



February 10, 2021

Submitted Electronically

Alex H. Krist, MD, MPH
Chair, United States Preventive Services Task Force
c/o USPSTF Senior Project Coordinator
5600 Fishers Lane
Mail Stop 06E53A
Rockville, MD 20857

RE: USPSTF Draft Research Plan on Screening for Breast Cancer

Dear Chairman Krist and Task Force Members:

As an organization with a long history of advocating for quality in mammographic screening, and of encouraging women and their health care providers to utilize proven screening methods to save lives, the American College of Radiology (ACR)—a professional organization representing more than 40,000 radiologists, radiation oncologists, interventional radiologists, nuclear medicine physicians, and medical physicists—appreciates the opportunity to provide input into the USPSTF draft research plan for breast cancer screening.

We recognize that the opportunity for public comment has not always been afforded as part of USPSTF's processes (pre-2009), and we encourage thoughtful consideration of the comments received. We believe that the processes of the Task Force, the quality of its recommendations, and ultimately the public's trust in the recommendations would be enhanced by maximizing the input of breast imaging specialists and other experts, and ensuring transparency throughout your deliberations. Accordingly, we reiterate the following general comments relating to the process of the Task Force as well as providing specific recommendations related to the draft research plan.

GENERAL COMMENTS

The Task Force Process Should be Fully Open, Balanced and Transparent

Although the Task Force was created for the purpose of providing supplemental guidance to primary care physicians, USPSTF recommendations now have far broader public policy implications. They are being used to influence national screening program guidelines, federal and private sector coverage policies, as well as direct-to-consumer screening recommendations. With the passage of the Affordable Care Act, the USPSTF was explicitly granted a prominent role in Centers for Medicare and Medicaid Services' coverage decisions and in the establishment of preventive service coverage requirements for private insurers. With such substantive policy issues at stake, the public trust demands that the USPSTF recommendation-development process be entirely transparent, consistent with other federal agencies that create policy and promulgate regulations.

While we understand that the Task Force is not a formal Federal Advisory Committee and is not statutorily bound to abide by the Federal Advisory Committee Act or the Administrative Procedures Act, we believe that the Task Force should embrace the public transparency and accountability protections afforded by these Acts. With millions of lives affected, it is imperative that critical decisions affecting citizens' access to preventive healthcare services not be made behind closed doors without the benefit and protection of well-established federal agency transparency requirements.

In addition to the broad process protections afforded by the APA and FACA, we urge the Task Force to be transparent in its methodology. The Task Force should disclose the input received as part of its public comment periods – those with which they disagree as well as any with which they agree – and explain its analysis of public comments, as well as its rationale for accepting or rejecting the input provided by the public. Further, as the Task Force examines evidence and conducts its analysis, it should disclose and clearly explain (1) the evidence it uses to make its recommendations; (2) their rating of the strength of that evidence (SOE) and; (3) the criteria used to make the SOE determination.

The Task Force should engage experts in breast imaging

The Draft Research Plan is foundational to Task Force deliberations in that it establishes the evidence that will be reviewed. The critical review and analysis of the evidence should be undertaken with breast imaging experts for whom the scientific literature is familiar and the subject matter well understood. Expert peer review is an important tool in parsing out the strengths and limitations of scientific research and in moving the science of medicine forward. The Task Force should take advantage of the insights provided by expert peer review as it gauges the strength and weakness of the studies it considers.

We would also like to use this opportunity to request, once again, that the Task Force utilize expert consultants in breast imaging throughout the review process. Breast Imaging experts have a high degree of familiarity with the relevant research and the downstream scientific literature that provides important context and understanding. Certainly, USPSTF's processes can only be

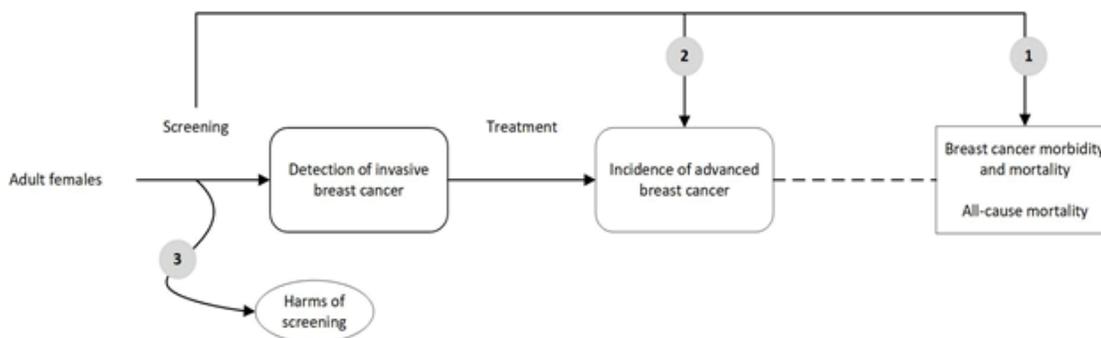
improved by the inclusion of experts who are familiar with the research in their field of specialization and who understand its merits and limitations. Selection of such experts should not be made in a manner that reinforces a bias against screening mammography; the deliberative process is enhanced when open discussion and debate are embraced. ACR welcomes the opportunity to recommend subject matter experts to you.

ACR also cautions against an approach that discredits participation of subject matter experts through a blanket-assertion of conflict of interest (COI) for some individuals, while not acknowledging undeclared COIs of others. Federal Advisory Committees have long reflected the understanding that true experts are rarely entirely free of conflicts. Conflicts should be fully disclosed but should not preclude participation in scientific discussion. Moreover, in the interest of transparency, we urge that unresolvable disagreements arising out of Task Force discussion and deliberations should be made public to facilitate further discourse and informed shared patient-centered decision-making.

With respect to the proposed research plan, ACR proposes the following considerations/suggested modifications:

SPECIFIC COMMENTS

ACR Comments on Proposed Analytic Framework



- As the proposed framework is pictured, it appears that “treatment” is expected to impact the incidence of advanced breast cancer. It may be expected to impact advanced breast cancer after diagnosis, and it may be expected to impact morbidity and mortality. The proposed framework should be revised to reflect that treatment affects more than incidence of advanced breast cancer. It affects harms to patients, mortality, and morbidity as well.
- The proposed framework should clarify the timepoint at which “incidence of advanced breast cancer” is measured. The illustration is not clear as to whether it is measured at the time of initial diagnosis but before treatment, or at any point within the patient’s lifetime.

- The “**benefits of screening**” is missing from the illustration. In a balanced review, the “harms of screening” and “benefits of screening” should both be included. Although mortality reduction is the major benefit of screening, there are additional benefits of screening. These include a reduced likelihood of requiring chemotherapy, fewer mastectomies, reduced anxiety and reassurance from either a true negative test result (confirming breast-healthy status) or a true positive test result (knowing that cancer was diagnosed and treated earlier with less likelihood of recurrence). Quality of life issues such as pain, suffering, and anxiety from living and ultimately dying from metastatic breast cancer, loss of productivity due to metastatic disease and death, unnecessary treatment and testing to document metastatic disease, as well as loss of support by either a spouse or parent should be included in the methodology.
- The arrow towards “**harms of screening**” suggests that DCIS diagnoses will be included within the harms but excluded from the potential benefits, since only detection of invasive breast cancer is included within the proposed analytic framework leading to any benefits. This introduces bias into the draft research plan and should be corrected. DCIS detection should be considered as a potential benefit (KQ 1 and 2). The diagnosis of DCIS is associated with treatment impact, the synchronous and subsequent incidence of invasive breast cancer, and breast cancer morbidity and mortality (Narod 2015). The evidentiary basis for excluding DCIS from the potential benefits of screening is lacking.
- The **harms of not screening** should also be considered in the proposed analytic framework.

ACR Comments on Proposed Key Questions to be Systematically Reviewed

- The DRP does not specify how all-cause mortality (ACM) will be evaluated given that no randomized controlled trials (RCTs) for screening were powered for ACM or included ACM as an endpoint. It is also not clear why ACM is relevant. The taskforce should reconsider assessment of ACM.
- Each of the key questions specifically cite “personalization based on risk factors”. However, the randomized controlled trials of screening mammography did not preferentially recruit and/or enroll based upon specific risk factors (other than gender and age). It would seem to be a foregone conclusion that USPSTF will state that there is insufficient evidence regarding personalized screening based on risk factors. This shortcoming should be considered at the outset and addressed in the final research plan.
- Prior USPSTF screening for breast cancer recommendations have explicitly excluded some groups of women at highest risk. The current draft research plan does the same. The research plan needs to address how it will guide consideration with respect to women

who may be at intermediate risk or high risk (for reasons other than genetic mutation or history of chest radiation at a young age or history of high-risk breast lesion).

- Most women who develop breast cancer have no family history of breast cancer. Accordingly, it is unclear why the draft research plan identifies “family history” as a specific subgroup for review (Key Questions 1-3)
- We strongly encourage consideration of risk factors beyond age, breast density, race/ethnicity, and family history.
- As noted in comments on the proposed analytic framework re: advanced breast cancer, it is unclear at what timepoint advanced breast cancer is measured (initial diagnosis? any occurrence?). The DRP should clearly specify this.
- As noted above, harms of not screening and harms of treatment as well as reduced harms of treatment should be included as part of the systematic review.

ACR Comments on Proposed Contextual Questions

- It is unclear how equipoise will be considered in the analysis. Black women were under-represented in the RCTs which are the most robust data regarding effectiveness of screening. Recommend the DRP specify if/how models will be adjusted to account for this issue.
- The DRP should specify how the steady increase in incidence of breast cancer in black women will be incorporated into the analysis. Incidence of breast cancer among black women was significantly lower in the 1960s-1980s when RCTs were conducted.
- The DRP should specify whether RCTs from Canada or other countries are to be considered in the analysis of screening comparative effectiveness for women in the United States if the populations are significantly different.
- The Task Force should consider (and the DRP should reflect) research and/or tools to increase utilization of risk-appropriate breast cancer screening behaviors including supplemental screening in women at high risk and regular screening mammography in women at average risk. Underutilization of screening, including screening mammography, is a serious public health issue and warrants a dedicated research plan by the USPSTF.

- Proposed Contextual Question 3 addresses risk assessment tools for use in average-risk screening populations. Most women do not know their level of risk, because they have not been offered risk assessment by their health care providers. As a result, women presenting for screening mammography should be expected to have a distribution of risk. If risk assessment tools are to be considered, they should be considered for women at average, intermediate, and high risk and the draft research plan should be revised accordingly. The draft plan does not exclude all subsets of high-risk women within the proposed exclusion criteria listed under the Proposed Research Approach.

- Regarding Proposed Contextual Question 5, we note that the last edition of BI-RADS provides the following comment on breast density: “The Committee on BI-RADS® indeed is aware of recent and continuing investigations of percentage breast density as an indicator for breast cancer risk, and by eliminating percentage ranges we do not intend to compromise or impede any such research. We simply recognize the reality that interpreting physicians will continue to use density categories in mammography reports as they have done over the past many years, independent of BI-RADS® guidance on percentage breast density. We further recognize that both subjective estimates and planimetry measurements of breast density based on area as depicted on (2-D) mammograms are imprecise indicators of the volume of dense tissue, which may be measured using (3-D) cross-sectional breast imaging modalities. We await publication of robust volume-based breast density data, using validated percentage cut points (not necessarily quartiles) that are readily and reproducibly determined at imaging, before again indicating percentage ranges for BI-RADS® density categories. We also urge avoidance of numbers to classify breast density instead of BI-RADS® terminology in order to avoid confusion with BI-RADS® assessment categories, which are numbered.”

See also Destounis S, Arieno A, Morgan R, Roberts C, Chan A. Qualitative versus quantitative mammographic breast density assessment: Applications for the US and abroad. *Diagnostics* 2017; 7(2):30.

ACR Comments on Proposed Research Approach

General Comment

- As an overarching comment, we feel it important to note that the exclusion of clinical examination indicates that the Task Force will not be able to comment for or against clinical examination.

Comparisons:

- The evaluation should include the strategy of no screening at all.

Outcomes:

- KQ1 and 2 should include interval cancers, because longer screening intervals and less supplemental screening have both been shown to increase interval cancers.

Timing:

- KQ1 and 2 should include the same bullet points as KQ3 e.g. lifetime.
- Regarding KQ3, the DRP should include the harms of underdiagnosis (cancers that are detected later and in more advanced stage because screening was not performed) to fully address comparative effectiveness. The harms of underdiagnosis include increased anxiety, increased treatment, increased costs, increased morbidity, increased mortality and decreased quality of life.

Setting:

- As noted above, black women and other minority populations were under-represented in the RCTs which are the most robust data regarding effectiveness of screening. This will need to be accounted for.

ACR Comments on Study Design

- KQ1, 2, and 3 should include the identical study design options. By excluding observational and cross-sectional studies from KQ1 and 2, the DRP reflects a bias that will result in omitting a large amount of data regarding potential benefits from screening.
- The United States does not track the initial method of detection with specific patients (screening mammography, physical examination, patient symptom etc.) in any large database. The DRP should clarify how “individual participant data meta-analysis” will be performed and what sources will be used.
- Although mortality reduction is the major benefit of screening, there are additional benefits of screening. These include a reduced likelihood of requiring chemotherapy, a greater likelihood of surgical treatment options and fewer women requiring mastectomy. Other factors should also be reviewed, such as reduced anxiety and reassurance from either a true negative test result (confirming breast healthy status) or a true positive test result (knowing that cancer was diagnosed and treated earlier with less likelihood of recurrence).

Other ACR Comments/References

The following references are instructive with respect to recommendations for breast cancer screening and are commended for your consideration.

Annual vs Biennial screening

Mainiero MB, Moy L, Baron P, Didwania AD, diFlorio RM, Green ED, Heller SL, Holbrook AI, Lee S, Lewin AA, Lourenco AP, Nance KJ, Niell BL, Slanetz PJ, Stuckey AR, Vincoff NS, Weinstein SP, Yepes MM, Newell MS. ACR Appropriateness Criteria® Breast Cancer Screening. *Journal of the American College of Radiology* 2017;14(11): S383-S390.

Monticciolo DL, Newell MS, Hendrick RE, Helvie MA, Moy L, Monsees B, Kopans DB, Eby PR. Breast Cancer Screening for Average-Risk Women: Recommendations from the ACR Commission on Breast Imaging. *Journal of the American College of Radiology* 2017;14: 1137-1143.

Monticciolo DL, Newell MS, Moy L, Niell B, Monsees, B, Sickles EA. Breast Cancer Screening in Women at Higher-Than-Average Risk: Recommendations from the ACR. *Journal of the American College of Radiology* 2018;15: 408-414.

Life Years Gained by Screening Women aged 40-49 years

Mainiero MB, Moy L, Baron P, Didwania AD, diFlorio RM, Green ED, Heller SL, Holbrook AI, Lee S, Lewin AA, Lourenco AP, Nance KJ, Niell BL, Slanetz PJ, Stuckey AR, Vincoff NS, Weinstein SP, Yepes MM, Newell MS. ACR Appropriateness Criteria® Breast Cancer Screening. *Journal of the American College of Radiology* 2017;14(11): S383-S390.

Monticciolo DL, Newell MS, Hendrick RE, Helvie MA, Moy L, Monsees B, Kopans DB, Eby PR. Breast Cancer Screening for Average-Risk Women: Recommendations from the ACR Commission on Breast Imaging. *Journal of the American College of Radiology* 2017;14: 1137-1143.

Monticciolo DL, Newell MS, Moy L, Niell B, Monsees, B, Sickles EA. Breast Cancer Screening in Women at Higher-Than-Average Risk: Recommendations from the ACR. *Journal of the American College of Radiology* 2018;15: 408-414.

Digital Breast Tomosynthesis as a Primary Screening Method for Breast Cancer

Mainiero MB, Moy L, Baron P, Didwania AD, diFlorio RM, Green ED, Heller SL, Holbrook AI, Lee S, Lewin AA, Lourenco AP, Nance KJ, Niell BL, Slanetz PJ, Stuckey AR, Vincoff NS, Weinstein SP, Yepes MM, Newell MS. ACR Appropriateness Criteria® Breast Cancer Screening. *Journal of the American College of Radiology* 2017;14(11): S383-S390.

Alabousi, M, Wadera A, Al-Ghita MK, Al-Ghetaa RK, Salameh J, Pozdnyakov A, Zha N, Samoilov L, Sharifabadi AD, Sadeghirad B, Freitas V, McInnes MD, Alabousi A, Performance

of Digital Breast Tomosynthesis, Synthetic Mammography and Digital Mammography in Breast Cancer Screening: A Systematic Review and Meta-Analysis, *JNCI: Journal of the National Cancer Institute* 2020; Online publication ahead of print. <https://doi.org/10.1093/jnci/djaa205>

Ciatto S, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S, Tuttobene P, Bricolo P, Fanto C, Valentini M, Montemezzi S, Macaskill P. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. *The Lancet Oncology* 2013;14(7):583-589

Thank you for your consideration of our comments. Please contact Gloria Romanelli at ACR (703-716-7550) with any questions or to discuss this matter in more detail.

Sincerely,

A handwritten signature in black ink, appearing to read "William T. Thorwarth, Jr. MD, FACR". The signature is written in a cursive style with a large, stylized initial "W".

William T. Thorwarth, Jr. MD, FACR
Chief Executive Officer
American College of Radiology