National Comprehensive Cancer Network®

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United States Preventive Services Task Force
5600 Fishers Lane
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RE: United States Preventive Services Task Force Draft Recommendation Statement on Screening for Breast Cancer

To the Members of the United States Preventive Services Task Force:

The National Comprehensive Cancer Network® (NCCN®) appreciates the opportunity to comment on the United States Preventive Services Task Force (USPSTF) Draft Recommendation Statement on Screening for Breast Cancer as it relates to NCCN's mission of improving and facilitating quality, effective, equitable, and accessible cancer care so all patients can live better lives. NCCN thanks the USPSTF for its efforts to provide evidence-based recommendations about breast cancer screening. NCCN is pleased to provide information, recommendations, and resources as USPSTF considers its updated recommendation.

NCCN Background

As an alliance of 33 leading academic cancer centers in the United States that treat hundreds of thousands of patients with cancer annually, NCCN® is a developer of authoritative information regarding cancer prevention, screening, diagnosis, treatment, and supportive care that is widely used by clinical professionals and payers alike. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a comprehensive set of guidelines detailing the sequential management decisions and interventions that currently apply to 97 percent of cancers affecting patients in the United States.

NCCN Guidelines® and Library of Compendia products help ensure access to appropriate care, clinical decision-making, and assessment of quality improvement initiatives. NCCN was recognized by CMS in 2016 and renewed in 2021 as a qualified Provider Led Entity (PLE) for the Medicare Appropriate Use Criteria (AUC) Program for the development of AUC and the establishment of policy and decision-making for diagnostic imaging in patients with cancer. NCCN Imaging Appropriate Use Criteria (NCCN Imaging AUC™) include information designed to support clinical decision-making around the use of imaging in patients with cancer and are based directly on the NCCN Guidelines®. NCCN Imaging AUC™ include recommendations pertaining to cancer screening, diagnosis, staging, treatment response assessment, follow-up, and surveillance. The NCCN Drugs & Biologics Compendium (NCCN Compendium®) has been recognized by CMS and clinical professionals in the commercial payer setting since 2008 as an evidence-based reference for establishment of coverage policy and coverage decisions regarding off-label use of anticancer and cancer-related medications. The NCCN Biomarkers Compendium® has been referenced as a coverage mechanism and source of evidence by local Medicare Administrative Contractors and serves as a resource for payers, providers, and health care entities navigating the rapidly changing evidence-base for medically necessary biomarker testing in oncology. The NCCN Biomarkers Compendium® contains information derived directly from the NCCN Guidelines to support decision-making around the use of

biomarker testing in patients with cancer. The NCCN Biomarkers Compendium is updated continuously in conjunction with the NCCN guidelines to stay evergreen.

NCCN imposes strict policies to shield the guidelines development processes from external influences. The "firewall" surrounding the NCCN Guidelines processes includes the following: financial support policies; panel participation and communication policies; guidelines disclosure policies; and policies regarding relationships to NCCN's other business development activities. The guidelines development is supported exclusively by the Member Institutions' dues and does not accept any form of industry or other external financial support for the guidelines development program. The NCCN Guidelines are updated at least annually in an evidence-based process integrated with the expert judgment of multidisciplinary panels of expert physicians from NCCN Member Institutions. The NCCN Guidelines are transparent, continuously updated, available free of charge online for non-commercial use, and are available through a multitude of health information technology (HIT) vendors.

Expanded Age Group

The USPSTF proposes to update the B grade recommendation for biennial screening mammography to include women (including transgender men and non-binary individuals assigned female at birth) ages 40 to 49. The NCCN Clinical Practice Guidelines for Breast Cancer Screening and Diagnosis® recommend annual screening mammography age 40 and over for those at average risk as a Category 1 recommendation, the highest available category in the NCCN Clinical Practice Guidelines. As such, NCCN applauds the USPSTF for this first step to improve access to appropriate breast cancer screening for those aged 40 to 49. Although screening women ages 40-49 will benefit all races and ethnicities, minority women may experience even greater benefit because they are more likely to be diagnosed with aggressive breast cancer subtypes at earlier ages. The proposed update will expand identification of breast cancer at earlier stages, offering the potential to improve care outcomes and save lives. **NCCN supports screening mammography in women beginning at age 40.**

Goals of Screening Mammography

Early detection of breast cancers with regular screening mammography decreases breast cancer mortality and treatment morbidity. Modeling data from the Cancer Intervention and Surveillance Modeling Network (CISNET) Breast Cancer Working Group were provided by the USPSTF for decision analysis.[i] **CISNET data cited by the USPSTF demonstrate that the greatest median breast cancer mortality reduction (41.7%) results from annual screening mammography or annual screening digital breast tomosynthesis (DBT) in women ages 40 to 79.**[i] Annual screening for women ages 40-79 maximizes the breast cancer deaths averted and life-years gained. Biennial screening, initiation of screening at older ages (45 or 50), and cessation of screening at age 74 results in less mortality reduction, fewer lives saved, and fewer life-years gained. **The NCCN urges the USPSTF to revise their draft recommendations from biennial screening and cessation of screening at age 74 to annual screening at age 40 until an age when comorbid conditions limit life expectancy.**

The NCCN suggests the USPSTF re-consider their metric of a "more favorable trade-off" or "more favorable balance of benefits to harms".[ii] The harms outlined by the USPSTF focused on false-positive screens, benign biopsies, and over-diagnosed cases.[ii] Recalled screening examinations are correctly termed "incomplete"

examinations per the Mammography Quality Standard Act, not "false -positive". Most patients recalled from screening mammography only undergo additional mammography or ultrasound imaging. Only 1-2% of patients undergoing screening mammography will be recommended to undergo a needle biopsy.[iii] The cited CISNET data demonstrate a very broad range of over-diagnosis estimates, consistent with the known difficulty in accurately estimating the degree of over-diagnosis.[i] Perhaps most importantly, the harms of not undergoing screening were not presented. For example, women with screen-detected breast cancers are less likely to require mastectomy and chemotherapy.[iv] It is incorrect to suggest that a lack of screening equates to a lack of harms. **The balance of benefits to harms is a subjective opinion from the panel. Nor does the "balance" necessarily reflect the consensus or values of individuals eligible for screening mammography.** Following the prior USPSTF recommendations statement for biennial mammography, over 80% of mammograms in women undergoing screening DBT in a large cohort from the BCSC were annual mammograms rather than biennial mammograms.[v] Furthermore, women are highly tolerant of false positive results, with 63% tolerating 500 or more per life saved and 37% tolerating 10,000 false-positive results per life saved.[vi] The NCCN believes the USPSTF should recommend that each patient and her health care provider be given the opportunity to weigh the benefits and harms to make an informed decision tailored to that specific patient.

Frequency of Screening

The USPSTF draft recommends biennial rather than annual screening mammography. NCCN respectfully disagrees with this recommendation. To realize the greatest reductions in breast cancer mortality and morbidity, NCCN recommends annual screening. The NCCN Panel believes that the benefits of annual mammography outweigh the risks.

New USPSTF commissioned CISNET model results show that for 1000 patients undergoing screening digital breast tomosynthesis ages 40-74, biennial screening results in 30% mortality reduction and 165 life-years gained (LYG).[i] In comparison, annual screening results in 37% mortality reduction and 217 LYG, a 23% and 32% improvement, respectively, compared to biennial. Interval cancer rates are lower among people undergoing annual screening.

The estimated cumulative risks of recall from screening mammography and benign biopsies are higher with annual compared to biennial mammography. The extent of overdiagnosis is unlikely to substantially change with screening interval, especially in women with fewer competing comorbidities, because an over-diagnosed cancer that exists at one year (annual screening) would still be present on a mammogram performed at 2 years (biennial). **The NCCN panel believes that the lower mortality and morbidity of annual screening outweighs the harms. NCCN urges USPSTF to re-consider and update the final recommendation to annual screening for patients beginning at age 40.**

Upper Age Limit

The draft USPSTF screening recommendation states the current evidence is insufficient for screening mammography at age 75 and above. The NCCN Guidelines for Breast Cancer Screening® do not include an upper age limit for screening and encourage the USPSTF to reconsider the inclusion of an upper age limit. NCCN acknowledges that there are limited RCT data regarding screening of older adults, because most trials for breast screening used a cutoff age of 65 or 70 years.[vii,viii,ix] However, observational studies and computer

models show mortality benefit in older women.[x] For example, the cited CISNET data for women ages 75-79 demonstrate an incremental mortality reduction and improvement in LYG, compared to cessation of screening at age 74.[i] Annual screening results in greater improvement compared to biennial screening irrespective of age. Considering the high incidence of breast cancer and increasing population of older women, screening mammography should be considered as long as the patient remains in good health. Irrespective of age, mammography screening should be individualized, weighing its potential benefits and risks in the context of each patient's overall health and estimated longevity. If a patient has severe comorbid conditions limiting her life expectancy and no intervention would occur based on the screening findings, then the patient is unlikely to benefit from screening, regardless of age. **NCCN respectfully requests that the USPSTF re-consider an upper age limit on screening and instead encourage shared decision making between clinicians and patients.**

High-risk Groups

NCCN recognizes that the USPSTF recommendations are targeted to people at average risk. **NCCN respectfully requests that the USPSTF re-frame their inclusion and exclusion criteria for the "Patient Population under Consideration" for this draft recommendation statement.** The NCCN disagrees that "these recommendations apply to persons with a family history of breast cancer (i.e., those with a first-degree relative with breast cancer) and to persons who have other risk factors such as having dense breasts". The NCCN Guideline for Breast Cancer Screening and Diagnosis® specifically recommends that patients undergo breast cancer risk assessment which may include the use of validated statistical models that incorporate multiple known risk factors. NCCN guidelines recognize that patients may have an elevated lifetime breast cancer risk assessed by models largely dependent upon *family history*. Patients at elevated risk may benefit from more intensive screening regimens beginning at earlier ages.

While NCCN recognizes that the USPSTF recommendations are geared toward the average risk population, they are often used as a health policy tool and, as such, may inadvertently cause access barriers for those at increased risk for whom additional screening may be medically necessary. A similar challenge recently occurred in the context of opioid prescribing. The United States Centers for Disease Control and Prevention (CDC) released prescribing guidelines for opioids targeted to primary care physicians serving the general population. These guidelines were then applied broadly by payers and government officials causing inadvertent harm to patients with cancer and survivors. To remedy this, the CDC updated their guidelines to refer readers to other guidelines such as NCCN and ASCO for specific patient populations and clarified their guidelines were intended for the general population. NCCN has recently heard from patient advocates that USPSTF guidelines are also often misapplied by policymakers and payers in a way that can harm access for high-risk populations. NCCN respectfully requests that USPSTF consider incorporating a similar statement as the CDC to ensure that access to appropriate and medically necessary screening is not impeded for high-risk patient populations.

NCCN respectfully suggests that USPSTF consider referring readers to other organization guidelines with recommendations for higher risk populations. NCCN notes that the NCCN Guidelines for Breast Cancer Screening and Diagnosis® and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic® include specific screening recommendations unique to higher risk populations including those with risk factors such as family history, hereditary risk, and a history of thoracic radiation therapy.

Inclusive Language

NCCN thanks the USPSTF for including language within full draft recommendation clarifying that the recommendation applies to all individuals assigned female at birth including transgender men and non-binary persons. In recent years, NCCN has launched an initiative to include gender inclusive and respectful language throughout our Clinical Practice Guidelines. NCCN appreciates that the USPSTF clarifies the patient population to whom this recommendation applies. NCCN further recommends incorporating this inclusive and clarifying language into the recommendation itself.

NCCN appreciates the opportunity to comment on the USPSTF Draft Recommendation Statement on Screening for Breast Cancer. NCCN is happy to serve as a resource and looks forward to working together to advance access to equitable, high-quality cancer care.

Sincerely,

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s%2040%20to%2074%20years.&text=The%20USPSTF%20concludes%20that%20the,age%2075%20years%20or%20older.

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