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REVIEW

Genetic evaluation and testing for hereditary forms of cancer in the era of next-generation sequencing

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ABSTRACT

The introduction of next-generation sequencing (NGS) technology in testing for hereditary cancer susceptibility allows testing of multiple cancer susceptibility genes simultaneously. While there are many potential benefits to utilizing this technology in the hereditary cancer clinic, including efficiency of time and cost, there are also important limitations that must be considered. The best panel for the given clinical situation should be selected to minimize the number of variants of unknown significance. The inclusion in panels of low penetrance or newly identified genes without specific actionability can be problematic for interpretation. Genetic counselors are an essential part of the hereditary cancer risk assessment team, helping the medical team select the most appropriate test and interpret the often complex results. Genetic counselors obtain an extended family history, counsel patients on the available tests and the potential implications of results for themselves and their family members (pre-test counseling), explain to patients the implications of the test results (post-test counseling), and assist in testing family members at risk.

KEYWORDS

Genetic counseling; genetic testing; informed consent; high-throughput nucleotide sequencing; neoplastic syndromes, hereditary

Introduction

An estimated 5% to 10% of cancers have a hereditary component1. There are over 35 hereditary cancer susceptibility syndromes, many with overlapping phenotypes. The use of next-generation sequencing (NGS) in the setting of a hereditary cancer clinic provides the opportunity to test for a growing number of cancer susceptibility genes in an efficient and cost-effective way. It is now possible to evaluate the entire differential diagnosis for a patient and family with a single laboratory specimen. This decreases the time to a potential diagnosis and reduces testing fatigue for patients, families and providers2,3. The knowledge gained through the use of NGS is increasing our understanding of the natural history of hereditary cancer syndromes and contributing to the expanding phenotypes associated with individual cancer susceptibility genes4,5. While the ability to test for multiple cancer susceptibility genes at one time is attractive and even exciting, this new technology brings challenges that must be addressed in the pre-test genetic counseling session.

Genetic counseling in oncology

Genetic counselors are professionals with a Master’s degree entailing extensive training in the medical, laboratory, and research applications of genetics. Genetic counseling training also includes the study of counseling principles related to risk communication, facilitated decision-making, the impact of chronic illness, bereavement, cultural sensitivity and family communication of genetic risk. Genetic counseling is defined by the National Society of Genetic Counselors (NSGC) as "the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease"6.

Genetic counseling is a key component of the evaluation for possible hereditary cancer risk. The importance of genetic counseling in the oncology setting is acknowledged by the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), American College of Medical Genetics and Genomics (ACMG), and the U.S. Preventative Services Task Force (USPSTF)3,7-9. A comprehensive genetic evaluation includes assessment of personal and family history for features consistent with a hereditary cancer syndrome, review of available medical records (typically pathology and imaging reports, results of
genetic testing -somatic or germline- on the patient and affected family members, consultation notes and physical exam findings), deriving a differential diagnosis, and discussion of available testing options with coordination of testing if appropriate and available. Genetic counseling also involves education about the natural history of the condition, inheritance patterns, implications for family members and review of medical management recommendations for the individual and family regarding cancer screening and prevention. The possibility of environmental contributors to cancer risk must also be ascertained.

Established referral criteria for genetic counseling and risk assessment for a possible hereditary cancer susceptibility are1,10,12,13: (1) patients or first-degree relatives (parents, full-siblings, children) who meet established criteria for a hereditary cancer syndrome; (2) relatives with cancer or related health issues indicative of hereditary cancer syndrome must be on the same side of the family; (3) close relatives considered for evaluation of hereditary cancer syndromes are first- and second-degree relatives (aunts, uncles, nieces, nephews, half-siblings, grandparents, grandchildren); (4) individuals with a personal cancer diagnosis or other features of hereditary cancer susceptibility syndrome are most informative for genetic testing (e.g. a mother diagnosed with breast cancer at age 40 who is now 54 over her daughter who is 24 and concerned about her breast cancer risk); and (5) individuals with a known family history of a mutation in a cancer susceptibility gene.

To assist practitioners with the identification of individuals appropriate for genetic counseling referral, the ACMG and NSGC developed practice guidelines for cancer predisposition assessment. The guidelines are organized both by tumor type and as a list of common cancer predisposition syndromes.

Most hereditary cancer conditions are inherited in an autosomal dominant pattern. A three- to four generation pedigree is a critical tool in tracing the history of cancer through a family. Particular attention should be paid to age of onset of cancer, primary cancer site, current ages and ages at the time of death for all family members. Ethnicity of both maternal and paternal lineages should be recorded. Limitations to family history analysis such as limited family structure, unknown medical information due to lack of contact or adoption, the early death of family members due to non-cancer related issues, and the possible masking of sex-influenced cancers must be taken into account. Mutations may be de novo, as in the case of 10%-25% of individuals with APC gene mutations and 20% of individuals with VHL mutations. Although less common, the possibility of recessive inheritance in the cases of MUTYH mutations or Constitutional Mismatch Repair Deficiency syndrome must also be considered.

**Genetic testing for cancer susceptibility**

Genetic counseling and risk assessment for hereditary cancer susceptibility does not always lead to genetic testing. Not all individuals wish to pursue testing and not all family and medical histories warrant testing. Genetic testing should be offered however, when the following conditions are met: (1) the individual has a personal or family history suggestive of a hereditary cancer syndrome; (2) test results can be adequately interpreted; (3) test results will influence the medical management of the individual or their family members; and (4) testing is accompanied by informed consent.

Although risk assessment tools exist to estimate the likelihood that a patient may carry a mutation in a particular cancer susceptibility gene, there is no absolute threshold that must be met to consider genetic testing. While risk models can be used as guidelines, it is the clinical judgment of the oncology and genetics care providers that should determine the appropriateness of genetic testing in a given situation. This is of particular importance in risk assessment for non-white populations as most models were validated in populations with European ancestry.

Individuals considering genetic testing for hereditary cancer should be informed about the potential risks, benefits and limitations of genetic testing relevant to their situations. Genetic testing in the oncology setting in the absence of adequate pre- and post-test genetic counseling by a qualified genetic professional has been shown to result in misinterpretation of test results leading to inaccurate assessment of cancer risks and inappropriate medical management. Individuals undergoing testing without genetic counseling may not be fully informed of the potential implications of test results for them or their family members, resulting in psychological distress when the cancer risks and management recommendations are made known. Furthermore, providers without experience in oncology genetics training have ordered the wrong test or unnecessary testing leading to misuse of healthcare dollars. In some cases, erroneous testing and subsequent misinterpretation of results has led to an incorrect recommendation to expand or reduce cancer screening or risk reduction measures. For specific case examples see reviews of Bonadies and Brierley.

The process of informed consent for genetic testing for inherited cancer susceptibility is well described. In
order for an individual to give fully informed consent for genetic testing, the following educational elements must be provided: (1) information on the specific gene(s) or gene mutations(s) being tested including a description of associated cancers and other potential health risks; (2) inheritance patterns associated with genes being tested. Individuals should understand risks to their children and other family members; (3) implications of possible test results: positive, negative, or uncertain [variant of unknown clinical significance (VUS)]. Interpretation of each result in the context of the patient’s personal and family histories should be discussed as clinical impact of result will vary depending on whether or the individual tested has a personal diagnosis of cancer and if testing was for a known familial mutation. Individuals should understand the possibility that test results may not be informative in defining their cancer risk; (4) use of test results for medical management for the individual and their family members. Review of options and limitations for cancer surveillance and risk reduction based on possible test results; (5) psychological impact of testing including the potential risks and benefits of testing as they relate to the individual and their family. Discussion should include potential anxiety related to test results, concern for self and family members, and feelings surrounding the possibility of uninterpretable results; (6) technical aspects of testing-estimated time to results, accuracy of methods used, limitations of the technology in detecting certain mutations; (7) laboratory policy on the use of de-identified DNA following test completion; (8) economic considerations-individual cost of proposed testing; (9) plan for disclosure of results and confidentiality of results; (10) potential risks and protections related to insurance and employment discrimination on the basis of genetic test results; and (11) laboratory policy regarding re-analysis of VUS as more information is learned.

Table 1 provides examples of genes that may be included in each group.

| Penetrance | Genes |
|------------|-------|
| Low or unknown risk | BRCA1, BRCA2 |
| Moderate risk | TP53, STK11 |
| High risk | APC, CDH1 |

There are two major categories of NGS cancer panels. The first, with arguably the most clinical utility, includes panels that are specific to a tumor type or organ system. This type of panel is useful in the evaluation of families with multiple cases of the same type of cancer who may have previously tested negative for the most common hereditary risk factors or in individuals for whom the differential may be broad2. Consider the case of a patient who presents with 10 or more colon adenomas at age 40 where possible diagnoses include Lynch syndrome, attenuated familial adenomatous polyposis (AFAP) and MUTYH-associated polyposis.

The second category of NGS panels is pan-cancer panels that include a variety of cancer types. Pan-cancer panels may focus on common cancers including genes for breast, ovarian, uterine, colorectal, gastric, and pancreatic cancers and melanoma. More extensive pan-cancer panels incorporate genitourinary, brain, endocrine, hematologic, and a growing number of other cancer types. In its 2015 statement, the ASCO affirmed that there may be situations in which an individual’s personal or family history of cancers requires the simultaneous evaluation of multiple high-penetrance genes with established clinical utility3. Situations appropriate for consideration of multigene panel testing would be when an individual’s personal or family history meets testing criteria for multiple hereditary cancer syndromes or an individual has a personal history of multiple cancer diagnoses. Cases of limited family size or unknown family medical history or a high index of clinical suspicion for an individual who does not meet standard testing criteria would also merit consideration of a multigene panel. Finally, individuals who previously had negative or inconclusive testing for specific genes, but have medical histories concerning for hereditary cancer susceptibility may benefit from additional testing with a multigene panel2.

**Gene panel testing in oncology**

The use of NGS for multigene panel testing has raised new issues in genetic counseling and providing informed consent. In the context of a pre-test genetic counseling session it would be impossible to thoroughly review all of the potential cancer and health risks associated with individual genes on 10, 20, or 100 gene panels. Therefore modifications to the existing informed consent process have been proposed4,5. Genes on NGS cancer panels may be classified into 3 groups based on penetrance: high risk, moderate risk and low or unknown risk2-5. Opinions vary, but generally high-penetrance genes are considered to confer a lifetime risk for cancer of 50% or greater. Moderately penetrant genes confer a lifetime cancer risk of 20% to 50% or a 2 to 4-fold increase above the general population risk29. Low- or unknown-penetrance genes may have limited or conflicting evidence2,4,5.
finding mutations in genes without well-established medical management guidelines. Individuals with a family history of cancer could learn that they have a mutation, but there is no additional recommended screening available to them. The knowledge of a gene mutation coupled with the uncertainty of management guidelines, as in the case of a mutation in a low-penetrance gene, could become a significant source of anxiety for patients. This possibility and the potential patient reactions to this scenario should be explored in pre-test counseling. Post-test counseling and management should be based on personal and family history. Individuals should be encouraged to contact their genetic counselor/clinician every 1-2 years as more specific cancer risk and management information is expected to be learned over time.

Similar counseling challenges arise when an individual has a pan-cancer panel including genes not known to be related to the specific types of cancers found in the particular individual or their family. The possibility of finding a mutation in a gene that could indicate risk for a "new" cancer that has not yet been identified in the family must be included in pre-test education. For example, an MSH6 mutation indicating Lynch syndrome could be found in a woman undergoing testing due to a family history of early-onset breast cancer and no previous known history of

Table 1  Categories of gene panels

| Panel category                  | Examples of genes                                                                 | Penetration       | Quality of management guidelines                                                                 | Cancer and associated health risks                                      | VUS rate      | Implications for relatives                        |
|--------------------------------|----------------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------|----------------------------------------------------|
| Site/or organ system-specific  |                                                                                   |                   | Strong evidence-based clinical actionable guidelines for management of cancer and related health risks | Risk profiles well-defined                                                | Low 2%-10%    | Quantifiable risk and risk management profile      |
| Panel - e.g. breast cancer     | **BRCA1, BRCA2, APC, PTEN, TP53, MLH1, MSH2, MSH, PMS2, STK11, CDH1, MUTYH**     | **High**          |                                                                                                   |                                                                          |               |                                                    |
| High penetrance genes only     |                                                                                   |                   |                                                                                                   |                                                                          |               |                                                    |
| High and moderate penetrance   | The genes above plus ATM, CHEK2, PALB2                                            | **Moderate**      | Moderate evidence for increased surveillance at certain cancer sites                                | Risk profiles defined for some cancers, but the full spectrum of risks undetermined | Moderate 10%-20% | Incomplete risk and management profile            |
| genes clinically actionable     |                                                                                   |                   |                                                                                                   |                                                                          |               |                                                    |
| Low penetrance/newly           | The genes above plus RAD50, RAD51C, RAD51D, BRIP1, BARD1 POLE, POLD1              | **Low or unknown**| Lack of evidence-based guidelines. Management based on personal and family history and literature review | Suspected but uncertain cancer risks                                     | High>20%      | Poorly defined                                    |
| described genes                |                                                                                   |                   |                                                                                                   |                                                                          |               |                                                    |
| Multiple organ systems panel   |                                                                                   |                   | Varied evidence or case-based management depending on gene mutation identified                    | Varied potential for identifying a mutation in a highly or moderately penetrant gene that does not currently fit the known medical history | High>20%      | Depends on the gene                                |
| Pan-cancer panel               | Various combinations of high-, moderate-, and low-penetrance genes                | Unknown to high   | Varied potential for identifying a mutation in a highly or moderately penetrant gene that does not currently fit the known medical history |                                                                          |               |                                                    |
colo-rectal, endometrial, or ovarian cancers. The standard management recommendation would be for that individual to begin colonoscopy every 1-2 years over age 30 and to consider a prophylactic hysterectomy and bilateral salpingo-oophorectomy upon completion of childbearing. Is that same level of intervention and invasive screening appropriate for a patient with no known family history of colon cancer who happened to have a multigene cancer panel?

Additional challenges in test interpretation present with the co-occurrence of mutations in high- and moderate-penetrance genes. The potential gene-gene interactions and their relative contributions to the overall cancer risk is currently unknown. Counseling in these situations should be guided by what is known about the specific gene mutations present. Medical management should be based on standard guidelines for high-penetrance genes and family history.

Further complicating the counseling for NGS cancer panels is informing individuals about the likelihood of an inconclusive result or VUS. The VUS rate increases with the addition of moderate-penetrance and low-penetrance genes. In some cases a panel test could show multiple VUS in different genes. The standard medical management recommendation for a VUS is to manage the individual based on their personal and family medical history, rather than the potential implications of the VUS. This can be a difficult concept for a patient who is looking for an explanation for the cancer in their family. There is also the possibility of harm if a VUS is incorrectly interpreted as being deleterious and medical intervention is enacted based on that erroneous interpretation.

Finally, a number of genes found on cancer panels can have very different health implications when inherited as part of a recessive disorder (e.g. ATM-ataxia telangiectasia, BRCA2 and PALB2-Fanconi anemia). Reproductive implications of possible gene mutations should also be part of pre-test education when genes associated with recessive disorders are included in a test under consideration.

Using multigene panels in common hereditary cancers

Common hereditary cancers with overlapping and expanding phenotypes are obvious targets for NGS panels. Panels are readily available, relatively inexpensive, and offer a measure of convenience for both patients and practitioners. However, careful genetic evaluation may identify unique physical or family history characteristics that make targeted gene testing or at least tiered testing the best approach. Common cancer types where NGS panels are increasingly utilized due primarily to overlapping phenotypes include breast and ovarian cancer (Table 2), isolated ovarian cancer, gastrointestinal cancers/polyposis, and pancreatic cancer (Table 3).

Breast and ovarian cancer

Referrals for possible Hereditary Breast and Ovarian Cancer (HBOC) are among the most common indications seen in the cancer genetics clinic. HBOC is caused by mutations in the BRCA1 and BRCA2 genes and remains the primary consideration for individuals with a personal or family history of early-onset breast cancer, multiple relatives with breast cancer, male breast cancer, and breast and ovarian cancer in the same lineage. The current prevalence estimate for BRCA1 mutations is 1 in 300 and for BRCA2 is 1 in 800. There are several populations identified with founder mutations in these genes. The most well-known is the Ashkenazi Jewish population in which 1 in 40 individuals is expected to have a BRCA1 or BRCA2 mutation. Mutations in BRCA1 and BRCA2 are associated with an increased risk for early-onset breast cancer, multiple primary breast cancers, epithelial ovarian, fallopian tube or primary peritoneal cancer, male breast cancer and increased risks for melanoma, prostate and pancreatic cancers. The estimated lifetime risk (to age 70) for breast cancer in women with BRCA1 mutations ranges from 46%-65% and from 43%-45% in women with BRCA2 mutations in pooled analyses. Earlier estimates of risk based on highly-penetrant families put the risk of breast cancer to age 70 in the 80% range.

Risks for ovarian, fallopian tube and primary peritoneal cancers are approximately 39% by age 70 in women with BRCA1 mutations and 11% by age 70 in women with BRCA2 mutations. Breast cancers with triple negative pathology (estrogen and progesterone receptor and HER2-neu negative) are associated with an increased risk for BRCA1 gene mutations, although BRCA2 mutations have also been found in women with triple negative breast cancer. Women with ovarian cancer have a 13%-18% likelihood to have a BRCA1 gene mutation. Men with BRCA gene mutations have up at an 8% lifetime risk of breast cancer. Approximately 15%-20% of men with breast cancer at any age will have a BRCA gene mutation. Men also have an increased risk for aggressive prostate cancers. Increased rates of both pancreatic cancer and melanoma have been reported in men and women with BRCA gene mutations.

Referral for HBOC evaluation should include those
individuals with personal history or first-degree relative with: (1) breast cancer <50; (2) triple negative breast cancer diagnosed <60; (3) two or more primary breast cancers in the same person; (4) ovarian, fallopian tube, or primary peritoneal cancer; (5) Ashkenazi Jewish ancestry with breast or pancreatic cancer at any age; (6) male breast cancer; and (7) three or more individuals with breast, ovarian, pancreatic or prostate cancers (Gleason score >7) (all three individuals should not have prostate cancer)\textsuperscript{10}.

For individuals who have a classic history of several family members across multiple generations with early-onset breast cancer with or without ovarian or other HBOC cancers, analysis of the \textit{BRCA1} and \textit{BRCA2} genes with traditional Sanger sequencing and deletion and duplication analysis is an appropriate starting point for testing. However, evaluation for HBOC should include consideration of other hereditary

\textbf{Table 2} Examples of breast and ovarian cancer susceptibility genes on NGS panels

| Gene                | Syndrome                                      | Breast and ovarian cancer                  | Phenotype MIM number                  |
|---------------------|-----------------------------------------------|--------------------------------------------|--------------------------------------|
| \textit{BRCA1, BRCA2} | Hereditary breast and ovarian cancer          | Breast, ovarian, male breast, pancreatic, and prostate cancers, melanoma | 604370, 612555                       |
| \textit{CDH1}       | Hereditary diffuse gastric cancer              | Lobular breast, diffuse (signet ring) gastric, signet ring colon cancers | 137215                              |
| \textit{EPCAM, MLH1, MSH2, MSH6, PMS2} | Lynch syndrome                               | Colorectal, endometrial, ovarian, gastric, small bowel, urothelial, and pancreatic cancers, glioblastoma, sebaceous carcinoma, possible breast cancer risk | 613244, 609310, 120435, 614350, 614337 |
| \textit{PTEN}       | Cowden syndrome/PTEN hamartoma syndrome       | Benign skin lesions (trichilemmomas, oral papillomas, acral keratosis), gastrointestinal hamartomas, breast, thyroid endometrial, colon, and renal cancers, gastrointestinal hamartomas | 158350                              |
| \textit{STK11}      | Peutz-Jeghers syndrome                        | Breast cancer, gastrointestinal hamartomatous polyposis, mucosal pigmentation, colorectal, gastric, small bowel, cervical, and testicular cancers, ovarian sex cord tumors | 175200                              |
| \textit{TP53}       | Li-Fraumeni syndrome                          | Childhood cancer, sarcoma, brain tumors, adrenal cortical tumors, breast cancer (early-onset), colorectal cancer, leukemia, other cancers | 151623                              |
| \textit{ATM}        | Monoallelic-unnamed biallelic-ataxia telangiectasia | Elevated breast and pancreatic cancer risks | 114480-breast cancer susceptibility, 208900-biallelic ataxia telangiectasia |
| \textit{CHEK2}      | Unnamed                                       | Elevated breast, colon and prostate cancer risks | 604373-breast and colorectal cancer, 114480-breast cancer susceptibility, 176806-prostate cancer susceptibility |
| \textit{PALB2}      | Unnamed                                       | Elevated breast and pancreatic cancer risks, suspected male breast cancer risk | 114480-breast cancer susceptibility, 612248-pancreatic cancer susceptibility |

MIM: Mendelian inheritance in man, http://www.omim.org
| Gene          | Syndrome                              | Clinical features                                                                 | Phenotype MIM number |
|--------------|---------------------------------------|-----------------------------------------------------------------------------------|----------------------|
| **Gastrointestinal cancer** |                                       |                                    |                      |
| APC          | Familial adenomatous polyposis/attenuated familial adenomatous polyposis | Colonic and gastric polyposis, colon, duodenal, pancreatic and papillary thyroid cancers, childhood hepatoblastoma, medulloblastoma, desmoid tumors, congenital hypertrophy of the retinal pigment epithelium (CHRPE), osteomas, dental abnormalities, fibromas, epidermoid cysts | 175100               |
| BMPR1A, SMAD4 | Juvenile polyposis syndrome           | Juvenile-type hamartomatous polyps, colon (predominant), gastric, small bowel and pancreatic cancers | 174900               |
| CDH1         | Hereditary diffuse gastric cancer     | Lobular breast, diffuse (signet ring) gastric, signet ring colon cancers            | 137215               |
| EPCAM, MLH1, MSH2, MSH6, PMS2 | Lynch syndrome                      | Colorectal, endometrial, ovarian, gastric, small bowel, urothelial, and pancreatic cancers, glioblastoma, sebaceous carcinoma, possible breast cancer risk | 613244, 609310, 120435, 614350, 614337 |
| MUTYH        | Biallelic-MUTYH-associated polyposis  | Colorectal polyposis, colon cancer, possible breast cancer risk                     | 608456               |
| PTEN         | Cowden syndrome/PTEN hamartoma syndrome | Benign skin lesions (trichilemmomas, oral papillomas, acral keratosis), gastrointestinal hamartomas, breast, thyroid endometrial, colon, and renal cancers, gastrointestinal hamartomas | 158350               |
| STK11        | Peutz-Jeghers syndrome               | Breast cancer, gastrointestinal hamartomatous polyposis, mucosal pigmentation, colorectal, gastric, small bowel, cervical, and testicular cancers, ovarian sex cord tumors | 175200               |
| TPS3         | Li-Fraumeni syndrome                 | Childhood cancer, sarcoma, brain tumors, adrenal cortical tumors, breast cancer (early-onset), colorectal cancer, leukemia, other cancers | 151623               |
| CHEK2        | Unnamed                               | Elevated breast, colon and prostate cancer risks                                   | 604373-breast and colorectal cancer, 114480-breast cancer susceptibility, 176806-prostate cancer susceptibility |
| **Pancreatic cancer** |                                       |                                    |                      |
| APC          | Familial adenomatous polyposis/attenuated familial adenomatous polyposis | Colonic and gastric polyposis, colon, duodenal, pancreatic and papillary thyroid cancers, childhood hepatoblastoma, medulloblastoma, desmoid tumors, congenital hypertrophy of the retinal pigment epithelium (CHRPE), osteomas, dental abnormalities, fibromas, epidermoid cysts | 175100               |
| BRCA1, BRCA2 | Hereditary breast and ovarian cancer  | Breast, ovarian, male breast, pancreatic, and prostate cancers, melanoma           | 604370, 612555, 614320-BRCA1 pancreatic cancer risk, 613347-BRCA2 pancreatic cancer risk |
| CDKN2A       | Pancreatic cancer/ melanoma syndrome  | Pancreatic cancer and melanoma                                                     | 606719               |
| EPCAM, MLH1, MSH2, MSH6, PMS2 | Lynch syndrome                      | Colorectal, endometrial, ovarian, gastric, small bowel, urothelial, and pancreatic cancers, glioblastoma, sebaceous carcinoma, possible breast cancer risk | 613244, 609310, 120435, 614350, 614337 |
syndromes in which breast and ovarian cancers are component cancers\textsuperscript{32}.

If no \textit{BRCA1} or \textit{BRCA2} mutation is found in a "classic" HBOC family, a multigene panel could be an appropriate next step. Some laboratories offer the option to analyze \textit{BRCA1} and \textit{BRCA2} first and automatically reflex to a larger breast/ovarian susceptibility gene panel if \textit{BRCA1} and \textit{BRCA2} analysis fails to identify a gene mutation. The knowledge of additional cancer history in the family or lack thereof, may help expand the differential diagnosis and determine the next step in the evaluation. Individuals without a classic HBOC presentation (e.g. clusters of later-onset cancers, limited family structure, or early-onset breast cancer with a multiple other cancer diagnoses in the family) may be candidates for consideration of a multigene cancer susceptibility panel as a first-tier test.

Other well-defined high-penetration genes associated with breast cancer susceptibility and often found on high-penetration breast cancer panels are \textit{CDH1}, \textit{TP53}, \textit{PTEN}, and \textit{STK11}. These genes are associated with known genetic syndromes which have defined medical management guidelines. Lifetime risks for breast cancer are similar to those seen in \textit{BRCA1} and \textit{BRCA2} mutation carriers. \textit{CDH1} is associated with a lifetime risk for lobular breast cancer of approximately 40\%\textsuperscript{48}. \textit{PTEN} mutation carriers have a 25\%-85\% lifetime risk for breast cancer\textsuperscript{49,51}. \textit{STK11} mutation carriers have a 30\%-54\% lifetime risk for breast cancer and a 21\% risk for ovarian sex cord tumors\textsuperscript{52,53}. Breast cancer is the most common tumor in individuals with \textit{TP53} mutations with an estimated risk of 24\%-31\%\textsuperscript{54,55}. All of the syndromes associated with these genes have other tumor associations and phenotypic features that might, with careful pedigree and medical history analysis, suggest that syndrome specific testing is the appropriate initial test with consideration of reflexing to a panel test if no mutation is found. Summaries of associated tumor types and other phenotypic features are found in Table 2.

Moderately penetrant genes often included on breast

### Table 3 (continued)

| Gene    | Syndrome                               | Clinical features                                                                 | Phenotype MIM number                                                                 |
|---------|----------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| \textit{PRSS1} | Hereditary pancreatitis              | Chronic pancreatitis, pancreatic cancer                                         | 167800                                                                              |
| \textit{STK11} | Peutz-Jeghers syndrome     | Breast cancer, gastrointestinal hamartomatous polyposis, mucosal pigmentation, colorectal, gastric, small bowel, cervical, and testicular cancers, ovarian sex cord tumors | 175200-260350-pancreatic cancer                                                   |
| \textit{TP53} | Li-Fraumeni syndrome               | Childhood cancer, sarcoma, brain tumors, adrenal cortical tumors, breast cancer (early-onset), colorectal cancer, leukemia, other cancer | 151623-260350-pancreatic cancer                                                     |
| \textit{ATM}  | Monoallelic-unnamed biallelic-ataxia telangiectasia | Elevated breast and pancreatic cancer risks                                         | 114480–breast cancer susceptibility, 208900-biallelic ataxia telangiectasia     |
| \textit{PALB2} | Unnamed                               | Elevated breast and pancreatic cancer risks, suspected male breast cancer risk     | 114480-breast cancer susceptibility, 612248-pancreatic cancer susceptibility     |
| Endometrial cancer |                        |                                                                                   |                                                                                     |
| \textit{EPCAM, MLH1, MSH2, MSH6, PMS2} | Lynch syndrome                  | Colorectal, endometrial, ovarian, gastric, small bowel, urothelial, and pancreatic cancers, glioblastoma, sebaceous carcinoma, possible breast cancer risk | 613244, 609310, 120435, 614350, 614337                                          |
| \textit{PTEN}  | Cowden syndrome/PTEN hamartoma syndrome | Benign skin lesions (trichilemmomas, oral papillomas, acral keratosis), gastrointestinal hamartomas, breast, thyroid endometrial, colon, and renal cancers, gastrointestinal hamartomas | 158350                                                                              |
| \textit{TP53}  | Li-Fraumeni syndrome               | Childhood cancer, sarcoma, brain tumors, adrenal cortical tumors, breast cancer (early-onset), colorectal cancer, leukemia, other cancer | 151623-260350-pancreatic cancer                                                     |

MIM: Mendelian inheritance in man, http://www.omim.org
cancer susceptibility gene panels are ATM, CHEK2, and PALB2. Mutations in these genes increase the risk for developing breast cancer over the benchmark 20% lifetime risk\(^{29,56,57}\) used to determine MRI screening eligibility\(^{58}\) and may imply increased, but as yet undefined, risks for other tumor types\(^{59-66}\). Mutations in these genes justify increased screening, especially in situations where there is a personal or family history of breast cancer. However, with a list of other potential associated cancers (Table 2) that are not well-defined, additional medical management recommendations should be based on family history.

Lower penetrant and emerging genes included on breast and ovarian cancer panel testing vary by laboratory but frequently include BARD1, BRIP1, MRE11A, NBN, NF1, RAD50, RAD51C, and RAD51D. For the individual who had a personal and family history of multiple breast cancers, including early-onset breast cancer and multiple generations of affected individuals, does a mutation in one of these lower penetrance genes fully explain the cancer risk in the family? Perhaps not. Some familial clusters may be due to shared environmental risk factors as well as shared mutations in low to moderate-penetrance breast and ovarian cancer susceptibility genes\(^ {32}\). As data accumulates over time, more specific predictive and management information may become available. It is therefore important to impress upon the patient the need to contact the clinic regularly to see if new information is available relevant to their situation.

### Isolated ovarian cancer

Approximately 15% of women with invasive ovarian cancer have a detectable mutation in the BRCA1 or BRCA2 genes\(^ {42,67}\) and testing for BRCA1 and BRCA2 genes is recommended for all women diagnosed with ovarian cancer\(^7\). More recently a growing number of ovarian cancer cases are attributed to mutations in the Lynch syndrome genes, notably MSH6\(^ {68,69}\). A recent study found more than one in 5 ovarian cancers to be associated with a germline gene mutation and >30% of women studied had no family history of breast or ovarian cancer\(^ {42}\). Mutations in a growing number of other genes have been found in ovarian cancer patients including: ATM, BARD1, BRIP1, CHEK2, MLH1, MRE11A, MSH6, NBN1, PALB2, PMS2, PTEN, RAD50, RAD51C, and TP53\(^ {42,68,70}\). This expansion in the number of genes under consideration in ovarian cancer risk suggests that consideration of a panel-based testing approach for ovarian cancer patients is warranted.

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### Gastrointestinal cancer

Multigene cancer panels may have the greatest clinical utility in the setting of gastrointestinal cancer history where the phenotypic overlap is significant and the differential diagnosis includes multiple genes. Up to 6% of colorectal cancers may be due to a defined high-risk syndrome\(^ {71}\). Lynch syndrome alone has 5 genes (EPCAM, MLH1, MSH2, MSH6, and PMS2). Tumor screening such with immunohistochemistry (IHC) studies may identify genes to target, but does not definitively rule out a role for evaluation of all 5 genes. A NGS panel may now be preferred as a frontline evaluation for Lynch syndrome in the event that IHC testing is unavailable\(^3\). Many families with colonic polyposis and features of Lynch syndrome are not found to have mutations in APC, MUTYH, or the 5 Lynch syndrome-associated genes. Recent studies have identified mutations in the POLE, POLD1, and other polymerase genes in such families leading to a diagnosis of polymerase proofreading-associated polyposis (PPAP)\(^ {72,73}\). With this emerging evidence of additional genes with phenotypic overlap of more common hereditary colorectal cancer/polyposis syndromes, panel testing may be a time and cost-effective approach to genetic evaluation\(^ {74}\). Panel testing with careful consideration to the genes included should be considered in the event that initial gene specific testing for an individual meeting the diagnostic criteria for familial adenomatous polyposis (FAP), Attenuated FAP, MUTYH-associated polyposis, or Lynch syndrome is negative.

### Pancreatic cancer

Approximately 5%-10% of pancreatic adenocarcinoma is familial (2 or more affected first-degree relatives)\(^ {75}\). Several genes have been associated with increased pancreatic cancer risk including BRCA1, BRCA2, CDKN2A, PALB2, PRSS1, STK11, and the Lynch syndrome genes\(^ {66,76}\). Recent studies using multigene cancer panels to screen pancreatic cancer patients identified mutations in the ATM, BARD1, BRCA1, BRCA2, CHEK2, FANCM, NBN, MLH1, MSH2, MSH6, and TP53 genes\(^ {59,60}\). The American College of Gastroenterology currently recommends testing for BRCA1, BRCA2, PALB2, CDKN2A and ATM for all familial pancreatic cancer cases adding the genes for Peutz-Jeghers syndrome, Lynch syndrome and hereditary pancreatitis if the clinical history is suggestive of these conditions\(^ {77}\).
Conclusions

The expansion of knowledge regarding genetic contributions to cancer risk and the advent of NGS panels for cancer susceptibility genes makes genetic testing more affordable and appropriate to consider for larger numbers of individuals and families. The use of multigene panels in oncology have the potential to expand our knowledge of the spectrum of cancers and additional health risks associated with both rare high-penetrance susceptibility genes and moderately penetrant and newly described genes. Phenotype expansion and definition will help modify and create medical management guidelines for gene carriers. Providers using multigene panels are encouraged to participate in registries such as the Prospective Registry of Multiplex Testing or PROMPT registry to advance research in this area. It is especially important that peoples of diverse ancestry are included.

While the ability to analyze multiple cancer susceptibility genes is attractive, the complex nature of the analysis and interpretation require an in depth understanding of the genetic susceptibility to cancer risk, careful analysis of the patient and family medical histories and ability to appropriately interpret the results in the context of individual and familial risk as well as medical management. Individuals undergoing genetic testing for cancer susceptibility must be fully informed about the potential implications of the information to be learned. The pre-test counseling and informed consent process becomes even more complex when describing the benefits, limitations and potential for VUS associated with multigene panels. Genetic evaluation for inherited cancer susceptibility should be a collaboration between oncologists, clinical geneticists and genetic counselors. Genetic counselors are uniquely trained to provide the genetics education and support to patients and families in the oncology setting and are best suited to spend the time necessary for individuals to make fully informed decisions about genetic testing for cancer susceptibility.

Conflict of interest statement

Christine Stanislaw, and William R. Wilcox have no conflicts. Yuan Xue is an employee of Fulgent Diagnostics, a genetic testing company.

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