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Using lessons from breast, cervical and colorectal cancer screening to inform the development of lung cancer screening programs

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Abstract

Multiple advisory groups now recommend that high-risk smokers be screened for lung cancer by low dose computed tomography. Given that the development of lung cancer screening programs will face many of the same issues that have challenged other cancer screening programs, the NCI funded Population-based Research Optimizing Screening through Personalized Regimens (PROSPR) consortium was used to identify lessons that have been learned from the implementation of breast, cervical and colorectal cancer screening that should inform the introduction of lung cancer screening. These lessons include the importance of developing systems for identifying and recruiting eligible individuals in primary care, ensuring screening centers are qualified and performance is monitored, creating clear communication standards for reporting screening results to referring physicians and patients, making sure follow up is available for abnormal tests, avoiding overscreening, remembering primary prevention, and leveraging advances in cancer genetics and immunology. Overall, this experience emphasizes that effective cancer screening is a multistep activity that requires robust strategies to initiate, report, follow-up, and track each step as well as a dynamic and ongoing oversight process to revise current screening practices as new evidence about screening is created, new screening technologies are developed, new biological markers are identified, and new approaches to health care delivery are disseminated

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Screening high-risk smokers for lung cancer with low dose computed tomography (CT) scans reduced lung cancer mortality by 20% in the National Lung Screening Trial (NLST) and has been recommended by the United States Preventive Services Task Force, the American Cancer Society and other advisory organizations.¹⁻⁴ Given these recommendations, health care systems and public health programs across the US are considering the development of screening CT programs.⁵ Although these programs will encounter lung cancer specific issues, they will also face many of the same issues that have challenged other cancer screening programs, including breast, colorectal, and cervical cancer screening. The Population-based Research Optimizing Screening through Personalized Regimens (PROSPR) is an NCI-funded consortium that brings together expertise in the delivery of breast, cervical and colorectal cancer screening to improve the multi-stage process of cancer screening. (Figure) This cross-screening multi-site collaboration was used to identify lessons that have been learned from the implementation of these cancer screening programs to inform the introduction of lung cancer screening. These lessons include:

1. Develop systems for identifying and recruiting eligible individuals in primary care

Engagement of primary care systems has been critical for the implementation of breast, cervical and colorectal cancer screening programs. A key step in this engagement is the development of clear consensus guidelines about who is eligible for screening and the linkage of those guidelines to feedback about screening rates among eligible groups. For breast, cervical, and colorectal cancer screening, current eligibility criteria are based upon age and gender, which are recorded in all electronic medical records (EMRs) and easily translated to reminder systems. Attempts to develop more complex eligibility criteria, such as risk based guidelines, have been hampered by difficulties in collecting and using the necessary data in primary care practices.

For lung cancer screening, determining eligibility will require information on smoking history in addition to age; for example, current guidelines generally recommend screening patients with more than a 30 pack-year history of smoking and less than 15 years of smoking abstinence.² Thus, an important first step is to ensure that the most common EMRs enable the efficient collection of current and past smoking history in a format that can be used by a computerized algorithm. Investment in EMR optimization can also facilitate screening implementation by defining the role of the multiple members of the primary care medical home in identifying and counseling eligible individuals, as well as the coordination of screening orders and follow up across practice sites (e.g. specialty and primary care)- two areas that remain a challenge for breast, colon and cervical cancer screening.

2. Ensure screening centers are qualified and performance is monitored

Generalizing the benefits seen in the NLST across the US requires attention to the quality of care provided by screening providers. Although there are no comprehensive national quality assurance programs for colorectal or cervical cancer screening, the 1992 Mammography Quality Standards Act (MQSA) is a highly successful model for establishing and maintaining quality assurance for image-based screening.⁶ MQSA defines multiple quality

measures including equipment performance, personnel qualification, and screening process outcomes that are tracked and benchmarked at the facility and physician level each year.

The NLST protocol and quality assurance manual provides qualification standards for CT scanner testing and performance and for facility technologists, radiologists and physicists that serves as a template for this effort. The American College of Radiology built upon this to develop an accreditation that, if widely adopted, could insure the technical quality of lung screening examinations nationally.⁷ Expansion of this effort to include experience and qualification of providers, similar to what is required for breast cancer screening by MQSA, would strengthen accreditation. The CMS requirement that screening providers submit data to an accredited registry is also an important step in this direction, as is the development of accredited registries by organizations such as the American College of Radiology and the creation of a common language for screening outcomes and process step by the PROSPR consortium.^{8,9}

3. Create clear communication standards for reporting screening results to referring physicians and patients

The development of assessment standards played a critical role in reducing variability in the communication of screening results for mammography (BI-RADS) and Pap smears (Bethesda system).^{10,11} These categorizations guide clinical recommendations for short interval follow up, more intensive testing and possible biopsy. The American College of Radiology has developed a corresponding approach for lung cancer screening (LungRADS) and follow up is needed to ensure it is adopted by screening providers.¹² The implementation of an assessment standard can also promote efficient management of screening results in the primary care setting. Although 24% of patients in the NLST had a positive screen, the vast majority requires only follow up imaging.¹ Clear reporting standards tied to follow up recommendations will allow those patients to be managed without referral to specialty care, thereby preserving access when specialty consultation for biopsy consideration is needed. This effort may also provide impetus to revisit result reporting for colorectal cancer screening, where there is currently no universal standard for communicating endoscopy and pathology findings.¹³ Another potential advance that could benefit other forms of cancer screening would be the development of simple and effective language for the communication of results to patients about what was found and the implications of that finding including follow up of abnormal results.

4. Make sure you can finish what you start

The success of any screening program is dependent on the appropriate follow-up of suspicious lesions and oncologic evaluation and treatment when a cancer is diagnosed. Individuals who are poor, less educated and from certain minority groups tend to be heavier smokers and at higher risk for lung cancer and of barriers in accessing and paying for any follow-up tests, procedures and/or treatment.¹⁶ Federal policy has made important advances in the financing of breast and cervical cancer screening programs over the last decades through the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), which provides free or low-cost mammograms and Pap tests to all low-income, uninsured,

and underserved women in the US. The Breast and Cervical Cancer Prevention and Treatment Act is used by all 50 states to cover treatment for women diagnosed with cancer via the NBCCEDP through Medicaid.¹⁷ Similar policies should be developed for lung cancer screening to avoid the state-by-state gaps in adequate coverage and lower rates of colorectal cancer screening among the un- and under-insured.

5. Remember primary prevention

Perhaps not surprisingly, health care entities are better designed to deliver health care than to prevent the need for health care. Thus, the introduction of a screening program has the potential to distract from upstream, primary prevention efforts that may have an even greater effect on mortality. For example, mammography screening is a standard quality metric for health insurance quality incentive programs but there has been little attention to counseling around reducing alcohol intake and increasing exercise, despite evidence that these behaviors reduce breast cancer risk.¹⁴ Given the undisputed primacy of tobacco cessation programs to reducing lung cancer mortality, tobacco cessation should remain central to all lung cancer screening programs. Efforts to advance the capture of data on tobacco counseling in EMRs should enable monitoring counseling rates within lung cancer screening programs.

6. Avoid overscreening

Cancer screening programs can reduce cancer mortality but also incur the risk of false positive tests, over-diagnosis, and over-screening. Breast and cervical cancer screening are now widely recognized to lead to substantial rates of false positive and ambiguous test results, some of which lead to morbidity from unnecessary biopsies, procedures, and/or treatment.^{18,19} Although determining rates of over-diagnosis is challenging, up to a third of lesions detected in breast and cervical cancer screening and classified as cancer may never have progressed clinically.^{20,21} Over-screening has been a growing concern with evidence that indicates tests are being used too frequently for cervical cancer screening in low-risk women, for colorectal cancer screening among the Medicare population, and for patients with limited life expectancy.^{22–24}

Minimizing the burden of these adverse events for lung cancer screening can be facilitated by several early steps. Educational materials developed for patients and referring clinicians should be clear about the risks of false positive screening results, how to resolve most abnormal results without invasive procedures, and approaches to managing the anxiety that often accompanies them. Treatment recommendations should be evidence-based and tied to growing information about variation in natural history, recognizing that some lesions currently classified as malignant may progress very slowly if at all. Recent data suggest that while only 20% of non-small cell lung cancers found in the NSLT may represent over-diagnosis, that proportion may be as high as 80% for bronchoalveolar cancer.²⁵ Lung cancer screening quality assurance programs should consider monitoring for over-screening as well as other screening outcomes.

7. Don't forget biology

The implementation of screening programs occurs within the broader context of ongoing research into cancer susceptibility and development. The identification of cancer susceptibility genes, such as *BRCA1* and *MSH1*, has enabled genetic testing and intensive screening for breast and colon cancer among individuals who carry a pathogenic variant.²⁶ The identification of human papillomavirus (HPV) as a causal agent of cervical cancer and information on HPV acquisition and natural history have transformed cervical cancer prevention including the development of HPV testing and HPV vaccines.¹⁹ Advances in understanding lung cancer biology may also have a major impact on lung cancer screening in the future. Analyses of genomic alterations in non small cell cancer have provided insight into the pathways and genes implicated in cancer initiation and progression as well as the development of targeted therapies.²⁷ Although research into the use of genomics to inform the lung cancer screening process is just beginning, recent studies have demonstrated the presence of genomic alterations consistent with loss of tumor suppressor genes and activation of oncogenic signaling pathways in pre-malignant lesions as well as cytologically normal airway epithelium from patients with cancer.^{28–30} Furthermore, a recent report found *KRAS*, *TP53* and *EGFR* mutations in areas of atypical adenomatous hyperplasia and in paired circulating DNA.³¹ In the future, these and other approaches may prove useful for predicting which nodules are likely to be aggressive cancer, monitoring response to chemoprevention or other preventive interventions and even as a primary screening tool.³²

Conclusion

Early detection through screening programs has been proven to reduce mortality from breast, cervical, colorectal and lung cancers. Although this evidence supports the dissemination of screening programs for these cancers, successful implementation of a screening program is challenging. Experience with breast, cervical and colorectal cancer screening can provide useful guidance for the implementation of lung cancer screening programs that maximize quality, value and effectiveness. This experience demonstrates that cancer screening is a multistep process, not a one-time event, and robust strategies are needed to initiate, report, follow-up, and track each step in the process. Furthermore, delivery of cancer screening requires a dynamic and ongoing oversight process to revise current screening practices as new evidence about screening is created, new screening technologies are developed, new biological markers are identified, and new approaches to health care delivery are disseminated.

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REFERENCES

1. Aberle DR, Adams AM, et al. National Lung Screening Trial Research T. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011; 365:395–409. [PubMed: 21714641]

2. Moyer VA. Force USPST. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2014; 160:330–338. [PubMed: 24378917]
3. Wiener RS, Gould MK, Arenberg DA, et al. An Official American Thoracic Society/American College of Chest Physicians Policy Statement: Implementation of Low-Dose Computed Tomography Lung Cancer Screening Programs in Clinical Practice. *Am J Respir Crit Care Med.* 2015; 192:881–891. [PubMed: 26426785]
4. Wender R, Fontham ET, Barrera E Jr, et al. American Cancer Society lung cancer screening guidelines. *CA Cancer J Clin.* 2013; 63:107–117. [PubMed: 23315954]
5. Eberth JM, Sercy E. Implementation of Lung Cancer Screening in the United States: Changing Trends Based on a Survey of Society of Thoracic Radiology Members. *J Thorac Imaging.* 2015; 30:W60–W62. [PubMed: 26447869]
6. Legislative Issues. American College of Radiology, 2014. <http://www.acr.org/advocacy/legislative-issues>.
7. Kazerooni EA, Armstrong MR, Amorosa JK, et al. ACR CT accreditation program and the lung cancer screening program designation. *J Am Coll Radiol.* 2015; 12:38–42. [PubMed: 25455196]
8. Services CfMaM. , editor. 2015. Decision Memo for Screening for Lung Cancer with Low Dose Computed Tomography (LDCT).
9. 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. *J Natl Cancer Inst.* 2015; 107 djv120.
10. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA.* 2002; 287:2114–2119. [PubMed: 11966386]
11. Liberman L, Menell JH. Breast imaging reporting and data system (BI-RADS). *Radiol Clin North Am.* 2002; 40:409–430. v. [PubMed: 12117184]
12. Lung CT Screening Reporting and Data System (Lung-RADS™). <http://www.acr.org/Quality-Safety/Resources/LungRADS>.
13. Lieberman D, Nadel M, Smith RA, et al. Standardized colonoscopy reporting and data system: report of the Quality Assurance Task Group of the National Colorectal Cancer Roundtable. *Gastrointestinal endoscopy.* 2007; 65:757–766. [PubMed: 17466195]
14. Kushi LH, Doyle C, McCullough M, et al. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin.* 2012; 62:30–67. [PubMed: 22237782]
15. Rigotti NA, Quinn VP, Stevens VJ, et al. Tobacco-control policies in 11 leading managed care organizations: progress and challenges. *Effective clinical practice : ECP.* 2002; 5:130–136. [PubMed: 12088292]
16. Jamal A, Homa DM, O'Connor E, et al. Current Cigarette Smoking Among Adults - United States, 2005–2014. *MMWR Morb Mortal Wkly Rep.* 2015; 64:1233–1240. [PubMed: 26562061]
17. French C, True S, McIntyre R, Sciulli M, Maloy KA. State implementation of the Breast and Cervical Cancer Prevention and Treatment Act of 2000: a collaborative effort among government agencies. *Public Health Rep.* 2004; 119:279–285. [PubMed: 15158107]
18. Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false positive screening mammograms and clinical breast examinations. *New England Journal of Medicine.* 1998; 338:1089–1096. [see comment]. [PubMed: 9545356]
19. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet.* 2007; 370:890–907. [PubMed: 17826171]
20. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med.* 2013; 367:1998–2005. [PubMed: 23171096]
21. Holowaty P, Miller AB, Rohan T, To T. Natural history of dysplasia of the uterine cervix. *J Natl Cancer Inst.* 1999; 91:252–258. [PubMed: 10037103]
22. Saraiya M, Berkowitz Z, Yabroff KR, Wideroff L, Kobrin S, Benard V. Cervical cancer screening with both human papillomavirus and Papanicolaou testing vs Papanicolaou testing alone: what screening intervals are physicians recommending? *Arch Intern Med.* 2010; 170:977–985. [PubMed: 20548011]

23. Goodwin JS, Singh A, Reddy N, Riall TS, Kuo YF. Overuse of screening colonoscopy in the Medicare population. *Arch Intern Med.* 2011; 171:1335–1343. [PubMed: 21555653]
24. Lee SJ, Boscardin WJ, Stijacic-Cenzer I, Conell-Price J, O'Brien S, Walter LC. Time lag to benefit after screening for breast and colorectal cancer: meta-analysis of survival data from the United States, Sweden, United Kingdom, and Denmark. *Bmj.* 2013; 346:e8441. [PubMed: 23299842]
25. Patz EF Jr, Pinsky P, Gatsonis C, et al. Overdiagnosis in Low-Dose Computed Tomography Screening for Lung Cancer. *JAMA Intern Med.* 2013
26. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol.* 2015
27. Buettner R, Wolf J, Thomas RK. Lessons learned from lung cancer genomics: the emerging concept of individualized diagnostics and treatment. *J Clin Oncol.* 2013; 31:1858–1865. [PubMed: 23589544]
28. Nakachi I, Rice JL, Coldren CD, et al. Application of SNP microarrays to the genome-wide analysis of chromosomal instability in premalignant airway lesions. *Cancer Prev Res (Phila).* 2014; 7:255–265. [PubMed: 24346345]
29. Gustafson AM, Soldi R, Anderlind C, et al. Airway PI3K pathway activation is an early and reversible event in lung cancer development. *Sci Transl Med.* 2010; 2:26ra5.
30. Ooi AT, Gower AC, Zhang KX, et al. Molecular profiling of premalignant lesions in lung squamous cell carcinomas identifies mechanisms involved in stepwise carcinogenesis. *Cancer Prev Res (Phila).* 2014; 7:487–495. [PubMed: 24618292]
31. Izumchenko E, Chang X, Brait M, et al. Targeted sequencing reveals clonal genetic changes in the progression of early lung neoplasms and paired circulating DNA. *Nature communications.* 2015; 6:8258.
32. Kensler TW, Spira A, Garber JE, et al. Transforming Cancer Prevention through Precision Medicine and Immune-oncology. *Cancer Prev Res (Phila).* 2016; 9:2–10. [PubMed: 26744449]
33. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A.* 2001; 98:10869–10874. [PubMed: 11553815]

Figure.**Screening Process**

Derived from 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. J Natl Cancer Inst 2015