Timely Follow-Up of Positive Cancer Screening Results: A Systematic Review and Recommendations From the PROSPR Consortium

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Abstract: Timely follow-up for positive cancer screening results remains suboptimal, and the evidence base to inform decisions on optimizing the timeliness of diagnostic testing is unclear. This systematic review evaluated published studies regarding time to follow-up after a positive screening for breast, cervical, colorectal, and lung cancers. The quality of available evidence was very low or low across cancers, with potential attenuated or reversed associations from confounding by indication in most studies. Overall, evidence suggested that the risk for poorer cancer outcomes rises with longer wait times that vary within and across cancer types, which supports performing diagnostic testing as soon as feasible after the positive result, but evidence for specific time targets is limited. Within these limitations, we provide our opinion on cancer-specific recommendations for times to follow-up and how existing guidelines relate to the current evidence. Thresholds set should consider patient worry, potential for loss to follow-up with prolonged wait times, and available resources. Research is needed to better guide the timeliness of diagnostic follow-up, including considerations for patient preferences and existing barriers, while addressing methodological weaknesses. Research is also needed to identify effective interventions for reducing wait times for diagnostic testing, particularly in underserved or low-resource settings.

Keywords: breast, cervix uteri, colon, early detection of cancer, early diagnosis, lung, mass screening, neoplasm

Introduction

The Institute of Medicine (now the National Academy of Medicine) identified improving the timeliness and patient-centeredness of care as important unmet health care priorities.\(^1\)\(^-\)\(^3\) Screening has been shown to reduce the risk of death from some cancers and is currently recommended at grade A or B by the US Preventive Services Task Force (USPSTF) in eligible persons for breast, cervical, colorectal, and lung cancers,\(^4\)\(^-\)\(^7\) which enables full coverage of those services under the Affordable Care Act.\(^8\) To realize the benefits of screening, and depending on the type of test used, an individual with a positive screening result must undergo follow-up diagnostic testing, to guide clinical decision making.\(^4\)\(^-\)\(^7\),\(^9\)\(^-\)\(^18\) However, there is considerable variation in the time to receipt of follow-up diagnostic testing among patients with positive screening results,\(^19\)\(^-\)\(^23\) and it is unclear how such differences influence cancer outcomes. The ideal timing of follow-up testing is unknown.

For several reasons, conventional wisdom has been to deliver diagnostic follow-up for a positive screening with minimal delay. First, cancer may progress over time from precancerous or early (more curable) tumors to advanced (less curable) cancer.\(^24\) Prompt diagnostic testing enables detection earlier in the course of carcinogenesis and thus may reduce mortality risk.\(^25\) Second, prompt diagnostic testing is part of
patient-centered care\textsuperscript{1,3} and may reduce worry from uncertainties about the procedure.\textsuperscript{26-31} Third, provider-related or system-related delays in follow-up may increase the likelihood that diagnostic testing may not occur at all because of new logistical hurdles, such as changes in patient contact information or insurance coverage.\textsuperscript{32} However, the assumption that quicker is always better is largely unproven in terms of patient outcomes. Rapid follow-up efforts may require more health care resources to implement and need to be weighed against the benefits and opportunity costs.\textsuperscript{33} Thus, evidence is needed to guide clinicians and health systems on the timeliness of diagnostic testing after a positive screening test.

This systematic review aimed to identify evidence from the published literature to inform recommendations for clinical practice and quality improvement on the timeliness of diagnostic testing for positive cancer screening results. We evaluated the following key question: What is the association between the time from the positive screening result and receipt of diagnostic testing on the risk of cancer progression and death for breast, cervical, colorectal, and lung cancers?

**Methods**

This review was conducted by a transdisciplinary team of cancer-specific experts in the Population-Based Research Optimizing Screening Through Personalized Regimens (PROSPR) Consortium supported by the National Cancer Institute. PROSPR is comprised of research centers at diverse health care systems across the United States.\textsuperscript{34} Our review focused on breast, cervical, colorectal, and lung cancers because of existing recommendations and policies on screening\textsuperscript{4-8} and thus the need for guidance on follow-up evaluation after a positive screen.

**Conceptual Framework**

Our review was guided by an analytical framework that was drawn from the conceptual model of the screening process developed by the PROSPR Consortium.\textsuperscript{35} We focused on the steps between the receipt of a positive screening result and cancer diagnosis and death (Fig. 1). Thus, our literature search sought to identify studies that addressed cancer diagnosis or cancer mortality as the outcome. We considered studies on intermediate outcomes, such as precancerous lesions or tumor size, as reasonable proxies where direct evidence was lacking.

**Selection Criteria**

To be included, articles had to be written in English; published in a peer-reviewed journal between January 1, 1998 and December 31, 2017; and indexed in MEDLINE; and must have been conducted in an average-risk population, except in lung cancer; used study designs that provided empirical evidence, such as randomized controlled trials, cohort or case-control, systematic review, or meta-analysis; and evaluated our key question. The timeframe includes the date of some of the earliest screening guidelines for currently used strategies,\textsuperscript{36} and it seemed likely that relevant literature before 1998 would be included in more recent publications. We also included modeling studies but excluded publications that were unlikely to provide empirical evidence, such as commentaries, editorials, and opinion pieces. DISCLOSURES: This study was supported in part by awards (no. R01CA213645, U54CA163262, U54CA163261, and U54CA 164336) from the National Cancer Institute of the National Institutes of Health. Anna N. A. Tosteson reports grants from the National Cancer Institute during the conduct of the study. Douglas A. Corley reports grants from National Cancer Institute during the conduct of the study. Katrina Armstrong reports grants from the National Institutes of Health during the conduct of the study and personal consulting fees from GlaxoSmithKline outside the submitted work. The remaining authors made no disclosures.

The views expressed here are those of the authors only and do not represent any official position of the National Cancer Institute or the National Institutes of Health. No part of this study has been presented in any form. Chyke A. Doubeni is a member of the US Preventive Services Task Force (USPSTF). This article does not necessarily represent the views and policies of the USPSTF. Stacey A. Fedewa is employed by the American Cancer Society, which received a grant from Merck Inc for intramural research outside the submitted work; however, her salary is solely funded through American Cancer Society funds.

doi: 10.3322/caac.21452. Available online at cacancerjournal.com

\begin{figure}
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\caption{Analytic Framework for the Systematic Review on Time to Diagnosis After Positive Screen. This model indicates how the timing of diagnostic testing can impact the pathways between (1) the positive screening test and cancer mortality and (2) the positive screening test and cancer diagnosis.}
\end{figure}
pieces (see Supporting Material 1 for specific inclusion and exclusion criteria).

We sought to restrict our review to studies on asymptomatic patients who were undergoing screening, which included studies in organized screening programs. However, we considered studies of wait time from symptomatic presentation to diagnosis or treatment to provide context, because the underlying biologic processes may be similar in asymptomatic patients.

**Data Sources and Search**

We used a systematic search strategy for each cancer type that included general screening terms (eg, diagnosis, screening, early detection of cancer), cancer-specific screening terms (eg, mammogram, cytology, Papanicolaou [Pap] test, fecal immunochemical test [FIT], or low-dose computed tomography [LDCT]), terms capturing time to diagnostic testing (eg, time, follow-up, compliance, completion, biopsy), general terms for positive results (eg, abnormal, positive, suspicious), and cancer-specific terms for positive results (eg, breast cancer, high-grade squamous intraepithelial lesion, adenocarcinoma, or lung nodule). To enhance complete capture of published literature on our key question, the cancer-specific teams reviewed references in articles and existing guidelines and other relevant peer-reviewed literature identified in publications in their professional networks or collaborative work. The search criteria were then refined to improve results (see Supporting Material 2 for search terms). We performed 4 separate standardized searches in MEDLINE, one for each cancer type.

**Data Extraction**

Articles retrieved through the search were screened by 2 trained reviewers for inclusion criteria using standardized procedures. Disagreements were resolved by 2 senior team members (K.A.R. and N.B.G.) with adjudication by a third (C.A.D.) when necessary. Eligible unique articles were then reviewed by each cancer-specific expert group to generate evidence summaries (breast cancer, K.A. and A.M.M.; cervical cancer, C.M.W. and P.E.C.; colorectal cancer (CRC), C.A.D., D.A.C., and E.A.H.; and lung cancer, C.A.D. and A.V.). The quality of the evidence for each cancer was evaluated with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group taxonomy. We used Cochrane tools for assessing the risk of bias in cohort studies, which we rated using the ROBINS-I (Risk of Bias in Nonrandomized Studies-of Intervention) criteria as low, moderate, serious, or critical. We provide summaries under each cancer type, but the small numbers of eligible articles precluded a formal meta-analyses. In each study assessed, we also examined whether confounding by indication was likely present.

**Definitions of Confounding by Indication in Follow-Up Diagnostic Testing**

Confounding by indication occurs when the clinical reason for an intervention or treatment (the predictor) is related to the outcome under study. In the specific context of time of diagnostic testing for positive cancer screening results, clinicians may prioritize follow-up testing for more severe screening findings or for patients who report symptoms in addition to a positive screen. For example, patients with highly suspicious findings on LDCT may be followed more quickly; such patients are at higher risk of more advanced or fatal disease. This type of confounding would distort a positive association between time to diagnostic testing and cancer mortality, such that estimates from analyses are attenuated, null, or even reversed to falsely suggest that a longer wait time is protective.

**Definitions of a Positive Screening Test Result**

We used consensus definitions to standardize the review across cancer types (Table 1). A positive screening was defined as the result or set of results from a screening test or tests in an eligible, asymptomatic person that indicated the need for a confirmatory diagnostic test (such as imaging, visualization, and/or biopsy). A diagnostic test was defined as a test used to determine the presence or absence of precancerous abnormality or invasive cancer after a positive screening result. An imaging or endoscopic test performed as follow-up for a positive screen was considered a diagnostic test even if a biopsy was not performed. However, tests performed as part of multistep screening processes or to triage an abnormal screening were not considered diagnostic testing: examples include repeat mammogram for an American College of Radiology Breast Imaging-Reporting and Data System (BI-RADS) score of 0, follow-up testing for a single positive human papillomavirus (HPV) DNA test with normal cytology, or surveillance for some lung nodules.

**Results**

The results of the search are shown in Fig. 2 and Table 2 and are presented along with evidence syntheses under each cancer type. Each section begins with an overview of screening processes followed by the evidence summary, contextual information, and recommendations offered by the PROSPR group.

**Breast Cancer**

*Overview of screening and diagnostic testing for breast cancer*

Breast cancer is the most common cancer and the second leading cause of cancer death in US women, with more advanced disease and lower survival in black women. Breast cancer risk is related to age, family history, inheritable genetic susceptibility (including breast cancer 1 [BRCA1])
and BRCA2 gene mutations), and other risk factors, such as reproductive factors, breast density, obesity, alcohol intake, and exposure to hormones or radiation.64 Screening for breast cancer is recommended at grade B for women ages 50 to 74-years by the USPSTF, but recommendations vary across public health and professional organizations’ guidelines on ages to start and stop screening.7,13,65

Mammography is the primary screening modality for breast cancer and has been recommended by various groups since the 1970s.36 Findings on breast cancer screening are generally reported using the BI-RADS, with categories 4 or 5 recommended to receive a core needle or open surgical biopsy.9,10 Ultrasound and stereotactic-guided core needle biopsy has a sensitivity greater than 97% and specificity from

### TABLE 1. Summary of Definitions of Positive Screening, Choice of Diagnostic Testing, and Test Characteristics

| CANCER TYPE | POSITIVE SCREENING TEST CRITERIA | DIAGNOSTIC TESTS | TEST PERFORMANCE CHARACTERISTICS |
|-------------|----------------------------------|------------------|-----------------------------------|
| Breast      | Mammography with BI-RADS 4 or 5  | Core needle biopsy | Sensitivity, 87%; specificity, 98% (Wang 201743) |
|              |                                  | Fine-needle aspiration biopsy | Sensitivity, 74%; specificity, 96% (Wang 201744) |
|              |                                  | Open biopsy       | Sensitivity, ≥98% (Dahabreh 201442) |
| Cervical    | HPV-16 and ASC-US+ (Massad 201343)b | Colposcopy-directed biopsy | Sensitivity, 60.6% (95% CI, 54.8%-66.6% (Wentzensen 201544) |
|              | ≥LSIL (Massad 201343)b            | Single biopsy     | Sensitivity, 85.6%; 95% CI, 80.3%-90.2% (Wentzensen 201544) |
|              | HPV-16/HPV-18 in women ≥ 25 y (Huh 201545) | Two biopsies | Sensitivity, 95.6%; 95% CI, 91.3%-99.2% (Wentzensen 201544) |
|              | Persistent (≥12 mo) hrHPV+ (Massad 201343) | Three biopsies | Sensitivity, 95%, specificity, 86% (Knudsen 201646) |
| Colorectal  | Positive guaiac FOBT, FIT, or multitarget DNA | Colonoscopy | Sensitivity, 95%, specificity, 86% (Knudsen 201646) |
| Lung        | LDCT indicating suspicious nodule or nodule that has increased in size since prior scan | Imaging (PET scan) | Sensitivity, 97%, specificity, 78% (Gould 200147) |
|             |                                  | Sputum cytology   | Sensitivity, 66%; specificity, 99% (Rivera 201348) |
|             |                                  | Lung biopsy       | Sensitivity, 90%; specificity, 97% (Rivera 201348) |

Abbreviations: +, positive; ≥LSIL, low-grade squamous intraepithelial lesion or more severe cytologic abnormalities; ASC-US, atypical squamous cells of undetermined significance; BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; CTC, computed tomographic colonography; FIT, fecal immunochemical test; FOBT, fecal occult blood test; hrHPV, high-risk human papillomavirus; HPV, human papillomavirus; LDCT, low-dose computed tomography; PET, positron emission tomography. *Test characteristics were calculated relative to the following gold standards: breast cancer, surgical biopsy; cervical cancer, the presence of any high-grade squamous intraepithelial lesion identified in at least 1 of 4 biopsies; colorectal cancer, tandem colonoscopy; lung cancer, modified gamma camera, semiquantitative and qualitative methods or semiquantitative methods only (imaging); histologic confirmation or follow-up ≥1 year (sputum cytology and lung biopsy). †Management options may vary if the woman is pregnant or is ages 21 to 24 years. ‡Test characteristics vary by the number of biopsies taken.
92% to 99% for cancer diagnosis, with open biopsy as the standard (Table 1). Core needle biopsy without imaging guidance has lower sensitivity (91%) but similar specificity to that of open biopsy. Serious harms are relatively uncommon (<1%) and include bleeding, infection, vasovagal reactions, and procedure-related anxiety. The risk of harms is lower with core needle than with open biopsy.

Quality metrics based on expert opinion for the time between a positive screening result and biopsy include the National Quality Measures for Breast Centers (NQMBC) program of the National Consortium of Breast Centers, Inc, and the Breast and Cervical Cancer Early Detection Program (BCCEDP), which is supported by the Centers for Disease Control and Prevention. These guidelines include both the time for resolution of an indeterminate (BI-RADS 0) and positive (BI-RADS 4/5) mammogram. BCCEDP sets a benchmark of 60 days or less from screening to diagnosis, while the NQMBC ranks participating centers against each other and aims for each center to perform above the 25th percentile on 75% of measures. The National Accreditation Program for Breast Centers does not address time to diagnostic testing.

### Evidence synopsis for breast cancer

The search yielded 898 unique articles for breast cancer and, after initial screening, 31 articles were selected for review, and 3 were deemed acceptable by the breast cancer team, including a multimodel microsimulation study on breast, cervical, and colorectal cancers by PROSPR investigators in collaboration with the CISNET (Cancer Intervention and Surveillance Modeling Network) group (see Supporting Material 3 for a list of final included articles).

Olivotto et al examined the association between the time interval from a positive screening mammogram to diagnostic testing and tumor characteristics among 4465 women diagnosed with breast cancer in 5 Canadian organized breast cancer screening programs between 1990 and 1996 (Table 3). On average, women with mammograms that were more suspicious for cancer had diagnostic testing sooner than those who had less suspicious results (31 days for high suspicion vs 47 days for others; \( P < .0001 \)). In regression models controlling for level of suspicion, compared with diagnostic testing at 29 to 84 days after the positive result, there was no statistically significant difference in risk for tumor size greater than 10 mm or for lymph node metastases among women who underwent diagnostic testing at 85 to 140 days or 141 to 364 days after the positive screening examination. Those with a 365-day to 728-day wait time had significantly increased odds of tumors greater than 10 mm (odds ratio [OR], 1.51; 95% confidence interval [95% CI], 1.05-2.16) and of lymph node metastases (OR, 2.16; 95% CI, 1.48-3.15). The associations were even greater for a 729-day to 1092-day wait time.
| STUDY                  | COUNTRY    | STUDY DESIGN | SAMPLE SIZE, NO. | RISK OF BIAS | DAYS FROM POSITIVE SCREEN TO DIAGNOSIS | OUTCOMES MEASURED | ASSOCIATIONS: OUTCOME, OR, OR RR (95% CI) |
|-----------------------|------------|--------------|------------------|--------------|----------------------------------------|-------------------|------------------------------------------|
| Breast cancer         | Canada     | Retrospective cohort | 4465            | Serious      | Median, 41 d                           | OR (95% CI): Reference category, 29-84 d interval |
|                       |            |              |                  |              |                                        | Tumor size >10 mm |
|                       |            |              |                  |              |                                        | 0-28 d, 1.59 (1.36-1.87) |
|                       |            |              |                  |              |                                        | 85-140 d, 0.88 (0.66-1.17) |
|                       |            |              |                  |              |                                        | 141-364 d, 1.17 (0.88-1.56) |
|                       |            |              |                  |              |                                        | 365-728 d, 1.51 (1.05-2.16) |
|                       |            |              |                  |              |                                        | 729-1092 d, 2.11 (1.15-3.86) |
|                       |            |              |                  |              |                                        | Lymph node involvement |
|                       |            |              |                  |              |                                        | 0-28 d, 1.37 (1.16-1.62) |
|                       |            |              |                  |              |                                        | 85-140 d, 0.98 (0.67-1.42) |
|                       |            |              |                  |              |                                        | 141-364 d, 1.19 (0.84-1.69) |
|                       |            |              |                  |              |                                        | 365-728 d, 2.16 (1.48-3.15) |
|                       |            |              |                  |              |                                        | 729-1092 d, 3.19 (1.84-5.55) |
|                       | France     | Retrospective cohort | 1984            | Serious      | Mean ± SD; High suspicion lesions, 59 ± 47 d; low suspicion lesions, 78 ± 52 d |
|                       |            |              |                  |              |                                        | OR (95% CI): Reference category, <30 d interval |
|                       |            |              |                  |              |                                        | Tumor size >10 mm |
|                       |            |              |                  |              |                                        | 30-90 d, 1.37 (0.91-1.63) |
|                       |            |              |                  |              |                                        | 90-180 d, 1.32 (0.86-1.96) |
|                       |            |              |                  |              |                                        | >180 d, 1.77 (1.02-2.85) |
|                       |            |              |                  |              |                                        | Lymph node involvement |
|                       |            |              |                  |              |                                        | 30-90 d, 0.99 (0.67-1.42) |
|                       |            |              |                  |              |                                        | 90-180 d, 1.41 (0.98-1.98) |
|                       |            |              |                  |              |                                        | >180 d, 2.01 (1.29-3.03) |
|                       | United States | Microsimulation modeling | NA            | n/a          | 0-365 d, simulated                     | RR/LYG: Reference category, 0 d interval |
|                       |            |              |                  |              |                                        | Late stage at diagnosis* |
|                       |            |              |                  |              |                                        | 90 d, RR = 1.08 |
|                       |            |              |                  |              |                                        | 365 d, RR = 1.26 |
|                       |            |              |                  |              |                                        | LYG |
|                       |            |              |                  |              |                                        | 90 d, 17.3% |
| Cervical cancer       | United States | Microsimulation modeling | NA            | n/a          | 0 to 365 d, simulated                  | RR/LYG: Reference category, 0 d interval |
|                       |            |              |                  |              |                                        | Late stage at diagnosis* |
|                       |            |              |                  |              |                                        | 90 d, RR = 0.99 |
|                       |            |              |                  |              |                                        | 365 d, RR = 0.98 |
|                       |            |              |                  |              |                                        | LYG |
|                       |            |              |                  |              |                                        | 0.8% |
| STUDY        | COUNTRY       | STUDY DESIGN        | SAMPLE SIZE, NO. | RISK OF BIAS | DAYS FROM POSITIVE SCREEN TO DIAGNOSIS | OUTCOMES MEASURED | ASSOCIATIONS: OUTCOME, OR, OR RR (95% CI) | Abbreviations: | elevated; ↓, decreased; CI, confidence interval; CRC, colorectal cancer; IQR, interquartile range; LYG, life-years gained; n/a, not applicable; NA, not available; OR, odds ratio; RR, relative risk or hazard ratio; SD, standard deviation. aLate stage indicates distant or regional disease or stage III or IV disease at diagnosis. |
|--------------|---------------|---------------------|------------------|--------------|----------------------------------------|-------------------|------------------------------------------|----------------|
| Corley 201754 | United States | Retrospective cohort | 70,124           | Moderate     | Median [IQR], d 37 [23-62 d]            | OR (95% CI): Reference category, 9-30 d interval | CRC diagnosis 31-60 d, 0.92 (0.83-1.02) |                  |
|              |               |                     |                  |              |                                        |                   | 61-90 d, 0.95 (0.82-1.10)                 |                  |
|              |               |                     |                  |              |                                        |                   | 91-180 d, 0.98 (0.82-1.16)                |                  |
|              |               |                     |                  |              |                                        |                   | 181-270 d, 1.03 (0.99-1.72)               |                  |
|              |               |                     |                  |              |                                        |                   | 271-365 d, 1.48 (1.05-2.08)               |                  |
|              |               |                     |                  |              |                                        |                   | >365 d, 2.25 (1.89-2.68)                  |                  |
| Rutter 201851 | United States | Microsimulation modeling | NA               | n/a          | 0-365 d, simulated                       | RR/LYG: Reference category, 0 d interval | Late stage at diagnosis a 90-d, RR = 1.03 |                  |
|              |               |                     |                  |              |                                        |                   | 365 d, RR = 1.11-1.12                     |                  |
| Meester 201655 | United States | Microsimulation modeling | 10 million, simulated | n/a          | 0-365 d, simulated                       | LYG 90 d, 2.0%-2.7% | Reference category, 0-14 d |                  |
| Lung cancer  |               |                     |                  |              |                                        | CRC incidence 10.3% Higher risk for every 30-d interval |                  |
| Sonavane 201758 | United States | Retrospective cohort | 462              | Serious      | Median [IQR], 132 d [49-484 d]          | Lung cancer death OR (95% CI): For each 180-d interval, 1.06 (0.90-1.20) |                  |
(OR, 2.11 [95% CI, 1.15-3.86] and 3.19 [95% CI, 1.84-5.55], respectively) (Fig. 3).\textsuperscript{49,50,54}

Ganry et al analyzed 1984 women who underwent screening in the Somme area in France and had intermediate-suspicion or high-suspicion screening results between 1996 and 2000, and 159 of those women were diagnosed with breast cancer on follow-up.\textsuperscript{50} The authors reported a shorter time to diagnostic testing for high-suspicion than for intermediate-suspicion screening results. Compared with diagnostic testing within 30 days, women who had an interval greater than 180 days to diagnostic testing had a significantly increased risk for tumor size greater than 10 mm (OR, 1.77; 95% CI, 1.02-2.85) and of lymph node metastases (OR, 2.01; 95% CI, 1.29-3.03) (Table 3).\textsuperscript{49-51,54,55,58} There was a statistically nonsignificant, increased risk of larger tumor size and lymph node metastases in those who had an interval from 90 to 180 days to diagnostic testing.\textsuperscript{50}

Finally, the PROSPR multimodel microsimulation study evaluated the effect of time to diagnostic testing after an abnormal mammogram. That study suggested no

\begin{figure}
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\caption{Association Between Intervals for Diagnostic Testing and Outcomes for (A) Breast Cancer (Olivotto et al, 2002\textsuperscript{49}; Ganry et al, 2004\textsuperscript{50}) and (B) Colorectal Cancer (Corley et al, 2017\textsuperscript{54}). T indicates tumor size; 95% CI, 95% confidence interval.}
\end{figure}
difference in the lifetime risk of breast cancer for wait times of 90 days to 1 year, but the relative risk (RR) for late-stage disease was 1.08 at 90 days and 1.26 by 1 year. The modeling yielded a 17.3% decrement in estimated life-years gained (LYG) when diagnostic testing occurred at 90 days.51

**Contextual evidence for breast cancer**

Literature on wait times in breast cancer diagnosis for women who present with breast cancer–related symptoms provides indirect evidence for the key question. A 1999 systematic review of 87 studies found that women with wait times of 3 to 6 months or longer had lower 5-year survival after diagnosis (OR for death, 1.47 [95% CI, 1.42–1.53] compared with less than 3 months).67 That review was updated with an additional 26 articles that included studies examining the association between time to diagnostic testing from symptoms, stage at diagnosis, and survival.68 Although the majority of these studies demonstrated an association between longer wait times and poorer survival, several recent studies either did not find an association or found that patients with longer wait times had better survival, likely because of confounding by indication.

**Conclusion and strength of evidence for breast cancer screening**

Overall, there was limited evidence for a specific, optimal time to diagnostic testing after a positive screening mammogram. One study50 suggested a nonsignificant increase in disease outcomes risk as early as 90 days after the positive screen date, whereas another did not observe worse outcomes until after 365 to 728 days. Thus, the current evidence is not sufficient to determine a precise timing for diagnostic testing, and the quality of evidence is low because of the small number of studies with inconsistent results, which used observational data and had evidence of confounding by indication.69 Therefore, the current published literature does not confirm or refute the 60-day threshold set by the BCCEDP. Given evidence of an increase in risk after 90 days, the 60-day goal set in the Centers for Disease Control and Prevention quality guidelines is a reasonable target for quality improvement after a positive breast cancer screening. Beyond existing practice standards, our conclusion reflects biologic plausibility of disease progression with prolonged wait times, the need for diagnostic testing to occur before discernible increases in risk, and consideration of potential patient anxiety and preferences.

**Cervical Cancer**

**Overview of screening and diagnostic testing for cervical cancer**

In the United States, an estimated 12,820 women were diagnosed with cervical cancer and 4210 women died of the disease in 2017.64 Persistent infection by oncogenic HPV is the primary etiologic factor in cervical cancer.64 HPV types 16 and 18 account for 70% of cases worldwide, and an additional 10 to 12 HPV strains cause the remaining 30%. Cervical cancer thus is potentially preventable through vaccination against HPV. Current screening practices take advantage of the extended, multistep carcinogenic process of progression—from incident, to persistent HPV infection, through cervical intraepithelial neoplasia, to invasive disease—that occurs over an average of 20 to 25 years.70,71

Cervical cancer screening is recommended as grade A by the USPSTF.5 Screening, historically with the Pap test, is credited with large reductions in cervical cancer incidence and mortality over decades.5,15,36 Recent guidelines include recommendations for HPV-cytology cotesting every 5 years among women ages 30 to 64 years, with a shift toward HPV-only testing,43,45 which is included in the new USPSTF recommendations.

The definition of a positive screen depends on age, the presence of persistent high-risk HPV infection, and the severity and persistence of cytologic abnormalities.14,15,18,43,72,73 A low-grade squamous intraepithelial lesion (LSIL) or more severe cytology or a finding of HPV-positive atypical squamous cells of undetermined significance (ASC-US) is an indication for colposcopy in the United States.18,74 Many other countries, especially those with organized screening programs, follow mild abnormalities like LSIL (watchful waiting) until there is evidence of persistence. Increasing prevalence of HPV vaccination and the identification of new biomarkers may change screening and diagnostic practices.75,76

Colposcopy is the primary diagnostic approach for a positive cervical cancer screen (Table 1)41–48 and includes endocervical sampling when endocervical canal extension is suspected, such as atypical glandular cells or adenocarcinoma in situ.49 Colposcopy performance is variable because of subjectivity in where and how many biopsies are taken, and low-quality procedures may lead to false reassurance.77–79 Colposcopy sensitivity ranges from 60.6% for a single biopsy to 95.6% for 3 biopsies (Table 1).41–48 Current practice guidelines recommend no biopsies in low-risk women without visible acetowhite lesions; biopsy of all acetowhite lesions; and consideration for forgoing colposcopy in favor of treatment in women at very high risk for cervical precancer and cancer (such as at least 2 high-grade cytology or high-grade colposcopy findings and/or a positive HPV16/HPV18 result).80,81

Harms from colposcopy are relatively few but include bleeding, infection, and minor discomfort from prolonged speculum examination, application of acetic acid, and biopsy.82 Women may experience anxiety before, during, and after colposcopy.27 Colposcopy identifies cervical intraepithelial neoplasia 2, which may regress83,84 but typically
triggers excisional treatment\(^4\), which can increase the risk of preterm births by 2-fold.\(^85\)-\(^87\)

Recommendations on time to diagnostic testing exist in several countries based on expert consensus.\(^88\) Metrics for time to diagnostic testing for a positive cervical screening in the United States were implemented by the BCCEDP.\(^89\) The interval set by the BCCEDP was originally 60 days or less but was subsequently changed in 2009 to 90 days or less based on expert opinion and pragmatic considerations of the ability of different health systems to achieve timely follow-up.\(^53\)

**Evidence synopsis for cervical cancer**

The final literature search yielded 2601 unique articles for cervical cancer; 23 articles were selected for review after initial screening, and only the multimodal microsimulation study was deemed relevant.\(^51\) The PROSPR multimodel microsimulation study found that longer times to colposcopy led to lower lifetime benefit of screening, with 1.4% fewer cancers prevented at about 90 days. There was an estimated decrement of 0.8% and 1.4% in LYG with 90-day and 180-day intervals to colposcopy, respectively, compared with immediate follow-up (Table 3).\(^49\)-\(^51,54,55,58\)

**Contextual evidence for cervical cancer**

As with other cancers, the severity of abnormalities has been associated with follow-up of a positive Pap test and poorer outcomes; thus, women suspected to have a higher likelihood of severe disease may receive follow-up sooner.\(^90\) Minority and uninsured women and those with lower socioeconomic status have a lower probability of completing follow-up after a positive screening test result,\(^69,91\) and they also have a higher risk of disease.

**Conclusion and strength of evidence for cervical cancer**

The available evidence on the optimal time to diagnostic testing is of very low quality primarily because of the absence of published empirical studies. However, the risk of cervical cancer is higher in underserved populations, likely because of failure to screen or inadequate follow-up of abnormal cytology, and a modeling study suggests disease progression with longer wait times.\(^23,92\) The current convention is to perform colposcopy within 30 days for suspected invasive disease, within 60 days for high-grade cytology, and within 90 days (but not exceeding 180 days) for women with lower grade cytology (such as persistent HPV with ASC-US and LSIL).\(^93\)-\(^96\) Because lesions with a low probability of invasive cancer may regress or progress only slowly over time, the urgency of follow-up after a positive cervical cancer screen appropriately depends on the severity of the abnormality, and the 90-day BCCEDP benchmark is a reasonable target for quality improvement, with shorter time intervals if there is suspected invasive disease or high-grade cytology.

**Colorectal Cancer**

**Overview of screening and diagnostic testing for CRC**

CRC ranks third in the number of new cancer cases reported annually and is the second leading cause of cancer death among US men and women combined.\(^64\) CRC risk is most strongly related to age and genetic susceptibility, including Lynch syndrome, as well as lifestyle-related factors.\(^64\) CRC screening is recommended as grade A by the USPSTF.\(^4\) Screening takes advantage of well-defined precancerous states and the slow progression to invasive disease. Screening has been shown to reduce the risk of death\(^97\)-\(^99\) and is recommended by major national groups.\(^4,11\)

Guideline-recommended tests for screening average-risk individuals beginning at age 50 years through ages 75 or 84 years, depending on prior screening history and life expectancy, include FIT, fecal DNA, computed tomography (CT) colonography, sigmoidoscopy, and optical colonoscopy. FIT and guaiac-based fecal occult blood tests (gFOBT) are the most widely used tests worldwide and are recommended either annually or biennially. CT colonography and flexible sigmoidoscopy are both less commonly used in the United States. Colonoscopy performed every 10 years is the most commonly used screening test in the United States and can both observe and perform diagnostic evaluation of detected lesions at the time of screening. To realize the benefits of noncolonoscopy screening, a positive result requires diagnostic colonoscopy with biopsy or polypectomy, as appropriate. The estimated sensitivity and specificity of colonoscopy are 95% and 86%, respectively, but depend on the type and size of lesions (Table 1)\(^41\)-\(^48\) and also vary across performing providers.\(^100,101\)

Harms of colonoscopy are relatively uncommon and vary in severity from minor to major. Harms increase with age, comorbidity, and the use of polypectomy and are mainly gastrointestinal events (such as bleeding or perforation) and cardiovascular events (such as myocardial infarction or angina, arrhythmias, cardiac arrest and syncope, hypotension, or shock).\(^30,102\) There is also procedure-related fear.\(^28,29\)

There are few published guidelines or quality metrics for the completion of diagnostic testing after a positive CRC screen. A 2006 Canadian Association of Gastroenterology consensus panel recommended 60 days or less from positive screening to colonoscopy.\(^56\) The Veterans Health Administration (VHA) policy sets a 60-day target for the completion of diagnostic colonoscopy from the date of the positive fecal test result\(^57\); the evidence brief for that policy identified only one small study, which we included in our contextual literature.\(^103\)

**Evidence synopsis for CRC**

The final literature search yielded 597 unique articles for CRC; after initial screening, 80 articles were selected for
review, and 3 were deemed acceptable by the CRC team (see Supporting Material 3 for a list of final included articles), including 2 modeling studies.\textsuperscript{51,55}

In the largest available study, Corley et al examined the relationship between time to colonoscopy and risk of any CRC and late-stage CRC in a retrospective cohort of 70,124 patients who had a positive FIT within Kaiser Permanente Southern or Northern California’s organized screening programs between 2010 and 2014 (Table 3).\textsuperscript{49-51,54,55,58} Compared with patients who received colonoscopy 8 to 30 days after a positive FIT, the study found a trend toward increasing CRC risk after 180 days that became statistically significant at greater than 270 days (OR, 1.48; 95% CI, 1.05-2.08) (see Fig. 3). Similar times for significant increases in risk were observed for late-stage disease.\textsuperscript{54,104}

Meester et al\textsuperscript{55} used a well-known and validated microsimulation model, which has been used to inform the USPSTF, to simulate an average-risk cohort of 10 million US adults ages 50 to 75 years undergoing annual FIT screening. Those authors estimated the effect of time to diagnostic colonoscopy on disease progression and CRC mortality. The simulated CRC incidence without screening was 64.8 cases per 1000, and mortality was 26.8 per 1000. Compared with receiving diagnostic testing within 2 weeks of a positive FIT (incidence, 35.5 cases per 1000), each additional month interval was estimated to increase both CRC incidence and mortality by 0.1 per 1000 (a 0.3% and 1.4% monthly increase and 4% and 16% increase with a 12-month wait time, respectively). The results were similar for fecal-DNA screening but were twice as large for gFOBT.\textsuperscript{55} The PROSPR multimodel study used 2 separate CRC modeling strategies side by side. That study reported an RR from 1.01 to 1.02 for lifetime disease risk at 3 months (compared with immediate diagnosis), an RR of 1.05 at 12 months, an RR of 1.03 for late-stage disease risk at 3 months, an RR from 1.11 to 1.12 at 12 months, and an estimated decrement of 2.0% to 2.7% in LYG with a 3-month interval to diagnostic testing.\textsuperscript{51}

Contextual evidence for CRC

In a small observational study (n = 231), Gellad et al examined the association between the timing of diagnostic testing after a positive gFOBT and the risk of colorectal neoplasia.\textsuperscript{103} The median time to colonoscopy was 201 days, and the authors observed that each additional 30-day wait time for colonoscopy increased the odds of detecting any colorectal neoplasia (OR, 1.10; 95% CI, 1.02-1.19), but they did not evaluate specific time intervals, and there was no statistically significant association when the analysis was restricted to advanced neoplasia (OR, 1.07; 95% CI, 0.98-1.18).\textsuperscript{103} A VHA study examined the time between referral for colonoscopy and CRC diagnosis between 2000 and 2005 in 269 veterans at a single center.\textsuperscript{105} The number of days between referral to CRC diagnosis was greater than 90 days in 30% of patients. A shorter time to cancer diagnosis was associated with the presence of symptoms and abnormal laboratory findings. An interval greater than 40 days was correlated with lower mortality risk (hazard ratio [HR], 0.61; 95% CI, 0.39-0.96) but became statistically nonsignificant after adjustment for tumor stage (HR, 0.75; 95% CI, 0.47-1.21). An analysis restricted to 100 patients who were referred as a result of a positive screen (FOBT or sigmoidoscopy) did not find a statistically significant association, but the estimates were not reported.\textsuperscript{105}

Conclusion and strength of evidence for CRC

Overall, there was limited evidence for a specific optimal time to diagnostic testing after a positive screening noncolonoscopy result for CRC. There is empirical evidence from a single study of increased risk for CRC incidence and higher stage in a dose-response fashion for wait times greater than 180 days. Modeling results support these findings, suggesting the potential for increased risk with each additional month of wait time for diagnostic testing. The quality of evidence was low because of the small number of empirical observational studies, but there was some support from modeling studies.

The current published literature does not confirm or refute the 60-day threshold for follow-up of a positive CRC screen set by the VHA and the Canadian panels.\textsuperscript{56,57} The current evidence is not sufficient on the precise timing for diagnostic testing. However, given evidence of an increase in risk after 180 days and modeling estimates suggesting a monotonic increase in risk over time, a 90-day goal is a reasonable target for quality improvement for positive CRC screening results, depending on the resources available and colonoscopy capacity, but wait times longer than 180 days should be avoided. This conclusion reflects biologically plausible disease progression with prolonged wait times, the need to perform diagnostic testing before discernible increases in risk, the heterogeneity of disease detected by some screening tests (FIT and gFOBT are better at detecting cancers than precancerous lesions), existing practice standards, the available evidence, and consideration of the potential for patient anxiety and preferences.

Lung Cancer

Overview of screening and diagnostic testing for lung cancer

Lung cancer is the most common and most lethal malignancy in the United States, with disproportionately high mortality rates in some populations, such as black men.\textsuperscript{54,106} Lung cancer is caused primarily by tobacco use, thus the high prevalence of comorbid, tobacco-related conditions. Screening for lung cancer using LDCT is recommended by
the USPSTF and other national groups based primarily on the National Lung Screening Trial results. The USPSTF recommends annual screening as grade B in those ages 55 to 80 years who have a smoking history of 30 pack-years or greater, are current smokers or have quit in the past 15 years, and are willing and able to undergo surgery. Medicare limits coverage to those ages 55 to 77 years and requires documented shared decision making before screening and for clinical details to be provided to a registry, partly because of the risks from high false-positive rates. The American Academy of Family Physicians does not formally endorse lung cancer screening and concluded that the evidence was insufficient.

LDCT results are classified using the Lung CT Screening Reporting and Data System (Lung-RADS). Lesions classified as Lung-RADS 4B or 4X (and some 4A lesions) require a chest CT or positron emission tomography–CT (PET-CT) and tissue confirmation using CT-guided or bronchoscopy-guided biopsy. The approach and procedures used for diagnostic confirmation (such as flexible bronchoscopy with transbronchial needle aspiration, endobronchial ultrasound-guided-needle aspiration, transthoracic fine-needle aspiration or biopsy, thoracoscopic pleural biopsy, mediastinoscopy, sputum cytology, or thoracentesis) depend on the clinical and radiologic findings. There are several emerging technology refinements (such as navigational bronchoscopy) to aid in the diagnosis of peripheral lesions.

The overall sensitivity and specificity of PET-CT are 96.8% and 77.8%, respectively (Table 1). The sensitivity and specificity of procedures for tissue sampling depend on the type, size, and location of the lesions; the sensitivity of flexible bronchoscopy is about 88% for central lesions, and the sensitivity of transthoracic needle biopsy is about 90%. Harms from diagnostic procedures vary across procedures used and are more common in older patients who have comorbid conditions, such as chronic obstructive pulmonary disease. Pneumothorax is the most common harm and is reported in 5% of image-guided pleural biopsies and 15% of needle biopsies but only about one-half require chest tube. Other harms include hemorrhage, hypoxemia, bradycardia, and death. There is also short-term procedure-related anxiety.

Few published recommendations exist on benchmarks for the timing of diagnostic testing after a positive lung cancer screen, and there is high variability in the definition of wait intervals used in the current literature. The RAND Corporation recommended diagnostic confirmation within 60 days of presentation. The American College of Chest Physicians recommended “timely and efficient” delivery for patients with suspected or known lung cancer and emphasized consideration for competing needs for resources to set local performance metrics. The United Kingdom recommends urgent referral (defined as 2 weeks or less) to a specialist for patients with suspected cancer on a chest roentgenogram or CT.

Evidence synopsis for lung cancer

The final literature search yielded 883 unique articles for lung cancer; after initial screening, 27 articles were selected for further review, but only one was deemed relevant (see Supporting Material 3 for a list of final included articles). Sonavane et al examined the association between time to diagnostic testing and tumor stage and survival over 7 years of follow-up in 462 National Lung Screening Trial participants who had a positive baseline LDCT and were diagnosed with lung cancer within 3 years (Table 3).

Many patients received diagnostic testing greater than 12 months after the LDCT. Patients with less aggressive LDCT findings (such as nodules less than 10 mm, pure ground glass nodules, or nodules with smooth margins) took longer to receive diagnostic testing. There were fewer stage I and II cancers (55% vs 76%) or adenocarcinomas (53% vs 78%) in the lowest quartile of time to diagnostic testing than in the highest quartile (P < .005), thus the lung cancer death rate was highest in the first quartile (44%, 25%, 30%, and 26%, for quartiles 1 through 4, respectively). There was no statistically significant association of time to diagnostic testing with lung cancer death (OR, 1.06 [95% CI, 0.90-1.20] for each additional 180-day interval) after adjustment for tumor characteristics and LDCT findings.

Contextual evidence for lung cancer

In a Japanese study of 198 patients who had lung cancer diagnosed through screening roentgenograms, the 5-year survival rate was lower in those with a 1-year wait time for follow-up (21%; n = 45) than in those who had sooner follow-up (51%; n = 153; HR, 2.15; 95% CI, 1.20-3.84). Another Japanese study of 83 patients who had screening-detected lung cancer reported a difference in survival between those diagnosed with a clinical staging interval less than 4 months after the screening result and those who took longer to be diagnosed (P = .05).

In a Canadian study, Byrne et al used retrospective data to evaluate tumor size and stage in patients who had biopsy-confirmed nonsmall cell lung cancer (NSCLC) during 2 periods of differing waiting times for diagnostic confirmation after positive imaging tests (n = 66 in 2009 [48 days; interquartile range (IQR), 29.0-84.0 days] vs n = 85 in 2011 [81.0 days; IQR, 41.0-139.5 days]). Tumor size and stage were higher in the group with a longer median wait time (P < .001). A small study (n = 29) reported an increase of up to 373% in tumor size over a median 54-day period (range, 18-131 days) of workup, consistent with the estimated doubling time of 20 to 300 days for NSCLC. In a US cohort study of 482 consecutive
patients with NSCLC who had a median interval; of 16 days (IQR, 6–43 days) from imaging to diagnosis, Yorio et al found no association between time to diagnostic testing and overall survival. Some low-quality studies have reported paradoxical findings of lower mortality risk with longer delay in receipt of care, likely reflecting quicker follow-up for those with more severe LDCT results.

**Conclusion and strength of evidence for lung cancer**

Available evidence on the optimal time to diagnostic testing for lung cancer is of very low quality, primarily because of the paucity of studies assessing time to diagnosis on the key question in an LDCT screening population. However, indirect evidence is consistent with the notion that patients who have suspected lung cancer detected at screening should undergo diagnostic workup soon after the positive result, but the evidence is insufficient to provide a specific timeframe for the diagnostic workup to occur. The RAND Corporation–recommended 60-day timeframe provides a reasonable target for quality-improvement efforts.

In efforts to improve the quality of care for lung cancer screening, consistent with biologic plausibility and patient-centered care, those with Lung-RADS 4B or 4X findings should undergo timely follow-up diagnostic evaluation with PET-CT and/or biopsy and workup should be performed within 60 days of the positive result date to reduce the risk of disease progression. This recommendation does not apply to nodules for which surveillance is indicated.

**Summary Discussion**

This review evaluated the current evidence on the association between timing of diagnostic testing after a positive screening result and risk of progression of precancerous lesions or cancer and mortality for 4 cancers for which screening is recommended at grade A or B by the USPSTF. We found limited direct evidence in the published literature on our key question, due mainly to a small number of studies and the presence of confounding by indication. Additional supporting evidence came from studies in nonscreening populations that examined time from onset of symptoms to diagnostic testing or treatment or when screening was performed using tests that are not recommended in the United States. The available evidence suggests an increased risk of cancer, later stage cancer, or mortality with increasing time between a positive cancer screening result and receipt of diagnostic testing; however, the patterns differ across cancers, and specific thresholds remain unclear.

**Gaps in the Evidence of Time to Diagnostic Testing**

The primary gap in the evidence is the paucity of studies on the key question with sufficient power to examine effect of wait times on mortality from the specific cancers. Randomized clinical trials are infeasible for assessing the effect of delay in diagnostic testing after a positive screen because of ethical concerns. There are several challenges of observational studies, principally confounding by indication, as defined previously, from prioritizing the follow-up of patients who have high-suspicion screening results or concurrent symptoms. Consequently, observational studies may show a null or reverse association between time to diagnostic testing and cancer outcomes, especially during the early phases of follow-up, as reported in many studies. For instance, in one study of screening mammograms, the higher the level of suspicion for cancer, the shorter interval to diagnostic testing (31 days for high suspicion vs 47 days for other; P < .0001); thus women with a higher likelihood of cancer on mammograms were worked up more quickly. Both Myrdal et al and Annakaya et al reported that a longer delay from symptom to treatment initiation was correlated with a better prognosis for NSCLC. Another study indicated that patients who had longer wait times between referral and treatment had a higher proportion of earlier stage lung cancer. Studies of time to diagnostic testing may be less susceptible to bias or confounding for screening results that are only reported qualitatively as positive or negative. Unlike cancer screening results that report lesion phenotype based on the probability of cancer diagnosis (eg, BI-RADS, Lung-RADS, or colonoscopy), the results from fecal-based CRC screening tests are only reported qualitatively as positive or negative. A positive FIT simply signifies the presence of occult blood; studying outcomes in that population in large, closed systems with centralized, organized screening programs that are able to track patients over time may be less subject to confounding, provided the timing of follow-up by patients or providers is not influenced by the presence of symptoms. In addition, natural experiments (such as those occurring during the roll out of screening programs or natural variations in practice patterns) may provide insights on the impact of time to diagnostic testing. Because of the limited evidence base, several existing recommendations on time to diagnostic testing are based on either historical patterns of care, consideration of patient-centered care, expert opinion, or policy mandates.

Well-calibrated natural history models can provide valuable insights on the effect of time to diagnostic testing, but findings from such studies depend on the specification of the model parameters and should be interpreted with caution. We did not have modeling estimates on lung cancer screening, because it was not included in the first phase of PROSPR, and we are unaware of any other microsimulation models that address our key question. Thus, additional modeling studies are needed to inform decisions on the
effect of delay on the benefits and harms of lung cancer screening.

We included only published studies in our review, which is subject to publication bias. However, we found evidence for and against timely diagnostic testing, which argues against substantial publication bias.

**Other Considerations on the Recommendations for Timeliness of Diagnostic Testing**

Despite the limitations of the current literature, strong biologic plausibility and the available evidence support the notion that longer waiting times from a positive screen to diagnosis diminish the benefits of screening. Earlier time to diagnostic testing decreases the risk of progression of preneoplastic disease to cancer and from early-stage to late-stage cancers. Another consideration is the possibility that the longer the time period between positive screening and diagnostic evaluation, the higher the potential that patients may change contact information, insurance coverage, or providers, further complicating coordination of care and follow-up. In addition, some patients may never receive follow-up after a positive test and only receive confirmatory diagnosis after symptoms appear. These issues directly influence the likelihood of successful cancer prevention or cure. There is also the potential for worry or anxiety about the uncertainty of a cancer diagnosis from a positive result.

For those reasons, some systems offer same-day follow-up for positive mammograms. An analysis of 18,245 women in the NQMBC program indicated that the median time to diagnostic testing was 6.5 days (IQR, 4.0-10.5 days) from a positive mammogram. The median time to diagnostic testing from a positive mammogram decreased by 2 days in the BCCEDP between 1996 to 2000 and 2001 to 2005. Immediate follow-up may not be feasible for other cancer types because of greater resources needed for same-day evaluation and the need for preparation and transition to different settings to continue care. Some diagnostic procedures, such as colonoscopy, require special preparation, sedation, and additional personnel.

**Improving Diagnostic Testing After a Positive Screen**

There is a strong national imperative to improve the timeliness of care. There is consistent evidence that the overall proportions of people receiving follow-up and the times to follow-up testing after a positive screen are generally suboptimal and vary across populations and health systems.

Studies in the PROSPR Consortium show that the probability of undergoing diagnostic colonoscopy after a positive fecal test plateaus at approximately 80% after 6 months in systems with highly organized screening and at lower levels in systems with less organized follow-up. Less than 75% of women receive follow-up within variously defined time metrics after an abnormal cervical cancer screening.

These suboptimal rates may reflect appropriate shared clinical decisions to forgo further testing, or they may stem from social, cultural, financial, structural, or other barriers at individual, provider, or system levels. Such factors include low socioeconomic status, employment status, rurality, perceived discrimination, or health-related stigma. Provider-related and system-related problems with care delivery are crucial. The method of result notification (with telephone and letter notification associated with longer delays than in-person notification), as well as the use of navigators, rapid diagnostic units, and organized screening programs, influence the timeliness of follow-up. Procedures that reduce the number of interfaces involved (such as use of core needle biopsy rather than open biopsy for abnormal mammograms) may reduce the time to biopsy.

Thus, overcoming barriers to timely follow-up likely will require multilevel interventions to mitigate multiple barriers, but evidence is limited regarding effective interventions. A recent systematic review of interventions to improve follow-up of positive FIT found only limited evidence that supported the use of patient navigators or giving providers reminders or performance data. Other studies also suggest a role for patient navigation as well as the use of electronic health record flags, counseling, and education. Improving electronic health record “cross-talk” across different health systems also may minimize losses to follow-up.

**Conclusions**

The effectiveness of cancer screening is predicated upon performing diagnostic testing to confirm the absence or presence of precancer or cancer and the stage of disease when cancer is found. Failure to do so undermines the benefits of screening and may lead to poor cancer outcomes. Furthermore, attention to timely follow-up is a critical part of routine clinical care. Current evidence shows that diagnostic testing is being prioritized based on the severity of findings when available but also suggests that longer wait times for diagnostic testing may be harmful. Overall, the evidence suggests that the risk for poorer cancer outcomes rises with longer wait times, which supports performing diagnostic testing as soon as feasible after the positive result. However, evidence for specific times for diagnostic testing is limited across cancers, and the available evidence does not confirm or refute existing guidelines that set targets for quality improvement. Local benchmarks may take available resources into account. More research is needed to provide evidence-based metrics for optimizing follow-up timing.
that best balances benefits and harms (at both patient and system levels) and patient preferences. It is crucial for future studies to address methodological weaknesses in current studies: principally, confounding by indication. Research is needed to guide interventions on reducing the time to diagnosis for vulnerable and minority populations and for patients who have identified barriers to timely follow-up. 

Acknowledgements: We thank Jessica Chubak, PhD for helpful comments on the article.

References
1. Kaplan GS. Health care scheduling and access: a report from the IOM. JAMA. 2015;314:1449-1450.
2. Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: The National Academies Press; 2001.
3. Institute of Medicine. Transforming Health Care Scheduling and Access: Getting to Now. Washington, DC: The National Academies Press; 2015.
4. US Preventive Services Task Force. Bibbins-Domingo K, Grossman DC, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2016;315:2564-2579.
5. Moyer VA, US Preventive Services Task Force. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;156:880-891, W312.
6. Moyer VA, US Preventive Services Task Force. Screening for lung cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160:330-338.
7. Sui AL, US Preventive Services Task Force. Screening for breast cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2016;164:279-296.
8. Koh HK, Sebelius KG. Promoting prevention through the Affordable Care Act. N Engl J Med. 2010;363:1296-1299.
9. Brueining W, Fontanarosa J, Tipton K, Treadwell JR, Lauanders J, Schoelles K. Systematic review: comparative effectiveness of core-needle and open surgical biopsy to diagnose breast lesions. Ann Intern Med. 2010;152:238-246.
10. D’Orsi CJ, Sickles EA, Mendelson EB, et al. American College of Radiology (ACR) BI-RADS Atlas, Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology; 2013.
11. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin. 2008;58:130-160.
12. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395-409.
13. Offeniger KC, Fontham ET, Etzioni R, et al. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. JAMA. 2015;314:1599-1614.
14. Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin. 2002;52:342-362.
15. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathol, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012;62:147-172.
16. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2017: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2017;67:100-121.
17. Wender R, Fontham ET, Barrera E Jr, et al. American Cancer Society lung cancer screening guidelines. CA Cancer J Clin. 2013;63:107-117.
18. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ; ASCCP-Sponsored Consensus Conference. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA. 2002;287:2120-2129.
19. Chubak J, Garcia MP, Burnett-Hartman AN, et al. Time to colonoscopy after positive fecal blood test in four US health care systems. Cancer Epidemiol Biomarkers Prev. 2016;25:344-350.
20. Eggleston KS, Coker AL, Luchok JK, Meyer TE. Adherence to recommendations for follow-up to abnormal Pap tests. Obstet Gynecol. 2007;109:1332-1341.
21. Laiyemo AO, Doubeni CA, Pinsky PF, et al. American Cancer Society guideline for breast, cervical, and colorectal cancer screening: examining fears, attitudes, and medical mistrust in an ethnically diverse sample of adults 50 years and older. Am J Health Promot. 2012;26:295-300.
22. Green AR, Peters-Lewis A, Pencacc-Lima S, et al. Barriers to screening colonoscopy for low-income Latino and white patients in an urban community health center. J Gen Intern Med. 2008;23:834-840.
23. Lin JS, Piper MA, Perdue LA, et al. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2016;315:2576-2594.
24. Humphrey L, Defiebach M, Pappas M, et al. Screening for Lung Cancer: Systematic Review to Update the US Preventive Services Task Force Recommendation. Evidence Synthesis No. 105. Agency for Healthcare Research and Quality Pub. No. 13-05188-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2013.
25. Khakbazan Z, Taghipour A, Latifnejad Roudsari R, Mohammadi E. Help seeking behavior of women with self-discovered breast cancer symptoms: a meta-ethnographic synthesis of patient delay (serial online). PLos One. 2014;9:e10262.
26. Racz JM, Holloway CM, Huang W, Hong NJ. Improving patient flow and timeliness in the diagnosis and management of breast abnormalities: the impact of a rapid diagnostic unit. Curr Oncol. 2016;23:e260-e265.
27. Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health. Population-based Research Optimizing Screening Through Personalized Regimens (PROSPR). Bethesda, MD: National Cancer Institute; 2018. healtharedelivery.cancer.gov/prospr/. Accessed January 3, 2018.
28. Beaber EF, Kim JJ, Schapira MM, et al. Unifying screening processes within the PROSPR Consortium: a conceptual model for breast, cervical, and colorectal cancer screening [serial online]. J Natl Cancer Inst. 2013;105:dv120.
29. American Cancer Society. Chronological History of ACS Recommendations on Early Detection of Cancer. Atlanta; GA: American Cancer Society; 2013.
30. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-926.
National Quality Measures for Breast Centers, National Consortium of Breast Centers Inc. nqmbc.org/become-a-certified-quality-breast-center/. Accessed October 24, 2017.

53. Centers for Disease Control and Prevention. National Breast and Cervical Cancer Early Detection Program (NBCCEDP) Monthly Newsletter. Atlanta, GA: Centers for Disease Control and Prevention; 2009.

54. Corley DA, Jensen CD, Quinn VP, et al. Association between time to coloscopy after a positive fecal test result and risk of colorectal cancer and cancer stage at diagnosis. JAMA. 2017;317:1631-1641.

55. Meester RG, Zauber AG, Dubeni CA, et al. Consequences of increasing time to coloscopy examination after positive results of colorectal cancer screening test. Clin Gastroenterol Hepatol. 2016;14:1445-1451, e1448.

56. Paterson WG, Depew WT, Pare P, et al. Canadian consensus on medically acceptable wait times for cancer care. Can J Gastroenterol. 2006;20:411-423.

57. Peterson K, Carson S, Humphrey L, Helfand M. Patients with Positive Screening Fecal Occult Blood Tests: Evidence Brief on the Relationship Between Time Delay to Coloscopy and Colorectal Cancer Outcomes. VA-ESP Project 09-199. Portland, OR: Evidence-Based Synthesis Program (ESP), Coordinating Center, Portland VA Medical Center; 2013.

58. Sonavane SK, Pinsky P, Watts J Jr, et al. The relationship of cancer characteristics and patient outcome with time to lung cancer diagnosis after an abnormal screening CT. Eur Radiol. 2017;27:5113-5118.

59. Byrne SC, Barrett B, Bhatia R. The impact of diagnostic imaging wait times on the prognosis of local cancer. Can Assoc Radiol J. 2015;66:53-57.

60. Denning DJ, O’Connell RM, Bishop L. Angiographic follow-up of positive cancer screening biomarkers. BMJ. 2018;68:7-11.

61. Fitchett J, Ware RE, O’Connell RM, Bishop L. The relationship of cancer characteristics and patient outcome with time to lung cancer diagnosis after an abnormal screening CT. Eur Radiol. 2017;27:5113-5118.

62. Asch S, Kerr E, Hamilton E, et al. Lung cancer diagnostic and treatment intervals in the United States: a health care dispari- ty? J Thorac Oncol. 2009;4:1322-1330.

63. Asch S, Kerr E, Hamilton E, et al. Lung cancer. In: Asch S, Kerr E, Hamilton E, et al., eds. Quality of Care for Oncologic Conditions and HIV: A Review of the Literature and Quality Indicators. Santa Monica, CA: RAND Corporation; 2000:133-171.

64. Baldwin DR, White B, Schmidt-Hansen M, Champion AR, Melder AM; Guideline Development Group. Diagnosis and treatment of lung cancer: summary of updated NICE guidance [serial online]. BMJ. 2011;342:d2110.

65. Siegel RL, Miller KD, Jemal A. Cancer stats- tistics, 2018. CA Cancer J Clin. 2018;68:7-30.

66. Expert Panel on Breast Imaging. Mainiero MB, Moy L, et al. ACR Appropriateness Criteria breast cancer screening. J Am Coll Radiol. 2014;11(8):S38-S40, 2017.

67. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. Lancet. 1999;353:1119-1126.

68. Caplan L. Delay in breast cancer: implica- tions for stage at diagnosis and survival [serial online]. Front Public Health. 2014;2:87.

69. Durham DD, Robinson WR, Lee SS, et al. Insurance-based differences in time to diagnostic follow-up after positive screening mammography. Cancer Epidemiol Biomarkers Prev. 2016;25:1474-1482.
based colposcopy practice. J Low Genit Tract Dis. 2017;21:230-234.

82. Khan MJ, Werner CL, Darragh TM, et al. ASCCP colposcopy standards: role of colposcopy, benefits, potential harms, and terminology for colposcopic practice. J Low Genit Tract Dis. 2017;21:223-229.

83. Castle PE, Schiffman M, Wheeler CM, et al. ASCCP evidence for frequent regression of cervical intraepithelial neoplasia grade 2. Obstet Gynecol. 2009;113:18-25.

84. Trimble CL, Plantadosi S, Gravitt P, et al. Spontaneous regression of high-grade cervical dysplasia: effects of human papillomavirus type and HLA phenotype. Clin Cancer Res. 2005;11:4717-4723.

85. Castanon A, Landy R, Brocklehurst P, et al. Risk of preterm delivery following increasing depth of excision for cervical intraepithelial neoplasia in England: nested case-control study [online report]. BMJ. 2014;349:g6223.

86. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, et al. Obstetric outcomes after conservative treatment for cervical intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet. 2006;367:489-498.

87. Sasiemi P, Castanon A, Landy R, et al. Risk of preterm birth following surgical treatment for cervical disease: executive summary of a recent symposium. BJOG. 2016;123:1426-1429.

88. Mayeaux EJ Jr, Novetsky AP, Chelmow D, et al. Systematic review of international colposcopy quality improvement guidelines. J Low Genit Tract Dis. 2017;21:249-257.

89. Ryerson AB, Bernard VB, Majors A. National Breast and Cervical Cancer Early Detection Program: Summarizing the First 12 Years of Partnerships and Progress Against Breast and Cervical Cancer. edc.gov/cancer/nbcedp/pdf/national_report.pdf. 2017. Accessed January 3, 2018.

90. Egleston KS, Koker AL, Das IP, Cordray ST, Luchok KJ. Understanding barriers for abnormal Pap smear, follow-up care for abnormal Pap tests. J Womens Health (Larchmt). 2007;16:311-330.

91. Tahmaz F, Muller HG, Wang JL, Zhang W, Howell LP. Timeliness and follow-up patterns of cervical cancer detection in a cohort of medically underserved California women. Cancer Causes Control. 2010;21:411-420.

92. Janerich DT, Hadjimichael O, Schwartz PE, et al. The screening histories of women with invasive cervical cancer, Connecticut. Am J Public Health. 1995;85:791-794.

93. Canadian Partnership Against Cancer, Pan-Canadian Cervical Screening Network. Cervical Cancer Screening in Canada: Setting Targets for Program Performance. Summary Report: 2013. Toronto, ON: Canadian Partnership Against Cancer; 2013.

94. Canadian Partnership Against Cancer. Cervical Cancer Screening in Canada: Monitoring and Evaluation of Quality Indicators. Results Report: January 2011-December 2013. Toronto, ON: Canadian Partnership Against Cancer; updated July 2016.

95. International Agency for Research on Cancer, CPO Piemonte and University Hospital “Città della Salute e della Scienza” Turin, Mass Screening Registry/Finnish Cancer Registry. Cancer Screening in the European Union: Report on the Implementation of the Council Recommendation on Cancer Screening. Lyon, France: International Agency for Research on Cancer; 2017.

96. Mayeaux EJ Jr, Novetsky AP, Chelmow D, et al. ASCCP colposcopy standards: colposcopy quality improvement recommendations for the United States. J Low Genit Tract Dis. 2017;21:242-248.

97. Dounbi CA, Corley DA, Quinn VP, et al. Effectiveness of screening colposcopy in reducing the risk of death from right and left colon cancer: a large community-based study. Gut. 2018;67:291-298.

98. Akinw T, Woolfdrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. Lancet. 2017;389:1299-1311.

99. Hewitson P, Glassziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. Am J Gastroenterol. 2008;103:1541-1549.

100. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med. 2014;370:1298-1306.

101. Fedewa SA, Flanders WD, Ward KE, et al. Lagtimes in diagnosis and treatment of colorectal cancer: a population-based cohort study. Ann Intern Med. 2017;166:857-866.

102. Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy with polypectomy. Am J Gastroenterol. 2005;11:4717-4723.

103. Wattacheril J, Kramer JR, Richardson P, et al. Time from positive screening fecal occult blood test to colonoscopy and risk of neoplasia. Dig Dis Sci. 2009;54:2497-2502.

104. Dounbi CA, Corley DA, Levin TR. Time to diagnostic testing after a positive colorectal cancer screening test [letter]. JAMA. 2017;318:483.

105. Waittcheril J, Kramer JR, Richardson P, et al. Lagtimes in diagnosis and treatment of colorectal cancer: determinants and association with cancer stage and survival. Aliment Pharmacol Ther. 2008;28:1166-1174.

106. American Cancer Society. Cancer Facts & Figures 2018. Atlanta, GA: American Cancer Society; 2018.

107. American Academy of Family Physicians. Clinical Preventive Service Recommendation: Lung Cancer. Patient Care. Leawood, KS: American Academy of Family Physicians; 2014. aafp.org/patient-care/ clinical-recommendations/all/lung-cancer. html. Accessed December 3, 2017.

108. Roetzelheim RG, Gonzalez EC, Ferrante JM, Pal N, Van Durme DJ, Krischer JP. Effects of health insurance and race on breast cancer treatment and outcomes. Cancer. 2000;89:2202-2213.

109. American College of Radiology. Lung CT Screening Reporting and Data System (Lung-RADS). Reston, VA: American College of Radiology; 2014. acr.org/Quality-Safety/Resources/LungRADS. Accessed January 8, 2017.

110. Belanger AR, Akulian JA. An update on the role of advanced diagnostic bronchoscopy in the evaluation and staging of lung cancer. Ther Adv Respir Dis. 2017;11:211-221.

111. Benamore RE, Scott K, Richards CJ, Entwistle JI. Image-guided pleural biopsy: diagnostic yield and complications. Clin Radiol. 2006;61:700-705.

112. Jacobsen MM, Silverstein SC, Quinn M, et al. Timeliness of access to lung cancer diagnosis and treatment: a scoping literature review. Lung Cancer. 2017;112:156-164.

113. Ost DE, Jim Yeung SC, Tanoue LT, Gould MK. Clinical and organizational factors in the initial evaluation of patients with lung cancer: Diagnosis and Management of Lung Cancer, 3rd ed. American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 suppl):e121S-e141S.

114. Kashiwabara K, Koshi S, Itokama N, Nakahara O, Tanaka M, Toyonaga M. Outcome in patients with lung cancer found on lung cancer mass screening roentgenograms, but who did not subsequently consult a doctor. Lung Cancer. 2003;40:67-72.

115. O’Rourke N, Edwards R. Lung cancer treatment waiting times and tumour growth. Clin Oncol (R Coll Radiol). 2000;12:141-144.

116. Ost DE, Gould MK. Decision making in patients with pulmonary nodules. Am J Respir Crit Care Med. 2012;185:363-372.

117. Myrdal G, Lambe M, Hillerdal G, Lamborg K, Agustsson T, Stahle E. Effect of delays on prognosis in patients with non-small cell lung cancer. Thorax. 2004;59:45-49.

118. Annakkaya AN, Arbak P, Balbay O, Bilgin C, Erbas M, Bulut I. Effect of symptom-to-treatment interval on prognosis in lung cancer. Tumori. 2007;93:61-67.

119. Comber H, Cronin DP, Deady S, Lorcain PO, Riordan P. Delays in treatment in the cancer services: impact on stage and survival. Ir Med J. 2005;98:238-239.

120. Haas J, Kaplan C, McMillan A, Esserman LJ. Does timely assessment affect the anxiety associated with an abnormal mammogram result? J Womens Health Genet Based Med. 2001;10:599-605.

121. Kreyzer-Dekker CM, van Esch L, de Vries J, et al. An abnormal screening mammogram causes more anxiety than a palpable lump in benign breast disease. Breast Cancer Res Treat. 2012;134:253-258.

122. Kaufman CS, Shockney L, Rabinowitz B, et al. National Quality Measures for Breast Centers (NQMC): a robust quality tool: breast center quality measures. Ann Surg Oncol. 2010;17:377-385.

123. Richardson LC, Royalty J, Howe W, Helsel W, Kammerer W, Benard VB. Timeliness of breast cancer diagnosis and initiation of treatment in the National Breast and Cervical Cancer Early Detection Program, 1996-2005. Am J Public Health. 2010;100:1769-1776.

124. Tejeda S, Darnell JS, Cho YI, Stolley MR, Markosian TW, Calhoun EA. Patient barriers to follow-up care for breast and
cervical cancer abnormalities. J Womens Health (Larchmt). 2013;22:507-517.

125. Yabroff KR, Breen N, Vernon SW, Meissner HJ, Freedman AN, Ballard-Barbash R. What factors are associated with diagnostic follow-up after abnormal mammograms? Findings from a US National Survey. Cancer Epidemiol Biomarkers Prev. 2004;13:723-732.

126. Rojas C, Zhou MK, Khamis HJ, Amesse L. Analysis of patterns of patient compliance after an abnormal Pap smear result: the influence of demographic characteristics on patient compliance. J Low Genit Tract Dis. 2013;17:298-302.

127. Perez-Stable EJ, Afable-Munsuz A, Kaplan CP, et al. Factors influencing time to diagnosis after abnormal mammography in diverse women. J Womens Health (Larchmt). 2013;22:159-166.

128. Carter-Harris L. Lung cancer stigma as a barrier to medical help-seeking behavior: practice implications. J Am Assoc Nurse Pract. 2015;27:240-245.

129. Carter-Harris L, Hermann CP, Schreiber J, Weaver MT, Rawl SM. Lung cancer stigma predicts timing of medical help-seeking behavior. Oncol Nurs Forum. 2014;41:E203-E210.

130. Dunn J, Garvey G, Valery PC, et al. Barriers to lung cancer care: health professionals' perspectives. Support Care Cancer. 2017;25:497-504.

131. Chiarelli AM, Muradali D, Blackmore KM, et al. Evaluating wait times from screening to breast cancer diagnosis among women undergoing organised assessment vs usual care. Br J Cancer. 2017;116:1254-1263.

132. Plotogea A, Chiarelli AM, Mirea L, et al. Clinical and prognostic factors associated with diagnostic wait times by breast cancer detection method [serial online]. Springerplus. 2014;3:125.

133. Baron RC, Melillo S, Rimer BK, et al. Intervention to increase recommendation and delivery of screening for breast, cervical, and colorectal cancers by healthcare providers a systematic review of provider reminders. Am J Prev Med. 2010;38:110-117.

134. Selby K, Baumgartner C, Levin TR, et al. Interventions to improve follow-up of positive results on fecal blood tests: a systematic review. Ann Intern Med. 2017;167:565-575.

135. Battaglia TA, Bak SM, Heeren T, et al. Boston Patient Navigation Research Program: the impact of navigation on time to diagnostic resolution after abnormal cancer screening. Cancer Epidemiol Biomarkers Prev. 2012;21:1645-1654.

136. Markossian TW, Darnell JS, Calhoun EA. Follow-up and timeliness after an abnormal cancer screening among underserved, urban women in a patient navigation program. Cancer Epidemiol Biomarkers Prev. 2012;21:1691-1700.

137. Brookhart MA, Sturmer T, Glynn RJ, Rassen J, Schneeweiss S. Confounding control in healthcare database research: challenges and potential approaches. Med Care. 2010;48(6 suppl):S114-S120.