

COMMENTARY

Cancer Models and Real-World Data: Better Together

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Abstract

Decision-analytic models are increasingly used to inform health policy decisions. These models synthesize available data on disease burden and intervention effectiveness to project estimates of the long-term consequences of care, which are often absent when clinical or policy decisions must be made. While models have been influential in informing US cancer screening guidelines under ideal conditions, incorporating detailed data on real-world screening practice has been limited given the complexity of screening processes and behaviors throughout diverse health delivery systems in the United States. We describe the synergies that exist between decision-analytic models and health care utilization data that are increasingly accessible through research networks that assemble data from the growing number of electronic medical record systems. In particular, we present opportunities to enrich cancer screening models by grounding analyses in real-world data with the goals of projecting the harms and benefits of current screening practices, evaluating the value of existing and new technologies, and identifying the weakest links in the cancer screening process where efforts for improvement may be most productively focused. We highlight the example of the National Cancer Institute-funded consortium Population-based Research Optimizing Screening through Personalized Regimens (PROSPR), a collaboration to harmonize and analyze screening process and outcomes data on breast, colorectal, and cervical cancers across seven research centers. The pairing of models with such data can create more robust models to not only better inform policy but also inform health care systems about best approaches to improve the provision of cancer screening in the United States.

An overarching goal of health policy is to advance high-quality care and discourage low-quality and harmful care. Ideally, health policy decisions are evidence based. While information about intermediate or short-term outcomes is often available from clinical studies, policy decisions often must be made in the absence of data on the long-term consequences of care. Cancer screening policies provide a good example of this. The natural history of a cancer can extend over decades, and consequently it can take

10 years or longer to assess the impact of new cancer screening interventions on long-term (eg, mortality) outcomes. Screening programs are often adopted based primarily on short-term outcomes, such as screening test sensitivity and specificity, under the assumption that detection of precancerous lesions and early-stage cancers will reduce cancer incidence, morbidity, and mortality.

In the absence of long-term empirical data, decision-analytic models (eg, decision trees, cohort models, and microsimulation

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models; hereafter “models”) have emerged as an approach to synthesize existing data to make long-term projections either as we await new evidence or under “what if” scenarios that are otherwise unfeasible or unethical to evaluate in clinical studies. Models have been influential in informing clinical guidelines in the United States, including the US Preventive Services Task Force (USPSTF) recommendations on screening for breast (1), colorectal (2), cervical (3), and lung (4) cancers. The key to effective modeling is integrating high-quality data. In this Commentary, we discuss the synergies between cancer models and emerging research networks that leverage data on health care utilization through the increased adoption of electronic medical record (EMR) systems. We highlight as a recent example the Population-based Research Optimizing Screening through Personalized Regimens (PROSPR) consortium, a National Cancer Institute (NCI)-funded multisite collaborative focused on studying the processes of screening for breast, cervical, and colorectal cancers across a diverse range of US health care settings.

Strengths and Limitations of Modeling

Like any methodological approach, models have both strengths and limitations that must be considered when used to inform clinical guidelines (5,6). One strength is that models are explicit, systematic, and quantitative: Modelers can describe the data used in model development, the structural and analytic assumptions that are made, and the ability of the model to represent the decision problem at hand. Models can incorporate information about the natural history of disease, the ability of tests to detect and diagnose disease, the effectiveness of treatments, and screening participation patterns to project the health impact of interventions under real-world or hypothetical conditions. Additionally, the inclusion of information on resource use and costs enables evaluation of the budget impact and value (ie, cost-effectiveness) of interventions. Because no single empirical study can address all factors relevant to screening, the process of model-building requires multiple data sources and is inherently transdisciplinary (7). Because models piece together available information about disease processes and interventions, they can also help researchers identify what factors are most influential on important outcomes, uncover critical gaps in the state of the science for a specific research question, and assess the value of new information on policy decisions (8).

The primary challenge is that model validity depends on the availability of high-quality data that inform model inputs, structures, and assumptions. Effective modeling requires rigorous specification of model parameters and transparency in underlying assumptions. Cancer natural history models typically require technical information on the progression of existing precancer stages, tumor growth, and survival. Ideally, models would also integrate behaviors at the patient, provider, facility or health systems levels, such as screening adherence, diagnostic referral rates, waiting times, and costs of care. For example, to accurately model screening as currently practiced in a population, understanding the screening behavior of individuals over time would be desirable: At what age do individuals initiate screening? How often do people fail to return to evaluate a positive test result? How frequently do people screen, and is the screening interval related to patient characteristics (eg, age, sex, race/ethnicity), test results (eg, a positive screen), or disease risk? How does screening adherence (ie, initiation, return for follow-up, and rescreening) correlate within individuals? Such data would facilitate the evaluation of personalized screening recommendations by examining the risk-benefit tradeoff in

patient subgroups with specific behaviors and characteristics. Given the complexity of screening practices and behaviors and the relative ease with which to simulate “ideal” conditions (ie, perfect adherence to screening regimens), model-based evaluations to date have fallen short of comprehensively incorporating detailed process data reflecting screening “as practiced.”

Research Consortia

In recent years, several large research consortia, including the Breast Cancer Surveillance Consortium (BCSC) (9), the Cancer Research Network (CRN) (10)—and more generally the Health Care Systems Research Network (HCSRN), formerly known as the HMO Research Network (HMORN), (11) and the National Patient-Centered Clinical Research Network (PCORnet) (12)—have undertaken the daunting task of identifying and analyzing important factors related to health care, including the quality and delivery of care and patient outcomes, through multidisciplinary teams and approaches. These data resources assemble millions of observations, usually from multiple institutions, containing individual-level data on demographics, risk factors, and clinical encounters and outcomes. Cancer modeling groups, including members of the Cancer Intervention and Surveillance Modeling Network (CISNET) consortium, have engaged in active collaborations with these research networks to take advantage of these data to enhance model inputs, including prevalence of risk factors, test characteristics, short-term screening outcomes, and costs (13,14). The increasing use of EMR systems in health care delivery settings will further increase opportunities to study and characterize real-world health care practice and to incorporate these findings into decision models.

The PROSPR consortium is a relatively new consortium focused on informing and improving cancer screening processes for breast, colorectal, and cervical cancers through a multisite collaboration (15–18). The PROSPR consortium comprises seven research centers, as well as a statistical coordinating center, geographically dispersed across the United States representing a spectrum of health care institutions, ranging from large health plans to population-based state registries. PROSPR data describe real-world screening practice at multiple levels, including patient (eg, demographic, risk factors), provider (eg, specialty), and facility (eg, location, availability of reminder systems) levels. Unlike other cancer networks to date, the PROSPR consortium has specified comparative effectiveness research as a requisite and central project goal. With five of seven research centers using decision-analytic modeling for such projects, the PROSPR consortium serves as an example of how cancer networks can work closely with models to integrate data.

Modeling Applications Through the PROSPR Consortium

The pairing of decision-analytic models with data from large-scale research consortia provides an important opportunity to enhance model quality by grounding analyses in real-world settings and issues; in turn, models can identify high-priority areas for health improvement through projections of both the short- and long-term comparative effectiveness of screening approaches.

As demonstrated with other research networks, there are several fundamental ways that data from the PROSPR consortium can strengthen existing models and stimulate novel models, including: 1) illuminating both systematic and random between-person variability to inform natural history models; 2) providing directly observed information, derived from clinical records, on

individual-level screening behaviors in the general population to quantify the effectiveness and value of current screening practices and to determine the influence of particular factors and alternative scenarios on outcomes; 3) providing evidence on variation in care at provider and system levels, which can be used to assess the potential impacts of adopting “best practices” more widely; 4) linking screening practice with outcomes to test model predictions and assess external validity, an important step in model-based evaluations (19); and 5) providing opportunities for comparative modeling (ie, cross validity (19)) in which independent modeling teams use common, core data inputs to address specific research questions and compare results across models. Model applications within the PROSPR consortium have begun to capitalize on these opportunities and include both policy evaluations and advances in modeling methodologies and approaches.

Policy Questions

Table 1 provides an overview of the types of models that are being used to address a range of policy questions across PROSPR Research Centers (20–26). Common themes of analyses for the different cancer sites include: 1) quantifying the long-term consequences of current cancer screening as practiced in different health organizations and systems; 2) projecting the singular and interactive effects of different breakdowns along the screening process to help inform where to prioritize investments to improve screening impact; 3) evaluating the comparative and cost-effectiveness of newly available or anticipated technologies related to detection, diagnosis, and treatment of cancer; and 4) examining the influence of screening factors on health disparities across subgroup populations (eg, by race/ethnicity) and evaluating interventions to alleviate disparities. For example, the cervical cancer model has been used to simulate current screening practice in New Mexico and quantify the inefficiency compared with national guidelines (24). Likewise, the colorectal cancer models are being used to predict the number of lives saved by the timely follow-up of positive fecal occult blood test (FOBT) results.

Model Validation Exercises

Models can be used to simulate many aspects of the disease process that are observable, which enables assessments of model validity against empirical data. Data that are not used directly in model development (ie, as direct inputs or in model calibration) may be used to evaluate the predictive validity of the models. For example, cumulative risk of high-grade precancerous lesions following abnormal Pap smear results are outputs of the model that can then be compared against outcomes from real-world practice (27,28). Models can be used to predict the number of cancers detected in the next year, stratified by age (and sex for colorectal cancer) and past screening history; for breast cancer, models can also predict stage distribution by breast density, screening frequency, and age. Data describing the cumulative risk of a false-positive FOBT over a 10-year program of screening (29) could also be used to validate assumptions about within-person correlation of these tests over time. These types of evaluations are critical for validating models that are used for policy development.

Opportunities for Comparative Modeling

Research networks are ideally poised to provide common data elements harmonized across contributing research centers that can be used for comparative modeling exercises. PROSPR

estimates of screening processes (eg, screening rates, loss to follow up) can be incorporated into multiple models and used to predict and compare the impact of screening as practiced on cancer incidence and mortality. Because models make different assumptions about unobservable disease processes, comparative modeling provides more robust predictions than those obtained from a single model. Comparative modeling within the PROSPR consortium can be facilitated by the fact that several of the PROSPR modeling groups are also members of the CISNET modeling consortium that has for many years focused on comparative modeling across multiple cancer organ sites, including those studied in PROSPR (1,20,30).

Transdisciplinary Collaboration

Advancements in cancer-related research require expertise from distinct fields. Within the PROSPR consortium, disease modelers have the opportunity to collaborate directly with researchers in the fields of clinical medicine, health services, epidemiology, health disparities, behavioral science, biostatistics, and operations research. These specialists can assist modelers by providing both expertise to inform modeled processes and data that will make models more robust; in turn, modelers can guide future work in these fields by revealing insights into disease processes and interventions to prevent and treat disease. Importantly, these collaborations will help to strengthen the methodologic toolkit of comparative effectiveness research methodologies currently practiced in applied cancer prevention and control research.

Challenges

Data from cancer research collaboratives, including PROSPR, provide a basis for improving our understanding of—and therefore our ability to accurately model—screening as practiced. However, it takes a considerable amount of time to accrue data that are mature enough to describe longitudinal screening patterns that can be used for model inputs. This issue is most readily apparent for colorectal cancer screening because colonoscopy screening intervals can be as long as 10 years. It also takes time to collect data describing long-term outcomes that can be used for model validation. As these data accrue, models can and should be validated against shorter-term clinical outcomes, such as false-positive rates and rates of screen-detected cancers. While data quality is likely to be high in large research networks given the extensive data quality assurance processes in place, the data are observational in nature, making causal inference challenging; as a result, efforts must be taken to adjust for biases in the data or alternatively to capture these biases (if the source of bias is known) or explore potential sources of biases in the simulations. Finally, while the data networks might include diverse healthcare settings, it is likely that the range of settings does not reflect the full spectrum of how and where care is delivered in the United States, and therefore data may not be generalizable to all settings.

Conclusion

In spite of these challenges, perhaps because of them, it is important to move forward with modeling as part of large cancer research consortia and initiatives. These consortia provide rich repositories of real-world data that can be leveraged in decision-analytic modeling to create more robust models to not only

Table 1. Overview of models and policy questions in the PROSPR consortium

Lead investigator(s), PRC	Model type	PROSPR data source	Example analysis or policy question related to PROSPR	PROSPR data elements used for modeling	Model outcomes
Breast cancer					
Anna Tosteson, Dartmouth/Brigham and Women's Hospital	Decision tree	Dartmouth-Brigham clinical provider network	What are high-value targets for screening process improvement?	Screening abnormality rates; rate and timing of screening abnormality follow-up	Near-term measures of process outcomes (eg, resolution of initially abnormal mammograms)
Brian Sprague, University of Vermont	Microsimulation (20–22)	Vermont Breast Cancer Surveillance System	What changes in the harm/benefit balance for breast cancer screening strategies would result from the development of accurate prognostic markers that could minimize overtreatment of DCIS?	Screening test characteristics, by imaging modality and patient characteristics	Long-term outcomes from screening and use of diagnostic tests (eg, breast cancer mortality, QALY, costs, false-positive tests, treatments avoided)
Amy Trentham-Dietz and Oguzhan Alagoz, University of Wisconsin			What are the potential effects of new imaging modalities (eg, digital breast tomosynthesis) on the detection of DCIS and rates of overdiagnosis associated with breast cancer screening?	Cancer characteristics, by age and method of detection	
Natasha Stout, Harvard Medical School				Distribution of treatments received, by age and cancer characteristics	
Cervical cancer					
Jane Kim, University of New Mexico/ Harvard T. H. Chan School of Public Health	Microsimulation (23,24)	New Mexico HPV Pap Registry	What are the benefits, harms, and cost-effectiveness of current cervical cancer screening practice, compared with established guidelines?	Screening process measures: Screening intensity by age HPV triage test utilization, by preceding Pap result Compliance to diagnostic visit (ie, biopsy), by preceding Pap result Compliance to precancer treatment, by preceding biopsy result Cumulative risk of high-grade precancer	Harms (eg, colposcopy/biopsy rates), costs, and health benefits (eg, reductions in lifetime cancer risk and mortality, gains in LY/QALY) Cost-effectiveness of current practice vs predicted outcomes with guidelines-based screening Net monetary benefits of improving breakdowns along screening pathway
			What are priority investments in improving current failures in the screening process?		
			How do model outputs compare against empiric screening outcomes (ie, model validation)?		
				Following abnormal Pap results, by age, by HPV genotype, over five-year period	
Colorectal cancer					
Carolyn Rutter, RAND Corporation	Microsimulation (20,25,26)	Group Health Research Institute	What is the effectiveness of colorectal cancer screening as practiced in reducing mortality?	Screening process measures: Uptake of screening Time between screening tests Types of screening tests used Time to follow-up of positive tests results	Long-term outcomes from screening, including reductions in cancer incidence and mortality attributable to screening
Ann Zauber, Kaiser Foundation Research Institute/ Memorial Sloan Kettering	Microsimulation (20)	Kaiser Permanente Northern and Southern California			

* DCIS = ductal carcinoma in situ; HPV = human papillomavirus; LY = life-years; PRC = Population-Based Research Optimizing Screening through Personalized Regimens research center; PROSPR = Population-Based Research Optimizing Screening through Personalized Regimens research center; PROSPR = Population-Based Research Optimizing Screening through Personalized Regimens research center; PROSPR = Population-Based Research Optimizing Screening through Personalized Regimens research center.

better inform policy but also guide health care systems about best approaches to improving the delivery of cancer screening. PROSPR's study of variability in these outcomes at multiple levels (eg, patient, provider, health system) may enable models to identify influential points within the screening process in terms of high impact on population-level outcomes and areas where improvement efforts may be most productively focused.

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Notes

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