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MAKING SENSE OF THE MAMMOGRAPHY CONTROVERSY: WHAT WOMEN NEED TO KNOW

JOINT HEARING

BEFORE THE

SUBCOMMITTEE ON PUBLIC HEALTH

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS
UNITED STATES SENATE

AND THE

SUBCOMMITTEE ON LABOR, HEALTH, AND HUMAN SERVICES, AND EDUCATION

OF THE

COMMITTEE ON APPROPRIATIONS
UNITED STATES SENATE

ONE HUNDRED SEVENTH CONGRESS

SECOND SESSION

ON

EXAMINING THE CONFLICTING FINDINGS REGARDING MAMMOGRAPHY USAGE AND UPDATE RECOMMENDATION GUIDELINES, BASED ON THE MOST CURRENT SCIENTIFIC DATA, ON THE USE OF MAMMOGRAPHY IN BREAST CANCER DETECTION

February 28, 2002

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C O N T E N T S

STATEMENTS

FEBRUARY 28, 2002

	Page
Mikulski, Hon. Barbara A., a U.S. Senator from the State of Maryland, opening statement	1
Specter, Hon. Arlen, a U.S. Senator from the State of Pennsylvania, opening statement	2
Harkin, Hon. Tom, a U.S. Senator from the State of Iowa, opening statement	8
Reed, Hon. Jack, a U.S. Senator from the State of Rhode Island, opening statement	10
Von Eschenbach, Andrew, M.D., Director, National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services, prepared statement	14
Berry, Donald A., M.D., Chairman, Department of Biostatistics, Anderson Cancer Center, Unibersity of Texas, Houston, TX; and Harmon J. Eyre, M.D., Chief, Medical Officwer and Executive Vice President ofr Research and Medical Affairs, American Cancer Society, Washington, DC	44
Prepared Statements of:	
Donald A. Berry, M.D.	46
Harmon J. Eyre, M.D.	52
Visco, Fran, President, National Breast Cancer Coalition, Washington, DC; Carolyn D. Runowicz, M.D., Vice Chariman, Department of Obsttretrics and Gynecology, Saint Luke's Roosevelt Hospital, New York, NY, On Behalf of the American College of Obstretricians, and Gynecologists; and LaSalle Leffall, Jr., M.D., Chairman-Elect, Susan G. Komen Breast Cancer Foundation, Dallas, TX	65
Prepared Statements of:	
Fran Visco	67
Carolyn D. Runowicz, M.D.	73
LaSalle D. Leffall, Jr., M.D.	76

ADDITIONAL MATERIAL

Articles, publications, letters, etc.:	
Danish Study	21
Claudia I. Henschke, PhD., M.D.	88
Letter to Senator Specter from UPMC Health System	89
Agency for Healthcare Research and Quality	89
Food and Drug Administration, Department of Health and Human Services	92
Letter to Senators Kennedy and Gregg from the Oncology Nursing Society	94
Samuel B. Wallace	96

MAKING SENSE OF THE MAMMOGRAPHY CONTROVERSY: WHAT WOMEN NEED TO KNOW

THURSDAY, FEBRUARY 28, 2002

U.S. SENATE,
SUBCOMMITTEE ON PUBLIC HEALTH, COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS, AND SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The joint hearing convened at 2:28 p.m., in room SD–106, Dirksen Senate Office Building, Hon. Barbara Mikulski, presiding.

Present: Senators Mikulski, Harkin, Murray, Reed, Clinton, Specter, and Frist.

OPENING STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. [presiding]. Good afternoon.

This is a joint hearing between the Subcommittee on Public Health of the Health, Education, Labor, and Pensions Committee as well as the Appropriations Subcommittee on Labor, Health and Human Services, and Education.

We are holding a joint hearing because of the advocacy of the members and the way that both the authorizing and appropriating committees have worked together.

The title of this hearing is "Making Sense of the Mammogram Controversy: What Women Need to Know."

As chair of the hearing, I wish to yield to the ranking member of the Appropriations Committee, Senator Arlen Specter. Senator Specter is co-chair of the Steel Caucus, and he, along with other Steel Caucus members, has a meeting with the President in about 20 minutes.

As a Senatorial courtesy, we would like him to go first, because he is going to go and be representing thousands of steel workers, and as a member of the Steel Caucus, Senator, my thoughts go with you. I will hold the fort here at the committee, and I know you will with the President.

I would ask my colleague to proceed, and I just want to emphasize what a bipartisan effort this is, helping women to be protected from the ravages of breast cancer, and what a strong advocate Senator Specter has been for the empowerment of women in being able to have the health care they need.

Senator?

OPENING STATEMENT OF SENATOR SPECTER

Senator SPECTER. Thank you very much, Madam Chairperson, for your initiatives and your leadership in convening this important hearing, and thank you for yielding to me for a few moments.

Senator Mikulski and I have just come from the Ellipse. It is about 35 degrees outside in Washington today, and there was a rally of some 25,000 steel workers who came to urge the President to impose tariffs to allow the steel industry to revitalize itself. Senator Mikulski and I spoke there, and we are glad to be indoors for a few minutes at this time.

As Senator Mikulski has said, the President has scheduled a meeting of the Steel Caucus of which I am vice chairman, and we will be meeting with the President shortly to make the case as to why we ought to stop subsidized and dumped steel from coming into the United States, costing the bankruptcies of many corporations, the loss of hundreds of thousands of jobs and impairing our capacity for national defense.

But I wanted to be here for at least a few minutes this morning, and I will return if I can before the hearing is concluded, on this very important subject of mammography.

I chaired the appropriations subcommittee which funded the Department of Health and Human Services in 1997, when a controversy arose as to whether there should be mammograms for women between the ages of 40 and 49 and, in my capacity as chairman of that subcommittee, initiated a series of hearings on the subject and became personally convinced that the mammograms could be helpful—not necessarily but possibly so, that if a noninvasive screening process could detect breast cancer at an early age and save lives, and the statistics are just devastating as to how many women die of breast cancer each year, it ought to be available.

The issue came before the appropriations subcommittee because it was a matter of cost. Senators ought not decide medical questions; we ought to leave that to the experts. But when it comes to the issue of establishing priorities on where expenditures ought to be allocated, that is the prerogative of the Members of Congress of the House and Senate.

We decided that we could afford it, and that is part of what Senator Harkin and I have done on many of these important medical issues. Senator Harkin and I have taken the lead on funding for NIH from $12 billion a year to $23 billion a year. We are a rich and powerful country, and we can afford that. And the funding for cancer has increased enormously, including funding for breast cancer. Of the $2.1 trillion which is spent by the United States Government each year, none is spent for a better purpose than to try to eradicate breast cancer, prostate cancer, eliminate Alzheimer's, Parkinson's, and heart disease. There is nothing more important than health.

So I am pleased that these hearings have been convened. Let us take a fresh look at the matter. There is some potential if someone has a mammogram and there is a false positive, but my own personal view after studying the matter in great detail is that that is of lesser consequence than the availability of screening to detect

cancer at an early stage where it can be successfully treated. And I believe that the United States Government has the funding to make such mammography available for women ages 40 to 49; but reconsideration is always fine.

Since I have to leave, I want to introduce Ms. Fran Visco, who is president of the National Breast Cancer Coalition and a member of the board of directors. President Clinton appointed her as a member of the President's Cancer Panel. She has a degree from Saint Joe's and a law degree from Villanova Law School, and she is a Pennsylvanian, which gives us special pride.

While I am at it, I want to note the presence of the distinguished new head of the National Cancer Institute, Dr. von Eschenbach, who comes from South Philadelphia. It is a high honor to be director of the National Cancer Institute, and it may be an even higher honor to be from South Philadelphia.

Thank you very much, Senator Mikulski.

Senator MIKULSKI. Thank you, Senator, and good luck to you in your meeting with the President. Give him my regards that it is a bipartisan effort. We have got to be Team USA here.

Thank you.

In my own opening statement, I want to say that the title of this hearing is "Making Sense of the Mammogram Controversy: What Women Need to Know," and what women need to do.

Today we are here to examine the very troubling controversy about the effectiveness of screening mammography. Women are hearing conflicting scientific studies. Some studies say that mammogram save lives. Others say they do not. This is incredibly frustrating for American women. Many are confused, exasperated, and apprehensive, both about breast cancer and now about the information they are getting about mammography. They do not know what to do, whom to believe, or where to go.

I am very concerned myself. I called this hearing to get answers for American women. What should they do? Where can they get information they can rely upon?

Also, in the absence of conclusive information, I am worried that insurance companies will wiggle out of providing this coverage, saying that it is no longer a mandate for prevention but a personal option. I do not believe that mammograms should be equated with nose jobs. I do believe that mammograms save lives, and we need to know when is the best time to get them.

There are conflicting studies. Recent work by biostatisticians in Denmark concluded that there is no reliable evidence that regular mammograms save lives. Here in the United States, the Physicians' Data Query Screening and Prevention Board—which, by the way, is an independent group of experts created and funded by the National Cancer Institute—has come up with these observations. They have signalled yellow flashing lights about whether mammograms provide any benefit to women. These findings conflict with other studies showing that screening mammograms can reduce breast cancer deaths by 30 percent.

Then, in the atmosphere of these conflicting studies, last week, Secretary Tommy Thompson affirmed the Department's traditional position that regular mammograms do benefit women and cited the Preventive Services Task Force. But at that time, Secretary

Thompson, a longstanding advocate of women's health, did not give us data.

Many other organizations like the American Cancer Society also continue to recommend screening mammograms.

So today, we want to hold a hearing. This is not a debate. It is a presentation of views in which we hope we can clear the air and clear up what women should do. I understand dissent in the scientific community and difference of opinion about particular studies, but this conflict is exasperating. Women do not know whom to believe or what they should do.

My own position is that I would rather be safe than sorry. But I also have the means to pay for a mammogram. What about women who do not have the ability to pay? What happens if insurance companies decide to stop paying? And in the absence of clarity, I am concerned that conflicting studies will give women pause rather than pursuing prevention.

We do need new tools and techniques regardless of the efficacy of mammograms. Right now, what we do know is that the mammogram is the best tool we now have—but it should not be the only tool. Hopefully, there will be more in the future. We need new tools and accurate testing to make sure they work. We cannot afford to have the same controversy over and over again.

The Institute of Medicine has recommended improving the development and adoption of new technologies as well as maximizing the technology currently available for breast cancer detection. These recommendations should be seriously considered.

At the same time that we look at new technologies, we have to make sure that mammograms, regardless of when we are advised to get them, are safe. That is why in 1992, I led the way to ensuring that we had Mammogram Quality Safety Standards to be sure that they are safe and accurate, to avoid, of course, the terrible situation of false negatives. These Mammogram Quality Standards are now up for reauthorization, and we hope to be able to expedite that and look forward to any comments that others wish to make.

This hearing brings together the Public Health Subcommittee and the Labor-HHS Appropriations Subcommittee to look at these issues. I am happy to say that I am joined by Senator Tom Harkin, who chairs the Labor-HHS Appropriations Subcommittee. Senator Harkin is a longstanding advocate for doubling the funding for the NIH budget, to ensuring that American people have access to health care and the cures that they help pay to discover, and at the same time, when women were not even included in the clinical trials, he was a real Galahad to make sure we created the Office of Women's Health at NIH and had the money in the Federal checkbook so that we could pursue those issues of research in breast and ovarian cancer.

So, Senator Harkin, we thank you for being here, and of course, we welcome Dr. Andrew von Eschenbach.

[The prepared statement of Senator Mikulski follows:]

PREPARED STATEMENT OF SENATOR MIKULSKI

Today we are here to examine a troubling controversy about the effectiveness of screening mammography. Women are hearing about conflicting scientific studies. Some say mammograms save

lives. Others say they don't. This is incredibly frustrating for women. Many are already apprehensive about breast cancer. Now they don't know what to do or who to believe.

I am frustrated myself. I called this hearing to get some answers for American women. What should they do? Where do they get information they can trust? We also don't want insurance companies to wiggle out of providing this coverage because they say the data is inconclusive.

Recent work by statisticians Dr. Peter Gotzsche and Ole Olsen of the Nordic Cochrane Center in Denmark concluded that there is no reliable evidence that regular mammograms save lives. This finding conflicts with other studies showing that mammograms reduce breast cancer deaths by about 30%. Here in the United States, the Physicians' Data Query Screening and Prevention Board, a panel of independent experts created and funded by the National Cancer Institute, has signaled its yellow flashing lights about whether mammograms provide any benefit to women. Last week, Secretary Tommy Thompson reaffirmed the Department's position that regular mammograms do benefit women. Many other organizations, like the American Cancer Society, also continue to recommend screening mammograms.

I understand dissent in the scientific community and differences of opinion about particular studies, but this conflict is exasperating. Women don't know who to believe or what they should do—do they get a mammogram or not? My position is that I would rather be safe than sorry, but I have the means to pay for a mammogram. What about women who don't have the ability to pay and whose insurance companies may decide to stop paying for mammograms? In the absence of clarity, I'm concerned that these conflicting studies give an excuse to insurance companies to stop paying for mammograms.

I'm not mandating an outcome, but this is very troubling. I speak for the women of the Senate and I salute the wonderful men who are so supportive and real champions like Senators Harkin, Specter, and Frist.

Mammography is the best tool we have now, but it is not the only one and there will be more in the future. We need new tools and accurate testing to make sure they work. We cannot afford to have this same controversy over and over. A report last year by the Institute of Medicine recommended improving the development and adoption of new technologies, as well as maximizing the technologies currently available for breast cancer detection. These recommendations should be seriously considered.

Mammography is not perfect, but it is the best screening tool we have now. Mammograms must be as safe and accurate as possible. A mammogram is worse than useless if it produces a poor-quality image or is misinterpreted. That's why I have fought over the last ten years to make them even better. The Mammography Quality Standards Act (MQSA) that I authored has improved the quality of mammograms in this country over the last ten years. MQSA has brought facilities nationwide into compliance with federal quality standards. Before MQSA, tests were misread, women were misdiagnosed, and people died as a result of sloppy work. This year Congress must reauthorize the Mammography Quality Standards

Act, because women must continue to have safe, quality mammograms. Until there are more effective screening tools, mammography is still the front line against breast cancer.

This hearing brings together the Public Health Subcommittee and the Labor/HHS Appropriations Subcommittee to look at this issue of great importance to women. I look forward to the testimony of our witnesses and the expertise they bring. I extend a warm welcome to Dr. Andrew von Eschenbach, the new Director of the National Cancer Institute, as he testifies at his first hearing. I also enter into the record statements from the Food and Drug Administration and the Agency for Healthcare Research and Quality that are valuable contributions to this hearing. Whether or not to get a mammogram is a decision faced by millions of women. They are looking for answers and recommendations based on sound science, and they deserve no less.

Senator MIKULSKI. Before I turn to Senator Harkin, I would like to note that Senator Olympia Snowe, a dear colleague, will not be able to attend today. For more than 20 years in the House and the Senate, we have been paired up as advocates in terms of helping not only to race for the cure but to race for every other tool we had to be able to find a cure and for prevention.

Senator Snowe has sent a statement for the record, and I ask unanimous consent that it be included in the record.

[The prepared statement of Senator Snowe follows:]

PREPARED STATEMENT OF SENATOR SNOWE

Chairwoman Mikulski, Chairman Harkin, thank you for inviting me to join you and your committees today for this very important hearing, as we try to make sense of the controversy surrounding the merits of mammograms. Having worked with both of you over many years on this issue, I am pleased to have this opportunity to continue our joint efforts to improve women's health.

The uncertainty around the merits of mammography has gone on for almost 25 years, beginning in 1977 when the National Cancer Institute stopped recommending mammograms for women in their 40s. Since then, there have been three additional reversals of the policy on mammography for this class of women . . .

And what has all of this back and forth accomplished? Well it's done only one thing well, and that's create confusion and uncertainty on a matter that's central to a woman's health. As this debate wears on, women are becoming more and more uncertain of what science and what good health practices dictate they should do to be a partner in the fight against cancer, using the best weapon we all know of . . . early detection. Putting aside for a moment the controversy surrounding mammograms, no one can argue that early detection is not a critical component in the fight against breast cancer. Finding breast cancer earlier through mammography and earlier treatment has led to a steady decline in death rates. Not coincidently, as the number of women who received mammograms doubled, the average size of a tumor when it is originally detected has shrunk from three centimeters to two. And both common sense and experience tells us that detecting the tumor earlier, when it's smaller, improves the ability to treat the cancer *before* it spreads.

Women have certainly taken the importance of routine mammograms and early detection to heart, playing an active role in their health maintenance by getting their annual or bi-annual screening. In fact, according to the 2000 Behavioral Risk Factor Surveillance System, the percentage of U.S. women aged 40 and older who had a recent mammogram was almost 63 percent.

And why are women consistently going for these screenings? Consider the everyday experience of women, knowing not only the grim statistics that one in eight women will develop breast cancer in their lifetime, but also—all too often—having personal experience in confronting the devastation of breast cancer, when facing the diagnosis of a grandmother, mother, sister, or friend. I know the impact my mother's diagnosis had on me, as an eight-year old, and the impact her death from the disease had on inspiring me to make combating breast cancer a top priority.

And yet, the debate about the efficacy of mammograms has thrown a shadow over the one tool available to women to protect themselves. The latest round in this debate began last fall, when the British medical journal, The Lancet published a Danish study which re-examined and confirmed the authors' original opinion that "there is no reliable scientific evidence that screening for breast cancer reduced mortality." Having been active in this debate throughout my tenure in Congress and as the author, with Senator Mikulski, of the 1997 resolution adopted unanimously by the Senate highlighting the need for accurate guidelines for mammography for women in their 40s, I am concerned, but not surprised, that this controversy has arisen again.

My concern led me, along with Senator Mikulski, to write to the Acting Director of the National Cancer Institute requesting that NCI, among other things, clarify the conflicting findings and recommend updated guidelines for the use of mammography in breast cancer detection. We have also been in contact with the newly-appointed Director, Dr. von Eschenbach, who is appearing today. Dr. von Eschenbach has been very receptive to our concerns and has indicated his intent to be active on this issue.

We did not need to wait too long for this action, as last week, NO endorsed the recommendation of Health and Human Services Secretary Thompson, affirming the current recommendation that women in their forties get a mammogram once every year or two. These strong endorsements of routine mammograms were a definitive signal as to the position of the public health infrastructure. While their statements are encouraging, as long as the controversy remains in the national press, it will continue to weigh heavily on women and their families, on a matter that is too often of life and death.

It is my sincere hope that this hearing will be the beginning of the end of the almost twenty-five year controversy surrounding the value of mammography. Certainly, we all recognize that there is no "silver bullet" in the fight against breast cancer—or any cancer for that matter. But, in order to fight this fight the best we can, it's critical that we use all the tools in our arsenal. Today, early detection of cancer through mammograms represents a powerful weapon in the war against cancer and I hope and trust that through investments in research we will continue to develop new and better

weapons to fight cancer. But until that day comes, I urge the witnesses here today to continue their efforts to make this a reality. Thank you.

Senator MIKULSKI. Senator Harkin, I will now turn to you.

OPENING STATEMENT OF SENATOR HARKIN

Senator HARKIN. Senator Mikulski, thank you very much, first for your dynamic and great leadership on so many issues that affect the health and welfare of the people of our country, but especially on this issue. You are more than generous in your remarks about my work in this area, but I can assure you that I am just following your lead.

Senator Mikulski correctly stated that in 1992 she authored the legislation that provided for standardization and quality in terms of mammograms and the interpretation of mammograms. So I know that what is transpiring right now is of the utmost importance to her, as it is to all of us. But she really took the lead on this, and I just want to thank her for her foresight 10 years ago in addressing this issue.

I also want to thank you, Senator Mikulski, for your work on our committee to make sure that we get the funds needed for intervention and especially for research. We made a commitment 5 years ago as a Congress, the Senate and the House, that we were going to double funding for NIH over 5 years and with the budget this year we will accomplish that goal. Of course, a great deal of that goes into research on cancer and also into breast cancer research.

I think that what we have to keep in mind is that we have an epidemic in this country of breast cancer. This is an epidemic by any yardstick or measurement. One out of every nine women in America will get breast cancer in their lifetime. Every 3 minutes, a woman is diagnosed with breast cancer in this country. Every 13 minutes, a woman dies of breast cancer in this country. That is an epidemic.

I know these are statistics and we frequently throw out figures and statistics. But these statistics involve real people. One reason I have been so involved in this is—and I am frank to admit it—personal. My only two sisters died of breast cancer at quite an early age. They had young families. Had they had early intervention and early screening, I daresay they would have lived a lot longer and would be alive today.

Now I have nieces, my sister's daughters, who, because both of their mothers died of breast cancer, I some time ago advised—I should not say I advised them because I am not a doctor—but I counseled them about getting early mammogram screenings because of perhaps some genetic susceptibility or something like that. So they started to have mammograms at an early age. One of them called me the other day and said, "Uncle Tom, what am I supposed to do now?" I said, "I don't know, but we will get the answers."

Just yesterday I had a conference call with a number of doctors and nurses and breast cancer survivors in my State of Iowa. I think the consensus was clear, Senator Mikulski, as you stated in your statement, that there is no confusion and no dissension among any of them. They believe mammograms are a very useful tool. They are not the cure-all; they are not the only thing to do. But

combined with self-examination and annual physicals, mammograms can be the key to early detection. And we all know that early detection and early intervention means a woman can live longer and have a better quality of life.

So I hope we can clear up some of this. I am sorry I came in a little late, Madam Chair. I just heard you say that we are not here to debate or anything like that. I understand that, but I think we are here to shed some light on these studies. We are here to find out from the experts and from breast cancer survivors, people who have been involved in this for a long time—I see Fran Visco out there—who can give us some guidance and direction and who can reassure the women of this country of what they should do to protect their health and make sure they get early screening and early intervention.

So Madam Chair, let me again thank you for taking the lead in this. Thank you for pulling our two committees together to look at this and to have what I think is a very, very vital hearing at this point in time.

Thank you, Madam Chair.

[The prepared statement of Senator Harkin follows:]

PREPARED STATEMENT OF SENATOR HARKIN

Thank you, Senator Mikulski and thank you for joining me in chairing this joint hearing on the benefits of mammography. I am pleased that we have such a distinguished panel of witnesses with us this afternoon. I particularly want to welcome the new director of NCI, Dr. Andrew von Eschenbach, who is making his first appearance before our subcommittee.

Breast cancer is a disease I take very seriously. I lost my only two sisters to this killer. Sadly, they contracted the disease at a time when regular mammograms and improved treatment methods were not widely used or available. I'm convinced to this day had they gotten regular screenings, they would have lived longer lives.

We have a breast cancer epidemic in this country. Every three minutes, a woman is diagnosed with breast cancer, and every 13 minutes, a woman dies from the disease. We need to wage a war against this epidemic. And as with any war, you want all the tools in your arsenal to maximize your chance of victory. And so while there have been conflicting studies, I believe we need to keep screening mammography in our arsenal. In fact, for women age 50 to 69, there is strong evidence that screening with mammograms on a regular basis reduces breast cancer deaths by 25 percent to 30 percent.

I have read quite a bit about the new study by a pair of Danish researchers. I have also heard that this has led to a lot of confusion by woman facing the decision of whether to be screened regularly.

Yesterday, I talked by phone to a number of clinicians and breast cancer survivors in Iowa. There was no confusion with them. These Iowans, who work with patients every day feel very strongly about the benefits of mammography and the early detection that it provides. Every one of them had a personal story about an Iowan, whose cancer was detected early by a mammogram, and is now doing very well. They all agreed that access to mammography is critical. Especially for Medicare beneficiaries.

So I believe we need to redouble our efforts to maintain women's access to screening. That means improving Medicare's unacceptably low reimbursement rates and continuing to expand the breast and cervical cancer screening program.

But, let me be clear, mammography is not a cure all. We need to continue our efforts to improve treatments and eventually develop a vaccine or cure for breast cancer. That is the ultimate victory. And the key is research. A decade ago, the Federal Government spent barely $90 million on breast cancer research. Today, I am proud to say, we've increased that investment to about $800 million. That investment is leading to new discoveries about the causes of breast cancer and its prevention, detection, diagnosis, treatment and control.

Given the stakes, I'm very interested to hear from the experts we have here today. With that, I'll turn to my colleague, Senator Specter, for his opening statement.

Senator MIKULSKI. Thank you, Senator Harkin.

Senator Reed?

OPENING STATEMENT OF SENATOR REED

Senator REED. Thank you very much, Madam Chairman.

I simply want to commend you for taking the initiative along with Senator Harkin on this very important issue and simply add to your praise of both Senator Harkin and Senator Specter for their role over many years in trying to ensure that we have the resources to provide support in this very important area.

But ultimately, your leadership, Madam Chairwoman, has been the critical factor, I think, in this whole debate. I am here to learn and to listen, and with that, I will yield back my time.

Senator MIKULSKI. Thank you.

At this time I submit for the record statements from Senator Jeffords and Senator Hutchison.

[The prepared statement of Senators Jeffords and Hutchison follow:]

PREPARED STATEMENT OF SENATOR JEFFORDS

Madam Chairwoman, I want to commend you for holding this timely hearing on the quality of mammography screening. I also would like to extend a warm welcome to the panel of expert witnesses here today. I look forward to your testimonies so that we may all gain a better understanding of the current controversy surrounding mammography. It is my hope that this and other sessions like it will lead us all to better, more informed solutions in the fight against cancer. We have made remarkable progress in the areas of research, diagnosis and treatment over the 30 years since we first declared the "war on cancer", but much more remains to be done. In my own home state of Vermont, the American Cancer Society estimates nearly 3,000 new cancer cases, including hundreds of new breast cancer cases in the year 2002 alone.

Recent studies have raised questions and left doubts for millions of women and their loved ones about the efficacy of mammography screening. Given these new uncertainties, I think it is all the more important that the public gets the best information and analysis

available. We must continue to make accurate information available, and we need to avoid confusing the women for whom this issue is so vitally important. I hope, as we all do, that we will soon arrive at answers to the many questions before us on this matter. In the end, the most important conclusion to reach will be one that offers more effective screening and treatment options for women.

This week I was pleased to join Senator Dianne Feinstein, yourself Chairwoman Mikulski and many of our other colleagues in cosponsoring The National Cancer Act of 2002. It is a modernization and enhancement of the original National Cancer Act of 1971, which was a result of President Richard Nixon's "war on cancer." This legislation would increase funding for the National Cancer Institute (NCI), provide incentives and increased compensation for researchers and physicians, and improve and expand the recruitment and training of health care workers who serve in underprivileged areas and areas with high rates of cancer. A major provision of the bill would allow the NCI to fully fund 40 percent of the research grant applications received, which is considerably higher than the current level of 28%.

In a time when cancer is claiming the lives of over 500,000 Americans per year, and 1 in 8 women will develop breast cancer in the course of their lives, it is clear to me that we must continue to increase our investments in life-saving cancer research. Thank you for organizing these important hearings today, and I am looking forward to learning more from our witnesses. I know it will help us as we move to reauthorize the Mammography Quality Standards Act.

PREPARED STATEMENT OF SENATOR HUTCHISON

Thank you, Mr. Chairman. I am glad we have the opportunity today to disseminate the correct information in regards to mammography. It is important for women to know that mammography is an important tool in our fight against breast cancer.

I am a cosponsor on Sen. Feinstein's cancer legislation which was introduced yesterday. This legislation addresses the issue of mammography. It mandates that everyone has a right to receive a mammogram who is 40 years of age or older or is at high risk of developing breast cancer. We understand the importance of mammography enough to put it into legislation. It is our responsibility to further ensure that the public is encouraged to take the steps necessary to detect cancer at an early stage.

I am concerned after reading the recent Washington Post (February 17th) article that women will not be encouraged to get a mammogram. The head of general medicine at a Seattle hospital stated that she was not pressuring women to have a mammogram. If there are questions or misinformation at that level of expertise, then what is the general public thinking? Women don't necessarily want to have one in the first place and if an "out" is presented to them, then they may take it.

This is why I reiterate that it is important that we get the correct information out about mammography and that screening should start at 40. More than 2,600 women in Texas will be diagnosed with breast cancer this year and it would be greatly disturb-

ing to have these numbers rise higher when we are just beginning to win the battle.

I hope at this hearing today we clarify the issues for ourselves and the public.

Senator MIKULSKI. We are now going to turn to our first witness, Dr. Andrew von Eschenbach, who is director of the National Cancer Institute at the National Institutes of Health. He is the 12th director of the NCI and comes as an academician, a scholar, a researcher, and a clinician. His area of expertise has been prostate cancer, but he has also been a consulting professor in the department of cancer biology at M.D. Anderson Cancer Center and has led a faculty of more than 1,000 cancer researchers and clinicians, as well as serving in the Navy. There are many things that can be said about his articles and his very hard work.

We really welcome you, Dr. von Eschenbach. We are going to count on you for your expertise and your leadership on this topic.

We will now turn to you. Thank you.

STATEMENT OF DR. ANDREW VON ESCHENBACH, DIRECTOR, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. VON ESCHENBACH. Thank you, Senator, and good afternoon, distinguished members of the subcommittees.

I am very pleased to present my first official testimony as director of the National Cancer Institute and to do so on the important public health issue of mammography and to provide guidance on both the scientific and clinical dimensions of this problem, and to also make clear why the National Cancer Institute remains committed to its use of mammography as one tool in our fight against breast cancer.

I ask that my full written statement be included in the hearing record.

Senator MIKULSKI. Without objection.

Dr. VON ESCHENBACH. I am joined today by Dr. Peter Greenwald, director of the National Cancer Institute's Division of Cancer Prevention, and by Dr. Barbara Reimer, director of our Division of Cancer Control and Population Sciences. These two individuals have worked tirelessly on this issue and have contributed so much to our understanding of early detection strategies.

Along with the millions of women threatened by breast cancer, we at the National Cancer Institute are grateful to you, not only for your addressing this issue today but for all the effort you have expended in the past to help make more effective early detection and treatment options available to women.

As you know all too well, cancer is a complex disease, and our solutions to this menace are likewise complex but also deliberate. As scientists and clinicians, we examine, we evaluate, we learn, and we intervene, and through it all, we continue to drive forward toward our goal to save lives and to eliminate suffering.

This has been the story with our continuing struggle against breast cancer. Many years ago, we embarked on this journey to save the lives of women with breast cancer by detecting the disease early, when we could apply more effective therapies. Our tool ini-

tially for early detection was breast examination to detect a lump; then, in the 1960's, x-ray detection using mammography began to be employed, especially in North America and Europe.

From the 1960's to the 1980's, seven randomized clinical trials that enrolled over 400,000 women were conducted to determine whether mammography, when used as a screening tool in women with no symptoms or sign of breast cancer, would then result in decreased mortality from breast cancer.

These data have been subsequently analyzed, examined, and reexamined by organizations like the National Cancer Institute, the American Cancer Society, the American College of Radiology, the U.S. Preventive Services Task Force, and many others. These reviews ultimately led the National Cancer Institute and the American Cancer Society to together issue a recommendation in 1997 that mammography was beneficial to women in saving their lives from breast cancer, beginning with examination starting at age 40.

As you have mentioned, Senator, a recent critique of these major clinical trials has reawakened the debate by casting doubt on the absolute value of mammography. While my written testimony provides more specific details, the bottom line is that the National Cancer Institute has reviewed this latest analysis and, after careful and serious deliberation, we have concluded that the weight of evidence continues to show that mammography saves lives through early detection, which permits treatment of the disease at an earlier stage.

This conclusion is shared by the U.S. Preventive Services Task Force, an independent panel of private sector experts in prevention and primary care that is sponsored by the Agency for Health Care Research and Quality.

Senators, allow me to be clear in my testimony. As the director of the National Cancer Institute, who is also an investigator, a clinician, and a cancer patient, I want to assure you and the women of this Nation that we are being vigilant regarding evaluation of all information on early detection of breast cancer; that we are dedicated to continuously improving the diagnosis and treatment of this disease to save lives; and finally, to reaffirm the following recommendation that, beginning in their forties, women should be screened for breast cancer with mammography every one to 2 years.

In my written testimony, I have provided you with detailed information regarding our vigilant examination and monitoring of the data, our insights into the debate among the experts, and I have enumerated many of the programs that are being sponsored by the National Cancer Institute to improve early detection and treatment of breast cancer.

Today in my oral testimony, I would like to focus on what I believe is the crux of the issue. In this first chart, the women of this Nation need to know that while we are far from declaring victory, we are headed in the right direction. In the past 10 years, overall mortality rates from breast cancer continue to fall. We first saw this encouraging trend in 1989, with the decreasing death rate of 1.4 percent per year. More recently, the decrease has sharpened to 3.2 percent per year.

There are significant declines for all ages, and this reduction in death rates has resulted over time in 38,000 saved lives. We have a long way to go, particularly to address the gap between white and black women. But we must ensure that as we go forward, this downward trend that we see here continues.

There are multiple factors that can be attributed to this decline. We also need to understand that it is a complex interaction of both the value of early detection, namely, the application of mammography, and the application of better therapies that are being developed and applied to women who are diagnosed with breast cancer. This is an equation in which both factors leading to that decline are important. Experts may argue about the degree to which one of those factors may or may not be contributing to the outcome, but clearly, both factors are of importance, and both factors must remain in the equation, because without detection, treatment is not possible.

At the same time, we must remember that we have to continue to focus on further downturn in that curve, and in that regard, we must continue to monitor information to determine better methods of early detection; we must at the same time contribute to more improved methods of therapy so that together, they will result in the most appropriate outcome that you have asked for, namely, that we save lives of women with breast cancer.

I would like to once again reassure the women of this Nation that the National Cancer Institute stands today by its recommendation of mammography screening beginning in women in their forties, and that we are doing everything we can so that tomorrow, we can improve prevention, screening, treatment, and supportive care so that we will continue these encouraging trends in survival that we have seen over the last decade.

I thank you for the opportunity to testify about this vitally important topic, and I will be pleased later to respond to your questions.

[The prepared statement of Dr. von Eschenbach follows:]

PREPARED STATEMENT OF ANDREW VON ESCHENBACH, M.D.

Good afternoon, members of the Subcommittees. I am Andrew von Eschenbach, M.D., Director of the National Cancer Institute (NCI). I am pleased to present my first official testimony as the new Director of NCI before these distinguished Committees on the very important public health topic of mammography.

I would like to begin with a very concise summary of the position of NCI and the Department of Health and Human Services (HHS) on mammography and our current plans. I will expand on these later in my testimony. Let me assure you that NCI is collaborating with other agencies within the Department, including the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Disease Control and Prevention (CDC), to ensure that together we are providing the latest science, clinical recommendations, and programs to prevent, screen, diagnose, and treat breast cancer.

Breast cancer mortality continues to fall, and that is very good news. Death rates from breast cancer first began to decline in 1989 at 1.4 percent per year. More recently the decrease has improved to 3.2 percent per year. This is a significant decline for all ages. Unfortunately, the decline began later (1993) and is lower for Black women, whose breast cancer death rates are 33 percent higher than rates for all women.

We feel confident that mammography has contributed to this decline, but mammography alone has not driven this trend. Advances in therapy, including adjuvant therapy (both hormonal and chemotherapy) and chemoprevention approaches (such as tamoxifen) have also played a role. Unfortunately, the current debate appears to be focused on this single component in the equation. What we need to keep in mind

is that many factors taken together are responsible, all are important, and we cannot eliminate any from our current approach to breast cancer. Women need unimpeded access to prevention, screening, treatment, and supportive care to win their battle against breast cancer, and we need to keep our focus on the sum of the equation: longer life coupled with better quality of life.

NCI continues to recommend mammography screening for women beginning in their forties. This is consistent with the recently released report of the U.S. Preventive Services Task Force (USPSTF), an independent panel of private-sector experts in prevention and primary care sponsored by AHRQ. On February 21, 2002, HHS Secretary Tommy Thompson released an updated recommendation from the USPSTF that recommended screening mammography every 1–2 years for women ages 40 and over. As Secretary Thompson stated, "I believe that this recommendation reaffirms the importance of mammography and should substantially allay concerns about its value in safeguarding the health of women."

Everyone agrees that mammography detects early tumors when they are smaller, detects more tumors, and gives a woman more options for treatment. These benefits are substantial by themselves. The controversial issue is whether it saves lives in the long run. We have reviewed the evidence and the USPSTF recommendation, and we conclude that the weight of the evidence shows that mammography saves lives through early detection and treatment at an earlier stage. We will continue to monitor and consider any new information about mammography. However, mammography as a screening technology is only one tool, and we are pursuing a strong research agenda to develop other methods, such as improved imaging techniques, to design better ways to screen for breast cancer in the future. We will continue to work closely with other Institutes and Centers of the National Institutes of Health (NIH), organizations, and breast cancer patient advocates to ensure that research findings are translated quickly into effective interventions.

How do we know what we know about mammography? The use of x-ray imaging for the detection of breast cancer came into use in the 1960s, following technological advances that resulted in better images that were easier to reproduce and interpret. Initially used to assist in diagnosis, mammography was also studied for its potential use as a screening tool. Several randomized clinical trials of mammography have been conducted since 1963, and as these studies have been completed and the data analyzed, the findings have added to the total body of evidence we have today. At various times in the past decades, different organizations such as the American College of Radiology, the American Cancer Society, NCI, and others have reviewed the available data on screening mammography, have drawn conclusions about the strength of that evidence, and have made recommendations or statements about its appropriate role and use. Specifically, in 1993 NCI convened a workshop of experts to examine the available literature and data on screening mammography and to issue a statement of the strength of that evidence. At that time, the NCI concluded that the evidence supported mammography for women over age 50 but not under age 50.

In the intervening years, more data were obtained on the women who participated in the trials, and there were now enough women who had entered the trials in their 40s to more accurately assess the impact of mammography for women in their 40s. In 1997, there was a National Institutes of Health consensus conference where an extensive review was reported of all of the available information on screening mammography. Following that meeting and subsequent deliberations by our respective boards of advisors, both NCI and the American Cancer Society (ACS) released modified breast cancer screening recommendations. As of 1997, both NCI and ACS recommend mammography for women starting at age 40, although on somewhat different screening intervals. Both organizations also emphasized the importance of informed decision making about mammography.

The critique by Olsen and Gotzsche that was published in The Lancet last fall reviewed the seven randomized clinical trials of mammography that were done in the 1960s through 1980s. They considered technical details of the trials, such as how women were randomized into mammography and control groups, and whether breast cancer as a cause of death was determined accurately. The authors found technical problems in five of the clinical trials, all of which had shown a reduction in mortality associated with mammography; they therefore called into question the value of mammography.

The NCI has reviewed very carefully the Olsen and Gotzsche critique, and we have concluded that their review does not warrant a departure from our current recommendation on mammography. Over 400,000 women took part in the seven randomized clinical trials that were reviewed by Olsen and Gotzsche. They examined each of these trials and identified potential flaws that could have influenced the findings in several of the studies. They gave little weight to the reported benefits

from five of the seven trials and went on to conclude that the totality of evidence did not support screening mammography. However, difference of opinion among experts regarding design of these studies does not in itself prove that the conclusions are wrong. After careful deliberation of the arguments, the NCI has concluded that the value of mammography has not been refuted.

Let me give you two examples of what Olsen and Gotzsche said and why we disagree. The first clinical trial of mammography was begun in New York City in the 1960s. It was state-of-the-art at that time. Olsen and Gotzsche pointed out that after the participants were randomized into two groups, one group to be screened and the other not to be screened, a larger number of women were excluded from the group to be screened than from the unscreened group. This suggested the possibility that women diagnosed with breast cancer before the study began could be included in the screened group, but not in the unscreened group, resulting in a bias that would make it appear that mammography was useful, when this might only have been an artifact of study design. A scientific clinical trials expert who worked on this trial corroborated that during the nineteen-year follow-up period, any woman with breast cancer diagnosed prior to the onset of the study was excluded from both groups. This would correct for the potential bias suggested by Olsen and Gotzsche.

A second claim by Olsen and Gotzsche was that in several studies, the cause of death in the mammography screened group was more often called "died with breast cancer," while in the comparison group, women were classified as "died of breast cancer." They claimed that this could also be a bias in favor of mammography. However, this is also what you would see if mammography were in fact saving lives. Therefore, the NCI concluded that Olsen and Gotzsche have not refuted the evidence that mammography saves lives.

The authors also failed to consider that since the time these trials were conducted, there have been improvements in mammography and the technique of biopsy as well as in treatment. We have learned much about breast cancer biology since this time—we now think that if tumors are detected when small in size, they have not yet developed many blood vessels, and are less likely to be aggressive or to metastasize. Mammography can detect these small tumors and also can detect the earliest form of breast cancer, called ductal carcinoma in situ, and surgery can remove these lesions.

Olsen and Gotzsche's analysis is not the first one to scrutinize the underlying data in these studies. Other expert groups have conducted intensive reviews of the studies and have reaffirmed previous findings of a mortality reduction benefit, most notably the recent report of the USPSTF.

Large workshops and consensus conferences have been convened in an attempt to reach agreement on what the data actually say, and we have all witnessed the difficulty and frustration that ensue from these efforts to both reach agreement on the meaning of the data and also to craft a statement that accurately reflects the meaning. Simply put, this is not an easy task, and the conclusions reached by Olsen and Gotzsche are at variance with other reviews by expert groups.

The National Cancer Institute has compiled a very comprehensive database about cancer called Physician Data Query (PDQ), that contains the latest available information about cancer prevention, screening, diagnosis, treatment, genetics, supportive care, and clinical trials. Independent PDQ advisory boards have been retained by NCI to carry out periodic evaluations of the body of scientific data and its usefulness for drawing conclusions about the state of cancer care.

At its last meeting, the PDQ screening and prevention editorial board discussed The Lancet review and felt that Olsen and Gotzsche made some valid points about the quality of the trials. However, no modifications to the current PDQ statement of evidence on breast cancer screening have been made at this time; we expect that specific recommendations will be discussed at the next meeting of the editorial board in March 2002.

WHAT IS NCI DOING?

The NCI is committed to improving health outcomes for women with breast cancer. As part of the commitment, we will continue to strive to monitor new information as it emerges and to communicate what we learn. NCI has taken a number of steps to improve our effectiveness in these areas. First, I have asked two of NCI's division directors, Dr. Peter Greenwald, Director of the Division of Cancer Prevention, and Dr. Barbara Rimer, Director of the Division of Cancer Control and Population Sciences, to lead the new NCI Breast Screening Working Group. This group has three major tasks: one, to monitor and evaluate new information on mammography and how best to communicate the message; two, to monitor NCI's research

program on imaging and molecular technologies for early detection; and three, to assess basic biology as it pertains to early detection (for example, molecular methods to differentiate indolent from aggressive tumors).

Second, NCI has requested that the Institute of Medicine (IOM) review the evidence related to mammography and advise us on their interpretation of the evidence. This complements an ongoing initiative of the IOM to periodically update their year 2000 report entitled, Mammography and Beyond. This report examines the current state of the art in early breast cancer detection, identifies promising new technologies, and how best to move the field of breast cancer screening forward.

Third, the NCI Breast Cancer Surveillance Consortium (BCSC), a cooperative agreement between the NCI and investigators at medical research centers across the country, is evaluating the performance of screening mammography in community practice in the United States. This research collaboration links data from mammography registries with data on cancer outcomes from pathology laboratories or cancer registries. The Consortium consists of eight research sites located in seven states, plus a Statistical Coordinating Center. As of April 2001, the Consortium's database contains information on 2.2 million screening mammographic examinations and 28,000 breast cancer cases. This is a tremendous resource that can tell us much more about how mammography is performed in community practice.

The Breast Cancer Surveillance Consortium supports a wide-ranging portfolio of research projects that use population-based databases to evaluate the performance of screening mammography in community practice. Researchers at individual sites conduct analyses using data collected at their sites. In addition, all sites transmit their data to a centralized Statistical Coordinating Center located at the Group Health Cooperative site. This allows Consortium researchers to conduct analyses across sites using pooled data.

Research in the Consortium examines issues such as the effect of breast density and hormone replacement therapy on the accuracy of screening mammography, the relationship of mammography assessment with final recommendations for diagnostic evaluation, biologic characteristics of breast cancers detected by mammography screening, and rates of detection of ductal carcinoma in situ among screened women. Anticipating the need to track the diffusion of new screening technologies in clinical practice, the Consortium is developing measures for tracking the use of digital mammography, which is a promising emerging technology, and will serve as a model for tracking the diffusion of other new technologies as they emerge.

POPULATION DATA SUPPORT A BENEFIT FOR MAMMOGRAPHY

In addition to data from clinical trials, we also have data from our population-based Surveillance, Epidemiology and End Results (SEER) registries that can be used to track new cases and deaths from breast cancer and to examine these in relation to changes in mammography use over time. NCI also has created a national collaboration of some of the Nation's leading statisticians, called Cancer Intervention and Surveillance modeling NETwork (CISNET), to examine important questions about trends in breast cancer and other diseases by using the latest modeling methods. Although preliminary, recent work by the statisticians leads to the following conclusion: breast cancer incidence rates by stage showed a decline of later stage disease and larger size tumors and an increase in smaller, early stage tumors and pre-invasive cancers. Modeling this shifting of cases to earlier tumors with better prognosis predicted a decline in mortality during recent years, accounting for about one-quarter to one-third of the observed decline in breast cancer mortality since 1990. The important fact is that back in the late 1980s, our statisticians predicted that if mammography rose over the next decade, there would be a subsequent decrease in mortality. We are now seeing that decrease.

BEYOND MAMMOGRAPHY

There is no doubt that thousands of women are alive today because their breast cancers were treated successfully after having been detected by mammography. There also is no doubt that we have plenty of opportunity for improvement. We need better ways to detect breast cancer in its very earliest stages and to prevent its further growth. While mammography is the best technology we have available today, it has limitations. Tumors that exist, especially in dense breast tissue of younger women or located close to the chest wall, may be missed (false negative), while in other women there may be indications that cancer is present when it is not actually present (false positive), leading to a series of additional procedures such as repeat mammograms and/or biopsies. The debate about the role of mammography will continue until we have a better technology that more accurately predicts a woman's

risk of developing breast cancer, and NCI is supporting a broad range of research on promising new approaches to breast cancer screening and early detection.

Imaging research supported by NCI is advancing on several fronts. Along with efforts to improve conventional and digital x-ray mammography, NCI also supports research for several other technologies such as magnetic resonance imaging (MRI), ultrasonography, positron emission tomography (PET), and single photon emission computed tomography (SPECT). Already, with these technologies, scientists can "see" and monitor biological processes taking place in living tissues such as blood flow, oxygen consumption, and glucose metabolism.

A major research effort is under way to capitalize on the abundant discoveries in cancer biology and create imaging technologies that can noninvasively detect and display the actual molecular events taking place in the body. Molecular imaging will allow researchers to detect altered gene products and tumor-specific receptors or enzymes. The ability to visualize molecular pathways involved in the development of tumors is expected to enable researchers to detect and stage tumors more easily, to select more effective treatments, and to predict the effectiveness of new drugs. Some specific examples of research supported by NCI:

Digital Mammography.—In 2001, the American College of Radiology Imaging Network (ACRIN), a group of researchers sponsored by NCI, launched the largest study ever to compare conventional and digital mammography. The Digital Mammographic Imaging Screening Trial, involving 49,500 women in the United States and Canada, will compare digital mammography to standard film mammography to determine how this new technique compares to the traditional method of screening for breast cancer.

Magnetic Resonance Imaging.—An imaging modality making use of a magnetic field and radio-wave signals linked to a computer to create detailed images of areas inside the body without the use of radiation. Each MRI produces hundreds of images of the breast from side-to-side, top-to-bottom, and front-to-back. A radiologist then interprets the images. Breast MRI is not used for routine breast cancer screening, but clinical trials are under way to determine whether MRI is valuable for early detection in certain groups, such as young women at high risk for breast cancer and women with a previous history of breast cancer.

Positron Emission Tomography.—PET creates computerized images of chemical changes that take place in tissue. NCI-sponsored researchers are evaluating the usefulness of PET to detect tumors in dense breasts. A clinical trial is also evaluating the usefulness of PET results compared with the findings from other imaging and diagnostic techniques. This trial is also studying the effectiveness of PET in tracking the response of a tumor to treatment.

Computed Tomography (CT).—Computed tomography creates a series of detailed cross-sectional x-rays of areas inside the body taken from different angles. The images are then turned into two- and three-dimensional pictures by a computer program. This technique is also called computerized tomography (CT) and computerized axial tomography (CAT). Several NCI-funded investigators are studying the use of dedicated breast CT devices as both a screening and diagnostic tool for the detection of breast cancer.

Magnetic Resonance Spectroscopy (MRS).—MRS has the ability to distinguish cancerous tissue from normal tissue and benign growths. MRS can show the presence and relative quantities of the chemicals comprising tissues of each type, and can characterize even small tumors. As a result, MRS can make it easier to detect breast cancer at even earlier stages. A number of NCI grantees are exploring use of MRS in breast cancer.

Optical Imaging.—Optical imaging refers not only to the use of visible light but also to radiation just beyond the visible—ultraviolet and near-infrared. Several researchers are evaluating the potential of using visible or near infrared light to scan the breast for abnormalities alone and in conjunction with other imaging technologies and the possibility of combining such information with other techniques. For example, NCI is supporting projects that superimpose optical signals from small breast cancers onto MRI scans of the breast.

Computer-Aided Detection (CAD).—CAD involves the use of computers to bring suspicious areas on a mammogram to the radiologist's attention. Through a number of grants, NCI is funding research that will develop computer-aided diagnosis methods to assist radiologists in diagnosing breast cancer from mammograms. It is hoped that CAD will improve radiologists' ability to interpret mammograms so that both the number of missed cancers and the number of women unnecessarily sent to biopsy can be reduced. A number of grantees are exploring the use of CAD in breast cancer. Currently, there are two FDA- approved CAD methods that are commercially available.

Imaging Agents.—The NCI's Development of Clinical Imaging Drugs and Enhancers (DCIDE) program will foster and speed the development of promising imaging agents, such as contrast agents, and their translation from laboratory to clinic. NCI will make its pre-clinical development resources available to competitively selected developers of a promising diagnostic agent or probe in order to remove a recognized barrier between laboratory discoveries and their entry into the clinic. To further aid in the development of promising imaging agents, NCI is launching a program to fund early clinical trials of novel imaging probes and agents. One of the agents under development in this program is a nanoparticle that specifically targets angiogenic vessels. This could potentially play a role in cancer detection, staging, and monitoring of therapy for breast cancer.

In addition to imaging technology, NCI is investing in new biologic tests to improve our ability to identify cancer cells in their earliest possible stages of development. Among the research being supported:

Molecular Analysis.—NCI's Innovative Molecular Analysis Technologies Program (IMAT) supports the development of non-invasive techniques for identifying molecular changes that distinguish cancer cells from normal cells. More than 100 research projects are under way, focusing on new approaches to analyze DNA, RNA, and proteins.

Proteomics: Finding Protein Patterns.—Proteomics is the systematic study of protein expression and function. In the Clinical Proteomics Program, a joint initiative of NCI and FDA, researchers are discovering differences in patterns of protein in the blood from cancer patients compared to people without cancer and applying this knowledge to early detection of breast cancer.

Biomarkers.—NCI's Early Detection Research Network (EDRN) is the first comprehensive network to develop and validate early detection markers for cancer. Researchers are studying a variety of molecules, proteins, genes, and other biological substances that may be the earliest warning signs that normal cells are on the road to becoming cancerous. Their discoveries are then translated into methods for detecting warning signals, sometimes even before full-blown cancer can develop.

Finding Fingerprints of Cancer Cells: The Molecular Classification of Tumors.—All cells have unique "signatures"—special characteristics related to which genes are active and which proteins or other products the cell manufactures. During the transformation of a normal cell to a cancer cell, the cell's signature changes, and the change becomes a signal of the presence of cancer. Researchers are developing profiles of molecular alterations in human tumors, such as breast cancer, using DNA, RNA, or protein-based technologies. This technology holds promise for improving the early detection, diagnosis, and treatment of cancer.

Over the years, researchers have focused on examination of cells shed by breast tissue into the ducts. Investigators have now developed techniques for collecting nipple aspirates and ductal lavage and hope that it may be possible to evaluate suspicious breast masses detected by mammography by analyzing these secretions. It may be possible to spare at least some women the need to undergo a surgical biopsy.

These are by no means established techniques, and it would be more accurate to say that they are being "explored" rather than "used" in breast cancer diagnosis. There are now a number of investigators around the country who have methods that enable them to collect these specimens, but there is no consensus yet on how they should be analyzed. The NCI is currently funding research through its exploratory grant programs to determine which substances or characteristics of cells present in these specimens will correlate reliably with the presence of absence of cancer in the breast. The research also includes development of new analytic technologies to detect particular alterations. This research has not yet progressed to a stage where large-scale clinical trials are ready to proceed.

NCI also supports a number of resources for the research community ranging from tissue banks to registries to shared funding for national monitoring programs.

COMMUNICATING ABOUT MAMMOGRAPHY

It is not enough to make discoveries. We also must turn those discoveries into interventions that benefit people and communicate that information so women can use it to make important decisions about their health. The investments that NCI, ACS, CDC, and AHRQ made in the 1980s and 1990s led to effective interventions to enhance use of mammography. There is a solid armamentarium of effective interventions, and we have seen the former Black-white differences in mammography use disappear. There still is under-use of mammography among some groups, including older and Hispanic women. We are now working with the CDC, ACS, and other organizations to disseminate the effective interventions.

NCI has several projects in place to improve the ways we communicate the results of research and to take advantage of new communication technologies. One example is a research project funded by NCI and AHRQ studying how to communicate about the benefits and limitations of screening tests. Researchers are also developing tools to help women ask the important questions and to examine their own preferences. These research efforts are exploring the capacity of new communication technologies, including online and other interactive health communication tools, to address women's questions.

CONCLUSION

Multiple factors come together in an equation that leads to longer and better lives for breast cancer patients. All of our current tools are important, and all must be improved because the outcome, although better than in the past, is not yet what it should be. We must retain what is adequate and appropriate but strive to discover what is better. Many of the new technologies now under development hold real promise. Detecting the molecular changes that lead to cancer will give us the opportunity to intervene in the disease process more effectively. Like you, I am impatient for these new approaches to prove themselves. The lives of our mothers, daughters, wives, sisters, and friends are at stake. We cannot allow ourselves to become complacent, accepting the status quo. Yet, we must not ignore the fact that our best available technology today, mammography, does save lives.

I thank you for this opportunity to testify about this vitally important topic. I will be pleased to respond to your questions.

Senator MIKULSKI. Thank you very much, Dr. von Eschenbach.

I just want to be sure—it is the National Cancer Institute's position that women should continue to get annual mammograms starting at age 40?

Dr. VON ESCHENBACH. Every one to 2 years, Senator, is our recommendation. Whether there is a difference between every year or between one and 2 years is still not absolutely determined, but at least every one to 2 years.

Senator MIKULSKI. Thank you.

You are familiar with the Danish study done by two very eminent biostatisticians. Because of logistics, they could not come today, although we acknowledge the cooperation of the Danish Embassy, and with unanimous consent, I am going to enter their study into the record.

[Document follows:]

Public health

Is screening for breast cancer with mammography justifiable?

Peter C Gøtzsche, Ole Olsen

Summary

Background A 1999 study found no decrease in breast-cancer mortality in Sweden, where screening has been recommended since 1985. We therefore reviewed the methodological quality of the mammography trials and an influential Swedish meta-analysis, and did a meta-analysis ourselves

Methods We searched the Cochrane Library for trials and asked the investigators for further details. Meta-analyses were done with Review Manager (version 4.0).

Findings Baseline imbalances were shown for six of the eight identified trials, and inconsistencies in the number of women randomised were found in four. The two adequately randomised trials found no effect of screening on breast-cancer mortality (pooled relative risk 1·04 [95% CI 0·84–1·27]) or on total mortality (0·99 [0·94–1·05]). The pooled relative risk for breast-cancer mortality for the other trials was 0·75 (0·67–0·83), which was significantly different (p=0·005) from that for the unbiased trials. The Swedish meta-analysis showed a decrease in breast-cancer mortality but also an increase in total mortality (1·06 [1·04–1·08]); this increase disappeared after adjustment for an imbalance in age.

Interpretation Screening for breast cancer with mammography is unjustified. If the Swedish trials are judged to be unbiased, the data show that for every 1000 women screened biennially throughout 12 years, one breast-cancer death is avoided whereas the total number of deaths is increased by six. If the Swedish trials (apart from the Malmö trial) are judged to be biased, there is no reliable evidence that screening decreases breast-cancer mortality.

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See Commentary page xxxx

Introduction

After heated controversy, there now seems to be general acceptance that the benefit of screening for breast cancer with mammography has been well documented.[1] Large randomised trials, including a total of half a million women, have been carried out in New York, USA;[2] Edinburgh, Scotland;[3] Canada;[4,5] and Malmö,[6] Kopparberg,[7] Östergötland,[7] Stockholm,[8] and Göteborg[9] in Sweden. A meta-analysis of an update of the five Swedish trials, which used data from individual patients, was particularly influential. It showed that screening lowered mortality from breast cancer by 29% in women aged 50–69 years.[10]

The findings of a 1999 epidemiological study were therefore surprising. It found no decrease in breast-cancer mortality in Sweden,[11] where screening has been recommended since 1985. The observed decrease in number of deaths from breast cancer was 0·8% (not significant), whereas the expected decrease was 11%. Although that study can be criticised,[12,13] it raises once again the issue of the reliability of the evidence that screening is effective.

We therefore reviewed the methodological quality of the mammography trials and the Swedish meta-analysis, and did a meta-analysis ourselves. We focused on the three most important sources of bias in randomised trials: suboptimum randomisation methods, lack of masking in outcome assessment, and exclusion after randomisation. We paid special attention to the quality of the randomisation, since bias caused by suboptimum randomisation methods can be larger[14,15] than the treatment effects that might be detected if a screening programme is beneficial.

Methods

We searched the Cochrane Library with the terms "breast-neoplasms/all" or "breast next cancer" and "screening" and "mammography" and extended the search with authors' names and other terms as appropriate to capture updates of the trials. When necessary, we asked the investigators for details about the randomisation method, in particular whether the assignment process was concealed so that no-one could foresee which assignment the next cluster or woman would get before actual recruitment. We also asked for baseline characteristics that could show whether the screening group was similar to the control group in terms of important prognostic factors such as age, symptoms at entry, family history of breast cancer, socioeconomic status, and previous examinations for breast cancer. We noted whether all randomised women had been accounted for in the results and whether the cause of death had been assessed by a panel unaware of screening status. We also sought data on the morbidity associated with screening, defined as reported events that had occurred in at least 100 women.

Meta-analyses were done with Review Manager (version 4.0; available from http://www.cochrane.dk; accessed on Dec 20, 1999). A fixed-effects model was used unless the test for heterogeneity gave p<0·10; 95% CIs are presented.

Results

Randomisation methods and exclusions

In the New York trial, pairs of women were matched and the pairs were randomised.[16] The allocation method is not clear—"every nth woman was placed in the study group, the paired (n+1) woman in the control group".[16] Because of the matching in pairs, the number of randomised women should be exactly the same in the study group and in the control group. This was not the case, and the number of women is unclear. It has been described as "about 31 000",[16] 30 000,[17] 30 131,[2] 31 092;[18] and 30 239[19,20] allocated to the study group, and 30 756,[20] 30 765,[19] and 30 565[2,16] allocated to the control group. There was also an important imbalance in exclusions after randomisation. Women were excluded if breast cancer had been diagnosed before entry to the trial, and this

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status was more completely ascertained for the screened women; thus, the final study cohort was smaller than the control cohort (30 131 *vs* 30 565).[2,16] This difference introduced bias in favour of the screening group. Close similarity between the study and control groups has been claimed,[16,21] but in the table of seven selected characteristics presented in justification for this claim, we calculated imbalances for previous lump in the breast ($p<0{\cdot}0001$), menopause ($p<0{\cdot}0001$), and education ($p=0{\cdot}05$); there were no differences for age, religion, marital status, or pregnancies. These findings are incompatible with an adequate randomisation.

The allocation method of the Edinburgh trial is poorly described; 87 general practices were cluster randomised,[22] but the allocation was later changed for three of them.[23] The screening and control groups differed substantially at baseline; only 26% of the women in the control group were in the highest socioeconomic stratum, compared with 53% in the screening group.[22] Thus, the randomisation method was grossly inadequate, even for a cluster analysis.

In the Canadian trial, women were randomised individually.[24] Names were entered successively on allocation lists, in which the intervention was noted on each line. The randomisation could therefore be subverted. However, checking of whether this had happened was also possible, and a thorough review concluded that there could not have been enough cases of such subversion to affect the reported results.[25] Moreover, the two compared groups were similar at baseline in terms of self-reported symptoms, including lump, family history of breast cancer, marital status, livebirths, menopause, education, and place of birth.[26,27] We found no data on the age distribution.

In the Malmö trial,[5] women in each birth-year cohort were randomly arranged according to a computer program, and those on the first half of the lists were invited for screening (Ingvar Andersson, personal communication). Thus, the allocation method was apparently adequately concealed. No baseline data are available, but we estimated from the other Swedish trials that the mean age was similar in the two groups.

A sort of continuation of that trial, called Malmö Mammographic Screening Trial II,[28] has been published in brief; it was randomised and had death from breast cancer as the endpoint, but it did not have a formal protocol, and because of an administrative error, all women born in 1934 were included in the screening group (Ingvar Andersson, personal communication). Because the report mixes follow-up data from a subgroup of the original trial with data from this new cohort, and since some women were not randomised, the published data cannot be included in a meta-analysis. No baseline data are available.

In the Stockholm trial,[8] randomisation was according to date of birth; women born on days 11–20 of any month constituted the control group. The number of randomised women is not clear. The number of controls is given as "c. 20 000" in an early report,[29] and as 19 943 in the final report.[8] There is a substantial discrepancy between the numbers in the final report and the meta-analysis of the Swedish trials[10] in which the number of randomised women fell from 40 318 to 38 525 (a decrease of 4·5%) in the screening group, but increased from 19 943 to 20 651 (a rise of 3·6%) in the control group. This inconsistency cannot be explained by the curious fact that women born on day 31 of any month were excluded after randomisation despite being offered mammography "to simplify the numerical comparisons",[30] since that approach led to a study group size of 39 164 women. We cannot understand how the number of randomised women in the control group can increase. Some 40-year-old women were excluded from the meta-analysis, which was based on age at randomisation and not on birth-year cohorts as most of the trials had used, but this exclusion would lead to a decrease as it did for the other three Swedish trials for which we could check the numbers (Malmö −1·9% *vs* −1·9%,[5] Kopparberg −1·3% *vs* −2·0%,[31] and Östergötland −0·2% *vs* −0·7%[7]). We calculated from a table divided into five age categories[30] that the study women in Stockholm were, on average, 0·18 years younger than the control women ($z=2{\cdot}73$, $p=0{\cdot}006$, Mann-Whitney test). This imbalance at baseline indicated that the randomisation method was inadequate.

In Göteborg, randomisation was partly by day-of-birth cluster (18% of participants) and partly individual.[9] We calculated from a table divided into 11 age categories[9] that the study women were, on average, significantly younger than the control women by 0·09 years ($z=2{\cdot}39$, $p=0{\cdot}02$), which shows that the randomisation method may have been inadequate.

Cluster randomisation was used in Kopparberg and Östergötland.[12] The population in these counties was divided into 19 blocks which were further divided into two or three groups on unspecified criteria. These groups were then randomised. We were unable to find a description of the randomisation method. In Nyström and colleagues' meta-analysis, the cluster randomisation method was said not to have introduced bias.[10] However, the justification for this statement was a reference to an unpublished lecture.[10] The meta-analysis is unlikely to have taken the clustering into account, since we obtained the same point estimate and the same narrow CI for breast-cancer mortality as in the meta-analysis when we based our analysis on individual women. We therefore used women as the statistical unit and calculated from a table divided into eight age categories[31] that the study women in Kopparberg were, on average, 0·45 years older than the control women ($z=5{\cdot}50$, $p<0{\cdot}0001$). There was also an imbalance in Östergötland ($z=4{\cdot}04$, $p<0{\cdot}0001$), the study women being 0·27 years older than the control women.[7] The number of randomised women (aged 40–74) is not clear: for example, the number in the study group in Östergötland has been reported as 39 034[32,33] and 38 491;[7,34] the total number of randomised women in the two trials has been reported as 134 867[32] and 133 065.[7,34]

Baseline data were not reported in the Swedish meta-analysis.[10] 3 years after the report was published in *The Lancet*, however, a report in a specialist journal stated that the mean age in the screened groups was 55·05 years compared with 54·54 years in the control groups.[35] Since the SD for age in the Swedish trials was 10 years,[7,31] the age difference was highly significant ($z=12{\cdot}7$, $p=3\times10^{-37}$). This extremely skewed distribution is incompatible with the hypothesis that the women were distributed to the screening and control groups according to a truly chance procedure.

We estimated whether the Malmö trial had an imbalance at baseline like the other four Swedish trials. We used the number of women as reported in the meta-analysis and the mean ages as estimated above. We took account of the fact that women in Göteborg were

	Randomisation produced similar groups	Account of number of patients consistent
Malmö	Yes	Yes
Canada	Yes	Yes
Göteborg	No	Yes
Stockholm	No	No
Kopparberg	No	No
Östergötland	No	No
New York	No	No
Edinburgh	No	Yes

Table 1: **Mammography screening trials according to methodological quality**

randomly allocated to study and control groups in the approximate ratio of 1·2 in the 39–49-year age-group and 1·6 in the 50–59-year age-group.[9] We had no data on age for the 50–59-year group, but since the imbalance in age in the 39–49-year group was numerically small, we used a mean age of 54 for both study and control groups. For Malmö, we used 57 years as estimated mean age in the study group, similar to the Kopparberg and Östergötland trials.[7,31] This approach yielded a mean age in the study groups of 54·93 years, very close to the 55·05 years reported in the meta-analysis. Since the mean age in the control groups was 0·51 years lower, that in the Malmö control group was estimated to be 56·85 years. The difference of 0·15 years is not significant (z=1·53, p=0·13) which suggests that the randomisation method in Malmö was adequate. In summary, our findings suggest that only the trials from Malmö and Canada were unbiased (table 1).

Diagnosis of deaths from breast cancer

Knowledge of screening status may affect the judgment of cause of death. Masked assessment of cause of death was used only in the trials from Canada and Malmö, but in the Swedish meta-analysis[10] all deaths from breast cancer were assessed with masking of screening status. Deaths from breast cancer diagnosed before entry to the trial were generally excluded from analysis. Such exclusions can lead to bias when the first round of screening identifies cancer in women who have already noted a tumour in their breast if these women are subsequently excluded. The New York trial excluded more cancers in the screening group than in the control group.

All-cause mortality

The imbalance in age at baseline in the Swedish trials is important. Nyström and colleagues reported in a specialist journal[35] that the screened women had an increased risk of death (relative risk 1·05; 15 695 women died of 156 911 in the screening groups *vs* 11 887 of 125 866 in the control groups). Nyström and colleagues did not test whether this increased mortality was significant, nor did they give a CI. They argued that because breast-cancer mortality constitutes less than 5% of the total mortality, such an analysis "would require very large cohorts and is therefore impossible in practice".[35] We based our calculation on number of randomised women (the meta-analysis investigators had used person-years) and found a relative risk of 1·06 (95% CI 1·04–1·08, p<0·0001). The investigators adjusted their calculation for age, after which the relative risk was 1·00. In *The Lancet* report of the meta-analysis,[10] the investigators had included the same total numbers of deaths but reported only the age-adjusted risk without mentioning that an adjustment had been made or that there was an increased risk of death without adjustment.

The pooled relative-risk estimate for the two unbiased trials (Malmö and Canada) was 0·99 (0·94–1·05), which was very close to the estimate for Malmö alone (0·99 [0·93–1·05]), since that study reported 3586 deaths, compared with only 1147 in Canada (relative risk 1·08 [0·84–1·40]).

	Number randomised		Number of deaths from breast cancer		Relative risk (95% CI)
	Screening	Control	Screening	Control	
Randomisation adequate					
Malmö[6]	21 088	21 195	63	66	0·96 (0·68–1·35)
Canada[5,27]	44 925	44 910	120	111	1·08 (0·84–1·40)
Total	66 013	66 105	183	177	1·04 (0·84–1·27)
Randomisation not adequate					
Göteborg[8]	11 724	14 217	18	40	0·55 (0·31–0·95)
Stockholm[4]	40 318	19 943	66	45	0·73 (0·50–1·08)
Kopparberg[7]	38 589	18 582	126	104	0·58 (0·45–0·76)
Östergötland[7]	38 491	37 403	135	173	0·76 (0·61–0·95)
New York[3]	30 131	30 565	153	196	0·79 (0·64–0·98)
Edinburgh[1]	22 926	21 342	156	167	0·87 (0·70–1·08)
Total	182 179	142 052	654	725	0·75 (0·67–0·83)

Table 2: **Relative risk of death from breast cancer in screened versus control groups**

Mortality from breast cancer

The two trials with adequate randomisation methods and baseline comparability (table 1) had similar estimates for the relative risk of death from breast cancer with 95% CIs that overlapped substantially, showing lack of heterogeneity (table 2). The combined relative-risk estimate was 1·04 (0·84–1·27).

The six trials that had not been adequately randomised had more favourable outcomes with screening than these wo trials, and their results were homogeneous (p=0·23 for test of heterogeneity). The pooled relative risk was 0·75 (0·67–0·83). This estimate is significantly different from that for the two adequately randomised trials (z=2·60, p=0·005).

If the Göteborg trial, which was the least biased trial of the six, was moved from the second group to the first, the relative-risk estimate changed little (0·94 [0·76–1·17]). However, since this change creates heterogeneity (p=0·08), this trial should probably not be moved. If all eight trials are analysed together (which would be inappropriate), heterogeneity is also introduced (p=0·05).

Morbidity

Total numbers of interventions were identified only in the trials from Malmö[6] and Stockholm.[29] Surgery was significantly more common in the screening groups for radical mastectomy (relative risk 1·23 [1·08–1·40]) and for mastectomy or lumpectomy (1·35 [1·20–1·52], as was radiotherapy (1·25 [1·04–1·50]). A similar tendency was seen in the Canadian trial, in which only surgery done within the framework of the trial was reported. In that trial, the proportion of benign findings in biopsy samples was two to four times higher in the mammography groups throughout the whole screening period.[5] We found no data from Edinburgh and New York and data only from the screened group for the other trials.

Discussion

The effect of screening programmes, if any, is small and the balance between beneficial and harmful effects is very delicate. It is therefore essential that such programmes are rigorously evaluated in properly randomised trials.

Unfortunately, the randomisation process failed to create similar groups in six of the eight trials of mammographic screening. Our analyses focused on age as a marker for imbalance, since this variable was the only baseline information we had available for the Swedish trials.

Cluster randomisation was used in several of the trials, but the number of clusters was insufficient, which is well illustrated by the Edinburgh trial.[22] The proportions of women in the highest socioeconomic stratum differed substantially between the screening and control groups, and, as expected, there was a pronounced relation between social group and total mortality, which may explain why total mortality was much lower in the screening group (relative risk 0·85 [0·79–0·92]). Attempts were made to remedy this shortcoming,[3] but adjustments cannot fully compensate for faulty methods. First, adjustment for unknown or unmeasured confounders is impossible. Second, adjustment for one confounder may create imbalance for another, since confounders are rarely fully correlated. For example, adjustment for age in the Swedish trials might seem reasonable; however in the New York trial, age was evenly distributed whereas several other prognostic factors were not.[16,21] Which adjustments should then be preferred for that trial? There must have been many other imbalances in prognostic factors at baseline in the Swedish trials, and there is a strong probability that other adjustments would have produced other results, both more and less extreme than a relative risk of 1·05 for the increase in total mortality with screening. Thus, the third important problem with adjustments is the risk of biased analyses when results of trials which were meant to be randomised but were found not to be so are adjusted post hoc.

The credibility of the Swedish meta-analysis is greatly weakened because it did not report that there were important imbalances at baseline in four of the five trials; that there was increased mortality in the screened groups; and that an adjustment for age had been made without being described.[10] The last point is particularly important, since readers would not have expected any adjustment to have been made in a meta-analysis of hundreds of thousands of women in which adjustments would not change anything, provided that the trials had been properly randomised. Shortly after the publication of the meta-analysis, Skrabanek obtained the mortality rates from the primary author and drew attention to the increased mortality in the screened groups[24] (10·0% *vs* 9·4%; relative risk 1·06). In their response,[37] Nyström and Larsson did not mention the imbalance in age, but defended the relative risk of 1·00 reported in the meta-analysis by comparing the observed number of deaths in the screened groups with the expected number in the population (15 695 *vs* 15 710). They also noted that the relative risks for total mortality in the individual trials were 0·98, 0·98, 0·99, 1·00, and 1·00. It is quite impossible, however, to have such rates for the individual trials and then an increased mortality of 1·06 (as we calculated) for the pooled analysis. Swift[38] noted subsequently that "a more precise and apt comparison is that between the mortality rates in the exposed and control groups". In response to this indisputable fact Nyström and Larsson wrote that "we prefer (see our response to Skrabanek) standardised relative risks to crude relative risks".[39] This reply is remarkable since the whole idea of randomisation is to make unbiased analyses possible, but it was another 3 years before Nyström and colleagues admitted publicly that the analysis of total mortality had been adjusted for age.[35]

Another serious flaw in the mammography trials is the fact that the number of randomised women was inconsistently reported for four of the six trials with inadequate randomisation methods. This inconsistency is not only odd, but it also raises further doubts about the validity of these trials.

The two trials with adequate randomisation found no effect of screening on mortality from breast cancer, not even a tendency towards an effect. By contrast, the pooled effect of the six trials with inadequate randomisation was highly significant. There was no overlap of the CIs for these two effect estimates. This lack of overlap is remarkable. Such disparate effects of subgroups of similar trials in a meta-analysis are very rare, and a strong warning signal that something is wrong. The explanation in such cases is generally methodological. In fact, the difference between the two point estimates, 1·05 and 0·75, is in good agreement with the results from empirical, methodological research. Randomised trials with inadequate or undescribed allocation methods exaggerate the estimated intervention effect by 33–41%, on average.[14,15] The bias can be even larger in cohort studies. For example, a meta-analysis of cohort studies of hormone replacement therapy showed protection against coronary heart disease (relative risk 0·50 [0·43–0·56]),[40] which was not confirmed in a large randomised trial (0·99 [0·80–1·22]);[41] again, there was no overlap of the 95% CIs.

The Canadian trial has been subjected to a fair amount of criticism, probably because it had the most negative results of the eight trials. The criticism has been rebutted;[26] somewhat ironically, this trial seems to be the one that is by far the best documented. A persistent criticism has been that an effect would be difficult to find because the breasts of all women in the age-group 50–59 years were physically examined regularly. This criticism is unwarranted because mammography will identify many tumours that are too small to be detected on physical examination alone. Furthermore, any effect of physical examination is likely to be small. A study of 122 471 women found no effect of regular self-examination of the breast on breast-cancer mortality after 9 years of follow-up, even though twice as many of the intervention group consulted an oncologist.[42] In addition, Kerlikowske's meta-analysis found that the regular clinical examinations in the non-Swedish trials had no influence on the relative risk.[43] We also much doubt the importance of the fact that the Canadian trial was not community based. Proper randomisation ensures the internal validity of a trial, and if mammography were effective, an effect should also be seen in a selected part of the population. Finally, the quality of the mammography has been criticised as being poor,[26] but the tumours found in the Canadian trial were smaller, on average, than those found in the Swedish trials.[44]

The study reports provided very few data on morbidity associated with screening. Some might argue that an increased occurrence of surgery, chemotherapy, and radiotherapy in the screened group is only natural and that, in the long run, over decades, the interventions would become less drastic because the tumours would be detected earlier. However, another point of view is that screening would be expected to increase morbidity in the

long run because of false-positive findings, cell changes that may never develop into cancer, and cancers that will develop so slowly that the woman dies of other causes before the cancer becomes apparent.

We could not assess psychological morbidity related to false-positive findings because this feature was not reported in the trials. In the USA, Elmore and colleagues[45] estimated that 49% of screened women will experience at least one false-positive mammogram during ten screening rounds and that 19% will be subjected to biopsy.[45] In the Swedish trials, false-positive rates of 4–6% have been reported,[9,28,29,31] corresponding to an average risk of 40% of a false-positive mammogram during ten rounds.

We conclude that screening for breast cancer with mammography is unjustified.

On the one hand, those who believe that the Swedish trials are unbiased have to accept from the data that screening for breast cancer with mammography causes more deaths than it saves. The total mortality in the five Swedish trials was 10%,[10] the relative risk of death was 1·06, and the Swedish meta-analysis showed a difference in breast-cancer mortality of 0·1% after 12 years of follow-up.[10] The data therefore show that for every 1000 women screened throughout 12 years, one breast-cancer death is avoided but the total number of deaths is increased by six.

On the other hand, those who believe the Swedish trials (apart from the Malmö trial) are biased have to accept that there is no reliable evidence that screening decreases breast-cancer mortality.

There is a need for further follow-up of the two unbiased trials and for detailed scrutiny of the other trials to see whether subgroups of women can be identified who have been properly randomised.

Contributors

Peter C Gøtzsche did the data searches and most of the analyses and wrote the drafts of the paper. Both researchers read the key articles critically and Ole Olsen contributed importantly to the final article.

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Review

Herb-drug interactions

Adriane Fugh-Berman

Concurrent use of herbs may mimic, magnify, or oppose the effect of drugs. Plausible cases of herb-drug interactions include: bleeding when warfarin is combined with ginkgo (*Ginkgo biloba*), garlic (*Allium sativum*), dong quai (*Angelica sinensis*), or danshen (*Salvia miltiorrhiza*); mild serotonin syndrome in patients who mix St John's wort (*Hypericum perforatum*) with serotonin-reuptake inhibitors; decreased bioavailability of digoxin, theophylline, cyclosporin, and phenprocoumon when these drugs are combined with St John's wort; induction of mania in depressed patients who mix antidepressants and *Panax ginseng*; exacerbation of extrapyramidal effects with neuroleptic drugs and betel nut (*Areca catechu*); increased risk of hypertension when tricyclic antidepressants are combined with yohimbine (*Pausinystalia yohimbe*); potentiation of oral and topical corticosteroids by liquorice (*Glycyrrhiza glabra*); decreased blood concentrations of prednisolone when taken with the Chinese herbal product xaio chai hu tang (sho-saiko-to); and decreased concentrations of phenytoin when combined with the Ayurvedic syrup shankhapushpi. Anthranoid-containing plants (including senna [*Cassia senna*] and cascara [*Rhamnus purshiana*]) and soluble fibres (including guar gum and psyllium) can decrease the absorption of drugs. Many reports of herb-drug interactions are sketchy and lack laboratory analysis of suspect preparations. Health-care practitioners should caution patients against mixing herbs and pharmaceutical drugs.

"Poisons and medicines are oftentimes the same substances given with different intents."
Peter Mere Latham (1789–1875)

Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another. Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component. Synergistic therapeutic effects may complicate the dosing of long-term medications—eg, herbs traditionally used to decrease glucose concentrations in diabetes[1] could theoretically precipitate hypoglycaemia if taken in combination with conventional drugs.

Herbal medicines are ubiquitous: the dearth of reports of adverse events and interactions probably reflects a combination of under-reporting and the benign nature of most herbs used. Experimental data in the field of herb-drug interactions are limited, case reports scarce, and case series rare. This lack of data is also true of drug-drug interactions: published clinical studies are mainly case reports (controlled trials are scarce, since the random assignment of patients to trials that examine unintended effects is not ethical). The true prevalence of drug interactions is substantial but unknown. One study of 1000 elderly people admitted to a hospital from the emergency department found that 538 patients were exposed to 1087 drug-drug interactions; 30 patients experienced adverse effects as a consequence of these interactions.[2] In clinical practice, polypharmacy is common, and to the mixture physicians prescribe, patients add various over-the-counter medications, vitamins, herbs, and foods. All ingested substances have the potential to interact.

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Source and extent of review

Sources for this review include MEDLINE 1966–98 (searched under MeSH terms "drug interactions" combined with "herbal medicine", "traditional medicine", "Chinese traditional medicine", "African traditional medicine", "Ayurvedic medicine", "Oriental traditional medicine", "Unani medicine", and "Arabic medicine"); EMBASE 1994–99 (searched under the same terms); reference dredging; and my own files on the subject.

Many reports of herb-induced interactions lack crucial documentation on temporal relations and concomitant drug use. Perhaps the most serious problem encountered in analysing such reports is the consistent absence of any effort (beyond that of reading the label) to establish a positive identification of the herb involved, and to exclude the effect of contaminants or adulterants. Unless noted otherwise, the reports mentioned herein did not include chemical analyses.

This review was limited to the most commonly used medicinal plants, and to clinical reports (animal studies

WHAT'S NEW
From the U.S. Preventive Services Task Force

AHRQ Publication No. APPIP02-0016 *February 2002*

Screening for Breast Cancer

What Does the Current U.S. Preventive Services Task Force (USPSTF) Recommend?

- Recommends screening mammography every 1-2 years, with or without clinical breast examination, among women aged 40 and older.
- Women should be informed of potential benefits, limitations, and possible harms of mammography in making decisions about when to begin screening.
- Concludes that there is insufficient evidence to recommend for or against routine clinical breast examination alone to screen for breast cancer.
- Concludes that there is insufficient evidence to recommend for or against teaching or performing routine breast self-examination.

Why Did the USPSTF Revisit This Topic?

In 1996, the USPSTF recommended routine screening for breast cancer every 1-2 years, with mammography alone or mammography plus annual clinical breast examination, for women aged 50-69. At that time, the USPSTF found insufficient evidence to recommend for or against routine mammography or clinical breast exam for women younger than age 50 or older than 70. The USPSTF also concluded at that time that there was insufficient evidence to recommend for or against the use of clinical breast exam or breast self-examination alone. Since then, new studies and extended follow-up from earlier trials have provided important new information on the benefits and harms of breast cancer screening for both younger and older women.

In 2001, approximately 40,200 women died of breast cancer.

Prevalence and Risk

Breast cancer is the most common cancer among women in the United States and, after lung cancer, is the second leading cause of cancer-related death. In 2001, an estimated 192,200 American women were diagnosed with breast cancer for the first time, and 40,200 women died from the disease.

What's New from the U.S. Preventive Services Task Force is a series of fact sheets based on work of the U.S. Preventive Services Task Force (USPSTF). The USPSTF systematically reviews the evidence of effectiveness of a wide range of clinical preventive services—including screening, counseling, and chemoprevention (the use of medication to prevent disease)—to develop recommendations for preventive care in the primary care setting. This fact sheet presents highlights of USPSTF recommendations on this topic and should not be used to make treatment or policy decisions.

More detailed information on this subject is available in the USPSTF Recommendations and Rationale. The complete evidence considered by the USPSTF will be summarized in a Systematic Evidence Review and Summary of the Evidence, which are currently undergoing final revisions, and will soon be accessible on the Agency for Healthcare Research and Quality's (AHRQ) Web site (http://www.ahrq.gov/clinic/uspstfix.htm), through the National Guideline Clearinghouse (http://www.guideline.gov), and in print through the AHRQ Clearinghouse (1-800-358-9295).

The risk of developing breast cancer increases with age after age 40 but is even greater at age 50 and older. Among the individual risk factors, other than age, that increase the risk of developing breast cancer, the strongest are a family or personal history of breast cancer and biopsy-confirmed atypical hyperplasia of the breast.

Potential Benefits and Harms of Screening for Breast Cancer

Screening for breast cancer poses both potential benefits and potential harms. Although all the studies of mammography have limitations, the USPSTF concluded there was fair evidence that mammography screening every 1-2 years could reduce breast cancer mortality by approximately 20% to 25% over 10 years. The evidence is strongest for women between the ages of 50 and 69, but the USPSTF concluded benefits were likely to extend to women 40-49 as well.

The balance of potential benefits and harms varies with age. Because of a lower risk of breast cancer, the benefits of regular mammography are smaller for women younger than 50, and the balance of benefits and harms is closer. In older women, however, the benefits are larger, the risk of false-positive results is smaller, and the balance of benefits and harms is more favorable.

The USPSTF found fair evidence that mammography screening every 1-2 years significantly reduces mortality from breast cancer for women ages 40 and older.

For more information on breast cancer and breast cancer screening, please visit the healthfinder™ Web site at: http://www.healthfinder.gov

Note: When discussing breast cancer screening with patients, clinicians should refer patients to mammography screening centers with proper accreditation and quality assurance standards to ensure accurate imaging and radiographic interpretation. A listing of accredited facilities is available at: http://www.fda.gov/cdrh/mammography/certified.html

U.S. Department of Health and Human Services

AHRQ
Agency for Healthcare Research and Quality
www.ahrq.gov

USPSTF
U.S. Preventive Services Task Force

The USPSTF is an independent panel of experts who represent the fields of family medicine, obstetrics-gynecology, pediatrics, nursing, prevention research, and psychology. Members of the current USPSTF are:

Alfred O. Berg, MD, MPH
Chair
Janet D. Allan, PhD, RN, CS
Vice-chair
Paul S. Frame, MD
Charles J. Homer, MD MPH
Mark S. Johnson, MD, MPH
Jonathan D. Klein, MD, MPH
Tracy A. Lieu, MD, MPH
Cynthia D. Mulrow, MD, MSc
C. Tracy Orleans, PhD
Jeffrey F. Peipert, MD, MPH
Nola J. Pender, PhD, RN
Albert L. Siu, MD, MSPH
Steven M. Teutsch, MD, MPH
Carolyn Westhoff, MD, MSc
Steven H. Woolf, MD, MPH

fixation and equidistant from the quadrant borders. The patient was asked whether the targets appeared equally and truly red or if one appeared duller. Seventh was the central red-field test, in which a red target 5 mm in diameter was first used kinetically to ascertain the boundary of the central red field. The target was then presented statically to multiple points within the central 20° field. At every position the patient reported whether the target was clearly seen as red.

Full-threshold automated static tests of the visual fields were done on all patients with the Humphrey Visual Field Analyser 640 (Allergan Humphrey, San Leandro, CA) with the 24/2 programme. Fields were assessed in accordance with published criteria[2] by a second ophthalmologist (PGG), who was masked to the results of confrontation tests and to the diagnosis.

The median age of patients was 67·5 years (range 17–88). 89 patients (64%) had defects in their visual field detected by automated perimetry, most defects were small or shallow (table 1). In identification of loss of visual field, the sensitivity of all seven confrontation tests combined was 76% (95% CI 66–85), most of which was accounted for by the central red-field test, with a sensitivity of 73% (63–82) (table 2). The least sensitive test was quadrant finger counting, with a sensitivity of 35% (25–46). The specificity of all confrontation field tests was 100% (93–100).

Most confrontation tests are not sensitive enough to identify small or shallow defects in the visual field. The most sensitive method was examination of the central 20° visual field with a small red target. No patients with field defects missed by the central red-field test had the defects identified by examination of the peripheral field, but three had them identified by red colour comparison. The combination of these two tests thus achieves the overall sensitivity of 76%, with no loss of specificity.

Assessment of the central visual field is usually sufficient to identify defects,[3] since central field representation greatly dominates all levels of the visual pathway.[4] Isolated peripheral field defects that do not produce abnormality of the central field are rare.

That red targets are more effective than white seems to be because colours act as dim white stimuli and are therefore closer to the visual threshold, not because of a specific effect of colour itself. White stimuli give the same sensitivity as red when matched for size and intensity.[5] In practice, it is easier to recognise abrupt colour change of a red target than a change in intensity of a dimmer white target.

The central red field and the red-colour comparison tests should be essential components of the examination of visual fields to confrontation. Subjective description of the examiner's face and quadrant finger counting are not very sensitive, but might quickly identify a substantial loss in visual field, and should thus be included as initial tests. Traditional kinetic boundary tests with fingers or mounted targets are time consuming and do not enhance the sensitivity of the examination. The specificity of confrontation tests is high, suggesting that the causes of identified field defects are usually real and therefore warrant explanation.

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Cochrane review on screening for breast cancer with mammography

Ole Olsen, Peter C Gøtzsche

In 2000, we reported that there is no reliable evidence that screening for breast cancer reduces mortality. As we discuss here, a Cochrane review has now confirmed and strengthened our previous findings. The review also shows that breast-cancer mortality is a misleading outcome measure. Finally, we use data supplemental to those in the Cochrane review to show that screening leads to more aggressive treatment.

Lancet 2001; **358:** 1340–42
See Commentary page 1284

We previously assessed the results of the seven randomised trials of screening mammography, and concluded that screening is unjustified because there is no reliable evidence that it reduces mortality.[1] We reassessed this finding in a Cochrane review[2] in which we paid close attention to the standard dimensions of methodological quality of trials: the randomisation method, baseline comparability, exclusions after randomisation, and unbiased assessment of outcome (see protocol for the Cochrane review [issue 3, 2001, Cochrane Library]). Additionally, we noted whether early introduction of screening in the control group had occurred. Details of the trial assessments are presented in our review.[2] On the basis of these assessments, we classified the quality of the available trial data into four groups: high, medium, poor, and flawed.

We found that the results confirmed and strengthened our original conclusion. No trial data were of high quality, two were of medium quality (Malmö and Canada), three were of poor quality (Two-County, Stockholm, and Göteborg), and two were flawed (New York and Edinburgh). The review provided evidence that assessment of cause of death is unreliable and biased in favour of screening. Even when endpoint committees masked to group assignment were used, uncertain causes of death were significantly more commonly ascribed to breast cancer than to other causes in the control group. The credibility of this finding is supported by another meta-analysis, which showed that radiotherapy reduces local recurrence by two-thirds.[3] Treatment of early cancers by tumourectomy and radiotherapy might increase the likelihood that deaths among screen-detected breast cancer cases will be misclassified as deaths from other causes,[3] particularly other cancers.[3] We noted that the two trials with medium-quality data failed to find an effect of screening on deaths ascribed to any cancer, including breast cancer (relative risk 1·02 [95% CI 0·95–1·10]). The estimate for the trials with poor-quality data was similar (1·00 [0·91–1·10]). Furthermore, the greater use of radiotherapy in screened women than in controls[3] is expected to increase overall mortality because of cardiovascular adverse effects.[3] These deaths were not

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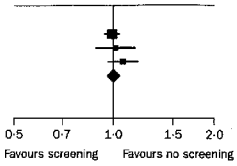
Study	Screened Number of deaths/ number of women	Not screened Number of deaths/ number of women	Relative risk* (95% CI)	Weight (%)	Relative risk* (95% CI)
Malmö 1976	2537/21 088	2593/21 195		70·08	0·98 (0·93–1·04)
Canada 1980a	418/25 214	414/25 216		11·22	1·01 (0·88–1·16)
Canada 1980b	734/19 711	690/19 694		18·70	1·06 (0·96–1·18)
Subtotal	3689/66 013	3697/66 105		100·00	1·00 (0·96–1·05)

Test for heterogeneity: χ^2=1·80, df=2 (p=0·41)
Test for overall effect: z=0·05 (p=0·96)



All-cause mortality in medium-quality screening trials after 13 years
*Fixed-effects model.

counted as deaths related to screening in the trials we assessed.

The main outcome measure in the screening trials was breast-cancer mortality. This choice seems rational, since larger trials would be needed to show an effect on overall mortality. However, we showed that the assumption that a demonstrated effect on breast-cancer mortality can be translated into a reduction in overall mortality rests on suppositions that are not correct.[2] The only reliable mortality estimates are therefore those for overall mortality. The relative risk of overall mortality was 1·00 (0·96–1·05) in the two trials of highest methodological quality (figure).[2] The Swedish trialists have recently reported an updated mortality estimate for the four Swedish trials:[4] this estimate was also 1·00 (0·98–1·02) after adjustment for imbalances in age that had occurred despite attempts at randomisation.[1,2] Thus, although the trials were underpowered for all-cause mortality, the reliable evidence does not indicate any survival benefit of mass screening for breast cancer.

In our previous paper,[1] we divided the trials into two groups on the basis of methodological quality. We reported that the effect estimate for breast cancer mortality in the two best trials was significantly different from that for the five poor-quality trials, which is a sign that something is wrong. In our latest review, we therefore omitted the trials from New York and Edinburgh from the analysis of the poor-quality trials, since they are flawed.[2] However, there was still a significant difference between the two estimates for breast-cancer mortality. The two best trials failed to find an effect of screening on deaths ascribed to breast cancer (relative risk 0·97 [0·82–1·14) after 13 years, whereas the three remaining trials with poor-quality data found a marked effect (0·68 [0·58–0·78]; p=0·001 for the difference between the two effect estimates). Given the strong heterogeneity, results from the different quality groups should not be combined.

The largest effects on breast-cancer mortality were reported in trials that had long intervals between screenings (Two-County trial), that invited many women to only two or three screenings (Two-County and Stockholm trials), that started systematic screening of the control group after 3–5 years (Two-County trial, Göteborg trial, and Stockholm trial) and that had poor equipment for mammography (New York trial). This surprising situation suggests that differences in reported effects between the trials are related to the methodological quality of the trials and not to the quality of the mammograms or the screening programmes.[2]

We have also confirmed, with additional data (see www.thelancet.com), which the editors of the Cochrane Breast Cancer Group have elected to defer from publication until further editorial review has been completed, our earlier finding[1] that screening leads to more aggressive treatment, increasing the number of mastectomies by about 20% and the number of mastectomies and tumourectomies by about 30%. The greater use of surgery was not merely an initial phenomenon caused by the tumours detected at the prevalence screen, but seemed to persist. The increased mastectomy rate in the trials might be higher than in current practice, since there has been a general policy change towards fewer mastectomies. However, screening identifies some slow-growing tumours that would never have developed into cancer in the women's remaining lifetimes, as well as cell changes that are histologically cancer but biologically benign. Furthermore, carcinoma in situ does not always develop into invasive cancer, but since these early lesions are often diffuse, women are sometimes treated by bilateral mastectomy. Therefore, the increase in surgery rates could also be an underestimate, since reoperations and operations in the contralateral breast seemed not to have been included. Furthermore, "better" diagnostic methods—eg, better mammograms—could lead to additional overtreatment because of detection of even more early or questionable lesions. Quality assurance programmes could possibly reduce the surgical activity to some degree, but the problem cannot be avoided.

Our earlier report[1] has been criticised,[5,6] especially for its emphasis on imbalances in baseline variables. However, the main reason for the ongoing controversy is probably that our opponents keep referring to the criticisms of our paper without referring to our reply.[7] Furthermore, they seem to have ignored this sentence in our paper: "Our analyses focused on age as a marker for imbalance as this was the only baseline information we had available for the Swedish trials".[1] We have not postulated that the baseline imbalances per se caused the inflated effect, but we used the imbalances as markers of poor trial methodology[7]—an approach that led us to new important information about the trials.[2] Contrary to what the critics assert,[6] the fact that that there was no age imbalance in the two best trials was confirmed in the correspondence that followed our *Lancet* paper, and we believe that all relevant criticism has now been addressed in our review.[2]

We have provided detailed evidence on the mammography screening trials, and hope that women, clinicians, and policy-makers will consider these findings carefully when they decide whether or not to attend or support screening programmes. Any hope or claim that screening mammography with more modern technologies than applied in these trials will reduce mortality without causing too much harm will have to be tested in large, well-conducted randomised trials with all-cause mortality as the primary outcome.

This study was funded by the Danish Institute for Health Technology Assessment. The review is available at http://image.thelancet.com/lancet/extra/fullreport.pdf

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Molecular diagnosis in a child with sudden infant death syndrome

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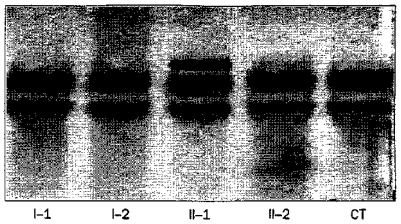
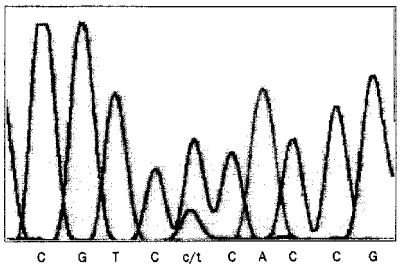
Although sudden infant death syndrome (SIDS) has been associated with long QT syndrome—a genetic disorder that causes arrhythmia—a causal link has not been shown. We screened genomic DNA from a child who died of SIDS and identified a de-novo mutation in *KVLQT1*, the gene most frequently associated with long QT syndrome. This mutation (C350T) had already been identified in an unrelated family that was affected by long QT syndrome. These results confirm the hypothesis that some deaths from SIDS are caused by long QT syndrome and support implementation of neonatal electrocardiographic screening.

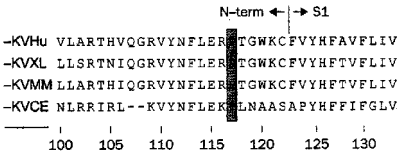
Lancet 2001; **358:** 1342–43

Sudden infant death syndrome (SIDS) is a common diagnosis in children who have died in the first year of life.[1] Several non-specific changes in behaviour have been recommended in an attempt to reduce the number of children who die from SIDS; however, to implement targeted preventive strategies, specific causes need to be identified. SIDS has been associated with long QT syndrome (LQTS),[2,3] a genetic disorder causing arrhythmia, and one of the main causes of sudden cardiac death in young children.[4]

Results of a prospective study of 34 000 newborn babies showed that 50% of children who died from SIDS had a QT_c that was higher than normal, and that a prolonged QT interval (which does not necessarily infer LQTS) increased the risk of SIDS by 41 times.[2] Two hypotheses could explain how an infant could be affected by this genetic disease, and still have parents with a normal QT interval: either a de-novo mutation or mutation that is incompletely penetrant. A de-novo mutation of the cardiac sodium-channel gene associated with LQTS was identified in a child with near-SIDS,[3] suggesting that the former hypothesis is correct. However, a diagnosis of LQTS has not been made in a child who died from SIDS without having had an elec







Genetic analysis of *KVLQT1* gene
(Top) Single strand conformation polymorphism analysis of a PCR reaction amplifying the region of the *KVLQT1* gene that contains the coding sequence for P117. The abnormal conformer of the PCR product potentially containing the mutation can be seen in the extra band in the child with SIDS (II-1) compared with only two bands seen in those with wild type (I-1, father; I-2 mother; II-2 sister; CT, healthy control). (Middle) Results of DNA sequencing analysis of the same fragment, showing the heterozygous single nucleotide substitution of the P117L mutation. (Bottom) Alignment of P117 in different species showing that this residue is highly conserved in *KVLQT1* homologues. Hu=human, XL=*Xenopus laevis*, MM=*Mus musculus*, CE=*Caenorhabditis elegans*, S1=first transmembrane segment.

Our results relate to two Italian familes, both of whom had the same genetic mutation. In one family, an infant died of SIDS, and in the other, several members had LQTS. A genetic analysis of the infant who died from SIDS identified a point mutation (C to T at position 350; figure), which led to a non-conservative aminoacid substitution with leucine replacing a highly-conserved proline at position 117 of the KVLQT1 protein. This mutation was not found in 800 reference alleles of Italian origin. Both the parents and the sister had a normal electrocardiogram, with QT_c values below 405 ms, and no one had the P117L mutation. Paternity was confirmed, thereby establishing a de-novo mutation. Our results provide evidence that in a child who died from SIDS,

Senator MIKULSKI. My question is this, Doctor. You have read the Danish study of Drs. Olsen and Gotzsche, and also the PDQ, which is really an advisory board to the NIH and NCI, has also raised yellow flashing lights. Could you give us your comments and analysis of the Danish study, and if you care to comment on PDQ,

from which a board member will testify later. You have just said it clearly, and the position has been clearly since 1997. We welcome your commentary on these two studies that essentially dispute what you have just said.

Dr. VON ESCHENBACH. In summary, the investigators that you address looked at the seven randomized trials, made decisions about certain aspects of those trials in terms of how much they would weight them or include them in a combined analysis of the information called the meta-analysis. Based on their judgments and decisions about the relative value of some of those studies, they eliminated some of them from the ultimate analysis. Then, when they applied their meta-analysis, they concluded that the information was not significant enough to warrant continued support of mammography.

Other statisticians, other experts, have looked at their analysis and have raised concerns about many of the judgments that they made on a statistical basis. So there is a difference of opinion among the experts as to how one should evaluate those seven combined trials.

Other experts have looked at that information and have concluded, as the U.S. Preventive Services Task Force has, that the data still supports the value of mammography in the equation that I pointed out and must continue to remain an important part of that equation.

So the issue here, Senator, is a difference in statistical interpretation and methodology. From the scientific perspective, there is value in that argument. From the clinical perspective, however, one must conclude that there is no indication that mammography should not be in that equation based on that analysis, even if you might want to argue whether it is providing the major part of that equation or a component of it.

Senator MIKULSKI. Doctor, I have time for one more question. Essentially what you are saying is that one group of biostatisticians came to one set of conclusions and another has come to another, both competent people.

Dr. VON ESCHENBACH. Correct.

Senator MIKULSKI. We are now again into lack of clarity—I am not saying from you—and my question is do you think—there have only been seven studies over 40 years in terms of the efficacy of mammograms in early detection—do you think it is time to do another study?

Dr. VON ESCHENBACH. No, I do not.

Senator MIKULSKI. Could you comment on that, because it would then seem like we need a study to settle the disputes about the other studies.

Dr. VON ESCHENBACH. Those studies over that period of time enrolled over 400,000 patients, and over that period of time, much has changed with regard to the State of the art of mammography and our State of the art with regard to breast cancer care.

To attempt to repeat that kind of study in which there would be a randomization whereby women by the flip of a coin or by chance would be assigned to either mammography or no mammography would not at this point in time be a viable or rational study, in my opinion, one that would not likely be able to be carried out at this

point in time and certainly not, I believe, under our current structure.

Senator MIKULSKI. But, Doctor, isn't that true of any clinical trial? Some get the treatment, and some do not; some get the diagnosis, and some do not.

Dr. VON ESCHENBACH. In terms of being able to attract a sufficient number of patients to the trial and in terms of being able to get them to accept a randomization by the flip of a coin as to whether they would or would not get mammography, I have and I believe others have serious concerns that that kind of trial could not effectively be carried out in a reasonable period of time to get a conclusive answer to the question; while in the meantime, where we believe we should be focusing our efforts is on even better methods of detection than mammography and to look at newer technologies and their applications in the kinds of clinical trials you are describing.

Senator MIKULSKI. You raise a very good point. Unfortunately, my time is up. I think other of my colleagues will raise other issues. But I thank you; I think we are on our way to clarification.

Senator Harkin?

Senator HARKIN. Thank you, Senator Mikulski.

I have looked very carefully at the study that was done by Olsen and Gotzsche, and it seems to me that first of all, these were mammographies that were done in the 1960's and 1970's and maybe in the early 1980's. I do not know if they got into the 1980's or not, but it was sometime in that time frame. As you have stated, we clearly have better mammography technologies now than we had at that time.

Second of all, Olsen and Gotzsche, as I understand it, looked at the technical details of how the studies were set up. If I am not mistaken, others have looked at their study and basically refuted some of their findings based upon what happened later on in the clinical trials. I am sorry, I am just a layman speaking here—I am not a doctor or a biostatistician or anything like that. But it seems to me, as I read through their study, that Olsen and Gotzsche, looked at one part of the data from the clinical trials, and based upon that, they said there was not conclusive evidence of the value of mammography. They did not really look at all the data. At least, that is my layman's way of interpreting it. And based upon some statistical analysis they had done about how the groups were selected and who was screened and who was not screened, they reached these decisions. But they did not take into account that those things were adjusted for, if I am not mistaken, later on. Those anomalies, whatever they might have been, were adjusted for later on.

Am I somewhat correct in that?

Dr. VON ESCHENBACH. Yes, Senator, you are quite on track with regard to your interpretation, as I also see it, and I believe that on the next panel, there will be experts far more sophisticated than I with regard to biostatistics. But I am in agreement with your interpretation.

Senator HARKIN. I know that to the general public this sounds like a lot of gobbledegook, and it is sometimes beyond my comprehension, too. But if you read the Danish study and really get

into it, I am finding out that they just looked too narrowly at the data from the clinical trials. Second, they did not take into account the new technologies and the development of better mammography screening that we have today.

Now I want to follow up on what Senator Mikulski was just getting to when her time expired. She spoke about future methods of breast cancer screening and new types of technologies. Could you elaborate a little bit on that and perhaps the time frame we are looking at?

Dr. VON ESCHENBACH. At the present time, the National Cancer Institute is supporting one trial that is looking at the value of digital mammography versus standard mammography as a method of improved detection. Other technologies that are being evaluated include PET scanning, or the use of positron emission tomography, and the evaluation of the function of lesions; magnetic resonance imaging is also being employed; and techniques whereby we are beginning to understand the biologic basis of tumors; even aspirates from the nipple that enable us to look at cells may be a way of detecting cancer in its earlier stages.

So there are multiple methodologies that are being evaluated in the kinds of trials that Senator Mikulski is referring to.

Senator HARKIN. Dr. von Eschenbach, the National Cancer Institute recently announced the development of a new blood test—for detection of ovarian cancer. I believe it is a blood test that patients can take.

Dr. VON ESCHENBACH. Correct.

Senator HARKIN. Is there anything underway in terms of research that might lead to some kind of blood test for early detection of breast cancer?

Dr. VON ESCHENBACH. Well, that is one of the methodologies that, as it is validated in ovarian cancer, needs to be more broadly applied, and the underlying technique certainly opens up the hope that this would be applicable to many cancers, including breast.

Senator HARKIN. Of course, the ultimate goal of all the money that we have been putting into breast cancer research is to hopefully find a means of prevention, a vaccine or some other treatment that would be a preventive measure for breast cancer. Is there anything along those lines that you can tell us about?

Dr. VON ESCHENBACH. I think that what we are looking at, Senator, in that equation is that we would like to attack this problem at multiple places along the spectrum, including the ability to prevent it. We now know that there are agents that have been developed that can be preventive for breast cancer; tamoxifen and relaxifen are being clinically tested, and new drugs are also being developed that would perhaps have less toxicity, yet at the same time be able to provide that preventive effect as well.

So I want us at the National Cancer Institute to have a multipronged attack or approach that looks at detection, diagnosis, treatment, and prevention, so that ultimately, we eradicate the deaths that we are seeing from this disease.

Senator HARKIN. Thank you, Doctor.

Senator MIKULSKI. We have now been joined by Senator Bill Frist, the only physician currently serving in the U.S. Senate, who

has brought such keen insight to all of our committee deliberations and is the ranking member of the Public Health Subcommittee.

Senator Frist, I would like to turn to you. Senator Specter was here, but he had a meeting with the Steel Caucus with the President, and Senator Snowe was unable to come. So we are glad to see you.

Senator FRIST. Thank you. I would just ask that my opening statement be made part of the record, and I apologize for being a few minutes late.

Senator MIKULSKI. Without objection.

[The prepared statement of Senator Frist follows:]

PREPARED STATEMENT OF SENATOR FRIST, M.D.

During the past few weeks, there have been seemingly conflicting and often confusing reports about the benefits of mammography screening. I believe today's hearing will go a long way toward providing more clarity. It is important that women have as much credible information as possible about mammography as a breast screening tool so that they can make informed and appropriate decisions about their health.

I want to extend a special welcome to Dr. Andrew von Eshenbach of the National Cancer Institute. I understand that this is your first time testifying before Congress. I am very pleased that you are here today.

It is confusing for many Americans to read a report in the local paper 1 week about a recent study stating that mammography may not be beneficial, and then to read statements by public officials the next week stating that the government still recommends mammographies. Women can easily be confused about what they should be doing in the interest of their own health.

In many ways, it would be easier to communicate with the public about how to take care of their health if there existed one static, scientific document which stated exactly what should be done, by whom, at what time, and at what place. However, science is a constantly evolving field, with new information being added daily regarding new therapies and new ways of looking at diseases. As we gain more information about how to diagnose, treat, and or even cure many illnesses, we must interpret new research, evaluate it in the context of other studies, and challenge our scientific and medical assumptions.

Unfortunately, making the right health care choices becomes particularly difficult when there are conflicting research studies. During those tumultuous times, we generally rely on public health and health care experts to assist us in wading through the information and drawing appropriate conclusions, to provide guidance to the general public about appropriate health care choices. For mammography, the story is no different. Scientists and statisticians have been debating the relative merits of mammography as a screening tool for a number of years. In the mid-1990's, for example, there was a great deal of controversy over whether women in their 40's should receive mammographies. After more definitive studies became available and were analyzed, the National Cancer Institute eventually decided to recommend screening for women in their 40's.

Last fall, the issue once again came front and center when Danish scientists reviewed seven leading studies of mammography screening and concluded that there were significant questions about the quality of the research—ultimately questioning whether using mammography as a screening tool results in a reduction of breast cancer deaths. This one study produced a flurry of discussions about the validity of mammography as a screening tool and the message that we should be sending to women about its value. However, as is the case with all studies, research must be put in the context of what has already been learned.

That is why I was encouraged when the U.S. Preventive Services Task Force, an independent panel of experts in primary care and prevention that systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services, last Thursday released new recommendations regarding mammography, based on a review of eight randomized, controlled trials. These recommendations call for screening mammography with or without clinical breast examination, every two years for women ages 40 and older, as well as clarifying recommendations regarding breast self examinations. Their previous recommendations, in 1989 and 1996, endorsed mammography for women over age 50.

Although the Task Force's recommendations provide guidance about the overall value of mammography for breast cancer screening, it does not endorse mammography as the perfect screening tool. We need continued research to improve the detection of breast cancer lesions and differentiation between cancer lesions and other non-cancerous lesions. Moreover, as better diagnostic tools to detect early-stage tumors are developed, additional research will be needed to guide our decisions about recommended treatment options. Finally, as we all are aware, the answer is not just to detect breast cancer but also to both prevent the incidence of the cancer and to appropriately treat any detected tumors. We must work to not only diagnose, but also to prevent and cure the diseases.

Additionally, we must continue efforts to ensure that women receive quality mammography services without reducing access to those services, which is why it is important that we strengthen the Mammography Quality Standards Act (MQSA). I appreciate the testimony from the National Breast Cancer Coalition and the Susan G. Komen Foundation about this vital program, and I look forward to working with Senator Kennedy, Senator Gregg, Senator Collins, and my other colleagues on this Committee to reauthorize this important law.

Senator FRIST. First of all, welcome, Dr. von Eschenbach. I know this is your first hearing. The position that you have assumed is one that is very, very important to millions and millions of Americans, as you well know. I appreciate your sacrificing a practice of taking care of patients one-on-one for public service, for what is a terribly important position and initiative. Whether it is in the Patient Bill of Rights or coverage of clinical trials for cancer or for preventive medicine or for Medicare reform modernization, what we do with cancer is right at the center of all of these debates. I am delighted to have you before us today, initiating that discussion, so people can get to know you and you can get to know them.

You and I have had the opportunity to talk about a number of issues. Mammography is an issue that we are spending a lot of time on today and a very important issue that, as has been mentioned, has been debated and discussed again and again—we are going to continue to discuss it to find just the appropriate place. As I can see from your chart, we see the change in mortality and the various parameters that are there. A and B will continue to change, as will C, over time, and that is the importance of these hearings.

In my couple of minutes, let me just ask you to expound a bit on translational research. I think it is very important—and I know that you feel very strongly about it—to make sure that the basic research findings that are so remarkable, that we have invested in in a doubling fashion at the National Institutes of Health, are translated into the types of diagnostic and treatment procedures, like mammography, like treatment for breast cancer.

Could you share with us a little bit of your philosophy and what you hope to see happen; feel free to use mammography as an example of the importance of translational research.

Dr. VON ESCHENBACH. Thank you, Senator. I would be delighted to share that with you, and I think that breast cancer is a very important example of the opportunity and the challenge that translational research provides us.

Specifically, one of the problems with mammography is the question as to whether we are detecting some breast cancers that, by their very nature, would not be virulent or aggressive and would then threaten a patient's life.

We do not yet have a way of being able to accurately, totally, completely determine or predict that, so we must treat any cancer that we find as a dangerous cancer requiring significant intervention.

Hopefully, as we begin to understand how cancer cells develop at the genetic level and why they behave the way they do based on their interactions with other cells, when we understand that at the basic, fundamental, biological level, we can design interventions that can interfere with, change, or alter that behavior, and we may then be able to use that information to define the aggressive cancers, treat them aggressively, to find the cancers that do not have those molecular-genetic characteristics and treat them in a more benevolent but effective fashion.

So translational research will significantly improve the rational application of our treatments.

Senator FRIST. And what will that do to the protocols, and what can be recommended? How will that change those protocols?

Dr. VON ESCHENBACH. One of the important ways that I think it will change the protocols is that before a patient enters into a protocol, we can use the molecular and genetic information to stratify them, if you will, to separate them into high-risk and low-risk groups and then apply the particular treatment strategy or the protocol that we are testing; but we will know much more precisely the basis upon which we are gathering that information.

Senator FRIST. Thank you.

Madam Chairman, I think I will forego; I know we have a number of other panels to hear from.

Senator MIKULSKI. Thank you very much, Senator. That was an excellent question.

I would now like to turn to Senator Jack Reed.

Senator REED. Thank you very much, Madam Chairman.

Thank you very much, Doctor, for your testimony. At the core of today's hearing is a controversy about the efficacy of mammography in screening. Stepping aside from that, besides the advice that you are giving women today to continue the screening, is there other advice that you might give in terms of perhaps starting younger in terms of screening, or a different approach to it that would avoid the question of the efficacy of the tests and the statistical debate we are having today?

Dr. VON ESCHENBACH. No, Senator. We set the threshold at 40 as what we believe to do the optimal or reasonable level at which we can recommend it and apply it. Now, again, the research that I alluded to earlier in terms of understanding the disease will hopefully lead us to be able to identify women who are at much higher risk than normal or average, and in those women, we may need to modify or change the recommendations as we go forward so we can detect them even sooner or earlier. But that is a work in progress, and we have not yet reached the point where we can make it a uniform recommendation.

Senator REED. You have experience in several different medical conditions, cancer, etc. Is there a similar controversy in other areas, for example, in terms of prostate or other cancers, where the testing regime and the efficacy are also debated as they are with mammography?

Dr. VON ESCHENBACH. Yes, sir, unfortunately, there are, and I personally was deeply involved in the issue of formulating guidelines for men for the use of prostate-specific antigen. As with mammography, in that situation, there is even less data or information upon which to make hard, specific, scientific recommendations.

I think what we are faced with as clinicians responsible for the lives of patients with cancer is to apply the science, but at the same time use clinical judgment and arrive at the best recommendation we can today given the information that we have.

The information on mammography is far better than the information for PSA and prostate cancer, and we are basing our recommendation to American women on what we have available as the best information.

Senator REED. But I would suspect that both of these areas have helped in terms of your analysis, that having experience in several different fields has helped inform your judgment about your recommendation today.

Dr. VON ESCHENBACH. What is most gratifying to you and to us is the fact that in both of these diseases, we are seeing a decline in mortality; we are seeing a decline in death rate. That gives us hope and a bit of comfort that we are at least on the right track. We are nowhere near where we need to be, but we are heading in the right direction.

Senator REED. Finally, Doctor, you indicated in your testimony the disparity between the incidence of in African American women and white women, Caucasian women. What role does mammog-

raphy play in this disparity, and what might be other contributing factors?

Dr. VON ESCHENBACH. There are two very interesting observations that can shed some light on the answer to that question. One is that we are beginning to see the gap narrow between the mortality rate for black women and white women, so we are improving, we are closing that gap, and we are making progress. That coincides with the fact that there has been greater utilization of mammography among black women. So that hopefully, those are coincident. I cannot prove them to be cause and effect, but they are coincident, and they are both encouraging.

Senator REED. Thank you. One final point, Doctor. I do not know much about South Philly, but are you the only von Eschenbach in South Philly?

Dr. VON ESCHENBACH. My mother's maiden name was de Alfonso.

Senator REED. Now I understand, now I understand. Thank you, Doctor. The record is now complete. I yield back.

Dr. VON ESCHENBACH. Thank you, Senator.

Senator MIKULSKI. Senator Murray?

Senator MURRAY. Thank you very much, Madam Chairman, first for having this hearing, which I think is so important today, but also for your long-time work on the issue of breast cancer. We have been here before, debating this issue—Senator Hutchison remembers—and frankly, we have been through it too many times, and I think the bottom line is that women need to know what they can do to fight breast cancer, and unfortunately, this debate too often comes down to a debate between numbers versus women, and we have allowed abstract statistical data to confuse and distort the issues.

I want to thank all the witnesses who are here today, especially the advocates, for the tremendous work that you do on behalf of so many women. I appreciate your continuing efforts to make sure that women have access to early screening and diagnosis.

Madam Chairman, it seems to me, unfortunately, that we have allowed this controversy to shift the focus away from prevention and access to health care. This is not just an issue for women in their 40's or 50's, but for women who are in their 20's and 30's who want to know what they can do today to prevent breast cancer. I hope we do not lose our focus on that issue.

One issue that concerns me very much is that we do know that through better information and access, more women are getting regular mammograms, and we know that that has helped to boost survival rates; but we also know that access has not improved equally across the board for all women. Minority women have a much lower screening rate; in fact, the screening rate for Asian and Native American women is really dismal. I know there are many factors that contribute to those low rates, but I am very worried that the current conflicting and confusing messages are not going to help our efforts to expand access.

Doctor, if you could just tell me what you think we need to do to make sure that this current controversy does not hinder our efforts to improve access for minority women, I would appreciate hearing your thoughts on that.

Dr. VON ESCHENBACH. Thank you, Senator Murray.

We have tried to be very clear in our message so that we do not continue to contribute to some of the concern. At the same time, we are paying a great deal of attention within the National Cancer Institute, particularly through Dr. Reimer's division, to messages and communication and education so that patients do in fact have appropriate and timely and accurate information; and we are learning and studying how to reach out as effectively as we possibly can to various communities so that we can provide that appropriate message in the appropriate way.

Senator MURRAY. I think that that is extremely important to do. Especially when information that comes out that is conflicting, it automatically offers women the excuse that they are looking for. So I think we need to especially now, at times like this, reach out again and make sure we are doing and saying what we need to do to make sure that women get screened.

Let me ask you another question. We always focus on what age do you start having a mammogram every year, and we need to really get that message out; it is very important. But I am also very concerned about what we should be telling women who are in their 20's about what they can do now, before they start worrying about getting a mammogram when they are 40. What are we learning today that women can be doing even when they are young teenagers that will help decrease their risk of getting breast cancer?

Dr. VON ESCHENBACH. Well, we do not have the absolute cause and effect kinds of relationships where we can say that if you absolutely do this, we can guarantee that you will not have a problem. But we do recognize certain associations—for example, diet being one of them—and we are obviously encouraging a healthy lifestyle with regard to diet and exercise as part of that preventive process.

What we need to do is research that will help us identify women who are at high risk early in life and also identify the most effective preventive methods, not just in terms of lifestyle but some of the biologic interventions that are safe and appropriate. Our whole area of cancer prevention is directed toward trying to identify those kinds of interventions and then apply them appropriately in women at high risk.

Senator MURRAY. Good. I really appreciate that, and I hope that we do not allow these kinds of discussions to refocus away from making sure that we are doing that, because I really think that that is the much better answer in the long run, what we can do when we are younger so that breast cancer is not such a concern for women who are older.

I have one other comment and question. I think there is another issue that has really been ignored in this debate, and that is the role that mammography has played not just in improving survival rates but in improving quality of life for breast cancer victims. The written statement of Dr. Leffall, who is the chair-elect of the Susan G. Komen Breast Cancer Foundation, shows that because of mammography, tumors have been detected earlier and smaller.

Now, that is a huge benefit that I think has been lost in this debate, because options to mastectomy significantly improve quality of life and allow for a faster and quicker recovery.

Can you talk a little bit about how mammography and early diagnosis have impacted quality of life for breast cancer patients?

Dr. VON ESCHENBACH. Thank you for pointing that out. I think that from the quality of life point of view, over and above just the mortality argument or discussion that we have been having, from the patient's point of view, that is an extremely important contribution. By detecting cancers earlier, one can then apply therapies that are going to be less mutilating and have less of an impact on quality of life, and that in itself is a major goal and objective for us. So I concur completely with your emphasis on that particular aspect of the issue.

Senator MURRAY. Thank you very much, Doctor. I really appreciate your coming and providing the testimony today.

Madam Chairman, again, I really want to thank you for holding this hearing to clarify this issue once again and to help us focus on what we can do to make quality of life better for all women in this country.

Senator MIKULSKI. Thank you very much, Senator Murray, for your compliments but most of all for your ongoing advocacy.

I invited the two Republican women who are not on the committee to join us today because of their longstanding advocacy on this issue. As I said, Senator Snowe and I have worked on this since we were in the House, but Senator Kay Bailey Hutchison is here, and Doctor, you will be interested to know that the women of the Senate have really worked on women's health on a bipartisan basis and particularly on the issues of breast and ovarian cancer. Senator Kay Bailey Hutchison has been an advocate in helping me get the Mammogram Quality Standards that were necessary, and of course, she is from the home State of the outstanding Komen Foundation. And also, you are on the Labor-HHS Committee on Appropriations, so you are also a member of this. I am sorry.

Senator HUTCHISON. That is right, Madam Chairman, and you and I, of course, have worked on many cancer issues and trying to fund cancer research.

But to give you the real background—I feel like it is deja vu all over again—in 1994, the Government representative came forward and said women should not have mammograms until they are 50. Well, Senator Mikulski called a hearing, and every, single woman Member of the Senate came and upbraided the Government official, who was sitting at that table by himself just like you are, and said how could you send this kind of mixed message. We have been working for years now to at least get early detection for women, because that is all we have—we do not have the cure—and finally, after about a month or so after that hearing, the entire NCI cratered, and everybody said, "No, no, no—40—we think that is probably the most prudent thing to do. Women should have mammograms at the age of 40."

Well, fast-forward to about a month ago, and we see the results of the study that say that mammograms are really useless and might even cause harm. I was looking at that, just astonished that we could be once again mixing our message based on, apparently, trials that were done in 1985. Now, there may have been other things that went into that, but we are talking about 1985 trials, and we are saying, well, you can do without a mammogram, and maybe walking is just as good as getting a mammogram.

Well, here we are again, and Dr. von Eschenbach, I am so glad that you have clarified very quickly that 40 is the recommendation, because I know that we have saved lives. Everyone in this room knows that by early detection, we have saved lives. We also have put hundreds of millions of dollars into research to try to find the cure, and you will be in a pivotal position to help us find that cure so that we will not have to talk about mammogram anymore; we will cure this, and then perhaps we will not have to deal with cancer of this kind again, and we can move on to something else.

But for now, I would ask you how you view this study that is based on these 1985 trials that came from the Danish researchers that would indicate that false positives are a reason not to go forward and do the only thing we know that will allow the early detection of a cancer tumor.

Dr. VON ESCHENBACH. There are two answers that I might offer, Senator. One is that certainly as we have improved the technology of not only mammography, but the ancillary studies that can be used to follow up mammography, including the ability to biopsy under ultrasound, we have actually been able to improve on the false positive concern, if you will.

So I think that additional progress is improving some of those previous concerns and issues.

The other thing that I think your question comes out, to come back to my example, is that we are seeing a decline, and if you want to use the number 6 per 100,000 as that decline, one could—and I think the debate has been around whether it is 3 plus 3 equals 6, or 2 plus 4 equals, and there is an argument around the relative value of mammography—but I believe we all conclude that mammography needs to be a part of that equation, that it is continuing to add to that equation, and whether there is an argument among statisticians as to whether it is 3 plus 3 or 2 plus 4, the important point is that it is contributing and must remain a part of the equation.

Senator HUTCHISON. Anyone who has had a mammogram knows that you wonder which is worse—getting the mammogram or getting the cancer—but having said that, is there anything harmful that can be done in a mammogram, or maybe a wrongly given one, but is there in general a harmful effect of a mammogram?

Dr. VON ESCHENBACH. I believe that the greatest issue is in fact the discomfort and the humiliation that may go along with the examination, but other than that, other harms would be negligible, in my opinion.

Senator HUTCHISON. Well, thank you, and I do hope that you will use your position to help us find the cure, because that is what has been missing for all these years that we have worked to try to eradicate breast cancer as a leading cause of deaths among women.

Thank you.

Dr. VON ESCHENBACH. Thank you, Senator.

Senator MIKULSKI. Now we turn to Senator Clinton, one of the newer members of the committee but certainly one of our most active.

Senator Clinton?

Senator CLINTON. Thank you very much, and thank you for holding this hearing.

And thank you, Dr. von Eschenbach, for now being in the hot seat for quite some time. I appreciate your clarification—I am sorry that I missed your testimony, and I just want to ask three brief questions just to be sure that I can accurately report to my many constituents who are deeply concerned about the controversy and also about the high prevalence of breast cancer in many parts of New York, higher than the national average.

Is it fair to say that your testimony today reflecting the NCI position is that all women should get regular mammograms after the age of 40, or is it that women should be provided with information about the benefits and risks which they then, in consultation with their doctors, make their own decisions?

Dr. VON ESCHENBACH. We are recommending that it be a combination of both the performance and availability of the mammogram along with the education and understanding of the implications of it. I believe that both of those are important, but I would not leave out the mammogram as a primary part and the initial part of that recommendation.

Senator CLINTON. But a woman who is a potential recipient of a mammogram really has no independent way of determining the efficacy or the quality of the mammogram; so if I am asked by a constituent after this hearing what did Dr. von Eschenbach say should be done, what is my short answer?

Dr. VON ESCHENBACH. Beginning at age 40, you ought to have a mammogram every 1 to 2 years.

Senator CLINTON. OK, great. I just want to be absolutely clear about that.

As to the second issue with respect to the quality and the efficacy, we will be reauthorizing the Mammography Quality Standards Act, recertifying it, I think this year. Will you be able to provide us with specific suggestions as to any modifications of the Act that might be helpful to address this controversy and increase the quality standards? I think there has been some debate about whether or not the MQSA has really lived up to its promise. Can you offer any suggestions as to what we can do to modify it when we reauthorize the Act?

Dr. VON ESCHENBACH. At this point, I could not, Senator, but I would be happy to provide that to you in subsequent information and material that would give you the kind of documentation that you need for an intelligent recommendation from me.

Senator CLINTON. That would be very helpful, because one of the things which is happening in New York, and I assume it is happening elsewhere, even before the back and forth of the last month or so, is that many physicians' offices and freestanding mammography clinics were eliminating the service because the reimbursement was insufficient to pay for the physician time, the technician time, and the overhead costs.

So we have many parts of my State where it is very difficult to access a mammogram, and what I am worried about is that in light of this controversy, we will see more and more insurance companies determining that they will no longer cover the cost of mammography, concluding that because it is somewhat in dispute as to its importance, it is no longer a covered service.

So I am hoping that your very straightforward statement that it is still the recommendation of the National Cancer Institute that women, staring at the age of 40, have mammograms, will give us the ammunition we need to avoid further cutbacks in access and reimbursement, which I am very concerned about.

So I join the other members of this panel in thanking you for your testimony, thank you for taking on such an important task, because certainly those of us who have been involved in this issue for some time—and I see my friend Fran Visco out there—know that we have to do even more to find ways of preventing and curing breast cancer and that mammography is a tool in that fight, but it is not the principal weapon that we need to utilize.

So thank you very much for being here.

Dr. VON ESCHENBACH. Thank you, Senator. You said it far better than I did. Thank you.

Senator MIKULSKI. Thank you very much, Dr. von Eschenbach. If you would like to hang around, we would really welcome you at the end, perhaps, if you have any concluding observations.

Dr. VON ESCHENBACH. Thank you, Senator.

Senator MIKULSKI. I will say to my colleagues that we have two excellent panels, one that we will call up now, which includes Dr. Donald Berry and Dr. Harmon Eyre.

Dr. Berry is from the PDQ, and Dr. Eyre is from the American Cancer Society. They will be followed by a panel that will include the National Breast Cancer Coalition, a clinician representing the American College of Obstetricians and Gynecologists, and also a physician representing the Komen Foundation.

Dr. Berry is an international expert and is the chairman of biostatistics at the University of Texas. He is also a principal investigator on a project funded by the National Cancer Institute to assess the relative contribution of screening mammography, tamoxifen, and chemotherapy in terms of the drop in breast cancer.

We invited Dr. Berry to come and speak as a member of the Physicians' Data Query Screening and Prevention Board, the PDQ, which has raised some yellow flashing lights about the efficacy of mammograms.

Dr. Harmon Eyre has a career-long interest in cancer research. He comes to us with an academic career in medical oncology. He has degrees from Utah and Hopkins. He has been recognized by the American College of Surgeons. We really welcome him to present the views of the American Cancer Society.

Dr. Berry, we would like you to kick the panel off and give us the perspective of the PDQ, and then we will turn to questions.

STATEMENTS OF DR. DONALD A. BERRY, CHAIRMAN, DEPARTMENT OF BIOSTATISTICS, M.D. ANDERSON CANCER CENTER, UNIVERSITY OF TEXAS, HOUSTON, TX; AND DR. HARMON J. EYRE, CHIEF MEDICAL OFFICER AND EXECUTIVE VICE PRESIDENT FOR RESEARCH AND MEDICAL AFFAIRS, AMERICAN CANCER SOCIETY, WASHINGTON, DC

Mr. BERRY. Thank you very much, Senator, and good afternoon. Thank you for inviting me to this important hearing.

Just a word about Dr. von Eschenbach. I will say some things that disagree with Dr. von Eschenbach. I had the pleasure of serv-

ing with him on the faculty at M.D. Anderson for 2 years, and as a result of that have come to respect his opinion, his clinical abilities, and his person, and there is no one in medicine whose opinion I respect more than his.

I serve on the PDQ Screening and Prevention Board. We discuss published literature and decide how to modify our website accordingly. This website is used by physicians and the lab public, so with respect to Senator Clinton's question, the women in her State can long onto the PDQ website and get information about screening benefits and risks.

We assign levels of evidence to our statement. We are independent of the NCI. We are not advisory to the NCI. We do not establish guidelines. We do not make official recommendations.

At a recent PDQ meeting, we discussed as a matter of course this paper that has been mentioned and referred to by Senator Mikulski and others by Olsen and Gotzsche that critiqued the randomized trials of screening mammography. We agreed with some of the criticisms but not with all. Our current statement indicates that the benefits of screening are uncertain, and based in part on this study, the plan is to modify the statement to add that the existence of a benefit is itself uncertain.

The deficiencies with which we agreed are discussed in detail in my written report, which I ask to be included as part of the record. In each case, there was evidence of a bias favoring screening, but not all trials were subject to these biases.

Briefly, first, women with pre-existing breast cancer were preferentially excluded from the screening group. Second, attribution of cause of death was not blinded. Third, in three of the Swedish trials, the timing of the control mammogram slipped, increasing the time to country breast cancer in the control groups. This is a technicality which we can get into if you would like, but it is an important bias. And fourth and finally, there have been no independent audits of the Swedish trials. In contrast, the Canadian trial which showed no screening benefit has been thoroughly audited.

In my report, I explain how people can differ in their evaluation of evidence toward screening. At least 90 percent of what we know in medicine is the result of clinical observation, with the rest derived from randomized control trials. Experience is a great teacher, but when inferring the benefits of screening, clinical observation is flawed.

Women with breast cancer detected mammographically have extremely good prognoses—extremely good prognoses—in comparison with those having cancers detected in any other way. But this does not mean that screening reduces mortality in itself. I explain why this is so in my report, and I discuss the associated biases. Hence the need for randomized trials.

How impressive are the results of the trials? Suppose we ignore the Canadian trial which showed no screening benefit and take the results of the Swedish trials at face value. The most recent data from Sweden show a 21 percent reduction in breast cancer mortality. This is a paper that has been accepted to appear and is currently under embargo by the journal, so I cannot be too specific about it, but the 21 percent figure appeared in the press, and this

is a lowering of the 30 percent figure which occurred earlier, and it applies to all ages; there is no distinction between less than 50 and greater than 50.

This is a relative risk reduction. One way to convert it into a more meaningful absolute measure of risk is to ask the corresponding increase in life expectancy. Out to 18 years of follow-up in the Swedish trials, this increase is about 4 days per women screened. In contrast, quitting smoking adds years to life expectancy.

What should we tell women? The answer is the truth. The benefits of screening are uncertain, and women should know this; they should be informed of the possible benefits and risks along with the associated uncertainties and decide about screening for themselves. I discuss the risks of screening in my report, and I hope you ask me about that.

Where do we go from here? We cannot do another randomized trial in this country—I completely agree with Dr. von Eschenbach—but there are several steps that we can take, and there are developments being pursued. One is that we should provide women with aids so they can make informed decisions about screening. Second, the Swedish trial should be independently audited.

Third, there is an NCI-sponsored program called CISNET that addresses the question that Dr. von Eschenbach put up on the board regarding the decrease in breast cancer mortality, trying to apportion the relative contributions of screening mammography, hormonal therapy, and advances in chemotherapy.

The fourth is the most promising of all. We know little about the biology of the disease, as Dr. von Eschenbach indicated, but we are learning. Cancers may manifest their metastatic potential when they are tiny, say, when they total only a few million cells, or they may start sloughing off their tumor cells for traveling through the rest of the body when they have become large enough to be detected mammographically. Screening would be effective in the second case, but not the first. We are learning fast about the biology of the disease, and soon will be able to decide which.

I thank you for the opportunity to discuss this very important issue in women's health, a topic to which I have dedicated and will continue to dedicate my career. I am happy to answer questions.

Senator MIKULSKI. Thank you very much, Dr. Berry.

[The prepared statement of Mr. Berry follows:]

PREPARED STATEMENT OF DONALD BERRY

EVALUATING THE EVIDENCE OF BENEFIT FOR SCREENING MAMMOGRAPHY

I serve on the PDQ (Physicians' Data Query) Screening and Prevention Editorial Board. We write statements for the NCI Website http://www.cancer.gov/cancer__information/ regarding screening for cancer and preventing cancer. However, we are independent of the NCI. Our statements are intended for and are accessible by physicians and the general public. We meet approximately six times per year to discuss recently published literature and on the basis of the available information we decide whether and how to modify our Website statements. We assign levels of evidence to our statements. Contrary to reports in the press, we are not advisory to the NCI, we do not establish guidelines, and we do not make official recommendations.

I will give my understanding of the discussions and intentions of the PDQ Board. However, I have not been elected to be a spokesperson for the Board and so I do not have the right to speak for other members of the Board.

My introduction to today's topic was my appointment five years ago to an NIH Consensus Development Conference Panel on Breast Cancer Screening for Women Ages 40–49. 1 had no ax to grind then and I have none now. My life is dedicated to understanding and fighting cancer—breast cancer in particular. I am intimately involved in the prevention and treatment of this horrible disease. Nothing would please me more—professionally and personally—than to have a tool that eliminates breast cancer or that turns it from a disease that kills into one that is chronic but can be controlled.

THE RANDOMIZED TRIALS

At the January 2002 PDQ Board meeting we considered an article authored by Drs. Ole Olsen and Peter Gotzsche of the Nordic Cochrane Collaborative and that appeared in The Lancet in October 2001. This article critiqued the randomized trials that have been conducted to evaluate the benefits of screening mammography and cited a number of deficiencies and flaws. Many of these were known previously and there was little original information in the review. However, it served to put the trials' deficiencies into perspective and led us to re-evaluate the credibility of the trials. We decided to revise our breast cancer screening statement and to refer to the Olsen-Gotzsche article. The plan is to discuss and possibly finalize the revision at our meeting in March. The current version of the statement indicates that the estimates of the benefits of screening are uncertain. Therefore, in a sense the revision will be minor. However, we plan to indicate that the existence of benefit is itself uncertain.

Olsen and Gotzsche reviewed the seven randomized trials. One was conducted in Canada, one in New York, one in Edinburgh, Scotland and the other four in Sweden. The PDQ panel discounted some of the deficiencies pointed out by Olsen and Gotzsche but we agreed with others. In the first category, most of us (1) felt that their focus on all-cause mortality (rather than breast-cancer specific mortality) was too strong, (2) that imbalances in randomization were not a major concern (except in Edinburgh) and (3) regard the use of mammograms in the control groups (to coincide with the end of the screening period) of three of the Swedish trials to be a reasonable design strategy. From our perspective the trials had four types of major deficiencies. They applied to some but not all of the trials. The first three are potential sources of bias favoring the screening group and in each case there is some evidence of actual bias in the trials.

(1) Women with pre-existing breast cancer were preferentially excluded from the screening group. The problem was most severe in the New York trial in which 853 women in the screened group and 336 in the control group were excluded because they had breast cancer at the time of randomization. Excluding women with breast cancer is not unreasonable, but the numbers excluded in the two groups would be about the same had there been no bias. If these women had been included and only 9 percent of the differential of 517 women died of their disease, the breast cancer mortality rate would have been higher in the screened group than in the control group.

(2) Attribution of cause of death was made with knowledge of whether the woman was in the screened group. Blinding assessment of cause of death to assigned intervention is fundamental in good clinical trial practice. For example, an assessor might be more likely to attribute a death to lung cancer if the woman's cancer was detected through screening and to metastatic breast cancer if the woman had been in the control group. There is evidence that this bias was real. The numbers of deaths have changed in unusual ways from one report of the trial results to the next: The number of breast cancer deaths in the control group always increases over time but it sometimes decreases in the screened group.

(3) In three of the Swedish trials women in the control group were supposed to have a mammogram, which was scheduled at the time of the last mammogram in the screened group. Then, deaths due to breast cancer in the control group would be counted only if they were diagnosed at or before this mammogram and in the screened group if they were diagnosed at or before the last mammogram. This design is reasonable. But the scheduled control mammogram slipped in all three trials, allowing for more time to detect cancers in the control group. The slippage was by as much as 18 months. As a consequence, the control group in the Göteborg trial had 21% more breast cancers detected than did the screened group. Such an observation seems impossible (in an unbiased design) because mammography is very good at finding breast cancers.

(4) No independent audit of trial results. Having an independent audit is a generally accepted in medical research and it is essential for a trial to be credible. For example, the FDA routinely audits clinical trials that provide the basis for an exper-

imental drug's safety and efficacy. None of the Swedish investigators have opened their results to external inspection (but some have recently indicated their willingness to do so).

The Canadian trial was subject to none of these biases. It has been extensively audited and its data are openly available for external examination. Both parts of the Canadian trial (one admitted women in their 40s and the other admitted women in their 50s) found a higher breast cancer mortality rate in the screened group, although the increase was not statistically significant. The other trials fell prey to one or more of the biases, although it is not known whether there were biases in the first part of the Malmö trial.

HOW CAN PEOPLE DIFFER SO IN THEIR EVALUATION OF EVIDENCE?

Physicians learn by experience. At least 90 percent of what is known in medicine today is the result of clinical observation, with the remaining knowledge deriving from randomized clinical trials. Experience is a great teacher. But when it comes to inferring the benefits of screening, clinical observation is fundamentally subject to flawed interpretation.

Women with breast cancer detected mammographically have extremely good prognoses in comparison with those having cancers detected in any other way. Mammographically detected tumors are smaller and are less likely to have spread to the axillary lymph nodes. Since women whose breast cancers were found by a mammogram do so much better, there is a tendency to attribute the benefit to mammography. Unfortunately, this logic is wrong. The fallacious aspect is not simply a nuance—it is a mistake that gives rise to profound misconceptions. And it is a logical lapse to which doctors and patients alike can fall prey.

Suppose temporarily that screening mammography has no survival benefit. Clinicians would still see precisely what they do see. Consider a 50-year-old woman who has breast cancer and who is destined to die of her disease at age 60. However, she does not yet know that she has breast cancer. It would be found on a mammogram if she were to have one, and she would live for ten years with breast cancer. But without a mammogram it would show up clinically only when its symptoms become apparent, say at age 55. So without a mammogram she lives for only five years after her cancer is discovered. The discrepancy between ten years and five years results from what is called *lead-time bias*. It means that women whose cancers detected by mammography live longer than do those detected otherwise, and this is true even if screening has no true benefit.

There is another kind of bias—called length bias—that is even more important in magnitude, but it is not as easy to understand. It is related to the fact that breast cancer is a heterogeneous disease. Again, assume temporarily that screening has no survival benefit. We understand some of the factors that give rise to this heterogeneity, but not all of them. Some cancers grow rapidly and others take a more indolent course. Suppose just for the sake of discussion that there are two kinds of cancers: half grow fast and the other half grow slowly. We cannot determine which is which and so we treat them similarly. Suppose that after their cancer is detected via mammography, patients having the first type live an average of five years and patients with the second type live an average of 35 years (not counting causes of death other than breast cancer). So the average survival for women whose cancers are detected by mammograms is about 20 years. In the absence of mammography the first type of cancer might show symptoms with only three more years to live (a lead-time of two years). Some portion—say one half—of the women who harbor the slowly growing tumors will die of other causes before it is discovered. The other half of these women will discover them with 24 more years to live, say, a lead-time of 11 years. There will be 25 percent fewer breast cancers in the non-mammography group. Two-thirds will live an average of three years and one-third will live an average of about 24 years, for an overall average of ten years. So women diagnosed with mammography live about ten years longer than those detected otherwise. This enormous difference is pure artifact since we assumed that screening had no benefit.

The above assumptions were simplified to make a point. No one thinks that there are only two kinds of breast cancer. But everyone recognizes that the disease is heterogeneous. Length bias and lead-time bias are present regardless of the form of heterogeneity. Together they account for enormous differences in apparent survival, as measured from the date of diagnosis, between screened and unscreened cancer patients. These differences are so large that they are detectable by physicians in their everyday practices. No wonder physicians are persuaded of screening's benefits. But the observed benefits may be completely spurious. In other words, apparent survival from diagnosis may be longer, but life expectancy may not change at all. Hence the need for randomized trials.

RELATIVE RISK VS. ABSOLUTE RISK

If there is a benefit of screening then the benefit is modest. To see this, ignore the criticisms of the trials and take their results at face value. The benefits evinced vary considerably from one trial to the next. Outside of the Canadian trial (which showed no benefit), the highest quality results are from the Swedish trials. The most recent results (out to 18 years) of the Swedish trials show a reduction in breast cancer mortality of 21% (over all ages) in favor of screening. The value 21% is a *relative risk* reduction, which is convenient as a statistical measure of benefit. But relative risk is difficult to interpret clinically. One measure of *absolute risk* is to convert the 21% into expected life gained per woman screened. In the first 18 years following initiation of screening in the Swedish trials the average gain is about 4 days. (In contrast, quitting smoking adds years to one's expected lifetime.) Of course, only those women who are eventually diagnosed with breast cancer share in any benefit. Suppose 10% of the women get breast cancer eventually. Then each woman with cancer gains an average of about 40 days. How this is apportioned among the women diagnosed with cancer is not clear. From the trial results it is impossible to distinguish whether (i) each breast cancer patient gains exactly 40 days, (ii) fewer than one percent of patients gain 18 years or more and the rest gain nothing, or (iii) something between these two extremes. Put another way, it is not possible to know whether a small proportion of lives are saved by screening or a large number of women have their lives extended by a small amount, or some combination of the two.

WHAT SHOULD WE TELL WOMEN?

The short answer is "The truth." The benefits of screening are uncertain and women should be told this. They may be confused. Confusion is a legitimate state of knowledge, one that may be appropriate in this case. It is a mistake and it is patronizing to women to pretend that we know something we do not. Women have a right to hear about the risks of screening and about the uncertainties regarding the benefits of screening. They should hear all points of view and then decide for themselves. Making this decision will not be easy for some women. We should provide them with decision aids that will inform them of what is known and help them weigh the benefits and risks.

The risks of screening may seem minor but they are important nonetheless, and they are common. From four percent to ten percent of women screened are found to have an abnormal result. The ensuing recommendations range from a follow-up mammogram to having a biopsy. Eighty to 95 percent of the abnormalities turn out to be benign. Obviously, not having cancer is good news, but an estimated 28 million women have mammograms each year, and so a million or more go through the anxious experience of an abnormal test until the final result is known. After ten mammograms the cumulative risk of a false positive result is about 50 percent and about 1 in 6 have biopsies that turn out to be negative. In addition, we know that screening misses about 15 to 25 percent of breast cancers.

Another potential consequence is overdiagnosis. Some breast cancers that may never have progressed become symptomatic during a patient's lifetime. We don't know which of these cancers will progress and so essentially all women with screening-detected breast cancer are treated surgically, with or without radiation. This may result in unnecessary surgery for some women. Of course, even this serious consequence may be acceptable if the test is saving the lives of other women.

A problem with setting guidelines such as those we have now is that it conveys the message to physicians that screening is an imperative health measure. A woman who decides that the risks outweigh the benefits should not be made to feel that her decision is somehow irrational. A 58-year-old woman from New Jersey sent me the following lament: "Sadly, in my experience anyway, I have found it impossible to have a rational conversation with a physician, where my concerns are respected on the topic of mammograms, as the NYTimes article says a patient should have. Doctors get belligerent and almost hostile if I say I have reservations about getting a yearly mammogram. The upshot is that I don't feel I have a good relationship with a physician, and that is not good. A good scientist is not afraid to express uncertainty on a topic or to discuss a topic openly. I'm afraid the practicing physicians who I have come across do not have that scientific mind-set."

WHERE TO GO FROM HERE?

It is not possible to do another randomized trial, at least not in the United States. Women want either to be screened regularly or not. Few would let a coin toss make

their decision. However, there are developments that may help elucidate the issue, and steps that we can take.

(1) Provide women with decision aids in which they are informed of the benefits and risks, including uncertainties, and helped to weigh them in making a decision.

(2) Audit of the Swedish trials. A positive consequence of the PDQ's position and the ensuing discussion in the press was reported by John Crewdson in the Chicago Tribune of January 31, 2002: Several of the Swedish investigators "announced last week that they would release their detailed data, including patient files, to researchers at the U.S. National Cancer Institute or another international body." (Hopefully, the recently announced NCI guidelines will not lead to the Swedes withdrawing this offer.) If an audit of these trials examines the biases and confirms the recently announced 21% reduction in breast cancer mortality then I for one will agree that screening has a benefit.

(3) Cancer Intervention and Surveillance Network (CISNET). This is an NCI-sponsored program that considers a variety of cancers. I am one of seven Principal Investigators considering breast cancer. Breast cancer mortality in the United States has decreased by nearly 15% over the last decade. This coincides with the wide scale introduction of screening mammography. It also coincides with the dramatic upsurge in the use of tamoxifen and improvements in chemotherapy. We use statistical modeling to conclude how much screening mammography, hormonal therapy and chemotherapy have contributed to this decrease. Of special interest is the possibility of synergism between screening and treatment. For example, it may be that treatment with tamoxifen and chemotherapy has more benefit when a tumor is discovered by a mammogram at an earlier stage. We use annual data concerning who got screened, who used tamoxifen, etc. An advantage of this approach is that it applies to mammography actually used in practice in the late 1980s and into the 1990s, which may have been better than that used in the randomized trials. Another advantage is that we assess effectiveness in the context of actual clinical practice rather than in the possibly artificial world of clinical trials.

(4) The third development is the most promising of all. Our understanding of the biology of breast cancer has increased greatly in recent years, but we still know relatively little. Breast cancer would not be fatal if it were to stay in the breast. Its lethality stems from its penchant for traveling to and setting up shop in other places in the body, such as in bone, the lungs, liver and brain. The question is, When does it do these things? Perhaps cancers manifest their metastatic potential (or not) when they are tiny, say when they total only a million or so cells. If so then they will have dispatched their malevolent messengers from the breast to the rest of the body before even the best mammography can detect their presence. Or it may be that they start sloughing off tumor cells only when they become large enough to have been detected and removed. We know little about such matters. And we know little about the relationship between the biological characteristics of tumors and how to treat them. These issues are being addressed by researchers around the world. Research progress will help us better understand the relationships between biological markers, early detection and treatment. Especially exciting are the genomics and bioinformatics revolutions. These are in their infancies and are well funded, but they deserve all the attention they have received.

Thank you for the opportunity to discuss this extremely important issue in women's health, a topic to which I have and will continue to dedicate my career. I would be happy to answer questions or provide further details.

Senator MIKULSKI. Dr. Eyre?

Dr. EYRE. Good afternoon, Madam Chairwoman and distinguished members.

As chief medical officer at the American Cancer Society, I am honored to be here today and want to thank you for the opportunity to testify about the strong science supporting the value of mammography in saving lives.

The American Cancer Society is the largest community-based health organization dedicated to preventing cancer, saving lives from cancer, and diminishing suffering from cancer.

We have established very ambitious goals for the year 2015 to reduce the incidence and death rates of cancer as well as improve the quality of life of cancer patients. In order to do that, cancer prevention and early detection is a critical aspect of this strategy.

You have heard from Dr. von Eschenbach about the magnitude of the breast cancer problem, but one fact he did not give you which I think is astounding is that a woman who dies of breast cancer in America loses 19 years of life due to premature death, as judged by average life expectancy. As a medical oncologist and cancer specialist, I have personally taken care of over 1,000 patients with breast cancer and witnessed the suffering that occurs to patients and their families from breast cancer, and I believe that we are making vast progress in this country, saving thousands of lives from breast cancer, and I hope to not see that reversed.

We too would add our encouragement behind the U.S. Preventive Services Task Force's recent affirmation of mammography and believe that it adds to the scientific evidence behind it. The scientific evidence supporting mammography in reducing breast cancer death rates is solid, and I would like to share just a few comments about the Society's position on this.

Over 100 years ago, it was hypothesized by a French physician that breast cancer began as a single focus, gradually began to spread, went through the lymphatic channels into the vascular channels, resulting in the death of the person. This concept has been verified and gives rise to the notion that if you can find it early enough, surgical removal of the cancer results in cure.

It was not until the 1950's, however, that we began to find mammography able to detect early breast cancer, and this gave rise in the 1960's, actually, to the HIP study in New York City which was the first large-scale randomized trial, with 62,000 women randomized to mammography and clinical breast exam versus usual care. The result of that study after follow-up was a 30 percent reduction in death rate in breast cancers in the study group compared to the control group.

Before moving on, I would like to discuss with a little bit of evidence the data on size and stage of cancer. If you find early disease—no lymph node involvement, no disseminated disease—5-year survival of breast cancer in America is 97 percent. In contrast, if you find breast cancer when it has already demonstrated spread, 79 percent of those women will die in that first 5 years. Our goal is survival, and the scientific evidence has repeatedly demonstrated that screening can help achieve this goal.

Following the HIP study, the American Cancer Society and the National Cancer Institute launched a major nationwide demonstration project, the BCDDP, in which at 10 centers, 280,000 women were screened from 1973 to 1980, and comparing the results of those individuals to the results of the population revealed a substantial reduction in mortality.

Subsequent to those trials, there have been studies in Great Britain, in Sweden, and in Canada. Almost all of those studies except the Canadian studies have demonstrated a statistically significant reduction in mortality. The Cochrane group, as you know, has recently criticized these studies. We find their analysis flawed. We do not agree with the fact that those studies had substantial imbalances within them, and in fact the Cornell group pointed out in the Malmo study that Senator Harkin referred to that if you had just followed the people longer, there was a significant reduction in

mortality, and the Cochrane group did not even acknowledge that second report.

We believe that mammography is not a perfect test; it has flaws. It is an interim effort to help control breast cancer, and as we progress—and we applaud Dr. von Eschenbach's scientific studies, and we are funding scientific studies into finding answers as to how to present cancer, how to block it from occurring, and if it occurs, how to cure it—it will only be then that we will get the final control. But in the meantime, mammography is of value in reducing the death rate from breast cancer, and the American Cancer Society applauds and continues to support this effort with information to patients, to women, and with the recommendation that women 40 and over should have annual mammograms.

Thank you.

[The prepared statement of Dr. Eyre follows:]

PREPARED STATEMENT OF HARMON J. EYRE, M.D.

Good afternoon, Madam Chairwoman, Mr. Chairman, Senator Frist, Senator Specter, and distinguished members of both Committees. I am Dr. Harmon Eyre, Chief Medical Officer and National Vice President for Research and Medical Affairs of the American Cancer Society. I am honored to be here today, and I want to thank you on behalf of the more that 28 million volunteers and supporters of the Society for the opportunity to testify about the strong scientific evidence supporting the value of mammography in saving lives from breast cancer. The American Cancer Society commends you for conducting this very timely and important hearing.

I respectfully asked that my comments be submitted for the record.

The American Cancer Society is the largest nationwide community-based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives and diminishing suffering from cancer through research, education, advocacy and service. We have set ambitious goals for the year 2015 to reduce the number of people dying from and being diagnosed with breast and other types of cancer, and to significantly improve the quality of life for all cancer patients, survivors, and their families. While we believe that national achievement of these goals is possible, increased awareness and utilization of cancer prevention and early detection tools is critical to our success.

Madam Chairwoman and Mr. Chairman, before setting out to explain the American Cancer Society's view on the benefits of mammography, I would like to take a moment to call attention to the terrible impact that breast cancer is having on women in this country. This year, 203,500 new invasive cases of breast cancer will be diagnosed, and an estimated 40,000 women will die of the disease. On average, a woman dying of breast cancer loses approximately 19 years of life she might otherwise have had. The human face on those statistics translates into families watching a loved one struggle with advanced, unsuccessfully treated disease, and a family and community that ultimately are left to mourn her loss. As a physician and medical oncologist, I have treated thousands of breast cancer patients in my career and observed first hand the heartbreak this disease visits on families and loved ones. Over the years, I have also witnessed the progress we have made, so that fewer women are dying from breast cancer. I do not wish to see our country lose the ground we have gained.

To this end, we are hopeful that the recent announcement of the U.S. Preventive Services Task Force's update of their breast cancer screening guidelines and their endorsement of mammography for women ages 40–69, will add to the weight of the wide-scale rejection of the recent mistaken notion that mammography is valueless.

Madam Chairwoman, Mr. Chairman, and members of both committees, the scientific evidence supporting the value of mammography in effectively reducing deaths from breast cancer is solid, and I appreciate having the opportunity today to share with you the Society's view on this important subject.

THE ORIGINS OF EARLY DETECTION IN BREAST CANCER

The importance of detecting localized breast cancer is well established. It was first recognized in the mid-18th century by a French physician who proposed that breast cancer originated as a localized disease that subsequently spread through lymphatic channels to the general circulation. This key concept established the idea that sur-

gery, if performed early, offered the potential to cure breast cancer. Effective means of early detection eluded us, however, until the early 20th century when it was first demonstrated that breast disease could be detected with x-rays, allowing for diagnosis of breast cancer even before symptoms, such as lumps, could be detected by a woman or her physician.

As you well know, the path toward turning a promising idea into a practical solution can be a time consuming journey in the scientific world, because of the high standards of scientific evidence that are required. Promising work in breast imaging continued through the first half of the 20th century, eventually leading to a turning point in the early 1960s when Dr. Philp Strax, a radiologist in one of the Health Insurance Plan of Greater New York medical groups, proposed a large-scale study to evaluate the potential of mammography and clinical breast examination to reduce deaths from breast cancer. Professor Sam Shapiro, Director of Research and Statistics at the Health Insurance Plan, and Dr. Louis Venet, a surgeon with experience in clinical breast examination screening programs, later joined him as co-investigators. This study became the Health Insurance Plan of Greater New York Project, historically known as the HIP Study, and was initiated in December 1963. It was the first randomized, controlled trial to evaluate the efficacy of breast cancer screening with clinical breast examination (CBE) and mammography. Approximately 62,000 women aged 40–64 were randomly assigned to two groups: the study group was offered annual clinical breast examination and two-view mammography for four years, and the control group received usual care.

The fact that this study was a randomized controlled trial is important because, with respect to cancer screening, it is critical to know whether the actual act of screening is the factor making the difference in saving women's lives. The ideal study would be one in which you had two identical groups of people, with the only difference between them being whether they were screened. Obviously, a study like that is impossible. Therefore, the next best thing is to randomly assign a large group of individuals to either the group that is offered screening or the group that receives usual care. If our randomization has succeeded, and the study is well organized to maintain the integrity of equality between the study group and the control group, then we come very close to the theoretical ideal of two identical groups. Randomization of the women in the study controls for factors we know about and factors we don't know about that could bias our findings. It helps us demonstrate whether or not screening, and not some other factor, is the reason death rates are reduced.

The HIP study was a dramatic turning point. It offered hope for the first time that through intervention we could reduce the number of women who died from breast cancer. The randomized HIP study demonstrated that there were approximately 30% fewer breast cancer deaths in the study group compared with the control group. Without question, the results of the HIP study ushered in a new era in breast cancer control, one in which there would be increasing emphasis on detecting and treating breast cancer before the onset of symptoms. However, scientists are rarely willing to recommend wholesale change in health policy based on one study.

THE LOGIC BEHIND EARLY DETECTION

Before I talk about the next series of studies, I want to quickly discuss the logic behind early detection and the relationship to the underlying biology of breast cancer. Breast cancer is a progressive and systemic disease, in which our ability to treat and cure a small tumor is much greater than our ability to treat and cure a larger tumor. Treatment is easier and the outcomes are better, when the cancer is caught before there is lymph node involvement and before the cancer has metastasized, or spread, to distant organs. There is no more consistent and straightforward measure of a breast cancer patient's prognosis than the size of the tumor. A few statistics to put this in perspective: When breast cancer is still localized—meaning that it has not spread to other organs—97 percent of patients survive for five years or more. Once the disease has spread to other organs, however, prognosis is bleak, with 79 percent of patients dying within five years. Our goal is survival—and scientific evidence demonstrates that screening can help us achieve the goal of lives saved. Indeed, the important role screening plays in reducing breast cancer deaths has been demonstrated repeatedly.

PROMISING CONCEPT TO PROMISING SOLUTION: THE IMPORTANCE OF ROUTINE BREAST CANCER SCREENING

As I mentioned, the HIP study was not enough on its own to recommend screening to the general population. Before recommending screening to the general population, we would have to not only know that screening works, but that it was possible to implement an effective screening program in the community. The results of

the landmark HIP study led the American Cancer Society and the National Cancer Institute to collaborate on a larger project to determine the practicality of bringing mammography screening to women at the community level. This project, known as the Breast Cancer Detection Demonstration Project, or BCDDP, screened over 280,000 women at 29 centers between 1973 and 1980. Participation rates were high over the course of the study and final analysis underscored the importance of mammography screening—nearly half of all breast cancers in this study were found by mammography alone.

Furthermore, among study participants, breast cancers were diagnosed at more favorable, early stages when compared with breast cancer cases among women nationwide during the same period. Most importantly, overall long-term survival has been much better among participants in the screening study. The bottom line is that, based on these two studies, we now had enough scientific evidence to say that mammography was an effective tool to detect breast cancer early, and breast cancer deaths would be reduced if we detected the disease before it had spread. Mammography was a tool that could make a difference.

Thanks to the groundbreaking results of the BCDDP and the HIP study, the Society determined that there was sufficient evidence to promote routine breast cancer screening in the U.S. as a public health initiative in 1980. As the largest national health organization devoted to reducing cancer incidence and deaths, the American Cancer Society is well recognized as a primary resource for cancer screening guidelines. Our screening guidelines are established through a rigorous scientific review process and are re-evaluated at least every five years. We have reviewed the scientific evidence relating to mammography repeatedly since 1980, and we have continuously concluded that while improvements in technology are certainly welcome, mammography remains the best tool we currently have to detect breast cancer early. In fact, as the Institute of Medicine recently concluded, mammography presently is the gold standard by which breast cancer is detected early.

As I mentioned, evaluation of mammography has continued. Between 1976 and 1982, six additional randomized controlled trials were initiated in Edinburgh, Sweden, and in Canada. While there are differences in the results, all of these studies (with the exception of the Canadian studies) show a benefit from breast cancer screening with mammography, both with and without clinical breast examination. In fact, the trials show a statistically significant reduction in breast cancer death by about 25–30 percent for women aged 40 and older and similar benefits for women in their forties compared with women aged 50 and older.

The accumulation of evidence from randomized trials over the years has strengthened the science behind breast cancer screening. In fact, one remarkable observation from the trials is that in the group offered screening, the observed reductions in the mortality rate in each trial are consistent with reductions in the rate of advanced breast cancer when compared with the control group. Put simply, the studies showed that detecting breast cancers early increases the chances of survival.

It is important to note that trial results derive from controlled environments. It is also necessary to demonstrate whether true benefits are being achieved under real-life circumstances. In Sweden where screening is a national health priority, those women receiving regular screening have been shown to reduce their risk of dying from breast cancer by over 40 percent compared with women who do not get regular screening—a fact that should not be ignored.

REVISITING COMPLEX QUESTIONS: REPORTS FROM CORNELL UNIVERSITY AND COCHRANE

Madam Chairwoman and Mr. Chairman, as you know, in spite of the overwhelming evidence, mammography has not been without its detractors. Recently, two of these detractors have been able to gain widespread media attention and cause great confusion among the public about the value of mammography. I am speaking of course about the Cochrane Review on Screening for Breast Cancer as published in the Lancet. In my view, this current confusion is a regrettable development that is harmful to women. Given the weight of evidence from the trials and the reductions in breast cancer death rates observed in real life instances, the conclusions of the Cochrane Review are quite frustrating to many in the scientific community. Indeed, the Cochrane conclusions are at odds with the most fundamental understanding of breast cancer as a progressive disease. Moreover, these conclusions run contrary to decades of supporting scientific evidence from the individual trials, meta-analyses, observational studies and case series, national trends, and confirmatory, independent expert reviews conducted by medical and scientific groups in North American and Europe.

As you are probably aware, the Cochrane report rejected five of the seven major mammography trials as flawed. The researchers then claimed that the two remain-

ing trials showed that mammography was not beneficial. Inexplicably, one of the reports they selected was an early report of the Malmo study. The early report was made before there had been sufficient time for follow up and therefore did not show a difference in breast cancer deaths between the study group and control group when all deaths in each group were compared. For some unknown reason, the Cochrane review ignored a second later report of this study that had allowed sufficient time for follow up. This later report did indeed show that mammography was beneficial. In fact, it showed that there were 19% fewer deaths in the group offered screening.

Because most breast cancer deaths do not occur rapidly after diagnosis, experts in the evaluation of screening have known for years that a lengthy period of follow up in a screening study is necessary to observe a lower mortality rate if there is one. In fact, this very point was strongly made in a report in the Lancet only a few weeks ago by investigators from Cornell University. The Cornell investigators demonstrated that once a sufficient amount of follow up was allowed, even the first Malmo study shows a clear reduction in breast cancer deaths. In other words, the Cochrane analysis used incomplete data, making their conclusions suspect.

Knowing that the results of a scientific study can have a great impact on many aspects of health care and health policy, standards for conducting these types of studies are set high and are adhered to by most of the scientific community. Unfortunately, on close examination, it is evident that the Cochrane review does not adhere to some of these standards and is deeply flawed. Indeed, it appears that the review's investigators failed to perform a careful examination of the published literature—for example, missing the second Malmo report—and made arbitrary and inconsistent judgments about study quality. Moreover, the Cochrane analysis concluded that the only reliable endpoint for comparison was not death from breast cancer, but death from all causes.

Using death from all causes as the means for evaluating mammography effectiveness is far-fetched in the extreme. The trials were designed to demonstrate a difference in breast cancer deaths—not deaths from all causes. To demonstrate a difference in deaths from all causes, an enormous number of people would need to be enrolled in any trial. These trials were too small to individually demonstrate a difference in all cause mortality and were never intended to do so. Moreover, breast cancer screening cannot logically be expected to reduce deaths from hip fractures, diabetes, trauma, or other causes of death.

Furthermore, the Cochrane analysis alleges that some of the trials should be ignored because of possible bias and error in determining the cause of death. This assertion is simply wrong, since the level of error, due to dishonesty or incompetence on the part of blinded and non-blinded expert panels, would have had to be entirely habitual to change the results so completely. All told, the claims made by the Cochrane review are based more on conjecture than an actual demonstration of errors.

The authors of the Cochrane analysis are part of a group in the scientific community who hold that studies should look only at all-cause mortality, not on mortality from breast cancer alone. This train of thought is quite misleading, because the goal of any preventive health program is not to prevent death, which will occur eventually, but to reduce our chances of dying prematurely Breast cancer screening makes sense for women between the ages of 40 and 70 because breast cancer is a leading cause of death in that age group—it offers women the chance to save those 19 years of life that I mentioned at the beginning of my remarks.

This raises another point. Screening is an undertaking in which we test the many to find the few. No screening test is 100 percent accurate. In some cases, cancer will be missed during screening. In other cases, women will be told they need additional tests for abnormalities that ultimately turn out not be cancer. Providers must handle each step of the screening process with great sensitivity. Likewise, more education can be done to assure women that "false positives" are part of the pathway to a normal interpretation. A group of investigators at Dartmouth found that women are highly accepting of false positives as part of the process of saving lives from breast cancer. This does not mean we should not devote more attention to reducing the avoidable false positive rate, but it is important to note that many women understand the inevitability of false positives and accept them as part of the process of early detection.

Another criticism of mammography is that it detects ductal carcinoma in situ, or DCIS, a non-invasive cancer. In the course of screening for invasive breast cancer, we will detect DCIS. Since not all DCIS will progress to invasive disease, screening has been criticized for over treating DCIS.

Madam Chairwoman and Mr. Chairman, approximately a third of DCIS may progress to invasive disease and we do not know which will or will not progress.

The notion that detection of DCIS should be avoided, or that screening should be postponed until DCIS progresses to invasive disease betrays a fundamental misunderstanding about the biology of breast cancer and the interplay between disease progression and early detection. The intent of breast cancer screening is the detection of small invasive cancers in order to give women an advantage in fighting their disease. The challenge today and in the future is tailoring the treatment of DCIS to ensure that it is treated appropriately and that a woman is not put through a greater treatment ordeal than is necessary—but that's a treatment issue not a screening issue. The only option for avoiding the diagnosis of DCIS is not being screened for breast cancer, which would make no sense at all since the incidence rate of invasive breast cancer is many times greater than the chance of a diagnosis of DCIS.

All told, in addition to numerous critiques of the Cochrane Review in published literature by well-known experts on screening, no national or professional body has found that this review's conclusions are convincing. As additional reviews are published, and as additional national groups reject the review's flawed interpretation of the data, it is our hope that policymakers and others will devote more attention toward setting the record straight. Mammography, while not a perfect tool, is currently the best tool we have to catch breast cancer early and to reduce deaths from the disease.

NEXT STEPS

Madam Chairwoman, Mr. Chairman, and members of the Committee, we have made incredible progress towards reducing deaths from breast cancer in North America and Europe. Here in the U.S., after nearly two decades of a public-private partnership in health promotion, a majority of women aged 40 and older are receiving mammograms. The efforts to improve the quality of mammography, and in particular the importance of the landmark Mammography Quality Standards Act of 1992, which the Chairwoman authored, have assured every woman in this country of higher quality breast imaging. These efforts have produced results. The death rate from breast cancer has declined by over 20% in the last decade. According to the American Cancer Society, progress in the U.S. in breast cancer screening, improved therapy, and increased awareness means that there will be many thousands fewer women who will be expected to die this year from breast cancer than would have died if mortality rates were the same today as they were in 1989. Furthermore, new technology, such as digital mammography, computer-aided detection, and potentially MRI hold the promise for even more successful breast imaging technology—but at this time, mammography is the best tool we have.

The American Cancer Society will continue to provide information designed to inform women of the benefits and limitations of mammography screening. We are confident that, armed with information, women and their health care providers will continue to see mammography as the best current strategy to reduce death from this disease, and that those whose confidence was shaken by the recent media attention will regain their confidence as the authoritative and credible interpretation of the scientific data on mammography prevails. To this end, we urge women 40 and older to continue to follow the advice of their physician and be screened for breast cancer annually.

Madam Chairwoman, Mr. Chairman, and members of the Committee, thank you again for the opportunity to speak to you today.

Senator MIKULSKI. Senator Harkin, you chair the appropriations committee on the other part of this joint hearing, so why don't you kick off the questioning of this panel?

Senator HARKIN. Thank you very much, Madam Chair.

Dr. Berry, again, in layman's terms, let me try to propound this question. All things being equal, if a woman has the opportunity to have mammogram screening available to her after age 40—and she can obviously do a self-exam and have a physical every year—would it be your advice to her to skip the mammogram, assuming she can afford it, it is available and so on? Would you say just skip it, or would you advise her to have a mammogram as part of the toolbox that we talked about earlier of different things that we can do to try to detect breast cancer?

Mr. BERRY. I would not advise either way. I would discuss with the woman—as, for example, I have with my wife and daughters—what the benefits are, what the uncertainties are associated with those benefits, what the risks are—and the risks may be more important for one woman than for another women—and if that woman, including members of my family, decided to have a mammogram, I would support that to the utmost; if they decide not to, I would support that as well.

Senator HARKIN. Is it true—or, is it factual—that the earlier breast cancer is discovered, the higher the possibility will be—or probability will be—that a woman could successfully have that treated one way or the other—through surgical removal or whatever—and have a longer life span and a healthier quality of life than if that woman waited until the cancer had grown and metasticized?

Is that a factual statement or not? Do you want me to repeat it?

Mr. BERRY. No, no. I think I understand the question. If a woman has cancer—if somebody says to you, "I have cancer," and it was detected mammographically, that woman has incredibly good prognosis. If it is not detected mammographically she has poor prognosis. That does not mean that the mammogram did it.

As Dr. von Eschenbach indicated, there are tumors that are relatively indolent that are found with mammogram that may not ever be found in the course of the woman's life. Autopsy studies have shown in the United Kingdom that women have as much as 35 percent invasive disease that never affected their health.

There is a lead time bias. There is a lead time associated with mammography that if you find it earlier—it is a very compelling notion—if you find it earlier, you may be able to treat it better. Does it really turn into a benefit? That is what the randomized trials are about. But there is a lead time bias. If you look at a woman, and you find the woman let us say 5 years earlier, that woman is going to live 5 years longer after you have found the disease. That is one of the two biases I talked about in my report.

Senator HARKIN. In your statement, you say that "Women with breast cancer detected mammographically have extremely good prognosis in comparison with those having cancer detected any other way. Mammographically detected tumors are smaller and are less likely to have spread to the auxiliary lymph nodes."

Let me put it this way: I had a telephone conversation yesterday with some breast cancer survivors in Iowa, and one woman said about false indications, "Well, I would rather have a false positive than a false negative."

Mr. BERRY. Obviously.

Senator HARKIN. Obviously. So I do not know that there is any way to detect at an early stage whether a cancer is indolent or aggressive.

Mr. BERRY. So far not.

Senator HARKIN. So far not. Therefore, it would seem to me logical that if a woman could find a cancer earlier, not knowing whether it is indolent or aggressive, and it could be removed with the least invasive procedure, it would seem to me she would be far ahead, rather than waiting until later on.

Mr. BERRY. If you could find the first cell that mutated, there is no question. The issue is when between that time—and it becomes detectable by our current mammography—when between that time does it have a metastatic potential—and there, we do not know. It may already be doing its dastardly deeds when it is only a few million cells, when it cannot be detected mammographically.

Senator HARKIN. I do not know how to respond to that. It would still seem to me, again as a layman, that the earlier you can detect a cancer, the better your prognosis is going to be.

Mr. BERRY. There is no question about that. The question is does it translate into a benefit for mortality. There are examples—for example, the neuroblastoma issue, where we detected lots of cancer really early, and we found out that it did not convert into a mortality reduction.

Senator HARKIN. I guess we are playing some kind of a word game here. I do not like to put it in those terms, but it just seems to me, again, that if I have breast cancer, I know that if I wait it is going to metasticize at some point.

Mr. BERRY. Not necessarily.

Senator HARKIN. More often than not?

Mr. BERRY. No, no—well, actually, it depends on whether it is detected mammographically or otherwise. If it is detected mammographically, fewer than 50 percent will ever metasticize. If it is detected otherwise, something possibly greater than 50 percent.

Senator HARKIN. Well, if it is detected mammographically, and fewer than 50 percent metasticize, that is because something has been done, right? I mean, you do not just detect it with mammography and say, okay, we are not going to do anything. Something has to be done.

Mr. BERRY. Yes, but the question, Senator Harkin, is what has been done. Several things have been done. One is that you have found more cancer, and some of the cancer that you have found may be incredibly important to find. I am not saying that mammography is not good. It may be incredibly important to find. But some of what you find is not important to have found. The problem is, of course, that we cannot distinguish which.

Senator HARKIN. Okay. I know what you are saying you would say to women. You would tell them all the odds and let them make up their own mind.

Mr. BERRY. Yes.

Senator HARKIN. But we are lay people, you know; we are not scientists. We want to know odds-on what is the best thing to do. We look to the medical community for this kind of advice and guidance and direction. And what I am hearing from most of the medical people I spoke to yesterday is that, as I said in my opening statement, mammography is not the sole thing, but in combination with other things it is a useful tool for early detection. And the earlier you detect it, the better your prognosis is going to be.

Mr. BERRY. If a woman says, "OK, you have told me all this stuff and it does not make any sense to me. Just tell me whether to get a mammogram," and she says it to a doctor who has her best interest at heart, and the doctor says, "I think you should get a mammogram," and she does, that is fine. I very much encourage that.

But I want that woman to be exposed to—if she wants—all the information that she can digest.

Senator HARKIN. Thank you very much. My time is up.

Thank you, Madam Chair.

Senator MIKULSKI. Thank you. I think that was a very important exchange.

Senator/Dr. Frist?

Senator FRIST. Thank you both for your excellent presentations.

Dr. Berry, do you counsel patients at all?

Mr. BERRY. No, I do not.

Senator FRIST. Your training is a Ph.D. in biostatistics.

Mr. BERRY. That is correct.

Senator FRIST. You are being asked questions, really, that center on the doctor-patient relationship, and you are answering from statistical data and your analysis of those statistics.

Mr. BERRY. That is why I put it in terms of my family. My family listens to me—although not always.

Senator FRIST. I think that just for the audience, it is very important. If you hear a biostatistician looking at statistics and looking at the lead time bias and your explanation, which is very clear in your presentation and in your writing—I think we need to be very careful in posing hypothetical questions to you. If you just listen, you might say, here is a clinician who says he does not really—in terms of counseling patients regarding who should get a mammogram or not—and really, you should not be in that position to provide clinical advice to a particular patient. That is really what you are saying.

Mr. BERRY. That is correct. That is absolutely correct.

Senator FRIST. With that, if someone comes to a clinician and the clinician calls you on the phone, you will basically tell the clinician what you have written here. Once again, you are not going to say whether that patient should get a mammogram or not. Based on the data out there, would you ever feel comfortable being in a position of answering whether someone should get a mammogram—again, recognizing that you are not a clinician—as a patient or a woman who comes to you, or a husband, to the question of "Should I or my wife get a mammogram?" Are you comfortable advising them or counseling them at all, even given what you know?

Mr. BERRY. If somebody were to come to me and say, "I am putting myself in your hands; you are to decide whether I get a mammogram," I would run away.

Senator FRIST. I think that is right. I think that is the correct answer. But it is a position that physicians are in, because they are looking at the biostatistical data. It is clearly confusing to the American people and people around the world where the statistics are limited and do not give the full answer. In your written statement, you do say that "When it comes to inferring the benefits of screening, clinical observation is fundamentally subject to flawed interpretation." The implication of that to me is that one should not rely on clinical observation.

Mr. BERRY. In the context of screening. It is very important in the context of treatment. A doctor gives Mrs. Smith a treatment, and Mrs. Smith does well. He or she learns from that, and that is very important. What I am saying is you cannot learn in screening.

Senator FRIST. And the biostatistician through screening looks at large populations, which I think is potentially dangerous—inferring how you should treat a particular patient. That is the implication in your written testimony, and to me it is very dangerous as a physician to make that inference.

Could you just comment, because people are listening to your interpretation of biostatistics, and they are taking down what you should advise the individual woman. I think that is dangerous as a clinician. So I just want to ask for your response to help me understand that. And I think that is what Senator Harkin is struggling with as well. In his hypothetical question, you answered it appropriately, but I do not think it leaves the correct image of what we really want to answer, and that is an individual woman coming in asking should she get a mammogram or not.

Mr. BERRY. I think there is a distinction between talking about the individual as an abstract and the individual as a particular one.

Senator FRIST. Yes, I agree.

Mr. BERRY. The individual as a particular one, I completely agree. The individual as an abstract, I am interested in communicating with particular women, with women as individuals. These are not policy statements that I am interested in. Other members of the PDQ may differ from that. I am interested in a particular woman's decisions and what kinds of things she should consider. When it comes to an individual, Jane Smith, that is a whole different story.

Senator FRIST. I think that is really important for us to understand in the hearings. The advocates, I think, will really be talking about individuals. But as we look at biostatistics, it is confusing to me as a clinician because I am in the business of looking at, whether it is transplantation or large populations, what to infer down to the patient. When I read what you said, "But when it comes to inferring the benefits of screening"—which, again, you qualified—"clinical observation is fundamentally flawed or subject to flawed interpretation"—it is screening that is right. I did not pick it up, either; that is the benefit of mass screening. But when it comes to an individual patient, which is what both patients want and what physicians want, clinical observation may not be flawed because it really does very much determine what goes on with that particular patient, as you said, in that situation.

I do not want to belabor this, but again for the broad audience here, I think we have to be very careful in taking biostatistics and saying that basically, the observations which are applied to screening in a statement on policy of screening may not apply when it comes to the individual patient. Correct me if I am wrong.

Mr. BERRY. I agree.

Senator FRIST. OK. I will stop there.

Senator MIKULSKI. Are you sure?

Senator FRIST. Yes. Thank you.

Senator MIKULSKI. First of all, Dr. Berry, I want to thank you for being here. And know that the rigor of the questions in no way challenges you and your dedication to trying to provide for women from your perspective the best information they need. So please

know that the rigorous exchange is in no way challenging your commitment.

Mr. BERRY. Thank you very much I appreciate that.

Senator MIKULSKI. I just want that on the record, and I think we would all concur with that.

In time, I might come back to you, but I want to turn to the American Cancer Society and Dr. Eyre. I want to be clear on your testimony. Could you repeat what are the guidelines of the American Cancer Society for women to have or not have guidelines? What are the American Cancer Society's recommendations and the rationale behind them?

Dr. EYRE. Senator, thank you for the question. Far and away the most important guideline for breast cancer is that women age 40 and older who are at average risk should have an annual mammogram combined with a clinical breast exam by their doctor.

We also advocate for teaching breast self-examination beginning at age 20, and for women between ages 20 and 40, they should have a clinical breast exam by their doctor at least every 3 years.

Those are our screening guidelines for breast cancer. We also advocate cancer prevention guidelines that speak to some of the points that Dr. von Eschenbach talked about. They are nutrition, physical activity, and modest consumption of alcohol at most if a person drinks, in order to do what we know how to do to diminish a woman's risk.

We do have additional information about women at high risk, but that does not apply across the board.

Senator MIKULSKI. When you say "average risk," what does that mean. For the women and the men who love them watching this on TV or hearing reports on this, what would be an "average risk" as they are calculating what they should be discussing with their physicians?

Dr. EYRE. The average risk accounts for 70 to 80 percent of women in America. What we define as "high risk" are those individuals with first degree relatives with breast cancer, or those women who have had a breast abnormality such as atypical ductile hyperplasia on previous exams or biopsies, so that they fall into a high-risk group or the extremely high-risk group, those who have a genetic predisposition with the BRCA-1 or BRCA-2 gene.

So we are talking about average risk individuals as those women who do not fall into those high-risk categories.

Senator MIKULSKI. Dr. Eyre, prior to this hearing, some things were brought to my attention, and I do not have the data, but it goes to women on birth control and also women who have sought hormone replacement therapy.

You have spoken very clearly, thank you, on where there is a genetic predisposition. But information was brought to my attention that women either on the pill, and now particularly women who are taking hormone replacement therapy seem to have escalating breast cancer when there has been no genetic propensity and so on.

Could you comment on what you have heard and also what your comments might be on these issues related to hormone replacement therapy, in terms of the average risk and should I be getting a mammogram—particularly those young women who might be on the pill, women who are "going through the change."

Dr. EYRE. The American Cancer Society has followed 1.2 million Americans by using our volunteers to enroll these individual, and we now have 16-year follow-up data; half are women, and half are men. We have looked very, very carefully at the risk factors associated with breast cancer in women, including the two that you just mentioned, that is, birth control pills and hormone replacement therapy. With both prolonged use of oral contraceptives or prolonged use of hormone replacement therapy, the risk of developing breast cancer does increase over time. However, when you actually look at the fatality rates, those women do not have a higher death rate. There could be multiple answers for that. They may be being seen by their doctors more often, being examined, getting mammograms, or they could be having a cancer develop that is a less aggressive cancer, so that the actual death rate for women in those categories is nearly the same as those who do not take those hormones, either birth control pills or hormone replacement therapy.

Senator MIKULSKI. Would you encourage—and "you" meaning again the American Cancer Society—those women who are either on the pill or who have hormone replacement therapy to get annual or close to annual mammograms because of this emerging set of information?

Dr. EYRE. The American Cancer Society very clearly recommends that women discuss with their doctors all of their risk factors, being age, sexual status in terms of reproductive status and use of hormones, either as birth control pills or as hormone replacement therapy, their exercise level, their weight, etc, and together, all of those factors should be taken into account in determining health behavior, and one of those health behaviors is screening.

We think that that adds to the impetus for a woman to have an annual mammogram and an annual clinical breast exam.

Senator MIKULSKI. Thank you very much, Doctor. I think we could go through another whole line of questions particularly where a young women might start birth control at age 20, and would have 20 years of use of the pill by the time she hit 40. That, by my definition and I presume by yours, would be prolonged use and I think would raise this.

I am now going to turn to Senator Clinton for any questions she might have.

Senator CLINTON. Thank you, Madam Chairman.

I especially want to thank my colleagues, Senator Harkin and Senator Frist, for their very informative lines of questioning. I just have a few specific follow-up questions.

Dr. Berry, in your written testimony, you have a reference to the audit of the Swedish trials, and you have a parenthetical statement that, "Hopefully, the recently announced NCI guidelines will not lead to the Swedes withdrawing this offer." Could you explain what that means?

Mr. BERRY. Apparently—and I am going from what John Kuntzen said in the Chicago Tribune—the Swedes have agreed to open up their studies to audit and analysis from other international people, including the NCI, and this was apparently due to the controversy that has been going on in this country; they wanted to settle that controversy by doing what people have been asking them to do for many years. And I am concerned that they fol-

low through on that, and I hope that these proceedings and others do not slow down that impetus.

Senator CLINTON. Well, what would it be about the NCI guidelines that would lead them to withdraw the offer?

Mr. BERRY. Well, there may be no more reason to open it up. If there were——

Senator CLINTON. The fact that the NCI reiterated their guidelines.

Mr. BERRY. Yes.

Senator CLINTON. OK. It is not something in addition to that.

Mr. BERRY. No, no, no; just less uncertainty in this country.

Senator CLINTON. Well, I would hope that if there are any Swedes out there, you do not withdraw the audit offer, because it seems to me that we all have a common interest in trying to determine what the facts are insofar as that is possible.

Dr. Eyre, what are the international standards with respect to mammography? Are you aware of what the recommended standards are in Europe or in Canada at this point?

Dr. EYRE. They vary depending on the health care system and the recommendations that they make to the public. There are a number of countries, including Sweden, who recommend mammography at age 40 or age 50, depending on the criteria that they use and on an every-one-to-two-year basis. Great Britain recommends mammography; a number of other countries do. Some in Europe do not recommend mammography. The issue primarily before this last discussion about the quality of the randomized trials has been on a cost-benefit analysis basis rather than on an issue of reduction in mortality.

There are some countries in the world where breast cancer is much less common—in Asian countries—than it is in European or North American countries, so for many of them, it would be less important because of the decreased frequency, or the burden of the disease is less.

In many European countries, the incidence and death rate of breast cancer exceeds that in the United States and Canada, and in those areas, some of them choose to do it, and some do not.

Senator CLINTON. Thank you very much.

I thank both of the panelists. I guess, having heard the testimony thus far and certainly having reviewed the written testimony, I think that although there may be questions and certainly additional work that needs to be done, and this is obviously something to be weighed, I think I would weigh heavily the clinical experience and recommendations of Dr. Eyre as well as NCI, and I think that until we learn otherwise, that seems to be the better course of action. I appreciate the testimony.

Senator MIKULSKI. Thank you very much.

Mr. BERRY. Senator Mikulski, can I just make one comment about something Dr. Eyre said, or is that out of order?

Senator MIKULSKI. No. As I said, it is a comment, but remember, this is not a debate.

Mr. BERRY. OK. It is an occupational hazard that I have that I complain about people who look at particular aspects of data that make a point that they want to make and ignore other aspects.

Dr. Eyre pointed to the Cornell study that addressed the Malmo trial and points out that if you look between years 8 and 11, you get a benefit for screening. What they do not point out is that if you look between years 3 and 6, you get a negative benefit for screening. In fact, the increase in mortality between those years was 58 percent—30 deaths versus 19 deaths. That study was really very flawed, much more flawed than any of the trials that we are talking about.

Senator CLINTON. Well, Dr. Berry, could I ask you—as far as I am aware, there are only two widely utilized other forms of screening—either self-exam or clinical physician screening—is that right?

Mr. BERRY. That is as far as I know, yes.

Senator CLINTON. Right. So this is a crapshoot, right? I mean, part of what we are trying to figure out here is that a lot of women either cannot or will not do self-exams, do not know what they find if they do them, and a lot of doctors may or may not have the same clinical judgment that their neighbor down the hall might have.

So in each of these instances with respect to screening, we are comparing, it seems to me, imperfect methods across the board. So part of what we are attempting to do—and I think Senator Frist's questions certainly got to this point—it is of very little benefit for most of us laypeople who are on the receiving end of conflicting advice to hear the difference between one and three and five and eight and the rest of it, when we have to make a judgment. And based on the best available information, and even based on many of the most unequivocal statements in your own written testimony, we put our odds with going ahead and having mammography, knowing, as we know, that it is not the perfect answer. It is like getting your teeth x-rayed; maybe the caries they find would never turn into something that you would have to have filled or have a tooth pulled, but you do the best you can with what information you have.

Senator MIKULSKI. Thank you, Senator Clinton.

This concludes this panel. We want to thank you for your testimony and your contributions.

We now turn to a panel that includes the advocacy groups and also testimony in behalf of the American College of Obstetricians and Gynecologists.

We welcome Fran Visco from the National Breast Cancer Coalition; Dr. Carolyn Runowicz on behalf of the American College of Obstetricians and Gynecologists, who is a constituent of Senator Clinton, and she will introduce here; and Dr. Leffall, chairman-elect of the Susan G. Komen Breast Cancer Foundation.

Fran has been introduced by Arlen Specter, but for all those who have been in the women's health advocacy arena for some time, she is a legend for her tireless and intrepid work to ensure that women have access to the best health care and the best information. She has received many awards and is herself a 14-year breast cancer survivor. We look forward to her testimony.

Senator Clinton, do you want to introduce the good doctor?

Senator CLINTON. Thank you very much.

It is my pleasure to introduce Dr. Carolyn Runowicz, who is the vice chairman of the Department of Obstetrics and Gynecology at Saint Luke's Roosevelt Hospital in New York. She faces the di-

lemma of what to tell her patients about mammography every single day, in fact, many times a day. She is speaking on behalf of the American College of Obstetricians and Gynecologists, and I am delighted that she could be with us on this panel.

Senator MIKULSKI. Thank you. We look forward to your testimony.

We turn also to Dr. LaSalle Leffall, who is chairman-elect of the Susan G. Komen Breast Cancer Foundation. He comes to us as the chairman of the Department of Surgery at Howard University, a position he has held for more than 25 years, and he is going to serve for 1 year as chairman of the Komen Foundation, which of course has been one of the leading advocacy groups, well-known for its Race for the Cure, and for not only raising money but also for raising consciousness, as is Ms. Visco's group, which represents 60,000 individual members and 500 groups in terms of grassroots advocacy in terms of access, accuracy, and also challenging a lot of the attitudes of the establishment.

Ms. Visco, we count you as a friend and an advisor, and we turn first to you. We are glad to see all of you.

STATEMENTS OF FRAN VISCO, PRESIDENT, NATIONAL BREAST CANCER COALITION, WASHINGTON, DC; DR.CAROLYN D. RUNOWICZ, VICE CHAIRMAN, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, SAINT LUKE'S ROOSEVELT HOSPITAL, NEW YORK, NY, ON BEHALF OF THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS; AND DR. LASALLE LEFFALL, JR., CHAIRMAN-ELECT, SUSAN G. KOMEN BREAST CANCER FOUNDATION, DALLAS, TX

Ms. VISCO. Thank you, Senator Mikulski and other members of the committee, for inviting me to testify and for holding this hearing.

You have described the National Breast Cancer Coalition, so I do not need to do that. But the question you have posed is "What do women need to know?" Of course, the ultimate goal that we all share is to save women's lives.

Unfortunately, over the years, mammography has come to be equated with breast cancer. Too many organizations, individuals, and policymakers focus their breast cancer work on how to get screening mammograms to healthy women. Yet you have heard and read much about where we are in breast cancer and what the future holds for this disease. We are learning more about the molecular basis of the disease. There is much more emphasis on how to prevent this disease from occurring to begin with. We are talking more about the environmental links to breast cancer. We are looking at targeted therapies. We are understanding that there are many different types of breast cancer, and we are beginning to learn how to treat them.

How do we detect breast cancer at its very early stages, and if so, do we know what to do with it?

These are many of the questions that we are working on today. It is an exciting time in breast cancer, and while we do not have answers, there is much work to be done that will take billions of dollars and much attention.

Yet we continue to spend billions of dollars on mammography. Where is this other money going to come from? These are priorities that must be set based on solid scientific evidence.

I want to make a couple of comments in response to statements that were made earlier. First of all, we must be clear that mammograms do not prevent breast cancer. We really do not know how to prevent breast cancer for any individual woman.

No. 2, the data show that there are more mastectomies in the groups in the trials that are screened by mammography than in the control groups. That is an important point when we begin to talk about quality of life in this issue.

Also, it is important to know that biostatisticians are experts in this debate; they are experts in looking at clinical trials, designing them, and interpreting data on which clinical decisions must be made.

But again, your question is "What do women need to know?" Well, they need to know the truth. Our goal should not be to provide a clear, simple message. Our goal here should be let us find the truth about what will save women's lives, and let us get that information and those interventions to women.

A clear, simple message, while comforting, is not necessarily correct. This is an incredibly complex issue, as you can tell—lead time bias, length bias. There are renowned scientists on every side of this issue, questions about the trials, many of which are important substantive questions; questions about how to interpret results, what are the risks—and a false positive is not the only risk of a mammogram—what are the benefits, how do we quantify them.

We cannot pretend that this complexity and these controversies do not exist, and it cannot be resolved simply by issuing a clear, simple guideline.

I am not going to address the complexities of the trials. I was a reviewer for the U.S. Preventive Task Force. I disagreed with their recommendations. I have spent a great deal of time analyzing the information, analyzing the data, and my written testimony addresses those issues—my written testimony which I submit for the record together with the Question and Answer that the National Breast Cancer Coalition has put together for the public on these issues.

I trust women. I think women are quite capable of understanding complexity and dealing with medical uncertainty. At the National Breast Cancer Coalition, we have developed a number of programs to educate the public about these issues, to give them the tools to enable them to deal with the uncertainty and to seize the power to make informed decisions. This includes the Q and A I referenced, a number of science and advocacy training programs.

So the goal is truth, not just clarity and a simple message; and the truth seems to be that there is uncertainty about the evidence or about the existence, or if it exists, the extent of the benefits of screening mammography. Some will say 30 percent reduction in mortality, others will say 20, some will say none. We have heard about lead time and length bias; do we save lives or simply add days to lives.

These are all legitimate issues that women are capable of understanding and making their own choices on.

I have just two more quick points. If the goal is to save women's lives, if we had taken the billions of dollars put into building an infrastructure for screening mammography and breast self-exam videos and shower cards, and provided health insurance for the women of this country, I think we would have saved many more lives.

A woman testified on behalf of the Coalition last year for the CDC treatment legislation about her support group sharing one prescription for tamoxifen because the other women did not have health coverage. That is the reality of what women with breast cancer are facing. And again, that would save more lives—I believe even the most ardent supporter of mammography screening would admit that.

So let us focus our efforts now on getting an independent review of the Swedish data on the screening trials by an organization such as MedicoLegal Investigations in the UK; let us get the best possible answer we can for women under the circumstances, and let us move on. Let us find out how to prevent this disease, how to detect it truly early, how to get nontoxic therapies, and how to get quality care to all women. And finally, let us reauthorize the Mammography Quality Standards Act, because diagnostic mammography will continue, as will screening mammography, and we need to make certain that it is done well.

Thank you very much.

Senator MIKULSKI. Thank you, Ms. Visco. As always, you raise eyebrows.

[The prepared statement of Ms. Visco follows:]

PREPARED STATEMENT OF FRAN VISCO

Thank you, Chairmen, members of the Senate Health, Education, Labor and Pensions Aging Subcommittee, and members of the Senate Appropriations Labor, Health and Human Services and Education Subcommittee, for your dedication and leadership in working with the National Breast Cancer Coalition (NBCC) in our fight to eradicate breast cancer.

I am Fran Visco, a breast cancer survivor, a wife and mother, a lawyer, and President of the National Breast Cancer Coalition.

The National Breast Cancer Coalition is a grassroots organization dedicated to ending breast cancer through the power of action and advocacy. The Coalition's main goals are to increase Federal funding for breast cancer research and collaborate with the scientific community to design and implement new models of research; improve access to high quality health care and breast cancer clinical trials for all women; and, expand the influence of breast cancer advocates in all aspects of the breast cancer decision making process.

On behalf of NBCC, which is made up of more than 600 member organizations and 70,000 individual members, I would like to thank you for the opportunity to testify today on this critically important issue.

I believe it's very important to put the current debate about the effectiveness of screening mammography in the right context. What this debate is really about is saving women's lives, and improving the quality of their lives—not about attacking or defending mammography. For decades, mammography has been linked to preventing breast cancer deaths. We used to think that the earlier we catch breast cancer, the easier it will be to treat. Yet, we are beginning to better understand the complexities of this disease. And we are realizing that the concept of early detection being the key to reducing mortality may not be the whole story. Some very small cancers can be very aggressive, regardless of when they are detected, and other big tumors caught later may never cause a death. We must consider screening mammography, not only in terms of how early and effectively it detects tumors, but also in terms of the impact early detection will have on a woman's treatment options in light of what we now know about this disease.

We also must be clear about the realities and limitations of the early detection tools that exist today. Currently, there is no truly early detection. Often, by the time a tumor is found, it has been in the breast for 6 to 10 years. The goal must be to detect the tumors at their earliest stage, or prevent them in the first place.

Mammography should be accepted for what it is: followed by treatment, it may extend the lives of some women who have breast cancer, but it does not prevent or cure breast cancer, and it has many limitations.

At best, this is simply not good enough. We need more reliable and less invasive tools developed to detect breast cancer. We need more targeted and more effective treatments for this disease and a better understanding of how one tumor differs from another. And, we need a clearer understanding of what causes this disease, and how to prevent it.

It is also important to keep in mind that this debate is not about diagnostic mammography (for women with symptoms of breast cancer), but about screening mammography (the healthy population of women). This issue must be considered in the context of the limited health care dollars available for breast cancer. What are the best use of resources to reduce mortality and improve quality of life for women?

The National Breast Cancer Coalition respects the difficult challenge in developing a public health message, which may differ from the personal decisions that individual women and their doctors will make. But, our goal today is to explain what we do and do not know about how to reduce breast cancer mortality. The truth is not always clear, but we believe that women deserve to be fully informed, and that they are capable of understanding the complexities around this disease.

BACKGROUND

The National Breast Cancer Coalition believes that the debate over the effectiveness of mammography in reducing breast cancer mortality is vitally important. For too long, mammography has been inextricably and erroneously linked with "prevention" of breast cancer. Mammography screening of women age 40 and above has become the standard of care for women in the United States. It has become a multibillion dollar business. Organizations exist solely to raise awareness about mammograms and breast self-examination. Legislation has proposed to teach high school students about breast self-examination. Campaigns directed to the public about the importance of screening are increasing in number. For much of the public, mammography is the most important, if not the only, issue in breast cancer.

Women are told that early detection saves lives. Yet, the evidence of mortality reduction from screening is conflicting and continues to be questioned by scientists, policy makers and some members of the public. Breast self examination has become part of the culture of breast cancer, even though there is no evidence whatsoever to support its efficacy.

The fact that breast cancer screening is now high on this nation's agenda must not color the analysis of the evidence. Recommendations on breast cancer screening must have as their goal saving women's lives, not preserving an infrastructure.

In my testimony today, I will make four major points.

First, I will explain NBCC's position on mammography screening.

Second, I will respond to the recent studies about what more we now know regarding the effectiveness of mammography reducing mortality.

Third, I will discuss what these new data mean for women, and for the decisions they must make.

Finally, I will give NBCC's recommendations for where we need to go from here.

THE NATIONAL BREAST CANCER COALITION'S POSITION ON SCREENING MAMMOGRAPHY

The National Breast Cancer Coalition has long acknowledged the limitations of mammography screening. For years, NBCC has said that mammography is not the answer to the breast cancer epidemic. Although it may be difficult to accept, it is vital that women know the truth about breast cancer screening and the false sense of security it provides. As breast cancer activists, NBCC welcomes the long overdue criticism and discussion of the effectiveness of existing breast cancer screening methods.

We must accept that we do not know how to detect breast cancer truly early or how to prevent or cure this disease. Instead, we should focus our attention on getting those answers. NBCC believes the goal must be to focus research efforts on true prevention and on stopping breast cancer from occurring altogether. We must work together to find new, more accurate ways to detect and treat this disease.

The Coalition also believes that women who have access to mammography must have access to treatment. Screening alone does not reduce mortality. It is for that reason that NBCC was proud to be the originators, and lead advocates on working

with Members of Congress, many who sit on your Committees, to enact the Breast and Cervical Cancer Treatment Act in the 106th Congress. As you know, this law ensures that low-income women screened and diagnosed with breast cancer through Federal programs can now have access to the treatment they need. NBCC had to fight four, very long, hard years to get women in this program treated as well as screened. There was a lot of opposition along the way, mainly because people were afraid that we were criticizing screening. This debate must not be about saving screening, but rather, about reducing breast cancer mortality. It is about women's lives.

NBCC also believes that mammography should be of the highest quality possible. The Coalition commends your Committees' leadership in enacting the Mammography Quality Standards Act (MQSA), which established minimum national quality standards for mammography facilities and personnel as well as a rigorous annual inspection program to ensure those standards are being met. We appreciated the opportunity to testify before Congress during reauthorization of this program in 1998, at which time we urged that the women be notified directly of the results of their mammogram, and that Congress continue to ensure the highest quality mammography by maintaining the rigorous inspection process initially contemplated.

NBCC supports reauthorization of this important program this year, and would be happy to provide the Committee with additional information or recommendations.

NBCC'S RESPONSE TO THE EVIDENCE

The National Breast Cancer Coalition's general position on mammography is that guidelines on mammography screening should only be issued if scientific studies prove that such programs save lives, and if the benefits outweigh the risks.

As your Committees know, there are seven published randomized trials of mammography screening. The oldest of these trials, the New York Trial, was conducted in the 1960's. Four of the trials were conducted in Sweden, one was conducted in Canada, one was conducted in the United Kingdom, and one was conducted in the United States. The seven trials are known as:

The New York trial or HIP trial—enrolled women 40–64
The Malmo trial—enrolled women 45–69
The Two-County trial—enrolled women over age 40
The Edinburgh trial—enrolled women ages 45–64
The Canadian trial (parts 1 and 2)—enrolled women ages 40–59
The Stockholm trial—enrolled women ages 40–64
The Goteborg trial—enrolled women ages 39–5

Two of these trials—the Malmo and Canadian trials—found that mammography did not benefit women. In these trials, the women who got mammography screening had the same breast cancer mortality as the women who did not. The other five trials found that mammography did benefit women and reduce breast cancer mortality by about 30% on average. Although a majority (five of seven) of the trials found that mammography is beneficial, we cannot simply conclude that mammography saves lives.

First, the reliability and quality of each trial must be evaluated. Some trials may have been poorly carried out, and some trials may not be applicable to the general population of women. Also, it is important to note that a majority of trials does not necessarily represent a majority in the number of individuals who participated in the trials.

Many scientists have critiqued these trials, however, the most thorough peer reviewed evaluation to date was recently conducted by Drs. Gotzsche and Olsen, Danish scientists affiliated with the well-respected Cochrane Collaboration. These scientists set out to review and evaluate all seven of the mammography trials to determine the quality of each. The authors had no conflicts of interest and were unbiased at the start of the review. Their findings were published in a recent issue of The Lancet medical journal as a systematic review.

The findings of the systematic review prompted an independent panel of experts (the PDQ screening and prevention editorial board) at the National Cancer Institute to conduct its own evaluation of the seven mammography trials. After its review, the panel concluded that there is insufficient evidence to show that mammography screening prevents breast cancer deaths in any age group of women. Moreover, it concurred with Drs. Goetze and Olsen that the Malmo and Canadian trials were the highest quality trials, and that they did not show that mammography reduces breast cancer mortality. Finally, the review found that mammography could also have negative effects—including more aggressive treatment and more unnecessary surgeries.

The authors of the systematic review do not state that there is proof that mammography is ineffective. Rather, the evidence is unclear.

Most recently, the U.S. Preventive Services Task Force (USPSTF) recommended screening mammography, with or without clinical breast examination, every one to two years for women ages 40 and over. The Department of Health and Human Services (HHS), and the National Cancer Institute (NCI), have endorsed these recommendations.

NBCC believes that these recommendations were premature and that the Task Force should not have made recommendations until the individual data is released by the Swedish investigators and analyzed by an independent review.

It seems clear that in a situation like the present, where data exist that could answer the questions posed, those data should be released and analyzed before recommendations are made. In addition, the fact that data exist that could help answer the question of whether screening results in fewer breast cancer deaths, but more deaths from other types cancer or other causes, should have compelled the Task Force to demand the data before it made recommendations.

Moreover, the Task Force relied on evidence to recommend screening mammography for women age 40–49 that clearly does not rise to a level sufficient to support screening. In fact, only one trial was designed to answer the question of screening in women aged 40–49, and it found no benefit. In the remaining trials, women in that age group were a cohort of the larger population. In previous recommendations, the Task Force did not recommend screening women in this age group; since there is no new data to show a benefit for these women, it is unclear why the Task Force changed its recommendation.

WHAT DOES THIS MEAN FOR WOMEN TRYING TO MAKE INFORMED HEALTHCARE DECISIONS?

The National Breast Cancer Coalition believes strongly that women deserve to know the truth. If the truth is that evidence is unclear, then they should know that. Progress in eradicating breast cancer means accepting uncertainty regarding best treatment and detection methods. Women and doctors have to understand, and live with this uncertainty, understand the risks, and make individual decisions.

This issue is not black and white. The public needs to accept uncertainty, and move toward educating themselves so they can make their own decisions on an individual basis. Women are capable of understanding that to date, no screening tool allows for truly early detection of breast cancer. Meaning, by the time a tumor is detected, it has been in the breast for 6–10 years. Women also need to understand that some cancers will never spread to other parts of the body, so detecting these cancers won't save lives—rather, treatment would be unnecessary, and possibly harmful. We just don't know.

WHERE DO WE GO FROM HERE?

First, the National Breast Cancer Coalition believes that the most useful thing we can do now is make certain that there is an independent review of the data. NBCC would like to first better understand what the results of these trials mean. The Swedish researchers must allow all of the individual data to be released to an independent reviewer like Medico Legal Investigations, Ltd. in Knebworth, England. This may resolve many of the concerns and questions raised by Drs. Gotzsche and Olsen, and may provide better answers about the effectiveness of mammography.

Second, the cost of mammograms cannot be ignored. Remember, we are not talking here about women who have been diagnosed with a disease. We are talking about the screening of a healthy population of women. Mammography screening is a multi-billion dollar expenditure. We must ask ourselves whether this is the best expenditure of finite dollars? Especially in light of the fact that we know using these resources to buy healthcare for underserved and uninsured women would unquestionably reduce mortality.

We must ask the critical questions: What is the best use of resources? What are the pros and cons? This is a debate that must happen. These are the issues that we must grapple with before we decide to just accept the status quo.

Finally, NBCC urges the public not to just sit and fret over the lack of clear consensus on mammography. Instead, we need to be advocating for more research and resources going towards true prevention and better methods of treatment and detection.

Precious time, resources and attention continue to be diverted away from promising research and funneled into an oversold panacea for breast cancer detection. The issue is about saving women's lives, not saving the institution of mammography. We

must continue to look ahead of the curve to see what more can be done regarding prevention and detection. Only then will we be able to eradicate this disease.

I want to thank these Committees for the opportunity to testify today. I have enclosed NBCC's Question and Answer document on mammography, and ask that it be included in the record. I would be happy to answer any questions.

Senator MIKULSKI. Dr. Runowicz, please.

Dr. RUNOWICZ. Good afternoon, Madam Chair and distinguished members of the subcommittee. I appreciate your invitation to testify today on behalf of the American College of Obstetricians and Gynecologists, or as it is better known, ACOG.

I am a practicing physician who is no stranger to dealing with concerned patients when scientific controversies raise questions about their health and safety. In this particular debate, I also wear a third hat—I am a 10-year breast cancer survivor.

The American College of Obstetricians and Gynecologists represents nearly 40,000 physicians dedicated to improving women's health care. Our members are seeing women on the front lines of the breast cancer struggle. We provide women with clinical breast exams, refer them most often for mammography, and often make the diagnosis of breast cancer. Some of us, like myself, are also gynecologic oncologists and assist in the treatment plan.

ACOG agrees that an extensive and objective reassessment of all mammography data may be justified. Until further reanalysis of the data is conducted, ACOG continues to recommend mammography screening every one to 2 years for women in their 40's and annual mammograms beginning at age 50.

We are here today because of publicity surrounding a study done by Danish researchers recently published in Lancet. The Lancet study questions one of the most widely held beliefs in preventive medicine—that screening healthy people for cancer and detecting it early saves lives. It is important to note that this is not a new study but a reanalysis of already existing published data.

Scientific debate on critical issues like this one is common. ACOG supports periodic, evidence-based, peer-reviewed analysis of all available data on mammography, including a review of studies like the one in Lancet. We take its criticism of prior mammography research very seriously, and we want to make sure that the Lancet study itself stands up to rigorous review.

In fact, the U.S. Preventive Services Task Force announced last week a different conclusion than that of the Lancet study. Their review of the data found that breast cancer deaths among women randomized to screening in seven trials that included women older than 50 showed a 23 percent reduction in mortality. And contrary to prior testimony that you have heard today, in 1993, an independent analysis of the actual data from the five Swedish trials cited in the Lancet study showed a statistically significant 24 percent reduction in breast cancer mortality in the screened group.

With such conflicting data, where do we go from here?

Initially, I think that all of us—Members of Congress, doctors, patients, journalists, researchers—need to understand the difference between the very rigorous standards that scientific evidence must meet to clearly prove the worth of a test and the proctocolitis of what must be done in physicians' offices when conclusive scientific evidence (1) is not yet available or (2) may never be available.

I make this second point because at this time and in the future, there would be clear ethical and moral problems in performing a randomized prospective clinical trial in breast cancer screening that medical scientists say are the highest qualify of scientific proof. How many women today would be willing to go without breast cancer screening in a clinical trial to prove or disprove a statistical point? We may have to live with a certain amount of uncertainty when it comes to the results of mammographic screening trials.

I also think we need to educate our patients about the facts behind the recent media hype—and that is what this is all about—media hype. While the Lancet study has raised several important issues, as a practicing physician, I have to look at this through the eyes of individual patients. I explain to patients that this debate has nothing to do with the effectiveness of breast cancer treatment. There is agreement that treatment saves lives. Instead, the debate is whether earlier treatment made possible by the early detection of tumors is better than later treatment.

I tell them that early treatment made possible by early detection does make a difference. I explain why I think the accumulation of research trial evidence over the years has strengthened the science behind breast cancer screening and that the data in aggregate demonstrate improved health outcomes, with benefits outweighing the harmful effects.

I discuss the recent controversy and my own recommendations. I explain that scientific debate on critical issues is common, but well-established guidelines should be followed unless there is compelling evidence to alter or abandon them.

The news stories have already had a large impact on patients. They are confused, and they express a loss of faith and confidence in mammography. Some even misinterpret the media coverage and take away the message that mammography is bad and even causes cancer.

Over the years, we have made significant strides in educating women about mammography by breaking down financial, physical, and psychological barriers to women seeking mammographic screening. I fear, as does ACOG, that these barriers might be reinforced by this negative attention and uncertainty generated by the media hype.

As already mentioned by Senator Mikulski, I and ACOG are also deeply concerned that the ongoing controversy might discourage health insurance plans from covering this important screening tool.

As frustrating as this controversy may be to women suffering from breast cancer, the silver lining is that it brings to light a goal that we all share—the need to be even more vigilant in supporting research efforts to enhance not just early detection, but treatment as well as prevention and finding a cure for breast cancer. Until then, mammography remains as one of a number of strategies that can help save or improve women's lives.

Even if the screening tests that we have now are not as good or as conclusive as we would like, they are the best we have at the moment. As a practicing physician, I would be derelict in my duties if I advised women to stop having mammograms.

On behalf of ACOG and my patients, I thank you for holding this hearing and for the opportunity to testify today. I would be happy to answer questions.

Senator MIKULSKI. Thank you very much, Doctor.

[The prepared statement of Dr. Runowicz follows:]

PREPARED STATEMENT OF CAROLYN D. RUNOWICZ, M.D.

My name is Carolyn D. Runowicz, and I appreciate your invitation to testify today. I appear before you on behalf of the American College of Obstetricians and Gynecologists (ACOG), and as a practicing physician who is no stranger to dealing with concerned patients when scientific controversies raise questions about their health and safety. In this particular debate, I also wear a third hat: I am a 10-year breast cancer survivor.

The American College of Obstetricians and Gynecologists (ACOG) represents nearly 40,000 physicians dedicated to improving women's health care. Ninety-five percent of board-certified obstetricians and gynecologists in the United States are members of ACOG. Our members are seeing women on the front lines of the breast cancer struggle: we provide women with clinical breast exams, refer them most often for mammography, and often make the diagnosis. Some of us, like myself, are gynecologic oncologists and assist in treatment plans.

I am currently Vice Chair of the Department of Obstetrics and Gynecology at St. Luke's-Roosevelt Hospital in New York City. I also serve as Director of Gynecologic Oncology Research for the Women's Health Service Line of Continuum Health Partners, Inc. and I am Professor of Obstetrics, Gynecology and Women's Health at Albert Einstein College of Medicine (AECOM). Since 1994, I have chaired the gynecologic subcommittee of the Breast Cancer Prevention Trials that are part of the National Surgical Adjuvant Breast and Bowel Project.

ACOG agrees that an extensive and objective reassessment of all mammography data may be justified. In fact, ACOG continually updates its own clinical recommendations by periodically reviewing all data. Until further reanalysis of the data is conducted, ACOG continues to recommend mammography screening every one to two years for women in their forties and annual mammograms beginning at age 50.

We are here today because of publicity surrounding a study done by Danish researchers, members of the Cochrane Collaboration, recently published in *Lancet* (referred to here as the *Lancet* study). The *Lancet* study questions one of the most widely held beliefs in preventive medicine: that screening healthy people for cancer and detecting it early saves lives. It is important to note that this is not a new study, but a re-analysis of published data.

Scientific debate on critical issues like this one is common. ACOG supports periodic, evidence-based, peer-reviewed analysis of all available data on mammography—including a review of studies like the one in *Lancet*. We take its criticism of prior mammography research very seriously, and we want to make sure the *Lancet* study itself stands up to rigorous review.

In fact, the U.S. Preventive Services Task Force (USPSTF) announced last week a different conclusion than that of the *Lancet* study. The USPSTF review of the data found that the pooled effect size of the combined trials was sizable and statistically significant. Breast cancer death among women randomized to screening in seven trials that included women older than 50 showed a 23 percent reduction in mortality.

In addition, an earlier independent analysis of individual-level data from the five Swedish trials cited in the *Lancet* study, conducted under the auspices of the Swedish board of health and published in 1993, showed a statistically significant 24 percent reduction in breast cancer mortality in the screened group.

With such conflicting data, where do we go from here?

Initially, I think all of us—members of Congress, doctors, patients, journalists, or researchers—need to understand the difference between the very rigorous standards that scientific evidence must meet to clearly prove the worth of a test, and the practicalities of what must be done in physicians' offices when conclusive scientific evidence (1) is not yet available, or (2) may never be available.

I make this second point because at this time and in the future there would be clear ethical and moral problems in performing the randomized, prospective clinical trials in breast cancer screening that medical scientists say are the highest quality of scientific proof. I ask you: how many women today would be willing to go without breast cancer screening in a clinical trial to prove or disprove a medical researcher's

point? We may have to live with a certain amount of uncertainty, when it comes to the results of mammographic screening trials.

I also think we need to educate our patients about the facts behind the recent media hype on the usefulness of mammography. While the *Lancet* study has raised several important issues and I am very interested in the scientific debate, as a practicing physician I have to look at this through the eyes of individual patients.

It is important to explain to our patients that this debate has nothing to do with the effectiveness of breast cancer treatment. There is agreement that treatment saves lives. Instead, the debate is whether earlier treatment made possible by early detection of tumors is better than later treatment.

Then I explain why I believe that early treatment does make a difference. I am very careful to explain to women that early diagnosis combined with early treatment translates for many women into a better future. I believe that early detection in most cases helps us to prolong women's lives, even those destined to die from breast cancer. Early diagnosis can affect the quality of women's lives in positive ways.

I explain why I think the accumulation of research trial evidence over the years has strengthened the science behind breast cancer screening. There has been an important decline in death rates from breast cancer, nearly 2 percent every year during the 1990s and nearly 4 percent since the mid-90s, which has been attributed to improvements in treatment and a trend towards earlier detection. In the 1980s, only 13 percent of U.S. women were getting mammograms and the average size of tumors was 3cm. By the late 1990s, 60 percent of women were having regular mammograms and the average size of tumors decreased to 2cm.

So, I note that although mammography is not a perfect screening tool, it is very effective. Mammography can have false-positive results, which may cause anxiety, biopsies, and cost—although these diminish from ages 40–70. However, the data in aggregate demonstrate improved health outcomes, with benefits outweighing the harmful effects.

I discuss the controversy and my own recommendations noting of course that the decision on whether to be screened is theirs. I explain that scientific debate on critical issues is common, but well-established guidelines should be followed unless there is compelling evidence to alter or abandon them.

The news stories have already had a large impact on patients. They are confused and express a loss of faith and confidence in mammography. Some misinterpret the media coverage and take away the message that mammography is "bad" and can even cause cancer!

Over the years, we have made significant strides in educating women about mammography by breaking down financial, physical, and psychological barriers to women seeking mammography screening. I fear that existing barriers and negative attitudes towards mammography might be reinforced by the negative attention and uncertainty generated by the media hype. It is too soon to know if women will turn away en masse from mammography and we will turn the clock back in the fight to treat breast cancer. I am also deeply concerned that the ongoing controversy about the value of screening mammography might discourage health insurance plans from covering this important screening tool.

As frustrating as this controversy may be to the women suffering from breast cancer, the silver lining is that it brings to light a goal I think we all share: the need to be even more vigilant in supporting research efforts to enhance not just early detection but also treatment, as well as prevention and finding a cure for breast cancer. Until then, mammography remains as one of a number of strategies that can help save or improve women's lives.

Even if the screening tests we have now are not as good or as conclusive as we would like, they are the best we have at the moment. As a practicing physician, I would be derelict in my duties if I advised women to stop having mammograms.

On behalf of ACOG and my patients, I thank you for holding this hearing and for the opportunity to testify today. I am happy to answer any questions.

Senator MIKULSKI. Dr. Leffall, we would be happy to hear your testimony in behalf of the Komen Foundation.

Dr. LEFFALL. Thank you very much, Senator Mikulski and other distinguished members of the committee.

As a surgeon oncologist and medical educator, I have devoted most of my professional life to the study of cancer. After I completed my surgical oncology training and Memorial Sloan Kettering Cancer Center and 2 years in the Army, I returned to Howard Uni-

versity in 1962 and have been there since then, so this is now my 41st year on the surgical faculty at Howard and my 41st year in the active practice of surgical oncology, and the major part of my practice consists of patients who have breast problems; thus my major interest in this.

The Komen Foundation was established some 20 years ago by Nancy Brinker to honor the memory of her sister, Susan Goodman Komen, who died of breast cancer at the age of 36. Today the Komen Foundation is the Nation's largest private funding sources of breast cancer research and community-based outreach programs.

Modern medicine is fully of uncertainty, but today the assault on mammography has created a cloud of confusion and an atmosphere of suspicion. It has also done a true injustice to American women who understand that screening is not prevention. We are not surprised, but certainly we are disappointed.

That said, we concur with the expert opinion of our times—mammography is an imperfect screening tool and one that should be made better. But we want to emphasize that we think it is the most appropriate thing now for women, screening mammography.

While we are working to unlock the secrets of what causes breast cancer and eventually prevent the disease for future generations of women, the Komen Foundation understands the realities facing women and their families today. Therefore, the Foundation applauds the mammography screening recommendations reported last week by the U.S. Preventive Services Task Force and the National Cancer Institute.

Affiliates of the Komen Foundation currently provide grants for more than 1,600 breast health education and breast cancer screening and treatment projects in their communities. In addition, the Komen Foundation Research Program awarded more than $20 million in grants during the last year alone to support cutting-edge research in institutions around the globe.

As someone who is on the front lines and seeing patients every day with breast problems, many of whom have breast cancer, I know firsthand how both mammography and breast cancer treatment have changed during the last 20 years. Mammography is better. The radiologists are better. The technicians are better.

Two of the crown jewels of health care policy in the United States, both of which came about in the last decade, are the Mammography Quality Standards Act and the CDC's Breast and Cervical Cancer Early Detection Program. Senator Mikulski, the Komen Foundation applauds your efforts and being a leader in the MQSA. It is so important to ensure the high quality of mammography for women. We know that quality mammography certainly saves lives.

Mammography screening to reduce breast cancer mortality must be sensitive enough to detect the disease. Poor-quality mammography reduces the sensitivity and specificity of the screening test. The use of dedicated, up-to-date equipment is key to the performance of high-quality screening tests. Since the MQSA enactment, women throughout this country have gained further confidence in their mammogram.

My next statement was alluded to by Senator Murray earlier today. In the early 1980's, when only 13 percent of women in the

United States were getting mammograms, the average tumor size at detection was about 3 centimeters. By the late 1990's, when 60 percent were getting mammograms, the average detected tumor size was 2 centimeters. For many women, early detection means the possibility of less invasive treatments in some cases as well as the option of breast conservation surgery instead of mastectomy.

In the past decade, breast cancer mortality rates have declined in the United States, and Dr. von Eschenbach showed that on his charts. This is due in large measure to early detection and timely treatment. That is important—early detection and timely treatment.

Regular mammography as part of a three-step breast health regimen that includes monthly breast self-exams and annual clinical exams saves lives. It enables women, as true partners in their health care, to become familiar with the normal look and feel of their breasts.

While mammography can sometimes lead to false negative results when a woman and her caregiver discover a suspicious lump that did not show up on a mammogram, further examination does not always entail surgery. We have means now of making a diagnosis with image-guided biopsies and tests like that.

There is also the risk of false positive results, and an abnormal mammogram is in fact not breast cancer, which may also result in further tests.

But while these risks may result in unnecessary procedures for some women, our constituents in America's communities tell us that even these serious consequences seem acceptable if they are faced with the possibility of a life-threatening disease.

We encourage the Senate to allow steadfast hearts and large minds to rule the day and advocate instead for the recommendation of the U.S. Preventive Services Task Force to take advantage of the only widely available screening tool currently proven to find breast cancers before they grow to the size that can be felt by hand.

The National Cancer Institute declares that the evidence will not support a change in their recommendations. We at the Komen Foundation will remain true to our recommendations as well.

Thank you for this opportunity to appear before you today, Senator Clinton and Senator Mikulski.

[The prepared statement of Dr. Leffall follows:]

PREPARED STATEMENT OF LASALLE D. LEFFALL, JR., M.D.

On behalf of the Susan G. Komen Breast Cancer Foundation, thank you Senator Mikulski, Senator Harkin, Senator Frist, and Senator Specter and other committee members here today, thank you for creating a forum for public discussion on the most recent debate on breast health.

The Komen Foundation is one of the largest private funding sources for breast cancer research today, and was begun by Nancy Brinker 20 years ago in honor of her sister, Susan Goodman Komen, who died of breast cancer at the age of 36. Helen Keller has long been a hero of Nancy's, and she once said, "Doubt and mistrust are the mere panic of timid imagination, which the steadfast heart will conquer, and the large mind transcend."

Modern medicine is full of uncertainty . . . This can be purposeful, however, for it is uncertainty which lends life its fascination when partnered with the desire to comprehend. But today, the assault on mammography has created a cloud of confusion, an atmosphere of suspicion, and an injured party of women. Discounting the power of uncertainty, the recent debate has thrust ambiguity upon this significant subject of public health. Unproductive reiteration of the relative merits of various

scientific inquiries has created confusion. We're not surprised, but we are disappointed.

Imagine two computers on one hand, and a couple of mastermind logicians on the other, testing which group analyzes chess moves more advantageously. Would you be surprised if your results were conflicting if one computer had a Pentium Chip, and the other did not?

The "Pentium Chips" of Mammography in the United States are the Mammography Quality Standards Act, the BCCEDP, and other new initiatives of the last decade. The vast improvements in film, machinery, training, and access are part and parcel to mammography's "Pentium Chip".

That said, we concur with the expert opinion of our times. Mammography is an imperfect screening tool. We are investing heavily in better technologies. Yet, we know improvements take time. So while we are working to improve early detection and eventually uncover true forms of prevention, the Susan G. Komen Breast Cancer Foundation applauds the mammography screening recommendations reported last week by the U.S. Preventative Services Task Force and the National Cancer Institute.

The Komen Foundation will continue to recommend the three-step approach to positive breast health including monthly self breast examinations beginning at age 20; clinical breast examinations at least once every three years beginning at age 20 and annually after age 40; and annual screening mammography beginning at age 40.

The Task Force's recommendations, underscored by Secretary Thompson's remarks, take us one step closer to clearing the confusion. Because, before women start canceling screening mammography appointments, we need clear guidelines for those making the decision today about their health care based on the best currently available information and technology. Until a foolproof mechanism of detection is widely available, the Komen Foundation strongly encourages women to continue having mammograms.

At the same time, the Komen Foundation will continue to focus research dollars on improving the quality of screening technology as well as research that will one day lead to a cure for breast cancer. The Komen Foundation Research Program awarded more than $2.4 million in grants last year to support institutions conducting cutting-edge imaging technology research.

In total, the Komen Foundation awarded $20 million in research grants last year in support of the fight against breast cancer, it's eventual cure, prevention and eradication. In addition, Komen Affiliates provided grants for more than 1,600 breast health education, screening and treatment projects in 116 communities across the country.

Since 1998, the Komen Foundation Research Program has funded grants to improve breast imaging technology totaling $3,320,927. We have also funded considerable research aimed at finding a way to cure or prevent breast cancer, to wit: proteins associated with breast cancer totaling $4,786,144; Angiogenesis totaling $754,148; Oncogenes totaling $1,845,348; Growth Factors totaling $4,051,553; Antibodies totaling $2,998,787; and BRCA genetic abnormalities totaling $2,082,024. Please find detailed information about grants in each category as an addendum to my testimony.

The benefit of early detection is undisputed, but with it comes the potential risks for additional procedures and/or over-treatment. "False-positive" results may lead to further imaging or biopsy that end up with a benign finding. When there are historic data (i.e., previous mammograms) for comparison, however, the rate of false positives can be decreased, thus the need for regular screening rather than a one-time view only.

The detection of breast cancers that may never have progressed to a dangerous stage during a patient's lifetime also counts toward the "risk" side of the equation. But since we don't know which breast cancers will progress, virtually all these women are treated surgically, with or without radiation and chemotherapy. And while these risks may result in unnecessary procedures or treatment for some women, our constituents in America's communities tell us that even these serious consequences seem acceptable if they are faced with the possibility of a life-threatening disease.

Mammography can also sometimes lead to false-negative results. For this reason, when a woman and her caregiver discover a suspicious lump that did not show up on a mammogram, it should be examined by other means—but that doesn't always entail surgery. There are well-accepted alternative ways of assessing whether a lump detected through clinical exam, or even an abnormal mammogram, is breast cancer other than through surgical biopsies. These methods include MRI, ultrasound, and ultrasound-guided or stereotactic (x-ray guided) biopsy. The cost of

making a breast cancer diagnosis is lowered dramatically by appropriate use of ultrasound and image-guided biopsies.

So, while we have the potential for false-negative and false-positive findings on the one hand, we have the case for early detection on the other. The larger the tumor, the longer or faster it has been growing. This often translates into more aggressive treatment, as larger tumors are more likely to have spread beyond the initial site. And even with more treatment, the survival chances of women with larger tumors is not as good as those with tumors smaller in size.

As previously stated, the Komen Foundation is funding research into new imaging technology with a goal of diminishing false-positive and false-negative outcomes. Further, and more critically, we are funding research to identify which tumors in which women are likely to spread aggressively and become life-threatening. Our funding of studies of molecular markers associated with breast cancer or other abnormalities, including inherited genetic changes, tumor growth factors and gene proteins, totaled nearly $3 million in 2001 alone.

In the early 1980's, when only 13 percent of women in the U.S. were getting mammograms, the average tumor size at detection was about 3cm. By the late 1990's, when 60 percent were getting mammograms, the average detected tumor size was 2cm. For many women, early detection also means the option of breast conserving surgery, instead of a mastectomy.

Mortality rates have also declined in the U.S. in the past decade. Some argue that lowered mortality rates for breast cancer may be attributable to better treatment options rather than early detection. It is intriguing however, to review data compare from countries that do and do not have national screening programs. The breast cancer screening program in Sweden is arguably the most comprehensive in the world. Denmark, Sweden's Scandinavian neighbor to the South, does not have a screening program. Germany also does not have a comprehensive screening program and never has. The U.S. has a growing program of mammography screening, with Medicare and Medicaid coverage, CDC programs, and private insurers.

The incidence of breast cancer per 100,000 population is lower in Germany than in the Sweden; lower in Denmark than in the U.S. Nonetheless, the ratio of mortality to incidence rate (which approximates the percentage of people who will die from the disease) is far lower in Sweden (22 percent) and the U.S. (23 percent) compared to Germany (32 percent) and Denmark (36 percent).

Country	Incidence	Mortality	Ratio
Sweden	81.03	17.48	22%
United States	91.39	21.22	26%
Germany	73.65	23.74	32%
Denmark	86.15	29.16	36%

Further, the rate of mortality decline in Germany and Denmark have not kept pace with the declines in the U.S. Between 1990 and 1996 (the last year of data for all four countries), breast cancer mortality declined 12 percent in the U.S. and 8 percent in Sweden, compared to 1 percent in Denmark and Germany.

Country	1990	1996	%change
Denmark	26.88	27.25	−1%
Germany	21.87	22.03	−1%
Sweden	17.80	16.39	8%
United States	22.54	19.75	12%

Dr. Gabriel Hortobagyi, of M.D. Anderson, believes that both early diagnosis and treatment play an important role in the decrease, stating, "The available data would indicate that early diagnosis would reduce risk of mortality by about 25–30 percent and that optimal adjuvant chemotherapy plus hormonal therapy would reduce risk of mortality by about 30–45 percent. However, neither approach has been applied to its full potential—not every woman between ages 40 and 65 has annual mammograms, and not everybody with primary breast cancer larger than 1cm receives optimal adjuvant systemic therapy." It is interesting to consider therefore, that the decrease in mortality observed in the U.S. may be only a fraction of the decrease one would observe, were both early detection and optimal timely treatment be available to all eligible women.

The Komen Foundation appreciates the significant role economics play in screening, and that new interventions must also be cost-effective. However, we cannot align ourselves with a "bottom line" philosophy, as therein the cheapest patient is

a dead patient. Thus, while we consider all screening and treatment with an eye toward cost-effectiveness, the Komen Foundation still puts faith in a procedure that yes, holds elements of uncertainty, but also holds proof of lives saved.

There are unanswered questions, not only behind mammography, but also behind its debate. What has really spurred this vigorous deliberation yet again? If the opponents of mammography vehemently deny substantial benefits, arguing instead that the risks tip the scales unfavorably, why then is there no call for a national "cease and desist" for all screening?

There is always a role for economics, but if that's the heart of this debate, then lay it on the table and have it examined objectively. If there's an argument for spending public and private dollars on research rather than screening, then it too should be aired for public examination.

To truly eradicate breast cancer, we must not only meet the immediate needs of women facing this disease today, but we must also invest in research for future generations. This is how grants are made at Komen—investing in tomorrow and today. But even then, the fight is not won. The greatest tragedy would be to discover that elusive cure or prevention and not be able to get it into the hands of each and every person who needs it, regardless of where they live or their ability to pay.

Clearly, the issues of risk and economics need to be spoken in a language women will understand. And for that, we encourage the members of these two committees to review this issue carefully to resolve the unanswered questions and confusion surrounding the risks of mammography. It is too hard to argue that a decrease in deaths of American women due to breast cancer is not related to a link in awareness and its sister messages of early detection and annual screening.

Women are in a quandary. Will you send the message to your mothers, sisters, aunts, wives and daughters to wait for a lump to be felt to find their breast cancer, even when we are able to find it much earlier? Public Health is in a quandary. Will even low-cost, effective screening methods be disallowed in a time of tightened healthcare budgets? And researchers are in a quandary. Will their years of research be allowed to go fallow due to politically motivated debate?

Rather, let us allow "steadfast hearts" and "large minds" to rule the day, and advocate instead for the recommendation of the U.S. Preventative Services Task Force: take advantage of the only widely available screening tool we currently have proven to find breast cancers before they grow to the size that can be felt by hand. The ACS sees no reason to change its screening recommendation. The NCI declares that the evidence will not support a change in their recommendations. We at the Komen Foundation will remain true to ours as well. Thank you for this opportunity to appear before you today.

Senator MIKULSKI. Thank you very much.

Senator Clinton, I am happy to do the wrap-up questions; if you want to go first and lead off this round, we are happy to have you do so.

Senator CLINTON. Thank you very much.

I want to thank the panelists. We have three extremely dedicated witnesses who have given their lives to this fight against breast cancer.

I could not agree more with the point that Fran Visco made about the inequitable distribution of resources with respect to dealing with breast cancer. In fact, most of our major health problems are more likely to fall disproportionately on the poor, on the people who do not have access to affordable, quality, reliable health insurance. I think that the National Breast Cancer Coalition's constant advocacy on behalf of more resources and better access has been an extremely important part of this debate, and I hope that it is not a point that is going to be forgotten, because we still have a lot of work to do.

I want to ask Fran about what the Coalition's current review of insurance coverage with respect to not only mammography but to breast cancer treatment in general has led you to conclude about any action that we need to be contemplating with respect to insurance coverage.

Ms. VISCO. I think one of the most important issues before the Congress now is coverage for oral anti-cancer drugs. As you know, breast cancer is primarily a disease of older women. Medicare does not cover tamoxifen, which is probably responsible for much of the decrease in mortality that you have seen in the charts that Dr. von Eschenbach put up. That is a critically important question in breast cancer, much more important than if a woman has to wait 3 months for a screening mammogram.

I also want to say that there is no way that the National Breast Cancer Coalition would let up on pushing for access to health care for all women and all Americans.

Another point that I need to have the opportunity to make is about breast self-exam. There is no scientific evidence that breast self-exams save lives. That is another infrastructure that has been built up in this country based on no evidence, and in fact the evidence that we are seeing now indicates that there may not be a difference in mortality through teaching breast self-exam.

Senator CLINTON. Thank you.

Dr. Runowicz, I really appreciate your perspective, both as a physician and as a breast cancer survivor yourself. What is the best way for us to dispel the confusion and to some extent even more than that, the despair that women feel about knowing what they are supposed to do and who they can believe and how they make the decisions. I think that what the American Cancer Society and the National Cancer Institute and others have said, which is, I think, putting it sort of simply, that you cannot let the perfect be the enemy of the good, and until we know something more than we know now, it is prudent to continue to recommend the same standards that we have adopted.

How do we get that message out?

Dr. RUNOWICZ. I think that is a very big challenge, and one article on the front page of The New York Times can undo all the good of all of the organizations. But I think that hammering home the same consistent message and letting patients know that controversy is what science is all about, and that is how we make new discoveries, but until we have other data that make us change these guidelines, these guidelines are based on good science, and we need to get that message out over and over again.

Senator CLINTON. I thank you for your role in doing that.

And Dr. Leffall, thank you for your years of service to patients and as an advocate and spokesman. From your perspective also dealing with patients and from the Komen Foundation work that you do, is there more that we could do in the Congress to try to convey more support for the clinicians' work that you and Dr. Runowicz and others are doing? How can we help you get the message out, and from your perspective, what additional steps should we be taking in funding to try to move the breast cancer debate beyond mammography to prevention and cure and some of the other issues that are at the root of it?

Dr. LEFFALL. We must always be concerned about those, Senator Clinton, prevention and cure. But one thing that I think you can do—so many of my colleagues who are radiologists are now telling me that they are no longer willing to perform mammography because the reimbursement they receive is not worth it from a prag-

matic point of view. They say, "I want to help patients"—that is why we are in medicine, to help patients—"and I do not get enough to pay the expense in my office."

So that is something that certainly can be done, but in addition to that, as long as we can continue to emphasize that until we have something better, the things that are based on science—and the mammography recommendations are based on scientific data—and we are not opposed to other people looking at those data to be sure that they are what they say they are, and if there is a difference of opinion, let us talk about it; let us not try to hide it. But that is something that we can do for the radiologists who perform mammography.

Senator CLINTON. Thank you, because as I said earlier, that is a big problem in New York and is becoming a real barrier to access, so that even if women are presented with all sides of this issue and make the determination that they want a mammogram, it is becoming harder to get one, either because of access or affordability.

Dr. LEFFALL. That is correct.

Senator CLINTON. I want to again thank Chairman Mikulski for holding this important hearing along with Chairman Harkin. It was a very important service.

Senator MIKULSKI. Thank you very much.

Senator Harkin?

Senator HARKIN. Thank you very much, Madam Chairman.

Dr. Leffall, regarding one point you just mentioned, I just want to say that I do have a bill in to increase that reimbursement rate for radiologists. I have been hearing from them, and just yesterday in Iowa the question was asked as to what does a mammogram cost. They said $100 to $120, somewhere in that range. I think the reimbursement is now around $75; is that right?

Dr. LEFFALL. Average.

Senator HARKIN. Average about $75?

Dr. LEFFALL. Yes.

Senator HARKIN. So you are right—a lot of people are just turning people away.

Dr. LEFFALL. They are not doing it anymore; that is correct, Senator.

Senator HARKIN. So I do have a bill in to get the reimbursement raised, and if I can find something to attach it to this year, I will attach it.

Dr. LEFFALL. Very well.

Senator HARKIN. I am wondering, though, if I will get comments on the floor that maybe this is not necessary. I don't know. Is it necessary? With the confusion that seems to be out there now, people will say, "Why do you want to increase the reimbursement rate to radiologists who do mammograms when we do not even know if mammograms are effective? Maybe we should not do it."

Dr. LEFFALL. But most groups in the United States believe that until we get something better, this is what we should continue to recommend. That is why the Komen Foundation is recommending it, ACOG, NCI, the American Cancer Society—because we believe that it is based on the available science that we have today. And we would like to emphasize that we are not opposed to a re-look

at the data to be sure that it is what we say it is, and let patients know the truth. We are not trying to hide the truth. But when you come up with something better—and Dr. von Eschenbach mentioned some things like the PET scan, MRI, digital mammography—when they prove to better, we can go to that, but until then, I think we should stick with what we have that we know can make the diagnosis early. And you have asked many questions today about early detection, which is extremely important.

Senator HARKIN. Fran Visco, we have worked together now for over 10 years.

Ms. VISCO. Yes, that is right.

Senator HARKIN. You said in your testimony that we have got to ask if mammography screening is the best use of finite dollars. Well, if not, then, what do we do?

Ms. VISCO. Well, I think we should use them to give health coverage to women. I think that women need to be reimbursed for their medicine. I think that more women need to have access to quality care. There are many areas that are looking at truly early detection, looking at how to prevent breast cancer, looking at nontoxic targeted therapies.

The mammography debate is sucking up all of our time, all of our dollars, all of our attention, all of our focus. There is so much more to eradicating breast cancer, and that is where we need to move those dollars.

Senator HARKIN. How much do we spend yearly on mammography?

Ms. VISCO. It is a multibillion-dollar number; exactly how many billions, I do not know. I have seen numbers recently, but they are not in my head; I know that it was many billions.

Senator HARKIN. Are most covered by insurance and Medicare—mostly Medicare?

Ms. VISCO. Probably. I do not know the answer to that question.

Senator HARKIN. I would like to find that out.

Senator MIKULSKI. But not for the poor. Senator, just in the interest of a little dialogue, you have Medicare covering mammography, but that is every other year—but at least it is something, and we spearheaded that. Then, those of us who have private insurance receive reimbursement, but again, you have got to watch your time on that, or they will not cover that. But for poor women, the only thing that we have is the breast and cervical screening program at CDC, which the women of Congress initiated and, Senator, you have been steadfast in helping provide the funds for it.

Did you hear what I just said? [Laughter.]

Senator HARKIN. I am sorry. Everybody is talking to me at one time.

Senator MIKULSKI. I said that for reimbursement, Medicare provides it for the women over 65 every other year; for other women, it is reimbursed through private health insurance, and again, it has age guidelines; third, for poor women, the only tool—and it is a down-payment tool—is for the breast and cervical cancer screening at CDC, and that is funded through——

Ms. VISCO. The treatment component that we worked on for 4 years and last year, we were finally successful in getting enacted into law, where women who are screened through the CDC pro-

gram, once they are diagnosed, become Medicaid-eligible for their treatment.

Senator MIKULSKI. That is right. But you fund in Labor-HHS the CDC program; but if it were not for your funding in the CDC program, poor women would not even have an option—and by and large, even there, it is still a rather spartan number of women who can participate. But even when they are screened, the Medicaid is also an option to the State.

Ms. VISCO. It is an optional program with the States, but the National Breast Cancer Coalition has been very successful over the past year in getting 39 States so far to opt in.

Senator MIKULSKI. Bravo, bravo for that.

Ms. VISCO. Thank you.

Senator MIKULSKI. But again, for poor women—you see.

Senator HARKIN. My staff tells me the amount spent on mammograms yearly is $3 billion. I assume that it is all covered by insurance and Medicare. So it is a sizeable sum of money. We are up to $800 million into research now; right?

Ms. VISCO. Yes.

Senator HARKIN. We finance $800 million for breast cancer research. So it is a lot of money for mammography.

Ms. VISCO. And remember, access to health care, too, for these women to treatment and to oral anti-cancer drugs—very important issues in breast cancer.

Senator HARKIN. Well, again, we're trying to clear this up and trying to get a definitive answer to women out there. What would you tell my nieces? Both of their mothers died of breast cancer. They are now in their late 30's now, maybe almost 40, and they have been getting breast cancer screening because of that. What would you tell them?

Ms. VISCO. I would tell them to go to the National Breast Cancer Coalition website and look at our question-and-answer, which lays out all of the issues on this very debate, and we would be happy to help them work their way through it, and then they can make up their minds about what they want to do. But I think women have the power and the capability to understand this complexity and to make a decision on what to do.

Senator HARKIN. I believe that is true also, but I think early detection right now is still the best.

Ms. VISCO. We may not know how to detect breast cancer early enough.

Senator HARKIN. I know that. I read that in your testimony.

Ms. VISCO. Believe me, I wish——

Senator HARKIN. And we are working on the blood test, as we did for ovarian cancer. That might be possible for breast cancer. They are working on it now. But in the meantime we do not have it. It might not be early enough, but finding it with mammography is earlier than detecting it during a physical exam.

Ms. VISCO. But the issue is does it make a difference, and that is the debate around the trials.

Senator HARKIN. I thought the answer to that was, all other things being equal, yes, it makes a difference. The earlier you detect it, the better the quality of life and the higher probability of having a longer life.

Ms. VISCO. Let me respond that the data do not necessarily show that in terms of length of life, but certainly quality of life. The data from the trials show that more mastectomies are performed in the group that is screened by mammography than in the control group, because we do not know how to treat very early breast cancer, and we tend to do mastectomies often in that population.

Senator HARKIN. Or lumpectomies, or something like that.

Ms. VISCO. Yes, but the data show that more mastectomies are done in the mammography screened group. That is the data.

Senator HARKIN. But that data from the sixties, seventies and eighties.

Senator MIKULSKI. And now we have new approaches.

Senator HARKIN. Yes, we have new approaches now. That is why I keep saying the Danish study does not take into account some of the new technologies and new interventions that we use now.

Ms. VISCO. OK. I know we can have this debate forever, and again, I believe that our Q and A lays out some of these issues, and perhaps it warrants a longer debate at another time. But sometimes breast cancer is not a very logical disease; it is a very complex disease.

Senator HARKIN. Well again I ask, as I asked the other panelists: all things being equal, if someone has the insurance coverage or if they are low-income and can get access to the breast and cervical cancer screening program, should they go ahead and have a mammogram?

Every single person I talked to yesterday in my State of Iowa answered yes. These were clinicians, doctors, nurses, and breast cancer survivors. Every single one said yes. I am not a doctor and I would not give advice, but I think one of the purposes of our hearing is to try to clear the air a little and get a little more clarity for the women of this country.

You are right, women can make up their own minds——

Ms. VISCO. Yes.

Senator HARKIN [continuing]. But it is very difficult to make up your mind when you are faced with a life-threatening illness, and the people in whom you put your trust and confidence do not have definitive answers or clear guidelines for you.

I keep coming back to my basic question: all other things being equal, is early detection better than later detection, and will mammography give you earlier detection?

Dr. Runowicz, what do you say?

Dr. RUNOWICZ. I would like to answer several of the questions that you have raised. On your nieces, there has been a breast cancer prevention trial that has been completed in this country and showed that tamoxifen prevented breast cancer, and there is the STAR study now. If they meet the eligibility criteria—and I do not think they will because they are not postmenopausal—but I would certainly encourage that they look into clinical trials and that they certainly discuss the issue of tamoxifen.

As far as right now, there is no compelling evidence to alter any of our guidelines. Every, single major institution, every, single major organization, is still saying "Stick with your guidelines," which are from age 40 to 50 every one to 2 years—some organizations are every year, such as the American Cancer Society; others

are every one to two, such as the National Cancer Institute, and the American College of Ob-Gyn—after 50, every year until there is another comorbid condition which precludes the sensibility of continuing mammography.

The debate here today is a statistical debate. The debate here today is media hype. The debate here today is The New York Times front page. That is why we are here today. We are not here because there is new data. We are here because there are statisticians who, in their own group, the Cochrane group, which is an excellent group—these two investigators did not have the entire group behind them, and the Lancet article that they published was not published with the entire backing of that group. Instead, that group published a separate article, and they have their website, where dissension from the two authors.

That is why we are here today—because somebody has reanalyzed data, and they have chosen, based on their statistical evaluation, that they wish to exclude other studies, to which other groups like the U.S. Preventive Services Health Task Force said no, we do not agree with their exclusions.

So looking at the raw data again—and it has been done in 1993—but looking at that raw data again will perhaps readdress these issues. But there is no compelling evidence, there is no new evidence, to alter our guidelines.

Was that clear?

Senator HARKIN. That is very clear.

Dr. LEFFALL. Senator, I would just like to echo—you asked the question about your nieces—without any question, I believe the answer is yes, please get the screening mammogram. And this is not saying you are opposed to any of the other things that have been mentioned today in terms of access to care. What could be more important than access to health care? It is one of the most important things. But today we are talking about the mammography debate, and it is a debate, a statistical debate.

But I think Dr. Frist, a colleague, mentioned it. When you are sitting with a patient, and that patient—once again, you go with a lot of information—they say, "You are asking me to make a decision in a few minutes, and you have spent your entire professional life studying this. I do not think you are being fair to me." I would get that when I used to go into a lot of detail; yet you try to inform patients. Patients should be informed. Patients are very intelligent. They should be informed. But when we cut through the chaff to get to the wheat—get the screening mammogram—that is the answer.

Senator HARKIN. Thank you all very much. I appreciate it.

Senator MIKULSKI. Before we conclude—because I said I would be the wrap-up questioner—I just want to reiterate essentially what has come out of this hearing and then have a final question for you, Doctor.

First of all, what we see is that the biostatisticians disagree. That is clear. And they will continue to look at data and analyze it.

Clinicians, those who have the lives of patients in their hands, do not disagree that clinicians agree and recommend in the most enthusiastic, unabashed, and unqualified way that we follow the existing guidelines that have been established by the National Can-

cer Institute, recently reaffirmed by the Preventive Services Task Force at HHS, and have also been the longstanding recommendations of the American Cancer Society.

So this hearing should not end without it being clear that those who are in charge of America's public health, its research institutes, the oldest cancer organization in the United States of America, and representing the clinicians all agree that if you are 40 or older, you should have a mammogram every other year, and if there is indication of greater risk, either genetically or because of medications, to pursue it.

That is where there is agreement. There is also agreement, whether it is among the biostatisticians or among the advocacy groups, where again there is disagreement.

But first of all, yes, we need access. We need access to women's health care. And as part of that, if you have access to health care, your doctor can then recommend what are the best next steps. It could be diabetes; it could be lung cancer, which is the biggest killer of women; it could be heart disease, etc. But we need access to health care, and then, access also to treatments, which means the way we need to look at our patients' bill of rights. I believe, Doctor, that ob-gyns should be designated also as primary care providers. You are the first and sometimes the only physician that women see, and you are the one who can say, "Wow, 20 years on birth control—we had better get you in now, even though you are 38 years old." So access is important.

Of course, this debate is moot for the poor because of limited access to health care and the even further limited nature of access to treatments, even where there is diagnosis. We have all heard that.

I thank all of you for mentioning the mammogram quality standards as well as the Cervical and Breast Screening Act at CDC.

Thanks to the advocacy groups, and Fran, I particularly want to mention your group. We really pushed for that. I take pride that I was one of the prime movers of that initially, and then we had these fine men of the Senate really support us. We now know that it has made a difference, and we welcome any views on the mammogram quality standards, so we thank you for that.

So that is where we agree. We agree that we have got to have our mammogram quality standards. We agree that we need research on new tools and on new treatments—but new tools and new treatments are a hollow opportunity if we do not have access to health care for women, and the start for what is the best way to go for whatever we confront really needs to start with access to health care.

So that, then, is where I think we agree, and I think if people ask me, "What do you think about all this, Senator?" I would say that we need to stay the course in terms of the existing guidelines until there is clear, compelling, and convincing evidence otherwise. We really need to pursue these mammogram quality standards as well as new research.

I am going to close with the access issue. I have raised this issue, as have Senator Clinton and others. We have got to be really careful that while we scientifically disagree, we do not end up discouraging health insurance plans from covering this important screen-

ing tool. It might not be the best tool right now, although it seems to be the only reliable, or at least pretty reliable, tool. In fact, we would like the health insurance industry to take a whole new, fresh look at women's health care and what they reimburse, starting with designating the ob-gyn as the primary care physician, along with other internists.

So we say to the insurance companies that we hope you have learned something, and we say most of all to American women that if you are over 40, get a mammogram; if you are under 40, let us find a way to get you in to talk to someone to see if you are at risk and go from there.

Thank you very much. I really want to thank everyone who presented their views today, and to the biostatisticians, thank you even for your disputed presentations, because they have caused us now to take a new look at where we are. So we thank you, and we encourage you to continue in your own good work.

This hearing stands adjourned.

[Additional material follows:]

ADDITIONAL MATERIAL

PREPARED STATEMENT OF CLAUDIA I. HENSCHKE, PHD, M.D.

Our testimony on behalf of mammography screening is based on our recent article published in The Lancet on February 2, 2002[1 2 3]. We there responded to the publication by Olsen and Gotzsche (also published in The Lancet, October 20, 2001) in which they concluded that of the seven major mammography studies, five were severely biased and thus could not be used to evaluate mammography. They stated that neither of the remaining two (Malmo and Canadian) studies considered to be acceptable showed a benefit.

In our paper, we focused on the Malmo and Canadian studies that Olsen and Gotzsche deemed acceptable to illustrate that they, among many others, ignored larger and even more fundamental flaws in their analyses and that this lack of understanding led them to produce misleading, falsely nihilistic evidence. These fundamental flaws are inherent in the currently prevailing approach to assessment of any screening test for cancer: the failure to continue screening long enough in a study for its benefit to become evident and the failure to assess that resulting benefit, namely the reduction of cancer deaths, during a relevant time period, that is, sufficient distant from the onset of the screening program. If the approach is flawed, conclusions drawn from such an evaluation will also be flawed.

We showed that in the Malmo study, mammography provided for a 55% reduction in the breast-cancer case-fatality rate in women 55 years and older and about a 30% reduction in those aged 45 to 54. This benefit, however, only became evident after six years of screening, that is from the seventh year of screening onward. It was only in the Malmo study that screening was not discontinued prematurely as had been done in the Canadian study.

It should be self evident that when a screening test picks up a cancer and this cancer is cured by the early intervention provided by the early detection, the death that would have otherwise occurred in the absence of screening would have been at some point in the future, typically years later. The better the screening test, the earlier the detection, the longer the time required before the evidence of the benefit becomes apparent. Thus, when assessing the screening benefit, screening must continue for sufficiently long to recognize the deaths which were prevented in the screened group as compared to the control group. Many studies have been done to evaluate mammography, yet we still are left in a state of confusion. This situation should not be repeated with screening for other cancers. Thus, we endorse these public hearings, but plead that before anything else, the fundamentals of research on screening for cancer be re-examined in open discussions. Some current examples of the now prevailing flawed approach are worth noting.

The National Cancer Institute (NCI) is about to embark on a new trial to evaluate spiral CT for lung cancer. This study will cost approximately $300 million (approximately the same amount the U.S. is planning to spend on rebuilding Afghanistan), will last 10 years, and its current design exhibits the same fundamental flaws that we have addressed. The ongoing PLCO (Prostate, Lung, Colon, Ovary) screening study currently underway, started in 1993 and projected to last until 2014, is the most expensive screening study ever performed by NCI until the recently contemplated spiral CT study. The PLCO costs approximately $150 million. It similarly ignores the fundamental principles we addressed. We therefore expect both of these studies to yield misleading results. In addition, these studies take so many years to complete that the screening they seek to evaluate may well be obsolete by the time the study is completed. For example, the lung component of the PLCO will evaluate the chest x-ray screening for lung cancer. In 1993 this may have been a reasonable consideration; by 1999, it was clear that spiral CT was far superior in detecting early lung cancer, and by 2014, even spiral CT likely will be outdated.

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[1] .abMiettinen OS, Henschke CI, Pasmantier MW, Smith JP, Libby DM, Yankelevitz DF. Mammographic screening: no reliable supporting evidence? Lancet 2002;358:404–06.

[2] .abMiettinen OS, Henschke CI, Pasmantier MW, Smith JP, Libby DM, Yankelevitz DF. Mammographic screening: no reliable supporting evidence? BM__1__www.theLancet.com.

[3] .abLetter to the editor. Lancet 2002, Feb 23. In press.

UPMC HEALTH SYSTEM,
PITTSBURGH, PA 15213–3180,
February 21, 2002.

Hon. ARLEN SPECTER,
U.S. Senate,
Washington, D.C. 20510.

DEAR SENATOR SPECTER: I am the Director of the Breast Program at the Magee-Womens Hospital/University of Pittsburgh Cancer Institute and the protocol chairman for the National Surgical Adjuvant Breast and Bowel Project STAR trial, the Study of Tamoxifen and Raloxifene that is funded by the National Cancer Institute. I understand that on February 28 you will be participating in a Labor, Health and Human Services and Education Appropriations Subcommittee and the Health, Education, Labor and Pensions Public Health Subcommittee joint hearing on mammography. As you prepare for this hearing, I wanted to bring to your attention another important weapon in our battle against breast cancer—breast cancer risk assessment.

While the debate over mammography is critically important, the statistics show that mammography alone is not enough. In addition to mammography and other tools for early detection, attention also needs to be focused on prediction and prevention—identifying those women who are at highest risk for breast cancer, and intervening to prevent them from developing breast cancer in the first place. Fortunately, women at high-risk now have several ways to reduce their risk and help prevent breast cancer. However, these options all involve difficult risk/benefit decisions, which heightens the importance of better predicting which women are most likely to benefit from early, preventative intervention.

One approach to refining our predictive abilities is to move risk assessment from statistics to science. Along with evaluating a woman's family history, age and other general risk factors, we now have biologically-based risk assessment tools to consider. For example, ductal lavage is a procedure in which the cells lining the milk ducts are collected and analyzed under a microscope to determine whether they are abnormal. Published studies demonstrate that high-risk women with atypical milk duct cells have a significantly increased, near-term risk of developing breast cancer. Using such individualized risk information, we can identify women at very high risk for breast cancer and better target our ability to offer them risk reduction options.

Because of my commitment to encouraging the routine practice of risk assessment among breast care specialists, I am currently serving as the chair of the Risk Assessment Working Group (RAWG), which consists of 13 leading breast specialists. On February 27, 2002, members of the RAWG will participate in the first risk assessment symposium of its kind at the 19th Annual Miami Breast Cancer Conference. At the conference, we will be presenting a consensus Risk Management Strategy, which will help guide breast specialists in the practice of risk assessment and the management of high-risk women. I have attached copies of two posters on breast cancer risk assessment and ductal lavage that will be presented at the Miami conference. Following the conference, the RAWG plans to broadly distribute the guidelines to the breast health community and pursue publication in a peer-reviewed journal.

As more prevention options become available for women at high risk of breast cancer, individualized risk assessment becomes increasingly important. I would like to stress, however, that neither risk assessment nor ductal lavage are substitutes for breast cancer screening. Rather, they are intended to serve as adjuncts to mammography and breast physical examinations. Early detection and preventative measures are both critical to our fight against breast cancer.

I hope that you will submit my letter to the record, so that you can share this important information about breast cancer risk assessment with your colleagues. Please feel free to call me at (412) 641–6500 if you have any questions or if I may be of further assistance to you or your staff. Thank you for your leadership on this and other important women's health issues.

Sincerely yours,

VICTOR G. VOGEL, MD, MHS, FACP,
Professor of Medicine and Epidemiology,
Director, Magee/UPCI Breast Program.

PREPARED STATEMENT OF THE AGENCY FOR HEALTHCARE RESEARCH AND QUALITY

The Agency for Healthcare Research and Quality (AHRQ) respectfully submits the following testimony on the effectiveness of screening mammography for the record.

Today's hearing is very timely in light of the recommendation from the U.S. Preventive Services Task Force (USPSTF) released last week on February 21, 2002, by HHS Secretary Tommy G. Thompson. The USPSTF is a leading independent panel of private-sector experts in prevention and primary care sponsored by AHRQ that conducts rigorous, impartial assessments of scientific evidence for a broad range of preventive services. In its new recommendation, the USPSTF endorsed screening mammography every 1–2 years for women ages 40 and over.

AHRQ's mission is to support research designed to improve the outcomes and quality of health care, reduce its costs, address patient safety and medical errors, and broaden access to effective services. The research sponsored, conducted, and disseminated by AHRQ provides information that helps people make better decisions about health care.

With this mission, AHRQ-funded research activities provide meaningful, evidence-based information on screening mammography to women and their clinicians. The Agency does this in three ways: first, supporting research that informs the quality of mammography and interpretation of mammograms; second, supporting a review of the up-to-date evidence on mammography screening by the U.S. Preventive Services Task Force (USPSTF); and third, developing evidence-based materials for patients and clinicians.

QUALITY MAMMOGRAMS

Screening mammography is an important tool for reducing deaths from breast cancer in women 40 and older. However, it is not a perfect tool. Because it is not as specific a test as it could be, false positives can occur which often require repeat screening and/or biopsies. This can cause significant anxiety among patients and their families, as well as unnecessary health care expenditures. In addition, problems with mammogram interpretation and communication of results to patients can result in cancers that are missed and treatment that is delayed.

As a result, the effectiveness and usefulness of mammography have been the subject of controversy for many years. AHRQ, along with other agencies of the Department of Health and Human Services, have worked to build the foundation of evidence for the effectiveness of mammography and to ensure that patients have access to high quality screening.

One of AHRQ's earliest activities in this area was the development of a clinical practice guideline on how to identify the elements of high quality mammography screening.

The guideline, developed in 1994 by an independent panel sponsored by AHRQ's predecessor, the Agency for Health Care Policy and Research, was entitled *Quality Determinants of Mammography*. The multidisciplinary panel that developed the guideline comprised radiologists, radiologic technologists, medical physicists, family practice physicians, a nurse, an obstetrician-gynecologist, a surgeon, a pathologist, an internist/oncologist, and consumer representatives. Many of these panel members also served on the original Food and Drug Administration (FDA) National Mammography Quality Assurance Advisory Committee.

The guideline provided information to clinicians on providing high quality mammography services and also gave patients information on how to determine the quality of the mammography services they received.

It is important to note that science and research are continually moving forward, and that medical practice must keep pace. In 2001, AHRQ reviewed the guidelines it had developed in the 1990s to determine which were still scientifically valid. Among those found to be out of date was the *Quality Determinants of Mammography*, a guideline that was published in 1994 and is therefore 8 years old.

Given the restructuring of AHRQ's guideline development activities in 1996, the evidence base for the guideline has not been updated since its initial release. A recent study sponsored by AHRQ has shown that the lifetime of a guideline is variable, but, generally, guidelines should be reviewed every 3 years

AHRQ now makes evidence-based guidelines available through the National Guideline Clearinghouse™ (NGC), an Internet-based compendium of more than 1,000 evidence-based clinical practice guidelines found at http://www.guideline.gov. At this time, the site contains 76 guidelines related to breast cancer and 23 related to mammography. AHRQ sponsors the NGC in partnership with the American Medical Association and the American Association of Health Plans. The NGC Web site provides the most current recommendations on screening mammography from leading guideline developers in the United States and around the world.

The NGC is an internationally recognized source of high-quality, evidence-based clinical information. Currently, NGC has approximately 55,000 user sessions and 950,000 hits a week. Guideline developers are contacted yearly to verify that their

guidelines are considered current. After 5 years, if the developer has not reviewed its guideline, it is withdrawn from the site.

RESEARCH ON MAMMOGRAPHY

AHRQ sponsors health services research that helps to inform the delivery and quality of health care services. The Agency has supported a number of important studies on the quality of mammography, its interpretation, and access to screening.

A study by Craig Beam, Ph.D., of the Medical College of Virginia, found that U.S. radiologists looking at the same mammogram are likely to interpret it quite differently. In their study sample, Dr. Beam and his colleagues found that some radiologists referred 100 percent of women with cancer for biopsy, while others referred only 47 percent. Inaccuracy in mammogram interpretation may mean that breast cancer goes undetected or is detected at a later stage, when it is more difficult to treat successfully.

Another AHRQ study, co-funded with the National Institutes of Health, is attempting to identify reasons for variability in the interpretation of mammograms. The study, led by Joann Elmore, M.D., at the University of Washington, is a unique collaboration among three geographically distinct breast cancer surveillance programs in the states of Washington, New Hampshire, and Colorado. This collaboration will permit the collection of breast cancer outcome and interpretive data on more than 500,000 mammograms from 91 facilities and 279 radiologists.

Dr. Elmore's study is especially timely because it takes place in the community setting where the majority of mammograms occur. Although mammography facilities are subject to rigorous accreditation standards regulated by the FDA, requirements do not include an evaluation of radiologists' accuracy levels in mammography or address the issue of variability in interpretation. Identifying the causes of variability of interpretation will be extremely important in enhancing the quality of screening mammography.

The Agency also is supporting research to understand barriers to breast cancer screening and improve access. For example, a study funded by AHRQ found that negative attitudes about mammography might play a role in the disproportionate number of breast cancer deaths among African American women compared with white women. Knowledge of screening recommendations and access to free mammograms were not enough to get some low-income black women to keep their mammography appointments. Most of the women who skipped their appointments said they were embarrassed or believed that a mammogram was unnecessary if they didn't have any symptoms.

Another study funded by AHRQ found that a major reason women cite for not undergoing breast and cervical cancer screening is that their physicians never recommend it. Older women, in particular, are less likely to be screened. This may be due in part to conflicting professional recommendations for screening older women, the many competing causes of mortality as women age, and possible negative attitudes about screening held by doctors and their older female patients.

An important element of AHRQ's research agenda is helping to ensure that the research it sponsors is translated into improved clinical practice. The first step in this translation is the publication of these findings in the professional literature. The Agency also works with professional and patient groups to disseminate the findings to those who can put them to work in routine medical practice.

NEW USPSTF MAMMOGRAPHY RECOMMENDATION

The debate over the usefulness of mammography has recently intensified. Much of this debate has focused on the critiques of the scientific literature on mammography screening by Olsen and Gotzche of the Nordic Cochrane Center in Copenhagen.

Over the last two years, the USPSTF has been reviewing the same scientific literature. The findings from this review were the foundation of the mammography recommendations released by Secretary Thompson on February 21.

Acknowledging that the scientific evidence is not perfect, but not as flawed as others have claimed, the USPSTF recommends screening mammography every 1 to 2 years for women age 40 and older. Evidence of benefit and reduced mortality is strongest for women aged 50–69, the age group generally included in screening trials.

The evidence was unclear on when women should have their first mammogram and how frequently they should be screened, so the Task Force recommends that women should discuss their personal preferences and the harms and benefits of mammography with their clinicians to determine when to start routine screening mammography and the optimal interval for screening.

AHRQ is working to get the new USPSTF recommendation translated into improved clinical practice and into information that will help reduce confusion and anxiety among patients.

As a start, AHRQ has made the new recommendation on mammography available on our Web site at http://www.ahrq.gov/clinic/3rduspstf/breastcancer/index.html. Also available are a fact sheet for clinicians and information for patients.

AHRQ also will use the Put Prevention Into Practice (PPIP) program to help get this information out to preventive services providers and patients around the country. PPIP, an AHRQ program, is designed to increase the appropriate use of clinical preventive services, such as screening tests, immunizations, and counseling, which are based on USPSTF recommendations.

CONCLUSION

AHRQ has a tradition of supporting and conducting evidence-based research and translating that research into improved clinical practice. The Agency also has led the way in providing evidence-based information for health care decision making for mammography, other important screening tools, and other clinical issues.

As HHS Secretary Tommy G. Thompson said on February 21, screening mammography can save lives. But this test is not perfect, and we need more research to improve the mammography and the interpretation of results. We also must ensure that women have the information they need to make decisions about their own health. Finally, it is particularly important that we continue periodic evaluations of the available scientific literature to ensure that medical practice and patient decision making are based on an up-to-date foundation of evidence.

Thank you very much for the opportunity to comment on this important issue, and we look forward to any questions that you may have.

PREPARED STATEMENT OF THE FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTRODUCTION

Madam Chairwoman, Mr. Chairman, members of the Committees, thank you forgiving the Food and Drug Administration (FDA or the Agency) this opportunity to present this statement for the record regarding Mammography Quality Standards Act (MQSA) of 1992.

BACKGROUND

The MQSA of 1992 was enacted in response to serious concerns about the quality of mammography. This procedure is an aid in combating the mortality associated with the growing incidence of breast cancer. In spite of the current controversy about the studies showing the benefits of mammography screening and in the absence of consensus about the scientific issues, the Department of Health and Human Services (HHS) and FDA support the conclusion reached by the U.S. Preventive Services Task Force. High quality mammography continues to be the best available tool for the early detection of breast cancer and MQSA provides our best assurance of that quality.

Mammography can reveal cancerous lesions up to 2 years before a woman or her doctor can feel a lump, and is a significant contributor to the current 5-year survival rate of 86 percent. Mammography represents life-saving ammunition in the war on breast cancer which is the most common non-skin cancer and, after lung cancer, the second leading cause of cancer deaths among women.

To achieve these benefits, all elements of the mammography system must be of high quality. Mammography is a highly challenging radiographic examination of the breast. The equipment must be capable of producing quality images and be maintained and operated by qualified individuals. Physicians who interpret these images must also be highly skilled. If the quality of mammography is poor, an incipient cancerous lesion may be missed. False negative diagnoses can delay early treatment and result in avoidable deaths. Poor quality mammography can also lead to false positive diagnoses, in which normal tissue is judged to be abnormal, resulting in needless anxiety for patients, costly additional testing, and unnecessary biopsies.

In the mid-1980s, indications of problems with the quality of mammography began to appear. Significant evidence came from a 1985 study known as the Nationwide Evaluation of X-ray Trends (NEXT), which was conducted by State radiation control agencies in cooperation with the FDA. Based on a survey of a representative national sample of mammography facilities, this study found that the image quality produced in perhaps as many as one-third of the facilities was less than desirable.

The findings from the NEXT study catalyzed efforts by the American College of Radiology (ACR), a private, non-profit association of radiologists, to create a voluntary mammography accreditation program. Begun in 1987, this program included an evaluation of the quality of clinical mammograms provided by facilities seeking accreditation. Although it is reasonable to surmise that facilities participating in this voluntary program were among the better facilities, ACR found that approximately 30 percent of the applicants failed on their first attempt to achieve accreditation.

Other evidence came from a 1990 General Accounting Office (GAO) study that reported that many mammography providers lacked adequate quality assurance programs. In 1992, hearings held by the Senate Committee on Labor and Human Resources revealed a wide range of problems with mammography services in the United States. These problems included poor quality equipment, lack of quality assurance procedures, poorly trained facility personnel, and inconsistent governmental oversight. At the same time, several States instituted programs to ensure that their residents were being provided with high quality mammography.

Despite these efforts, no national standards for providing safe, reliable, and accurate mammography were in place for the over 25 million American women who undergo the procedure annually. To rectify this situation, Congress enacted the MQSA on October 27, 1992, to ensure uniform high standards for mammography facilities, their equipment and personnel, and the quality of their mammograms. This law required all mammography facilities be certified by the Federal government after October 1, 1994, except for those facilities operated by the Department of Veterans Affairs (DVA). A separate law mandating a similar program governs DVA facilities. Responsibility for implementing MQSA was delegated to FDA by the Secretary of HHS on June 2, 1993.

IMPLEMENTATION

Faced with the task of certifying approximately 10,000 mammography facilities in less than 2 years, FDA published interim regulations in December 1993, which became effective in February 1994. As a prerequisite to certification, facilities had to be accredited by an FDA-approved accreditation body, the first of which was ACR approved in March 1994. Subsequently, four States, Arkansas, California, Iowa, and Texas, achieved approval as accreditation bodies.

FDA successfully met its demanding statutory deadline of certifying all qualified mammography facilities by October 1, 1994. While the interim regulations were in effect, FDA developed more exacting regulations, and the MQSA final regulations were published in October 1997, and became effective on April 28, 1999.

Another hurdle was obtaining qualified personnel to annually inspect the nearly 10,000 mammography facilities. FDA developed special training courses for both FDA and State personnel, and trained and eventually deployed 250 inspectors to conduct annual facility inspections. These inspections began in January 1995. During this time, FDA implemented the Mammography Program Reporting and Information System (MPRIS), a dynamic, interactive data system, designed to tie the pieces of the program together. MPRIS provides and tracks information on accreditation and certification of facilities, facility inspections, inspection violations, and the billing of inspection fees. MPRIS also allows inspectors to use uniform software on a laptop computer while in the field, and to directly upload inspection results to the headquarters database, thus streamlining the inspection process and facilitating data analysis. In addition, the database transmits daily certification information to the Centers for Medicare and Medicaid Services, thereby facilitating efficient facility reimbursement, and allowing consumers to search for certified mammography facilities by zip code.

In order to educate facilities about the regulations and how to comply with them, FDA published a quarterly newsletter that was mailed to facilities and other interested parties. The printed newsletter eventually evolved into web page updates and articles on matters of importance to facilities. A mammography website (www.fda.gov/cdrh/mammography) was created, a principal component of which is an extensive policy guidance help system.

DEVELOPING PROGRAMS

MQSA allowed States that desired to do so to take on the role of a certifying body, with FDA approval and oversight. In August 1998, the States as Certifiers (SAC) pilot was initiated with two participating States. During this time, regulations were promulgated and published in February 2002. These regulations will become effective in May 2002. Several additional States have expressed interest in the SAC program, and FDA expects this program to expand.

PROGRAM COMPLIANCE

Compliance with the final regulations continues to improve. Currently, 60 percent of all certified facilities are in total compliance with MQSA. The Government Performance Results Act goal for most serious violations is less than 3 percent. At this time, only 2.4 percent of facilities are exceeding the goal. This exemplary compliance rate can in large part be attributed to the program's extensive outreach efforts, including facility education by inspectors, and the availability, both on the web and in hard copy, of all guidance and policy determinations.

PROGRAM ASSESSMENT

In 1995 and 1997, the GAO evaluated aspects of the MQSA program. These favorable reports found that the initial impact of the new Federal law had been positive, while the report that looked at mammography inspections found that facility compliance was continuing to improve.

FDA performed facility satisfaction surveys under both the interim and the final regulations to review how facilities perceive the inspection process and the program's educational and guidance materials. Based on these results, it is clear that the vast majority of facilities see the MQSA inspection program as beneficial, particularly the educational approach of the inspectors that helps facilities identify areas for improvement.

FDA continues to fine-tune the MQSA program to better serve the mammography community, leading to higher quality care for the women of America.

REAUTHORIZATION

MQSA was reauthorized in October 1998, with the enactment of the Mammography Quality Standards Reauthorization Act (MQSRA). MQSRA mandated that patients be directly notified of their mammogram results, in lay language. The regulations were amended to reflect this mandate. Facilities quickly complied, and currently, there are almost no inspection violations in this area. In addition, a study published in the February 2002 American Journal of Roentgenology surveyed patients before and after this requirement went into effect. The study found that there was a substantial increase in the number of patients who reported timely receipt of mammography results, and a substantial decrease in patients dissatisfied with their results, all without an appreciable increase in patient anxiety.

Congress also requested FDA to determine if best-performing mammography facilities can maintain their high standards without the scrutiny of annual inspections. With input from the conference of Radiation Control Program Directors, FDA designed a demonstration program whereby citation-free facilities from States who agreed to participate were randomly assigned to study and control groups. Those study group participants would begin skipping their next annual inspection, beginning in May 2002. After data collection is completed in the summer of 2004, data analysis will be performed and a report will be presented to Congress in mid-2005.

Reauthorization of the appropriations authority for the Certification of Mammography Facilities would allow the Federal government to continue to ensure that all mammography facilities provide high quality mammograms as an aid in the early detection of breast cancer.

CONCLUSION

FDA has successfully implemented the MQSA program and has improved the overall quality of mammography by constructing and implementing an effective program that holds all providers of mammography to the same standard. The MQSA program in an invaluable tool in promoting public health and merits reauthorization.

ONCOLOGY NURSING SOCIETY,
PITTSBURG, PA 15220–2749,
February 26, 2002.

Hon. EDWARD M. KENNEDY,
U.S. Senate,
Washington, D.C. 20510.

Hon. JUDD GREGG,
U.S. Senate,
Washington, D.C. 20510.

DEAR CHAIRMAN KENNEDY AND RANKING MEMBER GREGG: On behalf of the more than 29,000 nurses and other health professionals of the Oncology Nursing Society (ONS), we are writing to inform you of our position on mammography screening for

breast cancer and our concern about the impact of the recent report published in the British medical journal, *The Lancet,* which concluded that no scientific support exists for breast cancer screening with mammography. For your reference, we have attached the ONS position paper on mammography, a public awareness ad supported by ONS on this issue, and a letter to the editor of the New York Times signed by ONS and numerous other cancer related organizations voicing concern regarding the impact that *The Lancet* article could have on public health.

ONS, the largest professional oncology group in the United States, exists to promote excellence in oncology nursing, teaching, research, administration; education in the field of oncology, and the provision of quality care to individuals affected by cancer. As part of our mission, we stand ready to work with policymakers at the local, state, and Federal levels to advance policies that will reduce and prevent suffering from cancer, including access to cancer detection tools that locate cancer early when both the chances of survival and treatment outcomes are highest.

Breast cancer is the leading cancer and the second leading cause of death from cancer in women in the United States. Additionally, for women between the ages of 15 and 54, breast cancer is the leading cause of cancer-related death. Early detection of cancer, including routine mammography screening, has been shown to decrease a woman's chance of dying from breast cancer. It is the position of ONS that:

- every woman has the right to make an informed decision about her need for mammography screening;
- baseline mammography must occur for all women by age 40;
- screening mammography must be provided every year for all women ages 40 and older who are at average risk for the development of breast cancer;
- women at higher than average risk due to genetic or lifestyle factors must have access to expert medical guidance to define the appropriate age to begin and the frequency of mammography screening; and
- mammography must be included as part of routine follow-up care to detect the recurrence in women who have been treated for breast cancer.

Although research continues to develop improved methods for early detection, at the present time, high-quality mammography coupled with adequate clinical breast exams remain the most effective means of early detection. ONS, like many in the cancer community, are concerned about the impact that *The Lancet* journal article will have on women's decision to be screened for breast cancer, that lives may be lost if women ultimately are dissuaded from having regular mammograms. Although the existing studies of mammography screening do have known limitations and even some flaws in design, ONS does not believe that any compelling evidence exists at this time that would warrant dropping the recommendation of mammography as a screening tool for the early detection of breast cancer.

ONS maintains that public and private health insurance plans, must continue to provide coverage of—and access to—age and risk appropriate mammograpy screening for all women who seek it. ONS will continue to monitor the research and await review by experts of these studies, as well as additional research in this area. To that end, we are hopeful that much of the doubt recently cast upon mammography will dissipate in light of last week's U.S. Preventive Services Task Force (USPSTF) recommendation calling for screening mammography, with or without clinical breast examination, every one to two years for women ages 40 and over. In addition, last week both the National Cancer Institute (NCI) and the U.S. Department of Health and Human Services (HHS) reaffirmed their support of mammography; these statements further validate the value of this important cancer screening tool.

ONS stands by its position that every woman has the right to make an informed decision about her need for mammography screening for the early detection of breast cancer. Should you have any questions or need more information regarding ONS' position on this important public health matter, please do not hesitate to contact us at (412/921–7373) or our Washington Health Policy Associate, Ilisa Halpern (202/857–8968).

Sincerely,

PAULA TRAHAN RIEGER, RN, MSN, AOCN, CS, FAAN,
President.

PEARL MOORE, RN, MN, FAAN,
Chief Executive Officer.

PREPARED STATEMENT OF SAMUEL B. WALLACE

MAMMOGRAMS DETECT CANCER SUGGESTED NEW SYSTEMIC & LOCAL ANTIBIOTIC THERAPY THAT IS EFFECTIVE AGAINST MICRO BREAST CANCER CELLS, THUS THERAPY WAS DEVELOPED BY SAMUEL B. WALLACE, AUTHOR OF THIS RESEARCH PAPER

Subject: Whether Mammograms save Breast Cancer Patient's lives? Distinguishing Cancer Detection and Cancer Therapy with emphasis on more precise Systemic and Local Therapy as I suggested in Subcommittee Hearings in 1979 in written testimony before Select Subcommittee on Cancer Research titled: "Frontiers in Cancer Research." Subcommittee on Health, House and Senate Committees Chaired by Senator Weicker and Chairman Natcher, May 1985 published in 1985 and 1986. Which were confirmed by the Five Year Clinical Trials of Dr. Bonadonna, an NIH Grantee as he reported in the Journal: CANCER RESEARCH, May 1988. The main point of the debate on this issue suggests to me that perhaps there should be two categories of Doctors—a Doctor of Medicine and an Doctor of Surgery. One would deal with the application of curative medicines and the other would deal with Surgical Procedures which also culminate in the saving of human lives. Thus far all in the field of Breast Cancer with the exception of Doctor Bonadonna place the emphasis on drastic or minimal surgery with the area of Cancer Metastasis all but forgotten or ignored. Thus the real issue seems to be justifying surgery rather than that of treating and cuing Micro Cancer.

MAMMOGRAMS ONLY DETECT CANCER—IT IS NOT CLAIMED THEY CURE IT

Proponents on both sides of the raging Debate all agree on one point and that is that Mammograms do detect Cancer better than any other medical device known to Medical Science. However, because the use of mammograms with concurrent Breast Cancer therapy of Surgery, radiation and chemotherapy does not produce a positive long lasting cure, the critics of the results of Cancer therapy suggest that perhaps mammograms should not be used because some forms of Cancer Therapy are not very effective. Thus, in Breast Cancer therapy for small Breast Cancer Tumors "the size of pencil points there is concern that Surgery followed by Radiation has produced only a very small increase in survival. While the benefits of early detection are unquestioned for larger sized tumors. It should be noted that the manufacturers of the Mammogram do not claim that their machine has any therapeutic value but only that it is capable of detecting even small cancer cells at close to the time of the breast cancer cells inception. Therefore the real issue is not about the Mammograms that successfully detect even the smallest cancer cells in a very early stage but the therapy that sometimes fails in curing the Breast Cancer.

The American Cancer Society in its 2nd Edition of Oncology 1996, Ch.12: Breast Cancer indicated at P. 296:

"Routine mammography (combined with good Breast Cancer Therapy) will reduce Breast Cancer Morality by at least 30%. No strategy has been shown to have a larger impact on breast Cancer Mortality and use of such techniques has not been as well established for any other disease:Day, N.E.: "Screening for Breast Cancer. British Medical Bulletin, 1991; 47: 400–415."

Time Magazine, February 18, 2002 in its article: Rethinking Breast Cancer P 50:

"Doctors know what to do when they find tumors the size of marbles—. . . surgery, radiation and chemotheopy. But what to do when the cancers are as (small) as pencil points? Do you treat them as massive tumors or do you leave them alone? 30 years ago these small tumors called "DCIS" were diagnosed in 6% of time. . . . Today it is approximately 20% largely because of detection . . ."

The questions asked by the writers of the February article on "Rethinking Breast Cancer" (Therapy) "do you treat small breast cancer tumors as you would massive tumors or do you leave them alone?" is not a difficult one to answer since it is obvious from their article that medicine has met with some success in treating large breast cancers, but not small ones. The obvious answer to that question is to find a *new way to cure small breast tumors.*

Small breast cancer tumors the size of pencil points generally begin in either the bone marrow and travel to the breast or begin in the small capillaries of the breasts that lead to the breast ducts. This poses a special problem for the breast Cancer Therapist. In the ordinary initial immune responses, the tissue macrophage and the smaller neutrophils in breast tissue called "histiocytes of breast tissue increase and immediately injest invading Bacteria and Viruses. Next, the neutrophils in the blood increase as a result of a combination of chemical released by the infected tissue. In acute infection, those Immune cells can act almost instantly. But in the case of precursor Cancer cells their action is much slower. There is a combination of chemical substance released from the infected tissue including neutrophils which carry natu-

ral antibiotics, toxicins and immune hormones as well as therapeutic antibiotics which are called "leucosytosis" inducing factor which diffuse from the precursor or tumor cells into the blood where it is transported into the Bone Marrow. This action also causes the circulating neutrophils carrying natural and man-made antibiotics to move to the targeted cancer infected tissue.

However, in the case of the small capillaries[1] which lead to the breast cancer ducts there are a number of barriers to the small capillaries which prevent the Antibiotics from being absorbed by the tissue and its capillaries which lead to the blood system. In addition, the small tumors because of their size and density of their tissue can not absorb the Antibiotic when it is applied directly.

Therefore, in order to treat small sized tumors or their precursors they must be treated by one of two routes by means of medication applied to the nose that enters 85% of the patient's blood supply and is truly systemic in that it treats the patient's entire blood system and entire glandular system. For most illnesses this is good therapy which produces the immediate activation of complement the beginning of the curative process which I indicated in Testimony Samuel B. Wallace, before Subcommittee of Health, House Ways and Means Committee Dec. 4th, 1975 was true for a wide variety of Viral, Bacterial and Protozoa Illnesses.

When there are barriers to Antibiotic therapy, such as the Blood Brain Barrier, as for example in the case of encephalitis of the brain, a slightly different approach is necessary for the best results. And this is true not only for Breast Cancer but also for of all things Lung Cancer where ordinary large cell treatment has not worked for small cell lung carcinoma. In both, the Bone and Bone Marrow are it would seem a far better route of application of the Antibiotic such as Penicillin or Tetracycline. And that is because in both instances the bone marrow which has access to virtually all the immune cells also has immediate access to the small carcinoma or precursors of Breast Cancer or Lung Cancer through the skeletal system which directly links both the Breast Tissue and the Lung Tissue including the small capillaries in each case! And this also has to do with the particular "Defensins" or natural antibiotic which are specific in neutrophils targeted for specific areas and tissues of the body as explained in a splendid article in the American Society of Microbiology News 5:56,315–320, 1990, the authors Robert Lehrer, Tomas Ganz and Michael Selsted, Professors of Medicine, (UCLA) explain @ 315: *"Researchers have found a variety of Peptides (naturally occurring Antibiotics in man) with Antibacterial, antifungal, antiviral and cytotoxic Activities*" called "Defensins" or natural antibiotics.

"Defensins" are "natural peptide antibiotics from neutrophils" or natural antibiotics produced by the human body to fight bacterial and viral infections including cancer and leukemia" (asm) are a key to understanding: how the natural immune response overcomes cancer.

In the recent past most Medical Textists while acknowledging that the Innate Immune System which they describe as: Antigen to Macrophage Activation and Macrophage to Complement Activation which in turn stimulates the activities of other Macrophages such as Neutrophils in the Innate Immune Response and the activity of NK Killer Cells and T Cells which kill Viruses in the acquired or Indirect response. But the Medical Textist do not explain the positive role of the chemotaxis role of Antibiotics particularly in the Innate Immune Response by the direct application of Antibiotics to the Macrophage which leads to the instant activation of Blood Serum Complement whose effects I discussed in my 1975 Testimony demonstrating that the Alveolar Macrophage when Penicillin and an Immune Hormone were combined and applied as Nose Drops good therapeutic results were obtained that cut in half the time it normally takes to produce a lasting cure. This therapy normally used 10% of the Physician's Desk reference recommended curative dosage for Anti-

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[1] N.Y. Times Feb. 12, 2002 D5 shows nonspecific therapy adds Antibiotics to all B.M. targeted cells!

/Id. N.Y. Times Feb. 12, 2003 Sect. D5: Showing mechanism by which Immune and Blood Cells are targeted to their destination by means of their receptors which attach to a matching receptor at a specific location in the nearby blood vessel which is near a specific tissue type such as the skin, GRR, GGH, or GTV protein cells, or the LVS, protein cells of the skeletal muscle which has a similar target receptor, such as the rib cage bones to which the Breasts are attached which are also linked to the arteries and veins in the Bone Marrow. It is important to note that many of these Immune Cells are Bone Marrow Macrophage which immediately ingest the Antibiotic when an Antibiotic is Injected into the Bones. Thus, the macrophage become essentially Antibiotic Macrophage which carry quantities of Antibiotics to the Cancer Infected area of the Breasts. See also: *Nature Immunology* 3, 189, Feb. 2002 "How GD94–NR G2A Receptors regulate T4 Cell Immune Response by Moser . . .; *NATURE MAGAZINE*, Feb. 2002, "Reporting that they have identified five area receptor codes which the matching Bone Marrow Blood vessels.

biotics. And I indicated that my 1975 Congressional testimony applied to: Viral, Bacterial and Protozoa Illnesses.

While I indicated in my 1985 Testimony that such Alveolar Macrophage Antibiotic Activation of complement could be important for the enhancement and protection of the entire Immune system and in order to produce a more "Systemic" form of Cancer Therapy citing the important Research of Umtae Kim on Metastasis. And indeed, Tonagawa won the Nobel Prize by discussing T Cell Acquired Immunity without discussing the Macrophage and Innate Immunity and the chemotaxic role of the Antibiotics in either form of Immunity.

The UCLA Professors of Medicine do discuss this important point in their article in the American Society of Microbiology on the "DEFENSINS" or "NATURAL ANTIBIOTICS" produced by the human body in the activation of the Macrophage which results in their activating complement, the beginning of the curative process in both the specific and acquired Immune Response. They also mention on page 316 of the same article that the same natural antibiotics have a I effect on tumors that have targets cells in the skeletal system and target cells in Cancer infected tissue: (paraphrased)

Defensins are newly defined family of broad spectrum Antibiotics found in the leukocytes of humans and other mammals. . . . Human neutrophils contain four principal Defensins. The four principal Defensins usually account for about 80% of the Neutrophils total Defensin content. The Defensins contain 30 to 50% of the total protein in human neutrophil's . . . granule."

. . . Neutrophils are made by stem cells in the bone marrow.

"Neutrophils are (also) Macrophages in the circulating blood. They are (highly flexible cells that enter infected tissues in large numbers (with) . . . the help of chemotactic stimuli. (Such as the Antibiotics) It is estimated that the Neutrophil Defensins account for as much as 7% of the protein content of the Neutrophils, themselves which approximates the standard standard dosage of Antibiotics. The Defensin delivery system by means of the neutrophil is more sophisticated than any yet constructed by the pharmaceutical industry.

The Human Defensins HNP-I . . . exert nonspecific cytoxicity against various human tumor cells that, depends on active target cell metabolism as found in the skeletal systems or bones and in the tissue, glands, and blood vessels. For that reason and because the Neutrophil Defensins account for as much as 7% of the protein content of the neutrophils themselves which is approximately the standard daily dosage of (some) Antibiotics, the Neutrophils and other Macrophage produce an extraordinary impact on the Immune system, singularly where most viruses and Cancer, and Leukemia Precursors are normally thrown off. And therapeutically when man made Antibiotic and Synthetic Immune Hormones are applied to the Immune systems directly related to the specific and systemic Immune, blood, glandular and skeletal immune systems.

Because as consequence of the neutrophils relation to humans immune system and because of the enormous impact they can exert on all immune systems for which they are targeted Neutrophils can be characterized as Macrophage that carry Antibiotics (natural or man-made) as do all Macrophage to all the areas of infection and inflammation caused by Virus, Bacteria and Protozoa including those caused by Cancer, Leukemia and AIDS Infections which are more in that they are also Immune responses that have gone wrong which have produced severe genetic mutations which effect the structure of the Immune and Metabolic systems in varying degrees.

Injection of Antibiotics into the surface of the cranium is a Bone Marrow Immune System Therapy which is not only important to those suffering from brain damage caused by ordinary diseases but also those caused by tumors. And it is safer and more effective less invasive than any other form of therapy. Particularly, surgery or radiation which one must recall are both very invasive Immune suppressing procedures. And in the recommended Antibiotic Therapy, the Macrophage and Neutrophils play a key role searching for damaged or diseased brain tissue which when found they instantly repair.

For example, I found in Brazil that encephalitis of the brain could be cured by simply Injecting Tetracycline into the cranium. On the other hand, at John Hopkins Hospital, the standard treatment for encephalitis of the Brain is removal of the diseased brain tissue which may result in paralysis and in some cases total disfunction of the brain. Therefore, a simple procedure of Injecting an Antibiotic into the cranium is a safe and effective therapy for Encephalitis of the Brain which utilizes the extraordinary properties of the Neutrophil Macrophage Immune Cell systems which includes their ability to find diseased or damaged tissue and to apply both natural and man made Antibiotics to that tissue when they are stimulated by the

chemotaxic effects of the added Antibiotics to the appropriate Immune System affected by Disease or Infection.

The "chemotaxic" effects on proteins including Immune blood cells causing their movement particularly in conjunction with epinephrine and the production of the ATP Enzyme and the release of C Amp the energy used to fuel cellular interactions play a critical role in the Immune response and cause Immune cells such as the Neutrophils or Macrophage to move toward the areas of Infection including areas where tumors or even small micro tumor precursors reside. This process is best understood when the event is severe inflammation which is described by the Physiologist Guyton in "Human Physiology" 1982, P.48:

"The tissue macrophage are the first line of defense against infection during its first hour. Neutrophils move from the nearby Bone Marrow and the circulating blood to the area of inflammation within a few hours after the onset of the infection where they often increase four to five fold. Which is the result of a combination of chemical substances that are released from the inflamed tissues called leukosytosis inducing factor. This factor diffuses from the inflamed tissue into the blood and is carried into the bone marrow . . . causing the release of many leukocytes, . . . especially large numbers of Neutrophils that are almost immediately transferred from the bone marrow storage pool into the circulating blood or directly from the bone marrow by way of its blood vessels to nearby targeted tissue which is inflamed.

When there is no inflammation the same basic process though considerably slower is basically identical. And what is noteworthy is that not only antigen or disease can initiate this macrophage-Neutrophil activation of complement, but that man made Antibiotics applied to macrophage can do the same thing, particularly when they are injected into the Bone of patients infected with cancer or leukemia.

While the standard procedure of removal of diseased brain tissue may cause the patient to be completely paralyzed or in some cases no longer living. In addition the costs of such surgical procedures are enormous—costing at least twenty thousand dollars per operation while the extremely safe injection of the Antibiotic into the surface of the cranium costs pennies per injection of Antibiotics and leaves the patient fully functional. Thus, such diseases of the brain can be treated by the man-made Antibiotics applied to the surface of the cranium where the neutrophils bearing Natural Antibiotics or "Defensins" also reside and are activated by the addition of man made Antibiotics causing the sensitized Neutrophil Macrophage Cells to seek the diseased brain tissue and to treat it effectively by causing the Activation of Blood Serum Complement. And given the proclivity of the Neutrophils and other Macrophage to seek damaged and inflamed tissue when stimulated, the addition of Injected Antibiotic to the bone marrow of the cranium could lead to good treatments for wide variety of Brain Damage caused Neurological diseases such as Multiple Sclerosis, Parkinson's Disease, Autism and Epilepsy. Direct Injection into the surface of the cranium is recommended.

This then is further indication that Injecting Antibiotics into the Bone Marrow, also for Breast Cancer Patients and small cell Lung Cancer would be effective in light of the role the natural Defensin Antibiotics play in the Bone Marrow Immune system responses to diseases of the brain an excellent therapy which imitates the natural Immune activity of the Natural Antibiotic Defensins in the Neutrophil Macrophages own immune response. The anatomy of the Bone Marrow Rib cage which are linked to the Breast tissue by means of common arteries and veins as well as the linkage of the rib cage veins to the Breast Cancer Glands and Blood Vessels also suggests that such treatment would be actually enhancing the normal immune response of the Breasts to potential malignancies which are often defeated by the normal immune response in that area.

The fact that this form of therapy has been tested in over 50 Clinical trials against Cancer and Leukemia as reported on the Japanese Internet in 1999 as I suggested in 1985 is also a strong indication that Injection of Antibiotics into the Bone for Breast Cancer is a reasonable alternative to the Invasive and Mutilating Procedures of Radiation and Surgery. The Antibiotic therapies are not only very effective but are also very inexpensive and invariably would yield good results in treating micro sized Breast Cancer Cell and would prevent metastasis as does Dr. Bonadonna's Breast Cancer Clinical Trials show . . . Dr. Bonadonna does not suggest the mild inexpensive and effective Antibiotic Bone Marrow therapy, perhaps because of NIH Policy which favors the unsafe and largely ineffective Bone Marrow Transplant Program which it sponsors. Thus there are two paths through which the Bone Marrow enter the nearby Breast tissue: One route is the application of the Antibiotic nose drops that treats the entire blood and glandular system which pass through the Breasts. Another is by way of the Microphage-Antibiotic entry by Injection into the rib cage beneath the Breasts where arteries and veins go into the near-

by Breast Tissue where they link with target areas in the Breast tissue. Both forms of Breast Cancer therapy are examples of Innate Immune Therapy.

All three forms of Innate Macrophage Therapy also activate an Acquired Immune response which embraces Acquired Immunity with the additional benefits of sensitized T Cells activity which along with the Macrophage and the NK Killer Cells are capable of destroying the Breast Cancer Tumors and Leukemia Viruses. In addition, the sensitized T Cell Acquired Immunity provides long term Immunity against Breast Cancer. It is also important to note that the Bone Marrow Immune system like the Lungs is linked to the Glandular System as well as the Blood System.[2] Therefore combining the systemic therapy of Penicillin Nasal Decongestant Nose Drops and Injection of Antibiotics into the rib cage proximate to the Breasts should lead to a very high cure rate for most forms of Breast Cancer including particularly the incipient DCIS which infect the Breast Ducts.

ECONOMIC IMPACT OF THIS INNATE ANTIBIOTIC THERAPY FOR BREAST CANCER

Those Professors of medicine are to be praised not for discussing a "new discovery" in medicine, but for their courage, candor and honesty in discussing a fact known to science and the entire American and European Pharmaceutical Industry since the early 1970's when Dr. Hamao Umezawa, Md. And Professor of Medicine Tokyo University indicated in the *Japanese Journal of Antibiotics 1977: 30 (Supp.):138–63 in an extensive article titled: "Recent Advances in bioactive microbial secondary metabolites"* that he had discovered "secondary derivative antibiotics" made in the human body by a process of screening human blood. A simple process used now by the American and European Pharmaceutical Companies in which Human Blood, Animal and Fish Blood and even plants, animals, and earth are screened by simple centrifugal force, which separates the samples according to their molecular weights.

What makes this method for Discovery of new Antibiotics produced by man, animals, fish and plants important to mankind is that it is extremely simple and extremely inexpensive to do as compared to the elaborate and costly procedures for discovery of Antibiotics by means of Enzyme or Protease Inhibitors a process used by Dr. Hamao, Umezawa to discover hundreds of Antibiotics that cure Cancer and Leukemia such as Bleomycin a beta lactam (penicillin) compound discussed by the NIH's Dr. Chabner as Editor of Oncology: Goodman's and Gilman's Pharmacology 1996 Edition. And why was the article by Professor Lehrer et al. of UCLA based on a lecture he gave in Houston, Texas in 1989 so significant? Because the NIH to this very day in the year 2002 still claims that the Antibiotics are incapable of Curing Viruses from the simple Asthma Virus to HIV I and III Leukemia! Despite Goodman's Pharmacology 2nd Ed. on page 1388 it authors indicating they do. Which adds immensely to the cost of government and private health program's. The NIH in taking the unscientific policy position that the Antibiotics (natural or man-made) are not Antiviral Agents despite the American Cancer Society and generally AMA doctors success in curing virally caused Cancer using hundreds of Antibiotics also contradicts a medical text that it authored in 1955: *Goodman and Gilman's. "The Pharmacological Basis for Therapeutics"*, 2nd Edition which on page 1346–1347 indicated that the Antibiotic Penicillin combined with a Nasal Congestant Nose Drops was a Cure for Asthma. Which I confirmed in Congressional Testimony before the Subcommittee of Health of the House Ways and Means Committee, Dec. 4th, 1975 before then Congressman Rostenkowski of Illinois. The result of the NIH's nonsci-

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[2] Arthur Guyton's: *HUMAN PHYSIOLOGY AND MECHANISM OF DISEASE*, 3rd Edition 1982, p.56. . . ."The complement System . . . is composed of 9 Enzymes which are normally inactive but which can be activated by Antigen-Antibody reactions or (Macrophage to Complement reactions) . . . 4. Chemotaxis (of complement): "One or more of the complement products cause chemotaxis of the Neutrophils and Macrophages, thus enhancing the number of macrophage and neutrophils in the area of the infection. 5. . . Complement often attacks structure of Viruses neutralizing them.

P.46: . . . Properties of Neutrophils, Macrophages and Monocytes: . . . The Neutrophils, Macrophage and Monocytes that mainly destroy invading Viruses, Bacteria and other invading infections. The Neutrophils can destroy Viruses even in the circulating Blood. Macrophage are mature monocytes which also destroy viruses.

P.48: . . . Tissue Macrophage, . . . the Alveolar Macrophage of the Lungs, the microglia of the Brain immediately go to work against infections and are the First Line of defense against infections in the first hour which also respond to inflammation of tissue including the elevation of temperature." (The fact that a Nasal Decongestant containing epinephrine combined with the Antibiotic Penicillin (called aptly by the Japanese: Penicillin Diversum) can activate Complement and reduce fevers that are caused by virus or bacteria with seconds of the Application of the Nose Drops is of great medical significance as I indicated in Congressional Testimony Dec. 4, 1975.) Also in the initial Immune response many neutrophils go from the Bone into the Circulating Blood and from thence to the Infected Tissue carrying Defensin Antibiotics.

entific policy is that today people who are infected with the Asthma rhino virus are given Antiviral Asthma Agents that cost $5,000 to $10,000 per year until they finally succumb to Asthma virus infection. Which means in Government Programs the Federal Treasury looses Billions of dollars annually and many patient's die from Asthma and other viral illnesses that can not be cured by means of the NIH's Antiviral Agents which the NIH admits can not cure Viral Illnesses. The UCLA Professors medicine who in their 1990 article published in the ASM News had showed great courage showing that the human body produces natural antibiotics which cure viruses. A finding similar to my own as I had indicated based on my own empirical tests in Brazil from 1969 to 1974 that man-made Antibiotics cure a wide range of ordinary viral illnesses in a shorter period of time using ten percent of the PDR required curative dosage which I reported in my Congressional Testimony Dec. 4th, 1975. I informed members of Congress and former Secretary of HH&S Ms. Shalala that the Antibiotics cure HIV I and III Leukemia in the 1980's and 1990's. I participated in two FDA Conferences of Physicians sponsored by David Kessler where I discussed the same Issues. And at an informal gathering on Capitol Hill I briefly discussed the Antibiotics effectiveness at an AIDS Conference in which Dr. Fauci was one of the officials present on stage.

THE ECONOMIC IMPACT OF USING SAFE AND EFFECTIVE ANTIBIOTIC THERAPIES

The economic impact to this approach to medicine is very positive. For Puerto Rico as was pointed out by a Ms. Pagan in *Health Care and Financing Review*/Summer 1983, Vol. 4, No.4: the Puerto Rican Public Health System is at least 95% more efficient than the stateside American Public Health System, (which I have personally experienced while teaching in Puerto Rico) because the Public Health System of Puerto Rico relies more heavily on Antibiotics.

This is similar to the experience of the Japanese, Canadians and Hawaiian Health Systems all of whom rely more heavily on Antibiotic Therapy which produce far more cures. Which leads me to believe that some thought should be given to directing medical studies to Medicines, only. Thus, a doctor could be a doctor of medicine or a doctor of Surgery. The Medical doctor's Education would emphasize the roll of medicines and the human immune response through the studies of Pharmacy and Immunology and Biochemistry. And would be for six years rather than twelve. Thereby reducing the cost of Medical School by 50%. While surgery would emphasize gross anatomy and physiology, surgical procedures and why it is important to treat surgical wounds immediately after surgery with antibiotics as well as always finding new techniques for the delivery of Antibiotics for the delivery of Antibiotics to various areas of the human body even when those techniques sometimes required minor surgery. This division of Medicine into two separate categories: "Doctor of Medicine and Doctor Of Surgery" would be more appropriate—so that more medicine oriented procedures could be developed through Biochemistry, Pharmacology, Immunology and Physiology for Doctors of Medicine. Which would lower the costs of both who would be required to study the essentials of the Medical Science and Pharmacy. At the same time those training to be Surgeons would also have their curriculum shortened because they would not have to be quite so knowledgeable about Medicine. Both disciplines would place emphasis on finding the cure of illnesses rather than on long esoteric studies attempting always to find the cause of disease. And those studying Medical Science only would have fully interrelated Science courses that related their individual science courses to Medicine as a whole.

BEST INNATE "SYSTEMIC" CURATIVE THERAPY: ANTIBIOTIC DECONGESTANT NOSE DROPS

Ordinarily Injection of Antibiotics into the veins is considered sound "Systemic" Therapy. However, that form of Therapy treats the Immune System through Veinular Blood System neglecting the glandular system. It is significant, that Penicillin and Tetracycline Nasal Decongestant Nose Drops That I Rediscovered in Brazil in 1969 or 1970 whose effectiveness against Bacteria, Viruses etc. I reported in Testimony before the Subcommittee on Health of the House Ways and Means Committee Dec. 4, 1975 is probably the best Curative Therapy for HIV I and III because I proved that a very wide range of illnesses were cured in a far shorter period of time with ten percent of the PDR's recommended Curative Dosage as well as Goodman and Gilman's: The Pharmacological Basis of Therapeutics 1955–1958 Edition, P. 1346–47: "A Cure for Asthma: Penicillin and a Nasal Decongestant" as well as the Spanish Pharmacopoeia 1993 edition: "Nasal Decongestant Cures Respiratory Illnesses" indicates that such Therapy is the most effective "systemic" therapy for a wide range of Viral and Bacterial Illnesses. And should always be used in "Systemic" Therapy for all forms of Cancer and Leukemia. That application of Antibiotic Nose Drops is the best form of "Systemic" Therapy is also shown because:

(1) Application of the Antibiotic Nose Drops treats the entire Glandular system to which the Lungs are attached as well as the entire Blood system through which Blood passes through the Lungs through the heart. That form of treatment is truly "Systemic" in that it enters into all the systems of the Immune System.
(2) This is also proven by empirical evidence because as is indicated in the Spanish Pharmacopoeia 1993: "A Nasal Decongestant Nose Drops combined with Penicillin Cures Respiratory Infections."
(3) My Empirical tests in Brazil indicate that it cures a wide range of Bacterial and Viral Illnesses. And that it reduces severe bacterial and viral fevers soon after it is applied as Nose Drops. This same form of therapy generally uses only ten percent of the normal initial curative dosage as recommended by the PDR which is 500 mg Penicillin for the treatment of Pneumonia, for example. The Nose Drops produce the same effect with only 50 mg of Penicillin, which begins the curative process immediately activating Blood Serum Complement, which is proved by its ability to reduce fevers as soon as it is applied as nose drops.
(4) Adriamycin has been designated by the American Cancer Society as the most effective Anti-cancer and Leukemia Agent, the Japanese Pharmaceutical Industry proved in Chemical Abstracts April 15, 1985 that PD-3; Penicillin Diversum combining synthetic epinephrine—Naphazoline Hcl in weak solution with Penicillin was 98% effective against Bone Cancer in vitro, the highest rating ever given an Anticancer Antibiotic in vitro.
(5) Other forms of Cancer such as Breast Cancer have been cured with the common Antibiotics such as Penicillin, Adriamycin and Bleomycin (a Penicillin complex compound)
(6) The Antibiotic Nasal Decongestant Nose Drops also act as an Amazing Immunological growth factor that can cause the Immature Stem Cells that proliferate in Leukemia Patients to begin growing once more which reverses the Leukemia proliferation process.

No other form of Systemic Therapy uses smaller quantities of Antibiotic to produce Cures in much shorter periods of time. See Testimony Samuel B. Wallace, Subcommittee of Health of the House Ways and Means Committee, Dec. 4th, 1975. Therefore, it is the best "Systemic" therapy for Breast Cancer, Bone Cancer and Leukemia is the application of the Antibiotic Nasal Decongestant Nose Drops which treats the Lung Immune System, the most powerful Immune System in the human body because it is directly linked to both the Blood and Glandular Systems. This is confirmed by a prestigious Cancer Research Institute in Japan as well as by NIH Grantee Dr. Bonadonna's five year Clinical Studies for Breast Cancer,[2] which has produced Cure Rates as high as 80% for Breast Cancer.

INJECTION OF ANTIBIOTICS INTO THE BONES IS THE BEST "LOCAL" (LOCAL—SYSTEMIC) ANTIBIOTIC THERAPY

. . .

In 1985, this author proposed an alternative to treating the Bone Marrow with medicines that were both safe and effective—namely, by Injecting Antibiotics into the Bone in my Testimony given before the Subcommittees on Health of the House and Senate Appropriations Committee May 1985. In that Testimony indicated that all forms of Cancer should be treated "Systemically" and "Locally" with the Curative Antibiotics and that the Antibiotics should be Injected into the bones of Cancer Patients in order to thoroughly treat such Patients and in order to prevent future reoccurrence and metastasis, citing the ten year work of Dr. Umtae Kim of the Rosewell Institute, Buffalo, N.Y. Injection of Antibiotics into the bone is the safest way to Administer Antibiotics and can even be given to new-borns before their veins are fully matured. My own research indicates that Injection of Antibiotics into the Bones, thus treating the bone Marrow Immune System is second only to the Nasal Decongestant Nose Drops in effectiveness. Thus, such treatment reduces a fever within approximately an hours time, while the Antibiotic Nasal Decongestant Nose Drops reduces the fever shortly after it is applied. Clinical Studies by Japanese Oncologists have proven that Injection of Antibiotics into the Bone is a very powerful and effective form of Cancer and Leukemia Therapy because there were in 1999 50 Clinical Trials where Injection of Antibiotics were given in the Treatment of Cancer and Leukemia. Therefore it would seem logical that this safe and effective Cancer and Leukemia Therapy would also prove effective against HIV III AIDS Leukemia which resides in the Bone Marrow as well of course in the Lymph Nodes, Blood and Glands. Therefore, the Best Form of Antibiotic "Local" Curative therapy for HIV III Patients is Injection into the four limbs and the surface of the cranium, as well as injection into the AIDS Patient's Lymph Nodes because:

(1) It is in the Bone Marrow that Immune Cells normally grow and where obviously HIV Leukemia suppresses the growth of normal immune cells including the B, T and Macrophages and particularly the T4 Immune Cells which play an important role in the Regulation of the Immune Cells in the Immediate Immune Response as well as influencing the role of the circulatory Lymphocytes. (Susumi Tonegawa the Noble Laureate emphasized that without the T Cells even in the case B Cell and macrophage complement activity that those responses without the T Cell participation would fail. (See Scientific American, October 1985, Tonegawa on the Molecular activity of the Immune Cells, Page 128. Therefore Injection of Antibiotics into the Bone treats the HIV AIDS Infection in its locus.

(2) The Bone Marrow Immune System is the second only to the Lung Immune System in its power to begin the Immune Response and then effecting a Positive result, which is a Cure. For example, applying a Nasal Decongestant Antibiotic as Nose Drops to the Lung Immune System initiates the Curative Process immediately as is shown by its ability to reduce Bacterial and Viral Fevers which is accomplished almost immediately. Reduction of Fevers by Injection into the Bones is accomplished within one or two hours far shorter times than is normal which generally takes four to six hours. See the Medical Physiologist, Arthur Guyton.

(3) Injection of Antibiotics into the Bone thus Treating the Bone Marrow Immune System has proven to be one of the most effective ways to Treat and Cure various forms of Cancer and Leukemia. See Japanese Internet 1999 showing 50 Clinical Trials where Antibiotics cured various forms of Cancer and Leukemia.

In May 1988, Dr. Bonadonna, a Surgeon at Instituto Tumari, Milan, Italy and also an NIH Grantee indicated in Cancer Research May 1988 Treating Breast Cancer "Systemically" and "Locally", produced over a five year period higher Cure Rates than with Surgery or Radiation. That modality of Breast Cancer Antibiotic Therapy has produced Cure Rates as high as 80% but has not been applied to other forms of Cancer and Leukemia by the NIH.[2]

THE EXISTENCE OF DEFENSINS IN THE HUMAN BODY MANUFACTURED BY MYELOID PRECURSOR CELLS IN THE BONE MARROW IS SIGNIFICANT FOR SEVERAL REASONS

The existence of Natural Human Antibiotics which are produced by myeloid precursor cells residing in the bone marrow and stored in the cytoplasm granules of mature cells that are capable of destroying bacteria and viruses is significant for several reasons:

First it destroys a fundamental fallacy where the NIH contradicted its own Text Goodman & Gilman's Pharmacology 2nd Ed. 1955–1958, Pharmaceutical Conferences in 1940 to 1950 and Armed Forces Records WWII and the American Cancer Society's and Japanese Doctors success in treating and curing Cancer and Leukemia Viruses with the Antibiotics. This contradictory conduct by the NIH is the basis for its reliance on ineffective and unsafe Antiviral Agents which have displaced low cost Safe and Effective Antibiotic Medicines that have long cured HIV I and sometimes HIV III Leukemia. This NIH fallacy has resulted in the World-wide AIDS Epidemic which has been characterized as Security Issue by the United Nations and may have resulted in the infection of more than 100 Million human beings.

Second, the displacement of the low cost safe and effective Antibiotic Medicines by the NIH's Unsafe and ineffective nostrums has resulted in the rise in the cost of Medicines from 5,000 fold to 20,000 fold and has produced many new categories of formally curable illnesses being reclassified as incurable. i.e. Asthma.

Third, the failure to make available synthetic Antibiotic Medicines has resulted in unnecessary loss of human life. And now animal life with the wholesale destruction of livestock caused by fear of infected animals who are now not given precautionary Antibiotics.

THE DISCOVERY OF TUMORICIDAL ALVEOLAR (LUNG) MACROPHAGE & NEUTROPHILS WHICH CARRY "DEFENSINS" OR NATURAL ANTIBIOTICS INDICATE IMMUNE CELLS COMBINED WITH ANTIBIOTICS CAN CURE CANCER, LEUKEMIA AND HIV I AND III

This author during the years 1970–1974 by his use of Innate Antibiotic Therapy (activation of Macrophage Direct activation of Complement) in Brazil discovered and described the effects of Antibiotic carrying Macrophage and Neutrophils activity in the Innate Immune Response. Which I describe in the Testimony of Samuel B. Wallace, Subcommittee of Health of the House Ways and Means Committee Dec. 4th, 1975, the effects of Antibiotic Macrophage and Neutrophil carrying Natural Antibiotics (Defensins). "The Antibiotic Nasal Decongestant Nose Drops" can:

1. Reduce Fevers to Normal Level: Viral, Bacterial and Protozoa Fevers instantaneously. Since, only the Macrophage can act instantaneously and the curative process begins with the activation of complement), the reduction of fever is an in-

dication that the curative process has begun which is a sure indication that serum complement has been activated instantaneously.

2. Can cure most Viral and Bacterial Illnesses in three days time. The more difficult illnesses can be cured in a third less time.
3. Curative dosage required to begin the curative process by activation of Complement is ten percent of the dosage recommended by *THE PHYSICIANS DESK REFERENCE*. For example PDR, recommends 500 mg Penicillin for Pneumonia, but using the Antibiotic Nose Drops the amount of medication required is ten percent of PDR recommendation or less than 5 mg per nose drop dosage.
4. Can cure most Virus, Bacteria or Protozoa Illness is a strong indication of a major break through in Medical Science. The discovery or rediscovery of an almost resistance free Curative therapeutic.

The four effects of the Innate Antibiotic Therapy: Immediate reduction of Viral, Bacterial and Protozoa, Fevers, the ability to cure most Viral, Bacterial and Protozoa Illnesses in three days, smaller curative dosages of Antibiotics which have the same effect as larger recommended dosages, and a medicine that can cure most illnesses is a very strong indication of better utilization of the patient's immune system and better placement of the medication in that immune system in achieving cures in a shorter period of time. And since only the Macrophage the predominant Immune System can act so swiftly to get natural and made Antibiotic to the locus of the Infection and beginning the curative process through the activation of complement. All of this is strong indication of a Direct Response of the Innate Immune system which is Macrophage to Direct activation of complement. Which begins the Curative Process.

On the other hand, the experiments of Kazuyoshi Imaizumi, N. Hasegawa et al. who found that stimulation of the Aleveolar Macrophage and Antigen Presenting Cells through the CD40 and CD40L complement receptors which expressed tumor cells could enhance the cytotoxic effect of macrophages and the Antitumor Immunity of the T Cells by using alfa Interferon Leukosyte fragments to stimulate Macrophage Antitumor activity against Lung Cancer cells were inconclusive and ambiguous.[3] Example: (Tested Macrophage prestimulated with Penicillin!)

The effectiveness of the Innate Macrophage Immune Therapy: Macrophage to direct activation of complement and its immediate therapeutic effects *is better tested against actual disease than against some remotely connected Antigen such as an Antibody or leucocyte particle. Which demonstrates far more effectively the ability of the Macrophage or other Immune Cells to act against Virus or Bacteria*. And a better

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[3] See *GAN TO KAGAKU RYOHO* 2000 July; 27(8): p. 1191–2000: "Tumor microcirculation and selective enhancement of drug delivery-clinical applications." Dept. of Internal Medicine, Sendai Shakaihoken Hospital . . . using Yoshida Sarcoma (Bone Marrow Cancer Tumors) functional differences in microcirculation between *tumor (tissues) and normal tissues were found by Suzuki et al. in (1977" . . ." It is very important after* chemotherapy to understand . . . the pathohistological changes in tumor(s) and (their) . . . repaired tissues, which present various clinical images." (Whether those "Clinical Images" have an effect on Mammographic Images is an open question that I would assume depends to some extent upon the degree of Tumor tissue density.) . . . In conclusion: "IHC (continuous infusion of Angiotensin II 'increased tumor blood flow') might be applied to all kinds of tumors to (including of course small cell Breast Tumors) to enhance the chemotherapeutic effects through selective increase of drug delivery to tumors."

This study at Sendai Hospital Japan was devoted to Cancer Tumor in general, and did not refer specifically to small Cell Breast Cancer or small Cell Lung Cancer. But it did note that there was a great difference in normal tissue and tissue that was infected with Cancer Tumors. And that differences in tissue made a difference in the effectiveness of the delivery of drugs to the area of tumor infection. It does therefore at least support my theory which was proven with respect to encephalitis of the brain that there are barriers to the delivery of medicines to tissue, such as the well known "Blood-Brain Barrier" and I believe the small capillaries of the Breast as well as the circulatory barriers to the Lungs. Which helps to explain why doctors have not met with success in treating Small Cell Breast Cancer or Small Cell Lung Cancer. The following three Papers borrowed from my own work on another Leukemia topic, I suggest from my own empirical studies in Brazil from 1969 prove the importance of the routes of Antibiotic Delivery in treating Cancer Tumors as well as the more common infections and neurological diseases titled:

BEST INNATE SYSTEMIC CURATIVE THERAPY ANTIBIOTIC DECONGESTANT NOSE DROPS

INJECTION ANTIBIOTICS INTO BONES BEST LOCAL (&SYSTEMIC) ANTIBIOTIC THERAPY

THE EXISTENCE OF DEFENSINS IN BODY MADE BY . . . PRECURSOR CELLS IN BONE MARROW IS SIGNIFICANT FOR SEVERAL REASONS

This author, Samuel B. Wallace has enclosed those three pages based on his Research in Brazil 1969 to 1974 because he believes they may be helpful in developing new methods for the delivery of Antibiotic Medicines in Breast Cancer and Cancer and Leukemia Therapy. All three pages have been tested by Samuel B. Wallace, in Brazil.

understanding of the effectiveness of an Antibiotic Therapy is better determined by the length of time that red blood serum complement is activated by the Macrophage which in turn has been activated by an Antibiotic or an Antibiotic combined with an Immune Hormone.

A more effective laboratory test of the Macrophage's ability can be determined by the number of new Antibiotics found in the Macrophage both natural (Defensins) and man-made after the Macrophage have activated Blood Serum complement.

Therefore, even though showing "stimulating the Alveolar Macrophage through its CD40 and CD40L Complement Receptors" is of great significance, it is of even more significance to demonstrate that an Immune Cell actually reacts to a specific disease by producing new natural antibiotics or Defensins to fight the disease. Or that it acts in general against a wide range of diseases of one type or another. Kazuyoshi et al. did use tumor cells in their experiment, but not Antibiotics in sufficient strength to strongly exhibit a tumoricidal effect! No curative dose! They, did not show Antibiotic to Macrophage: direct and instant activation of complement shown by the immediate reduction of fevers, and the cure of an extremely wide variety of bacterial, viral and protozoa illnesses in 1970 to 1974 for which many U.S. Pharmaceutical companies are today allegedly seeking to find a cure. And which led the Japanese Pharmaceutical Industry to dub this author's rediscovery ". . . Penicilium Diversum" Chem. Abstr,. April 15, 1985 and as being 98% effective against the deadly sarcoma "yoshida sarcoma" or bone marrow Cancer, is of more value to Medical science than the dubious discovery that an *esoteric cellular immunity* or acquired immunity fragment from a T cell Leukocyte Fragment also called "alfa interferon" has some impact on the macrophage because it means that *"researchers"* had failed to take into account the Macrophage's ability to do its most important work, its ability to Directly Activate red blood serum complement as well as its ability to reduce Viral Fevers and to achieve cure rates better than 90%, even though they nibbled around the edges of this discovery by proving that the Macrophage have Antitumoricidal properties by testing the Macrophages' Complement Receptors.

A better more Scientific approach would have been to test the complement receptors against some disease or virus said to be incurable such as Asthma or HIV AIDS using their approach or mine which consists of the Antibiotic stimulating the Alveolar Macrophages' Complement Receptors by showing that that approach actually activates red blood cell complement, thus beginning the Curative Process. The use of very weak or dubious indicators such as Interferon or Interleukin II–12 is of very little significance because those indicators, themselves, only produce cure rates of 5% or slightly better, while Antibiotics such as Penicillin or tetracycline alone or combined with synthetic Immune Hormones such as synthetic epernephrine produce cure rates against the same viruses. And the question remains that an experiment that uses a stronger stimulant the Antibiotics to "preserve" the Macrophage in culture, whether such "preservation" may have prestimulated the Macrophage before the test of the Macrophage's by means of weak CD-40 receptors and weak Interferon and Interleuken 2. Thus, invalidating the entire experiment.

[Whereupon, at 5:10 p.m., the joint hearing was concluded.]

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