting a higher risk of thromboembolic events and tumor promotion. A risk-mitigation strategy is being negotiated by the ESAs sponsors Amgen Inc. and Johnson & Johnson.

In Brief:

Moddelmog Steps Down At Komen For The Cure

SUSAN G. KOMEN FOR THE CURE announced the resignation of **Hala Moddelmog** as president and CEO. Moddelmog has served the organization since 2006 and has been credited with helping the organization's growth.

Susan G. Komen for the Cure founder, **Nancy Brinker**, will take on a more active leadership role in collaboration with the board of directors and the organization's senior leadership, the foundation said.

The Cancer Letter To End Print Production In 2010

The Cancer Letter will no longer be offered in a printed paper version starting in January, the newsletter's publisher announced this week.

All subscribers to the print edition will be moved to the online edition.

The elimination of print production is necessary due to rising costs for printing, paper, postage, and customer service, said Kirsten Boyd Goldberg, publisher of The Cancer Letter.

Letters have been sent to print subscribers explaining the action and how the newsletter plans to switch their subscriptions to online between now and the end of the year.

Print subscribers who misplace or don't receive this letter may contact Goldberg through the customer service form at http://cancerletter.com/contactForm.

The Cancer Letter has offered an electronic version of the newsletter since 1998, and most readers now view the issue online, Goldberg said.

Online subscribers receive an email each week with a link to the newsletter PDF file, which they can download to read on a computer screen using free Adobe Reader software.

Subscribers may print out one copy for their personal use.

The online version also enables readers to click directly on links to immediately jump to websites or documents mentioned in articles.

The newsletter has covered cancer research and drug development since December 1973, when it was called The Cancer Newsletter. It was renamed The Cancer Letter in January 1975.

Back issues are available online at http://cancerletter.com/tcl-newsletter.

The Cancer Letter, published 46 times a year, offers individual subscriptions for $375 a year, online group subscriptions for 20 users or less, and institutional subscriptions that enable cancer centers, universities, and companies to provide the newsletter's online version to all employees.

No Issue Next Week

The Cancer Letter will not be published next week due to the Thanksgiving holiday in the U.S.

The Cancer Letter will be published on Dec. 4, 11, and 18, and then the staff will take its annual three-week winter publication break. Publication will resume on Jan. 15.

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