Published in final edited form as:

Expert Rev Mol Diagn. 2017 January ; 17(1): 57–70. doi:10.1080/14737159.2017.1267567.

Care delivery considerations for widespread and equitable implementation of inherited cancer predisposition testing

Deborah Cragun¹, Anita Y Kinney^{2,3}, and Tuya Pal⁴

¹University of South Florida, Department of Global Health, College of Public Health

²University of New Mexico Comprehensive Cancer Center

³Department of Internal Medicine, University of New Mexico

⁴Department of Cancer Epidemiology, Population Sciences, Moffitt Cancer Center

Abstract

Introduction—DNA sequencing advances through next-generation sequencing (NGS) and several practice changing events, have led to shifting paradigms for inherited cancer predisposition testing. These changes necessitated a means by which to maximize health benefits without unnecessarily inflating healthcare costs and exacerbating health disparities.

Areas covered—NGS-based tests encompass multi-gene panel tests, whole exome sequencing, and whole genome sequencing, all of which test for multiple genes simultaneously, compared to prior sequencing practices through which testing was performed sequentially for one or two genes. Taking an ecological approach, this article synthesizes the current literature to consider the broad impact of these advances from the individual patient-, interpersonal-, organizational-, community- and policy-levels. Furthermore, the authors describe how multi-level factors that impact genetic testing and follow-up care reveal great potential to widen existing health disparities if these issues are not addressed.

Expert Commentary—As we consider ways to maximize patient benefit from testing in a cost effective manner, it is important to consider perspectives from multiple levels. This information is needed to guide the development of interventions such that the promise of genomic testing may be realized by all populations, regardless of race, ethnicity and ability to pay.

Keywords

Genetic testing; Inherited Cancer; Health Disparities; Next-generation Sequencing; Multi-gene panel testing

Address correspondence to: Dr. Tuya Pal, Department of Cancer Epidemiology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA, Tuya.Pal@moffitt.org, Tel: 813-745-3322.

Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

1. Introduction

Implementing genetic testing for hereditary cancer predisposition into clinical care holds great promise for reducing cancer associated morbidity and mortality. Approximately 5–15% of cancers have an inherited basis, including those of the breast, ovary and colorectum. Given that breast and colorectal cancers are among the most commonly diagnosed cancers in the U.S., genetic testing provides a great opportunity to prevent cancers or detect them early when they may be easier or less costly to treat.

For individuals, families and society to reap the benefits from genomic technologies, they must be aware of and have access to the genetic testing as well as subsequent preventive care. Poor implementation of genomic technologies can lead to increased health expenditures, without accompanying improvements in health outcomes. Poor implementation can even cause harm or increase existing health inequities. On the other hand, successful implementation of genomic technologies requires careful consideration of a variety of interrelated factors that impact advances in genomic technologies as well as access to both testing and preventive services.

Acknowledging evidence that multiple interacting factors impact health, the Social Ecological Model (SEM)^{1–3} organizes factors into multiple different levels as illustrated in Figure 1. Briefly, the individual level includes knowledge, attitudes, beliefs, preferences, values, sociodemographics, as well as genotype and phenotype of individual patients. Interpersonal-level factors include the healthcare provider, patient-provider interactions, and family networks/communication. Organizational level factors include health insurance plans, institutions (such as hospitals) and the processes employed by institutions to deliver and implement genomic technologies into health care. The community and policy levels include research institutions, support organizations, media, guidelines from national professional associations, laws, and regulations. In this article we incorporate an ecological approach, clinical experiences, and prior research to describe the evolution and impact of genetic/genomic testing along with many of the factors that should be considered for the widespread and successful implementation of genetic testing to identify and manage hereditary cancer predisposition.

2. Overview of current and emerging genetic testing approaches

With the completion of the Human Genome Project (HGP) in 2003 after 10 years and at an estimated cost of 2.7 billion dollars,^{4, 5} it was widely recognized that translation of the genome to routine clinical care would require more information. When the HGP began, DNA sequencing was performed through a chain-termination method (called “Sanger sequencing”) to accurately obtain long sequence reads (about 200 nucleotides),⁶ but limitations included high cost, restrictions in scale, and long turnaround time. During the HGP an approach called “shotgun sequencing” was developed to overcome some of the limitations to Sanger sequencing, including reductions in time and cost. Since then, there have been additional advances in DNA sequencing through the development of next-generation sequencing (NGS) technologies with costs of clinical whole genome sequencing (WGS) recently dropping to less than \$1,000.⁷

NGS-based tests have led to paradigm shifts in genetic testing, enabling us to test for multiple conditions simultaneously (called ‘multi-gene panel testing’) compared to the prior phenotype-directed approaches with sequential testing of one condition at a time through use of Sanger sequencing. At the same time that NGS-based technology has become increasingly used in clinical practice to evaluate patients for inherited cancer predisposition, several additional practice-changing events have occurred including: 1) implementation of the Affordable Care Act, 2) fall of the *BRCA* patent, and 3) celebrity disclosures.⁸ Additionally, compared to >\$4000 for testing for only *BRCA1* and *BRCA2* prior to the fall of the patent⁹, NGS has led to costs as low as \$250 for multiple inherited cancer genes including *BRCA*.¹⁰ In addition to the use of NGS-based sequencing for germline testing, it has also been used to sequence tumors to identify therapeutic targets which also has the potential to identify pathogenic variants if confirmed in the germline which would lead to inherited predisposition.¹¹ In fact, sequencing of over 1500 tumor samples identified germline pathogenic variants in known Mendelian disease-associated genes in over 15% of patients, the majority of which were in cancer susceptibility genes.¹² Consequently, care delivery issues surrounding potential germline significance of tumor sequencing results is highly important and complex issue as recently reviewed by Jain et al¹¹ and is not a focus of the current article.

Given the low cost and high availability, it is predicted that healthcare providers will soon routinely use genetic testing in the management of their patients.¹³ In fact, availability of large-scale genomic testing approaches, including whole genome sequencing (WGS) and whole exome sequencing (WES) led the American College of Medical Genetics (ACMG) to develop a policy statement to identify genes for which to report constitutional (inherited) mutations, regardless of the original indication for testing (called “secondary” or “incidental” findings).¹⁴ These 56 disease-associated genes (“ACMG-56”) include mostly inherited cancer and cardiac-related genes that were selected because actions can be taken by these individuals to reduce morbidity or mortality associated with these genetic risks. Per this policy, disclosure of pathogenic variants in these genes should not be limited by the age of the person being sequenced, which is an important consideration given that ACMG practice guidelines for genetic testing in minors recommends testing only if it impacts their medical management.¹⁵ Taken together, this policy represents an important beginning which is expected to evolve as evidence-based management options are determined for more genetic conditions and data is collected on optimal gene-based care delivery models.

3. Impact of the paradigm shift from syndrome-based to multi-gene testing for hereditary cancer

NGS-based multi-gene panel testing has led to a paradigm shift where multiple genes are simultaneously tested, including some genes which may not be clinically indicated per current guidelines, based on the patient’s personal and family history. These developments have resulted in significant changes to the delivery of genetic risk assessment services. Traditionally, a patient’s risk was evaluated based on personal and family history of cancer, ages of diagnosis, and other phenotypic features. Genetic counselors and other healthcare professionals then generated a differential diagnosis to determine a stepwise approach to

testing for genes for which there was a clinical indication, and focused their discussions based on cancer risks and management options for mutations in those specific genes. However, use of multi-gene panel tests eliminate the need to generate an extensive differential diagnosis. Thus, in contrast to using a stepwise genetic testing approach, the clinical practice paradigm has been shifting to a model where a patient is broadly consented about multiple hereditary cancer syndromes and the possibility of secondary findings and then tested.

Even though the need to generate an extensive differential diagnosis is no longer essential, it is important to recognize that a baseline proficiency in genetics remains crucial in choosing the appropriate test for the patient, interpretation of results, placing all results in proper clinical context (including unexpected positive results, variants of uncertain significance (VUS), and negative results), and making appropriate management recommendations. As such, the complexity of care based on genetic testing results is expected to become exponentially more complex.^{16, 17} With more genes tested simultaneously, the detection of more mutations (including secondary findings) and VUS results have increased.¹⁸ Furthermore, genes confer different levels of cancer risk, with varied levels of evidence to confirm cancer associations and risk stratification.^{9, 19, 20} Consequently, as our ability to test for more genes at a lower cost has been realized, these technical capabilities have surpassed our medical knowledge leaving several uncertainties and unanswered questions about some of the genes that are included in various multi-gene panel tests.

As outlined in Table 1, multi-gene panel tests for inherited cancer may include genes of high, moderate or unknown cancer risks.²¹ Mutations in high penetrance genes would typically be “actionable” as they generally lead to changes in guideline-based medical management, whereas mutations identified in moderate penetrance genes or those with unknown cancer risks may or may not warrant a change in care beyond that recommended based on the personal and family history of cancers. Cancer-related multi-gene panel tests generally fall into the three following categories: (1) inclusion of only high penetrance genes for specific cancer(s), (2) inclusion of high, moderate, and unknown penetrance genes for specific cancer(s), and (3) “comprehensive” cancer panels with inclusion of genes (often of variable penetrance) associated with multiple cancers or hereditary cancer syndromes.⁹ Additionally, several laboratories also offer the option of custom panels, where it is possible to choose the specific genes for which the patient is tested. Given that many labs offer multi-gene panel tests for inherited cancer predisposition in the U.S., it is not surprising that there exists substantial variation in the types of tests offered, platform used for testing, number of genes included on the tests, and methods used for interpretation of results.⁹

Prior studies indicate that multi-gene panel tests identify mutations in inherited cancer genes that are both expected and unexpected based on personal and family history.⁹ Specifically, there have been multiple studies to demonstrate scenarios in which the genotype (mutation result) does not match the phenotype (personal and family cancer history), suggesting that current understanding of genotype/phenotype associations based on targeted testing among only those meeting high risk criteria for a particular syndrome is incomplete.^{22–24} Consequently, the detection of these unexpected findings pose challenges to individuals, their family members, and healthcare providers. Finally, the higher rates of variants of

uncertain significance (VUS) results as more genes are tested may pose clinical challenges. The concern is that patients and/or providers may incorrectly assume a VUS is responsible for disease risk and this misconception could lead to inappropriate medical management. These and other potential concerns and benefits of implementing multi-gene panel tests are summarized in Table 2.

4. Individual Level Considerations in Genetic Testing for Inherited Cancers

This paradigm shift in genetic testing practices necessitates changes in the approach to genetic counseling of patients, recognizing that the optimal approach is currently unknown.²⁵ One approach adopted by many hereditary cancer clinics including our own incorporate a pre-test genetic counseling session during which the following is discussed: (1) a brief overview of multiple syndromes in general terms with discussion of specific conditions for which the patient may be at high risk based on personal and/or family history, (2) discussion of high penetrance (“actionable”) versus moderate penetrance (“not likely actionable”) genes, and (3) expectation of higher rates of VUS.¹⁸ A detailed discussion of specific conditions is deferred to the post-test session, during the disclosure of genetic test results.

Multi-gene panel testing has several potential benefits as well as challenges for patients as outlined in Table 2. Benefits include the potential to improve the detection rate of hereditary cancer syndromes, expand the range of clinical phenotypes associated with mutations in various genes and contribute to better understanding of the natural history of many of these conditions. However, there are also many uncertainties that must be conveyed to patients with regard to VUS results and mutations in genes where cancer risks are not well defined. Furthermore, it may prove challenging for patients who receive unanticipated results.

As multi-gene and whole exome/genome testing becomes more widely available, disparities that exist in the receipt of genetic testing for hereditary cancer^{26–31} are likely to remain an ongoing challenge. Currently, national practice guidelines indicate that all women diagnosed with breast cancer at or below age 50 should be offered Cancer Genetic Risk Assessment (CGRA) services which include genetic counseling and consideration of genetic testing.¹⁹ Among limited studies in Hispanics and/or Blacks,^{32–38} lack of awareness, cost concerns, competing life concerns and lower self-efficacy are key barriers to access. Awareness of genetic testing for hereditary cancer among Blacks (34.5%) and Hispanics (23.7%) is lower compared to NHW (54.4%)³⁹ yet when aware, interest in genetic services is high.⁴⁰ In fact, there was 100% acceptance of CGRA services among high risk patients recruited through a safety-net clinic of primarily underserved Hispanic women, and 96% of those offered genetic testing agreed.³⁸ Taken together, findings from us and others,^{38, 40–47} suggest that many minority patients are interested in pursuing CGRA services when given the opportunity and barriers are removed.

When considering follow-up care among individuals with hereditary predisposition to cancer from diverse populations, there remains little published data to evaluate disparities. The only published study of follow-up care among minority *BRCA* mutation carriers from a large African American kindred indicated that surveillance was preferred over risk-reducing

surgery.⁴⁸ Thus, more research is needed to ensure that once individuals are identified with high-risk cancer gene mutations they are able to access appropriate cancer surveillance and risk reducing options. Ultimately, the underuse of CGRA services among minority and socioeconomically underserved groups who also carry a disproportionate burden of early onset breast cancer⁴⁹ underscores the vital need to understand and address existing patient, interpersonal, institutional, and policy-level barriers through development and testing of interventions.

5. Interpersonal Level Considerations in Genetic Testing for Inherited Cancers

5.1. Healthcare Provider Considerations

When considering the increasing availability and use of multi-gene panel tests, it is important to recognize that providers' genomic self-efficacy and intention to order genetic testing may be impacted by the receipt of more complex test results and higher VUS rates that occur with multi-panel testing. Thus, provider-level factors are critical when considering the adoption rates of multi-gene panel tests and acting on positive results. Previously published data from us and others^{39, 50–53} suggest limited knowledge about cancer genetics among healthcare providers. In fact, providers indicate significantly less confidence about interpreting and counseling based on results of multi-gene panel tests, compared to single gene tests.⁵³ Furthermore, we and others^{26, 39, 40, 54–57} have demonstrated low genomic self-efficacy among providers, who indicate significantly less confidence about interpreting and counseling based on results of multi-gene panel tests, compared to single gene tests.⁵³ These findings highlight the importance of fostering provider-level involvement in the development of clinical decision support interventions to ensure that providers have accurate knowledge, self-efficacy, clinical skills, and resources needed to provide appropriate care based on family history and test results and that the interventions are acceptable, feasible and sustainable in different clinical contexts. Common provider-level barriers to guideline-concordant genomic care include: low levels of perceived clinical value of testing; gaps in genomic knowledge and skills (i.e., low genomic self-efficacy); and other competing clinical and educational priorities.^{58, 59} Despite this lack of knowledge and time constraints, healthcare providers generally welcome ongoing educational opportunities related to genomics.^{52, 60, 61}

Multi-gene panel tests have posed a number of challenges to healthcare providers, including higher rates of VUS results as more genes are tested, uncertainty in risks associated with some genes, and unexpected findings that do not match the patterns of cancers present in the family. For example, increasing use of multi-gene panel tests with testing for *TP53* amongst families without classic features of Li-Fraumeni Syndrome has led to detection of unexpected mutations, which is anticipated to result in expansion of the clinical phenotype.⁶² Consequently, clinicians and researchers are pursuing efforts to better understand how cancer presents among individuals who are unexpectedly found to have a *TP53* mutation. More information about cancer risks in these individuals is needed to further tailor medical care for these families. Another challenge occurs when mutations are identified in genes in which cancer associations remain unproven or in genes of moderate

penetrance. In these cases, appropriate medical management should generally be based primarily on personal and family cancer history rather than genetic test results, yet there is room for results misinterpretation and over- or under management in cases where providers misunderstand results;¹⁹ and providers may advise patients to undergo screening and/or surgery which may not be warranted. Consequently, it remains important to widely develop and foster programs to educate healthcare providers in the field of clinical cancer genetics, and promote both academic-community partnerships and multi-disciplinary care through which access to healthcare providers with expertise in genetics may be enhanced.

5.2. Patient-provider interaction

Interactions between patients and their healthcare providers play an important role in the utilization, access, and uptake of genetic testing. In fact, provider recommendation was the most important factor associated with genetic testing among a large sample of breast cancer survivors, with providers significantly less likely to discuss genetic testing with minority patients.⁵⁵ Moreover, a study of 3016 breast cancer survivors demonstrated lower patient-reported rates of physician recommendation for hereditary cancer testing among Black women, even after adjusting for mutation risk.⁵⁶ Furthermore, Black women with ovarian cancer had a 75% lower odds of provider discussion of genetic counseling than NHW women.⁶³ In contrast to the high hereditary cancer testing rates at academic centers,^{64, 65} much lower rates are reported through administrative data of commercially insured patients,³¹ suggesting that provider or system-level barriers contribute to low utilization rates among underserved populations including minorities and rural dwellers. Provider-level factors are salient, given that care for Blacks is concentrated among a relatively small number of providers who may face special challenges in providing high-quality care for their patients,^{66–69} and are less likely to order genetic testing for breast cancer.⁷⁰ Consequently, it remains important to better understand patient-provider interactions across all populations and develop interventions to address barriers.

5.3. Approach to ‘Next-Generation Counseling’ of high-risk patients

There currently remains a tremendous need to evaluate and refine new genetic counseling strategies to deliver genetic testing services and manage population needs, particularly as use of genomic testing technologies continues to increase. When considering evolving approaches to genetic counseling, it is beneficial to put approaches in the context of both existing behavioral theories and desired outcomes, particularly when disclosing genetic test results and communicating recommended risk management. The maximal value of hereditary cancer genetic testing will be realized only when risk notification translates into relevant actions taken by providers and patients who accurately interpret genetic risks, and understand evidence-informed guidelines or options to reduce risks.

Genetic counseling and testing provides an opportunity to motivate patients to adopt and sustain the behavioral changes necessary to reduce their cancer risks and improve health outcomes. The heightened personalization of genetic information has been posited to amplify motivation to engage in strategies to reduce their risk.⁷¹ Moreover, there have been high expectations that personalization of risk assessment afforded by genomics would hold great promise as a tool to motivate individuals to adopt risk reducing behaviors more

effectively than communicating disease risks using other types of risk information.^{72–74} Risk communication and health behavior change theories support these expectations suggesting that a positive genetic test result would increase the salience of risk, and in turn, intensify personal and familial risk perceptions thereby enhancing motivation.⁷⁵ However, available evidence suggests that simply communicating genetic test results and medical recommendations has modest to no effect on health behaviors.⁷⁶ This underscores the need for genetic service providers to adopt “next generation genomic counseling” approaches for motivating guideline-based care⁷⁷ to optimize outcomes among individuals and their families who are at risk for inherited cancer predisposition.

“Next generation counseling” supplements notification of genetic test results with theory-based behavioral interventions and motivational strategies tailored to the individual. Given the complexity of the relationships between genetic risk communication, informed decision making, and health behavior, it is often necessary to judiciously combine constructs from several theories or models that have been effectively used in prior research and apply them in “next generation counseling”.^{78, 79} Risk communication and behavior change are complex processes that often require multi-faceted interventions. The Extended Parallel Process Model (EPPM),^{80–85} Health Action Planning Approach (HAPA)⁸² and the Ottawa Decision Support Framework (ODSF)⁸⁰ may be useful in the context of inherited cancer risk communication. The EPPM is based on elements of Protection Motivation Theory,⁸¹ Theory of Planned Behavior⁸⁶ and the Health Belief Model.^{86, 87} Further, EPPM considers the role of emotions, cognitions and interpersonal influences on risk communication and behavior change. Briefly, EPPM focuses on channeling fear in a positive protective direction aimed at controlling the danger (e.g., getting a risk-reducing salpingo-oophorectomy) rather than controlling the fear (e.g., derogating the message and not taking action). Fear is aroused when individuals feel threatened (threat or risk appraisal process); they believe they and/or their family members are at risk for inherited cancer (perceived risk) and consider it a life-threatening disease (perceived severity). Individuals are more likely to engage in a danger control process (i.e., protection motivation) through uptake of risk reduction strategies if they believe that the desired course of action is effective in reducing their risks (response efficacy) and they have high levels of confidence in their ability to take such action (self-efficacy). Strategies for bolstering self-efficacy help patients emphasize facilitators and overcome barriers.^{88, 89}

While the EPPM focuses on strategies to promote motivation and increase intentions to engage in health behavior, HAPA recognizes that a substantial number of individuals are already motivated to engage in health behavior and form goal intentions, but fail to carry out those intentions.^{90–92} According to HAPA, successful behavior change involves both a pre-intentional motivational phase in which intention is formed and a post-intentional volitional phase in which intention is translated into action. To this end, the HAPA attempts to bridge the “motivation/intention–behavior gap” with a personalized and engaging action and coping planning component in the form of an implementation intention. Implementation intention suggests that patients are more likely to carry out an intended action if they identify when, where and how they will do so.⁹³ Thus, behavior change is more likely to occur if providers collaborate with patients to help them create action plans.

Recommended actions for individuals with hereditary cancer risks are sometimes influenced by individual-level patient considerations such as timing (i.e., at what age family planning is complete and a woman is ready to consider risk-reducing salpingo-oophorectomy) or preferences between two options (i.e., breast cancer surveillance or risk reducing mastectomy). Consistent with ODSF's conceptualization of decision support interventions, a central goal of cancer risk communication and behavior change counseling is to facilitate informed decision-making about risk reduction strategies, and prevent adverse psychosocial sequelae. Low levels of knowledge, and high decisional conflict can be impediments to informed decision making, thus these outcomes should also be considered.⁹⁴

Delivery style is important when implementing risk communication, behavior change and fear management interventions. There is strong evidence documenting the effectiveness of motivational interviewing (MI) in changing a broad array of health behaviors including cancer prevention behaviors. MI is a patient-centered counseling strategy based on autonomy and respect to help patients overcome their ambivalence, and strengthen motivation and commitment to taking action.^{95–99} MI enables genetic counselors to respond appropriately to patients' cognitive and affective responses to fear-arousing risk information such as discussing personal and familial risks of inherited cancer predisposition. There is evidence that MI reduces defensive responses (message rejection, paralyzing fear) after receiving fear-arousing cancer information and effectively motivates people to engage in preventive behavior.^{96, 100–104} MI is also culturally responsive because providers can incorporate the cultural and social context into the interaction; thus it is particularly well suited for minority and other underserved populations.^{105, 106} MI also draws on the patient's interpersonal resources to galvanize family support and communication about genetic risk and medical recommendations with their primary health care provider.

In addition to motivating use of guideline-based risk reduction strategies, next-generation genomic counseling can be used to promote family communication of genetic test results. Improving family communication and motivating relatives of mutation carriers to access clinical cancer genetic services is a priority for maximizing health outcomes and broad translation of genetics into preventive care delivery that can have a broad impact on population health.

5.4. Family-Level Considerations

Once an individual is identified to have a mutation in an inherited cancer predisposition gene, this information is very important to share with their at-risk (and often unaffected) family members so they too can be proactive with cancer risk management and prevention options if they are identified to also have the familial mutation. This is because most inherited cancer predisposing conditions are inherited in an autosomal dominant fashion, thus the risks of carrying a mutation among first- and second-degree relatives of a known mutation carrier are 50% and 25%, respectively. It is usually up to the first individual within the family identified with a mutation to share their positive genetic test result with their relatives. Studies to evaluate family sharing of genetic test results have primarily been on non-Hispanic white (NHW) populations at academic cancer centers where low rates of

testing have been reported,^{107–109} with even lower rates among Blacks based on very limited studies.^{110–112}

Multiple factors may influence communication of genetic risk information to family members, including lack of recognition that certain family members are ‘at risk’.¹¹³ Other factors include perceived responsibility to tell, relationship type, physical or emotional closeness, perceptions of whether relatives want to know, anticipation of relative’s reactions, personal emotions, and perceptions that discussing cancer is not accepted within the family.^{113–115}

Hereditary cancer testing rates among at-risk family members are generally low (ranging between 15–51%).^{107–109} Although studies have generally included limited racial/ethnic diversity among participants, one study reported that Black women (n=7) were significantly less likely to share test results.¹¹¹ A Bahamian study of *BRCA* carriers reported that <20% of at risk relatives came for free testing.¹¹² Additional research on family member testing among racial and ethnic minorities is necessary to identify the most promising ways to improve family risk communication and genetic testing uptake.

6. Organizational-level Considerations in Genetic Testing for Inherited Cancers

Several organizational-level factors threaten to further widen genomic disparities among underserved populations through their effects on healthcare access, health insurance coverage, and out-of-pocket costs.¹¹⁶ Major barriers to receiving and benefiting from hereditary cancer testing reported through an interview study of clinicians, insurance executives and patients included key organizational-level factors such as poor coordination of the timing of tests relative to treatment decisions and reimbursement-related disincentives, including high out-of-pocket costs.¹¹⁷ Furthermore, availability and quality of genetic services varies according across medical institutions as described in more detail below.

6.1. Medical Institutions

Although sometimes overlooked, differences in hospital procedures and hiring practices may impact genetic testing access and uptake. Clinical genetic service delivery varies by institution and by the types of providers who deliver these specialized services at various community hospitals or academic institutions.^{50, 51, 70, 118} Based on cross-sectional data, genetic service providers are more likely than other types of healthcare practitioners to provide patients with written summary information they can share with their family members; and observational studies suggest that family sharing letters increase family communication of test results and/or relatives’ use of genetic services.^{119, 120} Furthermore, one study of *BRCA* carriers reported lower testing rates among relatives treated at public hospitals compared to large cancer centers.¹¹⁰ Finally, not all institutions or geographic areas even have genetic professionals or offer genetic services as evidenced by a 2012 national survey of primary care physicians where over 53% indicated they did not have access to genetics experts.¹²¹

Evidence that institutional factors are influencing disparities in genetic testing is demonstrated through data published on the identification of individuals with hereditary colorectal cancer. Academic institutions and large cancer centers are more likely to have adopted an evidence-based method to systematically screen colorectal and/or endometrial tumors to identify individuals at high risk for Lynch syndrome,^{122, 123} the most common cause of hereditary colorectal and endometrial cancers. Additionally, there is great variability in procedures used to follow-up with patients after they are identified to be at high risk.¹²⁴ Furthermore, these procedural differences may impact the number of individuals who undergo confirmatory genetic testing for Lynch syndrome and are informed of steps that are proven to reduce morbidity and mortality related to Lynch syndrome.^{124, 125} Moreover, several institutions do not even track patient outcomes and had no routinized method of ensuring that patients were aware of their risks for hereditary cancer. Consequently, it remains important to develop automated measures, potentially through IT solutions, by which to improve identification and referral of high-risk populations who may then access genetic counseling and testing services.

6.2. Health Plans (Medicaid, Medicare, Private Insurers)

Insurance coverage for genetic testing varies greatly based on the type of testing (single-gene versus multi-gene), type of insurance, as well whether testing is ordered for diagnostic, preventive or informational purposes.¹²⁶ Despite the increasing use of multi-gene panel tests, many payers consider these tests investigational or experimental. Although most payers have coverage policies in place for *BRCA* testing, private insurers do not formally cover multi-gene panel tests despite their increasing availability.

Although Medicare has had limited coverage for preventive services, as the largest healthcare reimbursement system in the US its reimbursement policies are often closely followed by private insurers. Per Medicare guidelines, covered services encompass those that are ‘reasonable and necessary for the diagnosis or treatment of illness or injury’ and services exclude tests for screening ‘that are performed in the absence of signs, symptoms, complaints, or personal history of disease or injury.’ In contrast, Medicaid does not universally exclude genetic testing coverage among asymptomatic individuals, however state level management has led to variation in coverage across the country.

When considering private health insurance plans, criteria for coverage generally include that testing have direct influence on disease treatment management, diagnostic utility, or preventive measures for those at high-risk.¹²⁷ Policy exclusions often encompass testing for informational purposes, population screening in the absence of family history, and for minors tested for adult onset conditions. Despite these challenges, private insurance companies generally have broader reimbursement guidelines for genetic testing and services compared to public insurers.

Even if initial testing costs are covered, recommended interventions may not be accessible for some patients. Coverage for costly preventive services such as prophylactic surgeries are also not incentivized as the average individual in the US stays with their insurance company for less than 6 years.¹²⁷ Furthermore, without guaranteed future cost savings, there is potential to deter payers from covering the upfront costs of prevention. Consequently, it

remains important to evaluate cost-effectiveness of gene-based care, in order to maximize health benefits while minimizing non-guideline concordant care. Policies may also be needed to ensure appropriate services are covered by health plans.

7. Community- and Policy-level Considerations in Genetic Testing for Inherited Cancers

Several community- and policy-level factors have the potential to help alleviate genomic disparities among underserved groups through ensuring healthcare access, broadening health insurance coverage, and increasing levels of community engagement. Even as costs and availability of genetic testing decrease, other community- and policy-level factors will continue to influence whether the potential health benefits of genomic technology are fully, and equitably realized. Consequently, policy issues must be considered to minimize potential harms from implementing genomics into medicine.

7.1. Policies related to new genetic testing technology and secondary findings

The fall of the *BRCA* patent in conjunction with innovations in NGS technology have increased the availability of genetic testing at significantly decreased costs. However, this shift from single gene testing to multi-gene panel testing for inherited cancer predisposition has led to vague regulatory standards, with payers yet to adopt clear coding and reimbursement guidelines for panel-based testing.¹²⁸ Cited justification for lack of coverage for panels include limited data pertaining to clinical validity and clinical utility.¹⁹ Thus it remains imperative for research institutions to conduct comparative effectiveness and cost effectiveness studies to evaluate genetic testing approaches to define appropriate use of panels, in order to inform policy-level decisions related to new genomic advances.

WES and WGS will soon be cheaper than conducting a series of single gene tests and just as inexpensive as multi-gene panel testing. However, interpretation of the data is still in its infancy and there are several issues that should be addressed related to results interpretation and disclosure. Recognizing the increasing availability of WGS and WES, the ACMG set forth guidelines stating that whenever this testing is performed, laboratories offer to report results of 56 genes in 24 conditions regardless of the clinical indication for the testing. These conditions met the panel's criteria for clinical validity as they could provide medical benefit to the patient if the information was learned before the onset of symptoms. These findings are considered 'incidental' or 'secondary' if they are 'not apparently relevant to the diagnostic indication for which the sequencing test was ordered.'¹⁴ Although these recommendations were considered 'opportunistic screening' to promote access to additional actionable genetic information, there was no consideration of insurance reimbursement for both the test and subsequent follow-up care for those identified to have mutations, which leaves patients with the potential for greater harm¹²⁹ and widening of health disparities.

7.2. Policies influencing access to follow-up care and preventive services

The US health system is already fraught with widespread disparities, with genetic testing being no exception.¹³⁰ Even as genetic testing becomes more widely available, accessible, and affordable, this is not enough to reduce health disparities. Learning about a genetic

mutation and being unable to access preventive services may cause anxiety and other negative consequences and could further exacerbate cancer disparities. Racial minorities and those with lower socioeconomic status are more likely to be diagnosed with and die from cancer.¹³¹ After a positive genetic test, the inability to pay for preventive services in order to reduce cancer-related morbidity and mortality will only exacerbate disparities. Consequently, when making recommendations for coverage or access to predictive genetic testing, it is imperative for policy makers, insurance companies, professional organizations and advisory committees, and advocacy groups consider access to and reimbursement for preventive services.¹²⁷ It follows that initial cost/benefit considerations pertaining to genetic testing must factor into follow-up interventions in order to attain health benefits of testing.

Traditional payer coverage and reimbursement policies in the U.S. generally favor payment for diagnosis and treatment more often than prevention.¹²⁷ These policies make it necessary to pursue specific ad hoc coverage through an onerous process by which congress adds exceptions to ensure specific preventive services are covered (e.g., mammograms, colonoscopies, etc).¹³² With the passing of the Affordable Care Act in 2010, coverage for preventive services were substantially changed in the US. The two broad changes to reimbursement for genetic testing include: 1) private insurers must cover any preventive services recommended by the US Preventive Services Task Force (USPSTF), free of cost; and 2) all insurers must cover ten essential health benefits related to preventive and wellness services. Although these changes were made to improve access to and coverage of preventive services, gaps remain in coverage for genetic testing in those at risk for hereditary cancer predisposition. These include: 1) gender-specific recommendations, where men are explicitly excluded from the guidelines for *BRCA* testing thus there is no mandate for insurers to cover such testing in men; 2) the guidelines do not apply to individuals with a prior cancer diagnosis, as the scope of the evidence synthesis only includes asymptomatic individuals with no personal history of cancer; and 3) the guidelines do not address genetic testing for other hereditary cancer syndromes. Furthermore, the scope of the USPSTF recommendations made were solely focused on genetic counseling and testing, thus care following genetic counseling and testing were not part of these recommendations. When the preventive services provisions of the ACA went into effect, ambiguity arose regarding what insurance companies were required to cover, highlighting the opposing views between payers trying to minimize costs versus advocacy groups striving for broader interpretation.

7.3. Policies to maximize the value of testing

From both societal and patient-centered perspectives, the underuse and overuse of genomic testing and subsequent medical care should be avoided. In contrast, appropriate use of genomic testing and technological advances should be promoted as it can lead to high value in health care (i.e., beneficial health outcomes relative to costs).¹³³ Thus the costs and availability of genetic testing are not the only, and perhaps not even the most important consideration in discussions of genetic testing implementation. As genetic testing strategies evolve with the ability to test for many genes at relatively low or perhaps even no additional cost, secondary findings will be identified in genes unrelated to the presenting clinical phenotype. Although these findings may sometimes result in health value, early research has led to the growing recognition that return of secondary findings does not necessarily lead to

clinical health benefits and there is a need for more research in this area.^{134, 135} Existing efforts suggest that participants' and families' responses to genomic information can positively and negatively impact downstream utilization of health services.^{136, 137} This raises concerns that broader use of genomic tests may lead to wasted or inappropriate use of medical resources resulting in less cost-effective care or harm to patients. Ultimately, there remains a need to better understand the impact of integrating genomic sequencing into clinical care, to guide professional organizations and policymakers to develop approaches and policies to better ensure that the benefits of testing are maximized and provide value relative to direct and downstream costs.^{134, 135, 138}

Benefits from genetic testing do not arise from testing itself, but rather from appropriately acting on the information from testing; yet this is often dependent on their subsequent access to preventive care. In this regard, the policy recommendations made by both the American College of Medical Genetics (related to the reporting of secondary findings) and the Affordable Care Act (e.g. through mandating *BRCA* testing coverage in certain cases and relevant preventive services such as prophylactic surgery and enhanced surveillance) do not equate to insurance coverage for preventive interventions or automatically translate into improved health outcomes.¹²⁷ Variations in preventive services coverage threaten to exacerbate health disparities if only privileged segments of society can access these services and/or if these services do not extend to other hereditary cancer syndromes (such as Lynch syndrome) for which surveillance and treatments are also known to be effective at reducing cancer-related morbidity and mortality.

Finally, market and policy shifts have led to a rapidly growing demand for CGRA services, as results of genetic testing are increasingly incorporated into cancer care. With the evolution of genetic testing practices, deviation from the traditional in person genetic counseling sessions have resulted in alternate service delivery models including phone genetic counseling, which has great potential to improve accessibility to these specialized services.¹³⁹ In fact, telephone genetic counseling has been successfully used to increase reach and access to CGRA among a geographically diverse sample of high-risk women, without long-term adverse psychosocial consequences.^{43, 140, 141} Furthermore, results from prior studies have demonstrated that telephone genetic counseling may lead to cost savings compared to in person sessions.^{141, 142} In parallel, academic medical centers and commercial companies have increasingly started to offer telephone genetic testing options to increase the reach of CGRA services while improving accessibility.

8. Conclusions

Genetics is qualitatively different from other topics in medicine as it underlies all of pathophysiology, thus is the fundamental science of health and disease.¹⁴³ Emerging advances in genetics and genomics are increasingly influencing the healthcare environment with unprecedented opportunities for widespread implementation of genomic sequencing given the technological advances and plummeting costs. Successful and equitable implementation requires consideration of testing from multiple levels, including the individual-, interpersonal-, organizational-, community- and policy-levels as we have illustrated. Furthermore, we highlighted the importance of simultaneously considering and

addressing the longstanding disparities in receipt of genetic testing across populations as new genomic services are implemented in order to prevent existing disparities from increasing. Ultimately, there exists tremendous potential for genomic testing to prevent disease and positively impact health. However for the full promise of genomics to be realized, it is imperative to consider access to both testing services, implementation issues (including new care delivery models) and follow-up care across the population at large.

9. Expert Commentary

Advances in DNA sequencing technologies, in conjunction with policy changes, have led to a paradigm shift in germline genetic testing for inherited diseases. The practice paradigm of sequential testing when Sanger sequencing was used and the *BRCA* genes were patented is being replaced by the increasing use of multi-gene tests with an ever expanding option of genes for which to test at minimal or no additional cost. These changes have led to testing capabilities that have surpassed our knowledge about evidence-based management for individuals with mutations in: 1) genes in which limited data is available, and 2) previously characterized genes in lower risk individuals who unexpectedly are identified with a condition that does not match the indication for testing.

As we consider means by which to maximize patient benefit from testing in a cost effective manner, it is important to consider perspectives from multiple levels, including patient, provider and societal, as well as policy level factors. It has been widely recognized that that healthcare provider proficiency in genetics is limited with substantial need for education and decision support. The rapid advances in genomic testing, with point-of-care significance to cancer patients identified with inherited cancer predisposition has led to increasing demand for services with a limited workforce with specific content expertise in this area. Thus establishing and fostering an interface between genetics experts and other healthcare providers has become increasingly important so that more complex cases can be triaged to the experts and decision support is available for cases that may be more straightforward.

Advances in genomic testing for inherited cancer have led to policy-level changes to expand coverage for *BRCA* testing through the ACA based on the USPSTF recommendations, yet there are clearly areas that remain unaddressed, including those with mutations in other inherited cancer genes, those affected with cancer, as well as the provision of follow-up care coverage following testing. The latter issue is particularly important given that the benefits of testing do not result from testing itself but rather acting on the results following the detection of a mutation in an inherited cancer gene. Simultaneously, it is important to recognize that benefits from a societal perspective often differ from a payer perspective (where benefit is primarily measured at the patient medical health level, often without consideration of psychological or family benefits of testing). Thus there remains a great need to develop policies such that the greatest number of individuals may benefit from these tremendous advances in a cost effective manner. Specific areas that still require addressing are policies to enhance awareness, access and follow-up care across the entire population of high-risk individuals. Furthermore, patient utility from testing extends beyond personal health utility to improve their own outcomes to potential for testing to have psychological and other patient benefits including those to family members. Thus given the differences in

payer and societal perspectives when considering utility of genetic testing, it remains critical to generate population-level data regarding genomic testing implementation to inform development of evidence-based guidelines which equitably improve outcomes across all populations yet do not result in substantial wasted healthcare spending.

Finally, as genomic testing is implemented into routine healthcare, it is important to ensure that existing health disparities in gene-based care are not further widened. This may only be accomplished through focused efforts to better understand and develop interventions such that the promise of genomic testing may be realized by all populations, regardless of race, ethnicity and ability to pay.

10. Five-Year View

We expect that over the next few years as data is collected, compiled and analyzed, there will be additional information upon which evidence-based practice guidelines will be developed for genes that are currently less well understood. Furthermore, we expect expansion of the clinical phenotype as mutations in genes are detected in individuals without a characteristic personal and/or family history suggestive for that condition. This may also impact the evidence-informed guidelines for disease screening and prevention options.

Furthermore, we expect increasing use of WES and WGS as costs continue to drop and it comes to a point where these tests are less costly from a technological standpoint than multi-gene panel tests. Thus testing may no longer be focused on disease-focused phenotypes or even specialty-focused testing (e.g., cancer, cardiac, etc) and increasingly lead to potential to identify secondary findings. These changes will broaden the responsibility of providers who order the test to secure consent prior to testing and determine scope of analysis for each patient based on their preferences. It will also heighten the need to collaboration between primary care providers, healthcare providers across various specialties and genetics experts, given that interpretation of results may become increasingly complex and outside the scope of the testing providers expertise. Educational efforts and decision support tools will become critically important in order to enhance proficiency in genetics across all healthcare providers and empower both patients and providers with information upon which to base their gene-based healthcare decisions.

Finally, unless there are concerted efforts to implement genomics across underserved populations, disparities in gene-based care among racial and ethnic minorities, as well as rural dwellers, are expected to widen. This will require a focused understanding such that these disparities may be addressed at multiple levels such that the great promise of genetics to benefit health may be realized.

Acknowledgments

Funding

This paper was supported in part by a grant from the National Cancer Institute at the National Institutes of Health (1R01CA129142) and the University of New Mexico Comprehensive Cancer Center Support Grant: Development Funds (P30CA118100).

References

Reference annotations

* Of interest

** Of considerable interest

1. McLaren L, Hawe P. Ecological perspectives in health research. *J Epidemiol Community Health*. 2005; 59:6–14. [PubMed: 15598720]
2. Stokols D. Establishing and maintaining healthy environments. Toward a social ecology of health promotion. *Am Psychol*. 1992; 47:6–22. [PubMed: 1539925]
3. Stokols D. Translating social ecological theory into guidelines for community health promotion. *Am J Health Promot*. 1996; 10:282–298. [PubMed: 10159709]
4. Human Genome Sequencing C. Finishing the euchromatic sequence of the human genome. *Nature*. 2004; 431:931–945. [PubMed: 15496913]
5. National Human Genome Research Institute. The Human Genome Project Completion: Frequently Asked Questions. Available from URL: <http://www.genome.gov/11006943> [accessed Sept 6, 2013]
6. Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. *Proc Natl Acad Sci U S A*. 1977; 74:5463–5467. [PubMed: 271968]
7. Ray T. With \$999 Whole-Genome Sequencing Service, Veritas Embarks on Goal to Democratize DNA Information. *GenomeWeb*. 2016
8. Jolie, A. My Medical Choice. Available from URL: http://www.nytimes.com/2013/05/14/opinion/my-medical-choice.html?_r=0 [accessed July 18, 2013]
- 9 **. Hall MJ, Forman AD, Pilarski R, Wiesner G, Giri VN. Gene panel testing for inherited cancer risk. *J Natl Compr Canc Netw*. 2014; 12:1339–1346. Article gives a broad view of the salient issues pertaining to multi-gene panel testing, and compares it to prior sequential genetic testing approaches. [PubMed: 25190699]
10. Cho MK, Sankar P, Wolpe PR, Godmilow L. Commercialization of BRCA1/2 testing: practitioner awareness and use of a new genetic test. *Am J Med Genet*. 1999; 83:157–163. [PubMed: 10096590]
11. Jain R, Savage MJ, Forman AD, Mukherji R, Hall MJ. The Relevance of Hereditary Cancer Risks to Precision Oncology: What Should Providers Consider When Conducting Tumor Genomic Profiling? *J Natl Compr Canc Netw*. 2016; 14:795–806. [PubMed: 27283171]
12. Schrader KA, Cheng DT, Joseph V, et al. Germline Variants in Targeted Tumor Sequencing Using Matched Normal DNA. *JAMA Oncol*. 2016; 2:104–111. [PubMed: 26556299]
13. Ong FS, Lin JC, Das K, Grosu DS, Fan JB. Translational utility of next-generation sequencing. *Genomics*. 2013; 102:137–139. [PubMed: 23631825]
- 14 *. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013; 15:565–574. Article has widespread importance to genomic testing for inherited disease given its recommendations for selecting specific genes for which results should be shared regardless of the original indication for testing. [PubMed: 23788249]
15. Ross LF, Saal HM, David KL, et al. Technical report: Ethical and policy issues in genetic testing and screening of children. *Genet Med*. 2013; 15:234–245. [PubMed: 23429433]
16. Hiraki S, Rinella ES, Schnabel F, Oratz R, Ostrer H. Cancer risk assessment using genetic panel testing: considerations for clinical application. *J Genet Couns*. 2014; 23:604–617. [PubMed: 24599651]
17. Rainville IR, Rana HQ. Next-generation sequencing for inherited breast cancer risk: counseling through the complexity. *Curr Oncol Rep*. 2014; 16:371. [PubMed: 24488544]
18. Tucker T, Marra M, Friedman JM. Massively parallel sequencing: the next big thing in genetic medicine. *Am J Hum Genet*. 2009; 85:142–154. [PubMed: 19679224]
19. Genetic/Familial High-risk Assessment: Breast and Ovarian. Available from URL: http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf [accessed March 9, 2016]

- 20 **. Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol*. 2016 This article provides a framework by which to consider magnitude of cancer risks in the context of general population risks and existing evidence when advising those detected with mutations in moderate-risk inherited cancer genes.
21. Fecteau H, Vogel KJ, Hanson K, Morrill-Cornelius S. The evolution of cancer risk assessment in the era of next generation sequencing. *J Genet Couns*. 2014; 23:633–639. [PubMed: 24756768]
22. Norquist BM, Pennington KP, Agnew KJ, et al. Characteristics of women with ovarian carcinoma who have BRCA1 and BRCA2 mutations not identified by clinical testing. *Gynecol Oncol*. 2013; 128:483–487. [PubMed: 23262210]
23. Churpek JE, Walsh T, Zheng Y, et al. Inherited predisposition to breast cancer among African American women. *Breast Cancer Res Treat*. 2015; 149:31–39. [PubMed: 25428789]
24. Yurgelun MB, Allen B, Kaldete RR, et al. Identification of a Variety of Mutations in Cancer Predisposition Genes in Patients With Suspected Lynch Syndrome. *Gastroenterology*. 2015; 149:604–613.e620. [PubMed: 25980754]
25. Domchek SM, Bradbury A, Garber JE, Offit K, Robson ME. Multiplex genetic testing for cancer susceptibility: out on the high wire without a net? *J Clin Oncol*. 2013; 31:1267–1270. [PubMed: 23460708]
26. Jones T, Lockhart JS, Mendelsohn-Victor KE, et al. Use of Cancer Genetics Services in African-American Young Breast Cancer Survivors. *Am J Prev Med*. 2016
27. Bellcross CA, Kolor K, Goddard KA, Coates RJ, Reyes M, Khoury MJ. Awareness and utilization of BRCA1/2 testing among U.S. primary care physicians. *Am J Prev Med*. 40:61–66. [PubMed: 21146769]
28. Bellcross CA, Leadbetter S, Alford SH, Peipins LA. Prevalence and Healthcare Actions of Women in a Large Health System with a Family History Meeting the 2005 USPSTF Recommendation for BRCA Genetic Counseling Referral. *Cancer Epidemiol Biomarkers Prev*. 2013; 22:728–735. [PubMed: 23371291]
29. Trivers KF, Baldwin LM, Miller JW, et al. Reported referral for genetic counseling or BRCA 1/2 testing among United States physicians: a vignette-based study. *Cancer*. 2011; 117:5334–5343. [PubMed: 21792861]
30. Wood ME, Kadlubeck P, Pham TH, et al. Quality of cancer family history and referral for genetic counseling and testing among oncology practices: a pilot test of quality measures as part of the American Society of Clinical Oncology Quality Oncology Practice Initiative. *J Clin Oncol*. 2014; 32:824–829. [PubMed: 24493722]
31. Levy DE, Byfield SD, Comstock CB, et al. Underutilization of BRCA1/2 testing to guide breast cancer treatment: black and Hispanic women particularly at risk. *Genet Med*. 2011; 13:349–355. [PubMed: 21358336]
32. Sussner KM, Jandorf L, Thompson HS, Valdimarsdottir HB. Interest and beliefs about BRCA genetic counseling among at-risk Latinas in New York City. *J Genet Couns*. 2010; 19:255–268. [PubMed: 20151317]
33. Sussner KM, Jandorf L, Thompson HS, Valdimarsdottir HB. Barriers and facilitators to BRCA genetic counseling among at-risk Latinas in New York City. *Psychooncology*. 2013; 22:1594–1604. [PubMed: 22987526]
34. Sussner KM, Edwards T, Villagra C, et al. BRCA Genetic Counseling Among At-Risk Latinas in New York City: New Beliefs Shape New Generation. *J Genet Couns*. 2014
35. Gammon AD, Rothwell E, Simmons R, et al. Awareness and preferences regarding BRCA1/2 genetic counseling and testing among Latinas and non-Latina white women at increased risk for hereditary breast and ovarian cancer. *J Genet Couns*. 2011; 20:625–638. [PubMed: 21691939]
36. Adams I, Christopher J, Williams KP, Sheppard VB. What Black Women Know and Want to Know About Counseling and Testing for BRCA1/2. *J Cancer Educ*. 2014
37. Sheppard VB, Mays D, LaVeist T, Tercyak KP. Medical mistrust influences black women's level of engagement in BRCA 1/2 genetic counseling and testing. *J Natl Med Assoc*. 2013; 105:17–22. [PubMed: 23862292]

38. Komenaka IK, Nodora JN, Madlensky L, et al. Participation of low-income women in genetic cancer risk assessment and BRCA 1/2 testing: the experience of a safety-net institution. *J Community Genet.* 2015
39. Mai PL, Vadaparampil ST, Breen N, McNeel TS, Wideroff L, Graubard BI. Awareness of cancer susceptibility genetic testing: the 2000, 2005, and 2010 National Health Interview Surveys. *Am J Prev Med.* 2014; 46:440–448. [PubMed: 24745633]
40. Cragun D, Bonner D, Kim J, et al. Factors associated with genetic counseling and BRCA testing in a population-based sample of young Black women with breast cancer. *Breast Cancer Res Treat.* 2015
41. Kinney AY, Simonsen SE, Baty BJ, et al. Acceptance of genetic testing for hereditary breast ovarian cancer among study enrollees from an African American kindred. *Am J Med Genet A.* 2006; 140:813–826. [PubMed: 16523520]
42. Pal T, Bonner D, Cragun D, et al. A high frequency of BRCA mutations in young black women with breast cancer residing in Florida. *Cancer.* 2015
43. Kinney AY, Steffen LE, Brumbach BH, et al. Randomized Noninferiority Trial of Telephone Delivery of BRCA1/2 Genetic Counseling Compared With In-Person Counseling: 1-Year Follow-Up. *J Clin Oncol.* 2016
44. Benkendorf JL, Reutenauer JE, Hughes CA, et al. Patients' attitudes about autonomy and confidentiality in genetic testing for breast-ovarian cancer susceptibility. *Am J Med Genet.* 1997; 73:296–303. [PubMed: 9415688]
45. Hughes C, Gomez-Caminero A, Benkendorf J, et al. Ethnic differences in knowledge and attitudes about BRCA1 testing in women at increased risk. *Patient Educ Couns.* 1997; 32:51–62. [PubMed: 9355572]
46. Ramirez AG, Aparicio-Ting FE, de Majors SS, Miller AR. Interest, awareness, and perceptions of genetic testing among Hispanic family members of breast cancer survivors. *Ethn Dis.* 2006; 16:398–403. [PubMed: 17682241]
47. Vadaparampil ST, McIntyre J, Quinn GP. Awareness, perceptions, and provider recommendation related to genetic testing for hereditary breast cancer risk among at-risk Hispanic women: similarities and variations by sub-ethnicity. *J Genet Couns.* 2010; 19:618–629. [PubMed: 20798982]
48. Kinney AY, Simonsen SE, Baty BJ, et al. Risk reduction behaviors and provider communication following genetic counseling and BRCA1 mutation testing in an African American kindred. *J Genet Couns.* 2006; 15:293–305. [PubMed: 16865561]
49. American Cancer Society I. Cancer Facts & Figures 2016. Available from URL: <http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf> [accessed Apr 1, 2016]
50. Cragun D, Camperlengo L, Robinson E, Vadaparampil S, Pal T. Current Knowledge and Clinical Practices for Hereditary Breast Cancer Genetics and Genomics among Florida Providers. *Genetic Testing and Molecular Biomarkers (Accepted).* 2016
51. Pal T, Cragun D, Lewis C, et al. A Statewide Survey of Practitioners to Assess Knowledge and Clinical Practices Regarding Hereditary Breast and Ovarian Cancer. *Genet Test Mol Biomarkers.* 2013
52. Wideroff L, Vadaparampil ST, Greene MH, Taplin S, Olson L, Freedman AN. Hereditary breast/ovarian and colorectal cancer genetics knowledge in a national sample of US physicians. *J Med Genet.* 2005; 42:749–755. [PubMed: 15784723]
53. Blazer KR, Nehoray B, Solomon I, et al. Next-Generation Testing for Cancer Risk: Perceptions, Experiences, and Needs Among Early Adopters in Community Healthcare Settings. *Genet Test Mol Biomarkers.* 2015; 19:657–665. [PubMed: 26539620]
54. Anderson B, McLosky J, Wasilevich E, Lyon-Callo S, Duquette D, Copeland G. Barriers and facilitators for utilization of genetic counseling and risk assessment services in young female breast cancer survivors. *J Cancer Epidemiol.* 2012; 2012:298745. [PubMed: 23150731]
55. Jagsi R, Griffith KA, Kurian AW, et al. Concerns about cancer risk and experiences with genetic testing in a diverse population of patients with breast cancer. *J Clin Oncol.* 2015; 33:1584–1591. [PubMed: 25847940]

56. McCarthy AM, Bristol M, Domchek SM, et al. Health Care Segregation, Physician Recommendation, and Racial Disparities in BRCA1/2 Testing Among Women With Breast Cancer. *J Clin Oncol*. 2016
57. Birmingham WC, Hung M, Boonyasiriwat W, et al. Effectiveness of the extended parallel process model in promoting colorectal cancer screening. *Psychooncology*. 2015
58. Haga SB, Carrig MM, O'Daniel JM, et al. Genomic risk profiling: attitudes and use in personal and clinical care of primary care physicians who offer risk profiling. *J Gen Intern Med*. 2011; 26:834–840. [PubMed: 21311998]
- 59 *. Manolio TA, Chisholm RL, Ozenberger B, et al. Implementing genomic medicine in the clinic: the future is here. *Genet Med*. 2013; 15:258–267. Article outlines the various issues to consider as genomic testing for inherited disease is increasingly implemented into patient care. [PubMed: 23306799]
60. Vig HS, Armstrong J, Egleston BL, et al. Cancer genetic risk assessment and referral patterns in primary care. *Genet Test Mol Biomarkers*. 2009; 13:735–741. [PubMed: 20001580]
61. Carroll JC, Cappelli M, Miller F, et al. Genetic services for hereditary breast/ovarian and colorectal cancers - physicians' awareness, use and satisfaction. *Community Genet*. 2008; 11:43–51. [PubMed: 18196917]
62. Kamihara J, Rana HQ, Garber JE. Germline TP53 mutations and the changing landscape of Li-Fraumeni syndrome. *Hum Mutat*. 2014; 35:654–662. [PubMed: 24706533]
63. Meyer LA, Anderson ME, Lacour RA, et al. Evaluating women with ovarian cancer for BRCA1 and BRCA2 mutations: missed opportunities. *Obstet Gynecol*. 2010; 115:945–952. [PubMed: 20410767]
64. Schwartz MD, Lerman C, Brogan B, et al. Utilization of BRCA1/BRCA2 mutation testing in newly diagnosed breast cancer patients. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:1003–1007. [PubMed: 15824179]
65. Susswein LR, Skrzynia C, Lange LA, Booker JK, Graham ML 3rd, Evans JP. Increased uptake of BRCA1/2 genetic testing among African American women with a recent diagnosis of breast cancer. *J Clin Oncol*. 2008; 26:32–36. [PubMed: 18165638]
66. Bach PB, Pham HH, Schrag D, Tate RC, Hargraves JL. Primary care physicians who treat blacks and whites. *N Engl J Med*. 2004; 351:575–584. [PubMed: 15295050]
67. Jha AK, Orav EJ, Li Z, Epstein AM. Concentration and quality of hospitals that care for elderly black patients. *Arch Intern Med*. 2007; 167:1177–1182. [PubMed: 17563027]
68. Breslin TM, Morris AM, Gu N, et al. Hospital factors and racial disparities in mortality after surgery for breast and colon cancer. *J Clin Oncol*. 2009; 27:3945–3950. [PubMed: 19470926]
69. Hasnain-Wynia R, Baker DW, Nerenz D, et al. Disparities in health care are driven by where minority patients seek care: examination of the hospital quality alliance measures. *Arch Intern Med*. 2007; 167:1233–1239. [PubMed: 17592095]
70. Shields AE, Burke W, Levy DE. Differential use of available genetic tests among primary care physicians in the United States: results of a national survey. *Genet Med*. 2008; 10:404–414. [PubMed: 18496223]
71. Webster TH, Beal SJ, Brothers KB. Motivation in the age of genomics: why genetic findings of disease susceptibility might not motivate behavior change. *Life Sciences, Society and Policy*. 2013; 9:1–15.
72. Collins FS, Green ED, Guttmacher AE, Guyer MS. A vision for the future of genomics research. *Nature*. 2003; 422:835–847. [PubMed: 12695777]
73. Dzau VJ, Ginsburg GS, Van Nuys K, Agus D, Goldman D. Aligning incentives to fulfil the promise of personalised medicine. *Lancet*. 2015; 385:2118–2119. [PubMed: 25957453]
- 74 **. McBride CM, Birmingham WC, Kinney AY. Health psychology and translational genomic research: bringing innovation to cancer-related behavioral interventions. *Am Psychol*. 2015; 70:91–104. Article discusses multiple factors when considering clinical and public health translation as well as combining behavioral interventions with genomic test result disclosure to enhance motivation and optimize health outcomes. [PubMed: 25730717]
75. Keller M, Gordon E, Stack C, et al. Coriell Personalized Medicine Collaborative®: a prospective study of the utility of personalized medicine. *Personalized Medicine*. 2010; 7:301–317.

76. Hollands GJ, French DP, Griffin SJ, et al. The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. *Bmj*. 2016; 352:i1102. [PubMed: 26979548]
- 77 *. Mills R, Haga SB. Genomic counseling: next generation counseling. *J Genet Couns*. 2014; 23:689–692. An overview of genetic counseling practices, in the context of behavioural theories and evidence-based risk communication and behavior change strategies. [PubMed: 24026254]
78. Glanz K, Bishop DB. The role of behavioral science theory in development and implementation of public health interventions. *Annu Rev Public Health*. 2010; 31:399–418. [PubMed: 20070207]
79. Riekert, K., Ockene, J., Pbert, L. Springer Publishing Company, LLC. Handbook of health behavior change. 4th. New York, NY: 2014.
80. O'Connor AM, Jacobsen MJ, Stacey D. An evidence-based approach to managing women's decisional conflict. *J Obstet Gynecol Neonatal Nurs*. 2002; 31:570–581.
81. Rogers, R. Cognitive and physiological processes in fear appeals and attitude change: A Revised theory of protection motivation. In: Cacioppo, J., Petty, R., editors. *Social Psychophysiology*. New York, NY: Guilford Press; 1983.
82. Schwarzer R. Models of health behaviour change: Intention as mediator or stage as moderator? *Psychology & Health*. 2008; 23:259–262. [PubMed: 25160477]
83. Schwarzer R, Lippke S, Ziegelmann JP. Health action process approach - A research agenda at the Freie Universitat Berlin to examine and promote health behavior change. *Zeitschrift Fur Gesundheitspsychologie*. 2008; 16:157–160.
84. Witte K. Putting the Fear Back into Fear Appeals - the Extended Parallel Process Model. *Communication Monographs*. 1992; 59:329–349.
85. Witte K, Allen M. A meta-analysis of fear appeals: Implications for effective public health campaigns. *Health Education & Behavior*. 2000; 27:591–615. [PubMed: 11009129]
86. Ajzen I. The theory of planned behaviour: reactions and reflections. *Psychol Health*. 2011; 26:1113–1127. [PubMed: 21929476]
87. Janz NK, Becker MH. The Health Belief Model: a decade later. *Health Educ Q*. 1984; 11:1–47. [PubMed: 6392204]
88. Maloney E, Lapinski MK, Witte K. Fear Appeals and Persuasion: A Review and Update of the Extended Parallel Process Model. *Social and Personality Psychology Compass*. 2011; 5:206–219.
89. Murray-Johnson L, Witte K, Liu WY, Hubbell AP, Sampson J, Morrison K. Addressing cultural orientations in fear appeals: promoting AIDS-protective behaviors among Mexican immigrant and African American adolescents and American and Taiwanese college students. *J Health Commun*. 2001; 6:335–358. [PubMed: 11783667]
90. Gollwitzer PM. Implementation intentions - Strong effects of simple plans. *American Psychologist*. 1999; 54:493–503.
91. Kwasnicka D, Pesseau J, White M, Sniehotta FF. Does planning how to cope with anticipated barriers facilitate health-related behaviour change? A systematic review. *Health Psychology Review*. 2013; 7:129–145.
92. Schwarzer R. Self-regulatory Processes in the Adoption and Maintenance of Health Behaviors. *J Health Psychol*. 1999; 4:115–127. [PubMed: 22021474]
93. Sheeran P. Intention-behavior relations: A conceptual and empirical review *European Review of Social Psychology*. 2002; 12:1–36.
94. Services USDoHaH. , editor. *Quality AfHRA. Decision Aids for Cancer Screening and Treatment Comparative Effectiveness Review Number 145*. Rockville, Maryland: 2014.
95. Miller, WR., Rollnick, S. *Motivational interviewing : helping people change*. 3rd. New York, NY: Guilford Press; 2013.
96. Miller WR, Rollnick S. The effectiveness and ineffectiveness of complex behavioral interventions: impact of treatment fidelity. *Contemp Clin Trials*. 2014; 37:234–241. [PubMed: 24469237]
97. Moyers TB, Martin T, Manuel JK, Hendrickson SM, Miller WR. Assessing competence in the use of motivational interviewing. *J Subst Abuse Treat*. 2005; 28:19–26. [PubMed: 15723728]
98. Rollnick, S., Mason, P., Butler, C. *Motivational interviewing in healthcare: Helping patients change behavior*. New York, NY: The Guilford Press; 2008.

99. Rubak S, Sandbaek A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. *Br J Gen Pract.* 2005; 55:305–312. [PubMed: 15826439]
100. Hall K, Gibbie T, Lubman DI. Motivational interviewing techniques - facilitating behaviour change in the general practice setting. *Aust Fam Physician.* 2012; 41:660–667. [PubMed: 22962639]
101. Hall K, Staiger PK, Simpson A, Best D, Lubman DI. After 30 years of dissemination, have we achieved sustained practice change in motivational interviewing? *Addiction.* 2015
102. Kinney AY, Boonyasiriwat W, Walters ST, et al. Telehealth Personalized Cancer Risk Communication to Motivate Colonoscopy in Relatives of Patients With Colorectal Cancer: The Family CARE Randomized Controlled Trial. *Journal of Clinical Oncology.* 2014; 32:654–+. [PubMed: 24449229]
103. Pengchit W, Walters ST, Simmons RG, et al. Motivation-based intervention to promote colonoscopy screening: an integration of a fear management model and motivational interviewing. *J Health Psychol.* 2011; 16:1187–1197. [PubMed: 21464114]
104. Schwalbe CS, Oh HY, Zweben A. Sustaining motivational interviewing: a meta-analysis of training studies. *Addiction.* 2014; 109:1287–1294. [PubMed: 24661345]
105. Miller WR, Rose GS. Toward a theory of motivational interviewing. *Am Psychol.* 2009; 64:527–537. [PubMed: 19739882]
106. Miller WR, Rose GS. Motivational interviewing and decisional balance: contrasting responses to client ambivalence. *Behav Cogn Psychother.* 2015; 43:129–141. [PubMed: 24229732]
107. Sharaf RN, Myer P, Stave CD, Diamond LC, Ladabaum U. Uptake of genetic testing by relatives of lynch syndrome probands: a systematic review. *Clin Gastroenterol Hepatol.* 2013; 11:1093–1100. [PubMed: 23669308]
108. MacDonald DJ, Sarna L, van Servellen G, Bastani R, Giger JN, Weitzel JN. Selection of family members for communication of cancer risk and barriers to this communication before and after genetic cancer risk assessment. *Genet Med.* 2007; 9:275–282. [PubMed: 17505204]
109. Barsevick AM, Montgomery SV, Ruth K, et al. Intention to communicate BRCA1/BRCA2 genetic test results to the family. *Journal of family psychology: JFP: journal of the Division of Family Psychology of the American Psychological Association (Division 43).* 2008; 22:303–312.
110. Cheung EL, Olson AD, Yu TM, Han PZ, Beattie MS. Communication of BRCA results and family testing in 1,103 high-risk women. *Cancer Epidemiol Biomarkers Prev.* 2010; 19:2211–2219. [PubMed: 20699375]
111. Fehniger J, Lin F, Beattie MS, Joseph G, Kaplan C. Family Communication of BRCA1/2 Results and Family Uptake of BRCA1/2 Testing in a Diverse Population of BRCA1/2 Carriers. *J Genet Couns.* 2013; 22:603–612. [PubMed: 23666114]
112. Trottier M, Lunn J, Butler R, et al. Strategies for recruitment of relatives of BRCA mutation carriers to a genetic testing program in the Bahamas. *Clin Genet.* 2014
113. Wiseman M, Dancyger C, Michie S. Communicating genetic risk information within families: a review. *Familial Cancer.* 2010; 9:691–703. [PubMed: 20852947]
114. Chivers Seymour K, Addington-Hall J, Lucassen AM, Foster CL. What Facilitates or Impedes Family Communication Following Genetic Testing for Cancer Risk? A Systematic Review and Meta-Synthesis of Primary Qualitative Research. *J Genet Couns.* 2010; 19:330–342. [PubMed: 20379768]
115. Montgomery SV, Barsevick AM, Egleston BL, et al. Preparing individuals to communicate genetic test results to their relatives: report of a randomized control trial. *Familial Cancer.* 2013; 12:537–546. [PubMed: 23420550]
116. Cancer Action Network. Available from URL: <http://www.acscan.org/> [accessed June 1, 2016]
117. Weldon CB, Trosman JR, Gradishar WJ, Benson AB 3rd, Schink JC. Barriers to the use of personalized medicine in breast cancer. *J Oncol Pract.* 2012; 8:e24–31. [PubMed: 23180995]
- 118 *. Radford C, Prince A, Lewis K, Pal T. Factors Which Impact the Delivery of Genetic Risk Assessment Services Focused on Inherited Cancer Genomics: Expanding the Role and Reach of Certified Genetics Professionals. *J Genet Couns.* 2013 An outline of the expanding roles of genetics professionals with the widespread use of NGS-based tests for inherited cancer predisposition into routine care.

119. Dilzell K, Kingham K, Ormond K, Ladabaum U. Evaluating the utilization of educational materials in communicating about Lynch syndrome to at-risk relatives. *Fam Cancer*. 2014; 13:381–389. [PubMed: 24770865]
120. Suthers GK, Armstrong J, McCormack J, Trott D. Letting the family know: balancing ethics and effectiveness when notifying relatives about genetic testing for a familial disorder. *J Med Genet*. 2006; 43:665–670. [PubMed: 16371501]
121. Haga SB, Burke W, Agans R. Primary-care physicians' access to genetic specialists: an impediment to the routine use of genomic medicine? *Genet Med*. 2013; 15:513–514. [PubMed: 23306802]
122. Beamer LC, Grant ML, Espenschied CR, et al. Reflex immunohistochemistry and microsatellite instability testing of colorectal tumors for Lynch syndrome among US cancer programs and follow-up of abnormal results. *J Clin Oncol*. 2012; 30:1058–1063. [PubMed: 22355048]
123. Cohen SA. Current Lynch syndrome tumor screening practices: a survey of genetic counselors. *J Genet Couns*. 2014; 23:38–47. [PubMed: 23674164]
124. Cragun D, Debate RD, Vadaparampil ST, Baldwin J, Hampel H, Pal T. Comparing universal Lynch syndrome tumor-screening programs to evaluate associations between implementation strategies and patient follow-through. *Genet Med*. 2014
125. Heald B, Plesec T, Liu X, et al. Implementation of universal microsatellite instability and immunohistochemistry screening for diagnosing lynch syndrome in a large academic medical center. *J Clin Oncol*. 2013; 31:1336–1340. [PubMed: 23401454]
126. Graf MD, Needham DF, Teed N, Brown T. Genetic testing insurance coverage trends: a review of publicly available policies from the largest US payers. *Personalized Medicine*. 2013; 10:235–243.
- 127 **. Prince AE. Prevention for those who can pay: insurance reimbursement of genetic-based preventive interventions in the liminal state between health and disease. *J Law Biosci*. 2015; 2:365–395. Consideration of policies currently in place that impact both genetic testing and access to preventive care for inherited cancer predisposition, with a focus on how this may impact existing health disparities. [PubMed: 26339500]
128. Curnutte MA, Frumovitz KL, Bollinger JM, McGuire AL, Kaufman DJ. Development of the clinical next-generation sequencing industry in a shifting policy climate. *Nat Biotechnol*. 2014; 32:980–982. [PubMed: 25299915]
129. Rothstein MA. Currents in Contemporary Bioethics. *The Journal of Law, Medicine & Ethics*. 2012; 40:682–689.
130. Khoury, MJ. Why We Can't Wait: A Public Health Approach to Health Disparities in Genomic Medicine. Available from URL: <https://blogs.cdc.gov/genomics/2013/06/27/why-we-cant-wait/> [accessed June 1, 2016]
131. American Cancer Society I. Cancer Facts and Figures for African Americans 2013–2014. Available from URL: <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-036921.pdf> [accessed oct 7, 2013]
132. Boyd CE. Medicare: it's time to talk about changing it. *Ann Health Law*. 2010; 19:79–84. [PubMed: 21495552]
133. Porter ME. What Is Value in Health Care? *New England Journal of Medicine*. 2010; 363:2477–2481. [PubMed: 21142528]
134. Bennette CS, Gallego CJ, Burke W, Jarvik GP, Veenstra DL. The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. *Genet Med*. 2015; 17:587–595. [PubMed: 25394171]
135. Christensen KD, Dukhovny D, Siebert U, Green RC. Assessing the Costs and Cost-Effectiveness of Genomic Sequencing. *J Pers Med*. 2015; 5:470–486. [PubMed: 26690481]
136. Blumenthal-Barby JS, McGuire AL, Green RC, Ubel PA. How behavioral economics can help to avoid 'The last mile problem' in whole genome sequencing. *Genome Med*. 2015; 7:3. [PubMed: 25614766]
137. Blumenthal-Barby JS, McGuire AL, Ubel PA. Why information alone is not enough: behavioral economics and the future of genomic medicine. *Ann Intern Med*. 2014; 161:605–606. [PubMed: 25329206]

138. Gallego CJ, Shirts BH, Bennette CS, et al. Next-Generation Sequencing Panels for the Diagnosis of Colorectal Cancer and Polyposis Syndromes: A Cost-Effectiveness Analysis. *J Clin Oncol*. 2015; 33:2084–2091. [PubMed: 25940718]
139. Buchanan AH, Rahm AK, Williams JL. Alternate Service Delivery Models in Cancer Genetic Counseling: A Mini-Review. *Front Oncol*. 2016; 6:120. [PubMed: 27242960]
140. Kinney AY, Butler KM, Schwartz MD, et al. Expanding access to BRCA1/2 genetic counseling with telephone delivery: a cluster randomized trial. *J Natl Cancer Inst*. 2014; 106
141. Schwartz MD, Valdimarsdottir HB, Peshkin BN, et al. Randomized noninferiority trial of telephone versus in-person genetic counseling for hereditary breast and ovarian cancer. *J Clin Oncol*. 2014; 32:618–626. [PubMed: 24449235]
142. Chang Y, Near AM, Butler KM, et al. Economic Evaluation Alongside a Clinical Trial of Telephone Versus In-Person Genetic Counseling for BRCA1/2 Mutations in Geographically Underserved Areas. *J Oncol Pract*. 2016; 12:59, e51–13. [PubMed: 26759468]
143. Grosse SD, Khoury MJ. What is the clinical utility of genetic testing? *Genet Med*. 2006; 8:448–450. [PubMed: 16845278]

Key Issues

- Advances in DNA sequencing technology due to next-generation sequencing (NGS) in conjunction with policy shifts has resulted in plummeting costs of testing for inherited cancer predisposition.
- These advances have led to paradigm shifts in genetic testing approaches, with testing for multiple genes in parallel through multi-gene panel tests, whole exome sequencing, and whole genome sequencing, compared to the prior testing approach in which testing was generally performed sequentially for one or two genes or hereditary cancer syndromes at a time.
- Prior to NGS-based tests, cancer genetic risk assessment involved collection of comprehensive personal and family history to generate a differential diagnosis and proceed in a stepwise manner to test for genes for which a clear clinical indication existed.
- Increasing use of NGS-based tests have resulted in significant changes to the delivery of genetic risk assessment services, whereby the model has shifted to broad consent for patients for multiple hereditary syndromes and the possibility of secondary findings as well as a higher rate for detection of VUS results.
- Multi-gene panel tests identify mutations in inherited cancer genes that are both expected and unexpected based on the personal and family history, which can pose challenges to individuals, their family members, and healthcare providers.
- Consequently, it is imperative that as these emerging technologies are increasingly incorporated into routine patient care, testing be considered from multiple perspectives, including the individual, interpersonal, organizational, community, and policy levels.
- Furthermore, when considering the implementation of genetic testing, it is essential that access to follow-up care also be addressed given that the benefits of genomic testing do not result from testing itself but rather from patients acting upon results of testing through implementation of evidence-based care.
- Finally, with implementation of widespread genomic testing for inherited cancer predisposition, it is essential to understand and address existing disparities in gene-based care such that they do not further widen and all populations benefit from these tremendous advances.

Figure 1.
Social Ecological Model Illustrating Factors to Consider in Genetic Testing Implementation

Table 1

Three categories of genes found on Next Generation Multi-gene Cancer Panels

	High cancer risk “actionable”	Moderate cancer risk	Unknown cancer risk
Understanding of phenotype	Good to Excellent	Fair to Good	Poor
Management Guidelines	Published guidelines likely to exist, screening or prevention for many of associated cancer risks exist, mutation likely to change management	Guidelines unlikely to be published, screening may exist for associated cancer risks, mutation may or may not change management	Guidelines do not exist, difficult to make recommendations and therefore unlikely to change management
Examples of genes	<i>APC, BMP1A, BRCA1, BRCA2, CDH1, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11, TP53</i>	<i>ATM, CHEK2, PALB2</i>	<i>BARD1, BRIP1, MRE11, NBN, NBS1, RAD50, RAD51C, RAD51D</i>

Table 2

Pros and Cons of syndrome-based testing compared to multi-gene testing for hereditary cancer

Syndrome-based testing		Multi-gene panel testing	
pros	cons	pros	cons
Typically limited to common, high-penetrance genes for which clinical care guidelines exist. Guideline-based care reduces cancer-related morbidity and mortality for the most of the common hereditary cancer syndromes.	Missed opportunity for prevention of cancers or diseases caused by other “actionable” genes that are NOT tested, but for which there may be guidelines that would impact care and patient outcomes.	Higher yield of mutation positive results (including “incidental or secondary findings” in “actionable” genes) provides additional opportunities to reduce associated morbidity and mortality.	Higher chance of VUS results, or detection of mutations in genes in which treating providers have limited or no familiarity or genes that are “not actionable”, could result in guideline-discordant care (including both over and under treatment).
Given the lower likelihood of receiving unexpected or uninformative results (e.g., VUS), patients may experience lower levels of decisional conflict and psychological distress	Patients may desire more genetic information that would be available with broader genetic testing.	Additional information may be perceived as useful by patients. Even if information does not alter clinical care, finding a mutation in a moderate penetrance cancer gene may help to explain their cancer.	The higher chance for detection of a VUS or “incidental finding” may: 1) increase decisional conflict and psychological distress. For example, finding a mutation in a gene that does not fit the personal and family history may cause unnecessary worry.
Family history matches the gene mutation, making the information highly relevant.	Lower chance of finding a mutation in genes not included in the panel, thus reducing the opportunity for family members to benefit from additional genetic information.	More mutation positive results increases the opportunity to prevent or reduce symptoms of other hereditary diseases among family members.	Unexpected mutations in genes that don't fit the family history may not be perceived as useful to family members.
Reduced chance of overtreatment that can result from misinterpretation of VUS results or mutations in genes for which risks and healthcare guidelines are uncertain or unproven.	Failure to look for mutations in more genes, will result in missed opportunities to deliver guideline-concordant, cost-effective care to those with “secondary findings”.	Sequencing more genes may cost the same as testing fewer genes, but allows for the identification of mutation positive probands with “incidental findings”. This can lead to population-based prevention of other hereditary disease if guideline concordant care is received by patients and family members.	VUS results will outnumber mutation positives. VUS results and mutations in genes with which providers are less familiar may lead to guideline-discordant care, added expenditure of resources, and lower cost-effectiveness.