Population-based precision cancer screening: a symposium on evidence, epidemiology, and next steps

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INTRODUCTION

President Obama's Precision Medicine Initiative® (PMI) was announced in January, 2015 (1). Its goal is to enable a new era of medicine in which researchers, providers, and patients work together to develop care that takes into account individual differences in people's genes, environments, and lifestyles. The National Institutes of Health (NIH) has two major PMI mandates: to build a large national research cohort and to support precision medicine clinical trials to improve cancer treatment and study other aspects of oncology. Public health leaders, including National Cancer Institute (NCI) Acting Director Doug Lowy, have commented that precision medicine approaches have a place in cancer prevention and screening (2-4).

Cancer screening in the general population refers to the testing of asymptomatic, average-risk individuals. It is an important approach to cancer prevention and control but has limitations. At the heart of precision cancer screening is the notion that an individual's risk of disease, based on genetic factors, environmental and lifestyle exposures, and previous screening history, is positively correlated with the expected benefit that an individual will receive. If true, more precise risk assessment, coupled with modification of screening regimens based on risk, would lead to programs that result in more benefit and less harm than do today's programs.

The practice of precision cancer screening is not new. For example, screening guidelines and recommendations from leading bodies such as the United States Preventive Services Task Force (USPSTF), the American Cancer Society (ACS), and the National Comprehensive Cancer Network (NCCN) typically are conditional on age and sex, and for lung cancer, on smoking history. Two emerging research areas in precision cancer screening include the use of past screening history to recommend future screening regimens and the use of arrays of genetic information to allow varied screening regimens to be targeted to individuals based on personal

cancer risk. Implementation of certain proposed strategies should wait, however, until compelling evidence exists to indicate that such practices likely would increase the net benefit of screening programs and be acceptable to patients and clinicians. Metrics of benefit would need to reflect extension of life in those who are targeted for screening as well as consequences of missed cancers in those who would be excluded based on revised recommendations.

On September 29, 2015, NCI sponsored a symposium entitled "Precision Cancer Screening in the General Population: Evidence, Epidemiology, and Next Steps" (5). The goal was two-fold: to share the available evidence, practices, and challenges surrounding precision screening for breast, cervical, colorectal, lung, and prostate cancers, and allow for in-depth discussion among experts in relevant fields regarding how epidemiology and other population sciences can be used to move the field forward. By "general population," we refer to persons without previous diagnosis of cancer or pre-cancer and not known or suspected to be at markedly increased or decreased risk due to symptoms, highly penetrant genetic mutations, family history, or medical conditions known to increase cancer risk. In this paper, we report on symposium presentations and breakout group discussions, themes that emerged from the symposium, and thoughts regarding next steps.

CHALLENGES AND OPPORTUNITIES FOR PRECISION MEDICINE SCREENING FOR COMMON CANCERS

Morning sessions included overviews of NIH's PMI cohort, challenges and opportunities that would accompany precision cancer screening, and evidence and issues specific to each of the five cancers.

NIH's PMI Cohort

The multipurpose PMI cohort will provide data that can be used to explore precision screening strategies (1). One million volunteers will be recruited, provide a biospecimen, complete questionnaires, agree to share health information with researchers, and be recontacted for future research. The goals of the cohort that are of most relevance to precision cancer screening are quantification of risk associated with genetic and environmental factors (alone and in combination) and identification of biomarkers that can indicate degree of cancer risk.

Precision Cancer Screening in the General Population: Challenges and Opportunities

Risk assessment is central to precision screening. Once the distribution of risk in the general population is known, risk strata can be chosen, and each assigned a unique screening regimen. For example, different strata could have regimens that differ with respect to start and end ages, screening intervals, and screening modalities (6). Risk assessment can occur either before or after the first screening episode. A pre-screening approach enables selection of patients for risk-tailored regimens and could perhaps guide diagnostic evaluation decisions following abnormal screening exams.

Genetic and non-genetic risk factors could be used for risk assessment. To date, genome-wide association studies have identified over 90 breast cancer susceptibility variants (7), and the receiver-operating characteristic curve derived from a polygenic risk profile based on these variants has an area under the curve (AUC) of 0.65 (derived from data presented in (7)). Addition of non-genetic risk factors, like age at menarche, parity, age at first live birth, oral contraceptive use, body mass index, alcohol, smoking, personal history of benign breast disease, and family history of breast cancer in first-degree relatives, increases the AUC to 0.68 (8). In the hypothetical instance of restricting screening to women above the 30^{th} percentile of risk, addition of non-genetic factors would increase screen detection from 50% to 58% of all cases (derived from data presented in (7) and (8)).

Use of a precision screening strategy within the general population has the potential to improve the efficiency of screening programs and reduce adverse consequences. Examination of a possible risk-stratified screening strategy for breast cancer, with eligibility based on absolute risk calculated using age and polygenic risk score, suggests that the number needed to screen to prevent one cancer death could be reduced while detecting most cancers identified by a conventional age-based strategy (9). Modeling studies suggest that restriction of prostate cancer screening to men at higher than average risk based on polygenic information could reduce the proportion of screen-detected prostate cancers that are likely to represent overdiagnosis (10, 11). Evidence is lacking as to the impact on net benefit or harm of these strategies, and implementation clearly would pose numerous organizational challenges, most notably ascertainment of genomic information, and raise ethical and legal questions. Of great importance is that willingness of patients to accept such strategies is unknown.

Breast Cancer Screening

Most breast cancer screening recommendations for women in the general population specify starting and ending ages and screening intervals without regard to other individual characteristics, including breast cancer risk factors. Some organizations, including the ACS, recommend that cessation be based on life expectancy (12). Breast density is under consideration as a stratification factor, as it is associated with both increased breast cancer risk and decreased mammographic sensitivity; women with dense breasts could receive screening that begins earlier, occurs more frequently, or uses more sensitive modalities, either alone or as adjuncts to mammography. Certain published analyses that aimed to identify subgroups for whom screening before age 50 was beneficial suggest that women with extremely dense breasts may benefit from beginning screening in their forties (13) and by choosing an annual rather than biennial interval (14). No direct evidence supports use of supplemental ultrasound or MRI in the general population of women with dense breasts although modeling studies suggest that supplemental ultrasound following a negative mammogram may increase cancer detection but at the cost of substantially increased false-positive rates (15). Over 90 genetic susceptibility loci have been identified (7), but common genetic variants or polygenic risk scores are yet to be incorporated into screening recommendations; statistical modeling suggests, though, that they could decrease the number needed to screen while preserving the ability to identify most currently screen-detectable cancers (9). Given the modest contribution of genetic factors to breast cancer risk, environmental factors ought to be included in risk models used for stratification.

Cervical Cancer Screening

Virtually all cases of cervical cancer and precancer are caused by persistent infection with certain common sexually transmitted human papillomaviruses (HPV) (16). HPV infection is typically acquired in late adolescence and early adulthood, and most infections are controlled by the immune system or clear without intervention within a year or two. Women with persistent infection have increased risk of cervical precancer that can progress to invasive cancer. In the US, acceptable cervical cancer screening includes Pap testing, HPV DNA/RNA testing, or both (co-testing); the goal is to detect and treat precancer to prevent cervical cancer morbidity and mortality. It appears that the advent of HPV vaccination and accurate HPV tests will make the use of screening Pap alone obsolete (17).

An emerging strategy is to screen, using HPV testing only, women in the general population who are at greatest risk, based on age and prior screening experience. The negative predictive value of an HPV test is extremely high, and prospective observational studies combined with our understanding of the natural history of cervical cancer suggest that screening using HPV alone every three years or co-testing every five years provides a reasonable balance of efficacy and overtreatment, although there is widespread resistance in the US to a five-year interval (18, 19). Frequent HPV testing detects many new HPV infections destined to clear and co-testing leads to detection of cervical abnormalities that are especially prone to regression. Researchers are looking to discover and validate biomarkers that indicate high risk of precancer among HPV-positive women.

Colorectal Cancer Screening

Colorectal cancer screening recommendations in the US general population reflect a "menu" approach (20-22). The USPSTF 2016 guidelines (20) strongly recommend screening for individuals aged 50 to 75 years and provide seven acceptable strategies that reflect six unique modalities; no strategy is recommended over another. The guidelines state that the decision to be screened from ages 76 to 85 should take into account overall health and previous screening history. Data from the 2013 National Health Interview Survey indicate that only 58% of the US population was adherent with the 2008 USPSTF recommendations for colorectal cancer screening between 2010 and 2013, with rates of adherence lower among those who are less educated or have lower incomes (23).

The following scenario illustrates the type of challenges faced by clinicians when advising patients on colorectal cancer screening. A 55 year-old man has a history of two negative colonoscopies at ages 40 and 50. However, his father was diagnosed with colorectal cancer at age 40. The presence of family history at a young age suggests the need for continued screening, but the clinician contemplates recommending for future exams a less invasive modality or a 15-year interval between colonoscopies. Unfortunately, the information needed to assess the potential value of different scenarios for this patient is lacking. These data are critical for the successful implementation of precision screening, and as such, their collection must become a research priority.

Lung Cancer Screening

Lung cancer screening with low-dose computed tomography (LDCT) is recommended based on the results of the National Lung Screening Trial (NLST), which enrolled individuals at

high risk due to older age and extensive smoking history. LDCT screening reduced lung cancer mortality by 20%, corresponding to an absolute reduction of 3 lung cancer deaths per 1,000 screened (24). The baseline risk of death from lung cancer varied widely however, ranging from less than 0.55% in the lowest risk quintile to >2% in the highest quintile of the control arm, and 88% of the lung cancer deaths prevented by CT screening were observed in the three highest risk quintiles (25).

Models have been developed to estimate risk of lung cancer diagnosis and death (25-28). They facilitate precision screening by providing individualized risk estimates to be used during shared decision making visits. Other models are available to estimate risk of complications from diagnostic evaluation of a positive screen (29). A comprehensive shared decision making approach that provides risk information at all decision points in the screening process, from the choice to be screened to lung cancer treatment, would be clinically useful as well.

Precision screening for lung cancer could potentially benefit from the development of biomarkers that can be used to identify an especially high-risk target population, discriminate between patients with true positive and false positive test results, and discriminate between indolent and aggressive tumors. However, the molecular heterogeneity of lung cancer suggests that panels of markers will be necessary, and that tradeoffs between imperfect sensitivity and specificity will be unavoidable.

Prostate Cancer Screening

There have been two large-scale randomized controlled trials (RCTs) of prostate cancer screening in the general population using serum prostate specific antigen (PSA). The European Randomized Study of Screening for Prostate Cancer (ERSPC) reported a 21% relative reduction

in prostate cancer mortality at 13 years of follow-up, although the reduction was accompanied by a 57% increase in incident disease (30). In ERSPC, 781 men needed to be screened to prevent one prostate cancer death, and 27 additional prostate cancers had to be diagnosed. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial found no reduction in prostate cancer mortality (31). Despite methodological issues with both studies, the findings were used by the USPSTF to recommend against PSA screening and by the ACS to recommend informed decision making (32). Genome-wide association studies have identified 100 common prostate cancer variants, and while each confers a small risk, in combination they might produce useful risk stratification (33, 34). A screening program that targets men at or above the 50th percentile of genetic risk is predicted to detect over 75% of cancers (10). While many questions must be answered before such a targeted screening program could be introduced, the approach has the potential to maximize the benefit of screening while minimizing the harms.

CROSS-CUTTING ISSUES IN PRECISION CANCER SCREENING

In the afternoon, participants attended one of five breakout sessions. Each session was facilitated by a single researcher with expertise in the discussion topic. Topics were chosen to reflect broader issues surrounding precision cancer screening and its possible implementation.

Risk Prediction and Microsimulation Modeling

Risk prediction models can be used to identify individuals in the general population at differing risk for cancer death, and could be used to choose more or less aggressive screening regimens. Microsimulation modeling can compare outcomes arising from potential and varied screening strategies (35, 36). Epidemiologic methods and data can be used to improve conceptualization, construction, and implementation of these models. For example, van Hees et al developed a risk prediction model for colonoscopy screening in the elderly based on past screening history, family history of cancer, colorectal cancer risk factors, and comorbidity (37). Data derived from population science can provide information on disease complexity for models; for example, prospectively collected data on breast density would provide information to model how density changes over time. Unfortunately, commonly-used metrics of predictive performance, such as sensitivity, specificity, and AUC, are limited in their usefulness, and no unifying method of model assessment currently exists. Furthermore, model inputs are central to the value of any model; therefore, they must be chosen carefully and their limitations understood.

Health Services and Clinical Implementation

Because evidence concerning precision screening in the general population is just beginning to accumulate, it may be premature to discuss implementation. Nevertheless,

consideration of likely challenges is critical as we begin to discuss possible screening strategies. Expert groups convened by the Collaborative Oncological Gene-Environment Study (COGS) identified key ethical, social and logistical aspects needed to support incorporation of genetic information into population-based screening in European settings (38). Logistical aspects included the need to establish competencies in the healthcare community and assess acceptability and cost-effectiveness of stratified screening programs prior to implementation (39). In the US, implementation strategies will need to address those needs as well as challenges raised by the non-integrated structure of the healthcare system.

As exemplified by current challenges in healthcare delivery, screening strategies that are difficult to integrate into clinical workflows are unlikely to be successful, even if they can decrease cancer mortality in controlled environments. Implementation may further be hampered by the opportunistic way in which cancer screening is usually delivered in the US due to lack of centralized information on medical history, especially previous screening experience. It also will be necessary to respect values and preferences of patients with evidence-driven care. Implementation also will likely vary due to differences in provider and health care system practices, which will in turn impact patient experiences and outcomes, as well as quality improvement and metrics, provider and system incentives, and population health.

Leveraging Existing Data Sources and Infrastructure

Established epidemiological cohorts and screening registries can and will continue to provide invaluable and unique information for the development and evaluation of risk prediction models. Evaluating the risk of rare tumor subtypes and risk among population subgroups requires longitudinal data from very large cohorts. For evaluating precision screening, cohorts and

registries need to have information, at a minimum, on baseline genetic and non-genetic risk factors, detection method, prognostic tumor characteristics, and biospecimens for future genotyping. Data collection on provider and facility characteristics adds important information for multi-level modeling and confounder adjustment. It is imperative that data come from patients who are seen in settings representative of community practice so that findings are generalizable. Given the needed large sample size and long follow-up time, it will not be possible to compare all potential screening strategies using RCTs; therefore, observational data from large cohorts and registries, analyzed with causal inference methods, need to be used. Existing infrastructure also can provide a springboard for the efficient conduct of pragmatic comparative effectiveness trials.

Behavioral Aspects and Health Disparities

Health care disparities caused by geographic, socioeconomic, demographic and healthcare access factors may be exacerbated if not considered prior to implementation of precision cancer screening practices, should that ultimately occur. Behavioral and social sciences research is needed to address knowledge gaps in areas relevant to implementation. For example, data on patient risk factors often relies on patient self-report (40, 41), but accuracy of self-report varies across patient subgroups, with lower sensitivity and specificity observed for minority patients (42). Thus, methods to improve accurate reporting are needed. In addition, patient-centered communication and shared decision-making will be essential to help patients handle uncertainty (43, 44). Enabling effective communication will be particularly challenging for providers caring for patients with low health literacy or cultural barriers to acceptance. Precision cancer screening delivery cannot solely rest on already-overloaded physicians, and case

managers, nurse navigators, and genetics counselors could help to deliver information about screening choices. If a multidisciplinary team approach is employed (45, 46), responsibilities of each member must be defined and necessary resources identified. To facilitate healthcare delivery, electronic health records should provide clinical decision support; store information needed to identify high-risk patients, document provider recommendations and patient decisions, and track management of abnormal results. The existence of these capabilities, particularly in low-resource healthcare settings, may lessen or prevent disparities that often accompany screening implementation (47, 48) .

Evaluating Differential Effectiveness of Screening by Demographics, Genetics, and Other Factors

A prevailing strategy in precision screening in the general population is to identify subgroups that have varied cancer risk due to factors such as demographics, family history, and genetics. Receiving less attention is the possibility of differential effectiveness of screening for those groups. Differential effectiveness refers to the situation in which the mortality reduction attributable to screening, measured as a percent reduction, varies according to some identifiable factor. For example, the NLST showed no statistically significant differential effects on the lung cancer mortality percent reduction for age dichotomized at 65 years old, current versus former smoking status, or sex, although the observed mortality reduction for women (27%) was about three times that for men (8%) (49). This example highlights the difficulty in evaluating heterogeneous effectiveness, as screening trials rarely have sufficient power to detect interactions of typical magnitude. In addition, the small number of screening trials for a specific modality means it usually is not possible to test the reproducibility of findings, and often there are no

plausible explanations for potential differential effectiveness. Therefore, it is usually assumed that the mortality reduction is constant across major demographic or risk factor categories. This assumption seems reasonable unless there is a strong reason to believe otherwise or strong evidence to the contrary.

DISCUSSION

NCI's Precision Cancer Screening symposium provided a venue in which to educate attendees about the state of the evidence; it also provided a space in which important discussions surrounding next steps in precision screening research could occur. The symposium was not intended to produce recommendations, but the organizers did expect that themes would emerge as attendees, who represented multiple disciplines and had varied points of view, wrestled with the difficult issues that surround the possibility of moving such a complex and multi-faceted research agenda forward. The most prominent themes to emerge were strength of evidence and feasibility of implementation.

With regard to strength of evidence, some attendees felt that efficacy of precision cancer screening strategies for the general population could not be assessed without RCTs. Others felt that well-done observational studies and statistical modeling could provide useful information to make policy decisions if decisions were made carefully. Arguments for and against types of evidence were as expected. Those who felt that strategies must be tested in RCTs argued that screening always causes harm but benefit is never guaranteed (50). Those who felt that observational and statistical modeling data could suffice argued that it would be impossible to test all possible strategies with RCTs and that dissemination of precision screening strategies would likely happen before RCTs were completed, should trials occur. Each point of view can be defended, yet the solution to moving precision cancer screening forward likely rests on a compromise: some questions, perhaps those for which little data are available or represent new technology, will require RCTs, while others, perhaps those for which RCTs have been done to address over-arching or related questions, can utilize existing RCT data, cohort data, or cancer registries to inform modeling of screening harms and benefits.

With regard to feasibility of implementation, attendees pointed out challenges and possible approaches for the US. Attendees questioned whether the US health care system, already stretched thin, could handle incorporation of additional data needed to determine whether patients are at risk based on more complex information than age, for example. Others questioned how precision cancer screening would be implemented in US areas with fewer resources, such as those that are served primarily by safety net systems. Attendees pointed out that implementation issues are typically overlooked until efficacy has been assessed, but that concurrent assessment of patient acceptability and other implementation issues could allow for rapid uptake if precision screening strategies are shown to be of benefit.

Due to time constraints, health service changes that would need to accompany precision cancer screening in the US were not extensively discussed at the symposium, but were acknowledged as barriers to implementation. One needed change would involve "un-recommending" screening for segments of the US population identified through risk-stratification as being at low risk of cancer. That could in turn lead to elimination of the option to be screened for those who are dependent on health insurance to pay for preventive services. However, many cancer organizations, both research and advocacy organizations, continue to stress the centrality of screening for all to reduce the cancer burden, even as the harms of screening are better understood, quantified, and publicized. The contradictory messages that could result would leave the public confused and clinicians with yet another difficult, time-consuming task. Other changes would include reframing of cancer as a disease that in some instances is unlikely to be fatal, and one for which earliest detection may not always be necessary for cure. Perhaps the biggest challenge in moving forward with exploration of

precision cancer screening is to undo ingrained and historically-rooted, but not universally true, beliefs about cancer.

A fundamental tension exists in cancer screening: we need to screen as efficiently as possible but want to prevent as many cancer deaths as possible. Realistic manners in which to ameliorate that tension seem elusive. Precision cancer screening in the general population may prove helpful, but to rush to choose it at this point in time would be unwise. Additional discussion needs to occur to identify the high priority research areas in precision cancer screening and to map out plans to gather the necessary evidence to determine whether implementation is likely to be feasible and beneficial.

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