Cancer Screening and Genetics: A Tale of Two Paradigms

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Abstract
The long-standing medical tradition to "first do no harm" is reflected in population-wide evidence-based recommendations for cancer screening tests that focus primarily on reducing morbidity and mortality. The conventional cancer screening process is predicated on finding early-stage disease that can be treated effectively; yet emerging genetic and genomic testing technologies have moved the target earlier in the disease development process to identify a probabilistic predisposition to disease. Genetic risk information can have varying implications for the health and well-being of patients and their relatives, and has raised important questions about the evaluation and value of risk information. This paper explores the paradigms that are being applied to the evaluation of conventional cancer screening tests and emerging genetic and genomic tests of cancer susceptibility, and how these perspectives are shifting and evolving in response to advances in our ability to detect cancer risks. We consider several challenges germane to the evaluation of both categories of tests including defining benefits and harms in terms of personal and clinical utility, addressing healthcare consumers’ information preferences, and managing scientific uncertainty. We encourage research and dialogue aimed at developing a better understanding of the value of all risk information, non-genetic and genetic, to people’s lives.
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The United States Preventive Services Task Force (USPSTF), an independent panel of non-government experts in prevention and evidence-based medicine, has recently updated its 2005 review of research evidence and recommendations regarding genetic testing for mutations in the BRCA1/2 genes (1, 2), and is currently updating its 2009 breast cancer screening recommendations (3). BRCA1/2 testing represents a well-established form of genetic testing in the cancer context – these rare and high-penetrance gene mutations associated with hereditary breast and ovarian cancer were initially discovered in the early-1990s (4-7), and BRCA1/2 testing has been widely adopted. Genetic tests for such mutations differ from the types of cancer screening tests that the USPSTF usually evaluates – whereas the goal of conventional screening tests such as mammography, Pap testing, or PSA testing is to start the diagnostic process that will find treatable early-stage disease, predictive genetic tests of cancer susceptibility move the target earlier in the risk assessment and disease development process, and ultimately increase understanding about a person’s inherent predisposition to disease. As a result, cancer screening tests and genetic tests can be viewed as providing different types of risk information, which can have varying implications for patients’ health and well-being, as well as the health of their relatives. This difference prompts our consideration of the paradigms that are being applied to the evaluation of cancer screening tests as well as emerging genetic and genomic tests of cancer susceptibility, and how these perspectives are shifting and evolving in response to advances in our ability to detect cancer risks.

The Traditional Cancer Screening Paradigm

The evidence-based approach to cancer screening guideline decisions is rooted in the medical tenet to “first do no harm” because screening tests were developed for medical practice to examine individuals who exhibit no signs or symptoms of disease (8). Consistent with this view, the World Health Organization developed international standards regarding conditions that
should be met for a disease screening program to be considered appropriate at the population level (9). In the context of cancer screening, these conditions can be summarized into a few fundamental principles:

1) The target disease should be a common form of cancer, with high associated morbidity or mortality.

2) Screening test procedures should be acceptable, safe, and relatively inexpensive.

3) Treatment, capable of reducing morbidity and mortality, should be available and more effective when applied to early- versus late-stage disease.

Determining whether a screening test fulfills these principles of what we term the “traditional cancer screening paradigm” is a complicated process that depends upon the quality of the research evidence available, magnitude of the benefits, and degree of harms associated with the testing. The USPSTF is a national leader in determining whether a screening test fulfills these principles and ultimately bases its recommendations on the certainty of the net benefit (i.e., the benefits minus the harms) weighed against the magnitude of the net benefit. In general, a cancer screening test is recommended routinely when both the certainty and the magnitude of net benefit are high – with the benefits traditionally operationalized as reductions in morbidity and mortality (10). For example, the USPSTF 2009 evaluation of mammography concluded that women ages 50-74 should have routine mammography based on the estimation of a clear and large net benefit – reductions in cancer incidence and mortality deemed worth the risks of false-positive testing and overdiagnosis (8, 11). For younger women the net benefit was less certain and small, so the USPSTF recommended that women discuss their situation with a physician and decide on an individual basis.

The USPSTF also delved into evaluating predictive BRCA1/2 mutation testing in the general population of women without cancer in 2005 (12), and recently updated its review (1). For this updated review, its evaluative criteria focused on the primary benefit of reducing cancer incidence and mortality – outcomes consistent with the goals of conventional screening tests
and the traditional cancer screening paradigm (1). For women whose family history is associated with an increased risk for a deleterious \textit{BRCA1/2} mutation, the USPSTF found adequate evidence to suggest a moderate net benefit of testing and early intervention, and thus recommended (Grade B) routine genetic counseling, as well as subsequent \textit{BRCA1/2} testing when indicated by counseling. However, given the potential for harms of preventive management strategies and invasive screening, the USPSTF recommended against (Grade D) routine genetic counseling or \textit{BRCA1/2} testing for women whose family history is not associated with an increased risk for a deleterious \textit{BRCA1/2} mutation (1, 2).

\textit{An Emerging Genetic Paradigm}

The USPSTF is not the only group with an interest in, and process for, evaluating genetic tests; the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group was established in 2005 as a non-federal expert panel to develop an evidence-based strategy for evaluating genetic and genomic testing technologies for use in clinical practice (13). The EGAPP Working Group evaluates a variety of genome-based tests including predictive genetic tests for susceptibility to common and chronic diseases (note that to avoid duplication of efforts, \textit{BRCA1/2} testing has not been evaluated by this group), pharmacogenetic tests relevant to drug responsiveness, and diagnostic and prognostic genetic tests (13, 14). The EGAPP evaluation process is informed by the traditional cancer screening paradigm and the USPSTF methods – thus, they systematically consider the balance of benefits and harms, and the health outcomes of morbidity and mortality from disease (15). The EGAPP evaluation process is also informed by the ACCE model, a framework that outlines four critical components of a genetic test – the Analytic validity (ability to accurately measure the genotype of interest), Clinical validity (ability to detect or predict the clinical disorder of interest), Clinical utility (ability to significantly improve measurable patient clinical outcomes including morbidity and mortality), and Ethical, legal, and social implications of the test such as stigmatization or discrimination.
Both clinical and social implications, as well as their interaction, are considered in the EGAPP evaluation process and in the identification of relevant health outcomes. These health outcomes extend beyond traditional morbidity and mortality and span multiple outcomes relevant to behaviors, knowledge, and psychological well-being of individual patients, clinicians, families, and society (15).

This expanding universe of relevant health outcomes reflects an evolution of the traditional cancer screening paradigm in response to the challenges and demands highlighted by genetic technology. Whether evaluating conventional cancer screening tests or emerging genetic and genomic tests, the approach of identifying and weighing benefits and harms has remained critical for determining whether the test is appropriate for the population. However, a shift is occurring in terms of the specific benefits and harms evaluated. Although reductions in morbidity and mortality have been defined as key outcomes in the evaluation of conventional screening tests (and in the USPSTF evaluation of BRCA1/2 testing), the EGAPP process reflects a different perspective – one in which a more diverse and comprehensive set of health outcomes are considered in the evaluation of genetic tests. This is not to say that reductions in morbidity and mortality are irrelevant for genetic tests, but rather that genetic information provides a broader set of benefits than the disease risk for an individual, and these benefits may be meaningful to patients, their families, and communities, and are thus incorporated into the EGAPP evaluation process (15, 17). These broader benefits are considered because genetic and genomic testing technologies derive information from the mutations and variants present in an individual’s genetic code. An individual’s genetic code is complex, largely stable, and heritable, and the information derived from it can have far-reaching implications across the lifespan of an individual as well as their relatives. For example, this testing can provide knowledge that allows an individual and possibly her/his relatives to avoid unnecessary interventions, or that has implications for family planning or lifestyle decisions. Genetic and genomic tests provide a new dimension to the information we gather through other methods.
such as family history or physiological assessments, and by doing so have highlighted some of the diverse implications of health risk information that are useful to consider when contextualizing and evaluating various sources of such information (18).

This shift in the conceptualization of screening benefits is consistent with an expanding definition of clinical utility that considers aspects of “personal utility,” or the extent to which people find health information useful regardless of whether it leads to a reduction in morbidity or mortality (19-22). It can be argued that considering such benefits for genetic testing is appropriate because the information provided is ultimately about changing lives – not only changing the course of a disease. For example, individuals found to not carry their family’s deleterious BRCA1/2 mutation could move forward with less anxiety about the implications of their family history of cancer. Alternatively, individuals found to be mutation carriers can make reproductive decisions informed by this knowledge, as can subsequent generations within the family. As such, a variety of genetic testing outcomes can be considered for their benefits and harms: potential emotional reactions; quality of life; long-term planning and reproductive, career, and lifestyle decision making; perceptions of disease risk and control; communication of genetic findings to family members and their subsequent health behaviors; and adoption of appropriate preventive health behaviors and interventions (15). The EGAPP Working Group’s recommendations are ultimately based on measurable health benefits, yet the discussion of evidence related to these broader genetic testing outcomes that reflect aspects of personal utility is an important part of their decision-making process (23, 24). Social and behavioral research plays a critical role in providing evidence regarding these outcomes of genetic testing (25). For example, a substantive body of literature has explored the extent to which BRCA1/2 testing and result notification influences emotional outcomes including depression and anxiety. A meta-analysis of 21 studies demonstrated that BRCA1/2 testing does not produce long-term elevations in distress for most women, regardless of the test results received (26). Women who undergo BRCA1/2 testing and are found to be deleterious mutation carriers have also been
found to subsequently follow clinical recommendations for cancer prevention and detection. For example, in a sample of BRCA1/2 testers assessed at a mean of 5.3 years post-testing, mutation carriers were more likely to have undergone prophylactic surgery, used chemoprevention, and undergone screening with magnetic resonance imaging than were mutation noncarriers or those who received inconclusive results (27). Genetic testing may also have unforeseen positive effects on patients’ lives. It has been hypothesized that BRCA1/2 testing can promote “benefit finding,” or positive life changes such as a renewed appreciation for life, re-evaluation of priorities, and improved relationships; this prediction has received some empirical support (28).

Although the rationale for modifying the traditional cancer screening paradigm to encompass a broader spectrum of benefits and harms highlighted by the availability of genetic technologies is apparent, challenges do exist in applying this perspective to the development of evidence-based population-level recommendations. For instance, there are limitations in the types of empirical evidence available to inform recommendations. Although the USPSTF considers evidence from randomized clinical trials to be of the highest empirical quality (29), such studies are rarely available for most genetic tests. Observational, prospective studies that follow self-selected individuals electing to undergo genetic testing over time, and that adjust for the effects of relevant sociodemographic and medical confounding variables, are more likely to be available for evaluating various psychological and behavioral outcomes of genetic testing. Furthermore, whereas the traditional outcomes of morbidity and mortality are constant in their conceptualization and measurement across studies, such standardization is largely lacking for psychological and behavioral outcomes. These outcomes are reflected by numerous constructs (e.g., depression, anxiety, stigma, perceived risk), and there is little consensus regarding the best metrics for assessing these constructs (30, 31). An additional challenge is presented by the rapidly evolving genetic testing landscape – advances in gene sequencing technology (e.g., next-generation sequencing, whole genome and whole exome sequencing) have dramatically
increased knowledge about associations between genetic variation and various diseases, and there has been an increase in the availability of genetic testing and the marketing of such tests directly to the public. As a result, the opportunity and demand for testing is outpacing the research and its systematic evaluation. The EGAPP Working Group has strived to address this issue by developing methods for rapid reviews of emerging tests (13, 23), but many existing genetic testing technologies have yet to be formally evaluated. Furthermore, the EGAPP Working Group recognizes that, given limitations in available evidence and the subjective nature of some outcomes associated with personal utility, they will ultimately need to develop methods for incorporating patient preferences into their evaluation process (23). The development of such methods will be an important step toward integrating this evolution of the traditional cancer screening paradigm into the creation of evidence-based guidelines.

Overarching Challenges

Additional wide-ranging issues are affecting how the traditional cancer screening paradigm is being applied to the evaluation of both conventional screening tests and emerging genetic technologies. One major issue facing the medical community is the growing extent to which healthcare consumers desire personal health information. Earlier interests in accessing health information on the Web have evolved into something more personal, as interactive features of new data tools develop and the availability of health information increases. Patient portals such as PatientsLikeMe.com provide venues for people to interact with others who have the same conditions; mobile applications (apps) and personal health tracking tools support data capture and analysis of nutrition, exercise, and other behaviors that may be used casually, such as in pursuit of single health goals, or as a more formal data-informed approach to life, such as with Quantified Self movement devotees (32); the OpenNotes experiment encouraged patient access of medical records (33); and the HITECH Act’s Meaningful Use criteria require electronic health records to be used to interact with and engage patients (34). The common theme of
these examples is free and open access to more information, individualized information, and personal ownership of information – expectations that are not entirely consistent with an evidence-based approach to weighing information’s harms and benefits.

Topol (35) described the introduction of direct-to-consumer genetics products as the democratization of DNA, leading to the “realization that there will likely never be a ‘right time’ – after we have passed some imaginary tipping point giving us critical, highly actionable, and perfectly accurate information – for it to be available to the public” (Topol, 2012, Pg.119). The criteria of critical, actionable, and accurate information that have a longstanding importance in medical science are somewhat at odds with the tendency to emphasize information’s ability to promote patient empowerment and satisfy consumers’ health-related curiosity (36, 37). These differing perspectives have colored much of the media and public commentary regarding the recent downgrading of USPSTF recommendations for the use of mammography and PSA testing (38-40). Although providing all information may seem consistent with the concept of “personal utility,” experts caution against the potential harms of untested, unvalidated, or uninterpretable health risk information (41-43). Indeed, it is important to note that there is no personal utility if the information is incorrect, or if it only results in increased anxiety because there is no behavior to mitigate the disease risk or its implications. Information itself is not necessarily a benefit; rather, benefits are accrued when accurate information leads to improved health outcomes, however these outcomes may be defined. Nonetheless, determining how to balance consumer expectations for information against the need for well-defined and empirically-supported health benefits remains a challenge. In the face of this challenge, the traditional cancer screening paradigm has important strengths because it forces clarity regarding benefits and what “empowerment” means. Under this paradigm, people given information are empowered to choose or not choose a screening test with some knowledge of the net benefit of that choice. Moving the evaluation of genetic tests closer to demonstrating
clear clinical utility also has advantages, as the value of information becomes dependent on its harms as well as its benefits (41).

Uncertainty is a related and pervasive challenge. Determining the ratio of benefits to harms for a screening test is complex, and evaluation groups, clinicians, and patients must all grapple with uncertainties regarding the net benefit of cancer screening tests when the factors thrown into the balance are difficult to compare; for example, the adverse effects of false positive mammography among women who are healthy are difficult to balance against reduced mortality among women who have the disease. It is not always clear under which situations and for whom conventional screening tests and emerging genetic and genomic tests are likely to have the greatest benefit and least harm. Furthermore, scientific understanding regarding a test’s utility can change over time as new research evidence is obtained and synthesized and as new technologies are developed. It can be difficult for both clinicians and patients to know how to proceed when scientific evidence and expert opinions are incomplete, variable, or conflicting.

Some have addressed these challenges by considering patients’ preferences, goals, and values in the decision-making process. Indeed, the USPSTF has recommended shared and informed decision-making between patients and clinicians in instances where there is inadequate evidence regarding the net benefit of a conventional screening test, such as with the use of mammography in women ages 40-49 (11). In this case, the strict principles of the traditional cancer screening paradigm have been relaxed to accommodate uncertainty present in the situation, and to encourage clarification of an individual woman’s values (e.g., the relative importance of false-positive and false-negative testing).

Although there is some convergence of guideline development for conventional screening tests and genetic tests, the traditional evaluation of testing is changing in the context of disruptive genomic technologies such as clinical whole genome and exome sequencing. Contrary to predictive genetic tests of cancer susceptibility like BRCA1/2 testing that seek out a narrow set of mutations associated with a specific disease, clinical whole genome and exome
sequencing interrogate the entirety of a person’s genetic code to detect all known disease-associated variations. Although such sequencing is generally used as a tool to diagnose an unidentified disease or set of symptoms, it also reveals “secondary” or “incidental” results—information about thousands of gene variants associated with numerous diseases and outcomes of varying severity and actionability that are unrelated to the indication for ordering the sequencing, and which patients may have varying levels of interest in learning. Experts are grappling with how to manage the massive amounts of risk information provided, and with how to balance respect for patient autonomy in choosing to learn or avoid risk information against the clinician’s duty to disclose risk information that may potentially affect the well-being of patients and their relatives (44-46).

Recent guidance provided by the American College of Medical Genetics and Genomics (ACMG) states that clinicians must provide all patients with their sequencing results related to a minimal list of actionable genetic variants that (with appropriate medical intervention) could reduce morbidity and mortality (47, 48). In practice, this would mean that patients should be clearly educated on the likely harms and benefits of sequencing, and consent to such testing as a result of a shared and informed decision-making process. Yet, once patients have consented to testing, they would receive a specified set of results regardless of their preferences, goals, or values. Such a situation calls for a more open discussion of this shift in the consideration of patient choice and the value of risk information, as it is revolutionizing the problem of screening (49).

**A Call for Action**

We have examined how the traditional cancer screening paradigm has shifted and evolved in response to changes in our ability to detect cancer risks. Emerging genetic and genomic testing technologies have raised important questions regarding how to define the benefits and harms of risk information in terms of personal and clinical utility, address
healthcare consumers' preferences for information, and make decisions in the presence of scientific uncertainty. Yet, genetic risk information is neither unique nor exceptional in this way – these same questions are also relevant to the application and evaluation of conventional cancer screening tests. Ultimately, the need exists for a better understanding of the value of all risk information to people's lives.

Addressing these challenges will require multilevel efforts involving diverse stakeholders including national regulators overseeing genetic testing, policy makers suggesting guidelines, provider teams delivering care, and individuals at risk for disease. These multiple stakeholders make up the context of cancer care delivery (50) and personalized medicine (19, 51). As part of such efforts, researches should focus on determining the difference that risk information can make on the broad spectrum of outcomes of significance to both patients and clinicians, and the mechanisms and processes by which these outcomes are achieved. Morbidity and mortality are necessary outcomes to consider and will likely continue to play an important role in determining the coverage and reimbursement of medical services, but these outcomes are not likely sufficient for evaluating the benefits, harms, and utility of all risk information. Clinicians should also continue to be thoughtful about what kinds of information a screening test – conventional or genetic – will provide, and what the implications of this information are for their patients and for their own abilities to plan treatments, make decisions, and optimize care. Clinicians need to be cognizant of what specific outcomes they and their patients are each trying to achieve and whether those outcomes can be obtained by a given test, as enthusiasm for a test must be grounded in a clear understanding of its limitations and strengths, not based on false expectations or poor comprehension of its capabilities. Opportunities for discussions about the limitations, benefits, and harms of the information provided by screening tests – both familiar conventional screening tests and novel genetic and genomic tests – need to be supported by medical training, third-party payers, and policy. Similarly, patients' abilities to participate in a shared and informed decision-making process need to be reinforced by consumer education.
approaches that improve genomic literacy and the comprehension of probabilistic risk information and scientific uncertainty (52).

Efforts must continue to be made by evaluation groups such as USPSTF and EGAPP as the gap between conventional cancer screening tests and emerging genetic and genomic tests continues to narrow. For example, in response to the evolution of the traditional cancer screening paradigm, national bodies making recommendations might consider dimensions of personal utility by giving more weight to evidence regarding the benefit of testing to people’s lives, not just the effect of testing on morbidity and mortality. Furthermore, the balance of benefit and harm might shift as genomic risk information is applied as a means of risk-stratifying populations, resulting in screening recommendations that differ across risk strata in population-level cancer screening programs (53). Risk-based screening programs informed by established risk factors such as age and family history have previously been developed and implemented with demonstrated success (54), and recent discussions on this issue have proposed incorporating polygenic (i.e., results for multiple common genetic variants that individually confer a small degree of disease risk) information to identify patients at increased risk who may benefit from earlier or more frequent screening with conventional cancer screening tests (53, 55, 56). This personalized approach may hold promise, but will require an adequate evidence base and a thoughtful and timely evaluation process, one informed by the principles of the traditional screening paradigm and the lessons learned from its application to the challenges highlighted by genetic risk information.

Finally, professional organizations and policy makers need to have a willingness and ability to modify guidelines and regulatory frameworks as testing approaches, and our understanding of their various outcomes, continue to evolve. The importance of such flexibility has been recently illustrated in the domain of direct-to-consumer (DTC) genetic testing. Consumers have had substantial autonomy regarding the uptake of DTC genetic testing panels that assess a limited set of small nucleotide polymorphisms (SNPs), or genetic variants that are
common in the population and typically confer a small risk for a given health condition or characteristic (e.g., 57, 58). These DTC genetic testing panels, appealing to consumers’ desire for information and the concept of patient empowerment, quickly entered the marketplace and largely bypassed any systematic or evidence-based review of their effects on consumer outcomes. These tests have not met professional organization recommendations regarding evidentiary transparency (59), and the FDA has recently exercised their regulatory authority to stop the sale of these products until their clinical validity and utility are demonstrated (60), although hundreds of thousands of such tests have been sold with little understanding of their consequences. The decreasing costs of sequencing, constant pressures of consumerism, and anticipated benefits of personalized medicine suggest that in the future whole genome and exome sequencing may similarly be marketed directly to consumers (42). Yet, compared to these DTC genetic testing panels, whole genome and exome sequencing will provide an even greater amount of information that is more complex and could have more serious implications for the lives of individuals and their relatives. Researchers, clinicians, evaluation groups, professional organizations, and policy makers must be prepared to confront this challenge by working together to accumulate, interpret, and apply evidence about the various benefits and harms of these tests in a timely manner, and to reassess their conclusions as scientific understanding evolves.

With any screening test, there is a need for clear evaluative criteria and a consideration of the various outcomes that could be influenced by the test’s implementation. Valuable perspectives can be learned from the evaluation of conventional screening tests and emerging genetic and genomic tests – the traditional cancer screening paradigm acknowledges that not all information is useful, and the emerging genetic paradigm acknowledges that some information has a value in affecting lives rather than the course of a disease. As the number and availability of screening tests increases and the lines between risk prediction and disease
prevention become more blurred, we must continue to carefully consider these overarching issues and challenges.
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