The Cost-Effectiveness of Screening Mammography Beyond Age 65: A Systematic Review for the U.S. Preventive Services Task Force

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Breast cancer is the second leading cause of potentially avoidable cancer mortality among women.[1,2] Breast cancer is largely found in older women.[1,3] Presently, in the United States almost 50% of new cases and nearly two-thirds of deaths from breast cancer occur in 13% of the female population aged 65 or older (hereafter referred to as "older women").[1] By 2030, 1 in 5 U.S. women will be aged 65 or older.[4] This "graying of America"[5] will largely increase the absolute number of breast cancer cases among older women.[6] However, since few older women were included in the original screening trials, we have little primary data upon which to base recommendations.

This rapidly growing population group is primarily heterogeneous, with important age-related variations in comorbidity,[7–9] mammography sensitivity,[10,11] natural history of disease and tumor characteristics (eg, incidence of estrogen-receptor positive tumors that have better prognosis increases with age),[3,12–16] and morbidity associated with breast cancer and its treatments.[16–18] Many of these factors differ in their potential influence on the costs and yields of screening older women.

In such situations, cost-effectiveness analysis (CEA) can summarize the expected benefits (ie, life saving potential, improved quality of life), harms (ie, side effects), and costs of screening beyond age 65.[19–21] Prior CEA of breast cancer screening has generally demonstrated that reductions in mortality can be reduced at reasonable costs per life-year saved among women aged 65 and younger. It is unclear, however, if screening is cost-effective for women aged 65 and older.[10,22–27]

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We conducted a systematic review of published CEA to evaluate the costs and benefits of screening women aged 65 and older to help the U.S. Preventive Services Task Force's (USPSTF) deliberations regarding age limits for breast cancer screening.

Methods

The principles and rationale for our approach to conducting systematic reviews of cost-effectiveness studies have been described previously.[28] We reviewed original economic evaluations of breast cancer screening that included data for older women. We sought studies addressing the incremental cost-effectiveness of screening beyond age 65 compared to screening up to age 65.

We searched MEDLINE® from January 1989 to March 2002 and the British National Health Service Economic Evaluation Database (NHS EED) (http://agatha.york.ac.uk/nhsdhp.htm) from January 1994 to March 2002. We used the following search terms to capture studies related to breast cancer screening: 1) exploded Medical Subject Headings (MeSH®) "breast neoplasms" and "mass screening"; 2) "breast cancer" and exploded MeSH "mass screening"; and 3) exploded MeSH "mammography." To limit the search to studies relevant to screening in older women, we added the MeSH "aged." We used different strategies in each database to identify cost-effectiveness analyses. For our MEDLINE search, we added the exploded MeSH "cost-benefit analysis." In the NHS EED, we limited the search to "economic evaluations." We chose 1989 as a starting point because it marked the time period in which papers on cost-effectiveness of breast cancer screening began to appear. To identify studies not captured by our database searches, we manually searched the reference lists of retrieved articles and contacted selected authors and experts in the field to identify additional studies.

Two investigators independently reviewed each identified abstract, and potentially eligible articles were retrieved. Using information in the abstracts, we excluded studies that were not cost-utility analyses or cost-effective analyses, such as economic evaluations that did not quantify the health outcomes achieved for a given cost. We also excluded studies that reported only cost per patient screened or cost per type of cancer detected; studies without original analyses; studies that did not allow assessment of screening after age 65; and studies that were not performed from a societal perspective or the perspective of a third-party payer, such as Medicare or a national health system. When several publications reported results from the same cost-effectiveness model, we included more than 1 study if the studies contained different information. If several articles presented the same analyses, we selected the most comprehensive analysis and used the other articles for supplemental information. When the decision about whether to include a study was not clear from the title and the abstract, we evaluated the full article. A 4-member working group reached consensus regarding final inclusion or exclusion of articles. A summary of excluded studies is summarized in an Appendix available from the authors.

One reviewer extracted data into evidence tables. The results were checked by other members and discrepancies were resolved by consensus. Data were abstracted on the basis of a modeling approach; screening intervals; the assumptions of each study about the epidemiology and natural history of breast cancer; estimates of variables related to the effectiveness of screening, including test accuracy, adherence rates, and complication rates; estimates of the costs of screening, diagnosis, and treatment; the proportion of types of cancer and cancer deaths prevented by screening; and the effect of varying key parameters (sensitivity analyses).

For each study, we tabulated life-years gained and costs per person for different age groups. The evaluated strategies were ordered by effectiveness. Costs were updated to 2002 (U.S. dollars) using the Consumer Price Index for medical care.[29] Incremental cost-effectiveness ratios were then calculated comparing screening after age 65 to screening cessation at age 65.

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Results

Our initial searches identified 115 potentially relevant studies. There were 10 studies that met our inclusion criteria and included specific data on the cost-effectiveness of screening older women.[10,22,25–27,30–34] The most common reasons for excluding the remaining articles were lack of data on screening after age 65, not being a cost-effectiveness study, and duplicate publication.

The basic features of the 10 included studies are shown in Table 1. All were cost-effectiveness analyses with benefits expressed in life-days or life-years gained and costs expressed in U.S. (or other) dollars. Most studies expressed incremental results for extending screening to ages 75 or 80, compared to ceasing screening at age 65; 2 studies presented results as an average for screening from ages 50 to 74 or 79.[25,34] Each study considered the direct costs of care, including the costs of screening, diagnostic tests, and treatment. None of the studies considered patient time costs associated with screening, diagnostic, or surveillance procedures or for treatment of cancer. Costs and effects were discounted in all studies. Discount rates varied from 3% to 6%, with the most common rate being 5%. The variables used in the different studies were comparable to those noted in the USPSTF Summary of Recommendations.[35]

Overall, despite methodological differences, the cost-effectiveness results were fairly consistent. The results for biennial screening after age 65 generally indicate incremental costs of approximately $34,000 to $88,000 (2002 U.S. dollars) per life-year saved compared to stopping screening at age 65 (Table 1), with costs per life-year saved increasing after age 65. It was also cost-effective to screen women after age 65 if they had not been regularly screened prior to age 65.[27,32]

Most studies considered the average risk for developing breast cancer, but 1 study specifically tested results by level of risk for breast cancer (based on bone mineral density and a proxy for lifetime estrogen exposure).[27] Only 1 study presented results separately for older black and white women,[32] since black women have historically had lower screening rates and higher mortality rates than white women.[1,36] The remainder of the analyses explored results for women at average risk for breast cancer based on population incidence and mortality rates.

A key issue in evaluating the benefits of screening older women is that in this group, in addition to having an increased risk for breast cancer, the probability of developing other illnesses that can decrease life expectancy is also higher, offsetting survival benefits of early cancer detection. For example, if a woman has a small breast tumor detected at screening, but dies of a myocardial infraction the next year, screening had no benefit in extending life expectancy. Two papers in our review specifically addressed the effect of comorbidity on screening decisions.[30,32] One paper considered the situation for women with dementia,[30] and the other assessed the influence of congestive heart failure and hypertension.[32] These studies found that screening reduces breast cancer mortality in all but the sickest women. The remaining studies captured the effects of average numbers of comorbid conditions through use of general population mortality rates.

Detection of cancers or ductal carcinoma in situ (DCIS) that would not have become clinically evident (or not progressed to invasive disease) before death might be considered a screening-related harm or over-diagnosis. Depending on a woman's preference, living for a longer period with the diagnosis of breast cancer and the consequences of treatment (eg, scars, diminished arm mobility) can reduce a woman's quality of life, especially in cases where early detection and treatment do not extend life as a result of competing forces of mortality. These types of harms are not explicitly modeled in any of the studies in this review, and no study considered DCIS separately or made any assumptions about over-diagnosis. Two studies attempted to capture negative consequences of screening through quality adjustment of a woman's remaining years of life after cancer diagnosis.[27,32] However, the valuation of the quality of this time

(ie, utility, or preference value) was based on expert opinion, not directly by cancer patients or general populations of women.[19] Screening may also harm women who have a positive mammography result, but do not have cancer. One study incorporated the short-term disutility from anxiety and discomfort associated with a false-positive screen, and found that this did not alter the conclusions of the analysis.[32] The harms of operative mortality among women receiving treatment for breast cancer was only explicitly incorporated in 2 studies,[30,32] but was sufficiently low (< 2%) so as to not affect conclusions. Thus, in the studies included in this review, potential harms have been modeled incompletely.

If breast cancer is a slower growing neoplasm in older women than in younger women, then screening at intervals longer than 1 year may be a cost-effective option. Most base case analyses examined biennial screening intervals. The analysis by Mandelblatt and colleagues[32] considered a one-point-in-time screening decision, and the model by Eddy[26] included annual screening for a 10-year period. The analyses by Rosenquist and Lindfors[25,34] compared combinations of more frequent screening among younger women and longer screening intervals in older women. They concluded that the discounted cost-effectiveness of annual screening from ages 40 to 49, followed by biannual screening from ages 50 to 79, yields equivalent cost-effectiveness of screening annually from ages 50 to 79. However, the authors do not separately test different intervals after age 65 or 70. Making direct comparisons with the other studies difficult, de Koning and colleagues[22] include triennial screening, but only present the results for women aged 50 to 65.

In general, each model used data on stage-specific survival to simulate natural disease history. Only 2 studies made an explicit assumption regarding age-specific disease biology.[31,33] These authors assumed that the preclinical detectable phase increased from 1.8 years at age 35 to 2 years at age 50, and to 6.2 years at age 70. This assumption should favor screening, since fewer cases will rapidly progress and be missed by screening. However, as noted earlier, this also implies the possibility of longer intervals between screenings as women age. It also implies less virulent disease, leading to lower survival benefits in older than in younger women. Of note, the 2 studies that model age-specific disease behavior and the studies that use observed stage shifts with screening (ie, from regional to distant) come to similar conclusions about screening.

All studies assumed the same mammography test sensitivity for all age groups. Mammography has a higher sensitivity in older than in younger women.[10] The assumption of equivalent sensitivity across age groups underestimates effectiveness for older women. In addition, all studies used a single estimate of sensitivity for all rounds of screening. Prior studies have demonstrated that sensitivity is typically greatest in the first round of screening.[11] By including detection of prevalent (larger) tumors with incident (smaller) lesions, sensitivity values are overestimated, biasing results in favor of screening for all age groups.

With 1 exception,[22] all analyses assumed that 100% of women attended screening and adhered to diagnosis and treatment. If older women are less likely to adhere to screening than women aged 65 and younger, then costs will decrease. If the costs decrease in exact proportion to the benefits, then this will not affect conclusions. If either costs or benefits vary disproportionately, the cost-effectiveness ratio can be higher or lower. de Koning and colleagues[22] used the actual age-specific rates of participation seen in the Dutch trials (65% at age 70 and 45% at ages 71–75), and found that costs and benefits decreased proportionately with decreasing participation. If older women adhere to screening (and incur screening costs), but do not adhere to prompt diagnosis or recommended treatment, they will not fully benefit from earlier detection and cost-effectiveness ratios will increase. However, lower adherence could result in lower costs if women not using mammography do not develop breast cancer or die of competing causes prior to breast cancer surfacing.

Most sensitivity analyses varied 1 parameter at a time (1-way analyses). Parameters that caused cost-effectiveness ratios to vary significantly from the base case in sensitivity analyses included cancer

incidence rates (eg, women with a family history of breast cancer having about a 2-fold increase in incidence),[26,32] differences in assumptions about mortality reductions,[22,25,27,34] quality adjustment,[27] and discount rates for the oldest groups of women in poor health.[32] Discount rates reflect the fact that most people value present years of life more than future years. If older women value the present over the future to a greater extent than younger women, then screening may appear less favorable for older women compared to younger women. Kerlikowske and colleagues[27] explicitly tested the effects of increasing the discount rate from 0% to 15% (ie, increasing the preference for present vs future years). They found that among women valuing the present versus the future to the greatest degree (ie, discount rate of 15%) close to 1,000 women aged 69 to 79 would need to be screened to extend life by 1 year per woman. If women valued the future and the present equally (ie, 0% discount rate), then only 146 women would need to be screened to extend life by 1 year per woman.[27] Beyond time preferences, at the lower ranges of life expectancy, for women with a life expectancy of less than 5 years (eg, women ≥ age 85 with heart failure), the harms of screening outweigh the benefits.[32] Other parameters had less effect on results.

Discussion

The results of this review on cost-effectiveness literature are intended to aid in making clinical and policy guideline decisions on the optimal use of breast cancer screening for older women. Our review suggests that, over a range of assumptions, it remains cost-effective to screen older women for breast cancer every 2 years according to current medical spending. For instance, the incremental costs of $34,000 to $88,000 per life-year saved for screening beyond age 65, compared to stopping at age 65, are roughly comparable to the costs of $16,000 to $72,000 (1992 U.S. dollars) per life-year saved associated with mono-therapy of mild to moderate hypertension in non-elderly populations.[24,32] However, screening becomes more costly and harms begin to outweigh benefits in the sickest women, such as those with dementia or other comorbidities that limit life expectancy to that seen at around age 85 (ie, about 5 years). Additionally, screening is cost-effective if the biology of disease is similar to that seen in younger women (ie, if breast cancer is not a more benign disease in older women).

Screening may have a secondary benefit of detecting tumors at early stages to allow less risky operative procedures (eg, lumpectomy under local anesthesia compared to mastectomy under general anesthesia) and adjuvant therapies (eg, tamoxifen vs multi-drug chemotherapy). We know little about how older women approach decisions about treatment. Interestingly, in studies of older women, women's preferences regarding their post-operative quality of life affected their choice of initial breast cancer treatment.[37] In 1 study, older women with cancer detected by screening were more likely to feel that they had a greater choice of treatment (breast conservation vs mastectomy) than women with clinically detected cancer; older women choose breast-sparing surgery more often than mastectomy.[38]

Larger studies are needed to determine if having cancer detected by mammography actually increases the proportion of older women undergoing breast conservation versus mastectomy. At present, there are insufficient data to estimate the potential benefit of breast cancer screening for women who would have been clinically diagnosed at a later date, when they would have fewer treatment options. Additional data on preferences regarding quality of life after treatment for DCIS and for invasive lesions are also needed before we conclude that the benefits of screening outweigh the harms. New adjuvant therapy, such as aromatase inhibitors, could also change the overall cost-effectiveness of early detection and treatment through their non-cancer health effects (eg, improvements in bone density and reductions in deaths associated with hip fractures).

Assumptions about disease biology have important implications for devising optimal screening approaches for the older population. For instance, if tumors grow more slowly, with a pre-clinical detectable period of 6.2 years, as modeled by Boer and colleagues,[31] then screening intervals might

logically be extended from annual or biannual to every 3 to 5 years. The decrease in the number of mammography films (and evaluations for positive results) while maintaining the majority of the benefits of screening would result in more favorable cost-effectiveness ratios. If some aggressive tumors have a short pre-clinical phase, then even annual screening will have fewer benefits. It will be important to collect additional primary data on age-dependent disease history before recommending any changes in recommendations about breast cancer screening intervals for older women. For instance, age-stratified data on biomarker profiles, recurrence, and survival for women with similar stage and therapy might be used to draw inferences about key aspects of disease history. Another example of data to assess age-related differences in biology is comparisons of the size of tumors in women with clinically detected cancer and women with cancer detected by screening. Since it is not possible to directly observe the course of untreated disease in different age groups, indirect data can be used to estimate tumor doubling times and fatality in simulation models. Models are also useful to capture the wide range of individual variability in tumor biology that occurs at all ages.

Many women with an abnormal test result will not have cancer (ie, false-positive results). Elmore and colleagues[39] estimate that 56% of women screened annually, beginning at age 40, will be falsely identified as having cancer and will need to undergo additional films or tests. While the positive predictive value of mammography increases with age due to increasing incidence and improved test performance, the benefits of continuing to screen must be compared with potential distress related to having a false-positive screening result.

Some potential limitations in the studies we reviewed should be considered in interpreting our results. All analyses but 2[27,32] examined cost per life-year gained and did not account for differences in quality of life associated with screening, surveillance, or treatment for cancer. None of the studies specifically examined incremental results for screening women after age 80. Virtually all of the studies included a discount rate of 3% to 5% to reflect the fact that future savings are generally valued less than present savings. However, if, as suggested by Kerlikowske and colleagues,[27] older women value future years much less than the average (ie, have a higher discount rate, such as 10%), then it will be less cost-effective to extend screening beyond age 69. Clinicians could assess patients' individual discount rates by exploring preferences for future versus current years of life. Development of practical tools to aid providers in eliciting time preferences is an important area for future primary care geriatrics research.

Differences in model structure, assumptions about mammography effectiveness, data inputs for key parameters, and evaluated regimens limited our ability to draw definitive conclusions about the most effective and cost-effective age to stop screening older women. It is difficult to evaluate from the data presented in each report whether differences in the results related mainly to differences in the parameters used or diversity in the model structures. For instance, several reports assumed a fixed mortality reduction with mammography screening based on earlier clinical trials. However, some studies draw divergent conclusions about the effect of screening on observed population mortality trends,[40,41] while other studies model assumptions about benefit from data on actual differences in distributions of stage and other parameters before and after the advent of regular screening practices in the population. These observational estimates may be more robust than those based on specific effectiveness assumptions from clinical trial settings, especially since older women were underrepresented in the trials.[21]

We have also only considered strategies that assumed regular use of mammography. As our understanding of disease biology progresses, more complex strategies, including ones that triage women at some age (eg, age 65 or 70), based on presence of specific disease risk markers, genetic mutations, or disease-specific or health status-specific life expectancy, may yield more specific guidance for clinicians and policymakers. The latter guidelines would be most useful if accompanied by tools for rapid estimation of life expectancy based on age and comorbid conditions. New technologies, if more sensitive than mammography, and of similar or

lower cost, may also be useful in older women. No trial we identified studied the value of clinical breast examination. A long preclinical detectable period for low virulence disease could make this modality a cost-effective alternative to radiological imaging.

Uncertainty about how different model features are applied is also a potential limitation in drawing conclusions from this review. It would help guide screening policy if investigators were to participate in a validation exercise to compare intermediate and long-term model outcomes using a common set of variables for a common set of strategies. This would allow assessment of whether conclusions are robust, or if they were dependent on model structure and assumptions. The consistent finding that screening after age 65 reduces mortality from breast cancer at reasonable costs supports the general conclusion that screening should continue, especially if a woman is in good health. These findings are consistent with those of large population-based studies showing mortality reduction or down-staging benefits in women over age 75,[42–44] even those with moderate comorbidity,[45] and with the Summary of Recommendations of the evidence for the U.S. Preventive Services Task Force.[35] If the preclinical detectable phase of breast cancer is truly longer in older women than in younger women, a longer screening interval (ie, longer than every 2 years) might be more cost-effective.

This review has important implications for future research and policymaking. It supports the consensus view among major policymaking bodies that breast cancer screening is warranted for older women and those preferences for potential harms and benefits should be considered in screening decisions. Finally, it suggests that further research is needed to understand the parallel natural histories of breast cancer and aging, the impact of knowledge of a breast cancer diagnosis and getting treated for this disease on quality of life, time preferences, and rates of adherence with screening and treatment. These data will be important to define optimal approaches to avoiding cancer morbidity and maximizing active life expectancy in the older female population, which is growing.

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Table 1. Summary of Studies on the Cost-Effectiveness of Screening for Breast Cancer after Age 65

Author, Year, Reference	Time Horizon	Type of Model	Interval	Mammography Effectiveness	Sensitivity
Messecar, 2000[30]	Lifetime	Markov	Biennial	Based on SEER stage distribution§	95%
Rosenquist and Lindfors, 1998[34]	Ages 40–79	Markov	Annual ages 40–49, biennial ages 50–79	39% reduction in mortality with biennial for 50+; 13% for 40–49 yrs	Not stated
Lindfors and Rosenquist, 1995[25]	Ages 40–79	Markov	Annual ages 40–49, biennial ages 50–79	Mortality reduction varies by age; 4%–23% for ages 40–49; 23%–32% for ages 60–79	Not stated
Brown, 1992[10]	20 yrs starting at age 50	CANTROL Markov process	Biennial	Observed from RCTs ~30% reduction in mortality	Not stated
Boer et al, 1998[31]	Lifetime	MISCAN	Biennial; examines triennial	Observed from RCTs ~30% reduction in mortality	Varies by lesion size: 40% DCIS; 65% T1a; 80% T1b; 90% T1c; 95% ≥ T2
Boer et al, 1999[33]	Lifetime	MISCAN	Biennial; examines annual and triennial	Observed from RCTs ~30% reduction in mortality	Same as Boer et al, 1998[31]
de Koning et al, 1991[22]	1990–2017	MISCAN	Biennial	Observed from RCTs ~30% reduction in mortality	Same as Boer et al, 1998[31]

*CANTROL, a computer program to calculate outcomes (and costs); CE, cost-effectiveness; DCIS, ductal carcinoma in situ; HMO, health maintenance organization; Markov Model, a type of simulation program with recurring defined health states used to portray disease process; Mets, distant metastatic disease (ie, distant stage); MISCAN, microsimulation of cancer (a Monte Carlo simulation approach); RCT, randomized controlled trial; SEER, Surveillance, Epidemiology, and End Results; Tam, tamoxifen; T1a,b,c, tumor size.

† Year 2002 dollars based on the consumer price index.

‡ Incremental costs per additional life-year, compared to screening until age 65, unless otherwise specified.

§ Effectiveness based on stage is estimated by comparing stage distribution in the absence of screening to more favorable stage distribution in the presence of screening.

|| Ratio includes annual screening from ages 40–49, so overestimates results for women over age 50. Note that results are average results over the age range and do not allow separation of data for extending screening after age 65.

Table 1. Summary of Studies on the Cost-Effectiveness of Screening for Breast Cancer after Age 65 (cont)

Specificity	Costs†			Utility	Discount Rate	Cost-Effectiveness Ratio‡
	Screen	Diagnosis	Treatment			
95%	$118	$1,294	$40,475	.8 local .26 mets	5%	3.3 days saved for screening ages 75–79 (vs ages 65–74) healthy women; 1.5 days saved for women with dementia; cannot abstract CE ratio
Not stated	$72	$1,116	$7,991 (surgery only)	None	3%	$22,794–$27,248 average CE of screening for ages 50–79‖
Not stated	$110	$1,116	$7,991 (surgery only)	None	5%	$50,131 for biennial at ages 65–79 (approx vs stopping at age 59)¶
98.6%	$99	$2,520	Medicare costs: $21,287 local; $30,714 regional; $30,714 distant; $63,455 terminal care	None	5%	$50,400 for ages 70–75 vs ages 65–70; $54,000 for ages 75–80 vs ages 70–75
Not stated	$66	National Health Service costs	$34,860 advanced stage	None	6%	$5,910 for ages 65–69 vs stopping at age 64
Not stated	$66	National Health Service costs	$34,860 advanced stage	Surgery .89–93; tam .82; regional .63; mets .29	6%	$48,433 for ages 65–94 vs ages 50–64
Not stated	$66	National Health Service costs	$34,860 advanced stage	None	5%	$13,280 for ages 71–75 vs ages 65–70

continue

Table 1. Summary of Studies on the Cost-Effectiveness of Screening for Breast Cancer after Age 65 (cont)

Author, Year, Reference	Time Horizon	Type of Model	Interval	Mammography Effectiveness	Sensitivity
Eddy, 1989[26]	10 yrs	CANTROL Markov process	Annual	Unknown	Not stated
Kerlikowske et al, 1999[27]	Lifetime	Markov	Biannual	27% reduction in mortality (22%–32%); assume benefits continue for 5 yrs after cessation of screening	Not stated
Mandelblatt et al, 1992[32]	Cross section, 1 point in time	Markov	1 point in annual program	Based on SEER stage distribution§	75%

Table 1. Summary of Studies on the Cost-Effectiveness of Screening for Breast Cancer after Age 65 (cont)

Specificity	Costs†			Utility	Discount Rate	Cost-Effectiveness Ratio‡
	Screen	Diagnosis	Treatment			
98.6%	$194	Medicare costs: $21,287 local; $30,714 regional; $30,714 distant; $63,455 terminal care	Medicare costs: $21,287 local; $30,714 regional; $30,714 distant; $63,455 terminal care	None	5%	$34,188–$86,614 for screening for ages 65–75
Not stated	$108–$138	$451	Kaiser HMO costs: $31,258 DCIS; $45,220	None in base case; tested range in sensitivity analysis	3%	$87,887 for ages 70–79 vs stopping at age 69
90%	$146	N/A	N/A	None in base case; tested range in sensitivity analysis: local .9; regional .8; distant .5; short-term false-positive .10	None	Varies by age and health group

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