Genomics and Population Health Action Collaborative

Building the Evidence Base for Genomics in Public Health: Implications for Decision Making, Public Policy, and Population Health Planning

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INTRODUCTION TO THE ACTION COLLABORATIVE AND THE EVIDENCE WORKING GROUP

Since the completion of the Human Genome Project in 2003, researchers have been building an evidence base for the application of genetics and genomics in health and public health with notable successes in newborn screening and hereditary cancer. Given the great potential of precision health approaches and the announcement of the Precision Medicine...
Initiative, the Genomics and Population Health Action Collaborative (GPHAC) was formed in 2015 to identify potential areas where genomics and precision medicine could be further implemented to achieve near-term impact for population health. GPHAC’s two other main goals are to inform and communicate with population health policy makers and programs officials as well as to integrate evidence-based applications into practice at the clinical-public health interface. During the first year of the collaborative effort, two working groups – Implementation and Evidence – were formed to carry out the work of GPHAC, culminating in an online resource guide with tools for states interested in integrating genomics into their population health programs, specifically geared towards Lynch syndrome and hereditary breast and ovarian cancer (HBOC). The Implementation group focused on outcomes and metrics, examining the factors that contribute to success and readiness in implementing genomics programs at the public health level as well as potential barriers. The Evidence group focused its efforts on evidence assessment and horizon scanning to explore the impact of implementing genomics in public health, which is detailed in the following document.

HORIZON SCANNING: PURPOSE AND PROCESSES

Horizon scanning involves two processes: the identification of new and evolving health care interventions and the analysis of the potential impact of these technologies on clinical care, the health care system, patient outcomes, and costs. Horizon scanning is a critical initial step in evaluating new applications of genomics. In the field of genomics, tests and other applications tend to move rapidly from the discovery phase through analytic and clinical validation, but proceed more slowly, if at all, through studies demonstrating clinical utility, defined here as improvements in patient outcomes. Because undertaking systematic reviews and guideline development is a time and resource intensive endeavor, it is important to only begin these processes when there is a reasonably high likelihood that the selected application can be recommended unambiguously (either for or against) based on existing evidence. Horizon scanning helps to point health technology assessors and evidence evaluators in productive directions for future work, by giving them an overview of the landscape and maturity level of existing research.
Horizon scanning includes both identifying the evidence as it develops around given health applications, and analyzing the findings at a high level so that a general state of the evidence landscape, and how it is evolving, can be envisioned before proceeding with more in-depth investigations. On the level of individual genetic tests, analysis of horizon scanning results can help predict which applications are ready for guideline development (e.g., a test with plentiful studies identified that demonstrate good analytic and clinical validity, but no studies involving outcomes to support clinical utility, may not be ready for productive systematic review). Forecasts about the future of the field overall may be possible from analyzing groups of tests (e.g., estimating growth in number of genetic tests available for use in oncology versus other specialties). Horizon scanning typically includes periodic and systematic searching of both published scientific and available “grey” literature (the latter encompasses information not published in traditional scientific journals; examples of grey literature may include meeting abstracts, corporate press releases, blog posts, clinical trial registry data, regulatory filings, etc.).

Globally, there are many groups that perform systematic horizon scans for health applications and make their results freely available. In the U.S. the Agency for Healthcare Research and Quality (AHRQ) developed and operated a broad ranging systematic horizon scanning process from 2010-2015, to inform and plan activities of their Effective Health Care (EHC) program and provide the public with information on emerging health technologies (AHRQ, 2016). While the horizon scanning reports from this highly robust process often included emerging genetic tests, genomics is not an exclusive priority of this system.

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group operated a horizon scanning process that focused exclusively on genomic applications, in conjunction with the Centers for Disease Control and Prevention (CDC) Office of Public Health Genomics (OPHG) (EGAPP, 2010). Identified tests were used to develop clinical scenarios for topics that could potentially be reviewed and evaluated by the EGAPP working group. Topics were prioritized by EGAPP for development of summary reports according to scoring for numerous fields designed to estimate potential for impact in clinical and public health. Summaries were used in the decision making process to determine which topics would undergo systematic review and subsequent creation of guidelines. While the EGAPP prioritization by scoring and summary reporting is no longer operative, it was similar in several process characteristics to development of the current, and publically available, ClinGen “Actionability
Evidence-Based Summaries” (ClinGen, 2016). Identification and cataloging functions of the EGAPP system evolved into an OPHG horizon scanning process that continues to accumulate emerging genomic applications (Clyne et al., 2014; Yu et al., 2016). A key feature of the OPHG horizon scanning system is that the focus has shifted to studies and information on implementation of genetic testing on a population health level. This is expected to lead to enrichment of information collected on the later phases of translation from research to practice, with greater likelihood of addressing questions of clinical utility, at the cost of missing the more numerous studies of analytic and clinical validity. The organization and analysis phases of OPHG horizon scanning are evolving, primarily according to the form of a heuristic for categorizing genetic testing clinical scenarios according to levels of evidence, as described below.

As an aid to the analysis phase of the horizon scanning process for genomic applications, OPHG provides a high-level overview classification of genomic tests and family health history applications by levels of evidence (Dotson et al., 2014). This classification and ranking, denoted as the Tier Table Database\(^2\), is intended to inform and provide a starting point for researchers, health care providers and public health programs seeking an evidence base for genomic applications. However, the Tier Table Database is not an official endorsement or recommendation of any genomic technology by the CDC. The Tier System can be found online in the Public Health Genomics Knowledge Base website\(^3\).

The Tier System consists of three categories: Tier 1, Tier 2 and Tier 3 (Figure 1). Genomic tests in Tier 1 are either: a) required by the FDA in order to inform choice or dose of a drug, b) recommended in clinical practice guidelines based on systematic reviews, or c) covered by the Centers for Medicare and Medicaid Services (CMS) (Dotson et al., 2014). For example, when indicated through genetic counseling, genetic testing for \textit{BRCA1/2} mutations in women with a family history of certain cancers likely to be associated with \textit{BRCA1/2} mutations would be considered Tier 1. The primary basis for the classification in this case is a recommendation by the U.S. Preventive Services Task Force (Moyer, 2014).

\(^2\)For more information on the Tier Table Database, see: https://phgkb.cdc.gov/GAPPKB/topicStartPage.do (accessed June 15, 2016)

\(^3\)To view the Public Health Genomics Knowledge Base website, see https://phgkb.cdc.gov/GAPPKB/phgHome.do?action=home (accessed November 15, 2016).
Genomic tests in Tier 2 have either: a) relevant biomarkers mentioned in FDA drug labels without requiring testing, b) clinical practice guidelines addressing how to use the test, but not whether to test in given circumstances, c) clinical practice guidelines or systematic reviews find insufficient evidence regarding testing but do not discourage use of the test, or d) CMS covers testing with evidence development. Lastly, genomic tests in Tier 3 are either: a) cautioned against use by the FDA, b) clinical practice guidelines or systematic reviews, if existing, find insufficient evidence to support testing and discourage use of the test, or find at least adequate evidence to recommend against testing, c) not covered by CMS following evaluation, or d) no sources of synthesized evidence have been identified regarding testing (Dotson et al., 2014). It can be debated that tests evaluated and recommended against may not fit in the same Tier 3 category as those that have no synthesized evidence available. Classifying these features together in Tier 3 reflects the design of the system, targeting population level implementation as the desired endpoint, rather than use in research, or selected clinical applications.
TIER 1 TESTS

The translation of scientific and clinical knowledge into the realm of public health is complex and requires great care. Accordingly, the Genomics and Population Health Action Collaborative sought to begin their process by focusing on a select set of conditions in which medical, genetic and scientific knowledge were robust enough for possible application in the population at large. The action collaborative participants settled on three specific conditions in which there exists compelling arguments to warrant exploring the feasibility and net benefits of genetic screening of the general population: Hereditary Breast and Ovarian Cancer (HBOC), Lynch Syndrome (LS) and Familial Hypercholesterolemia (FH).

A number of persuasive factors led to the choice of these three conditions as the first candidates for exploring the extension of genetic testing into the realm of public health, including the robust medical knowledge about the conditions and about their underlying genetics. Each is caused by highly penetrant variants in a small set of genes and those who harbor pathogenic variants are at high risk of serious disease that threatens significant morbidity and mortality. However, critically, for those found by genetic testing to be at high risk, effective strategies by which to mitigate that risk are well established and supported by a strong evidence base (in the clinical realm).

Thanks to rapid advances in sequencing technology, genetic testing for FH, HBOC and LS is well established, increasingly affordable and has become a routine part of the care of many patients. This extensive experience has led to numerous professional clinical guidelines that inform genetic testing and reflect a robust consensus regarding management of those at risk. Moreover, due to the extensive application of testing in the clinical realm, the interpretation of pathogenic variants is well established in all three conditions.

While clinical testing and management of affected individuals cannot be directly translated to the public health realm, the concept of “cascade” testing, in which at-risk family members of those with pathogenic mutations undergo screening, can be seen as a “bridge” to inform population screening. In all three of the selected disorders, cascade family testing is recommended by evidence-based professional guidelines from organizations such as EGAPP and NICE, making these conditions particularly appealing as models for exploring the public health implications of genetic testing.
Importantly, none of the conditions upon which we are focusing is confined to a narrow ethnic group or to any specific ancestral background. Indeed, the aggregate prevalence in the US of HBOC, LS and FH may be as high as ~0.8% (each affecting 1/400, 1/400, 1/300 respectively), a very high figure when compared with other conditions routinely targeted for population screening. For example, the aggregate prevalence of these three conditions in the general adult population is nearly an order of magnitude greater than the conditions already targeted by newborn screening, an acknowledged success in public health, in which only about 0.1% of babies test positive.

The notion of extending genetic testing to the general, unaffected population has recently been supported for \( BRCA1/2 \) with recent evidence suggesting that at least in the homogeneous Israeli population, the penetrance in unselected individuals is equivalent to that seen in individuals identified clinically (Gabai-Kapara et al., 2014). However, it will be important to ascertain whether current global penetrance estimates, obtained primarily through the study of affected families, will remain unchanged in a heterogeneous population like the US once individuals are identified through screening. Other challenges that require study include how to ensure adequate understanding of both positive and negative results by those tested; assessing the financial benefits and costs of population genetic screening; and ultimately demonstrating its clinical utility.

Our robust understanding of these particular disorders, the high (and accelerating) frequency of genetic testing for them in clinical medicine and the existence of increasingly inexpensive testing, make Hereditary Breast and Ovarian Cancer, Lynch Syndrome and Familial Hypercholesterolemia ideal disorders upon which to focus current efforts to investigate challenges and explore the promise of genetic testing in public health.

**INTRODUCTION TO BRCA1 AND BRCA2-ASSOCIATED HEREDITARY BREAST AND OVARIAN CANCER**

In 2013, just over 3 million women in the United States were living with breast cancer (NCI, 2016d). Breast cancer is the most commonly diagnosed cancer among women, with approximately 230,000 new cases annually, and it accounts for an estimated 40,800 deaths each year (U.S. Cancer Statistics Working Group, 2016). Similarly, many women are affected by ovarian cancer, which is the leading cause of death among all gynecologic cancer
Statistics Working Group, 2016). Approximately 22,000 women are diagnosed each year, and 14,000 women die from the disease (U.S. Cancer Statistics Working Group, 2016).

In recent years, death rates from breast and ovarian cancer have been decreasing. From 2004-2013, breast cancer death rates fell an average of 1.9% annually while ovarian cancer death rates fell an average of 2.2% each year (NCI, 2016b). Though some of the biggest factors contributing to this decline are advanced treatment and awareness among patients, the decrease in death rates for breast cancer may partially be attributed to early detection as a result of preventive screening. Detecting cancer early can mean a patient has access to a greater array of therapeutic options and more time for effective treatment, thus increasing a patient’s chances of survival (NCI, 2015b).

Treating breast and ovarian cancer is extremely costly. In 2010, breast cancer cost the United States $16.5 billion, the highest cost of any cancer that year, while ovarian cancer cost the United States $5.1 billion (Mariotto et al., 2011). For some types of cancer, early detection can increase the likelihood of successful treatment, and therefore could help reduce some economic burden on patients and health care systems.

Approximately 90% of all cancers are considered to be sporadic, arising from gene damage acquired through environmental exposures, dietary factors, hormones, or aging, among other factors (FORCE, 2016). The acquired gene changes that result in sporadic cancers are not shared among relatives or passed on to subsequent generations. The other 10% of cancers are considered to be hereditary, and are driven by inherited mutations in specific genes. In the case of hereditary cancers, individuals across multiple generations of a family may be affected (FORCE, 2016). Hereditary cancer tends to occur earlier in life than sporadic cancer, is more likely to be bilateral or multifocal, is more likely to lead to multiple primary cancers, and exhibits autosomal dominant inheritance. Consequently, preventive screening at a younger age is recommended for people with a family history of hereditary cancer. In 2013, the United States Preventive Services Task Force recommended that women with a family history of breast or ovarian cancer should undergo family history screening followed by genetic counseling and testing to identify potentially harmful mutations in genes that are associated with hereditary cancer (USPSTF, 2013b).

Inherited mutations in two genes, breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2), account for 5 to 10 % of all breast cancers and 15% of all ovarian cancers (NCI,
2015a). BRCA1 and BRCA2 act as tumor suppressors in cells, helping to repair damaged DNA and prevent uncontrolled cell division (NCI, 2015a). In this way, BRCA1 and BRCA2 are instrumental in maintaining cell stability and the integrity of genetic information. Mutations in \textit{BRCA1} and \textit{BRCA2} can render the proteins less effective at repairing DNA and lead to uncontrolled cell growth (Deng, 2006). Mutations in the \textit{BRCA} genes thus alter the lifetime risk of developing breast and ovarian cancer. While the general population risk of developing breast cancer during an individual’s lifetime is approximately 12%, the lifetime risk of developing breast cancer in \textit{BRCA1} or \textit{BRCA2} mutation carriers increases to between 50-80% and 40-70% respectively (Table 1). Similarly, the general population risk of developing ovarian cancer during an individual’s lifetime is between 1-2% while the risk of developing cancer of the ovaries, fallopian tube, or peritoneal tissue in \textit{BRCA1} or \textit{BRCA2} gene mutation carriers is 39% and 10-17%, respectively. Some studies also indicate that BRCA1 and BRCA2 mutations may also may increase the lifetime risk of cancer at other sites including the prostate, pancreas, and colon (Table 1).

The body of evidence linking mutations in \textit{BRCA1} and \textit{BRCA2} with hereditary breast and ovarian cancer is strong and there may be an opportunity for public health programs to use that information to improve population health. For example, Healthy People 2020 is a science-based, 10-year national objective plan from the U.S. Department of Health and Human Services (HHS) designed to improve the health of all Americans by establishing benchmarks and monitoring progress for health improvement. Former HHS Secretary Kathleen Sebelius explained that, “[the] challenge and opportunity is to avoid preventable diseases from occurring in the first place.” In this spirit, when Healthy People 2020 was announced in 2010, HHS added a genomics topic area with the goal to improve health and prevent harm through valid and useful genomic tools in clinical and public health practices. Specifically, Healthy People 2020 aims to “increase the proportion of women with a family history of breast and/or ovarian cancer who receive genetic counseling” from a baseline of 34.6% to a target of 38.1% (HHS, 2014).
### Table 1. Impact of *BRCA1* and *BRCA2* mutations on lifetime risk of cancer diagnosis at specific sites.

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>General Population Lifetime risk, %</th>
<th>BRCA1 mutation carriers Lifetime risk, %</th>
<th>BRCA2 mutation carriers Lifetime risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>12.33†</td>
<td>50-80°</td>
<td>40-70°</td>
</tr>
<tr>
<td>Ovarian, Fallopian tube, and Peritoneal</td>
<td>1.3°</td>
<td>39 *</td>
<td>10-17°</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>0.13†</td>
<td>1-2°</td>
<td>5-10°</td>
</tr>
<tr>
<td>Prostate</td>
<td>15.02†</td>
<td>&lt;30°</td>
<td>&lt;39°</td>
</tr>
<tr>
<td><strong>Female and Male</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon/Rectum</td>
<td>4.66†</td>
<td>11 *</td>
<td>–</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>1.50†</td>
<td>1-3°</td>
<td>2-7°</td>
</tr>
</tbody>
</table>


### USPSTF ASSESSMENT OF *BRCA1* and *BRCA2*

In 1994, four years after initial evidence supported its existence, the *BRCA1* gene was cloned, and *BRCA2* was discovered one year later. Screening for *BRCA* mutations based on suggestive family history or ethnic background has become fairly common in clinical care, and some health care systems such as Kaiser Permanente have created and implemented clinical guidelines for counselling and testing around genetic breast cancer susceptibility. In 2004, the United States Preventive Services Task Force (USPSTF) decided to address *BRCA1* and *BRCA2* testing and commissioned a systematic evidence review by the Oregon Evidence-based Practice Center.

The USPSTF process involves creating an analytic framework and allows for reaching decisions based on a chain of evidence leading from screening to improvements in important health outcomes, such as mortality from breast cancer. The evidence review uncovered no studies directly addressing whether risk assessment and *BRCA1/2* testing reduce breast or
ovarian cancer incidence or mortality. However, there was sufficient evidence that women at increased risk for BRCA1/2 mutations could be identified, and that while there was insufficient evidence of whether testing itself was associated with important adverse health outcomes or ethical, legal and social consequences in high risk women, the magnitude of these potential harms were estimated to be small. Finally, based on fair evidence that prophylactic surgery for these women would significantly decrease the risk of breast and ovarian cancer, the USPSTF concluded that the benefits of counseling and testing might be substantial. The USPTSF concluded that benefits outweighed the harms and recommended women at increased risk for BRCA1/2 mutations be referred for genetic counseling and evaluation for testing. They also made a recommendation against screening women whose family history did not indicate an increased risk for BRCA1/2 mutations (USPSTF, 2013a).

The USPSTF updated their review and their recommendation in 2013 and added a recommendation that one of several family history screening tools be used to identify women at increased risk. They reaffirmed that these women should receive genetic counseling and if indicated, BRCA testing. They also reaffirmed that women who are not at increased risk based on their family history should not be counseled or tested. Based on this conclusion of the USPSTF’s systematic evidence review and recommendations, BRCA1 and BRCA2 testing was identified as a Tier 1 application, suitable for consideration of use in public health (USPSTF, 2013a). Under the Affordable Care Act, genetic counseling and BRCA1/2 testing using the latest USPSTF recommendation, is available without out-of-pocket expense to the patient in commercial health plans.

ASSESSMENT BY CLINGEN: BRCA1/2

The Clinical Genome Resource (ClinGen) is a consortium of researchers building an open-access and centralized resource defining the clinical relevance and actionability of genomic variants for use in precision medicine and research. ClinGen is funded by the National Institutes of Health (NIH) and represents a partnership between 75+ public, private and academic institutions collaborating to ultimately improve patient care through genomic medicine.\(^4\) Patients,

Clinicians, laboratories and researchers share genetic and health data, which ClinGen’s working groups use to address the following three questions:

1. Is this gene associated with a disease? (*clinical validity*)
2. Is this variant causative? (*pathogenicity*)
3. Is this information actionable? (*clinical utility*)

ClinGen’s Actionability Working Group (AWG) aims to identify genetic variants that confer a high risk of disease, yet also offer an opportunity for disease prevention or mitigation if an individual knows their risk. In order to do this, the AWG has developed a standardized, structured and transparent protocol to generate evidence-based Summary Reports and semi-quantitative metric (SQM) scores outlining the clinical actionability of gene-disease pairs. Clinical actionability can be defined as a known ability to employ a specific and effective intervention and avert a poor health outcome due to a previously unsuspected high risk of disease. The Summary Reports and SQM scores are publicly available in order to support the research and clinical communities in prioritizing the human genes with the greatest relevance for clinical intervention.5

The AWG’s Knowledge Synthesis Team (KST) gathers the knowledge base of clinical actionability for a genetic disorder and its associated gene through a formal and transparent literature review to create a Summary Report. The Summary Report is carried out in two stages.

In Stage I, the KST assesses whether a gene-disease pair meets the three criteria for minimal clinical actionability (see Box 1).

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**BOX 1**

**ClinGen Criteria for Assessing Minimal Clinical Actionability**

1. The genetic disorder must be clinically actionable in an undiagnosed adult
2. If penetrance or relative risk is known, there must be at least one pathogenic variant with moderate or high penetrance or at least moderate relative risk in any population
3. The resulting genetic disorder must be a significant health condition.

If the three Stage I criteria are met, a gene-disease pair proceeds to Stage II. If a gene-disease pair does not meet Stage I’s criteria, the AWG may decide by consensus to make an

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5For more information on ClinGen’s AWG, see https://www.clinicalgenome.org/working-groups/actionability/ (accessed October 27, 2016).
exception and move the pair to Stage II. If a gene-disease pair does not proceed to Stage II, no further action is taken. In Stage II, the KST documents and summarizes the key evidence related to the clinical actionability of the gene-disease pair, which eventually becomes the Summary Report. The Summary Report contains five aspects of clinical actionability for the gene-disease pair (see Box 2).

BOX 2
Five areas of clinical actionability assessed in ClinGen Summary Reports

1. The nature of the threat to health for an individual carrying a pathogenic allele of the given gene(s)
2. The effectiveness of available interventions for preventing or mitigating harm
3. The likelihood that the threat will materialize (the variant’s penetrance)
4. The nature of the intervention in terms of the burdens or risks placed on the individual based on the gene-disease pair finding
5. The chance that the underlying risk or disorder could escape detection prior to harm in the setting of standard care

The AWG then uses the evidence base provided in the Summary Report to score the clinical actionability of the gene-disease pair and associated, distinct clinical outcomes using a SQM. AWG assesses gene-disease pairs that have documented clinical outcomes and relevant interventions.

The SQM consists of four domains for clinical actionability that are each scored from 0 to 3 to indicate clinical actionability.

1. Severity of the outcome
2. Likelihood of disease
3. Effectiveness of the intervention
4. Nature of the intervention

A final actionability score is attained by summing the scores of the four domains, with a score of 0 indicating the least clinically actionable genetic variant, and 12 meaning the most clinically actionable. Additionally, the AWG grades the knowledge base for the disease and intervention effectiveness from A (substantial evidence) to D (controversial or poor evidence).
ClinGen’s recommendation for \textit{BRCA1} & \textit{BRCA2}

ClinGen assessed \textit{BRCA1} and \textit{BRCA2} and their association with Hereditary Breast and Ovarian Cancer (HBOC) for three possible disease/intervention scenarios: breast cancer/breast surveillance, breast cancer/mastectomy, and ovarian cancer/oophorectomy. When assessing the nature of the intervention, ClinGen took into consideration the severity and seriousness of risks associated with the intervention, with more aggressive procedures such as prophylactic surgery receiving a lower score than less aggressive surveillance measures.

Although ClinGen assessed the two genes separately, both \textit{BRCA1}\footnote{To view the Summary Report for \textit{BRCA1} and HBOC, see https://www.clinicalgenome.org/site/assets/files/3472/binning_hboc_05242016.pdf (accessed October 27, 2016).} and \textit{BRCA2}\footnote{To view the Summary Report for \textit{BRCA2} and HBOC, see https://www.clinicalgenome.org/site/assets/files/4680/binning_hboc_05242016.pdf (accessed October 27, 2016).} received the same total actionability score for each outcome pair. For breast cancer/breast surveillance, ClinGen assessed a total clinical actionability score of 10AA. For breast cancer/mastectomy, ClinGen assessed a total clinical actionability score of 9AA. Lastly, for ovarian cancer/oophorectomy, ClinGen assessed a total clinical actionability score of 8AA. The full list of scores from ClinGen can be found below in Table 2. ClinGen’s high scores for \textit{BRCA1} and \textit{BRCA2} and HBOC are significant because they highlight the potential to improve clinical outcomes in undiagnosed adults by preventing HBOC.

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>Outcome/Intervention</th>
<th>Severity</th>
<th>Likelihood</th>
<th>Effectiveness</th>
<th>Nature of the intervention</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{BRCA1}</td>
<td>Breast cancer/surveillance</td>
<td>2</td>
<td>3A</td>
<td>2A</td>
<td>3</td>
<td>10AA</td>
</tr>
<tr>
<td></td>
<td>Breast cancer/Mastectomy</td>
<td>2</td>
<td>3A</td>
<td>3A</td>
<td>1</td>
<td>9AA</td>
</tr>
<tr>
<td></td>
<td>Ovarian cancer/Oophorectomy</td>
<td>2</td>
<td>2A</td>
<td>3A</td>
<td>1</td>
<td>8AA</td>
</tr>
<tr>
<td>\textit{BRCA2}</td>
<td>Breast cancer/surveillance</td>
<td>2</td>
<td>3A</td>
<td>2A</td>
<td>3</td>
<td>10AA</td>
</tr>
<tr>
<td></td>
<td>Breast cancer/Mastectomy</td>
<td>2</td>
<td>3A</td>
<td>3A</td>
<td>1</td>
<td>9AA</td>
</tr>
<tr>
<td></td>
<td>Ovarian cancer/Oophorectomy</td>
<td>2</td>
<td>2A</td>
<td>3A</td>
<td>1</td>
<td>8AA</td>
</tr>
</tbody>
</table>

Table 2. Final consensus scores from ClinGen on the actionability of \textit{BRCA1} and \textit{BRCA2} pathogenic variants.
APPROACHES TO IDENTIFYING BRCA1 and BRCA2 MUTATIONS

The current National Comprehensive Cancer Network (NCCN) guidelines suggest the following individuals are at the highest risk for developing breast and other cancers caused by BRCA1/2 mutations: those who have a known mutation in BRCA1/2, have a known cancer susceptibility gene mutation that is shared among family members, have been diagnosed with either male breast cancer at any age or female breast cancer below age 50, have been diagnosed with triple-negative breast cancer under the age of 60, have had two or more primary breast tumors, have been diagnosed with ovarian or fallopian tube cancer or primary peritoneal cancer at any age, or are of Ashkenazi Jewish descent and have had any hereditary breast and ovarian associated cancers (HBOC) at any age. Current recommendations for identifying people with HBOC-related mutations focus on the individual patient level, relying on the physicians’ determination of the patient’s risk status and subsequent physician recommendation of appropriate testing and treatment. The population health approach, however, focuses on identifying all persons at-risk within a population to enact the most effective cancer prevention measures (Khoury and Galea, 2016). The population health approach still emphasizes individual patient-clinician communication. A prevention model may use two common methods for identifying all individuals at risk for diseases including HBOC: 1) screening all women for common alleles of BRCA1/2 regardless of risk status and current cancer diagnosis or 2) “cascade screening,” which is a systematic method of approaching relatives of symptomatic patients, who are likely to be asymptomatic, but affected, and offering expanded testing to their at-risk relatives.

An annual well-woman exam creates a potential opportunity to identify women who may be at risk for HBOC, allowing physicians to include comprehensive clinical examination, family history intake, breast imaging and offer genetic counseling or testing in their routine gynecological care. However, one problem is that many physicians do not request an expanded family health history that would help them identify individuals at risk for HBOC. Among those that do collect family health histories, a study investigating their use for determining a patient’s cancer risks revealed that physicians reported receiving unclear guidelines on the use of a family health history for prevention, limited time for researching complex genetic histories, and lack of confidence in ability to effectively use the data to guide treatments (Flynn et al., 2010). Further, physicians may not be trained in the proper interpretation of test results, and may not return
negative results to unaffected patients. Similarly, a 2011 study assessing physician’s knowledge of the appropriateness of ordering *BRCA* testing demonstrated that testing occurred more often among obstetricians and gynecologists who had been in practice up to 10 years, and more commonly among more affluent patients, demonstrating a notable gap in equitable testing policies and the potential to order inappropriate and expensive tests by providers who do not have detailed genetics knowledge (Bellcross et al., 2011). While the gap for lower income women who should be tested may be addressed by the Patient Protection and Affordable Care Act’s requirement to reimburse for tests that receive a US Preventive Services Task Force grade of A or B, hospital and insurance policy continues to lag in coverage and reimbursement.

Public health practitioners are focused on finding ways to detect hereditary cancer syndromes and prevent cancer among all individuals. One potential method for improving cancer prevention is through population level screening of all women regardless of family history or current cancer status for *BRCA1/2* mutations with known associations to breast or ovarian cancer incidence. This method has the advantage of potentially identifying many people and their families who would otherwise have gone undetected by traditional methods of screening. By identifying those women at high risk before they develop cancer, they may seek earlier, more comprehensive screening and in certain cases take advantage of preventive prophylactic surgery. Studies investigating previously undetected alleles in Ashkenazi Jewish populations have demonstrated that cancer risks for *BRCA1* and *BRCA2* mutation carriers detected through general population screening are as high as mutation carriers identified through personal or family history evaluations (Gabai-Kapara et al., 2014).

Population-level screening has several disadvantages including the overall cost of the testing, insurance reimbursement for women not at risk for HBOC, and lack of genetics professionals to help patients interpret results. The cost of testing a panel of mutations of known significance can be relatively high, and may still not capture all possible disease-causing alleles. Applied to every woman, the cost of population level screening would be astronomical. The studies that gave rise to population level recommendations are based on prevalence of three disease causing alleles in Ashkenazi Jewish families only, and individuals harboring such a mutation may take medically unnecessary action out of fear, creating additional health concerns as a consequence. Alternatively, by focusing on only a few highly penetrant alleles, individuals who test negative for these alleles may be missed even though they are still at elevated risk of
HBOC. Finally, the US Preventive Services Task Force (USPSTF) has given this approach a Grade D, recommending against it for identification of individuals with genetic susceptibility to HBOC. Considering the extra out of pocket costs, limited study populations from which population level screening recommendations arise, the USPSTF’s grade, implementation of widespread screening is not likely to become an option until the costs of testing decrease.

Alternatively, cascade screening involves offering genetic counseling and testing to at-risk relatives once a disease-causing mutation has been identified in a family member regardless of how the initial mutation was found. Cascade screening takes advantage of a system of cancer identification that is currently in place and adds provider education and awareness components to encourage referral to genetics providers who help patients and their families negotiate difficult diagnoses and help choose appropriate testing, allowing them to make informed medical decisions. Cascade screening augments the current identification system by increasing provider understanding and recognition of genetic counselors role in providing population level prevention mechanisms. Genetics providers take a detailed family health history, assemble a three generation pedigree, and use risk prediction models to identify the closest near relative to an affected patient. Advantages to this approach include limiting the number of individuals that need to be tested, and identification of a specific cancer-causing mutation that family members can then be tested for as cost saving measures. Further, once there is a known mutation, insurance companies will often reimburse at-risk family members for the cost of genetic testing, thereby reducing the out-of-pocket burden.

However implementation of cascade screening suffers from a lack of specialized providers who can provide these services especially in rural areas of the country. Individuals at high-risk may be missed by clinicians and therefore not referred for various reasons including patient unwillingness/inability to be tested, education programs that may not provide the best and most important information to providers, and low recognition of the benefits of genetic testing among non-genetics credentialed providers (George et al., 2015). Further, insurance reimbursement for genetic counseling and testing continues to be problematic due largely to unequal coverage among individual policies and company-wide policies that allow or deny genetic counseling and/or testing insurance claims. Though recommended by the Centers for Disease Control and Prevention’s Office of Public Health Genomics, effective implementation of cascade screening suffers from a lack of genetic counseling professionals who can work with patients to order and
interpret the correct genetic tests as well as hospitals and healthcare institutions that do not have adequate policies for integration of genomics into routine family care. Since cascade screening is dependent upon identifying an individual that has a medically actionable mutation, it is influenced by modes of inheritance, screening, depth, and penetrance of deleterious alleles which may complicate identification of individuals with relevant BRCA1/2 mutations.

INTRODUCTION TO LYNCH SYNDROME

Lynch syndrome, an inherited cancer predisposition syndrome, is one of the most common hereditary cancer syndromes (Sijmons and Hofstra, 2016). It is estimated that Lynch syndrome-causing variants appear in the general population at a rate of 1:370 (Hampel and de la Chapelle, 2011). Lynch syndrome is inherited in an autosomal dominant pattern and is caused by a germline pathogenic variant in one of the mismatch repair (MMR) genes: mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), mutS homolog 6 (MSH6) and PMS1 homolog 2 (PMS2). Lynch syndrome increases the risk of developing many types of cancer at an early age, such as colorectal, endometrial, stomach, and ovarian cancer (Table 4). Individuals with Lynch syndrome also have an increased risk of developing cancer of the hepatobiliary tract, urinary tract, small bowel, brain/central nervous system, and sebaceous glands in the skin (Table 4) (Kohlmann and Gruber, 2014). Despite this, many patients and physicians know very little about Lynch syndrome and its related cancer risks. In this case, genetic counseling can be important for helping individuals understand and mitigate their risks.
### Table 4. Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>MLH1 or MSH2</th>
<th>MSH6</th>
<th>PMS2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Risk</td>
<td>Mean Age of Onset</td>
<td>Risk</td>
</tr>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>52%–82%</td>
<td>44–61 years</td>
<td>10%–22%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>25%–60%</td>
<td>48–62 years</td>
<td>16%–26%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>6%–13%</td>
<td>56 years</td>
<td>≤3%</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>4%–24%</td>
<td>42.5 years</td>
<td>1%–11%</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>1%–4%</td>
<td>50–67 years</td>
<td>Not reported</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>1%–7%</td>
<td>54–60 years</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>3%–6%</td>
<td>47–49 years</td>
<td>Not reported</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>&lt;1%</td>
<td>1%–3%</td>
<td>&lt;50 years</td>
<td>Not reported</td>
</tr>
<tr>
<td>Sebaceous neoplasms</td>
<td>&lt;1%</td>
<td>1%–9%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Pancreas</td>
<td>&lt;1%</td>
<td>1%–6%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>


NOTE: MLH1, mutL homologue 1; MSH2, mutS homologue 2; MSH6, mutS homologue 6; PMS2, postmeiotic segregation increased 2; CNS, central nervous system. SOURCE: This table was referenced from the National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology for Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2016. © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed January 5, 2017. To view the most recent and complete version of the guideline, go online to www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Approximately 140,000 new cases of colorectal cancer (CRC) are diagnosed in the United States each year, with 3 to 5 percent being the result of a Lynch syndrome mutation (Genetics Home Reference, 2016h). CRC is the fourth most common type of cancer, behind breast, lung and bronchus, and prostate cancer, representing 8 percent of all new cancer cases in the United States (NCI, 2016c).

Lynch syndrome was first described in 1895 by Alfred Warthin as he documented the familial clustering of cancer (Lynch et al., 2015). In the 1960s, Henry T. Lynch and Marjorie Shaw assembled pedigrees for several families where cases of CRC were observed across generations. The term cancer family syndrome (CFS) was coined in 1971 for the familial clustering of cancer. Subsequent molecular studies of the genetic aetiology and pathogenesis of familial cancer cases led to the renaming of CFS to hereditary non-polyposis colorectal cancer.
(HNPCC) and Lynch syndrome in 1984 (Lynch et al., 2015). Although HNPCC and Lynch syndrome have historically been used interchangeably, there is current consensus that HNPCC is a misnomer given that the cancer predisposition syndrome increases the risk of developing many types of cancer beyond that of the colon and rectum (Weissman et al., 2011). Muir-Torre syndrome, characterized by skin tumors, and Turcot syndrome, characterized by brain tumors, are antiquated terms used to describe variations of Lynch syndrome.

**Molecular Basis of Lynch Syndrome**

During replication of short, tandem repeat sequences of DNA (microsatellites), it is possible for the two strands of DNA to become misaligned. Misalignment may lead to addition or subtraction of nucleotides that can lead to genome instability, if left unrepaired (Lynch et al., 2015). The MMR pathway is responsible for repairing these single-base-pair mismatches and small insertion or deletion loops (IDLs) that arise during DNA replication. The MSH2 and MSH6 proteins function as a mutation recognition complex that detects single-base-pair mismatches, and together they recruit proteins MLH1 and PMS2 to the damaged DNA (Kohlmann and Gruber, 2014; Lynch et al., 2015). The complex coordinates the activities of other proteins that repair DNA replication mistakes by correcting the mismatch or IDL (Genetics Home Reference, 2016a).

In 2009, Ligtenberg et al. demonstrated that mutations in the *MSH2* gene in some Lynch syndrome cases resulted from germline deletions of the 3’ end of *epithelial cell adhesion molecule (EPCAM)*, a gene that lies upstream of *MSH2* (Ligtenberg et al., 2009). Deletions in the 3’ end of *EPCAM* can lead to transcriptional read-through and downstream methylation of the chromosome. This aberrant methylation can subsequently result in the silencing of the *MSH2* gene (Kohlmann and Gruber, 2014). This change in the *MSH2* gene is referred to as an epimutation because it is a heritable change in gene activity associated with gain or loss of DNA methylation, not DNA mutation (Whitelaw and Oey, 2014). Although *EPCAM* is not an MMR gene, it is located nearby to one and thus has the potential influence the MMR repair process (Table 2). Given the role of *EPCAM* in potentially silencing MMR genes, screening for *EPCAM* deletions associated with *MSH2* epimutations is now also routine in genetic testing for Lynch syndrome (Lynch et al., 2015).
Table 5. Summary of Genes Associated with Lynch Syndrome.

Four mismatch repair genes (MLH1, MSH2, MSH6, PMS2) and the EPCAM gene are most strongly associated with Lynch syndrome-cancers. NOTE: MLH1, mutL homologue 1; MSH2, mutS homologue 2; MSH6, mutS homologue 6; PMS2, postmeiotic segregation increased 2; EPCAM, epithelial cell adhesion molecule.

SOURCE: Data used to generate this table taken from Kohlmann and Gruber (2014).

Germline mutations or epigenetic changes that inactivate MMR genes may prevent the production of MMR proteins or lead to abnormally short, altered or inactive versions of the proteins (Genetics Home Reference, 2016b). If MMR proteins are inactive, the MMR process may be defective, and thus unable to recognize and repair DNA replication errors. Consequently, the errors are replicated and permanently fixed in the genome (Lynch et al., 2015). When MMR is defective, somatic mutations may accumulate at an accelerated rate in cells. This may give rise to a phenotype denoted as high microsatellite instability (MSI-H) where 30% or more of a panel of microsatellites is mutated (Boland and Goel, 2010).

The MSI phenotype appears in 77 to 89 percent of tumors in patients with Lynch syndrome, thus it has become a useful marker to identify Lynch syndrome (Hampel, 2016). Lynch syndrome is definitively diagnosed when a germline or epimutation affecting an MMR gene is identified (Lynch et al., 2015). Thus, MSI analysis is the first step in identifying patients with Lynch syndrome. Alternatively, immunohistochemical (IHC) staining of the MMR proteins can be used to identify patients who are more likely to have Lynch syndrome and this test pinpoints which one to two of the MMR genes is likely mutated based on the proteins that are missing in the tumor (Boland and Goel, 2010).
Diagnosing Lynch Syndrome

There are three main models for diagnosis of Lynch syndrome that can highlight how early detection of Lynch syndrome may lead to better prognosis and survival rates for associated cancers (Figure 2). Traditional genetic counseling identifies individuals who are at risk of having Lynch syndrome based on personal or family history of cancer (Hampel, 2016). The Amsterdam I Criteria were developed in 1991 by the International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer as the first standardized guide to study and diagnose Lynch syndrome (Vasen et al., 1991). The criteria focused on identifying individuals with a strong family history of colorectal cancer at a young age of onset. In 1999, the Amsterdam Criteria were updated and published as the Amsterdam II Criteria to take into account new knowledge that Lynch syndrome could also be associated with extracolonic cancers (Vasen et al., 1999).

Lynch syndrome identification was revolutionized in 1993 when MSI was recognized as a key characteristic of Lynch syndrome tumors. The National Cancer Institute hosted a meeting and subsequently developed the Bethesda Guidelines in 1997, which took into account the clinical significance of MSI (Rodriguez-Bigas et al., 1997). Revised in 2004, the Bethesda Guidelines provide recommendations about which patient’s tumors should undergo MSI or IHC screening to identify Lynch syndrome (Umar et al., 2004).

Figure 2. Models to identify individuals with Lynch syndrome.

The models to diagnose Lynch syndrome facilitate the study and prevention of Lynch-syndrome associated cancers. The models have developed, and continue developing, as the biological, technological and sociological dimensions of Lynch syndrome are better understood. NOTE: Ls, Lynch syndrome; MSI, microsatellite instability; MMR, mismatch repair; IHC, immunohistochemical testing. SOURCE: Data used to generate this table taken from Hampel (2016).

The guidelines from traditional genetic counseling are useful as they provide uniform terminology and allow for comparison of study results in the literature (Figure 3). However, the different sets of criteria are difficult to apply in practice because they can be conflicting, they
require significant amounts of time from physicians, and they involve multiple steps (Hampel, 2016).

Lynch syndrome can also be identified through universal tumor screening, or reflex testing. This method involves universal tumor screening of all newly diagnosed colorectal cancer patients at the time they are diagnosed. Universal tumor screening tests for MSI or the presence of the MMR proteins (MLH1, MSH2, MSH6 and PMS2) through IHC stains. Tumors that exhibit MSI and are the result of Lynch syndrome may also require different treatment that could potentially result in a better outcome (Le et al., 2015). Future pharmacogenetics research may help to explain the relationship between an MMR gene mutation and the corresponding response to a chemotherapy or chemoprevention. This may be useful in order to better tailor treatment for patients with Lynch syndrome-associated cancers (Lynch et al., 2015). Universal tumor screening can be challenging because genetic counseling and follow-up genetic testing may not always be available, and health literacy barriers may prevent patient engagement in clinical cancer genetic services (Tomiak et al., 2014).

Lastly, Lynch syndrome can be identified through cascade testing. Cascade testing entails offering genetic counseling and testing to all the relatives of an individual diagnosed with Lynch syndrome starting with those most likely to have the mutation (first degree relatives) and moving on to more distant relatives only if their parent or sibling is found to have the familial mutation. If the family member with the mutation is willing to share their information, following the mutation through the family may be beneficial because the germline variant responsible for Lynch syndrome in the family is already known and intensive surveillance can lead to early diagnosis and prevention of cancer without additional panel testing (Hampel, 2016). Additionally, as an increased number of relatives receive genetic counseling and testing, universal tumor screening for Lynch syndrome may become increasingly cost-effective (Hampel, 2016). However, cascade testing relies on individuals sharing their genetic test results with their relatives and referring them to genetic testing. In a recent study of individuals who met the Amsterdam II Criteria, Patel et al. (2016) found that while 63 percent were aware of genetic testing for colorectal cancer, only 31 percent had been advised by a physician to undergo genetic counseling and even fewer had undergone testing themselves. Other socioeconomic, cultural, and religious factors may play into the decision to undergo testing or share information with at-risk family members, all of which can be potential barriers to implementation.
Lynch syndrome-associated cancers include colorectal, endometrial, stomach, ovarian, pancreas, ureter or renal pelvis, biliary tract and brain (usually glioblastoma) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel. Microsatellite-high (MSI-H) in tumors refers to changes in two or more of the five U.S. National Cancer Institute-recommended panels of microsatellite markers. MSI-H histology refers to the presence of tumor-infiltrating lymphocytes, Crohn disease-like lymphomatous reaction, mucinous or signet-ring differentiation, or medullary growth pattern. For the Bethesda Guidelines, there was no consensus among the Workshop participants on whether to include the age criteria in guideline 3. Participants voted to keep less than 60 years of age in the guidelines.

NOTE: CRC, colorectal cancer; FAP, familial adenomatous polyposis; LS, Lynch syndrome; MSI, microsatellite instability; MSI-H, microsatellite instability-high.

SOURCE: Data used to generate this table was adapted from Lynch et al. (2015).

ClinGen’s Recommendation for Lynch Syndrome

ClinGen’s AWG also reviewed the evidence of clinical actionability for individuals with another hereditary cancer disorder, Lynch syndrome. Lynch syndrome is caused by the inheritance of a defective mismatch repair gene product and is characterized by an increased risk of colorectal cancer (CRC) and other types of cancer including endometrial, gastric, urinary tract, brain, and ovarian. Microsatellite instability is observed in a majority of Lynch syndrome-associated CRC tumors, consistent with the loss or dysfunction of mismatch repair gene products. Lynch syndrome is the most common form of heritable CRC and is the cause of 1-5% of all CRC and 2% of all endometrial cancer cases. Lynch syndrome-associated CRC appears earlier in life than sporadic CRC, and is often more aggressive.

ClinGen assessed the evidence pertaining to the clinical actionability of Lynch syndrome-causing variants in five genes, \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2}, and \textit{EPCAM}. The AWG reviewed several interventions that are aimed at preventing CRC and reducing mortality in Lynch
syndrome patients. Specifically, these included risk-reducing surgery (e.g., prophylactic hysterectomy and salpingo-oophorectomy), aspirin regimens, surveillance mechanisms (e.g., colonoscopies, urinalysis, and transvaginal ultrasound with endometrial biopsy), genetic testing/screening of first degree family members, and lifestyle factors (e.g., smoking and obesity).

ClinGen went on to score 3 specific Lynch syndrome-associated outcome/intervention scenarios: (i) surveillance for CRC; (ii) surveillance for endometrial cancer, and (iii) risk-reducing surgery for endometrial cancer. The group cited evidence from a systematic review showing that regular colonoscopies led to a significant reduction in Lynch syndrome-associated CRC incidence, earlier detection of tumors, and a reduction in overall mortality. Similarly, there is a strong body of evidence that indicates that transvaginal ultrasound with endometrial biopsy may detect cancers and premalignant lesions of the endometrium. Surveillance for colorectal cancer in patients with Lynch syndrome received an actionability score of 10AA from ClinGen, while surveillance for endometrial cancer received a score of 8AA. Lastly, risk-reducing surgery to prevent endometrial cancer in those affected by Lynch syndrome received an actionability score of 9AB. The full list of consensus scores from ClinGen are listed in Table 3 below.

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>Outcome/Intervention</th>
<th>Severity</th>
<th>Likelihood</th>
<th>Effectiveness</th>
<th>Nature of the intervention</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>Colorectal cancer/ Surveillance</td>
<td>2</td>
<td>3A*</td>
<td>3A</td>
<td>2</td>
<td>10AA</td>
</tr>
<tr>
<td>MSH2</td>
<td>Endometrial Cancer/ Surveillance</td>
<td>2</td>
<td>3A*</td>
<td>1A</td>
<td>2</td>
<td>8AA</td>
</tr>
<tr>
<td>MSH6</td>
<td>Endometrial Cancer/ Risk-reducing surgery</td>
<td>2</td>
<td>3A*</td>
<td>3B</td>
<td>1</td>
<td>9AB</td>
</tr>
</tbody>
</table>

EVIDENCE ASSESSMENT OF LYNCH SYNDROME SCREENING BY EGAPP

The Evaluating Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG) was created as a CDC-hosted project to test the application of USPSTF-like evidence-based recommendations processes to genomic testing. In 2008, the EWG decided to evaluate the evidence supporting Lynch Syndrome testing in order to improve colorectal cancer outcomes. Lynch Syndrome, previously called hereditary non-polyposis colon cancer (HNPCC), was first described in a family in 1913 and further evaluated in two additional families in 1966. Family linkage studies and subsequent molecular research identified the group of cancer susceptibility genes associated with Lynch Syndrome (MHS2, MLH1, MSH6, PMS2). Using methodology similar to the USPSTF, the EWG used an analytic framework to guide a systematic evidence review to evaluate the strategy of offering genetic testing for Lynch syndrome to patients with newly diagnosed CRC in order to reduce mortality and morbidity family members. If the patient tested positive for Lynch syndrome, genetic testing of relatives would provide information that would guide enhanced cancer surveillance resulting in improved outcomes. The chain of evidence for this strategy, while indirect, was adequate for the EWG to conclude that the mortality and morbidity benefits of testing the patient and if indicated, family members, with enhanced cancer surveillance in those with Lynch syndrome, outweighed the harms. The EWG recommended this Lynch syndrome screening strategy.

Based on this conclusion of net benefit based on the outcomes of a systematic evidence review, Lynch syndrome testing for newly diagnosed CRC patients was identified as a Tier 1 genetic test, suitable for consideration that its use be supported by public health. This recommendation has unique features that make implementation challenging under our current health care payment and delivery systems. While new research provides support for testing the patient to help guide therapy, there was no directed benefit to the patient when EGAPP made the original recommendation. It was likely that some or all relatives would have a different source of health insurance (or no health insurance) and so information from once insurer/provider would need to direct the care provided and covered by others. These characteristics make this genetic testing strategy particularly suited for public health support, where working in the gaps between systems underlies the well-established methods used in outbreak investigations and communicable disease contact tracking and treatment.
LYNCH SYNDROME CASCADE SCREENING AND PUBLIC HEALTH

The U.S. public health community has called for more focus on chronic diseases, such as cancer. One objective of Healthy People 2020 is to “Increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic testing to identify Lynch syndrome (or familial colorectal cancer syndromes)”.

Public health control of infectious outbreaks has achieved great success through a process of index patient identification followed by contact elicitation to identify, evaluate, and treat exposed individuals. Advantages include efficient identification of individuals at highest risk, cost-effectiveness, and the ability to apply standard operating procedures such as informed consent to communicate sensitive health information for the benefit of others. ‘Cascade’ genetic screening uses an analogous approach of proband identification and family member contacting, evaluation, and management. In essence, the family is the ‘outbreak,’ but the transmission is genetic, not infectious.

Cascade genetic screening fits within an existing public health framework, the CDC’s health impact pyramid\(^9\) as a clinical intervention (Bowen et al., 2012). While cascade genetic screening is the norm in genetics practice, its implementation in the public health sphere has unrealized potential. As an activity near the top of the pyramid, cascade genetic screening requires relatively more individual effort for relatively less population impact. However, the high yield of case finding (particularly for a younger, unscreened population) and the availability of effective Tier 1 interventions mitigate against increased effort.

The cascade approach depends on effective methods to identify index cases (the family proband) with a diagnosis of cancer due to Lynch syndrome. Index case identification uses various combinations of tests on tumor tissue and germline (blood): immunohistochemistry, microsatellite instability, \textit{BRAF, MLH1} promoter methylation, and comprehensive mismatch repair gene (\textit{MSH2, MLH1, MSH6,} and \textit{PMS2}) testing. Screening algorithms employing these methods efficiently identify index cases and show that the prevalence of hereditary cancer is relatively high: 1 in 35 patients with colorectal cancer and 1 in 40 patients with endometrial carcinoma has Lynch syndrome (Bellcross et al., 2012).

\(^9\)The health impact pyramid applied to tier 1 genomics applications can be viewed at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4748713/figure/F1/ (accessed February 14, 2017).
The efficiency of cascade genetic screening also depends on the number of at-risk relatives identified per index case. Screening programs at Ohio State University resulted in the identification of about 3 relatives per proband (Hampel et al., 2008; Hampel et al., 2005). The efficiency of case-finding is markedly increased at this step based on relatedness to the proband (e.g., 50 percent risk for first-degree relatives). In addition, the cost of genetic testing for relatives is much lower than for the proband because analysis is targeted to the familial mutation rather than beginning with tumor testing followed by comprehensive germline mismatch repair gene testing. Decision analyses have found modeled screening programs to be cost effective, dependent on the laboratory screening algorithm used, and sensitive to the number of relatives of the program that are identified (Gudgeon et al., 2011; Mvundura et al., 2010).

Universal screening – Lynch syndrome index case identification in populations – has been implemented regionally by more than 30 health systems and on a statewide basis in Ohio (Bellcross et al., 2012; Hampel et al., 2008; Pearlman et al., 2016). Some experts say the point of readiness has been reached for universal Lynch syndrome screening across the United States (Modell et al., 2016).

The successful adaptation of universal Lynch syndrome screening into public health systems depends upon solving several implementation challenges (Khoury et al., 2012). While cascade testing might be implemented within public health systems, care will be carried out in health systems. Although the professional community of Lynch syndrome experts seems ready, a ‘willing constituency’ of health professionals and advocates is needed to carry out a truly universal program (Modell et al., 2016). However, education and awareness are lacking among non-experts, extending beyond clinicians and patients to healthcare system administrators, payers, and state and national public health entities and policy makers (Bellcross et al., 2012).

The genetic cascade model places responsibility for contacting positive screens with a genetic counselor (Gudgeon et al., 2011) – a role that can be adapted to public health systems. However, the rate of testing uptake by the proband and close relatives is an important determinant of the efficiency of cascade screening and is influenced by relationships within families and with healthcare providers. Best practices for communications that facilitate universal screening remain unclear.

In addition, since family members are often widely dispersed, care must be bridged across state health systems and private payers. Health insurance barriers to genetic testing may
limit genetic testing, and coverage for medical management is not assured. These implementation barriers might be less critical in states with a large multigenerational presence such as Utah or Pennsylvania. A multistage plan for U.S.-wide implementation might begin with additional pilots in such states, learning from the Ohio state example and addressing known barriers that might be solved on a statewide basis.

While many potential barriers remain in adapting cascade genetic testing to a public health model, multilevel factors have been elucidated and a research agenda has been proposed (Bellcross et al., 2012; Khoury et al., 2012).

**MODELING STRATEGIES AND EVIDENCE REQUIREMENTS FOR GENOMIC TESTING IMPLEMENTATION IN PUBLIC HEALTH SETTINGS**

The past two decades have witnessed the rapid translation of genomic discoveries from the lab to clinical and public health settings, including identification of rare but highly penetrant gene mutations that increase the risk of developing cancer, including mutations in *BRCA1* and *BRCA2* genes for breast and ovarian cancer and DNA mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*) associated with Lynch syndrome. In the recent past, panels of multiple common but low penetrance genes associated with breast cancer risk (“polygenic risk”) have also been identified. These advances may hold the potential to personalize cancer screening to maximize population health benefits and minimize harms by targeting those most likely to benefit if polygenic risk is predictive enough to stratify screening. However, the ultimate impact of initiatives to incorporate genomic advances into public health initiatives will depend on many factors including consideration of competing demands for resources, the population makeup and their prevalence of genomic risk (e.g., Ashkenazi Jewish, Mormon, Spanish ancestry Latinos), public uptake of testing, and health behaviors adapted in response to test results. For instance, if consumers obtain polygenic risk testing but do not use the information to tailor their screening regimens, then the promise of this new information may not be realized at the population level.

Decision making about implementation of public health programs could be facilitated by having high-quality data about the impact of dissemination of various genomic testing strategies to the population of interest under differing real-world strategies that consider the aforementioned factors. Unfortunately, there is often limited information on long-term outcomes,
direct comparisons among relevant alternative strategies, or comparisons incorporating individual or population preferences. Simulation modeling can be a useful research method to synthesize existing data and compare a broader range of alternatives than can be feasibly included in clinical trials or other studies (Moss et al., 2006; Nystrom et al., 2002; Tabar et al., 2000). Modeling can also determine a price point for surveillance tests following from genomic testing and how many individuals should be screened for a test to be considered cost-effective (Barzi et al., 2015; Knudsen et al., 2016).

The Cancer Intervention and Surveillance Modeling Network (CISNET) was launched by the National Cancer Institute in 2000 to provide public health decision makers with tools for synthesizing evidence to determine the impact of alternative cancer control strategies on US population incidence and mortality. The CISNET models have been used to evaluate a wide variety of public health cancer prevention and control strategies (Berry et al., 2005; Cronin et al., 2006; Knudsen et al., 2016; Lansdorp-Vogelaar et al., 2009; Mandelblatt et al., 2013; Mandelblatt et al., 2009; Mandelblatt et al., 2016; Naishadham et al., 2011; Near et al., 2012; van Ravesteyn et al., 2015; Vogelaar et al., 2006; Zauber et al., 2008) including several genomic testing interventions. One unique feature of CISNET is the use of a collaborative modeling approach where two or more groups have independently developed models, each with different structures and assumptions, but share a common set of input parameters, strengthening the inferences about the range of results (NCI, 2016a). The following narrative summarizes examples of how CISNET and other modeling has been used to evaluate programs using genomic testing for breast and colorectal cancer, and highlights the types of data needed to model outcomes expected in specific service area populations.

High Penetrance, Low Prevalence Mutations

In breast cancer, modeling has been used to determine the most efficient methods to identify individuals who should be tested for BRCA mutations, compare methods (and costs) of targeting genetic services (Lawrence et al., 2001; Schwartz et al., 2014), and understand the downstream impact of testing on population incidence and mortality. Models like BRCAPRO (Berry et al., 1997; Claus et al., 1998; Parmigiani et al., 1998) have been used to estimate the risk of an individual having a BRCA mutation, facilitating identification of those at highest prior probability of having a mutation, and thereby increasing the efficiency and yield of testing
programs. Models have also been used to compare the outcomes of different testing strategies. For instance, in the UK one model compared targeting all Ashkenazi Jewish women in the population versus only those with a family history of one or more first degree relative with breast or ovarian cancer. The investigators found that population screening of Ashkenazi Jewish women, who have higher rates of mutations than the general population, prevented more cancers and saved health care costs compared to only offering testing to those with a family history (Manchanda et al., 2015). In a general, non-Ashkenazi Jewish population, screening has not been found to be cost-effective. However, modeling has not been used to evaluate panel testing of BRCA mutations plus other more common but moderate risk mutations (e.g., CHEK2 mutations). This could be an interesting area for future modeling if public health programs are interested in this type of testing approach.

In terms of strategies for targeting services, one UK model determined that the most efficient (and cost-efficient) approach to delivery of BRCA testing was to identify unaffected relatives of cancer patients known to have a BRCA mutation rather than doing public outreach. Based on this result, the authors suggested that BRCA testing be integrated into oncology services rather than via public outreach (Slade et al., 2016).

CISNET models have also been used to evaluate the downstream effects of preventive management strategies on life expectancy of known BRCA mutation carriers, (Sigal et al., 2012) the costs and outcomes of adding MRI to mammography screening of mutation carriers, (Heijnsdijk et al., 2012; Plevritis et al., 2006; Saadatmand et al., 2013) and to develop online tools to guide decisions for BRCA mutation carriers (Schackmann et al., 2013). A non-CISNET model examined cancer incidence and survival, determining that prophylactic removal of the breasts and ovaries at age 25 provided similar survival as oophorectomy at age 40 and annual breast MRI screening from ages 25-69 (Kurian et al., 2012). In conjunction with professional recommendations, such results could be useful in setting priorities for local clinical practice policies.

Models have also been used to project the impact of population use of genetic testing to identify individuals at high risk of colorectal cancer. Lynch syndrome, for instance, accounts for approximately 3% of all colorectal cancers (Cunningham et al., 2010). Prediction algorithms such as PREMM\textsubscript{1,2,6} estimate the probability that an individual carries the most common gene mutations found in patients with Lynch syndrome (Ladabaum et al., 2011). Identifying Lynch
syndrome allows targeted colorectal cancer screening and care for the individual and detection and/or preventative care for first-degree family members. Microsimulation modeling of varying screening strategies for Lynch syndrome populations have found that general population screening strategies are not cost-effective. However, using predictive models in probands, followed by screening of those with a high probability of having Lynch syndrome and monitoring for colorectal cancer, is cost-effective (Barzi et al., 2015; Ladabaum et al., 2011).

**Low Penetrance, Common Mutations**

Discovery of multiple common low penetrance polymorphisms that increase risk of cancer (polygenic risk) has the potential to improve risk prediction beyond that based on non-genetic risk factors for breast cancer (Shieh et al., 2016). Thus, results of testing entire populations for polygenic risk could be used to stratify screening strategies based on risk, potentially improving the effectiveness and lowering the costs of screening (Chowdhury et al., 2013; Pashayan et al., 2013). However, adding polygenic risk testing to public screening programs would also increase the resources needed, including genetic testing and counseling services.

One CISNET colorectal cancer model estimated lifetime costs and effects of colonoscopy screening strategies targeted by risk level compared to the current use of uniform screening strategies for all individuals. The results indicated that risk-stratified screening had lower costs than uniform screening (exclusive of polygenetic test costs), while providing commensurate benefit. Future discovery of additional common genetic variants, combined with very high rates of public uptake, could theoretically increase the benefits and cost-effectiveness of risk-stratified screening if polygenetic testing remained reasonably affordable (Naber, 2016). Additionally, to maintain cost-effectiveness, individuals would need to agree to use screening based on their risk scores. Moreover, results of the model study assumed perfect adherence to screening. Future studies are needed to model potential health impact of screening strategies in scenarios involving assumptions that more closely approximate real world conditions of uptake and adherence.

**Data and Evidence Needed to Integrate Cancer Genomic Testing into Public Health Practice**

Modeling the population impact of alternative strategies for deployment of genomic testing in public health settings will require population data and evidence for each portion of care
delivery (Table 6). For instance, for each strategy modeled, it will be necessary to have data on the expected rates of uptake, especially among subgroups with less traditional access to genetic services. Of note, in one public health care setting, 96 percent of eligible low income, minority women agreed to counseling and testing for *BRCA* mutations (Komenaka et al., 2016). However, there is little data on uptake of genomic test offering or downstream actions based on test results among diverse populations. Models can also provide a variety of results (Table 7) which can be tailored to the needs of a particular public health agency and setting.
<table>
<thead>
<tr>
<th>Potential Data Sources</th>
<th>Population demographics</th>
<th>Age structure by race/ethnicity and gender</th>
<th>National Center for Health Statistics; CDC; State Department’s of Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population prevalence of mutations</td>
<td>Expected rate of mutations by race/ethnicity and gender</td>
<td>Literature</td>
<td></td>
</tr>
<tr>
<td>Uptake of mutation testing</td>
<td>Rate of uptake of testing and counseling</td>
<td>Literature</td>
<td></td>
</tr>
<tr>
<td>Genomic test performance</td>
<td>Analytical and clinical validity</td>
<td>Literature</td>
<td></td>
</tr>
<tr>
<td>Screening behaviors</td>
<td>Types of screening and rates among tested and untested groups by mutation results or risk.</td>
<td>NHIS; CDC; local BRFSS data</td>
<td></td>
</tr>
<tr>
<td>Prophylactic surgery</td>
<td>Rates of oophorectomy and mastectomy by age and race/ethnicity</td>
<td>Literature or local registries</td>
<td></td>
</tr>
<tr>
<td>Preventive drugs (e.g., tamoxifen for BRCA carriers)</td>
<td>Rates of use by age, race/ethnicity and mutation status</td>
<td>Literature</td>
<td></td>
</tr>
<tr>
<td>Treatment rates</td>
<td>By age, stage, and type of cancer</td>
<td>Published literature; registries</td>
<td></td>
</tr>
<tr>
<td>Cancer/disease survival</td>
<td>By age, race/ethnicity, molecular cancer subtype, treatment, and mutation status</td>
<td>SEER or local registry</td>
<td></td>
</tr>
<tr>
<td>Other cause survival</td>
<td></td>
<td>National Center for Health Statistics; CDC; State Department’s of Health; SEER [for cancer]</td>
<td></td>
</tr>
<tr>
<td>Utilities for health outcomes</td>
<td>Preferences for health states</td>
<td>Published literature or primary data collection</td>
<td></td>
</tr>
<tr>
<td>Costs</td>
<td></td>
<td>Medicare and Medicaid</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Exemplar Data Needed to Model the Impact of Genomic Testing in a Specific Service Area Population
<table>
<thead>
<tr>
<th>Genetic testing (and counseling)</th>
<th>Tested for mutations</th>
<th>Not tested for mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy A</td>
<td>Strategy B</td>
<td></td>
</tr>
<tr>
<td>Screening tests obtained</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening test results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• True positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• False positives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• False negatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• True negatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of biopsies for the number of false positives (unnecessary biopsies)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional imaging or testing for false positives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preventive surgeries obtained (if applicable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive cancers detected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-invasive cancers detected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types cancer diagnosed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• By Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• By biomarkers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Deaths (of life years and QALYS) from disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Deaths from other causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Deaths from all causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 7. Exemplar Model Outcomes**

In addition to modeling studies, decisions regarding implementation of genomic knowledge in public health will require a high level of broad-based primary evidence supporting clinical utility (from clinical and population-based studies, and their synthesis via systematic review and meta-analysis). Such evidence will help to ensure that the anticipated health impact and net health benefits are fully realized when the knowledge is used in health care practice (Rohrbach et al., 2006; Westfall et al., 2007). For instance, first it is necessary that there is evidence of an association between genetic markers and the health outcome of interest to identify
candidate applications. Next, clinical validity needs to be determined. After this evidence is conformed, then modeling, trials, or demonstration projects have the ability to demonstrate that a program using genomic information provides better outcomes than one that does not.

Thus, public health benefits can be expected when the efficacy of the intervention(s), the predictive ability of the genetic test, and the strength of the genetic associations are large enough for the genomic application to have health impact. This will be especially important for common but low risk polymorphisms. Also, these characteristics (large enough efficacy, predictive ability and genetic associations) should be replicated in multiple studies to confirm their generalizability.

**Summary**

Implementation of genomic applications in the public health arena requires sufficient evidence to support use, building upon the expectation that use of the genomic information will have a population health impact. When there is sufficient evidence to suggest use of a genomic test, modeling can be used to test the impact of alternative delivery scenarios on the population of interest. Microsimulation modeling done to date suggests that targeted screening on the basis of familial and genetic risk can decrease cancer mortality with few added resources. Thus, modeling can be useful to local and national public health agencies as they seek to determine whether to implement genomic testing, whom to target for testing, and how to structure services and plan for the downstream post-testing health care needs of the population. Modeling can also identify the likely drivers of program efficiency and cost-effectiveness. Information about the potential deaths averted from having genomic risk data could be useful in public communication to enhance targeted testing and/or launch lifestyle or other behavioral change campaigns for those with high disease risk based on genomic results.

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References


Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer. *JAMA Oncol.*


