10. Keen JD, Jorgensen KJ. Four principles to consider before advising women on screening mammography. *J Womens Health (Larchmt).* 2015;24:867-874.
11. Barratt A, Jorgensen KJ, Autier P. Reform of the National Screening Mammography Program in France [published online ahead of print October 30, 2017]. *JAMA Intern Med*. doi: 10.1001/jamainternmed.2017.5836.
12. Monticciolo DL, Newell MS, Hendrick RE, et al. Breast cancer screening for average-risk women: recommendations from the ACR Commission on Breast Imaging. *J Am Coll Radiol.* 2017;14:1137-1143.

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Reply to Opportunity Cost of Annual Screening Mammography

We thank Dr. Keen for responding to our article.[1] Much of his response is regarding cost, which is beyond the scope of our article and to our knowledge is not discussed in any of the national organization screening guidelines. We agree that more screening results in more direct financial expenditures for screening if the number of screening mammograms is used as a surrogate for cost. We also agree that more aggressive screening regimens result in more life-years gained and more breast cancer deaths averted. However, Dr. Keen's cost analysis is limited. Cost analysis of a screening program is complex and should not be restricted to insurer direct costs but rather should include the financial costs and burdens of not screening or screening less aggressively (ie, costs of alternative managements). These costs include lost productivity from increased morbidity and mortality (a major opportunity cost), the incremental costs of treating patients with later stage cancer, the cost of treating more cases of metastatic breast cancer, and the costs associated with symptomatic assessments of unscreened women. The economic cost due to lost productivity alone secondary to the (avoidable) death of a single woman in her 40s is $1.4 million, which equates to $1.4 billion per 1000 lives saved.[2] Medical insurers do not cover these large costs. The treatment of patients with metastatic breast cancer is estimated as $250,000 per woman.[3] Costs that are more difficult to estimate are those related to excess morbidity such as treatment-related cardiomyopathy, peripheral neuropathy, and lymphedema.

Another focus of Dr. Keen's letter is overdiagnosis. We explicitly stated in the "Methods" section why our article did not discuss overdiagnosis: "Because both CISNET [Cancer Intervention and Surveillance Modeling Network] modelers and the USPSTF [US Preventive Services Task Force] acknowledge that 'methods for estimating overdiagnosis at a population level are not well established' and 'Existing science does not allow for the ability to determine precisely what proportion of cancer diagnosed by mammography today reflects overdiagnosis, and estimates vary widely depending on the data source and method of calculation used,' the decision was made not to include overdiagnosis in this study's risk assessment."[1] However, because Dr. Keen raises the issue, we would like to stress that overdiagnosis is not reduced by screening less frequently or by initiating screening at a later age. There now is strong evidence that all cases of screen-detected invasive cancer and ductal carcinoma in situ, if untreated, remain suspicious and are detected at the time of the next screening, meaning that less intensive screening may delay but does not reduce overdiagnosis.[4] Therefore, overdiagnosis should not be used as a rationale for delaying initiation of screening until after age 40 years or for screening biennially instead of annually. Furthermore, Johns et al recently reported an overdiagnosis rate of only 0.3% in a large screening study from the United Kingdom after an appropriate follow-up period.[5]

Women considering screening mammography should be aware that the greatest reduction in breast cancer-specific mortality is achieved with annual screening mammography starting at age 40 years, with CISNET computer models demonstrating a nearly 40% reduction in breast cancer-specific mortality compared with only a 23% reduction associated with biennial screening of women aged 50 to 74 years.[1] Screening mammography decisions should be made by women, not for women.

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REFERENCES

1. Arleo EK, Hendrick RE, Helvie MA, Sickles EA. Comparison of recommendations for screening mammography using CISNET models. *Cancer*. 2017;123:3673-3680.
2. Bradley CJ, Yabroff KR, Dahman B, Feuer EJ, Mariotto A, Brown ML. Productivity costs of cancer mortality in the United States: 2000-2020. *J Natl Cancer Inst*. 2008;100:1763-1770.
3. Montero AJ, Eapen S, Gorin B, Adler P. The economic burden of metastatic breast cancer: a U.S. managed care perspective. *Breast Cancer Res Treat*. 2012;134:815-822.
4. Arleo EK, Monticciolo DL, Monsees B, McGinty G, Sickles EA. Persistent untreated screening-detected breast cancer: an argument against delaying screening or increasing the interval between screenings. *J Am Coll Radiol*. 2017;14:863-867.
5. Johns LE, Coleman DA, Swerdlow AJ, Moss SM. Effect of population breast screening on breast cancer mortality up to 2005 in England and Wales: an individual-level cohort study. *Br J Cancer*. 2017;116:246-252.

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Evaluation of Magnetic Resonance Imaging and Targeted Biopsy: The Difficulty of Finding the Right Reference Standard

We read with interest the study by Truong et al,[1] who have proposed a novel tool for predicting benign prostate pathology after a prior negative 12-core systematic biopsy. The study included 285 patients, and 46.3% had benign histological findings after targeted biopsy despite abnormal magnetic resonance imaging (MRI). This was defined as a false-positive MRI.

This approach highlights the most challenging and controversial aspect of evaluating a targeted biopsy: defining the clear reference standard. Because targeted biopsy is used in an interdisciplinary setting, all physicians involved (eg, urologists, radiologists, and pathologists) have a particular learning curve and must contend with uncertainty in the interpretation of their results.[2] Gaziev et al[3] elucidated this in a recent study showing that radiologists and urologists as well as technological differences could affect targeted biopsy results. In other words, using targeted biopsy results as the reference standard has clear limitations. If prostate MRI reveals suspicious lesions and the subsequent targeted biopsy yields benign histologic findings, there are theoretically 2 possible sources of error: the Prostate Imaging Reporting and Data System score is falsely high, or the targeted biopsy has failed to accurately sample the lesion in question. To underscore this, Cash et al[4] analyzed a subgroup of 61 patients with suspicious MRI findings, a negative targeted biopsy, and an additional random systematic biopsy, which still revealed a high rate of clinically significant prostate cancer. In this study, both the failure of the targeted approach to catch the suspicious lesion and the inaccurately positive MRI scores contributed to these findings.

Despite these limitations, the objective that Truong et al[1] tried to investigate with their study is still useful: persistent imaging and laboratory evidence for prostate cancer despite a negative biopsy is a common and vexing problem. The ideal setting for creating a predictive nomogram to this end would involve MRI analysis and corresponding biopsy results together with whole-mount specimens of the prostate to truly evaluate the diagnostic accuracy of the new technology. The drawback is that this would sample only those patients who ultimately went on to undergo radical prostatectomy, and thus a clear selection bias would be introduced. Thompson et al[5] studied this question with such a patient cohort, but they did not seek to develop a nomogram. The goal of developing and validating a standardized tool to help to reduce the number of unnecessary biopsies is clearly worthwhile, but we must take into account the underlying limitations of how these data were obtained.

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