J Genet Counsel (2014) 23:604–617
DOI 10.1007/s10897-014-9695-6

NEXT GENERATION GENETIC COUNSELING

Cancer Risk Assessment Using Genetic Panel Testing: Considerations for Clinical Application

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Received: 21 June 2013 / Accepted: 28 January 2014 / Published online: 7 March 2014

Abstract With the completion of the Human Genome Project and the development of high throughput technologies, such as next-generation sequencing, the use of multiplex genetic testing, in which multiple genes are sequenced simultaneously to test for one or more conditions, is growing rapidly. Reflecting underlying heterogeneity where a broad range of genes confer risks for one or more cancers, the development of genetic cancer panels to assess these risks represents just one example of how multiplex testing is being applied clinically. There are a number of issues and challenges to consider when conducting genetic testing for cancer risk assessment, and these issues become exceedingly more complex when moving from the traditional single-gene approach to panel testing. Here, we address the practical considerations for clinical use of panel testing for breast, ovarian, and colon cancers, including the benefits, limitations and challenges, genetic counseling issues, and management guidelines.

Keywords Cancer panels · Risk assessment · Breast cancer · Ovarian cancer · Colon cancer

Introduction

The development of next-generation sequencing (NGS) has significantly reduced the cost and increased the efficiency of gene sequencing, and the use of multiplex genetic testing is rapidly growing. Genetic cancer panels that assess risks of multiple different cancers and multiple different risk variants simultaneously are one example of how multiplex testing is being applied clinically. Cancer gene panels utilize this cost-effective technology by sequencing numerous targets associated with cancer risk (Meldrum et al. 2011). There are a number of issues and challenges to consider when counseling for genetic cancer risks, and these issues become exceedingly more complex when moving from the traditional single-gene approach to panel testing (Multiplex genetic testing. The Council on Ethical and Judicial Affairs and American Medical Association 1998). Since technological advances seem to be outpacing the clinical considerations of panel testing, it is important to address these issues and identify gaps in our knowledge as the demand for such tests continues to grow.

In this review of cancer gene panels, we sought to explore the issues pertaining to the development and provision of cancer panels. We first address how to determine the genes that should be included on a panel. We then assess the practical considerations pertaining to the clinical use of cancer panels, including the benefits, limitations and challenges, genetic counseling issues, and management guidelines. From this review of the literature, we developed the Einstein/Montefiore cancer gene panel for the assessment of breast, ovarian, and colon cancer risks.

Cancer Risk Genes

Breast cancer and colon cancer represent two of the most common types of cancers in the United States ("Common Cancer Types", n.d. http://www.cancer.gov/cancertopics/types/commoncancers#1. Both of these cancers have well characterized, high penetrance risk genes associated with them, and clinical genetic testing for risk assessment is available

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(Bonadona et al. 2011; Ford et al. 1994; King et al. 2003; Vasen et al. 2001). There are a number of other genes that have been associated with an increased risk for breast and colon cancer, some of which are part of well known cancer syndromes that confer high risk, while others have been less well studied and confer lower levels of risk. Many of these genes share molecular pathways and play a role in the repair of DNA damage, making them good candidates for cancer susceptibility genes.

FANC-BRCA Pathway

BRCA1 and *BRCA2* are well characterized genes associated with a significantly increased risk of breast and ovarian cancer (Ford et al. 1994; King et al. 2003). These genes are part of the Fanconi Anemia (FA)-BRCA Molecular Pathway. There are 14 genes identified in this pathway, and improved understanding of molecular mechanisms has led to the identification of new cancer susceptibility genes (Pennington and Swisher 2012). The FA genes work together in concert with *BRCA1* in a common DNA repair pathway. In response to DNA damage, ATM (ataxia telangiectasia mutated) and ATR (ataxia telangiectasia and Rad3-related) kinases activate the FA core complex comprising FANCA, B, C, E, F, G, L, and M, which then monoubiquinates FANCD2 and FANCI. This complex then interacts with other downstream proteins FANCD1/BRCA2, FANCN/PALB2, and FANCJ/BRIP1 to incite DNA repair through homologous recombination (Schwartz and D'Andrea 2010). BRCA1 has also been identified as an upstream regulator of the PALB2-BRCA2 complex, promoting its localization to DNA damage sites (Casadei et al. 2011). BRCA1 exists mostly as a heterodimer with BARD1 forming a ubiquitin ligase that is instrumental in BRCA1 response to DNA damage (Starita and Parvin 2006). Not surprisingly, *PALB2*, *BRIP1*, and *BARD1* gene mutations have been associated with an increased risk of breast cancer of 2–4 fold (Casadei et al. 2011; Seal et al. 2006; Stacey et al. 2006). Biallelic mutations in the *FANC* genes have been shown to cause Fanconi anemia, a rare disorder of chromosome instability and defect of repair of double-stranded breaks in DNA, resulting in childhood aplastic anemia, multiple congenital anomalies, and susceptibility to leukemia and other cancers. It is inherited in an autosomal recessive manner, except for an X-linked recessive subtype (Schwartz and D'Andrea 2010).

Also involved in the FANC-BRCA pathways is the *NBN* gene. Biallelic mutations in the *NBN* gene cause Nijmegen breakage syndrome (NBS), an autosomal recessive chromosome instability syndrome. Clinical features include microcephaly, growth retardation, intellectual disability, immunodeficiency, and increased risk of malignancy (Bogdanova et al. 2008). The NBN protein forms a complex with MRE11A and RAD50 producing the Mre11 complex necessary for repair of double stranded breaks in DNA (Desjardins et al. 2009; Heikkinen 2005). This complex co-localizes with BRCA1 as well as with FANCD2 in response to DNA damage (Wang et al. 2000). Heterozygous mutations in *NBN, MRE11A, or RAD50* have been found to be associated with an increased risk of breast cancer of about 2–4 fold (Bogdanova et al. 2008; Heikkinen 2005; Hsu et al. 2007). All of the genes in the FANC-BRCA pathway and those associated with NBS have been implicated in an increased risk of ovarian cancer, the magnitude of which has not yet been defined (Pennington and Swisher 2012).

CHEK2 Pathway

BRCA1 is also part of the *CHEK2* pathway. The *CHEK2* pathway plays an integral role in the prevention of cancer through its response to DNA damage. In response to DNA damage, ATM and ATR are activated, inducing the phosphorylation of the CHK2 protein. CHK2 interacts with the products of breast cancer susceptibility genes *BRCA1*, *TP53*, and *ATM*. *CHEK2* mutations have been implicated in the increased risk of both breast and ovarian cancer (Cybulski et al. 2011; Meijers-Heijboer et al. 2002; Tung and Silver 2011). *CHEK2* risks appear to be dependent on family history of breast cancer, with women who have a *CHEK2* mutation in the context of a positive family history of breast cancer (ie. both a first and second degree affected relative) having an even higher breast cancer risk than those without a family history (Cybulski et al. 2011; Narod 2010).

As one of the first responders to DNA damage, ATM plays a significant role in DNA repair. Homozygous mutations in *ATM* cause ataxia-telangiectasia, a rare autosomal recessive neurological disorder characterized by progressive cerebellar ataxia, immunodeficiency, and increased risk of malignancy ("Ataxia-Telangiectasia - GeneReviews", n.d http://www.ncbi.nlm.nih.gov/books/NBK26468/). Carriers of *ATM* mutations have been found to have a 2–4 fold increased risk of breast cancer (Swift et al. 1991; Thompson et al. 2005; Thorstenson et al. 2003). The tumor suppressor protein TP53 also plays a significant role in this DNA repair pathway. In response to DNA damage, it can induce cell senescence and apoptosis (Tung and Silver 2011). Homozygous mutations in *TP53* cause Li-Fraumeni syndrome characterized by significantly increased risk of both childhood and adult cancers including leukemia, soft tissue sarcomas, osteosarcomas, brain tumors, and adrenal cortical carcinomas ("Li-Fraumeni Syndrome - GeneReviews", n.d. http://www.ncbi.nlm.nih.gov/books/NBK1311/). Carriers of *TP53* mutations also have an increased risk of breast cancer (Birch et al. 1998; Chompret et al. 2000).

Mismatch Repair Pathway

The mismatch repair (MMR) pathway is the main pathway for the repair of base mismatch mutations resulting from errors in

DNA replication. The MMR pathway is comprised of several different proteins which include MSH1-6, MLH1, MLH2, MLH3, PMS1, and PMS2. Each protein has a unique role within the pathway. The MSH2 protein forms a heterodimer with MSH6 to repair single base substitutions and small insertion-deletions (indels), whereas the heterodimer between MSH2 and MSH3 is responsible for large indel repair. MLH1 forms heterodimers with PMS1, PMS2, or MLH3, each with specific repair roles (Martin et al. 2010; Peltomäki 2003; Wu et al. 2003). Germline mutations in MMR genes cause Lynch syndrome, or hereditary non-polyposis colorectal cancer (HNPCC), and greatly increase the risk for different types of cancers including colon, endometrium, ovary, gastric, and brain. The associated risks may vary depending on which gene is involved. The association between MMR genes and breast cancer remains unconfirmed (Barrow et al. 2009; Bonadona et al. 2011; Shanley et al. 2009). Since breast cancer is the most common malignancy in women, the presence of breast cancer in families with Lynch syndrome may be coincidental or there may be a subset of breast cancer which are indeed related to mutations in mismatch repair genes. Mutations in a non-MMR gene, *EPCAM*, can also lead to Lynch syndrome through its inactivation of *MSH2. EPCAM* deletion carriers appear to have a similarly increased risk of colon cancer as *MSH2* deletion carriers, however the risk of endometrial cancer is somewhat lower (Kempers et al. 2011; Ligtenberg et al. 2012).

Determination of Genes on a Cancer Panel

The research detailed above has informed the development of cancer genetic testing panels that are currently being offered clinically for the assessment of breast, ovarian, and colon cancer risk. In light of the Supreme Court decision to invalidate the gene patents held by Myriad BROCA ("Supreme Court," n.d. https://www.aclu.org/womens-rights/supreme-court-invalidates-patents-breast-and-ovarian-cancer-genes), more cancer panels that include *BRCA1* and *BRCA2* are expected to emerge in the future ("genetics/BROCA," n.d.; "Next-gen Cancer Panels," n.d.; "Comprehensive Cancer Panel," n.d. http://www.genedx.com/test-catalog/available-tests/comprehensive-cancer-panel/ "Myriad to Replace BRACAnalysis," n.d.). GeneDx offers a Breast/Ovarian Cancer Panel that targets 26 susceptibility genes, as well as a Colorectal Cancer Panel that targets 18 susceptibility genes (GeneDx, n.d.). Ambry Genetics offers a breast cancer panel (BreastNext) comprised of 18 risk genes, an ovarian cancer panel (OvaNext) comprised of 23 risk genes, and a colon cancer panel (ColoNext) comprised of 14 risk genes (Ambry Genetics, n.d. (http://www.ambrygen.com/tests/breastnext; http://www.ambrygen.com/tests/colonext; http://www.ambrygen.com/tests/ovanext). The University of Washington offers the BROCA Cancer Risk Panel comprised of 40 genes that assess the risk of cancer syndromes that include breast, ovarian, and colon cancer, as well as other types of cancer such as endometrial, pancreatic, endocrine, and melanoma ("genetics/BROCA," n.d. http://web.labmed.washington.edu/tests/genetics/BROCA). Sistemas Genomicos based in Spain has a 15 gene breast/ovarian cancer panel, as well as a variety of tests for colon cancer risk assessment (Sistemas Genómicos, n.d. https://www.sistemasgenomicos.com/web_sg/webing/areas-biomedicina-ugm3.php). CeGaT based in Germany has a 35 gene breast/ovarian cancer panel as well as a 17 gene colon cancer panel (Tumor Syndromes, n.d. http://www.cegat.de/Tumor-syndromes_l=1_171.html; Personal Communication).

From review of the literature, cancer gene databases, and existing panels, we developed a panel of genes that is representative of the available data on breast, ovarian, and colon cancer risks. The resulting Einstein/Montefiore panel strongly resembles what is currently being offered by other labs, illustrating that there is general consensus regarding what genes are appropriate to include when assessing high and moderately increased risks for these cancers (Table 1). Most of these genes participate in the molecular pathways detailed above, thus supporting their contribution to increased cancer risk. It is likely that in the future additional risk genes involved in these pathways will be identified, further expanding cancer risk panels.

Advantages of Cancer Panel Testing

Assessing genetic risk of a broad spectrum of cancer-predisposition genes using a single test has many advantages. Due to the genetic heterogeneity of most cancers, panel testing can be successfully applied to cancer risk assessment, and can convey greater sensitivity for assessing cancer risks compared to sequential genetic testing of individual genes. This personalized approach can provide a more objective risk, and is able to parse out who is at risk for a highly penetrant cancer syndrome, who is at moderate risk due to lower penetrance variants or multifactorial inheritance, and who is at average population risk (Gail 2011; Riley et al. 2012). This allows providers to more accurately weigh the risks and benefits of medical intervention, and affords those who would likely not benefit from intervention to be spared the potential risks, while providing those at high risk with potential risk reducing strategies (Gail 2011). For women whose a priori risk is close to a threshold level that would warrant intervention, incorporating additional factors into the risk assessment will likely change their risk classification, impacting clinical care decision-making (Mealiffe et al. 2010). Improving discriminatory accuracy of risk assessment can also aid clinicians in making more cost-effective decisions about testing and

Table 1 Cancer Gene Panels

Cancer Risk Genes	Cancer Risks	Ambry BreastNext, OvaNext, ColoNext	GeneDx Breast/Ovarian and Colon Cancer Panels	U Wash BROCA	Einstein/ Montefiore Panel
AKT	Breast, Thyroid			X	
APC	Colon, Small bowel, Thyroid	X	X	X	X
ATM	Breast, Pancreatic	X	X	X	X
AXIN2	Colon		X		
BARD1	Breast, Ovarian	X	X	X	X
BLM	Breast, Ovarian		X		
BMPR1A	Colon, Gastric	X	X	X	X
BRCA1	Breast, Ovarian	X	X	X	X
BRCA2	Breast, Ovarian, Melanoma, Pancreatic	X	X	X	X
BRIP1	Breast, Ovarian	X	X	X	X
CDH1	Breast, Ovarian, Colon, Gastric	X	X	X	X
CHEK2	Breast	X	X	X	X
EPCAM	Breast, Ovarian, Colon, Endometrial	X	X	X	X
FAM175A	Breast		X	X	
FANCC	Breast		X		
GALNT12	Colon			X	
GEN1	Breast			X	
GREM1	Colon			X	
HOXB13	Breast		X		
MLH1	Ovarian, Colon, Gastric, Endometrial, Brain	X	X	X	X
MRE11A	Breast	X	X	X	X
MSH2	Ovarian, Colon, Gastric, Endometrial, Brain	X	X	X	X
MSH6	Colon, Gastric, Endometrial, Brain	X	X	X	X
MUTYH	Breast, Colon	X	X	X	X
NBN	Breast	X	X	X	X
NF	Breast, Ovarian	X			
PALB2	Breast, Pancreatic	X	X	X	X
PIK3CA	Breast, Thyroid			X	
PMS1	Colon, Ovarian, Gastric, Endometrial, Brain				X
PMS2	Colon, Ovarian, Endometrial, Brain	X	X	X	X
POLD1	Colon, Endometrial			X	
POLE	Colon			X	
PTEN	Breast, Colon, Thyroid, Renal	X	X	X	X
RAD50	Breast	X	X	X	X
RAD51C	Breast, Ovarian	X	X	X	X
RAD51D	Breast, Ovarian	X	X	X	
RB1	Breast, Lung, Bladder, Melanoma				X
SMAD4	Colon, Gastric	X	X	X	X
STK11	Breast, Colon, Pancreatic, Gastric, Lung	X	X	X	X
TP53	Breast, Ovarian, Soft Tissue, Brain	X	X	X	X
XRCC2	Breast, Colon		X	X	

treatment by identifying those most likely to benefit from these interventions (Mealiffe et al. 2010; Williams et al. 2006).

Another significant benefit of cancer panel screening is the ability to assess risks in those who would not routinely come to attention because they do not meet the standard high risk criteria. This could be due to incomplete penetrance of the syndrome, sex-limited expression, or lack of or limited personal and/or family history (Rubinstein et al. 2009). Personal and family histories are routinely used to determine who would be appropriate for cancer genetic risk assessment. In the case of breast and ovarian cancer, models such as Gail, Couch, Frank, BRCAPRO, and the FHAT tool are used to

determine who would benefit from cancer genetic counseling and subsequent testing (Couch et al. 1997; Frank et al. 1998; Gilpin et al. 2000). The Gail model is an epidemiological model that predicts lifetime breast cancer risk, while the Couch, Frank, and BRCAPRO models are genetic models that predict the probability of being a *BRCA1/2* mutation carrier (Rubinstein et al. 2002). The FHAT tool uses family history to devise a cumulative score above which referral to genetic counseling is warranted (Gilpin et al. 2000). However, relying on these criteria may overlook those who carry significant cancer risks. It is now recognized that those who do not meet standard genetic testing criteria may still benefit from genetic risk assessment (Berliner et al. 2013). The American Society of Clinical Oncology (ASCO) recently updated their recommendations on genetic testing for cancer susceptibility in response to the rapid advancements in technology. Initially ASCO recommended that clinical genetic testing only be offered to those with a personal or family history suggestive of an inherited cancer syndrome. ASCO has since amended this recommendation indicating that those without a family history may be appropriate candidates for cancer susceptibility testing if analytic and clinical utility has been established, meaning that the results can be adequately interpreted, and can impact medical decision making and clinical outcomes (Robson et al. 2010).

In addition to extending genetic risk assessment to a wider population, cancer gene panels broaden the number of gene targets used to assess risk. Increasing the number of gene targets to include variants with lower frequency and lower penetrance provides a more comprehensive risk assessment and can further refine risk estimates (Meldrum et al. 2011). In the case of familial breast/ovarian cancer, *BRCA1* and *BRCA2* mutations account for only about 20 % of familial breast cancer cases (Hopper et al. 1999) and several other genes have been implicated in increasing the risk of familial breast cancer (Pennington and Swisher 2012). In the case of colon cancer, only 3–5 % of cases are caused by a highly penetrant heritable mutation (Burt 2007). Thus cancer gene panels may uncover risks not previously anticipated based on clinical presentation.

Challenges to Utilizing Cancer Panel Testing

Defining the Target Population

Although there are several advantages to utilizing cancer panels, there are also significant challenges to using this approach. The first challenge comes with defining the target population for this testing. When utilizing a gene panel that assesses risks of multiple different cancers, it is unlikely that an individual will meet criteria to warrant genetic assessment of all of these cancers. As indicated above, those without a personal or family history consistent with a hereditary cancer syndrome may still harbor risk-increasing mutations and may benefit from genetic assessment. In addition, many of the models used to assess risk are imperfect, and often lack sufficient discriminatory accuracy (Gail 2011). Therefore an argument could be made for providing this testing to a wider population who do not meet the standard testing criteria.

Interpreting Test Results

Interpreting and communicating the results of panel testing presents additional challenges. As with any genetic test, different types of results are possible with panel testing. These include a positive result in which a known pathogenic mutation is detected, a negative result in which no genetic variant is detected, and an ambiguous result in which a variant of uncertain significance (VUS) is detected. However when conducting tests on multiple targets simultaneously, interpreting these results is more complex. The effect of testing multiple targets on test performance must be considered, as false positive rates increase with an increasing number of tests, and also when testing a low risk population (Multiplex genetic testing. The Council on Ethical and Judicial Affairs and American Medical Association 1998"). In addition, the chance of detecting a VUS using panel testing is also greatly elevated, and there is limited information available on the impact of these rarer variants on risk (Walsh et al. 2010). With the broadening scope of genetic testing, dealing with VUS's has become increasingly problematic. To address this, in 2008 the International Agency for Research on Cancer (IARC, the cancer research branch of the World Health Organization) convened a Working Group on Unclassified Sequence Variants in high-risk cancer susceptibility genes. Recommendations were put forward for classifying uncertain variants in efforts to standardize this process and improve the clinical utility of testing for patients at increased risk for cancer (Tavtigian et al. 2008). Several different types of data may be used in assessing the pathogenicity of a variant. These can be divided into direct and indirect evidence. Direct evidence is that which is garnered from observation of disease and mutation transmission. Conditions that would increase the likelihood that a variant is pathogenic include co-segregation with the phenotype in families, a higher frequency of the variant in cases versus controls, occurrence in families with a stronger history of disease, and lack of co-occurrence with another known pathogenic variant (for a presumed dominant phenotype). Indirect evidence relies on the structural and functional features of the gene and protein, including the degree of species conservation, functional analysis of the mutated protein, and the predicted consequences of a particular sequence variation (Goldgar et al. 2008). The difficulty comes in trying to integrate the evidence in order to reach a consensus on variant classification. An integrated Baysian approach combines the various data to produce a quantitative

prior probability of pathogenicity. In the absence of quantitative measures of some types of evidence, qualitative measures can be used to reclassify variants, with a panel of experts assessing the quality of this evidence (Goldgar et al. 2008).

In the American College of Medical Genetics and Genomics (ACMG) recommendations for the interpretation and reporting of sequence variants, 6 categories of variants are delineated:

(1) sequence variation is previously reported and is a recognized cause of the disorder; (2) sequence variation is previously unreported and is of the type which is expected to cause the disorder; (3) sequence variation is previously unreported and is of the type which may or may not be causative of the disorder; (4) sequence variation is previously unreported and is probably not causative of disease; (5) sequence variation is previously reported and is a recognized neutral variant; and (6) sequence variation is previously not known or expected to be causative of disease, but is found to be associated with a clinical presentation (Richards et al. 2008). Once a variant is more accurately classified, decisions can be made regarding the best course of action for treatment and surveillance. The ACMG also presents guidelines for test reports documenting these variants. These reports should include (1) the gene analyzed and the presence or absence of a variant, the nature of the mutation, and whether it is conservative or non-conservative; (2) The category (1–6) within which the variants falls; (3) The basis upon which this classification was made; (4) Testing methodology and analytic sensitivity; (5) Available data on penetrance and expressivity of previously reported variants; (6) Strategies for further classification of novel variants (Richards et al. 2008). It is recommended that novel variants with unknown pathogenicity not be reported to the patient, but be studied within the research context in efforts to further refine the classification (Berg et al. 2011).

Risk Estimates

The ability to provide a genetic risk assessment is limited by the availability of data on the risks associated with genetic variants. For less penetrant, lower frequency variants, large prospective studies that provide lifetime risk estimates are generally lacking. Most published series are based on smaller homogeneous populations, and while the majority use a case–control design and express risks as odds ratios, some of the studies present risks in other formats such as cumulative lifetime risk, standard incidence rates, or absolute risk. This presents a challenge for how to present risks to patients. GeneDx categorizes genes based on level of risk, with "Significantly Increased Risk" genes having a relative risk≥4, "Moderately Increased Risk" genes having a relative risk of 2–4, and genes that confer an increased risk, the exact magnitude of which is unknown due to lack of data. Corresponding lifetime risk estimates are also provided ("Comprehensive Cancer Panel," n.d. http://www.genedx.com/test-catalog/available-tests/comprehensive-cancer-panel/). Ambry Genetics presents risks as either odds ratios or percentage lifetime risks depending on the gene ("Next-gen Cancer Panels," n.d. http://ambrygen.com/next-gen-cancer-panels). Our review of literature supports the high level of concordance in the risk estimates that are provided by these labs (Table 2).

When conducting multiple genetic tests simultaneously, it is quite possible that a patient may be found to carry more than one mutation in more than one gene. Interpreting these multiple risks constitutes another challenge to panel testing. Integrating SNP-associated risks has been based on additive models and has shown moderate discriminatory accuracy (Lalloo and Evans 2012; Rinella et al. 2013). However the formalism for combining higher penetrance genetic risk variants to yield a composite risk score for multigenic diseases has not yet been developed (Ng et al., 2009; Swan et al. 2010). Combining genetic risk factors with clinical risk factors into an integrated risk score is even more complex, but has been piloted by combining the Gail model risk score, which encompasses personal medical history, reproductive history, and family history, with a combined SNP risk score to yield a classification of breast cancer risk (Mealiffe et al. 2010). Such approaches may be used in the future once developed and validated for higher penetrance mutations, risk SNPs, and clinical risk factors.

Many of the genes on cancer panels confer risks for multiple different cancers. For those who are seeking testing primarily based on their risk for the most common heritable adult malignancies (breast, ovarian, colon), uncovering additional cancer risks may be an unanticipated outcome of the testing that should be discussed in the pre-test session. For genes that have distinct monoallelic and biallelic expression, the patient must be informed of the potential to identify not only personal cancer risks from having a mutation, but also the risk to have a child with a more severe autosomal recessive cancer syndrome, a scenario that would have important family implications (Rahman and Scott 2007). An example of this phenomenon is the *BRCA2* gene which in the heterozygous state confers an increased risk of breast and ovarian cancers, as well as other cancers, while homozygous inheritance causes a severe form of Fanconi anemia and a high risk of childhood cancers (Rahman and Scott 2007). Another example occurs with the mismatch repair genes, *MLH1, MSH2, MSH6, PMS2,* which in heterozygous form confer an increased risk for the colon cancer syndrome HNPCC, and in homozygous form causes mismatch repair deficiency syndrome which carries an increased risk of childhood cancers and skin lesions (Rahman and Scott 2007).

Communicating Results

It is important to communicate to patients that even if no pathogenic variant is detected by the panel, this does not

Table 2 Cancer Panel Risks

Genes	Breast		Ovary		Colon		References
	OR	Lifetime Risk	OR	Lifetime Risk	OR	Lifetime Risk	
FANC-BRCA Pathway Genes							
BRCA1	10–20X	50–85 %		35–60 %	4X		Ford et al. 1994; King et al. 2003
BRCA2	10–20X	50–85 %		12–25 %			King et al. 2003; Antoniou et al. 2003
PALB2	2–4X			increased			Bogdanova et al. 2008; Byrnes et al. 2008; Casadei et al. 2011; Cybulski et al. 2011; Heikkinen 2005; Rahman and Scott 2007; Seal et al. 2006; Stacey et al. 2006; Weischer et al. 2008; Pennington and Swisher 2012
BRIP1	2–4X			increased			
RAD51C	2–4X			increased			
BARD1	2–4X			increased			
RAD50	2–4X			increased			
NBN	2–4X			increased			
MRE11A	2–4X			increased			
MMR Genes							
MLH1				5–15 %		40–80 %	Barrow et al. 2009; Bonadona et al. 2011;"Lynch Syndrome" - GeneReviewsTM; Vasen et al. 2001
MSH2				5–15 %		40–80 %	
MSH6				5–15 %		40–80 %	
PMS2				5–15 %		15–20 %	Senter et al. 2008; Balmana et al. 2010
PMS1				increased		increased	Vasen et al. 2001; Nicolaides et al., 1994; Peltomäki and Vasen, 1997
EPCAM						40 %	Kempers et al. 2011; Ligtenberg et al. 2012
Syndromic Colon Cancer Genes							
APC						~100 %	Bisgaard et al. 1994; Burt et al., 1990
BMPR1A						40 %	Brosens et al. 2007; Howe et al. 1998; Howe et al. 2004
SMAD4						40 %	Brosens et al. 2007; Howe et al. 1998; Howe et al. 2004
Other Syndromic Genes							
CDH1		40–50 %					Guilford et al. 2010; Pharoah et al. 2001
PTEN		up to 85 %				18 %	Brownstein et al. 1978; Starink et al. 1986; Tan et al. 2012
STK11		30–80 %		20 %		30 %	Hearle et al. 2006; Boardman et al. 1998
RB1	3–4X						Marees et al. 2008; Fletcher et al. 2004
MUTYH	2X					2–3X	Rennert et al. 2012
CHEK2 Pathway							
CHEK2	2–4X		1.5X				Cybulski et al. 2011; Meijers-Heijboer et al. 2002; Tung and Silver 2011; Byrnes et al. 2008
ATM	2-4X						Swift et al. 1991; Thompson et al. 2005; Thorstenson et al. 2003; Byrnes et al. 2008
TP53		80–100 %		increased			Masciari et al. 2012; Chompret et al. 2000

remove the risks conferred by other factors such as personal medical history, family history, environmental exposures, and demographics. The patient may still be at increased risk over the general population, and additional screening and prevention measures may be warranted. Given the intricacies involved in panel testing and the range of possible complex results, a certified genetic counselor and/or medical geneticist should be an integral part of the testing process.

Another challenge to counseling for panel testing is that the implications of a positive result differ for each gene and variant detected. The type of cancer (expressivity) and level of risk (penetrance) associated with each mutation will be very different. Depending on the variant detected, the availability of risk-reduction, prevention, and treatment options, as well as other implications for the individual and family may also vary widely amongst the heritable cancer syndromes (Multiplex genetic testing. The Council on Ethical and Judicial Affairs and American Medical Association 1998; Rahman and Scott 2007). Communicating these intricacies to patients becomes increasingly difficult as more testing targets are added.

Informed Consent

Modifications to the standard informed consent process for single gene tests should be considered when counseling for panel testing. Communicating the same amount of detail for each gene in the panel that is usually conveyed with single gene testing would likely lead to information overload, in which there is too much information to absorb in a short time, potentially impeding patient understanding and decision making ability (Collins et al. 2001; White and Dorman 2000). In addition, the time needed to have a detailed discussion about each gene being tested may be prohibitive (Elias and Annas 1994). Given the vast amount of information that needs to be conveyed to patients prior to undergoing panel testing, innovative methods of communication will need to be developed to effectively explain risks and benefits, and to assess patient understanding (Domchek et al. 2013; Ormond et al. 2010; Tabor et al. 2012). Healthcare professionals beyond genetic counselors and medical geneticists will need to be trained to convey this information in order to meet the growing demand (Ormond et al. 2010).

Management Guidelines

For individuals who are at increased risk of cancer due to having a known cancer syndrome, a strong family history of cancer, or a significant personal medical history, established guidelines exist for increased surveillance and risk reduction options. The American Cancer Society (ACS) and the National Comprehensive Cancer Network (NCCN) provide recommendations for individuals at increased risk for breast and colon cancer based on a number of different factors (American Cancer Society, n.d. (http://www.cancer.org/cancer/colonandrectumcancer/moreinformation/colonandrectumcancerearlydetection/colorectal-cancer-early-detection-acs-recommendations; http://www.cancer.org/cancer/breastcancer/moreinformation/breastcancerearlydetection/breast-cancer-early-detection-acs-recs). For *BRCA1/2* mutation carriers, annual mammograms and MRIs are recommended, as well as consideration of prophylactic surgery and chemoprevention. Those carrying mutations for Lynch syndrome are advised to have a colonoscopy every 1–2 years starting at age 20–25 or 2–5 years prior to the earliest age of diagnosis in the family. For individuals who do not carry a known high risk mutation but are at increased risk of cancer due to family history, clinical recommendations are often based on a threshold level of risk above which it is warranted to offer surveillance and risk reduction strategies. For those with a strong family history of breast/ovarian cancer such that the lifetime risk is >20 %, annual mammograms are recommended beginning at age 30, with consideration given to MRI as well as prophylactic surgery and chemoprevention options. For those with a strong family history of colon cancer placing them at a 2X or higher lifetime risk, colonoscopy is recommended to begin at age 40 or 10 years prior to the earliest age of diagnosis in the family, and then repeated every 3–5 years. Uncovering cancer risk mutations in those with less compelling family histories could elevate their baseline empiric risks above the threshold of action, in turn providing them with surveillance and risk reduction options.

For lower penetrance genes that lack established management guidelines, the implications for clinical care are less clear (Robson et al. 2010). In these cases, existing recommendations for genes with comparable risk levels could be applied in order to guide future management. Therefore, testing these moderate risk genes does have clinical utility as it may modify baseline empiric risk conferred by family and medical history alone, providing a more personalized risk assessment. In addition, testing these genes in a cancer panel may uncover previously unknown risks of other cancers for which increased surveillance may benefit the patient.

Additional factors play a role in cancer risk and management recommendations and should be integrated with numerical risk in order to provide a comprehensive risk assessment. Other biological factors such as breast density may impact breast cancer risk and screening decisions. Higher breast density increases the risk of breast cancer and decreases the sensitivity of mammography, therefore adjunct methods of screening such as MRI or ultrasound are usually utilized in these cases (Saadatmand et al. 2012). Behavioral factors and comorbidities such as age, obesity, diabetes, heart disease, alcohol intake, and smoking impact cancer risk and should be taken into account in cancer risk assessment and management recommendations (Akushevich et al. 2011; Chlebowski 2002; Yasmeen et al. 2012). In addition, ethnic and cultural

differences, as well as personal preferences and values play a role in decision making about management options, and should be factored into the discussion (Julian-Reynier et al. 2001; Meiser et al. 2000; Trill and Holland 1993).

Knowledge of the molecular mechanisms of genes may also help guide management. For instance, many of the genes on the Einstein/Montefiore panel are involved in DNA repair such as *ATM, BRCA1/2,* and *p53*. Ionizing radiation induces double-stranded breaks in DNA, and carriers of mutations in DNA repair genes show increased radiosensitivity and increased risk of malignancy with radiation exposure. Therefore special consideration should be given to the use of ionizing radiation imaging techniques in those with DNA repair gene mutations (Bernstein et al. 2010; Heymann et al. 2010; Pijpe et al. 2012).

For gene mutations that lack established management guidelines and have uncertain clinical utility, genetic risk assessment can still provide benefit to patients. Personal utility can be an important factor for tests that lack standard therapeutic or preventive options (Secretary's Advisory Committee on Genetics and Health, Society 2006). For example, in individuals who chose to undergo susceptibility testing for Alzheimer's disease, a disease for which there is no proven cure or prevention, information-seeking was an important motivator for pursuing genetic testing (Hurley et al. 2005; Roberts et al. 2003). In addition, logistical and altruistic factors such as future planning, preparing family members, and contributing to research impact decisions about undergoing testing (Hurley et al. 2005; Roberts et al. 2003). Feeling more in control of one's health has also been cited as a motivating factor for pursuing susceptibility testing for complex disease (Gooding et al. 2006; Lerman and Croyle 1994).

Discussion and Future Directions

Technological developments in genetics and genomics have significantly advanced the field of cancer care in terms of risk assessment, targeted therapies, and prevention (Khoury et al. 2011). The use of cancer gene panels is one example of translational genomics that is rapidly being adopted into clinical practice. Khoury at al. (2007) outline a framework for the continuum of translational research in order to efficiently and effectively integrate genomic discoveries into clinical care. The first Phase (T1) entails the transformation of a gene discovery into a practical application, such as the development of a genetic test for a risk-increasing gene. Phase 2 (T2) assesses this genomic application in efforts to develop evidence-based guidelines for its clinical use. This is the most challenging and time-intensive phase of translational research as it involves assessment of analytic and clinical validity, clinical utility, as well as ethical, legal and social issues surrounding the genetic test. Phase 3 (T3) involves the application of evidence-based guidelines into clinical practice. T3 also has inherent challenges in terms of knowledge dissemination, integrating new practices into existing infrastructure, and actual adoption of the new technology. Phase 4 (T4) assesses population level outcomes research of the genomic application. In the case of gene panels that assess moderate risk genetic variants of lower frequency, we seem to be in both the T2 and T3 phases simultaneously. Although there may be some hesitation to move into Phase 3 prior to the completion of Phase 2, it is quite likely that both phases will occur simultaneously (Domchek et al. 2013). *BRCA* testing became clinically available as early as 1995 (Cho et al. 1999), and research pertaining to this testing is still ongoing (Donnelly et al. 2013; Narod et al. 2013; Sherman et al. 2013). Undoubtedly there is still much to learn about these lower penetrance cancer genes, and more research needs to be conducted concurrently with the availability of panel testing in order to maximize the clinical utility of such testing.

To address the difficulty in devising accurate and understandable risk estimates, future studies should assess how composite genetic models predict cancer risk. Prospective studies with large sample sizes are needed to determine the frequency and positive predictive value of less common variants (Ng et al. 2009), and it is important to recognize that it may be difficult to identify and accrue adequate numbers of individuals for such studies.

Another area of research that deserves attention is the psychological and behavioral impact of providing personalized genetic risk assessment using a panel test. Studies thus far have yielded mixed results regarding behavior change following genetic susceptibility testing for complex disease (Chao et al. 2008; "Getting personal" 2008; McBride et al. 2005; Vernarelli et al. 2010; Zick et al. 2005). In general, genetic risk assessment does not appear to have an adverse psychological effect on patients (Green et al. 2009; Schlich-Bakker et al. 2006). This could be explained by the fact that those who feel that they are at increased risk are more likely to undergo testing and are therefore more prepared for the results. They may also be using testing as a way to cope with concerns and uncertainties about their risk (Gooding et al. 2006). In the case of cancer panel testing however, risks for multiple different cancers may be uncovered, and the implications of the test results may be less clear. Therefore the motivations for undergoing panel testing and the psychological and behavioral responses to the results should be explored in order to design a genetic testing process that optimizes understanding and informed decision making for the patient, and also maximizes the clinical utility of the testing.

Conclusions

Cancer panel genetic testing enhances the benefits of genetic risk assessment by 1) extending testing to a wider population beyond those who meet standard genetic testing criteria and 2) broadening the number of gene targets to assess risk, providing a more comprehensive risk assessment. However there are also significant challenges and limitations to the use of cancer panels. Changes to the current paradigm of genetic counseling and testing for monogenic disease risk will need to be applied to accommodate the unique nature of panel testing. Although existing models of genetic counseling for risk assessment and current recommendations for the medical management of cancer risk can be used to guide the application of cancer genetic panels, more information about clinical validity, utility, and the outcomes of panel testing is needed to maximize the benefits of this testing.

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