Advancing Progress in the Development and Implementation of Effective, High-Quality Cancer Screening: Proceedings of a Workshop (2021)

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PROCEEDINGS OF A WORKSHOP

Erin Balogh, Sarah Domnitz, Margie Patlak, and Sharyl J. Nass,
Rapporteurs

National Cancer Policy Forum

Board on Health Care Services

Health and Medicine Division

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The forum wishes to express its gratitude to the expert speakers whose presentations helped further the dialogue on opportunities to improve the evidence base for and delivery of high-quality cancer screening. The forum also wishes to thank the members of the planning committee for their work in developing an excellent workshop agenda.

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Acronyms and Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AI	artificial intelligence
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare & Medicaid Services
CRCCP	Colorectal Cancer Control Program
CT	computed tomography
EDRN	Early Detection Research Network
ERSPC	European Randomized Study of Screening for Prostate Cancer
FDA	Food and Drug Administration
FQHC	federally qualified health center
HMO	health maintenance organization
HPV	human papillomavirus
LEEP	loop electrosurgical excision procedure
MPS	MyProstateScore
MRI	magnetic resonance imaging
MyPeBS	My Personal Breast Screening

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
PET	positron emission tomography
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PSA	prostate-specific antigen
RCT	randomized controlled trial
ROC	risk of ovarian cancer
SNP	single nucleotide polymorphism
TMIST	Tomosynthesis Mammographic Imaging Screening Trial
TVS	transvaginal ultrasound
UKCTOCS	UK Collaborative Trial of Ovarian Cancer Screening
USPSTF	United States Preventive Services Task Force
VHA	Veterans Health Administration
WHO	World Health Organization
WISDOM	Women Informed to Screen Depending on Measures of Risk

Proceedings of a Workshop

WORKSHOP OVERVIEW[1]

The aim of cancer screening is to reduce mortality and morbidity by detecting precancerous abnormalities or cancers early, when they are more likely to be effectively treated (NCI, 2019). While diagnostic testing is typically performed with the aim of understanding the cause of specific symptoms, screening is provided to individuals without any evident symptoms of the disease of interest. If abnormalities are detected through screening, additional follow-up testing and evaluation may be conducted to determine a diagnosis and whether treatment is appropriate.

Some cancer screening tests, such as those for colorectal cancer and cervical cancer, can detect precancerous abnormalities before they have progressed to cancer. If the precancerous tissue is excised, these screenings can reduce cancer incidence as well as deaths from these cancers. All effective cancer screening tests, including those for breast cancer and lung cancer, can enable earlier detection and thus earlier treatment, thereby increasing the likelihood of better health outcomes.

[1] The planning committee's role was limited to planning the workshop, and the Proceedings of a Workshop was prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of the individual presenters and participants, and are not necessarily endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they should not be construed as reflecting any group consensus.

However, cancer screening also carries risks. For example, there is the potential for false-positive results that could lead to unnecessary follow-up testing or surgery—interventions that carry their own health risks. Screening tests may also cause physical, psychological, and economic harms by identifying abnormalities that would never become symptomatic or life-threatening—a challenge referred to as cancer overdiagnosis.[2]

New technologies and improved understanding of the genesis and progression of various cancers have added to the enthusiasm for potential new strategies to improve screening and early detection of cancer. These strategies may enable a personalized or "precision" approach to cancer screening and apply such innovations as blood and urine tests (referred to as "liquid biopsies") or genetic testing of cancer risk. Research is also under way to evaluate refinements in current screening approaches, including determining optimal screening intervals, the ages at which screening should begin and end, as well as more specific estimates of the potential risks and benefits of screening for certain populations, such as racial and ethnic minority populations and people who have elevated risk for specific cancers (IOM and NRC, 2003; USPSTF et al., 2016). However, there remain significant challenges to developing, validating, and effectively implementing these new approaches. In addition, guidelines for screening issued by different organizations vary considerably with no clear way of deciding which guidelines are most trustworthy.

Another challenge is ensuring that patients fully understand the potential benefits and risks of cancer screening so that they can engage in informed and shared decision making with their clinicians regarding their options (IOM, 2013). In addition, there is a need to improve access to high-quality cancer screening and follow-up care, particularly in low-resource communities and among populations who are underserved or have numerous barriers to receiving care (NASEM, 2017).

To examine the challenges and opportunities related to improving current approaches to cancer screening, as well as the evidence base for novel cancer screening methods, the National Cancer Policy Forum held a workshop, Advancing Progress in the Development and Implementation of Effective, High-Quality Cancer Screening, on March 2–3, 2020, in Washington,

[2] Cancer overdiagnosis is "the detection of asymptomatic cancers, often through screening efforts, which are either non-growing, or so slow-growing that they never would have caused medical problems for the patient in the patient's lifespan. Some of the detected tumors may even resolve spontaneously without treatment. They therefore represent an important cause of overtreatment, which can involve serious harms and toxicities such as deaths from surgery, major organ deformation or loss, and second cancers from radiation or chemotherapy." See https://prevention.cancer.gov/news-and-events/news/qa-what-cancer (accessed June 9, 2020).

DC. This workshop convened a broad range of experts, including clinicians, researchers, statisticians, and patient advocates, as well as representatives of health care organizations, academic medical centers, insurers, and federal agencies. The workshop included presentations and panel discussion on topics such as:

- Current knowledge and key gaps in the evidence base for cancer screening
- Opportunities and challenges in developing, modeling, validating, and implementing new technologies and tests for cancer screening
- Strategies to help patients understand the potential benefits, risks, and costs of cancer screening and participate in shared decision making with their care team
- Opportunities to reduce disparities in cancer morbidity and mortality by facilitating patient access to high-quality screening and follow-up care

This workshop proceedings summarizes the presentations and discussions and highlights suggestions from individual participants regarding how to improve cancer screening. These suggestions are discussed throughout the proceedings and are summarized in Box 1. Appendix A includes the Statement of Task for the workshop. The agenda is provided in Appendix B. Speakers' presentations and the webcast have been archived online.[3]

Workshop speakers discussed many facets of high-quality cancer screening, but did not attempt to create a formal definition for quality in the context of cancer screening. Many dimensions of quality in cancer screening were discussed in detail by speakers with different areas of expertise. These dimensions included factors such as use of evidence-based screening recommendations, informed and shared decision making, high-quality acquisition and interpretation of test results, affordability and accessibility, and appropriate follow-up care for diagnosis and treatment.[4]

CANCER SCREENING: PAST AND PRESENT

"In the past, there was a lot of enthusiasm about cancer screening holding the potential for early detection to save lives. More recently, this has been

[3] See https://www.nationalacademies.org/event/03-02-2020/advancing-progress-in-the-development-and-implementation-of-effective-high-quality-cancer-screening-a-workshop (accessed May 30, 2020).

[4] The consensus study report *Delivering High-Quality Cancer Care: Charting a System in Crisis* highlighted six components of high-quality cancer care (see IOM, 2013).

BOX 1
Suggestions from Individual Workshop Participants to Improve Cancer Screening

Strengthening Understanding of Cancer Biology and Biomarker Development

- Improve understanding of tumor biology—for screen-detected and interval cancers—and the microenvironment surrounding tumors. (Albers, Kramer)
- Annotate collected biospecimens prospectively with the method of diagnosis to assess the natural history of screen-detected and interval cancers. (Kramer)
- Develop better animal models of tumor progression to gain insights into the early steps of tumor formation and progression. (Kramer)
- Capture biomarker data from various institutions and deposit centrally with a "data concierge" that could issue crowd-sourcing challenges to scientists. (Srivastava)
- Leverage large population-based health care systems to create data and biospecimen banks for biomarker discovery and validation research. (Ransohoff)
- Create more collaborative, integrated, multidisciplinary networks for biomarker development and validation. (Ransohoff, Srivastava)
- Allocate funding and build alliances to support large-scale, multi-institutional biomarker validation studies and to maintain biorepositories as a national resource. (Srivastava)
- Incentivize the use of sound scientific methods. (Ransohoff)
- Apply artificial intelligence to analyze large biomarker datasets. (Srivastava)
- Expand Food and Drug Administration oversight of cancer biomarker test development, especially multiplex tests (similar to the drug development process). (Chinnaiyan, Papadopoulos)

Identifying Potential Study Endpoints for Cancer Screening

- Consider whether metastasis could be a valid endpoint for cancer screening studies. (Albers)
- Consider interim outcomes—such as stage shifts of tumors—in decisions about whether to move forward with test development. (Menon, Papadopoulos, Rubenstein)
- Use stage shift as a study endpoint only if it is definitively linked to reduced cancer mortality or morbidity. (Krist)

Improving Clinical Validation and Implementation Research for Cancer Screening

- Design interventional studies to assess the risks and benefits of a screening test, with an initial prioritization of specificity rather than sensitivity. (Papadopoulos)
- Collect real-world evidence after implementation of a screening test to assess usefulness in clinical practice and effect on cancer mortality. (Papadopoulos)
- Use prospective, randomized controlled trials as the gold standard for evaluating benefits and harms of new cancer screening tests. (Kramer, Krist, Papadopoulos)
- Improve the diversity of participants in screening research and conduct subpopulation analyses to assess effectiveness and potential harms. (Brooks, Krist)
- Leverage health economics to inform cancer screening program design, implementation, and evaluation. (Mandelblatt)
- Design studies to assess individualized screening that is based on the patient's history, risk factors, and values. (Krist, Lichtenfeld, Miller)
- Use implementation research and root-cause analyses to identify elements that lead to success or failure in the cancer screening process. (Krist, Lichtenfeld, Percy-Laurry)
- Develop best practices for shared decision making for cancer screening. (Pentz)
- Evaluate de-implementation strategies for cancer screening in people who are older than the recommended age group. (Albers, Kramer)

Developing Cancer Screening Guidelines

- Increase transparency in guideline development by disclosing the methodology used and the sponsoring organization's sources of financial support. (Brawley, Krist)
- Form an independent organization that grades screening guidelines to inform primary care clinicians about the quality of the various guidelines. (Pentz)
- Abandon screening methods that are determined not to be effective, even if resources and effort have already been invested. (Krist)

Implementing Care Delivery Models to Facilitate Cancer Screening

- Address patient, clinician, and organizational factors to facilitate timely follow-up care after an abnormal screening result, and monitor with metrics. (Geiger, Miller, Schmeler)

continued

BOX 1 Continued

- Use automated algorithms to facilitate communication with patients and clinicians about screening and follow-up care. (Menon)
- Create specialty cancer screening centers to which patients could be directed—similar to specialty centers for surgery. (Brawley)
- Increase the time for shared decision making in preventive care visits by eliminating other low-value routine procedures. (Barry)
- Leverage patient portals to provide information and decision aids about screening to patients prior to their visit. (Barry, Jimbo, Pignone)
- Engage allied health professionals, community health workers, and patient navigators to help inform patients about cancer screening. (Miller)
- Increase cultural competency of clinicians to reduce bias. (Miller)
- Use digital technologies to enable patients to obtain information, make appointments, and communicate with their clinicians, and improve outreach to populations that are underserved. (Doubeni, Miller)

Enhancing Education and Communication About Cancer Screening

- Tailor decision aids to balance broad use, low cost, and adequate specificity for individual patients. (Barry)
- Train clinicians in shared decision making and how to use decision aids, and measure whether they are used appropriately and effectively. (Barry)

replaced by a somewhat more sobered view with the growing awareness of the potential harms of cancer screening," said Ruth Etzioni, member of the Public Health Sciences and Biostatistics Program at the Fred Hutchinson Cancer Research Center. However, she noted that "technology is opening up new possibilities to improve early detection of cancers, including early detection of cancers that we have [previously] never been able to screen for. Thus, it is a very pertinent time to have the conversation we are having today."

Otis Brawley, Bloomberg Distinguished Professor of Oncology and Epidemiology at Johns Hopkins University, described the history of the implementation of cancer screening as disheartening. In the 1950s and 1960s, he said, misinterpretations of Pap smears led to many women being inappropriately treated for cervical cancer when they did not have the disease. Similarly,

- Offer training and resources to help ensure patients have the opportunity to actively participate in shared decision making and make their wishes known to clinicians. (Barry)
- Educate patients and clinicians about cancer overdiagnosis due to screening. (Kramer)
- Ensure clinicians convey the potential risks and benefits of cancer screening to patients in an accurate, comprehensive, and understandable manner. (Lichtenfeld, Miller, Pentz)
- Remove the word "cancer" from the subset of indolent, screen-detected lesions that are very slow growing and likely to be overtreated. (Albers, Kramer)
- Refrain from using overly simplistic and misleading messaging such as "screening saves lives." (Darien, Kramer)
- Engage with health journalists to counter misinformation about screening. (Pentz)

Enhancing Insurance Coverage for Cancer Screening

- Provide improved insurance coverage for follow-up care, including diagnostic testing following abnormal screening results. (Miller, Pignone)
- Consider what insurance companies can do to improve cancer screening (e.g., supporting clinical studies and the development of decision aids). (Esserman, Geiger)
- Pay for the time primary care clinicians spend communicating about cancer screening with their patients and any follow-up care. (Lichtenfeld, Pignone)
- Ensure that clinicians do not have a financial interest in a patient's screening decision. (Pignone)

he added that when mammography was first implemented for breast cancer screening in the 1970s and 1980s, mammograms were often misinterpreted. As a result, some women who were treated for breast cancer did not actually have the disease. "Many people think screening is all about finding cancer and if a test finds cancer, that's all you need to do," Brawley said. "Many don't appreciate that there are harms associated with screening, and often the harms [of certain cancer screening tests] are better proven than the benefits."

Carolyn Rutter, senior statistician at the RAND Corporation, said that screening recommendations are based on an assessment of whether the potential benefits of the screening test outweigh the potential harms. She said the benefits can include lives saved, as well as cancers prevented, late-state cancers prevented, and quality-adjusted life-years gained. The harms include factors

such as false-positive findings that can foster unnecessary anxiety, inconvenience, and cost due to downstream interventions, including further diagnostic testing that could lead to unnecessary treatment, pain, hospitalization, or even death, she and Brawley noted.

Early detection of certain cancers can increase the 5-year survival rates of those cancers, said Arul Chinnaiyan, American Cancer Society Research Professor at the University of Michigan and investigator at the Howard Hughes Medical Institute (Etzioni et al., 2003). However, Brawley stressed that 5-year survival rates are an inappropriate metric to determine whether cancer screening is successful. Brawley explained that a screening test can give the appearance of increasing the survival of those screened without actually prolonging life or reducing mortality from the cancer being screened. He said this effect is known as *lead-time bias*, which refers to the overestimation of the duration of survival among people with screening-detected tumors—compared to those who present with signs and symptoms of the disease—when survival is measured from the point of diagnosis (Welch et al., 2016). In this case, detecting a cancer via screening appears to increase the length of time a person lives with cancer after detection, and thus appears to increase survival. However, this increase in time is because the cancer was found earlier than if screening had not been performed, rather than because life expectancy was extended out farther. Finding the cancer earlier "doesn't necessarily mean that the patient is going to die later," Brawley stressed. For example, studies of chest X-ray screening for lung cancer in the 1970s found increased survival among screened patients, Brawley said. However, a retrospective study conducted years later determined that the increased survival was an artifact of lead-time bias and did not translate into reduced mortality from the cancer (Marcus et al., 2006). Screening works when both the tumor is found earlier and as a result, the patient lives longer than they would have if the screening had not been performed, Brawley stressed.

Therefore, he said, the only valid way to judge the success of cancer screening is to determine whether it decreases the number of deaths from the cancer being screened. This requires a prospective, randomized clinical trial in which study participants are randomly assigned to receive screening or to not receive screening. Brawley said that well-designed clinical studies have demonstrated a cancer-specific mortality reduction through mammography screening for breast cancer; stool blood testing, sigmoidoscopy, and colonoscopy screening for colorectal cancer; Pap and visual screening for cervical cancer; and low-dose spiral computed tomography (CT) screening in those who are at high risk for lung cancer. He added that such a reduction in mortality has not yet been shown for prostate-specific antigen (PSA) testing for prostate cancer or various screening approaches for ovarian cancer.

Breast Cancer

The United States Preventive Services Task Force (USPSTF) currently recommends routine mammography screening biennially for women aged 50 to 74, Brawley reported.[5] However, the American Cancer Society currently recommends annual screening for women of average risk aged 40–54, then biennially after age 55 years (ACS, 2020a). Brawley explained that there is controversy as to whether mammography is an effective screening test for younger women aged 40 to 49 years old, as well as whether screening should be completed every year or every 2 years. For example, Brawley said that mammography is not as effective at detecting breast cancer among women with denser breasts, or in younger women. He added that mammography is most valuable when it is completed routinely, so that a current mammogram can be compared against a previous mammogram. The quality of the image and the skill of the radiologist interpreting the mammogram also influence the effectiveness of mammography (Smith et al., 2015).

Brawley said that overdiagnosis is a particular concern with breast cancer screening, because certain cancers detected by mammography do not need to be treated because they are dormant or grow slowly (Smith et al., 2015). Although population-based estimates suggest that overdiagnosis occurs, it is not clear which individuals have cancers that are going to progress, and which ones will not need treatment.

The death rate for breast cancer has declined by 40 percent in the United States from 1975 to 2017 (ACS, 2020b); experts attribute approximately 40–50 percent of this decline to screening programs, Brawley noted, while the remainder is due to improvements in treatment (Berry et al., 2005). Currently, approximately two-thirds of women in the United States over the age of 50 undergo regular mammography screening (CDC, 2020). Brawley said that one modeling study estimated that an additional 5,000–6,000 lives could be saved from breast cancer each year by 2025, if 90 percent of women were screened annually when aged 45–54 years and biennially when aged 55 years and above (Mandelblatt et al., 2013). Unfortunately, he said, nearly 40 percent of women in the United States receive less than optimal care once their breast cancers are diagnosed. If all women received optimal care—with no change in screening rates—the same study estimated that approximately 11,400 to 14,500 breast cancer deaths could be averted by 2025 (Mandelblatt et al., 2013). Brawley stressed that ensuring women receive optimal therapy is just as important as ensuring access to high-quality cancer screening.

[5] See https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/breast-cancer-screening (accessed June 15, 2020).

Colorectal Cancer

Currently, the American Cancer Society recommends one of the following colorectal cancer screenings for adults ages 45 years to 75 years: a stool sample test annually, sigmoidoscopy[6] every 3 to 5 years, or a colonoscopy[7] every 10 years, said Brawley. USPSTF currently recommends screening for adults ages 50 years to 75 years old, and that clinicians consider offering screening to adults ages 76 years to 85 years old, taking into account a patient's overall health and prior screening history.[8] The recommendation noted that there are numerous screening tests that could be considered—each with varying levels of evidence supporting their effectiveness, as well as different strengths and limitations—including stool-based tests, direct visualization tests (e.g., flexible sigmoidoscopy, alone or combined with stool tests; colonoscopy; and CT colonography), and serology tests (USPSTF et al., 2016). All abnormal findings from non-colonoscopy screening should be followed by a colonoscopy to confirm the presence of the cancer (Smith et al., 2019). Although stool DNA tests have become widely available over the past 5 years, Brawley said they have some problems with specificity,[9] which has necessitated more follow-up testing with colonoscopy for some individuals. It is estimated that, between

[6] Examination of the lower colon using a sigmoidoscope, or thin, tube-like instrument with a light and a lens for viewing, that is inserted into the rectum. It may also have a tool to remove tissue to be checked under a microscope for signs of disease. See https://www.cancer.gov/publications/dictionaries/cancer-terms/def/sigmoidoscopy (accessed June 17, 2020).

[7] Examination of the inside of the colon using a colonoscope, or thin, tube-like instrument with a light and a lens for viewing that is inserted into the rectum. It may also have a tool to remove tissue to be checked under a microscope for signs of disease. See https://www.cancer.gov/publications/dictionaries/cancer-terms/def/colonoscopy (accessed June 17, 2020).

[8] The Task Force is currently updating its recommendations for colorectal cancer screening. The Task Force is expanding its recommendation for colorectal cancer screening to adults aged 45–49 (the recommendation for this age group is grade B. See Box 5 for more information on how USPSTF rates the evidence for specific screening recommendations). The Task Force further recommends that clinicians selectively offer screening for colorectal cancer in adults ages 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small. In determining whether this service is appropriate for specific individuals, patients and clinicians should consider the patient's overall health and prior screening history (the recommendation for this age group is grade C). See https://uspreventiveservicestaskforce.org/uspstf/draft-recommendation/colorectal-cancer-screening3 (accessed December 22, 2020).

[9] Specificity refers to the percentage of people who test negative for a specific disease among a group of people who do not have the disease. No test is 100 percent specific because some people who do not have the disease will test positive for it (false posi-

2000 and 2014, colorectal cancer screening reduced colorectal cancer mortality by approximately 34 percent among individuals aged 50 years and older (Smith et al., 2019).

Cervical Cancer

Cervical cancer prevention, screening, and treatment has been remarkably effective at reducing the number of deaths from this cancer, said Kathleen Schmeler, professor in the Department of Gynecologic Oncology and Reproductive Medicine at the MD Anderson Cancer Center. Human papillomavirus (HPV) causes nearly all cervical cancers, and the availability of an effective vaccine against HPV, as well as both a variety of methods for cervical cancer screening[10] and a long latency period (~10 years) from when precancerous lesions are likely to progress to cervical cancer, facilitate prevention through timely treatment of early-stage disease.

However, Schmeler said that not everyone has access to timely cervical cancer screening and treatment. Worldwide, cervical cancer continues to be prevalent in low-resource countries (Arbyn et al., 2020). "A lot of these very high cervical cancer rates are due to not having access to screening and not having the systems in place to take care of the women who have a positive screening test result," she stressed. In 2018, the Director-General of the World Health Organization (WHO) put out a call to action to eliminate cervical cancer (WHO, 2020). The draft "Global Strategy" proposed three main pillars: (1) vaccinating 90 percent of girls by 15 years of age; (2) screening 70 percent of women with an HPV test at 35 and 45 years of age; and (3) treating 90 percent of women with cervical disease for precancerous lesions or invasive cancer (WHO, 2020).

Brawley reported that more than 4,000 women die from cervical cancer each year in the United States.[11] Women who have low incomes are at higher risk for developing cervical cancer, said Schmeler, in part because they may have challenges accessing adequate health care services, including cervical cancer screening and follow-up care. She noted that cervical cancer is still

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tive). See https://www.cancer.gov/publications/dictionaries/cancer-terms/def/specificity (accessed August 20, 2020).

[10] Different methods of cervical cancer screening include HPV DNA testing, Pap tests, and visual inspection of acetic acid staining.

[11] In the United States, approximately 13,800 women will be diagnosed with invasive cervical cancer in 2020. Hispanic women are most likely to get cervical cancer, followed by African Americans, American Indians and Alaska Natives, and whites. Asians and Pacific Islanders have the lowest risk of cervical cancer in this country. See https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html (accessed June 17, 2020).

prevalent in certain low-resource regions of the United States, including the Rio Grande Valley along the Texas–Mexico border. Women in this region are almost twice as likely to die of cervical cancer compared to those in the rest of the United States, Schmeler said. (See Patient Access to Screening and Follow-Up Care for more information on the cervical cancer screening, treatment, and prevention program in the Rio Grande Valley.)

Lung Cancer

Lung cancer screening with low-dose spiral CT can save lives among people who are at high risk of developing the cancer due to their smoking history, Brawley said. A prospective, randomized controlled trial (RCT) of annual lung cancer screening among individuals at high risk demonstrated a 20 percent reduction in the rate of lung cancer mortality (NLSTRT et al., 2011). But this study also found that for every 5.4 lives saved, 2 people had a complication due to an invasive procedure that was part of the follow-up to the screening, and 1 of those people died as a result of the procedure (NLSTRT et al., 2011). But Brawley cautioned that that the results of this study may not be generalizable, both because study participants were not representative of the general population and participating trial sites may differ from community practice settings (e.g., the trial was conducted at a variety of academic medical institutions, many of which are recognized for their expertise in radiology and in the diagnosis and treatment of cancer) (NLSTRT et al., 2011).

Approximately 136,000 Americans die from lung cancer every year (ACS, 2020b) and lung cancer screening has the potential to prevent approximately 12,000 deaths annually (Ma et al., 2013). However, Brawley noted that even if all people receive high-quality screening, it could lead to 1,500 to 1,850 deaths due to adverse events from invasive diagnostic interventions, such as biopsies and bronchoscopies. Rutter pointed to an Agency of Healthcare Research and Quality decision aid[12] that illustrates the potential benefits and harms of lung cancer screening. For example, the decision aid notes that among 1,000 individuals at high risk for lung cancer who are screened with low-dose CT:

- 3 deaths from lung cancer will be prevented
- 18 people will die from lung cancer
- 356 people will have a false alarm
- 18 of the people with a false alarm will have an invasive procedure, such as a biopsy

[12] See https://effectivehealthcare.ahrq.gov/decision-aids/lung-cancer-screening/static/lung-cancer-screening-decision-aid.pdf (accessed December 22, 2020).

- Less than 1 of the 18 people who have an invasive procedure will have a major complication (e.g., infection, bleeding in lung, collapsed lung)

In comparison, among 1,000 individuals at high risk for lung cancer who are not screened, 21 people will die from lung cancer.

Clinicians may also find it challenging to determine which patients may be good candidates for lung cancer screening, because they may be unfamiliar with assessing a patient's number of pack-years smoked (which is used to determine eligibility for cancer screening) and clinical decision support software is not always designed to collect such data, said Michael Pignone, chair of the Department of Internal Medicine at The University of Texas at Austin.

Prostate Cancer

Chinnaiyan said that prostate cancer is the most commonly diagnosed cancer in American men, and it is the second leading cause of cancer-related death in American men after lung cancer (ACS, 2020b). The PSA blood test has been extensively used to screen healthy men for prostate cancer, but clinical trials have yet to demonstrate the effectiveness of this screening test in reducing all-cause mortality (USPSTF, 2018). Chinnaiyan said PSA is a protein found in blood and serves as a marker of prostate epithelial cells, not prostate cancer. Thus, an elevated amount of PSA in blood could be due to prostate cancer, or it could be due to a host of other factors unrelated to cancer. The lack of specificity of the PSA test for prostate cancer causes many false positives that lead to further diagnostic testing, including prostate biopsies and imaging.

Peter Albers, professor of urology and chair of the Department of Urology at Heinrich Heine University, Düsseldorf, said a study funded in part by Cancer Research UK found that offering all men aged 50 to 69 a single PSA test did not prevent deaths from prostate cancer over an average of 10 years of follow-up: men who received the PSA test were 19 percent more likely to be diagnosed with prostate cancer, but they were no less likely to die from the disease (Martin et al., 2018; NIHR, 2018). As many as half of prostate cancers detected by a PSA test will not harm a patient during his lifetime (Fenton et al., 2018; Moyer and USPSTF, 2012; USPSTF et al., 2018). Follow-up biopsies and treatment of indolent tumors due to an abnormal PSA test result, however, carry significant risk of harming a patient. For example, treatment may cause sexual dysfunction and urinary incontinence, as well as emotional and financial burdens for patients, Chinnaiyan stressed (Fenton et al., 2018). J. Leonard Lichtenfeld, deputy chief medical officer at the American Cancer Society, said the standard for success after a prostatectomy is that the patient experiences urinary incontinence three times per day or less, "but when a man

is incontinent three times a day, I am not sure he considers that a success." Chinnaiyan added, "we need to reduce the number of men who are undergoing unnecessary prostate biopsies and treatment, and we don't need to be detecting low-grade disease [that is unlikely to cause patients harm]."

USPSTF does not recommend PSA screening for prostate cancer in men aged 70 years or older. For men aged 55 to 69 years, the Task Force has a Grade C recommendation that individuals should decide, based on their own values and preferences, whether to undergo screening after discussing with their clinicians the potential benefits and harms of screening in light of their family history, race/ethnicity, and other existing medical conditions. Clinicians should not screen men who do not express a preference for screening, USPSTF states. The Task Force further noted that "screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and erectile dysfunction" (USPSTF et al., 2018).

Whether patients receive a benefit from prostate cancer screening is heavily dependent on what they value, stressed Alex Krist, professor at Virginia Commonwealth University and co-director of the Virginia Ambulatory Care Outcomes Research Network. "Some men care very much about false positives, anxiety, incontinence, and impotence, while some men care very much about doing anything to prevent prostate cancer," Krist noted.

The National Comprehensive Cancer Network (NCCN) states in its guidelines that only a PSA level greater than 3 ng/mL and/or a very suspicious digital rectal exam should trigger a subsequent workup, Chinnaiyan said (NCCN, 2019). Brawley noted that because of the uncertainty of whether PSA screening results in more benefit than harm, the American Urological Association calls for an individualized approach and shared decision making regarding the risks and benefits of testing before it is undertaken, proceeding based on a man's values and preferences.[13] Brawley added that these discussions are "why the patient–physician relationship is important [for prostate cancer screening]."

Ovarian Cancer

Usha Menon, professor of gynaecological cancer at the University College London, said that invasive epithelial ovarian cancers encompass cancers that originate in the ovaries, fallopian tubes, and peritoneum (Meinhold-Heerlein

[13] See https://www.auanet.org/guidelines/prostate-cancer-early-detection-guideline (accessed December 23, 2020).

et al., 2016). For decades, clinicians have been using blood levels of the protein CA125 to monitor ovarian cancer progression, recurrence, and response to treatment because its levels rise with increasing numbers of tumor cells. But CA125 can also be moderately elevated for other reasons, such as benign uterine fibroids.[14]

Although some clinicians use blood levels of CA125 to screen women at high risk for developing ovarian cancer, clinical trials have not demonstrated that such screening can save lives. Surgery is required to confirm a positive test result, so there are significant harms linked to CA125 false-positive tests among women in the general population. Menon said that the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) found that 14 women out of 10,000 women who received longitudinal CA125 screening underwent unnecessary surgery (Jacobs et al., 2016). Among these women, there was a major complication rate of 3 percent. Repeating CA125 blood tests at more frequent intervals than are currently used could potentially lead to more effective ovarian cancer screening, Menon suggested.

Overdiagnosis

Most cancer screening tests developed in the past few decades have focused on high screening sensitivity[15] to enable more detection of life-threatening lesions, which in theory would make the screening beneficial, said Barnett Kramer, former director of Cancer Prevention at the National Cancer Institute (NCI). Unfortunately, the focus on sensitivity without also putting a high value on specificity led to overdiagnosis of cancer and the harms that can be associated with overdiagnosis, he said. He described overdiagnosis as "the diagnosis of cancers that were never destined to cause harm or death in the individual in whom they have been diagnosed…. It is, in essence, curing large numbers of people who didn't need to be cured in the first place." Etzioni defined overdiagnosis as the detection of cancer that would not have been diagnosed without screening and that is followed by death from another cause before the cancer would have been diagnosed due to clinical symptoms. "Overdiagnosis is one of the most serious harms of cancer screening that pres-

[14] See https://www.mayoclinic.org/tests-procedures/ca-125-test/about/pac-20393295 (accessed November 13, 2020).

[15] Sensitivity refers to how well a test can correctly detect a specific disease or condition in people who actually have the disease or condition. No test has 100 percent sensitivity because some people who have the disease or condition will not be identified by the test (false-negative test result). See https://www.health.ny.gov/diseases/chronic/discreen.htm (accessed November 12, 2020) and https://www.cancer.gov/publications/dictionaries/cancer-terms/def/sensitivity (accessed November 13, 2020).

ents a huge biological challenge and clinical dilemma," Kramer said. Kramer pointed out that not only can people be physically harmed by unnecessary follow-up due to being overdiagnosed, but they can also be psychologically harmed by being told they have cancer even though the cancer will not physically harm them.

Overdiagnosis drives up the incidence rate for cancers without lowering the mortality rate from those cancers. "What happens is survival and cure rates skyrocket, but there's no impact on the risk of actually dying of the underlying cancer," Kramer explained.

For example:

- In 1993, thyroid cancer occurred in approximately 5 out of 100,000 people in South Korea, Brawley reported. Over the next two decades, thyroid cancer screening became more common across the country and by 2011, the rate of thyroid cancer diagnoses was 15 times higher than in 1993. However, the death rate from thyroid cancer stayed the same over this time (Ahn et al., 2014).
- As more CT scans have been performed for nonspecific abdominal pain, more kidney cancers have been detected. This increased the incidence of kidney cancer between 1975 and 2015, but the mortality rate did not change, Kramer said (Welch et al., 2019).

Kramer noted that overdiagnosis tends to occur when a disease has a long silent period during which the patient does not experience symptoms and screening detects that silent disease (Welch and Black, 2010). Overdiagnosis is particularly likely for slow-growing cancers, or cancers that are unlikely to progress and may even regress without treatment, he said. A lack of knowledge about the natural history of many cancers and which subtypes are unlikely to cause harm also underlies overdiagnosis, but it has been difficult to gather that information because it is not easily observed, unlike the symptomatic portion of an illness, Kramer noted. "Almost everything we know about the natural history of cancer comes from the traditional symptomatic cases that gave cancer its well-deserved fearsome reputation as one of the worst diseases society has to deal with," Kramer said. "We need to change the terminology as we learn more about the natural history of the screening-detected lesions. We should be removing the word 'cancer' from the subset of tumors that we know are very slow growing and likely to be overdiagnosed in order to achieve better informed consent and informed decision making," Kramer said. "We can detect anything if we try hard enough, but the point is to make sure we don't do more harm than the benefit we hope to accrue," said Chyke Doubeni, director of the Mayo Clinic Center for Health Equity and Community Engagement Research. For example, in the cases of pancreatic cancer

and ovarian cancer, there is a fine balance between the potential benefit from screening and the risk from the invasive nature of the treatment. "The harms are just as important if not more important than the benefits and should be thought about first because if we don't, we may do more harm than good," he said.

Overdiagnosis also can occur if screening leads to incidental findings that require medical follow-up but prove to be harmless, such as some lung and cardiovascular abnormalities that can be found during lung cancer screening (Tsai et al., 2018), said Rebecca Pentz, professor of research ethics at the Winship Cancer Institute at the Emory University School of Medicine. One study found that nearly half of the per-patient reimbursement associated with a lung cancer screening program was related to the evaluation of incidental findings, she noted (Morgan et al., 2017).

Overdiagnosis in older adults also carries unique population-specific considerations because older adults may be at a greater risk of dying from causes other than the cancer for which they are being screened. Kramer described results from the National Health Interview Survey showing that a large percentage of women and men (18–60 percent, depending on the screening test) aged 85 years and older had undergone a cancer screening in the previous 2 to 10 years, even though they were unlikely to realize a benefit from screening due to their advanced age and an increased likelihood of dying from a cause other than the cancer that might be detected (DeSantis et al., 2019). "A lot of people get screened who shouldn't get screened," Kramer said.

NEW SCREENING TECHNOLOGIES AND STRATEGIES

Determining whether tumors are fast growing or slow growing and nonthreatening is a major area of research that holds promise for reducing the overdiagnosis of cancers due to screening, Brawley said. Opportunities include developing tests that could screen for multiple cancers simultaneously by detecting key cancer-related genetic sequences or proteins in blood or urine. Another innovation is to conduct more personalized screening that considers an individual's cancer risk factors, as well as fine-tuning screening strategies to detect more aggressive cancer subtypes.

Multicancer Screening

Many tumors shed detectable levels of DNA or RNA fragments into the bloodstream, creating the opportunity to develop a "liquid biopsy" if those cancer markers can be identified among the multitude of other fragments shed by healthy cells, said Nickolas Papadopoulos, director of translational genetics and professor of oncology and pathology at Johns Hopkins Univer-

sity (Bettegowda et al., 2014). Several characteristics of tumors are relevant to the development of an effective liquid biopsy. For example, late-stage tumors tend to shed more DNA fragments than do those from early-stage disease, Papadopoulos noted, so liquid biopsies tend to be most sensitive for metastatic disease. However, some types of cancers do not seem to shed any detectable levels of fragments into the blood, perhaps because they are dormant or slowly progressing, Papadopoulos said. In addition, successful detection of precancerous lesions has been limited, which could be an advantage because these tests might be less likely to overdiagnose cancers. Using a combination of markers to detect cancer in a liquid biopsy would likely increase test sensitivity, as it does with the Cologuard® test for colorectal cancer, he said.

A primary challenge of detecting cancer using a liquid biopsy is ascertaining exactly where the tumor is located in the body, Chinnaiyan said. One idea that has been proposed to address this challenge is to layer on additional tests for tissue-specific biomarkers to help locate the tumor (Campos-Carrillo et al., 2020). There are already companies pursuing these technologies, Chinnaiyan reported. He and his colleagues have been studying circular RNA in blood and urine for its potential to detect both the presence of cancer and what cell type the cancer originated from (Vo et al., 2019). The advantage of using circular RNA as a biomarker, rather than linear RNA, is that circular RNA tends to be stable in biospecimens, he said.

Brawley expressed concern about some liquid biopsy tests already being used for screening in some clinical settings. "There are already some folks who have been told they have cancer and the good news is we found it early. But the really bad news is we don't know where it is or what to do about it," Brawley said.

Papadopoulos agreed that liquid biopsy tests have unique challenges. To address the problem of locating a cancer detected by a liquid biopsy, he said he follows up each positive liquid biopsy test with positron emission tomography-CT (PET-CT) imaging. He added that his vision is to integrate liquid biopsy testing as a component of routine cancer screening, rather than having such testing replace existing screening techniques. However, Papadopoulos noted that there are several potential advantages of a multicancer blood or urine test. For example, patients are more likely to comply with having a single test on a regular basis than multiple screening tests for different cancers, especially if those other tests are more invasive and inconvenient, such as colonoscopies. In addition, a liquid biopsy is more likely to be accessible than a more involved screening procedure such as mammography, so it can be implemented for more populations and potentially be more cost effective, Papadopoulos said.

Personalized Screening

Breast Cancer

Breast cancer screening recommendations are largely based on age, which ignores the complexity of breast cancer risk, said Laura Esserman, surgeon and professor at the University of California, San Francisco. "Low-risk women are over-screened, resulting in false positives that lead to diagnostic mammograms and benign biopsies, while high-risk women are under-screened, missing lethal tumors," Esserman stressed. Breast cancer screening is also resource intensive, with a cost estimate of between $8 billion and $10 billion annually, she said (O'Donoghue et al., 2014).

There is a growing recognition that breast cancer is not a single disease, Esserman said. Some breast tumors are more aggressive and faster growing than others, so screening will have different benefits for women with different types of tumors (see Figure 1). In addition, germline mutations in nine genes are known to confer greater risk of developing breast cancer, and there are other known genetic mutations that raise the risk of developing cancer in general.

Taking all of this information together, Esserman said, screening should reflect the new understanding of breast cancer biology, especially because the cost of genetic testing has decreased to approximately the same cost as for a mammogram. She said it might be time to abandon the traditional one-size-

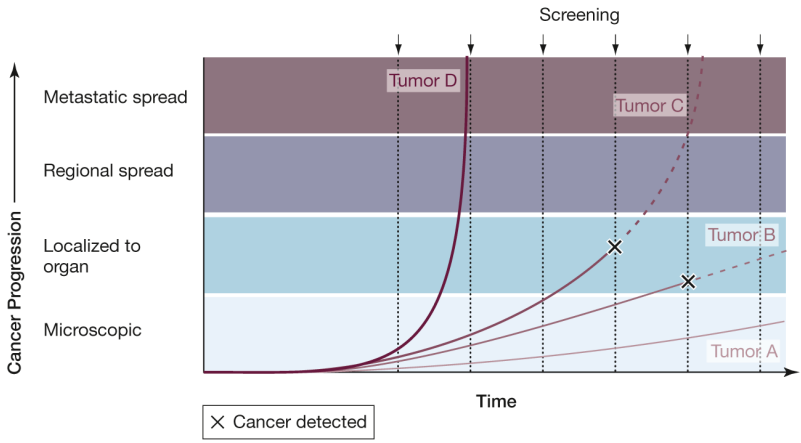

FIGURE 1 Breast cancer is not a single disease. Each tumor has a different trajectory of progression, and screening is not beneficial for individuals with tumors that progress rapidly.
SOURCES: Esserman presentation, March 3, 2020; Esserman et al., 2009.

fits-all approach to breast cancer screening and replace it with screening that leverages advances in the biology of breast cancer, risk assessment, and genetics that could potentially be more effective in finding clinically meaningful cancers. Such screening would be personalized for each individual woman, could be integrated with risk reduction strategies, and could be more efficient and cost-effective over the long term, Esserman added.

Esserman described several clinical trials aimed at personalizing breast cancer screening. She is currently leading the Women Informed to Screen Depending on Measures of Risk (WISDOM) study, which is designed to compare personalized risk-based breast cancer screening to annual mammography screening (Eklund et al., 2019). When she invites women to participate in the study, Esserman said she tells them, "Most women spend 30 to 35 years get-

BOX 2
WISDOM Risk-Based Breast Cancer Screening Trial

The WISDOM study, which aims to recruit 100,000 women in the United States, is comparing personalized risk-based breast cancer screening to annual mammography screening. The study seeks to determine whether personalized screening is as safe as annual screening, is more accepted by women, enables prevention, and has greater health care value. Study participants can choose to be in the randomized cohort or the observational cohort. Participants in the randomized cohort are randomized to receive either annual screening or personalized screening. Participants in the observational cohort choose which type of screening they wish to receive. As of this workshop, the study had enrolled more than 25,000 women, with more than 60 percent choosing to be in the randomized cohort.

The risk assessment used to tailor the personalized screening is based on validated risk factors such as exposures, lifestyle, breast density, mutations in 9 genes associated with breast cancer, and more than 300 single-nucleotide polymorphisms. Because the trial is studying risk-based screening and not a specific testing strategy, the researchers have the option of updating which tests they use to assess risk every 6 months. Esserman said, "As data matures and emerges, we incorporate it into the model. If there is a better breast density measure, then we would incorporate that. We tried to be very pragmatic in our approach." The investigators also plan to profile any breast tumors diagnosed in the trial to learn who develops which cancers, Esserman said.

ting mammography. Why not spend the next 5 years with us and help us get better answers for how best to screen you, your daughters, and your friends?" (See Box 2 for more information on WISDOM.)

Esserman described two other randomized, controlled trials aimed at combining innovative technology with a risk-based strategy to screen women for stage II breast cancer. The My Personal Breast Screening (MyPeBS) trial is being run across seven countries in Europe to compare the current standard breast cancer screening with a personalized strategy that screens high-risk women more often and low-risk women less often. Women in the lowest risk group (bottom 20 percent) do not undergo screening. TMIST (Tomosynthesis Mammographic Imaginging Screening Trial) compares 3-D mammography with conventional 2-D mammography to detect breast cancer

The trial is conducted virtually: participants register, complete questionnaires, and receive their screening plan entirely online. Genetic testing materials are mailed to their homes. "The trial comes to the participant and not vice-versa," Esserman noted.

Once a participant's combined risk is determined, she is given a recommendation for the age at which to start and stop screening as well as the frequency and modality of that screening. For women determined to be in the highest 2.5 percent of risk for developing breast cancer in their age group, a special decision tool was created that automatically integrates their individual risk information into visual representations and other information that compares their personal risk of developing breast cancer to others of the same age and race/ethnicity. It also provides them with information on interventions to lower their risk of developing breast cancer. "It can help make these women feel empowered as they learn what they can do to reduce their risk, which eases their anxiety," Esserman said. In a pilot test of the decision tool with 14 participants, 10 participants said they would be interested in lifestyle changes, and 6 participants said they would consider chemoprevention.

Esserman said the main grant for the study comes from the Patient-Centered Outcomes Research Institute, with insurers covering clinical costs of the trial. She has received another grant to increase participant diversity and accrual in the trial over 2 more years, and to translate the study materials into Spanish. She has also received funding to extend the WISDOM study to include female veterans. Esserman said she estimates that the WISDOM screening strategy will have a financial break-even point after 4 years and will be cost-saving thereafter.

SOURCE: Esserman presentation, March 3, 2020.

in women with no symptoms. All women in the trial will also be asked to submit blood and tissue samples, with the goal of personalizing breast cancer screening in the future based on genetics and other personal risk factors.[16]

Esserman also noted two recently completed clinical trials found that contrast-enhanced mammography performs better than 2-D or 3-D mammography when imaging dense breast tissue (Comstock et al., 2020; Destounis et al., 2015). Jeanne Mandelblatt, professor in the Department of Oncology and Medicine at Georgetown University, noted that 3-D is more expensive than 2-D mammography and may not be a good value given the limited gain in quality-adjusted life-years (Lowry et al., 2020). But Pentz added that 3-D mammography and 10-minute magnetic resonance imaging (MRI) may be better for some populations such as black women and younger women, both of whom typically have denser breasts (Comstock et al., 2020; Destounis et al., 2015; Rochman, 2015).

Prostate Cancer

Several workshop speakers called for improving prostate cancer screening beyond the traditional PSA test by adding MRIs, tests for genetic or protein markers for prostate cancer, and by taking age and other risk factors into account. "The PSA test has some challenges, so we should use it more intelligently," Albers said.

Albers said genetic changes occur over time, beginning in early-onset prostate cancer and continuing as the cancer becomes more aggressive (Gerhauser et al., 2018). For example, he said, it may be important to identify alterations in DNA repair genes early in the course of the disease. "There is a lot of scientific data that suggests that prostate cancer evolves over 20 to 30 years … so you have to be very precise in what you are diagnosing," Albers said.

Albers suggested several methods that might be used to improve detection of prostate cancer and reduce risk of overdiagnosis. These include tailoring screening by age-adapted risk groups and hereditary risk, as well as differentiating between aggressive and nonaggressive cancers prior to biopsy with multiparametric MRIs (which has not yet been systematically tested for screening but has been used for diagnostic testing), and analyzing serum or urine for molecular biomarkers associated with prostate cancer, such as hox gene expression and single nucleotide polymorphisms (SNPs). A combination of such tests could complement PSA screening, Albers noted. Chinnaiyan pointed out that the National Comprehensive Cancer Network guideline suggests that when PSA screening tests are positive, clinicians should consider other bio-

[16] See https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/tmist (accessed October 27, 2020).

marker tests or multiparametric MRI as alternatives to immediate biopsy. He reported that one test for early detection of prostate cancer—MyProstateScore (MPS)—combines results from serum PSA with levels of two other biomarkers in urine to predict aggressive prostate cancer and could potentially prevent many unnecessary biopsies (Sanda et al., 2017). "It's much better than PSA in discriminating low-grade from high-grade prostate cancer," Chinnaiyan said (Tomlins et al., 2016). Albers added that the European Randomized Study of Screening for Prostate Cancer (ERSPC) group and the Prostate Cancer Prevention Trial group have also developed apps for calculating personalized prostate cancer risk.

Albers described several clinical studies focused on refining PSA screening methods and guidelines. One large retrospective study found that men who had a PSA level greater than 1.6 ug/L at age 45 were far more likely to develop metastatic prostate cancer 25 years later than similarly aged men who had a lower PSA level (Assel et al., 2018). "This was astonishing because a small change in the elevation of this normal PSA value could predict many of whom in these 20,000 men would develop metastasis," Albers said.

Using this study as a baseline, Albers said he is conducting a clinical trial, PROBASE, that is randomizing 50,000 men to begin PSA screening at either 45 or 50 years of age. The hypothesis is that a PSA cutoff value would predict the 90 percent of men considered at low risk for developing prostate cancer so they would not need yearly or every-other-year PSA screening and could switch to screening every 5 years. The primary endpoint is to determine whether the initiation of screening can be delayed by 5 years. Other endpoints include determining whether overdiagnosis can be reduced and whether there is a change in metastasis rate after 15 years. "Ideally you could take three PSA values between 50 and 60 years and then predict that you will not develop prostate cancer for the rest of your life. This would be a good strategy for the 90 percent of low-risk patients," Albers said. Furthermore, Albers reported on another study in men aged 55 to 60 years old that found that a PSA level of less than 2 ng/mL was associated with only a 5 percent chance of developing clinically significant prostate cancer 13 years later (Kovac et al., 2020). Taken together, he said, "PSA baseline is not only able to detect cancer or to predict metastasis 25 years later, it can also indicate the probability of clinically significant cancers. Now we need long observational studies of these lower-risk cancers to determine when we should treat them." He suggested developing a new active surveillance strategy for such patients, perhaps using the new tests for molecular markers and MRI. Albers noted there are three other large studies in Europe (G2 Trial [Sweden], STHLM MR2 [Sweden], ProScreen [Finland]) that are assessing the benefits of adding biomarker tests, MRIs, and/or factoring in age to refine prostate cancer screening. "In the coming years, these trials will bring us a lot of information and hopefully help to decrease

the rate of overdiagnosis in prostate cancer," he said. In the meantime, Albers suggested that men with a low risk of developing prostate cancer could be screened with PSA testing every 5 years.

Ovarian Cancer

In an attempt to improve the performance of CA125 for the early detection of ovarian cancer, the UK team have used a longitudinal algorithm called risk of ovarian cancer (ROC) that considers longitudinal changes in CA125 blood levels to trigger more frequent CA125 testing, imaging, or surgery, resulting in a multimodal screening strategy rather than an isolated screening test (Menon et al., 2009) (see Figure 2).

She and her colleagues tested the strategy in the UKCTOCS randomized clinical trial of more than 200,000 postmenopausal women. She said that if not for using this strategy of looking at longitudinal change rather than a cutoff point, approximately one half of the ovarian cancers detected during multimodal screening would not have been identified (Menon et al., 2015). Improved detection results, compared with a cutoff point, were also found using other longitudinal CA125 algorithms, Menon reported (Blyuss et al., 2018).

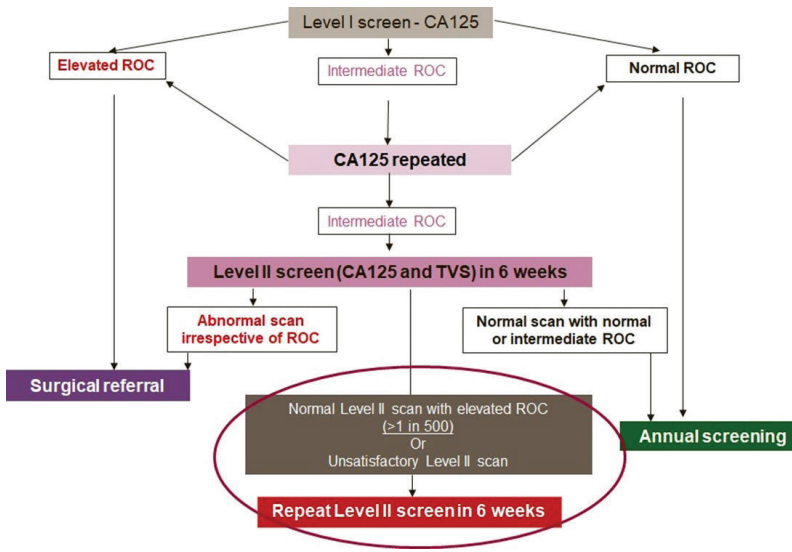

FIGURE 2 Strategy for multimodal ovarian cancer screening process in the UK Collaborative Trial of Ovarian Screening.
NOTE: ROC = risk of ovarian cancer; TVS = transvaginal ultrasound.
SOURCES: Menon presentation, March 2, 2020; Menon et al., 2009.

Menon noted that this screening strategy did not demonstrate a significant reduction in mortality from ovarian cancer unless prevalent cancers were excluded, but the data suggested that with further follow-up, a reduction in mortality might be identified in years 7–14 after onset of screening (Jacobs et al., 2016). In UKCTOCS, compared to the no screening control arm, in the multimodal screening group there was a significantly higher proportion of women who were diagnosed with earlier stage invasive epithelial ovarian, tubal, and peritoneal cancer (Jacobs et al., 2016). For example, she presented two individual case studies of study participants with rising but low levels of CA125 who, despite negative imaging findings, underwent surgery and were found to have early metastatic ovarian cancer, with extra ovarian lesions that could be easily removed. "The trial is teaching us that we have to focus on low-volume, surgically resectable metastatic disease as opposed to Stage 1 or Stage 2 for this cancer," Menon said. She noted that recent research has shown that many ovarian cancers rapidly become metastatic with little time spent in a precursor or localized tumor state, which makes early stage detection with screening less likely.

Menon said specificity for their multimodal screening strategy was 99.8 percent. She added that it also resulted in unnecessary surgery found 14 women out of 10,000 women who received longitudinal CA125 screening. Studies indicate that the multimodal screening strategy could potentially be cost effective, depending on the extent of the mortality reduction in the general population (Kearns et al., 2016; Menon et al., 2017; Moss et al., 2018), although it may only be cost effective in women at high risk of developing ovarian cancer (Naumann and Brown, 2018). Long term follow-up is ongoing in UKCTOCS, with results expected in January 2021, Menon noted.

CHALLENGES AND OPPORTUNITIES IN SCREENING TEST DEVELOPMENT AND VALIDATION

Chinnaiyan described five phases that he said a biomarker should pass through to go from discovery to clinical use (Pepe et al., 2001):

1. Preclinical exploration and initial studies to identify useful biomarkers.
2. Clinical assay and validation to determine the capacity of biomarkers to distinguish between people with cancer and those without.
3. Retrospective longitudinal phase to determine how well biomarkers detect preclinical disease. In this phase, the markers are tested against tissues collected longitudinally from research cohorts.
4. Prospective screening to identify the extent and characteristics of disease detected by the test and to determine the false referral rate.

5. Lastly, the biomarkers are evaluated in large-scale population studies on their ability to control cancer by their (a) role in detecting cancer, and their (b) overall impact of screening on the population.

He said this approach to biomarker development is used by the Early Detection Research Network (EDRN) (described in the next section).

Several speakers stressed that caution is warranted when evaluating biomarker tests for cancer screening. In a 2019 Medline search, Sudhir Srivastava, chief of the Cancer Biomarkers Research Group at NCI, said he found more than 60,000 papers published on cancer biomarkers each year, with 4,000 to 5,000 papers addressing biomarkers for early cancer detection, of which approximately 99 percent claimed to have greater than 90 percent sensitivity and specificity. Despite these results, Srivastava said that very few biomarkers are used in clinical care. He described the current state of biomarkers for cancer screening as akin to having "Water, water everywhere and not a drop to drink." Srivastava, Chinnaiyan, and David Ransohoff, professor of medicine at the University of North Carolina at Chapel Hill, provided several reasons for the lack of validated cancer biomarkers despite the extraordinary effort being made in biomarker discovery, as described further below. Problems can occur at any step of the biomarker development and validation process.

Preclinical Development

Chinnaiyan and Srivastava listed a number of points in the preclinical development of cancer biomarkers where errors can occur and mistakes can be made, such as lack of a defined clinical need; poor study design; lack of appropriate specimens and reagents; inappropriate statistical methods; bias, chance, and overfitting of data; failure to develop a reproducible assay; lack of validation; and incomplete protocol reporting. The invalid conclusions may still be published, Ransohoff said, if the protocol is not reported completely or if the scientific reviewers of the manuscript do not understand the biomarker technology well enough to assess whether the methods are appropriate. Furthermore, lack of protocol reporting will prevent other researchers from being able to reproduce the results,[17] Srivastava and Ransohoff both pointed out.

Another common mistake in biomarker studies is to test easier-to-acquire samples of late-stage cancer even though performance with early-stage cancer samples is critical for developing biomarkers for screening. "The vast majority of studies claim they are reproducible, but they are not really reproducible

[17] Reproducibility in science is defined as "obtaining consistent results using the same input data; computational steps, methods, and code; and conditions of analysis." See https://www.nap.edu/catalog/25303 (accessed December 23, 2020).

because they use convenience samples," Srivastava stressed. This is further compounded by a lack of understanding the biology underpinning many early-stage cancers, Srivastava pointed out. Because of the limited number of—and often inappropriate—biospecimens tested, many biomarker studies report unrealistic performance that fails to be replicated in other biospecimens, resulting in what Srivastava called "one-hit wonders."

Further complicating discovery is the selective publication of positive findings even though negative findings are also important because they help to improve the discovery and evaluation process, Srivastava said. Ransohoff expanded on this by noting that positive findings that are published in scientific journals can advance a scientist's career. Researchers do not deliberately falsify results, he said, but rather they succumb to "self-serving statistical sloppiness" in the absence of rigorous study design and analysis. Ransohoff stressed that this is a systems problem, and, citing Walter Deming, that "every system is perfectly designed to get the results that it gets." He said it is essential to ask what is wrong with a study design or study findings because such questions are critical to the progress of science. He quoted Richard Feynman, who said "Details that could throw doubt on your interpretation must be given, if you know them … if you know anything at all wrong, or possibly wrong—to explain it" (Feynman, 1974).

Lack of collaboration can also slow the progress of biomarker development. "It takes a multidisciplinary village to develop a biomarker," Srivastava said, and referred to the integrated collaborative approach of EDRN (see Box 3). But Ransohoff noted that when evaluating a new technology "asking what might be wrong can be especially difficult" because of the different perspectives of the various scientific disciplines involved in developing a test. Communication challenges can hamper such cross-disciplinary studies, he said.

Ransohoff also stressed the role that bias plays in the failure to validate biomarkers. He said bias occurs when the samples being compared differ systematically in some way other than having cancer versus not having cancer. Ransohoff said that bias in observational research is so difficult to avoid that researchers should consider "a study guilty until proven innocent." In preclinical biomarker discovery research, bias can occur in the selection of the biospecimens tested as well as in how they are analyzed, Ransohoff noted. Bias can be particularly tricky to detect if it occurs prior to sample analysis, such as differences in when or how cases and controls were obtained or stored. There can also be subtle differences in how samples are analyzed, which can introduce bias. For example, one study that analyzed serum for early detection of ovarian cancer was fatally flawed because the cancer specimens were analyzed using mass spectrometry on a different day than the control specimens, Ransohoff said. Mass spectrometry can drift over time, so the two groups were not truly comparable (Baggerly et al., 2005). Another study of a

BOX 3
Early Detection Research Network

The Early Detection Research Network (EDRN)[a] was established in 2000 by the National Cancer Institute (NCI) as a collaborative community to bring together dozens of institutions to help accelerate the translation of biomarker research into clinical applications, Srivastava said. EDRN has developed standard operating procedures for biospecimen collection and management, as well as a road map and study designs for clinical verification and validation.

EDRN includes biomarker development laboratories (which conduct biomarker discovery) and biomarker reference laboratories (which are generally certified under the Clinical Laboratory Improvement Amendments [CLIA]) to verify and develop the test for the putative biomarkers. These tests are then validated in EDRN's clinical validation centers. EDRN also leverages the expertise of many federal agencies, including the informatics system of the Jet Propulsion Laboratory, the National Institute of Standards and Technology, the Center for Prostate Disease Research, and the Pacific Northwest National Laboratory.

For its endeavors, EDRN relies on well-curated biospecimens at NCI, which are collected from multiple sites (to reduce bias) and include many samples from individuals with early-stage disease. EDRN also routinely tests biomarkers in other independent repositories of patient samples. The same samples are used to test multiple markers, which enables the evaluation of combinations of markers and saves time and resources.

Srivastava said EDRN promotes "data reproducibility and integrity, and we value negative findings because they help us improve our discovery and evaluation process." The network also provides checks and balances for unsubstantiated claims and data reproducibility, and it seeks to ensure that good biomarkers are further developed without regard to financial interests. EDRN also provides an economy of scale compared to the efforts of individual investigators.

With EDRN's support, 9 cancer biomarker diagnostic tests have gained approval from the Food and Drug Administration and 13 biomarker assay tests are available in CLIA-certified laboratories, although none are currently used for screening.

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[a] See https://edrn.nci.nih.gov (accessed June 2, 2020) and https://edrn.nci.nih.gov/resources/highlights (accessed June 2, 2020) for more information.

biomarker for early detection of prostate cancer was fatally flawed because the cancer biospecimens came from men whose mean age was 67, but 58 percent of the control group biospecimens were from women with a mean age of 35, Ransohoff said. Despite these glaring differences, the study went through the peer review process and was published (Villanueva et al., 2006). "The lesson is, even if you try to think about what might be wrong, you can miss it if you do not have experience in what to ask and where to look," Ransohoff said. He added, "There's no checklist of all possible biases to avoid. You must be thoughtful and motivated to ask what might be wrong in your research design to avoid fatal bias." But that can be challenging when multiple investigators with different expertise are involved in the research, he noted. "If each step requires different expertise, then that raises questions about communication, responsibility, and leadership," he said. Ransohoff concluded by stating, "The bottom line is: The promise in this field is great, but we need to explore it with stronger scientific methods."

Srivastava also described financial factors that hamper development and validation of biomarkers. These include the high costs of developing diagnostics, estimated at between $50 million to $143 million. Few companies are willing to invest such large sums into developing biomarker tests because they are considered high-risk ventures likely to yield a low, short-term return on investment. Consequently, discovery of biomarkers is largely done in academia, and funding for subsequent validation is inadequate. Although many academics rely on federal grants to conduct their research, government support for biomarker validation is lacking because validation proposals are not always hypothesis driven and score poorly in the current grant review process. In addition, validation often requires more time than the typical 5-year funding cycle of a federal grant, Srivastava said. Furthermore, Chinnaiyan added that it is hard to get academic credit for participating in this type of research.

Ransohoff described an example of a high-quality validation study that NCI conducted on five ovarian cancer blood tests for which researchers had claimed high sensitivity and high specificity but had yet to be validated. NCI designed a nested case-control study using serial blood samples from the biobank associated with the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) to compare the five new assays with the CA125 blood test to detect ovarian cancer in asymptomatic women. The study found the five new assays performed no better than CA125. Ransohoff said this type of validation study never would have been possible without NCI's large bank of high-quality biospecimens and the institute's power to induce investigators to perform head-to-head comparisons of these tests versus the CA125 test. "This is unlikely to happen with federal R01 grants or drug companies," Ransohoff said.

Demonstrating the Clinical Value of Screening

To demonstrate that a biomarker is effective for cancer screening, the biomarker has to be tested in a prospective clinical trial in the target population, Papadopoulos said. With some participants randomized into control arms, this study design can determine the clinical efficacy of the test. Papadopoulos said that endpoints for these types of trials need to be chosen carefully to help determine whether the test is likely to improve health outcomes and is thus worth the effort and cost to obtain regulatory approval. He noted that for some cancers, a screening test that causes a stage shift could make the cancer more treatable and could theoretically lower the risk of dying from that cancer, potentially making stage shift an endpoint worth evaluating.

Several speakers discussed the challenges in assessing the clinical value of a screening test, such as multiple types of bias, a nonrepresentative clinical population, insufficient time horizons in which to measure risks and benefits, findings that differ by subpopulation, and conflicting findings. As noted earlier, Brawley said that *lead-time bias* can contribute to an inappropriate assessment of a screening test because it may appear to increase survival; however, this increase in time can be attributed to the earlier detection of cancer.

Length bias is another type of bias that can occur during the clinical evaluation of a screening test. Length bias refers to the fact that screening is more likely to detect slow-growing, less deadly tumors, Brawley said. In contrast, screening is not likely to be beneficial for fast-growing, aggressive tumors because the tumor likely will have already spread by the time it is detected by screening and thus would be less treatable. Overdiagnosis is a form of length bias, Brawley said.

Selection bias can occur when people who volunteer for a trial are not truly representative of the general population. They may differ in overall health, health-seeking behaviors, or other characteristics, and thus the study results may not translate exactly to the real world, Menon said. For example, Menon said that in UKCTOCS, they had to extend screening and follow-up because the volunteer participants in the early years of the trial had one-third less the expected overall mortality compared to the equivalent UK general population (Burnell et al., 2011).

The study duration used to evaluate screening benefit significantly affects the degree of benefit that can be observed, Etzioni stressed. She noted that a study may not initially show much difference in the death rates between those screened and those not screened because screening conducted at the beginning of a new study may detect a number of cancers that already existed before the screening began, and they may be late-stage cancers that are less likely to be effectively treated. However, a difference in mortality rates between the screened and not-screened groups could become more pronounced with longer duration of study follow-up because new early-stage cancers will have

had time to appear, be detected, and effectively treated (Hanley, 2010). She stressed that lives saved over a long period of time may be dramatically higher than what is seen in limited duration trials. However, patients may ultimately have a different perspective on what timeline is important to them when considering whether to undergo screening, she said.

Etzioni described two main ways that reduction in cancer-specific mortality can be measured: *relative benefit* and *absolute benefit*. Relative benefit (also referred to as mortality rate ratio) is determined by dividing the number of deaths in the screened group due to a specific cancer by the number of deaths in the control group that did not receive the screening due to the same cancer, she said. Absolute benefit is the number of deaths in the control group minus the deaths in the screened group. Absolute benefit tends to be a lower number than relative benefit. For example, if there were 5 deaths per 1,000 men screened in the control group of a study and 4 deaths per 1,000 men in the screened group, the absolute benefit would be 1 life saved per 1,000 men screened, but the relative benefit is a 20 percent reduction in cancer mortality. Screening trials tend to emphasize relative benefit, whereas screening guidelines tend to rely more on absolute benefit, she said. "Benefit is usually presented as a single number, but it is a changing and moving target," Etzioni said. Ideally, benefit would be assessed in studies that followed participants for their entire lives but, Etzioni noted, "the time-limited nature of clinical trials means we cannot quickly determine absolute benefit, which is relevant to the policy setting." Menon pointed out that the United Kingdom has a new program called Accelerating Detection of Disease that aims to recruit up to 5 million individuals who will have various baseline and long-term data collected over many years to aid research on chronic diseases and cancer.

Demonstrating whether there is a benefit to screening can also be complicated by variability among different populations. For example, breast cancer screening might be more valuable for African American women because they are more likely to develop triple negative breast cancer, which tends not to respond to current breast cancer treatments, Lichtenfeld said. In addition, Krist noted that the benefits of screening may change if better treatments for cancer become available.

"Good test performance is not enough. We need to understand benefit and harm, which are very hard to quantify. This leads to an evidence gap that affects the development of sound health policies," Etzioni stressed. For example, she noted that in a study of a multicancer blood test developed by Papadopoulos and colleagues (CancerSEEK), the test was positive in 70 percent of 1,005 patients with eight types of cancer. The sensitivity was reported to be 69 to 98 percent in the detection of ovary, liver, stomach, pancreas, and esophagus cancers, all cancers for which there are no screening tests available for people of average risk (Cohen et al., 2018). Despite these tantaliz-

ing results, Etzioni stressed that there were several caveats to the study. For example, it was a retrospective study that was not designed to assess the value of the test for early detection even though such a test would be used in clinical practice to screen for cancers. Knowing that a test can detect cancer is only the first step, she said. Good analytical performance does not necessarily make a good test in clinical care, she said.

Another factor making it difficult to assess the value of cancer screening is conflicting findings in clinical trials due to differences in methods, Etzioni pointed out. She noted two large clinical trials of prostate cancer screening—one was conducted in Europe and showed a 20 percent reduction in prostate cancer mortality and one was conducted in the United States and showed no reduction in prostate cancer mortality. However, there were well-recognized differences between the two trials in their screening intervals, cutoff PSA levels for biopsy, compliance with biopsy recommendations, and other components, she said (de Koning et al., 2018; Otto et al., 2010; Schröder and Roobol, 2010). "These differences were very influential," Etzioni said.

USING MODELING TO COMPLEMENT CLINICAL EVALUATION OF SCREENING

Modeling Outcomes

Etzioni, Rutter, and Mandelblatt showed that modeling can be used to generate data from hypothetical trials, as well as to extend what is learned from traditional clinical trials, to provide information that policy makers can use to make screening recommendations. For example, modeling showed how the differences in study design in the prostate cancer screening trials previously described could lead to such different results, Etzioni said (de Koning et al., 2018). Model-based projections that analyze differences in the incidence of cancer between a control group and a screened group may also shed light on the natural history and progression of a cancer.

Rutter noted that it takes years to build and validate models but, once validated, researchers can use them to predict population-level lifetime risks and benefits of screening using a variety of interventions. For example, information about the prevalence of colorectal tumors and precancerous lesions can be modeled to estimate how long it may take for a colorectal tumor to initiate, grow to a specific size, and cause symptoms. In addition, information about how prevalence varies by age, sex, and race or ethnicity can be used to provide more personalized predictions about the impact of cancer screening. This is the type of information that underlies patient decision aids, Rutter said.

"Simulating optimal screening [practices through modeling] is important to inform what policy might be recommended, as long as what you are asking

people to do can be done in the real world," Rutter said. Alternatively, screening can be modeled based on what people realistically are likely to do, but this can be hard to predict, she noted. Realistic screening models have to consider access to high-quality screening as well as differences in treatments that could lead to differences in survival after screening.

Rutter provided several suggestions for reducing uncertainty in cancer screening models. To reduce uncertainty in predictions, the population size can be increased until the risks and benefits are estimated precisely. To reduce uncertainty about model assumptions and structure, Rutter suggested looking for consistency in results by using collaborative modeling and qualitative—rather than quantitative—comparisons. Uncertainty about unknown model parameters can be assessed with probabilistic sensitivity analysis that estimates or specifies a distribution for unknown model parameters and then samples from these distributions to predict risks and benefits. Such analyses are becoming more feasible with increasing computational capacity, she noted.

Modeling Cost-Effectiveness

Mandelblatt said that cost-effectiveness analysis models are defined as structured mathematical representations of all events in disease development and progression and their interactions with interventions for disease control and the associated costs. These models require defining every event that happens to patients, as well as the costs and probabilities linked to those events. She agreed with Rutter that it is important to consider uncertainty in models. Mandelblatt said that developing multiple cost-effectiveness models for the same problem of interest can facilitate identification of differences related purely to uncertainty in the input parameters or the structure assumptions of a model.

Mandelblatt stressed the importance of conceptualizing the problem of interest prior to designing a model, to make sure the model will address the right questions. She acknowledged that this may seem obvious but that it is important to emphasize nonetheless. This approach is similar to how USPSTF lays out its decision framework. She added that no single perspective represents the interests of all participants in value-based decisions about screening. Even the societal perspective, which may be best for society overall, may not be best for all participants.

Similar to the potential of study duration to affect observed mortality outcomes (see Challenges and Opportunities in Screening Test Development and Validation), the time horizon used in modeling cost-effectiveness should not be overlooked because some timelines are not long enough to consider all relevant outcomes needed to judge the value of some screenings, Mandelblatt cautioned. In addition, cost-effectiveness analyses will often be biased against

older populations and those with shorter life expectancies because they will have fewer life-years saved no matter what screening they undergo.

Mandelblatt noted that identifying the most efficient or cost-effective screening guideline is somewhat subjective. It varies according to availability of financial resources, screening program goals, needs of the target population, and preference for the balance of benefit to harm. She illustrated this using the following four examples:

Example 1: In CISNET analyses of the efficiency of mammography, Mandelblatt said they plotted the gain in life expectancy per 1,000 women screened against the number of lifetime mammograms per 1,000 women (Mandelblatt et al., 2009) (see Figure 3). This analysis—and a following one in 2016—indicated that the most efficient strategy was to provide mammogram screenings every other year (Mandelblatt et al., 2009, 2016). USPSTF, which does not base its recommendations on cost-effectiveness, decided to recommend screening every other year in women aged 50 to 74 to balance concerns about overdiagnosis among older women who are less likely to live long enough for the detected cancers to cause harm but who might suffer harm from the cancer treatment.

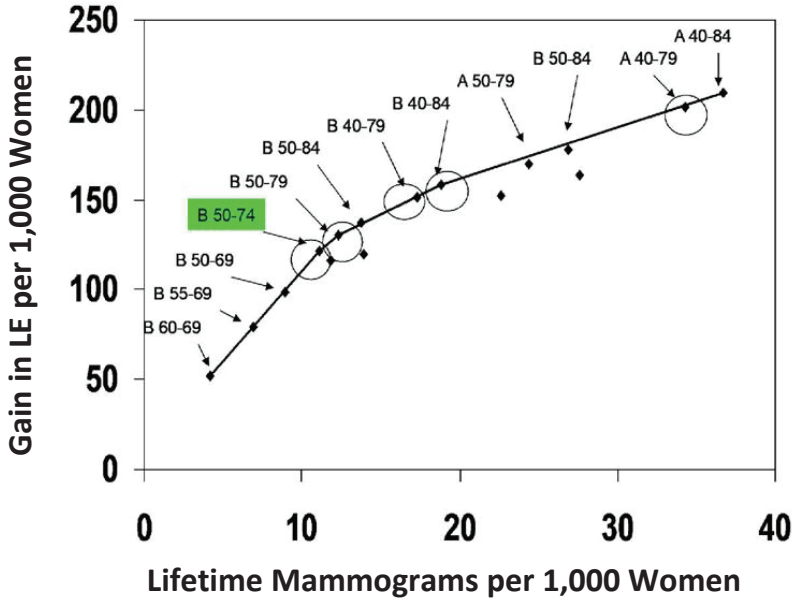

FIGURE 3 Modeling the efficiency of mammography.
NOTES: A is annual screening; B is biennial screening. Numbers refer to age ranges for which the annual or biennial screening would be performed. The green highlight shows the guideline USPSTF recommended in 2009. LE = life expectancy.
SOURCES: Mandelblatt presentation, March 2, 2020; Mandelblatt et al., 2009.

Example 2: Mandelblatt said the CISNET breast modeling teams worked with the CISNET prostate and colorectal cancer modeling teams to use modeling to examine the impact of comorbid conditions that can be an important determinant of screening benefits and harms. They used the models to estimate ages at which screening for prostate, breast, or colorectal cancer could be stopped based on an individual's level of severity of comorbid conditions (Lansdorp-Vogelaar, 2014) (see Figure 4). "Although these results are intuitive, clinicians do not necessarily have this type of guidance even though it is really important to consider," Mandelblatt said. She noted that CISNET models have been used for determining Medicare coverage, guideline recommendations, and to help construct patient decision aids for shared decision making in the clinic.

Example 3: Women who received radiation to the chest as part of their treatment for childhood cancer have a risk of developing breast cancer that is similar to women who carry a mutation in the BRCA1 gene, Mandelblatt said. Two models assessed mortality risk and cost-effectiveness of beginning breast cancer screening (mammography and/or MRI) in this population at various ages. The models made different assumptions about screening benefits and the added sensitivity of MRI beyond a mammogram; one model found several more years of life saved than the other model even though they were evaluating the same screening strategy (Yeh et al., 2019). "If we had published just one of these model analyses rather than both, you would have come to

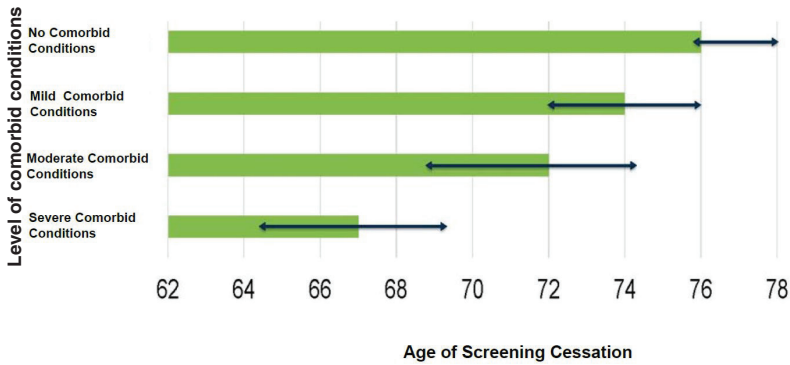

FIGURE 4 Age of screening cessation by comorbidity life expectancy.
NOTES: The green bars are the median ages, and the arrows are uncertainty bars of the ages that represent the range across all models and cancer sites. For no comorbid conditions, the lowest age of screening cessation across models and cancer sites coincides with median life expectancy.
SOURCES: Mandelblatt presentation, March 2, 2020; Lansdorp-Vogelaar, 2014.

very different conclusions. That is why collaborating with people to replicate your experiment is important," Mandelblatt stressed.

Doubeni said two common limitations of models are that they tend to assume (1) perfect adherence with screening, and (2) participant use of a high-quality screening facility where the harms from such screening are likely to be fewer than in a low-quality screening facility. "In minority populations, there is risk if we do not take that into consideration as we may be doing more harm than good," he added. He said he conducted a study that found African Americans are more likely to have cancers that develop between colorectal cancer screenings because of the poor quality of the screening. "These are things you cannot model, but I think are important for us to keep in mind," he said. Mandelblatt agreed that not only can the quality of screening differ between the real world and a model, but the quality of treatment can also differ.

GUIDING PRINCIPLES FOR DEVELOPING SCREENING RECOMMENDATIONS

Cancer screening recommendations are generated by advocacy organizations, medical professional societies, and other entities, such as USPSTF. Krist, a member of USPSTF, noted that preventive services are offered to healthy people who do not have symptoms of the health condition for which they are being screened. Most people will not develop the cancer they are screened for and therefore will not directly benefit from screening, but they are still at risk for the harms of screening. For that reason, he stressed, "We need to hold preventive services to a high bar before recommending them."

Krist said the process of determining cancer screening recommendations should be systematic, transparent, and free from conflicts of interest. It should also be based on the evidence of specific health outcomes and should consider both the benefits and harms of the screening, he said. The recommendations that result should be reproducible, Krist stressed, "So if you put different people together looking at the same evidence, they should be able to come up with the same recommendations." He also said recommendations should be clear and actionable for patients and clinicians, and they should respect patient values.

Krist said he recognizes that clinicians want definitive yes-or-no recommendations to clarify what they need to do for their patients, but he said sometimes this is not possible with the evidence in hand. Consequently, USPSTF grades the strength of the evidence underpinning their recommendations, sometimes leaving it up to clinicians and their patients to determine whether a specific screening should be carried out, based on professional judgment and patient preferences. Alternatively, it may grade the evidence as being insufficient to assess the balance of benefits and harms of a service. (See Box 4 for more detail on the process USPSTF uses to develop a recommendation.)

BOX 4
Recommendation Development Process of the United States Preventive Services Task Force (USPSTF)

Krist reported on how USPSTF develops its recommendations. USPSTF is an independent panel of volunteer experts in prevention and evidence-based medicine that makes evidence-based recommendations about clinical preventive services, including screening, counseling, and preventive medications, for adults and children with no signs or recognized symptoms of the disease in question. Its recommendations address services offered in the primary care setting or services referred by a primary care provider.

USPSTF makes recommendations based on rigorous review of existing peer-reviewed evidence, relying heavily on randomized controlled trials. USPSTF does not conduct any of its own research studies, although it systematically solicits input from relevant experts throughout its review process. Its evaluation of the benefits and harms of each service considers such factors as age and sex. USPSTF's screening recommendations require direct evidence that the screening reduces morbidity or mortality and thus improves health outcomes. Having an effect on intermediate outcomes (e.g., diagnosis or stage shift, in the case of cancer) is not sufficient. "It has to extend the length of life or improve the quality of life, not just increase survival time after diagnosis," Krist stressed.

USPSTF evaluates the quality of the studies it considers, including whether they have appropriate research design and whether the results are generalizable to the U.S. primary care population. It also assesses whether there are enough large studies with consistent findings to provide firm evidence for screening recommendations.

Once it has fully evaluated the studies, to grade its recommendations, USPSTF then considers the magnitude of the net benefit (benefits minus harms) of the preventive service as well as the certainty of that evidence. "A" and "B" grade recommendations indicate USPSTF recommends the use of the preventive service, in contrast to a "D" grade, which means USPSTF does not recommend clinicians use the intervention. A "C" grade is given for interventions that can be used in select populations, and an "I" grade is given when there is insufficient evidence to recommend for or against using the service (see the following Figure).

continued

BOX 4 Continued

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

FIGURE Definition of each recommendation grade of the United States Preventive Services Task Force (USPSTF) and suggestion for clinical practice.
SOURCES: Krist presentation, March 2, 2020. See https://www.uspreventiveservicestaskforce.org/uspstf/grade-definitions (accessed November 24, 2020).

Krist suggested that screening recommendations also be grounded in ethical principles, and Pentz expounded on those principles. She noted that identifying the risks and benefits of screening is a scientific process. However, weighing its harms and benefits has both statistical and ethical components "because you have to know how important those benefits and harms are to the people who will be screened," Pentz said. She said it is important to gather input from both experts and lay people, which could be in the form of diverse citizen juries or deliberative democracy techniques (Den Broeder et al., 2018; EPA, 2017; Safaei, 2015). Pentz provided one example of a 15-member citizen jury—balanced for sex, age, and education—that evaluated the PSA test for prostate cancer screening. The jury members were given a pamphlet of information and engaged with nine experts and with each other before being asked if they thought the National Health Service should discourage or recommend the PSA test for men aged 55 to 69 years old. Prior to this process, 60 percent of the 15 jurors—including all of the male jurors—thought that screening should be recommended, but afterward only 15 percent of the 15 jurors and 12 percent of the male jurors maintained that opinion (Mosconi et

Krist said USPSTF aims to have a reproducible, transparent process for developing its recommendations, beginning with anyone being able to nominate a topic for consideration via the USPSTF website.[a] Prior to finalizing its draft research plan on how it will search for the evidence for its recommendations, USPSTF seeks public comment and may adjust the plan according to those comments. It also solicits expert and public input on its draft recommendations prior to finalizing them. In the final report, every recommendation has a section specifying research gaps. There is also a section outlining clinical considerations, including a discussion of which populations are covered by the recommendation, as well as the need for future research to better inform screening recommendations for specific populations.

An annual report is provided to Congress describing what is known and what is not known. The National Institutes of Health (NIH) Office of Disease Prevention disseminates the report to other NIH funding agencies, which can use the information to inform future funding for grants. "Just like we need to know what the answer is, we also need to know what we don't know," Krist stressed. "Hopefully [funding opportunities will support] new research to fill the evidence gaps," he said.

[a] See https://www.uspreventiveservicestaskforce.org/uspstf (accessed December 23, 2020).

SOURCE: Krist presentation, March 2, 2020.

al., 2016). The jurors' concerns included the potential for false positives and false negatives, overdiagnosis, negative side effects of treatment, and the ratio of cost to benefit.

Once the harms and benefits have been weighed, there is still the conundrum of whether to apply public health ethical principles or clinical ethical principles when making a screening decision, Pentz said. Under the ethical principle of beneficence, public health ethics value what is best for the population at large, while clinical ethics value what is best for the individual. Similarly, public health ethics value justice for the population whereas clinical ethics prioritize justice for the individual. Public health ethics also have the additional principles of transparency and honest communication, which can be difficult to achieve because the public generally assumes that all screening is beneficial. Thus, patients need to be informed about the potential harms of screening so that they can understand the specific harms and benefits to weigh when making a decision about a particular screening test. Public health ethics also include the principle of reciprocity; that is, any harms should be appropriately compensated, Pentz reported (see Box 5).

BOX 5
Ethical Principles That May Apply to the Evaluation of Cancer Screening

Public Health Ethics Principles

- Emphasis is on the population
- Value what is best for the population at large (beneficence)
- Justice for the population
- Transparency
- Honest communication
- Reciprocity for harms resulting from screening
- When to apply: Screening benefit is high and risk is low

Clinical Ethics Principles

- Emphasis is on the individual
- Value what is best for the individual (beneficence)
- Justice for the individual
- When to apply: Screening benefit is low and risk is high or screening benefit and risk are equal

SOURCE: Pentz presentation, March 2, 2020.

In consideration of the ethical principle of non-maleficence, Pentz asked, "Can you harm an individual if it is a benefit to the population?" She said her personal opinion is that the answer is "yes" if the benefit to the population is very high and the risk of harm to an individual is very low. In that case, one should follow public health ethics. One such example is vaccination, where the benefits to the population vastly outweigh the harms to individuals, Pentz noted. "But what if the benefit and risk are equal or if the risk very high and the benefit is very low? Then clinical ethics principles should apply," she said.

When screening is of high benefit and low risk, compliance with ethical principles calls for an organized system of screening with regular patient contact and provisions for appropriate follow-up care, Pentz stressed. This is in contrast to opportunistic screening, she said, which depends on individuals having encounters with health care providers or on individuals initiating cancer screening on their own (Wender et al., 2019). When there are barriers to care (e.g., low income, less education, lack of health insurance, lack of geographical access to services, distrust in the health care system), an ethical and just screening system becomes less likely, even if it has the potential for high

benefit and low risk. (Barriers to screening are discussed further in the section Patient Access to Screening and Follow-up Care.)

When the risks and benefits of screening are equal and clinical ethics apply, then shared decision making between patient and clinician becomes critical and patient autonomy comes to the fore, Pentz noted. (For further discussion, see Shared Decision Making in the next section.) Clinical ethics also come into play when screening involves high risk and low benefit, Pentz said. This would entail not offering patients the screening unless they are uniquely at risk for the cancer that would be screened, she said. "Health care providers are not vending machines offering the same screening to every patient. As part of their ethical duty, they should offer only beneficial treatments and screenings," Pentz stressed. Regarding new screening technologies, Pentz said, "Bad science is bad ethics. Using good scientific methods to establish the risks and benefits is ethically required."

Brawley described what he termed an emotional conflict of interest that can adversely influence the development of screening guidelines. "There are groups out there for whom early detection and screening is of the utmost importance, but they don't understand basic concepts of screening," he said.

PATIENT DECISION MAKING

Shared Decision Making

"Trust begets shared decision making, and shared decision making begets trust," said Masahito Jimbo, chief of University Family Medicine Inpatient Service at the University of Michigan. Michael Pignone, chair of the Department of Internal Medicine at The University of Texas at Austin, said a high-quality, patient–clinician, shared decision-making process in the context of screening should include several key elements: patient engagement, patient recognition of the decision to be made, patient awareness of the alternatives and the potential benefits *and* harms of each option, awareness of the uncertainties in the decision, and consideration of the patient's preferences and values (Braddock et al., 1999). Pignone said, "You can't have a high-quality decision unless you have asked the patient about their preferences and values—not made assumptions based on what you think matters to patients, but actually asked them about what matters." Clinicians share information about risk and probabilities, but patients share information about what they care about, said Michael J. Barry, director of the Informed Medical Decisions Program at Massachusetts General Hospital. "It's a two-way transfer—not just patient education in one direction," he said. Both parties take steps to build a consensus about the preferred treatment and agree on the service to implement. Barry said a study he conducted found that across age, gender,

and education categories, most patients rate the importance of decision aids as very or extremely important (Wexler et al., 2015).

Pentz described the shared decision-making process as having seven phases: (1) bearings, (2) pathways, (3) amplification, (4) declaration, (5) enunciation, (6) enactment, and (7) emphasizing the importance of the patient's opinion (Bomhof-Roordink et al., 2019; Brown et al., 2004) (see Table 1 for a description of each phase). She noted it can be challenging to convey the complexity of screening to patients. For example, lay people often have difficulty understanding risk information, she noted. Even when patients are told the absolute risk of screening, their personal experience and frame of reference may lead a patient to overemphasize or underemphasize risks and benefits. Pentz said studies suggest that an evaluation of quantitative data does not generally play a role in patient decisions about risk (Lloyd, 2001; Reyna, 2004), while other research shows that individuals often overestimate the benefits and underestimate the possible risks of screening (Schwartz and Meslin, 2008). Jacqueline Miller, captain with the U.S. Public Health Service and medical director at the National Breast and Cervical Cancer Early Detection Program of the Centers for Disease Control and Prevention (CDC), added that people with low health literacy or numeracy may not understand or may be misinformed by information on screening, due to the level of interpretation that

TABLE 1 Phases of Shared Decision Making

Phases of Shared Decision Making	Definition
Bearing	Discusses the current health state and how screening fits in; ensures shared understanding of the present situation
Pathways	Explains both risks and benefits of screening
Amplification	Gives the patient the opportunity to express their reactions, thoughts, feelings, and to ask questions
Declaration	Provider makes an explicit screening recommendation
Enunciation	Patient articulates decision or delegates the decision to the provider
Enactment	Implements decision or describes next steps
Emphasizing the Importance of the Patient's Opinion	Invites the patient to become involved in the decision-making process and affirm the patient's opinion

SOURCES: Pentz presentation, March 2, 2020; Bomhof-Roordink et al., 2019; Brown et al., 2004.

can be required. Clinicians may also have personal biases that influence how they present information to patients. For example, Pentz said they do not want to believe that the tests they order could harm their patients, and a fee-for-service system tends to encourage more testing (Plutynski, 2012). Brawley stressed that the desire for screening "is based on a lack of rigor and a lack of appreciation of its limits as well as its benefits, even among clinicians. Some of us are just not truthful to ourselves." To achieve ethical shared decision making about cancer screening "we need to get the word out to overcome the pro-screening bias that has been the tradition in media and among health care providers and the public," Pentz emphasized. Pignone added that once a decision is made, patients should have the resources and support to carry out their decision.

Even though shared decision making involves consideration of a patient's values and preferences, Barry said that clinicians often misjudge those values and preferences. He noted a study showing that when physicians discussed with women the choice between a lumpectomy plus radiation versus a mastectomy and included a discussion of breast reconstruction, there was a lot of disagreement between what the physicians thought the patient was most concerned about and what the patients reported being most concerned about. For example, 71 percent of physicians thought keeping the breast was one of the most important considerations of their patients, while only 7 percent of the patients reported that it was (Lee et al., 2010). Barry said his colleagues refer to this as the "silent misdiagnosis of patient preferences." He quoted his colleagues who have written, "Many doctors aspire to excellence in diagnosing disease. Far fewer unfortunately, aspire to the same standards of excellence in diagnosing what patients want" (Mulley et al., 2012). Barry stressed that the patient is an expert on their values. He cited another study that found physician preference led to regional variation in how many patients were undergoing PSA testing; men living in Lebanon, New Hampshire, had less than a 4 percent chance of having a PSA test in the previous year, while men living in Miami, Florida, had more than a 58 percent chance of having a PSA test in the previous year. "It is very clear that this is driven by clinician, not patient, preferences. No one is born in Miami thinking they need a lot of PSA tests, but they get them," he said.

Barry said some of the variation between patient preferences on, for example, whether to have a PSA test, may be due to what he called "avoidable ignorance," which occurs when the facts are known, but the patients do not know the facts because they have not been given the facts or they do not retain or recognize the facts. He noted a study showing that less than half of patients correctly answered questions about cancer screening or risk of cancer diagnosis. For example, only about one-quarter correctly reported the low percentage of positive mammograms that result in a diagnosis of cancer, and only 17 percent

of patients reported correctly that a normal colonoscopy should be repeated after 10 years for someone of average risk (Fagerlin et al., 2010). "People aren't as well informed as we clinicians sometimes think they are," he said.

Jimbo noted that patient populations may experience shared decision making differently. For example, racial and ethnic minorities and patients who are less acculturated have been shown to have lower decision satisfaction, higher decision regret, greater knowledge gaps, and less trust in their clinicians and the health care system, while religion, spirituality, and family often play a greater role in their lives (Hawley and Morris, 2017). "Patients value different things," he stressed, noting marked differences have been found among various ethnic groups in the factors patients with breast cancer found very important when determining their surgical treatment (see Figure 5). Jimbo questioned whether traditional approaches to shared decision making might be too focused on (1) the individual while ignoring the role of the patient's family or significant other; (2) the transactional issues while ignoring the relational aspect of patient–clinician communication and the trust in the clinician's opinion that the relationship can engender; and (3) ignoring public health implications (Blumenthal-Barby et al., 2019).

Even when the shared decision-making process is implemented with the best of efforts, some patients do not want to be burdened with making their own decisions and prefer to be told what to do by their clinicians, Jimbo said. He said that one patient told him directly that he was a person who has to be told what to do. "He trusted my judgment," Jimbo said. However, he noted that a study found that less than 10 percent of patients have this preference of being told what to do (Murray et al., 2007).

Lichtenfeld stressed that messaging to patients should be both accurate and comprehensive. He noted that it is often not conveyed to women that HPV testing will not only reduce deaths from cervical cancer but also reduce unnecessary medical testing for pre-cancer diagnosis and treatment. "The problem is that we have catchy public health messages like 'Mammograms save lives' or 'Early detection saves lives' that fit well on a bumper sticker but really miss the complexity of screening," Esserman said. Brawley added, "Often the message is 'Get a mammogram' rather than 'Get a high-quality mammogram in a high-quality mammography program on a regular basis.'"

Patients can also be misinformed about screening due to direct-to-consumer advertising. Krist said that in a study he conducted of 1,000 wellness visits, he found clinicians spent an average of 2 minutes out of a 20-minute visit disabusing patients of direct-to-consumer advertising. Lichtenfeld added that a CDC analysis of direct-to-consumer advertising found that the advertising promoted additional testing that was not indicated by then-current standards (CDC, 2004). He said he also saw an Internet advertising campaign by a 3-D mammography company that told women to ask their clinicians why they

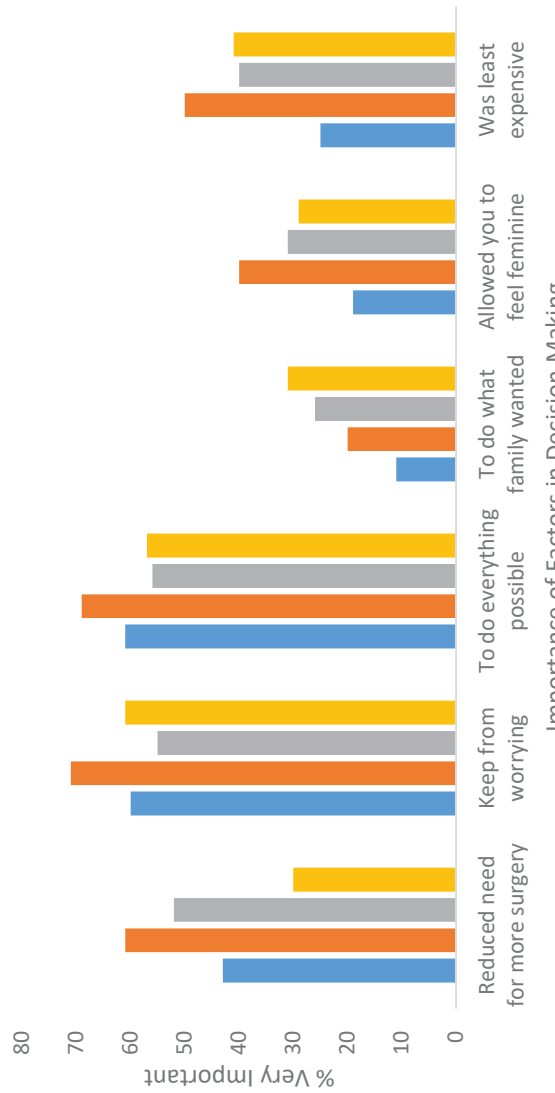

FIGURE 5 Proportion of patients with breast cancer indicating which factors were "very important" in their surgical treatment decision making, by race/ethnicity.
SOURCES: Jimbo presentation, March 3, 2020; Hawley and Morris, 2017.

are not up to date on using this new form of breast imaging for breast cancer screening (Szabo, 2019). On the other hand, Esserman pointed out that often there is a bias toward recommending new technologies on the part of clinicians even when those new technologies have not been shown to improve outcomes. She found in her own institution that clinicians were recommending 3-D mammography to women as being better than 2-D mammography, even though studies have not shown this and insurers were not covering it.

Although some patients are influenced by direct-to-consumer advertising, other patients may not trust the screening information given to them, especially if they perceive a conflict of interest or have distrust in biomedical research enterprise. Gwen Darien, executive vice president of patient advocacy and engagement at the National Patient Advocate Foundation, pointed out that HPV vaccine manufacturers extensively marketed the vaccine, which made some patients skeptical of the claims of benefit. "People want to trust their health care providers, but there is an ecosystem around clinicians that they may not trust," she said.

Several workshop speakers described a variety of logistical challenges in effectively communicating with patients about cancer screening. "Competing demands and time pressures are always important, especially in primary care where most of the decision making about cancer screening takes place. You are oftentimes competing with the patient's symptomatic complaints and their other chronic disease needs so communication about cancer screening has to be done efficiently as well as effectively," Pignone said. Esserman added that it can be challenging to do effective shared decision making with patients in a cost-effective way that is covered by insurers. Jimbo added that even in his health care system where primary care office visits are 40 minutes long for patients 50 years and older, he may have many different issues he needs to discuss with the patient during the visit. "If we have 20 things to talk about, do we really have time to talk about screening, too?" he asked.

To facilitate communication while also reducing time pressures, Pignone said that practitioners can deliver screening information and decision aids to patients before or after an office visit, or irrespective of an office visit, but few studies have assessed which option works best. Esserman agreed, saying studies measuring shared decision making during specific office visits may miss what is being done outside of that visit. Jimbo said that although information can be provided prior to an office visit, clinicians still need to set aside time during the visit to assess patient values and preferences regarding screening. He suggested that nonclinicians could provide information about screening prior to the patient meeting with the clinician, and Pignone suggested that a patient portal could be used. In addition, Pignone said there is limited recognition of the need for decision support overall. "Many people think they are informed well enough, but you don't know what you don't know," Pignone said.

Patient Decision Aids

Barry defined decision aids as tools designed to help patients participate in decision making by providing information on their options and helping them clarify and communicate the values they associate with different features of the options. He said a 2017 Cochrane review of more than 105 studies involving more than 30,000 participants found decision aids increased patients' knowledge, perception of involvement in decision making, accuracy of risk perceptions, and the consistency between patients' decisions and values (Stacey et al., 2017). Decision aids also decreased patients' feelings of being uninformed or unclear about their personal values, and they decreased the proportion of patients who remained undecided. Pignone noted the Agency for Healthcare Research and Quality (AHRQ) conducted a review of decision aids for cancer screening and found decision aids increased patient knowledge (Trikalinos et al., 2014). Barry said there are number of developers of patient decision aids, including AHRQ, Healthwise, and the Mayo Clinic. He added that the Ottawa Hospital Research Institute has an inventory of decision aids on their website,[18] and that the state of Washington has decision aid certification criteria based on international standards.[19] In addition, the National Quality Forum proposed the creation of national criteria for decision aids (NQF, 2016).

Barry cautioned that a decision aid may affect racially and ethnically diverse patient populations differently. For example, when Kaiser Permanente Washington introduced decision aids for hip and knee arthroplasty in 2009, they saw a substantial decrease in patients electing to have knee and hip replacements in their well-educated and perhaps overtreated population, Barry said. But when those same decision aids were used with African American patients being treated in Veterans Health Administration clinics in the Philadelphia area, the number of knee replacements increased (Arterburn et al., 2012; Ibrahim et al., 2013, 2017).

The usefulness of a decision aid may depend on how well it is tailored to the end user, Barry said. He said tailoring decision aids requires a balance of several factors, such as ensuring broad use, keeping expenses low to ensure access, and being specific enough to be useful for an individual patient. He said he designed his decision aid tools for patients with moderate health literacy to reach a broader population, noting that some decision aids use video, rather than relying solely on text, for patients who might have difficulty reading. He added that one study found differences in end-of-life decision making that were originally attributed to race and ethnicity but were actually due to

[18] See https://decisionaid.ohri.ca (accessed November 24, 2020).

[19] See https://www.hca.wa.gov/about-hca/healthier-washington/patient-decision-aids-pdas (accessed December 2, 2020).

differences in health literacy and could be overcome with the right decision aids (Volandes et al., 2008).

Pignone said his comparative trials of tailored decision aids versus more generic decision aids found that decision aid developers, in general, overestimate the need for precise information. He said that numbers used in decision aids "are salient but not as important as many of us coming from clinical epidemiology and a very quantitative background might think. I generally tend towards more simple information." On the other hand, he also cautioned about information being so generic in a decision aid that it is not relevant for some patients. "Don't give people information that is not relevant to them, and don't make it so complicated that the implementation of the decision aid becomes too challenging or even impossible," Pignone said.

Barry said he has found that decision aids have the most influence on patients who are undecided about a particular intervention. "You don't change many minds if people are pretty convinced ahead of time, but the people who are not sure can get off the fence," he said (Barry et al., 2015). Jimbo agreed, adding that if patients have already come to a decision on their own, then a shared decision-making process with their clinician may be superfluous.

PATIENT ACCESS TO SCREENING AND FOLLOW-UP CARE

Screening

Studies show that individuals with lower income and less education, and without insurance, are less likely to be up-to-date with screening, Pentz said (Carney et al., 2012; Damiani et al., 2015; White et al., 2017). She and Miller listed several barriers patients may encounter that impede their access to high-quality cancer screening. These include a lack of health services available in their community; inadequate health insurance or resources to pay for screening or treatment if cancer is detected; having other health issues, such as uncontrolled diabetes; and a legacy of self-reliance and the belief that no medical care is required or a fatalism that such care will not help (Beeken et al., 2011; Drew and Schoenberg, 2011). Pentz noted that several of these barriers have been found to influence patients who are eligible for and have the potential to benefit from lung cancer screening, but still choose to opt out of the screening (Carter-Harris et al., 2017). She added that as new screening technologies become available, there may be barriers to accessing them because they may not be available in some areas or they may be cost prohibitive for some patients (Newman and Yip, 2020).

Mistrust of the medical system is another barrier that has been shown to contribute to lower rates of colorectal cancer screening among African Americans, Pentz said (Adams et al., 2017). Miller added that patient distrust

of clinicians can be exacerbated by unconscious biases—that is, preconceived ideas the clinician has about the patient. For example, unconscious bias may lead a clinician to refrain from ordering screening tests if they perceive that a patient will not be able to afford them. "Justice demands that we attempt to remove all of these barriers," Pentz stressed.

Miller and Darien noted that the social determinants of health can be major barriers to accessing cancer screening and follow-up care. Darien said that competing priorities, such as a work, child care, or other caretaking responsibilities add to the patient burden of obtaining cancer screening. "We are not going to have appropriate cancer screening until we deal with the psychological, financial, life, and administrative burdens," Darien said. Jimbo agreed, adding, "We docs think health care is so important and should be the number one priority for every patient, but it is not."

Follow-Up Care

Ann Geiger**,** scientific director of Cancer Care Delivery Research in NCI's Community Oncology Research Program**,** noted that follow-up care after an abnormal screening result has multiple steps that can be complex from the viewpoint of a patient, clinician, and health care organization. These steps include a referral and making an appointment for follow-up care. She added that clinicians work in teams with processes that can help or hinder the efficiency and effectiveness of obtaining follow-up care, depending on how they are organized.

A sizable proportion of patients do not receive follow-up care after receiving abnormal findings from a screening test for breast, colorectal, or cervical cancer, Geiger said (Tosteson et al., 2016) (see Figure 6). Several studies have tried to identify factors that lead to differences in receiving timely follow-up care after an abnormal screening result. She said that the barriers to timely follow-up are similar to the barriers of cancer screening, including being older and sicker; a lack of or inadequate insurance coverage; high out-of-pocket costs; fear; insufficient understanding of the seriousness of the abnormal screening result; lack of transportation; competing demands (e.g., child care and work); inadequate social supports; scheduling difficulties; and not having a regular clinician or not trusting a clinician.

One study of follow-up care after an abnormal fecal test result in a safety net hospital serving a low-income population found that found 22 percent of cases lacking timely follow-up could be attributed to health care organizational errors, and an additional 18 percent was attributed to clinician factors, Geiger said (Martin et al., 2017). The organizational errors included staff inaction on processing the referral and scheduling difficulties (Martin et al., 2017). The clinician factors included lack of awareness of the abnormal test result and

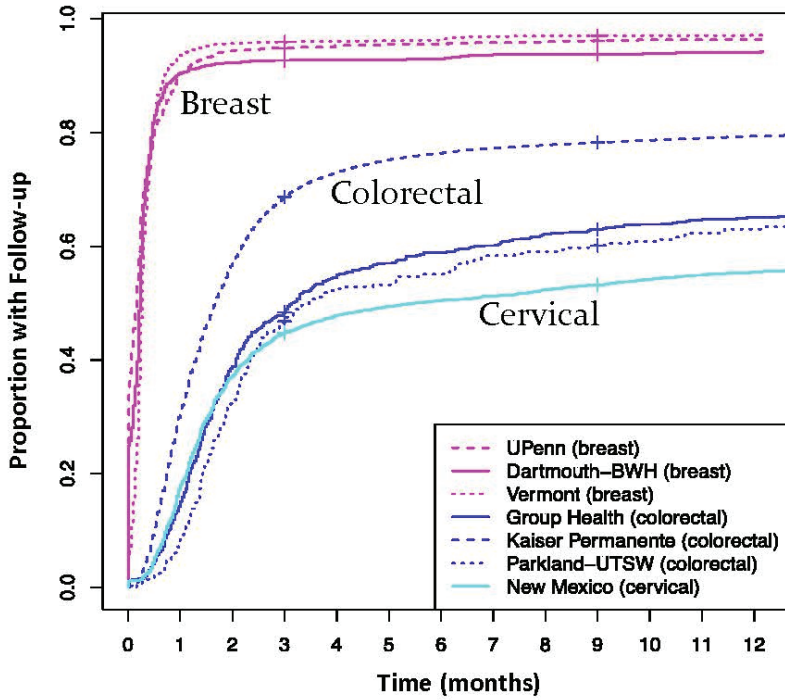

FIGURE 6 Variation in follow-up after an abnormal screening result, for breast, colorectal, or cervical cancer screening.
SOURCES: Geiger presentation, March 2, 2020; Tosteson et al., 2016.

failure to recommend a follow-up colonoscopy (Martin et al., 2017). "It may not be clear who is really supposed to follow up with the patients with all sorts of things dangling outside the clinical workflow," Geiger said. She described another study that found that the percent of patients who obtained a follow-up colonoscopy within 12 months after receiving an abnormal colorectal cancer screening result varied from 58 to 84 percent depending on which of four different health care systems the patient attended, even though all four systems were strongly committed to screening (Chubak et al., 2016). Failure to follow up on abnormal results within 10 months significantly increases the likelihood of being diagnosed with advanced stage colorectal cancer, she noted (Corley et al., 2017). "Different organizations achieve different outcomes. It is not just about patients and doctors," she stressed. Geiger emphasized that "we cannot hold patients accountable for all of this. We are going to have to address clinician, and more importantly, organizational factors. We need to make these environments work for follow-up." Geiger said she is increasingly

hopeful about improving the quality of follow-up care through research to identify best practices for integrating follow-up of abnormal screening results into the clinical workflow of teams. Brawley stressed that ensuring patient access to high-quality follow-up care is just as important as ensuring access to high-quality cancer screening.

Schmeler said she practices medicine in a low-resource area of the Rio Grande Valley along the Texas–Mexico border, where there are very high rates of cervical cancer relative to the rest of the United States and women are almost twice as likely to die of cervical cancer compared to those in the rest of the United States. She said some women who are undocumented or who have family members at home who are undocumented are afraid to travel to clinics for cervical cancer screening or follow-up care, even when the clinic is close to their home. Schmeler said most of her patients with advanced cervical cancer report having had a cervical cancer screening with an abnormal result in the previous 5 to 15 years, but they did not obtain follow-up care. (See Box 6 for a detailed description on work the MD Anderson Cancer Center is doing to facilitate access to screening and follow-up care in the Rio Grande Valley.)

BOX 6
Cervical Cancer Screening and Follow-Up Program at the MD Anderson Cancer Center

Schmeler reported on the MD Anderson Cancer Center's cervical cancer screening and follow-up program in the Rio Grande Valley, which is a rural area along the Texas–Mexico border. This population is 90 percent Hispanic, with many uninsured and undocumented individuals living in the area. About 40 percent live below the poverty line and less than 10 percent of eligible women undergo cervical cancer screening. The area also has a limited number of clinicians trained to care for women who receive abnormal cervical cancer screening results. Women in this region have nearly twice the likelihood of dying from cervical cancer as those in the rest of the United States.

To address this lack of screening and high rate of cervical cancer in the region, the MD Anderson Cancer Center, in collaboration with the University of Texas, initiated a cervical cancer screening and follow-up care program in 2015. The program takes a multipronged approach to preventing cervical cancer by providing a school-based vaccination program for human papillomavirus

continued

BOX 6 Continued

(HPV), community education and outreach, and increased access to cervical cancer screening with patient navigation. To address the paucity of clinicians in the region who treat uninsured patients, the program also works with a mobile clinic (van) and trains, educates, and supports local clinicians with telementoring video-conferences so they can effectively manage the follow-up care and treatment for women who receive abnormal screening results. All care is provided for free due to grant support.

To date, more than 1,000 middle school students have received the HPV vaccine free of charge, and nearly 20,000 women have been screened for cervical cancer. The program has significantly increased the number of women receiving proper treatment for pre-invasive cervical cancer, with more than 3,000 colposcopies or loop electrosurgical excision procedures (LEEPs) performed. Only one-third of this number of procedures was done in this region prior to the program opening. The program has been expanded to five other regions in Texas.

To further improve the program, the MD Anderson Cancer Center researchers are trying to develop new technologies to make screening, diagnosis, and treatment more streamlined so fewer clinic visits are needed. Currently in the United States, cervical cancer prevention may entail three clinic visits. The first visit is for a Pap test and HPV testing. If the Pap is abnormal, a second visit is required for colposcopy with a cervical biopsy. If the biopsy shows significant precancerous lesions, then a third visit is required to remove the lesions with a freezing technique, LEEP, or surgery. Each of these steps requires pathology services, which are expensive and may not be locally available, and in between each step is the risk that the woman may not return for her follow-up care.

To help eliminate steps, the program has developed and is testing a paper-based HPV test akin to a pregnancy test that can be administered by nonmedical staff, and a device for performing visual inspection to diagnose pre-cancerous lesions without removal of tissue or pathological analysis (Hunt et al., 2018). "Self-sampling HPV testing is going to be a game changer if we can get a cheap enough test because it will help us reach women who cannot travel, will not travel, or do not want to have an exam," Schmeler said, noting that many undocumented women are afraid of traveling. The program is also trying to align cervical cancer screening with family planning visits.

Doubeni stressed that "the evidence supports the conclusion that disparities exist because there is some fundamental difference in the way people access, use, and are able to benefit from screening and follow-up services." He added that bias and stigma play a role in perpetuating these inequities, and encouraged workshop participants "to think about how we can improve access to the right kind of cancer screening, prevention, and treatment for populations for whom, historically, access and treatment quality have been poor and who have [experienced] a history of social injustice."

POLICY SUGGESTIONS TO IMPROVE CANCER SCREENING

Workshop participants provided a range of policy suggestions to improve cancer screening. Some were related to research, development, and clinical testing of screening technologies and strategies, while others were directed at improving the screening guidelines development process. Suggestions were also made on how to change health care organization and delivery to meet screening needs, improve communication and education of patients and clinicians, and provide insurance incentives.

Research, Development, and Clinical Testing of Screening Technology

Research and Development

Krist stressed the necessity for greater awareness of what is needed for each step in the development and validation of cancer screening tests. "We need to think of this as a whole life cycle and not get stuck in one of its boxes—there is no free ride at any step of this," he said.

A critical gap to be filled at the very beginning is understanding the basic biology of the cancer being screened, several participants said. Albers stressed the need for better understanding of tumor biology to enable determination of who will truly benefit from early detection, especially for prostate and other cancers that may be present for decades before they cause clinically significant symptoms. Kramer added, "We need to know more about the underlying biology of tumors and their microenvironment—the molecular patterns that tell us with precision whether an individual has been overdiagnosed or not." He said that the molecular biology of a tumor provides information about natural history, and that studying the relatively healthy tissue surrounding the tumor can be helpful for learning how the organ as a whole is responding to the presence of the tumor. To aid such research, specimens should be collected and annotated prospectively with the method of diagnosis because the natural history of an asymptomatic case detected via screening is different from the natural history of a case detected after the patient experiences symptoms,

Kramer said. He suggested looking for molecular patterns in screen-detected cases, which are more likely to include overdiagnosed lesions, as well as in cases that develop between screening intervals, which are more likely to be aggressive cancers. Kramer also pointed out that active surveillance—which is offered to some patients with early-stage prostate cancer, Barrett's esophagus, and melanoma—could be informative of the natural history of indolent lesions. In addition, he suggested the need for better animal models of tumor progression to gain insights into the early steps of tumor initiation and progression.

Ransohoff and Srivastava offered suggestions to increase the availability of large volumes of data for study and analysis. Srivastava suggested that biomarker data be captured from various institutions and deposited centrally with a "data concierge," who could then issue a crowd-sourcing challenge so scientists can access and analyze the data and verify their findings. Ransohoff suggested leveraging large population-based health systems, such as health maintenance organizations (HMOs) or VHA, to create high-quality study participant and biospecimen banks for biomarker discovery and validation research. He said developing this kind of infrastructure is cumbersome, a bit risky, and expensive while also being unattractive to funders, although it may get easier in the future with wider availability of interoperable electronic health records and wearable health trackers.

Srivastava recommended creating more collaborative communities for biomarker development and validation, which requires a team effort over a long period of time. The communities could have an infrastructure akin to the National Clinical Trials Network and should include resources and integrated systems for new biomarker development and validation trials, along with the collaboration and coordination required to maintain a network of multidisciplinary groups and institutions. Srivastava stressed that this type of integrated approach is needed to adapt to the rapidly changing field of biomarker science. An integrated network would also be able to respond to Congressional directives on "recalcitrant cancers" (e.g., pancreas, liver, lung) and to the overdiagnosis of cancers.

Srivastava also suggested allocating adequate funding for conducting large-scale, multi-institutional biomarker validation studies and to maintain biorepositories as a national resource. "Public support for biomarker development is critical," Srivastava stressed, adding, "Public–private partnership is critical for accelerating progress. We need to build alliances, with support from investors around the country, to support large validation trials." Sara Brenner, associate director for medical affairs and chief medical officer for in vitro diagnostics at the Food and Drug Administration (FDA), added, "Any type of federal policies that encourage collaboration between the public and private sectors and encourage longitudinal thinking are going to lift all boats and help us get closer to achieving the end goal of improving patient outcomes."

To counter a lack of scientific rigor, Ransohoff suggested considering ways to motivate researchers to improve the strength of the science and to establish systems that incentivize sound scientific methods. He also suggested changing the culture of research enterprises so that it is routine to ask "What might be wrong?" when planning research, and to enable input from a broad range of expertise, such as clinical epidemiologists, biostatisticians, and experts in relevant technology and biology fields. Chinnaiyan suggested that the process for developing cancer biomarker tests, especially multiplex tests, should be more akin to the regimented process for drug development, in which FDA is highly involved.

Srivastava said artificial intelligence (AI) needs to be applied in biomedical settings to analyze the large amount of biomarker data that will be generated in the coming years. However, Ransohoff cautioned about the risks of algorithmic bias when using AI tools, especially in the absence of adequate data: "We still need the real world to anchor the variables we're trying to predict with machine learning. Machines learn from real data, but we don't have enough real data to work with." Etzioni added that a key challenge is the need for a gold standard for each level of disease status. "We need to know if people have the disease or not, and then we can use the records and images for AI and machine learning," she said. Mandelblatt summarized this challenge as "Big data equals big uncertainty." Although some commercial enterprises have made efforts to gather and use data to develop AI algorithms, this type of endeavor is not typically supported with research funding, Etzioni said.

Clinical Validation

Papadopoulos suggested that interventional clinical studies are needed to assess the risks and benefits of a test, with an initial prioritization of specificity rather than sensitivity. "Interventional studies are important because we have to know that when individuals were diagnosed with cancer and it was removed, the biomarker used in the test was in fact in the tumor. You need these types of studies and validation to be able to say that what you found in the plasma actually worked and detected the cancer," Papadopoulos said. He also suggested that real-world evidence be collected after approval of a test to assess the test's usefulness in clinical practice and whether it reduces cancer mortality.

Kramer and Krist cautioned that RCTs should remain as the gold standard for evaluating the benefits and harms of any new cancer screening test or strategy. Even the abundant real-world clinical data available from observational studies may not provide the reliable information about screening effects on cancer outcomes that are needed to make informed decisions, Kramer said. He described a study that found little correlation between the findings of

randomized clinical trials and observational studies comparing the same two treatment regimens for any diagnosis of cancer (Soni et al., 2019). Furthermore, the study found that the observational studies were more likely to show better survival outcomes than the RCTs (Soni et al., 2019). He stressed that overdiagnosis can lead to an increase in the survival rate for a given cancer, creating a cycle that reinforces a perceived benefit from screening. "It's very misleading and leads people to think there is benefit when there may be no benefit at all," Kramer said.

Krist said that conducting RCTs of cancer screening tests can be challenging because participants in the control groups may end up getting screened on their own, but he added that "I don't think we can get out of having some element of RCT data." Kramer said exceptions may occur, such as in the case of cervical cancer screening, where screening was clearly proven to be of benefit years before a randomized trial showed the benefit, and "all the stars were aligned." However, he stressed that such situations are rare.

Papadopoulos added that a "test may look good in retrospective studies by indicating more than 99 percent specificity, but retrospective studies are based on specimens for which it was already known who had the cancer, and the cancers were already symptomatic. So it is not representative of real life, which is why prospective studies are so important." But he noted that screening trials may require a timeline of 10 to 20 years to show a reduction in mortality. He said he did not think researchers would commit the effort and resources needed to develop liquid biopsy tests if they have to wait that long for trial results. Thus, he suggested assessing interim outcome measures that may serve as surrogate endpoints when making decisions about moving forward with a test, such as whether there is a downward stage shift of tumors detected in the screened group versus the control group. Wendy Rubinstein, director of personalized medicine at the Center for Devices and Radiological Health at FDA, agreed that a stage shift might be a valid surrogate endpoint, but that it would require careful statistical analyses that would ideally be collaboratively developed by a broad community to avoid the problems that arise when many different study methodologies are used. However, Krist noted that stage shift as an interim outcome measure may not be a valid surrogate for reduced cancer mortality or morbidity unless it can be definitively linked to one of those health outcomes.

Studying a new cancer screening test in patients with a high hereditary risk of developing the cancer of interest might speed up the development of new tests and improve the accuracy of assessing test sensitivity, Rubinstein, Brenner, and Menon suggested. Because these populations represent a very small fraction of those who develop these cancers, Brenner suggested that if markers for precancerous or cancerous conditions are consistent in both high-risk and general populations and also indicate the same pathway to cancer

development, then finding fewer cancers or a lower cancer mortality in the high-risk population undergoing screening might be sufficient to extrapolate the benefit to the general population. Menon noted that for a high-risk group, a stage shift might be a sufficient endpoint to start screening without waiting for the long-term evidence that it can reduce mortality rates. However, that would require defining what qualifies as "high-risk" and what it means to downstage cancer. She explained that it is hard to estimate downstaging in a high-risk population because it is difficult to decide who the comparator group should be.

When asked if USPSTF would consider data from a high-risk population to support screening in the general population, Krist responded that although the task force would consider such data in its assessment of test accuracy, it bases its recommendation of a test for the general population on a different level of evidence. Menon added that in the United Kingdom, screening recommendations for the general population are made by the UK National Screening Committee (comparable to USPSTF), whereas guidance on cancer surveillance for high-risk populations is provided by the National Institute for Health and Care Excellence (NICE), which is a separate independent organization.

Lichtenfeld emphasized the need for more precision screening, akin to the approach of the WISDOM trial. "We need to know who needs to be screened, how they need to be screened, and how to be more effective in our screening approaches," he said. Durado Brooks, vice president of cancer control interventions at the American Cancer Society, emphasized the critical need to include more minorities in screening studies and to conduct subpopulation analyses. For example, he stressed the importance of understanding the effectiveness and balance of benefits and harms of PSA testing in African American men and in men with a family history of prostate cancer. "We are only going to know [the answer] if we make sure that African American men and high-risk men are included in the trials," he said. Krist concurred and stressed the need to ensure good representation of all populations in clinical trials.

Mandelblatt suggested leveraging health economics to inform cancer screening program design, implementation, and evaluation.

Implementation Research

Susan Curry, professor in the College of Public Health and executive vice president and provost of The University of Iowa, said that although development of an effective screening test is important, effective implementation of the test is also key to effective screening. Several workshop participants recommended an increased focus on implementation research to address this challenge. Krist suggested that factors such as acceptability of a preventive service

and what is required to deliver that service could be assessed within an RCT evaluating the test. He added, "It's not just performing the preventive service that matters—doing it well is also important." Kramer added that the NCI Community Oncology Research Program was designed to assess the feasibility of screening and prevention interventions in real-world community settings.

Antoinette Percy-Laurry, health scientist for the implementation science team in the Division of Cancer Control and Population Sciences at NCI, added that NIH is working to optimize implementation science, and a recent NIH workshop highlighted the need for innovative methods to test implementation strategies. "We need strategies, methods, and techniques to help improve implementation outcomes like acceptability, adaptability, and sustainability," she said. She also suggested developing and testing strategies that address contextual factors in a population to help determine why a particular screening approach might work well in one community but not in another, and whether a successful intervention can be adapted to a particular population based on the context of that population.

Geiger pointed out that implementation science is in its infancy, with a focus on identifying and measuring key factors. "We will get there, but it is going to take time," she said. Miller added that CDC is working to develop implementation science in some of its cancer screening programs to determine what works well, how much it costs, how much staff time is required, and how to ensure the sustainability of interventions. She also noted the challenge of measuring how social determinants of health, such as insufficient housing or food, can influence the outcomes of screening programs. Lichtenfield suggested conducting more root-cause analyses to assess why patients do not receive regular screenings or appropriate follow-up care.

Pentz emphasized the need for research on best practices for shared decision making for screening. Kramer also stressed the need for de-implementation of cancer screening in certain circumstances, such as in older adult populations for whom the benefits do not outweigh the risks, stating: "The science of implementation is hard, but the science of de-implementation is different and even harder." Krist also noted the behavioral economics principle of the sunk cost fallacy. "As a society, we put a lot into developing and implementing a test. But if we find it doesn't work at any point, we need to abandon it. We should not continue to throw money, resources, and effort into something that we know is not right," he said.

Guidelines Development

Several participants made suggestions on how to improve the development and adoption of screening guidelines. Krist stressed the need for transparency in guidelines development because different groups use dif-

ferent methodologies to develop their guidelines. "If groups aren't explicit with their methodology, it's a fundamental flaw," he said. Krist noted that USPSTF's methods are published on its website. Brooks said that the American Cancer Society has also published the established methodology its uses to developing its screening recommendations. This methodology is similar to USPSTF, he said.

Clinicians and health care systems also need to be kept up to date with the most recent screening guidance, Pentz stressed. She noted that this can be challenging, because guideline developers may make varying or conflicting screening recommendations. She said that it would be helpful if an organization could grade the quality of guidelines to help better inform health care providers and patients of trustworthy guidelines.

Brawley expressed concern about conflicts of interest, both financial and emotional, in the development of cancer screening guidelines. He said some organizations that produce guidelines receive funding from companies that sell drugs, devices, or diagnostics relevant to the medical condition for which the organization is providing screening guidelines, thus creating a financial conflict of interest. "Organizations that put forth screening guidelines should fully disclose who they get financial support from," he recommended.

Brawley also cautioned that mistakes of the past should not be repeated. "We need to remember that those who don't appreciate history are destined to repeat it. We have overtreated and hurt people because we have not had enough scientific rigor and enough concern about ethics. Money drives too much of this," Brawley said.

Krist suggested that in the future it might be possible to make screening recommendations more personalized rather than population based. He suggested designing studies to facilitate personalized recommendations that maximize benefits, minimize harms, and prevent disease by meeting people's biological needs, personal values and preferences, and life needs.

Health Care Organization and Delivery to Facilitate Screening

Once a cancer screening test is clinically validated and recommended, the way in which health care is organized and delivered can create barriers to implementation. Schmeler said systems are needed not only to make sure patients are screened but to also ensure that patients with abnormal screening results receive the appropriate follow-up care for diagnosis and treatment. Stressing that screening impact is diminished when follow-up appointments are not conducted in a timely fashion, Gieger said studies have shown that patient navigators, reminders, and performance data for clinicians can all improve timely follow-up in asymptomatic adults with positive fecal blood test results (Selby et al., 2017).

Geiger noted the importance of monitoring performance and quality improvement in providing timely follow-up care. She said modified electronic health records are needed to support improved care delivery, and suggested using a publicly reported metric for how well health care facilities follow up on screening results. She noted that when leadership at an institution where she previously worked noticed there was more than a 21-day delay between the determination of an abnormal mammogram result and notifying the patient of that result, they found a way to reduce that lag time to 7 days. "Organizations can make changes if they are motivated to do so," Geiger said.

Miller pointed out that federally qualified health centers (FQHCs), which primarily care for underserved populations, work collaboratively with CDC to collect data on a number of parameters to improve the delivery of high-quality cancer screening and follow-up care, such as the time between an abnormal test result and follow-up diagnosis. She and Gieger said that these centers can serve as exemplars of monitoring and quality control measures that should be instituted in other health care systems. Stanton Gerson, director of the Case Comprehensive Cancer Center and professor at Case Western Reserve University, added that his cancer center placed patient navigators in the FQHCs "because the biggest issue was access to the hospitals. People were getting screened but not obtaining follow-up care. Our navigator groups work with patients to facilitate the patient getting to whichever hospital they would like for follow-up care."

Menon suggested using automated algorithms to facilitate screening and minimize manual data entry. The automated program used in her trial of ovarian cancer screening sent individual invitations to participate following transfer of electronic details of potential participants from national health service registries, checked automatically for participant eligibility when women responded, and scheduled appointments automatically. All blood tests were tracked using bar codes, and biomarker results were directly uploaded. Furthermore, classification of results and the scheduling of repeat tests or routine screening was automated, as was the mailing of results to patients and clinicians. Menon also stressed the importance of frequent direct communication between the coordinating center and participants.

To improve the quality of cancer screening, Brawley said there may be a benefit to create specialty screening centers where patients could be directed, similar to the designated specialty centers that exist for pelvic surgery and cardiovascular surgery. Albers noted that his study of prostate cancer screening identified substantial variation in pathology evaluation of biopsies and in the interpretation of MRI images. "This is a quality-of-care issue. If we introduce screening technology, we have to be sure that the quality is high," Albers said.

To increase the time available for shared decision making during preventive care clinic visits, Barry suggested eliminating some other procedures

performed during an annual visit that are driven by medical billing requirements but have not been shown to improve patient health. Pignone suggested making better use of patient portals for pre-visit preparations by both patients and clinicians so there is more time during clinic visits for high-quality shared decision making regarding cancer screening. Barry added that electronic health records could enable patients to access decision aids and input questions and feedback on their choices. Pignone said, "I am worried that electronic health records are becoming billing and administrative devices. In my health care system, the messages I receive from the portal are almost always about an upcoming appointment reminder, but they do not include what is going to happen during that appointment. I think we need to claw back that space for true clinical work." Jimbo agreed, adding, "What consumes the greatest visit time in shared decision making is the physician trying to impart knowledge to a patient. That can be removed from a visit if we can provide a free decision aid prior to or after the visit via a patient portal." Esserman pointed out that clinicians welcomed the WISDOM study's virtual provision of screening information to patients. "Ninety-eight percent of physicians were saying 'please have the discussion about breast cancer risk reduction because we don't have time and we are not experts at it,'" she said. Miller also suggested engaging allied health professionals, community health workers, and patient navigators to help inform patients about cancer screening.

Lichtenfeld suggested analyzing organizational systems to make certain that people have access to screening and do not "fall through the cracks" along the way. Improving access to screening can be especially challenging in rural areas that lack health care resources, Lichtenfeld said. Darien added that "we have to think about how we are failing patients in getting them through this whole process." She emphasized the need to alleviate administrative and financial burdens for patients.

Miller suggested that screening disparities could be addressed by increasing the cultural competency of clinicians and reducing bias. There are many populations for whom shared decision making will not help if clinicians are not addressing and respecting their cultural values, such as including family members in the decision-making process, if appropriate, she said. She added that clinicians need to reduce biases they may have about their patients. "People feel very uncomfortable if they think the health care provider is talking down to them," Miller said. She stressed the need to make sure patients feel comfortable and are understood in conversations with their clinicians. "Even if a patient speaks English, for example, it may not be their preferred language so it may still be beneficial to use a translator," she said.

Miller noted there are a number of evidence-based interventions available for health care systems and communities to improve access to, demand for, and delivery of screening services. She suggested reviewing the interventions

described in *The Community Guide*.[20] These interventions include offering after-hours clinics, using reminder systems for patients and clinicians, working with employers to allow their employees to have time off for screening, and bringing screening programs to work sites, pharmacies, and other easily accessible sites. She also suggested combining interventions to improve screening rates.

Miller noted that to improve screening, health care organizations do not have to develop new systems from scratch but rather can build on systems already in place, such as telehealth, community health clinics, electronic health records, as well as cancer screening programs supported by CDC. She said CDC has been successfully integrating evidence-based interventions into its colorectal and breast cancer screening programs. CDC's Colorectal Cancer Control Program (CRCCP)[21] increased screening rates in its participating clinics from 42.9 percent to 53.2 percent by the end of year four of the program, Miller reported. CDC's National Breast and Cervical Cancer Early Detection Program,[22] which provides screening services for low-income, uninsured, and underinsured women, contracted with more than 10,000 health care providers who screened 1.2 million women between 2014 and 2018, she added.

To increase patient demand for screening, Miller also suggested using digital technologies such as social media, apps, and telehealth to empower patients and make it easier for them to receive information, make appointments, and communicate with their clinicians, while also improving outreach to underserved and rural populations. Doubeni concurred that digital technologies might enable outreach to and easier access for underserved populations. Miller said the Internet holds great promise for facilitating communication about cancer screening, but she also noted that these digital technologies will only work for those patients who have access to Internet service. Furthermore, some patients may misinterpret or be misled by information sent to them via social media, Geiger and Miller added. They may also block text messages for screening reminders, Geiger noted. "I'm a real skeptic about social media being a solution," Geiger said. Schmeler added that the use of social media has pros and cons. For example, a lot of parents in the Rio Grande Valley had their daughters participate in the MD Anderson Cancer Center's HPV vaccination program because they saw a post on a parent Facebook group. But social media has also been used by anti-vaccine groups to target health care providers who support HPV vaccination, she said.

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[20] See https://www.thecommunityguide.org (accessed May 26, 2020).

[21] See https://www.cdc.gov/cancer/crccp/manuscripts/results-year-one.htm (accessed November 13, 2020).

[22] See https://www.cdc.gov/cancer/nbccedp/about.htm (accessed November 13, 2020).

Education and Communication

Barry suggested training clinicians in shared decision making and how to use decision aids, as well as measuring whether they are providing appropriate decision aid tools to their patients. The Centers for Medicare & Medicaid Services (CMS) has started doing this, he noted, and there are studies with insurance benefit designs that incentivize the use of a decision aid before a major procedure. Barry also suggested training for patients on how to be more assertive about making their wishes known.

Kramer stressed the necessity for educating both patients and clinicians about cancer overdiagnosis due to screening and changing the terminology of indolent tumors and other low-risk screen-detected lesions. "In order to achieve better informed consent and informed decision making, we should remove the word 'cancer' from the subset of tumors and lesions that are very slow growing and likely to be overdiagnosed," Kramer said. He noted this has already been done to some degree with ovarian and cervical lesions previously labeled as cancers and now called "ovarian tumors of low malignant potential" and "cervical intraepithelial neoplasia," respectively. "Language corrupts thought. As soon as you introduce certain words into the dialogue, it impedes informed decision making," Kramer stressed. He noted that Esserman has been pioneering the label "idle tumors" for tumors that have been classified as cancer by a pathologist but are very slow growing. Similarly, Albers questioned labeling low-grade prostate lesions as cancer. "If you tell a patient he has cancer, he behaves differently than if you don't name it [as cancer. We have to think carefully about terminology]."

Kramer also suggested steering away from using overly simplistic messaging such as "screening saves lives" because it is a strong driver of decision making. Instead, he suggested saying what is known (e.g., that the test has been shown to decrease the risk of dying from the target cancer and that it is not known yet if the screening will translate into increased life expectancy). When 1,000 people have to be screened for 10 years to save one person from dying from a cancer, as it does for PSA screening, "all it takes is losing one overdiagnosed person from [the adverse effects of] radiation, surgery, or chemotherapy to cancel out that benefit. We ought to be very rigorous in the application of our language," he said. Darien added that many public screening messages convey the notion that if someone undergoes the proper screening for cancer, they will be protected from that cancer. But if that individual is later diagnosed with that cancer, they feel betrayed. "We have to get away from talking about both life expectancy and the notion of protection," she said.

Pentz suggested interacting more with health care journalists as a means to counter misinformation about screening and to educate the public and health care providers. Kramer agreed, adding that he is part of a medicine-in-the-media program that offers a curriculum on cancer for journalists.

Pentz also stressed the importance of transparency and honesty in communicating the risks and benefits of cancer screening to patients. Lichtenfeld also emphasized the need for "truth in what we say about screening studies, and truth in how we apply study findings to populations." Miller stressed the need to make cancer screening more patient specific, based on the patient's history, risk factors, and values. She added that it is very important to make sure the patient understands the risks associated with screening tests, and to avoid glossing over the potential harms, such as complications from a biopsy or surgical procedure.

Miller also suggested that when meeting with medically underserved populations, clinicians should assess the issues and challenges these patients face and try to address them. For example, clinicians can help patients find follow-up care and address transportation needs and affordability of care. However, she also cautioned to be mindful and sensitive if a patient is not ready to move forward with screening or treatment. It is important not only to listen to patients but to communicate effectively using words they understand, Miller said.

Insurance Coverage

Geiger said that insurance coverage can help facilitate more effective cancer screening. Several workshop participants noted that a lack of or inadequate insurance coverage can prevent access to high-quality cancer screening and follow-up care. Miller said that screening is often provided for free, but if a patient then needs diagnostic tests or follow-up care, it may cost thousands of dollars. "That is a big barrier for people," she said. A lack of coverage for diagnostic testing can cause patients to delay follow-up care, during which time the cancer may progress and be less likely to respond to treatment, Miller noted. Pignone encouraged greater state uptake of Medicaid expansion to improve patient access to cancer screening. He also suggested modifying the Patient Protection and Affordable Care Act[23] to ensure that insurance covers not only cancer screening but also follow-up care. "The initial screening test and all subsequent follow-up care should be covered by the same copay," he said.

Lichtenfeld suggested more insurance coverage for the time that primary care clinicians spend communicating about cancer screening with their patients, noting that Medicare has made some changes over the past year to reimburse clinicians for engaging in shared decision making.

Pignone added that the clinician participating in a patient's screening decision should not have a financial interest in the clinical work that will

[23] Patient Protection and Affordable Care Act, Public Law 111-148, 111th Cong., 2nd Sess. (March 23, 2010).

result from that decision. For example, gastroenterologists benefit financially if a patient chooses a colonoscopy but not if the patient chooses a fecal blood test. A primary care clinician may not have the same conflict of interest, Pignone said.

Esserman suggested insurance companies could financially support the clinical studies needed to generate the data for determining which screening option is the best for patients, as well as financially support the development of decision aids. "We should be paying to generate better data and tools that help educate people before they come in for their clinic visit. If we don't incorporate that into our models for how we cover the cost of care, we will never make progress because people do what they are paid to do," she said.

WRAP-UP

Nicole F. Dowling, associate director for science in the Division of Cancer Prevention and Control at the National Center for Chronic Disease Prevention and Health Promotion at CDC, provided reflections on the workshop presentations and discussion. She said there is great potential to reduce cancer mortality through effective screening, but a recurring sentiment throughout the workshop was the "need to hold our preventive services to a high bar before recommending them to the population because many people will not reap benefits from screening, but all may be exposed to the potential harms. This includes the potential for overdiagnosis, which must be kept at the front of our minds." Simply finding cancer is not a measure of successful cancer screening, she said.

Dowling noted that cancer screening is not a one-time event, but a complex process that has numerous uncertainties, risks, and benefits. This workshop explored the multiple facets of cancer screening, from the initial scientific discovery of new cancer biomarkers to the follow-up care a patient receives after an abnormal finding in a screening test. She said there were many opportunities for improving the effectiveness of screening at the level of the individual, clinician, and organization, as well as opportunities to improve screening tests through increasing scientific knowledge and technology development. Dowling said there are no easy solutions but she identified several topics discussed during the workshop that are key to ensuring that effective screening tests are developed and implemented to enable better patient outcomes:

- Improving understanding of the natural history of cancer
- Strengthening the scientific rigor in the development and validation of potential cancer biomarkers by improving the understanding of early-stage disease, ensuring appropriate incentives for research, and engaging

appropriate expertise and leadership in cancer research, planning, investment, and infrastructure
- Continually conducting assessment of new screening technologies to avoid bias in their use
- Improving data quality and reducing potential bias in the evaluation of test performance and potential benefits and harms, which are very challenging to measure
- Addressing challenges in methodology and statistical analysis to accurately quantify benefits and harms of cancer screening, including consideration of the appropriate time horizon and variations in the target population, such as age, comorbidities, and cultural factors
- Ensuring that screening tests demonstrate a reduction in cancer mortality
- Engaging patients in the decision-making process so they feel informed about and included in their health care decisions
- Improving shared decision making through clinician training and patient education, use of decision aids, enhanced clinical workflow, integration of technology, and engagement of stakeholders in collaborations to generate new evidence
- Facilitating timely access to high-quality follow-up care and treatment
- Reducing the barriers to high-quality cancer screening and follow-up care by improving affordability, increasing access to services in the community, strengthening social supports, and taking actions at the health system and clinician level to reduce distrust of the health care system
- Creating a more personalized, risk-based approach to screening by taking into account biology and patient values

In closing, Dowling thanked the workshop participants for raising so many opportunities to think about how to advance the field of cancer screening.

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Appendix A

Statement of Task

A planning committee of the National Academies of Sciences, Engineering, and Medicine will organize and host a 1.5-day public workshop to examine current issues in the development and implementation of effective, high-quality cancer screening. The workshop will feature invited presentations and panel discussions on topics that may include

- Key gaps in the evidence base for cancer screening tests, as well as methodological and statistical challenges in assessing the potential benefits and risks of screening.
- Opportunities and challenges in developing, validating, and implementing new technologies for cancer screening tests, such as liquid biopsies and biomarkers of cancer risk.
- Strategies to help patients understand the benefits, risks, and costs of cancer screening and participate in shared decision making with their care team about screening options.
- Challenges in the clinical management of patients with premalignant lesions detected by screening.
- Opportunities to reduce disparities in cancer morbidity and mortality by facilitating patient access to high-quality screening and diagnosis in low-resource areas and among vulnerable populations.
- Strategies to ensure that screened patients diagnosed with cancer have timely access to high-quality cancer treatment.

The planning committee will develop the agenda for the workshop sessions, select and invite speakers and discussants, and moderate the discussions. A proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

Appendix B

Workshop Agenda

MARCH 2, 2020

7:30 a.m. **Registration**

8:00 a.m. **Welcome from the National Cancer Policy Forum**
Nicole Dowling, Centers for Disease Control and Prevention
Planning Committee Co-Chair

Stanton Gerson, Case Comprehensive Cancer Center
Planning Committee Co-Chair

8:10 a.m. **Session 1: Principles and Methods of Cancer Screening**
Moderator: Sue Curry, The University of Iowa

Overview of Cancer Screening
- Otis Brawley, Johns Hopkins University
- Barnett Kramer, National Cancer Institute

Frameworks for Assessing the Evidence Base for Cancer Screening Recommendations
- Alex Krist, Virginia Commonwealth University

Panel Discussion

9:30 a.m. **Break**

9:45 a.m. **Session 2: The Evidence Base for Cancer Screening: Key Gaps and Statistical and Methodological Challenges**
Moderator: Constantine Gatsonis, Brown University

Statistical and Methodological Challenges in Cancer Screening
- Ruth Etzioni, Fred Hutchinson Cancer Research Center

Quantitative Approaches to Summarizing the Benefits and Risks of Screening
- Carolyn Rutter, RAND Corporation

Assessing the Evidence Base for Cancer Screening as New Technologies Are Developed
- David Ransohoff, University of North Carolina at Chapel Hill

Health Economics of Cancer Screening
- Jeanne Mandelblatt, Georgetown University

Panel Discussion

11:45 a.m. **Lunch Break**

12:45 p.m. **Session 3: Opportunities and Challenges in the Validation and Implementation of Novel Screening Technologies**
Moderator: Sudhir Srivastava, National Cancer Institute

Challenges with Validation of Novel Screening Tests
- Arul Chinnaiyan, University of Michigan

Novel Screening Technologies and Approaches

Risk-Based Prostate Cancer Screening
- Peter Albers, Heinrich-Heine-University, Düsseldorf

Ovarian Cancer Screening
- Usha Menon, University College London

Noninvasive Multicancer Screening Using Liquid Biopsy
- Nickolas Papadopoulos, Johns Hopkins University

Panel Discussion
Speakers, plus:
- Hedvig Hricak, Memorial Sloan Kettering Cancer Center
- Wendy Rubinstein, Food and Drug Administration
- Sara Brenner, Food and Drug Administration

3:00 p.m. **Break**

3:15 p.m. **Session 4: Patient Access to High-Quality Cancer Screening and Follow-Up Care**
Moderator: Stanton Gerson, Case Comprehensive Cancer Center

The Screening Process: Ensuring Patient Access Among Vulnerable Populations
- Jacqueline Miller, Centers for Disease Control and Prevention National Breast and Cervical Cancer Early Detection Program

Patient, Clinician, and Organizational Barriers to Timely Diagnosis
- Ann Geiger, National Cancer Institute Division of Cancer Control and Population Sciences

Cervical Cancer Screening and Follow-Up Care Within the Challenging Context of U.S.–Mexico Border Communities
- Kathleen Schmeler, MD Anderson Cancer Center

Ethical Considerations in the Assessment of Cancer Screening Benefits and Risks
- Rebecca Pentz, Emory University

Panel Discussion

5:15 p.m. **Adjourn Day 1**

MARCH 3, 2020

7:30 a.m. **Registration**

8:00 a.m. **Session 5: Shared Decision Making and Communication in Screening**
Moderator: Alex Krist, Virginia Commonwealth University

Strategies to Promote Shared Decision Making
- Michael J. Barry, Massachusetts General Hospital

Decision Aids and Shared Decision-Making Implementation
- Michael Pignone, The University of Texas at Austin

Improving Cancer Screening Communication and Shared Decision Making Among Diverse Populations
- Masahito Jimbo, University of Michigan

Personalizing Cancer Screening Decision Making and Follow-Up Care
- Laura Esserman, University of California, San Francisco

Panel Discussion

9:45 a.m. **Break**

10:15 a.m. **Session 6: Participant Recommendations to Improve Cancer Screening**
Moderator: Otis Brawley, Johns Hopkins University

- Gwen Darien, National Patient Advocate Foundation
- Alex Krist, Virginia Commonwealth University and United States Preventive Services Task Force
- J. Leonard Lichtenfeld, American Cancer Society
- Jacqueline Miller, Centers for Disease Control and Prevention
- Rebecca Pentz, Emory University
- Sudhir Srivastava, National Cancer Institute

11:30 a.m. **Workshop Wrap-Up**
Nicole Dowling, Centers for Disease Control and Prevention
Planning Committee Co-Chair

11:45 a.m. **Adjourn**