THE CANCER LETTER

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FDA OHOP Director Richard Pazdur with his wife, Mary, in a video produced by NCCS

In Brief

Pazdur: "The Primary Endpoint of Any Trial Should be the Patient."

RICHARD PAZDUR and **ELLEN GOODMAN** were honored by the **National Coalition for Cancer Survivorship** for their contributions to cancer care at the "Focus on the Care" reception Oct. 21 in Washington, D.C.

Pazdur is the director of the FDA Office of Hematology and Oncology Products, and Goodman is a Pulitzer Prize-winning columnist, author and the founder of The Conversation Project, a national public health campaign focused on end-of-life care.

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ACS Recommends First Mammogram at 45, Transitioning to Biennial Screening After 55

By Paul Goldberg

The American Cancer Society published a breast cancer screening guideline that steers toward the middle course in deciding when mammography screening should start and how often it should be performed.

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Guest Editorial

Brawley on Mammography: What We Know, What We Don't Know, and What We Believe

By Otis W. Brawley

I have watched the rhetoric and heated debate about screening at age 40, now 45, and 50 for 25 years and am miffed that the discussion consistently ignores the obvious things we can do to save lives.

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ACS Recommends First Mammogram at age 45

(Continued from page 1)

• The ACS guideline now says 45 is a good age to get the first mammogram. In the past, the society recommended starting at 40. The U.S. Preventative Services Task Force gives a "C" rating to screening before age 50 (The Cancer Letter, April 24).

• Repeating mammograms every other year after age 55 is acceptable, the society now states. In the past, the society recommended annual mammography screening. USPSTF said screening should be biennial after age 50.

By steering toward the middle, the society triggered the ire of both the proponents of starting mammography at 40 and the proponents of starting at 50. On top of that, the guidelines caused consternation among supporters of annual screening and, predictably, from representatives of subspecialties that perform screening.

The ACS breast cancer screening guideline, which was published in JAMA Oct. 20, is important because it's the first to utilize pre-specified guideline-making procedures published in the same journal in 2011. The ACS guideline-making group commissioned a systematic review of the evidence by an independent center, the Duke University Evidence Synthesis Group.

"We recommend that a woman who understands that her risk for breast cancer is low in the early part of her 40s, but who places high value on doing everything she can to reduce mortality—even though her risk is low, and her risk of a false-positive is higher in her early 40s—may opt to start screening before age 45; whether it's 40, 41, or 42," said Richard Wender, chief cancer control officer at the American Cancer Society.

A conversation with Wender appears on p. 5.

Berry: "Arbitrary Starting Age"

"Breast cancer screening is all about uncertainty," said Donald Berry, professor of biostatistics at M.D. Anderson Cancer Center and co-founder of Berry Consultants, a statistical consulting company specializing in the Bayesian approach to medical statistics. "The benefits and risks of mammographic screening have been discussed ad nauseam. Both are uncertain but we know rather more about the risks. In terms of benefits, we have no idea at what age women should start screening or end screening, or if they should start at all.

"We know that breast cancer mortality in the U.S. population decreased by a third between 1990 and 2010. That is huge! It is due to some combination of widespread screening and advances in treatment.

"Treatment advances is probably the bigger contributor but its relative contribution is uncertain. The randomized screening trials were conducted mostly before the use of modern therapy. Perhaps modern therapies make screening redundant, or perhaps finding cancers early enhances the benefits of therapy. We don't know which.

"The new ACS guidelines are great, and for two reasons. First, they stress choice. Second, they come down between the recommendations of other groups. Both of these should convey to women that we just don't know what to recommend.

"The ACS age cutoff of 45 between 'choice' for 40-44 and 'should get' annual mammograms for 45-54 is curious. A 'follow-up analysis' in a 2002 pooling of the Swedish randomized trials showed a 15 percent reduction in breast cancer mortality in the former group and only a 7 percent reduction in the latter group. The Canadian randomized trials showed no mortality reduction in either group. Moreover, there's no empirical evidence that annual screening is better than biennial screening for women 45-54, or in any other age group for that matter.

"Rather than picking an arbitrary starting age the most honest recommendation we can make to women is that we don't know what to recommend. We should help them understand why that is so by communicating in an unbiased fashion the pros and cons of screening depending on age…and the associated uncertainties."

In an editorial in JAMA Internal Medicine, Karla Kerlikowske, of San Francisco Veterans Affairs Medical

Editor & Publisher: Paul Goldberg
Associate Editor: Conor Hale
Reporter: Matthew Bin Han Ong
Intern: Alberto Busch

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Center, wrote that "while the new ACS guidelines provide the opportunity to reduce screening harms, they have little added benefit in reducing lifetime risk of breast cancer death compared with the USPSTF guidelines because most of the benefit of mammography screening results from screening women aged 50 to 74 years, when breast cancer incidence and mortality are highest and mammography most efficacious."

In another JAMA editorial, Nancy Keating, of the Department of Health Care Policy at Harvard Medical School, and Lydia Pace, of the Division of Women's Health at Brigham and Women's Hospital, noted that the ability of mammography to save lives is modest. Thus, a better test would do more to reduce mortality than seeking greater utilization of mammography.

"For women in their 40s and 50s, randomized trial evidence suggests that screening mammography modestly decreases breast cancer mortality by approximately 15 percent," Keating and Pace wrote. "Thus, about 85 percent of women in their 40s and 50s who die of breast cancer would have died regardless of mammography screening. Moreover, because the risk of breast cancer is low for women in their 40s and to some extent women in their 50s, the modest relative benefit of 15 percent translates to a very small absolute benefit (approximately 5 of 10,000 women in their 40s and 10 of 10,000 women in their 50s are likely to have a breast cancer death prevented by regular mammography).

"Especially for average-risk women, decisions to undergo regular mammography screening must also consider the harms of mammography—most notably the possibility of overdiagnosis and resultant overtreatment (age-specific estimates of which are lacking) and also the risks of false positives and unnecessary biopsies (known to be greater in younger women and women screened more frequently).

"Ultimately, better screening tools are needed. The future of breast cancer screening is likely to entail a more personalized understanding of breast cancer risk, one that incorporates both published risk assessment tools using combinations of known risk factors with newer techniques such as genomics. If women who are at higher risk of aggressive breast cancer could be more accurately identified, for example, it would be possible to more definitively identify those women who are most likely to benefit from earlier and more frequent breast cancer screening and less likely to experience the related harms."

The ACS guidelines recommend:

• All women should become familiar with the potential benefits, limitations, and harms associated with breast cancer screening.

• Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 (strong recommendation*)

○ Women who are 45 to 54 years should be screened annually (qualified recommendation**)

○ Women who are 55 and older should transition to biennial screening or have the opportunity to continue screening annually (qualified recommendation)

○ Women should have the opportunity to begin annual screening between the ages of 40 and 44 (qualified recommendation)

• Women should continue screening as long as their overall health is good and they have a life expectancy of 10 years or more (qualified recommendation)

• The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age (qualified recommendation)

*A strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening.

**Qualified recommendations indicate there is clear evidence of benefit of screening but less certainty about the balance of benefits and harms, or about patients' values and preferences, which could lead to different decisions about screening.

Guidelines Get No Applause

The National Breast Cancer Coalition, a group that has been consistently skeptical about the role of mammography, said that although the new guideline moves closer to being evidence-based, it will not help women.

"The guidelines are a slight change from past ACS positions," NBCC President Fran Visco said in a statement. "While we at the National Breast Cancer Coalition appreciate that ACS is moving closer to the weight of the scientific evidence and in the direction that the data support, we do not believe this new interpretation of the data will in fact help women.

"The never ending discussion over mammography screening and the issuing of multiple screening guidelines only adds to the confusion for healthy women who want to make informed decisions. Both the 2015 U.S. Preventive Services Task Force Draft Guidelines and the new ACS mammography screening guidelines recognize that the strength of the scientific evidence for a reduction in mortality by screening, if any, is modest at best. And it is non-existent for most women.

"No matter how we parse groups into screen or not, use five-year or 10-year increments for guidelines,

or start at age 45 or 50, mammography screening will not have a major impact on breast cancer mortality. But it does take up most of the conversation about breast cancer. It is time to become aware of the fact that 40,291 women in this country and more than half a million women around the world will die of breast cancer this year and that number is projected to be 846,587 by 2035. And even if we screen all women, those numbers will not significantly change.

"Let's stop spending so much time on the issue of screening and focus instead on how to stop women and men from getting breast cancer in the first place, prevent its spread and stop deaths from breast cancer. We need to identify what makes a breast cancer tumor lethal so that when tumors are detected there will be no question about whether or not to treat it. Nonlethal tumors will no longer be treated with unnecessary and even harmful interventions. Let's focus on the areas of research that will help us reach those goals. It is within our power to know how to do these things…if we shift our focus and change the conversation to ENDING breast cancer."

The Susan G. Komen breast cancer organization said that the continuing debate over the timing of mammography fails to address several important issues.

"Although guidelines may differ regarding the age at which routine screening should begin, there is agreement that mammography is the best available tool for detecting breast cancer and that women and their health care providers should decide when those screenings should begin for individuals," said Judy Salerno, president and CEO of Susan G. Komen.

"First, the medical field is moving toward determining individual needs for screening based on a woman's risk, such as family history of breast cancer. Ultimately, women must have better and more accurate information about their individual risk for breast cancer so that they and their providers can make informed decisions about the screening schedule that is right for them.

"Second, it is estimated that about one-third of women who should be screened do not access these services. This means that we must take all steps necessary to ensure that women don't face economic or other barriers when their health care providers recommend screening. It's well established that early detection, combined with effective treatment, reduces mortality from breast cancer.

"Third—and this is a point we've made often—we absolutely must continue to invest in finding screening methods that are more accurate, cost-effective, easy-to-administer, and more widely available than mammography."

The American College of Radiology and Society of Breast Imaging said they continue to recommend that women get yearly mammograms starting at age 40.

"The new ACS guidelines show that if a woman wants to reduce, as much as possible, her risk of dying of breast cancer, she will choose yearly mammography starting at age 40," said Debra Monticciolo, chair of the American College of Radiology Breast Imaging Commission.

"A recent study in the British Medical Journal confirms this, showing that early detection of breast cancer is critical for improving breast cancer survival, regardless of therapy advances. Moving away from annual screening of women ages 40 and older puts women's lives at risk."

ACR and SBI said concerns about overdiagnosis are "vastly inflated."

"Published research shows that nearly all women who experience a false-positive exam endorse regular screening and want to know their status," said SBI President Elizabeth Morris. "The ACR and SBI agree with ACS that women 40 and older should have access to mammograms. We also recommend that women, 40 to 45, get screened and would expect that mammography critics would agree that Medicare and private insurers should be required to cover women 40 and older for these exams."

House Reps. Renee Ellmers (R-N.C.) and Debbie Wasserman Schultz (D-Fla.) said the discrepancies between the American Cancer Society and the USPSTF guidelines make it urgent to set aside implementation of the task force guidelines for two years, to allow scientists to sort out the differences. The two are co-sponsors of H.R. 3339—the Protect Access to Lifesaving Screenings Act

Said Ellmers: "Given the variance in screening recommendations among women's health groups and cancer organizations, I think it has become increasingly apparent that my current bipartisan legislation, H.R. 3339, the PALS Act, should swiftly move through the House of Representatives in order to eliminate barriers for patients seeking access to early intervention through life-saving screenings.

"The PALS Act advocates for a two-year freeze on current proposed USPSTF guidance [sic] so that providers, patients and lawmakers can address the differing recommendations for breast cancer mammography screenings. A two-year moratorium would pause implementation of the USPSTF's breast cancer screening recommendations and would assist in eliminating additional confusion for women who are seeking clarification on when and how often to receive mammograms.

"I will continue working with my colleagues

to advocate for the PALS Act so that we can ensure millions of women, young and old, have the resources and tools that they need in order to detect and defeat breast cancer."

Said Wasserman Schultz:

"These new guidelines should not discourage young women from taking control of their breast health and being their own advocates with their health care providers.

"Between these recommendations, the draft recommendations from the U.S. Preventive Services Task Force earlier this year and the recommendations of the Association of Obstetricians and Gynecologists, there is clearly ongoing debate about when individual women should begin mammograms. What is certain is that women must have the information and tools they need to understand the role mammograms have in their overall breast health.

"That is why we joined forces to introduce the Protecting Access to Lifesaving Screenings Act, H.R. 3339, which would place a two-year moratorium on implementing the USPSTF breast cancer screening recommendations. This two-year 'time out' would provide ample time for a thoughtful discussion about whether changes need to be made and how those changes will impact insurance coverage for women in their 40s. Insurance companies will be monitoring both the USPSTF and ACS guidelines closely, and it is essential for us to make sure that we have proper financial protection for women who need it for mammogram screening.

"The differing recommendations are confusing for women. That is why this moratorium is absolutely necessary. Without it, many women who need earlier screenings may not catch their cancer at its earliest onset.

"These new ACS guidelines also underscore that we must continue to empower young women with the tools, resources and information they need to detect, prevent and beat this deadly disease."

In another reaction, a young cancer survivor launched a Change.org petition urging ACS to retract the guideline.

"I was diagnosed with breast cancer on Nov. 11, 2014 at the age of 35, with no family history, no breast cancer gene, no symptoms, and no lumps. I asked for a mammogram and thankfully my GYN sent me and it was caught EARLY with a mammogram and ultrasound," the petitioner wrote. "If I waited until I was 40 years old, it would have been invasive and hard to treat."

There is no guideline that calls for mammography screening of asymptomatic 35-year-old women with no known risk factors.

Conversation with The Cancer Letter

Wender: ACS Guideline Hinges on Shared Decision Making

The Cancer Letter invited Richard Wender, chief cancer control officer of the American Cancer Society, to describe the rationale for the society's new guideline for breast cancer screening.

Wender spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

Paul Goldberg: *How's it going?*

Richard Wender: It's been a very intense couple of months now leading up to the release of the guideline and certainly post-release, responding to how it's been reported in papers and the response of many people around the country. We're working very hard to make sure the full message of the guideline has been communicated.

PG: *What's not been understood?*

RW: I think there are five major messages in the guideline.

Three of them have been addressed completely again with different perspectives in different media, but they've been addressed. One of them is that there's something important about the age of 45. At age 45, the guideline committee felt that breast cancer risk is high enough to argue that all women should begin routine screening if they haven't started before 45. Clearly, that statement has been captured and communicated.

The second message that many of the media outlets have communicated is that after menopause—and we use age 55 as the marker where almost all women have reached menopause—that they have the option to be screened every other year, and maintain almost all the benefit of screening.

The third message, which at times has been discussed, is that clinical breast exam is not the road to lower mortality—mammography is the road to lower mortality rates. Those three have been captured.

The most important one that has not been consistently addressed or mentioned is our recommendations for women at age 40. That's an important part of the guideline. We're going to work pretty hard going forward to make sure that people understand that part of the guideline.

And what the guideline says is that, at or around age 40, a woman should discuss with her physician—and the reverse is also true, physicians will have an obligation to bring this up to their patients. The onus will not just be on the woman, it will also be on the clinician to begin the discussion of mammography at age 40.

We recommend that a woman who understands that her risk for breast cancer is low in the early part of her 40s, but who places high value on doing everything she can to reduce mortality—even though her risk is low, and her risk of a false-positive is higher in her early 40s—may opt to start screening before age 45; whether it's 40, 41, or 42.

This guideline builds in more flexibility and personalization for women than our guideline in the past, certainly, and more personalization than I think in any other breast cancer screening guideline.

So that recommendation for the 40s is important. We understand that many women, some of whom may have risk factors, but some of whom may not, still place enormous value on avoiding—in fact I would say for many women, their highest priority is to do everything they can to reduce the risk of dying of breast cancer.

We want women to understand that their risk is actually quite low in the early part of that decade, and to understand that the likelihood that she will benefit from mammography is also quite low.

We also clearly state that there is benefit starting younger, and that a woman should be supported in starting annual screening before age 45. That's an important part of the message. It's interesting, because shared decision-making has been incorporated into several screening guidelines. Our lung cancer screening guideline recommends shared decisions; our prostate cancer guideline recommends shared decisions. But the message in breast cancer screening has been more difficult to communicate that there may be a period where a woman's personal preference is important, and should be considered.

PG: *Has there been any negative reaction as far as withdrawal of support for example?*

RW: We've had a lot of negative reactions. But here's a good way to look at it. Almost all the reaction that we've received—well, I think it's fair to say the vast majority of the reaction has been negative, often coming from women who had breast cancer at a young age. And also from the radiology community, and some reaction from other professionals who treat breast cancer primarily.

And we're working really hard to communicate all over the country directly with individuals, and directly with any organization that has reached out to us—most of them have been individuals—to answer their questions, to make sure that we listen and hear them clearly, to make sure they understand the process.

We fully understand that financial support is a personal discretionary decision. We're hoping that people keep their support with the American Cancer Society and work hard with us to recognize that guideline has the potential to build a unifying platform. It accommodates positive messages about mammography, but also informs clinicians and women about the times in their life when mammography is most likely to be beneficial.

PG: *You could, in principle, be cutting the revenues of the people performing the screening by as much as 50 percent or even more. You would think they would be upset for that reason as well.*

RW: No one has called us to say they disagree on the cause of revenue. The concerns we've had, I think, have been sincere. They feel very strongly about the importance about doing everything we can to reduce the death rates from breast cancer. And many of these people find patients with breast cancer every day and that does impact your perspective when that's what you do every day. We really value that.

We sent out the draft of this guideline to about 25 professional organizations, including all the organizations that are involved with treating patients with breast cancer. And we have received very helpful and useful comments back, which were incorporated into the guideline—chiefly, ways to communicate more clearly about it and to deliver the message.

I should mention that we've also received, far more quietly, and not so much through social media, but through personal emails, very supportive messaging—and I know that some radiologists, some academic centers, some people who are experts in screening, and individuals, are getting to understand the full scope of the guideline, and recognize that this does offer more flexibility in allowing a women to follow a preferred pathway, while at the same time confirming the potential to reduce death rates in all age groups.

One of the important messages of the guideline, which hasn't been focused on right now, but I think over time will become very important, is that this evidence review conducted by the Duke group and the guideline provide—I'm tempted to say a confirmation that cannot be challenged because it is so thorough and not terribly different from other recent evidence reviews that mammography is effective.

It does reduce mortality by at least 20 percent in all age groups tested. And in the newer observational trials, the benefit is even higher than that. As you know, there have been articles that have at least suggested that mammography has no meaningful benefit. So, I do think this guideline will provide a very solid basis for everyone, including those who have been very skeptical about mammography and those who have been very

excited about mammography to unite around a common appreciation of its value.

PG: *Did you about to follow all of the procedures that were pre-specified in the 2011 JAMA paper? For example, was it possible to look at the transparency of it, how the guideline was prepared, who said what when? That was a unique aspect [of the ACS process].*

RW: I was very impressed at how closely we followed exactly what was published in 2011. We refer to it regularly to make sure we were sticking to those steps, as close as was practically possible: the composition of the guideline committee, the commissioning of an independent evidence review that we chose through a competitive process, the choice of a specific validated model for rating evidence.

We stuck very closely to the grade system for evidence rating. We did not submit it for full public comment, but the 2011 paper did not say that we would do that. We said that we would solicit reactions for comment, but not—we chose to do that through organizations and experts, as opposed to full public comment, the way the [U.S. Preventive Services Task Force] does. But we've stuck to that.

I believe, in fact, I know, that the guideline proved—and that certainly I, as a sponsor of this guideline from the ACS standpoint—feel confident that we did an excellent job in sticking to this process.

PG: *Was the website functioning [to enable the public to follow the process of guideline-making]?*

RW: We did not post this on a public reaction website.

PG: *Is there a reason that it couldn't be done?*

RW: Frankly, there were some technical reasons; we're not set up to take the thousands of public comments as easily. That would require overcoming some technical barrier. The other reason is that we did get advice from members of the task force.

Almost all of the comments that potentially alter the guideline came through organizational response. I do think we're going to look at this again for our next guideline, whether having a method for full public comment might be possible and preferable.

PG: *There's this oversight committee. How were they involved?*

RW: They were involved in helping us design this process, but not in the writing of this guideline. In fact now that we're done, we are reconvening that oversight committee.

PG: *What would be the reason for that?*

RW: We want to review with them all of the steps, get their reaction to them, see if they would advise that we change any of them. This would have been done routinely no matter what.

We've been very intensely involved with writing the guideline and communicating about the guideline. Now that we're moving past that, now's the time to reconvene and review what we've done.

PG: *This is not the first guideline with the new approach, is it?*

RW: It actually is. The last one that we did was right after we had published the 2011 paper, and that was the lung cancer screening guideline; for that we used the hybrid model. I actually was the first author of that guideline and that was back in my volunteer days. And now that I compare the processes, I think that the fair statement is what I said: this is the first guideline that used the full IOM process.

PG: *Thank you so much for your guidance on this. Is there anything that we overlooked?*

RW: No, but again, the one message, I think, that for people trying to create a deeper and richer understanding of the guideline, there are important elements that accommodate multiple perspectives, but also empower women to make an individual choice, particularly in the times when the cancer is more rare. Because when cancers are more rare, the benefit of screening is lower.

That's why we think it's important to involve individual choice and values. But we hope to emphasize the fourth aspect of the guideline—that this is a discussion that should start at 40.

Guest Editorial

Brawley: Mammography—What we Know and What we Don't

(Continued from page 1)

All bodies (North American and European) that publish guidelines recommending screening say that all healthy women over 50 should get routine screening.

It is widely accepted that more than a third of American women over 50 do not get regular mammography and some do not get good quality mammography. It is also accepted that a good proportion of American women with diagnosed breast cancer do not receive good cancer treatment. It is a fact that the number of lives that could be saved by the logistical move of providing quality care to all is far greater than the number of lives that might be saved by screening all women in their 40s.

The following are my own views. They should be interpreted as the opinion of a physician who has studied

screening for nearly three decades and been concerned about ethics in medicine and doing the right thing to save the most lives and prevent the most suffering.

In 2011, the Institute of Medicine of the National Academies published a study with guidelines on the creation of trustworthy medical guidelines. The IOM study was commissioned because many of the healthcare guidelines of the past two decades were based on the opinions and prejudices of those writing the guideline and often not based in science. It was well known that some guidelines authors were clinicians with financial interests and limited expertise in the subject area. This was especially true of cancer screening guidelines.

The IOM's goal was to remove those with emotional and financial conflicts of interests from guidelines processes and replace them with a group of people who have objectivity and expertise. The IOM also said a guidelines committee should commission a structured review of the relevant scientific literature and each published research study should be graded. This is an important point. Some published medical studies are of very high quality, but some are not, some are biased. One can only get close to finding the truth by rigorously evaluating the quality evidence and discounting poor science.

The American public has been conditioned that all cancer screening is good. This is partly because cancer is understandably an emotional issue and partly because of a lack of understanding of complexity of cancer screening. There has long been a tendency to exaggerate the benefits of cancer screening and minimize or even ignore the harms associated it.

In the case of mammography for breast cancer, there have been years of overly simplistic messaging hyping the benefits and not recognizing the limitations. When I say limitations, I note that numerous expert panels have examined the data and agree that clinical trials suggest mammography reduces relative risk of death by 20 percent. Many expert panels agree that some observational studies suggest mammography may reduce relative risk of death by as much as 40 percent. This most optimistic assessment means mammography when done well does not benefit 60 percent of the women who need it.

Any criticism of mammography or mention of limitations seems to upset the real believers in screening. It is mistakenly viewed as anti-mammography and giving women an excuse not to get the test. Many in the lay and medical community have been allowed to believe mammography is near 100 percent. This is one reason why mammography is a leading cause of medical malpractice suits.

The above statement should not be construed as against the use of mammography, it is a plea for cautious, wise use of a technology that can be beneficial, but can also be harmful. A message we should be telling the public is: There is some benefit to mammography screening. But we do need a better screening test. Until a better test is developed, we need to wisely use the technology we have.

After nearly two years of study, a committee of experts commissioned by the ACS and using a modified IOM format issued a breast cancer screening guideline for women at average risk. The experts saw benefit in mammography screening saying it clearly reduces risk of death. That is "epi speak." The colloquial lay translation is "screening saves lives."

They also noted that breast cancer is relatively uncommon among women aged 40 to 44 and screening does not work well in populations where the disease of interest is uncommon. In this population at low risk for breast cancer, there are many false positives in order to detect the (relatively) few that can be helped by early detection. These objective experts examined the data and did not see that the benefits clearly outweigh the harms, when screening the entire population aged 40 to 44, but they do recognize that some women this age do benefit.

Largely overlooked in coverage of the announcement was an important detail. The panel said all women aged 40 to 44 should be informed of the potential benefits and potential risks of annual screening and be encouraged to make a choice. They chose not to be paternalistic. In an area where the science does not support a clear advantage versus harm for the general population, let the individual decide for herself. Screening should be tailored to the individual woman's concerns by the woman herself.

I would note that such informed decision making is not controversial in the world of prostate or lung cancer screening. The ACS recommendation even says those women aged 40 to 45 who want screening should not face financial barriers to getting that screening.

Some screening advocates seem unable to accept the fact that there are limitations to our current screening technologies even though there is significant consensus about this among experts. In recent years, 12 committees of screening experts in the U.S., Canada, or Europe have said that there is a problem in screening all women in their early 40s. Indeed, I cannot name a group of objective experts, who have gone through

a process of reviewing the scientific literature, and still support widespread screening of women in their early 40s.

This guideline applies to women of average risk. If we are truly interested in saving lives, we will support research to improve our ability to identify the young women who are at a high risk for breast cancer and likely to benefit from current screening technologies, and efforts to develop better screening tests.

I believe the new ACS guideline moves closer to revealing the truth about the strengths and weaknesses of breast cancer screening. It encourages women to make their own personal decision about screening. Mammography can save lives and we can use in wiser fashion to maximize its benefits and minimize its harms while supporting efforts to find a more effective test.

The author is chief medical officer of the American Cancer Society.

National Academy of Medicine Elects 80 New Members

The National Academy of Medicine elected 80 members during its annual meeting, including at least 17 whose work focuses on cancer treatment and research.

"Our newly elected members represent the brightest, most influential, and passionate people in health, science, and medicine in our nation and internationally," said Victor Dzau, president of the academy, formerly known as the Institute of Medicine.

"They are at the top of their fields and are committed to service. The expertise they bring to the organization will help us respond to today's most pressing health-related challenges and inform the future of health, science, and medicine. It is my privilege to welcome these distinguished individuals to the National Academy of Medicine."

Election to the academy is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service. This was the inaugural annual meeting as the National Academy of Medicine and the 45th year since the establishment of the Institute of Medicine.

The 70 new members and 10 new international members were elected by current active members, recognizing individuals who have made major contributions to the advancement of the medical sciences, health care, and public health.

A diversity of talent among NAM's membership is assured by its Articles of Organization, which stipulate that at least one-quarter of the membership is selected from fields outside the health professions—for example, fields as law, engineering, social sciences, and the humanities.

The newly elected members raise NAM's total active membership to 1,826 and the number of international members to 137.

The full list of new members is available here.

The newly elected members whose work focuses on cancer are listed below:

Christopher Austin, director of the NIH National Center for Advancing Translational Sciences. Austin joined NIH in 2002 as the senior advisor to the director for translational research at the National Human Genome Research Institute. He helped found and then directed the NIH Chemical Genomics Center (now the NCATS Chemical Genomics Center), the Therapeutics for Rare and Neglected Diseases program, Toxicology in the 21st Century initiative, and NIH Center for Translational Therapeutics.

Otis Webb Brawley, professor of hematology, medical oncology, medicine, and epidemiology at Emory University; and chief medical officer of the American Cancer Society. Previously, Brawley was medical director of the Georgia Cancer Center for Excellence at Grady Memorial Hospital in Atlanta, and deputy director for cancer control at Winship Cancer Institute at Emory University. He also previously served as a member of the ACS's Prostate Cancer Committee; co-chaired the U.S. Surgeon General's Task Force on Cancer Health Disparities; and filled a variety of capacities at the NCI. Brawley is also a member of the CDC's Advisory Committee on Breast Cancer in Young Women, has served as a member of the FDA's Oncologic Drug Advisory Committee, and chaired the NIH Consensus Panel on the Treatment of Sickle Cell Disease.

Amato Giaccia, Jack, Lulu, and Sam Willson Professor of Cancer Biology in the department of radiation oncology at the Stanford University School of Medicine. Giaccia is also director of the university's Cancer Biology Interdisciplinary Graduate Program. Giaccia was awarded an American Cancer Society Junior Faculty Research Award and the Michael Fry Award from the Radiation Research Society for his contributions on the molecular mechanisms of resistance promoted by the tumor microenvironment. Additionally, he was the recipient of the 2013 ASTRO Gold Medal.

D. Gary Gilliland, president and director of the Fred Hutchinson Cancer Research Center. He was also an investigator at the Howard Hughes Medical Institute, and previously was director of the leukemia program at the Dana-Farber/Harvard Cancer Center. He was also senior vice president and global oncology franchise head at Merck Research Laboratories.

Christopher Glass, professor of cellular and molecular medicine, professor of medicine, and Ben and Wanda Hildyard Chair in Hereditary Diseases at the University of California, San Diego. Glass's laboratory focuses on the biochemical and biological roles of transcription factors and their associated co-regulators in controlling macrophage differentiation and function and the pathogenesis of inflammatory diseases.

Michael Green, an investigator at the Howard Hughes Medical Institute; director of the cancer center and professor and chair of the department of molecular, cell, and cancer biology at the University of Massachusetts Medical School. Green's research has focused on regulation mechanisms of gene expression in eukaryotes, and the role of gene expression in various human diseases. He also uses transcription-based approaches and functional screens to identify new genes and regulatory pathways involved in cancer.

Murat Günel, the Nixdorff-German Professor, chairman of the department of neurosurgery, and professor of neurobiology and genetics at the Yale School of Medicine; and chief of the department of neurosurgery at Yale-New Haven Hospital. Günel's research interest is in treating brain aneurysms and vascular malformations with special emphasis on arterio-venous malformations and cavernous malformations. He also has expertise in occlusive vascular disorders such as carotid disease and gamma knife radiosurgery.

Beth Karlan, professor of obstetrics and gynecology; director of the Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute; and director of the division of gynecologic oncology at Cedars-Sinai Medical Center. Karlan also serves as the director of the Gilda Radner Ovarian Detection Program at Cedars-Sinai Medical Center.

Kenneth Kinzler, professor of oncology, director of the Ludwig Center, and associate director of basic research at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University. His research interests include the molecular genetics of cancer, APC and other genetic alterations in colon and rectal cancer, and experimental therapeutics. He has received the NCI MERIT Award, AACR Team Science awards in both brain and pancreatic cancer research, and the NCI Director's Service Award.

Vivian Lee, senior vice president for health sciences at the University of Utah, dean of the university's school of medicine, and CEO of University of Utah Health Care. Lee is a fellow and past president of the International Society for Magnetic Resonance in Medicine, and was elected to the American Society for Clinical Investigation.

Vasant Narasimhan, global head of development at Novartis Pharmaceuticals, in Basel, Switzerland. Narasimhan previously served as global head of development at Novartis Vaccines.

Nikola Pavletich, an investigator at the Howard Hughes Medical Institute; and Stephen and Barbara Friedman Chair of the structural biology program at Memorial Sloan Kettering Cancer Center. Pavletich's research has focused on the structural biology of oncogenes and tumor suppressors, as well as the structures and mechanisms of proteins that sense, signal, and repair DNA damage and on the cell cycle and associated growth regulatory pathways.

Alexander Rudensky, an investigator at the Howard Hughes Medical Institute; and chairman of the immunology program, and director of the Ludwig Center for Cancer Immunotherapy at the Memorial Sloan Kettering Cancer Center. Rudensky's lab is focused on the molecular mechanisms governing the differentiation and function of CD4 T lymphocytes and their role in immunity and tolerance. Rudensky received a Searle Scholar Award and a PharMingen Investigator Award from the American Association of Immunologists.

Richard Scheller, chief scientific officer of 23andMe Inc. Scheller is a member of the National Academy of Sciences and received the NAS Award in Molecular Biology. His research has focused on the cellular and molecular mechanisms of membrane organization and transport in eukaryotic cells.

Kevin Struhl, David Wesley Gaiser Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School. His research areas include Chromatin and other DNA-protein interactions; oncogenes and tumor suppressor genes; signal transduction; and transcription and gene regulation.

Richard Leo Wahl, Elizabeth E. Mallinckrodt Professor, chair of radiology, and director of the Mallinckrodt Institute of Radiology at the Washington University School of Medicine, in St. Louis. Wahl's work has focused on the development of FDG PET imaging in oncology in both preclinical and clinical

studies. He helped develop anatometabolic image fusion—fusion of PET with CT, SPECT or MRI—into hybrid images of cancer. He also is one of the inventors of radioimmunotherapy of lymphoma with anti-CD20 antibodies. He has also been an inventor of medical devices such as radionuclide-guided biopsy.

Nahum Sonenberg, elected as an international member, is the James McGill Professor in the department of biochemistry at the Rosalind and Morris Goodman Cancer Research Centre of McGill University, in Montreal, Canada. He is a Howard Hughes International Scholar, recipient of the Robert L. Noble Prize of the National Cancer Institute of Canada, and recipient of the Killiam Prize for Health Sciences. His research focuses on identification and characterization of the various translation factors involved in translation initiation; elucidation of the signaling pathways impinging upon translation; and discovery of physiological consequences of translational control.

Vice President Biden Calls For A National Commitment to Cancer Research Funding

Vice President Joe Biden, in a Rose Garden address announcing his decision to not run for president, called for a national commitment to end cancer—expressing that, were he to run and be elected, it would be a goal of his presidency.

"If I could be anything, I would have wanted to have been the president that ended cancer, because it's possible," Biden said Oct. 21. He said that his window of opportunity to mount a winning campaign had closed. "While I will not be a candidate, I will not be silent," he said.

His son, Beau Biden, the attorney general of Delaware, had been diagnosed with brain cancer and died in May of this year, at age 46.

"I believe that we need a moon shot in this country to cure cancer. It's personal. But I know we can do this," the vice president said.

"The president and I have already been working hard on increasing funding for research and development, because there are so many breakthroughs just on the horizon in science and medicine, the things that are just about to happen. And we can make them real with an absolute national commitment to end cancer, as we know it today.

"And I'm going to spend the next 15 months in this office pushing as hard as I can to accomplish this, because I know there are Democrats and Republicans on the Hill who share our passion, our passion to silence this deadly disease."

Margaret Foti, chief executive officer of the American Association for Cancer Research, said in a statement: "We extend our deepest sympathy to Vice President Biden and his family for the loss of his son Beau to cancer, and thank the vice president for his unequivocal support of cancer research during his announcement yesterday at the White House.

"The vice president is absolutely correct: We are at a turning point in cancer research, with many new advances in recent years and incredible breakthroughs on the horizon.

"However, while tremendous progress has been made against this insidious disease, our nation's ability to ensure future progress for cancer patients will require more research and more funding for the federal agencies that are vital for fueling progress against cancer, in particular the NIH, NCI, and FDA.

"Investments in these federal agencies will also help mitigate the immense economic cost of cancer. In the United States alone, it is estimated that the direct medical costs of cancer care in 2010 were nearly $125 billion, and that these costs will likely rise to $156 billion in 2020."

In Brief

Pazdur: "The Primary Endpoint Of Every Trial Should be the Patient"

(Continued from page 1)

Goodman received the inaugural Jessie Gruman Award for Patient Engagement, established with a grant from the Center for Advancing Health.

Pazdur received the NCCS Public Service Leadership Award in recognition of his research and leadership at the FDA as well as his career in developing oncology drugs for over 30 years.

"Rick was in the trenches doing the hard work," said Robert Califf, FDA deputy commissioner for medical products and tobacco, during the reception. "The willingness to establish order and try new things in this environment is not the easiest; I have a lot of admiration for that.

"An amazing balance has to be struck between different people and opportunity or new therapies, but also protecting them when things are not right. I think Rick has set an example there," said Califf, who was nominated by President Barack Obama to serve as the next commissioner of the FDA, pending

Senate confirmation.

"I think it's hard for people to appreciate the work of a clinician dealing with these things night and day as [Pazdur] did, now, not just working with drugs, biologics, immunotherapies, but also diagnostics, and how that fits together. But through all this technology, he's always got the patient at the front, setting an example for everyone at the FDA.

"Some of you might be aware that in the medical world, there's this cardiology-oncology thing that goes on, but I've been asking him, 'Rick, can you replicate what you've done in oncology in other fields?' He keeps saying, 'I'm interested in oncology.' And his route, that I'm really in awe of, is having an amazing group of people.

"Attracting people to work at the FDA is not the easiest thing in the world. The hiring system of the federal government is not necessarily the most facile to work with, but I think it's fair to say that he's put together the nation's leading academic oncology group at the FDA."

Pazdur said he did not plan on becoming an oncologist.

"Let me just start off with this oncology-cardiology 'thing' that Rob referred to," Pazdur said. "I don't think most know this, but early on in my career, I was going to become a cardiologist. I took an oncology rotation late in my internal medicine training and I fell in love with the field. So, it's cardiology's loss, oncology's gain. For me, oncology is a more fascinating field."

FDA's standards for regulating oncologic agents have been successful because OHOP invests in the professional growth of its personnel, Pazdur said.

"We have an amazing group of people who don't get lost in the weeds or minutia," Pazdur said. "We're focusing on big picture issues, we have camaraderie, and I hope, as a leader, I focus on every individual's career.

"I take a look at all of the review staff and many are in their 30s or early 40s—they are 'All My Children.' I attempt to develop their careers, and I want everyone—all of the physicians, basic scientists and support staff—to feel fulfilled and to feel their careers are being developed and built.

"I would like our staff to understand that I am for them. I have their best interest in mind. It's not about me—I don't need to give another talk, I don't need to get another award, I don't need to write another paper—it's about you, our FDA staff, and developing your careers."

Clinical trials and regulatory processes must be centered on the patient experience, which evolves over time, Pazdur said.

"The next thing I want to mention is 'the patient voice,'" Pazdur said. "What is the patient voice? I don't think there is a thing such as the patient voice. It is a collection—a chorus of many voices, of many different experiences—that may change during the course of an illness.

"For example, the way a patient looks at a clinical trial or treatment options when they are undergoing adjuvant therapy may be very different from a patient who has progressed through multiple therapies and may have few therapeutic options. Hence, the risk-benefit evaluation of the treatment and what types of endpoints may be very different.

"I think when we take a look at 'the patient voice,' there are things that all patients agree on. We all want clinical trials that really work for us.

"We want clinical trials that have more expansive eligibility criteria that reflect the patient populations who will be using these drugs. We want expanded access programs that work for us. We need to work on facilitating how patients get unapproved drugs.

"We need informed consents that are meaningful to patients—that aren't just page after page of legalese that patients don't read or don't understand. We need a better informed consent procedure.

"So it's about putting the patient in the forefront—that's what I see as the patient voice, or as I previously mentioned, 'the cry of the patient,' to make clinical trials more patient-focused.

"I'll just end by saying, what should be the primary endpoint of a trial? Should it be overall survival? Should it be progression-free survival? Should it be a response rate?

"Well, the primary endpoint of any trial should be the patient."

THE ASSOCIATION OF COMMUNITY CANCER CENTERS announced the six winners of its **2015 Innovator Awards**.

This year's winners are:

● Eastern Maine Medical Center Cancer Program, for improving efficiency, safety and the patient experience with location technology.

● Lancaster General Hospital and the Ann B. Barshinger Cancer Institute, for creating a Cancer Patient Support Fund for patients experiencing financial distress.

● Mary Washington Healthcare Regional Cancer

Center, for the center's focused "prehabilitation" program that couples physical therapy with holistic care that includes nutritional support, stress reduction strategies and nurse navigator intervention, which decreased hospital length of stay for thoracic oncology patients by 40 percent.

● PIH Health Comprehensive Community Cancer Program, for its nurse practitioner-run Lung Cancer Screening Program that utilizes an enrollment method that allows primary care practitioners to refer patients or for the patient to self-refer.

● Providence Cancer Center, which offers a supportive group model to deliver early and ongoing intervention and support throughout cancer care and creating a framework to talk about the impact of cancer on the family.

● The Seton Cancer Program of the Seton Family of Hospitals, for developing a standardized, integrated database of clinical and business metrics to measure, analyze and improve patient care and operational efficiency.

More details about each program are available on the ACCC website.

THE ASSOCIATION OF COMMUNITY CANCER CENTERS published a white paper, titled "What Will It Take? Five Essential Actions to Achieve a Positive Impact on Patient Care in the Integrated Healthcare Environment," at its 32nd National Oncology Conference, addressing patient care in a changing provider setting.

The five actions described in the white paper are: aligning stakeholders and requiring accountability; defining quality in a value-based reimbursement system and providing access to quality care; using non-traditional delivery systems such as telehealth and primary care physicians and non-physician providers to deliver cancer care; integrating the use of big data to drive treatment decisions; and moving to patient-directed care in which the patient is at the center of all decisions and systemic change.

"Increased integration will impact all aspects of an organization's cancer care delivery — cultural, operational, clinical and financial," said ACCC President Steven D'Amato. "Our focus in this newly integrated environment is to provide education for hospital systems and physician practices on how to offer the best collaborative oncology care in a seamless way for patients."

JODI DANIEL joined the firm **Crowell & Moring LLP** as a partner in its Health Care Group.

Daniel is the former director of the Office of Policy in the Office of the National Coordinator for Health Information Technology at the Department of Health and Human Services. Daniel served for a decade as the director at the ONC and 15 years at HHS, where she worked on changes in health information privacy and health information technology.

As the first senior counsel for health information technology in the Office of the General Counsel of HHS, Daniel developed HHS's foundational legal strategies and coordinated all legal advice regarding health IT for HHS.

"Jodi literally wrote the book—and all the rules—governing health information technology, including the complex HIPAA privacy and enforcement rules," said John Brennan, Jr., chair of the firm's Health Care Group. "Her experience in setting the regulatory framework and policies for both technology providers and adopters has supported innovation in areas including mobile health, remote devices and telehealth, and that insight will be of enormous value to our clients as they operate in this highly regulated space."

KIDS V CANCER was awarded the **2015 Peter F. Drucker Award** for Nonprofit Innovation for its role in the 2012 Creating Hope Act. Kids v Cancer was chosen out of 655 applicants from nonprofits.

The award is presented by the Drucker Institute and includes a $100,000 prize, made possible by the Coca-Cola Foundation.

"It is a great honor to be the 2015 recipient of the Peter Drucker Award for Nonprofit Innovation. We will use this recognition and award to continue our efforts to change the landscape of pediatric cancer drug development, including the passing The Advanced Hope Act and Kids Innovative (KIDS) Initiative," said Nancy Goodman, executive director of Kids v Cancer.

Since its passage in 2012, four companies have earned Creating Hope Act Rare Pediatric Disease Priority Review vouchers. Most recently, United Therapeutics Corporation announced the sale of its Creating Hope Act priority review voucher to AbbVie for $350 million. United Therapeutics earned the voucher for its development of Unituxin for neuroblastoma.

Drugs and Targets

Onivyde Regimen Approved for Metastatic Pancreatic Cancer

FDA approved Onivyde (irinotecan liposome injection), in combination with fluorouracil and leucovorin, to treat patients with metastatic pancreatic cancer who have been previously treated with gemcitabine-based chemotherapy. The agency previously granted Priority Review and orphan drug designations for Onivyde.

The effectiveness of Onivyde was demonstrated in a phase III, three-arm, randomized, open label study of 417 patients (NAPOLI-1) with metastatic pancreatic adenocarcinoma whose cancer had grown after receiving gemcitabine or a gemcitabine-based therapy. The study was designed to determine whether patients receiving Onivyde plus fluorouracil/leucovorin or Onivyde alone lived longer than those receiving fluorouracil/leucovorin. The monotherapy regimen in this study did not achieve its primary endpoint and, therefore, Onivyde is not indicated as a single agent.

Patients treated with Onivyde plus fluorouracil/leucovorin lived an average of 6.1 months, compared to 4.2 months for those treated with only fluorouracil/leucovorin ($p=0.014$, unstratified HR=0.68, 95% CI: [0.50-0.93]). There was no survival improvement for those who received only Onivyde compared to those who received fluorouracil/leucovorin.

In addition, patients receiving Onivyde plus fluorouracil/leucovorin had a delay in the amount of time to tumor growth compared to those who received fluorouracil/leucovorin. The average time for those receiving Onivyde plus fluorouracil/leucovorin was 3.1 months compared to 1.5 months for those receiving fluorouracil/leucovorin.

The safety of Onivyde was evaluated in 398 patients who received either Onivyde with fluorouracil/leucovorin, Onivyde alone or fluorouracil/leucovorin. The most common side effects of treatment with Onivyde included diarrhea, fatigue, vomiting, nausea, decreased appetite, inflammation in the mouth and fever. Onivyde was also found to result in lymphopenia and neutropenia. Death due to sepsis following neutropenia has been reported in patients treated with Onivyde.

The labeling for Onivyde includes a boxed warning to alert health care professionals about the risks of severe neutropenia and diarrhea. Onivyde is not approved for use as a single agent for the treatment of patients with metastatic pancreatic cancer.

Onivyde is marketed by Merrimack Pharmaceuticals Inc.

FDA approved Yondelis (trabectedin) for the treatment of liposarcoma and leiomyosarcoma that cannot be removed by surgery or is metastatic. This treatment is approved for patients who previously received chemotherapy that contained anthracycline.

The effectiveness of Yondelis, marketed by Janssen Products, was demonstrated in 518 clinical trial participants with metastatic or recurrent leiomyosarcoma or liposarcoma. Participants were randomly assigned to receive either Yondelis (345 patients) or dacarbazine (173 patients), another chemotherapy drug. Participants who received Yondelis experienced a delay in the growth of their tumor (progression-free survival), which occurred on average about 4.2 months after starting treatment, compared to participants assigned to dacarbazine, whose disease progressed an average of 1.5 months after starting treatment.

The most common side effects among participants who received Yondelis were nausea, fatigue, vomiting, diarrhea, constipation, decreased appetite, shortness of breath, headache, tissue swelling, a decrease in infection-fighting white blood cells, low blood platelet counts, low red blood cell count, elevated liver enzymes and decreases in albumin, a protein found in blood.

Yondelis carries a warning alerting health care providers of the risk of severe and fatal blood infections, muscle tissue breakdown, liver damage, leakage around the vein or catheter, tissue necrosis and heart failure. Patients with known hypersensitivity to trabectedin, a drug used to treat cancer, should not take Yondelis.

Health care providers are also encouraged to advise women of potential risks to a developing fetus when taking Yondelis. Women who are taking Yondelis should not breastfeed.

FDA granted de novo clearance to SonaCare Medical LLC to market the Sonablate 450 in the U.S. for the ablation of prostate tissue.

Sonablate is the first High Intensity Therapeutic Ultrasound device to receive FDA regulatory authorization for prostate tissue ablation. SonaCare expects to begin U.S. distribution this October.

Sonablate is the Company's second medical device to receive U.S. FDA regulatory authorization, complementing the 510(k) cleared Sonatherm laparoscopic HITU ablation device.