J Genet Counsel
DOI 10.1007/s10897-014-9714-7

NEXT GENERATION GENETIC COUNSELING

The Evolution of Cancer Risk Assessment in the Era of Next Generation Sequencing

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Received: 28 June 2013 / Accepted: 12 March 2014

Abstract Cancer genetics professionals face a new opportunity and challenge in adapting to the availability of cancer genetic testing panels, now available as a result of Next Generation Sequencing (NGS) technology. While cancer panels have been available for over a year, we believe that there is not yet enough data to create practice guidelines. Despite this, a year of experience allows us to provide our opinion on points to consider as cancer genetic counselors incorporate this testing technology into genetic counseling practice models. NGS technology offers the ability to potentially diagnose hereditary cancer syndromes more efficiently by testing many genes at once for a fraction of what it would cost to test each gene individually. However, there are limitations and additional risks to consider with these tests. Obtaining informed consent for concurrent testing of multiple genes requires that genetics professionals modify their discussions with patients regarding the potential cancer risks and the associated implications to medical management. We propose dividing the genes on each panel into categories that vary by degree of cancer risk (e.g. penetrance of the syndrome) and availability of management guidelines, with the aim to improve patient understanding of the range of information that can come from this testing. The increased risk for identifying variants of uncertain significance (VUS) when testing many genes at once must be discussed with patients. Pretest genetic counseling must also include the possibility to receive unexpected results as well as the potential to receive a result in the absence of related medical management guidelines. It is also important to consider whether a single gene test remains the best testing option for some patients. As panels expand, it is important that documentation reflects exactly which genes have been analyzed for each patient. While this technology holds the promise of more efficient diagnosis for many of our patients, it also comes with new challenges that we must recognize and address.

Keywords Genetic counseling · Neoplastic syndromes · Hereditary · Genetics · Medical · Next generation sequencing · Genetic testing panels

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Next-Generation Sequencing and Cancer Susceptibility Testing

As of June 1, 2013, nine laboratories in the United States were offering NGS cancer susceptibility gene panels, although at the time of completing this paper, several other laboratories announced intentions to release similar panels. We predict that the number of laboratories offering this testing service will continue to grow. Moreover, each laboratory may take a different approach as to the number of panels it offers and/or genes included on each panel.

The complexity of information that can come from a cancer gene panel is significant, yet given the growing number of cancer susceptibility genes with overlapping phenotypes and the potential time and cost savings of panel tests, we anticipate that cancer genetics providers will need to incorporate this technology into their genetic testing practices. Leaders in the cancer genetic community emphasize the importance of developing new models for providing genetic counseling to

Published online: 24 April 2014

patients considering cancer panel testing, to promote better informed consent (Domchek et al. 2013). Informed consent must be obtained under time constraints that are becoming more challenging in light of increasing patient volume and complexity of information to convey to patients. The purpose of this commentary is to highlight issues to consider when contemplating panel testing for cancer susceptibility and to propose a scheme for categorizing genes in order to facilitate informed consent and result disclosure.

Points to Bear in Mind When Considering Panel Testing for Cancer Susceptibility

As clinicians are faced with the decision of a single gene/syndrome test (e.g. *BRCA1/BRCA2* test) versus a cancer panel test (e.g. breast and/or ovarian cancer panel), there are multiple factors that need to be considered. For example, a cancer panel may lead to an improved detection rate for the causative gene mutation; however, depending on the finding, there may not be sufficient data in the medical literature to guide the clinician on how to medically manage that patient. In addition, the improved detection rate of a cancer panel should be weighed against a higher risk to find a variant of unknown significance (VUS). Lastly, each laboratories approach to a panel may differ, and therefore the ordering clinician will have several factors to consider when choosing between tests/laboratories (Table 1). There is not enough published literature to establish guidelines regarding which patients are best suited for a single gene/syndrome test versus a cancer panel test. Until such guidelines are established, the following factors should be considered when presenting a patient with genetic testing options and choosing which test to recommend.

Detection Rate

Gene panels may improve the detection rate of hereditary cancer syndromes. They may also expand the range of phenotypes associated with mutations in various genes and contribute to the understanding of the natural history of hereditary cancer syndromes. The traditional approach to genetic testing has involved analyzing a single gene or a few genes related to a single syndrome based on the pattern of cancers observed in a family. However, this method may have led to underrecognition of patients with mutations as between 30 % and 50 % of individuals with a mutation do not have a family history significant enough to warrant genetic testing (Meldrum et al. 2011). Gene panels allow for concurrent analysis of genes in which mutations confer variable levels of cancer risk and variable tumor spectrums, thus attending to syndromes with overlapping phenotypes and also addressing the limits of an uninformative family history.

Variants of Uncertain Significance (VUS)

The disadvantage of an improved detection rate is a greater possibility of identifying VUS's. A VUS is a genetic alteration whose association with disease risk is currently unknown. It is challenging for genetic counselors and other members of the healthcare team to consistently advise patients on appropriate medical management following the detection of a VUS and this may add to patient distress (Domchek and Weber 2008). The likelihood of identifying a VUS is proportional to the number of genes tested; therefore, gene panels inherently uncover more VUS's than single gene testing (Domchek et al. 2013). Laboratories should classify variants according to the American College of Medical Genetics (ACMG) guidelines and document supporting evidence regarding each variant's known or possible role in disease (Rehm et al. 2013).

While most labs that perform single gene testing report a VUS rate between 3 % and 5 % for genes such as *BRCA1* and *BRCA2*, labs that offer NGS panels report higher VUS rates. For example, Ambry Genetics reports through their website a VUS rate of 4 % in *BRCA1* and *BRCA2* analysis, but a VUS rate of 33 % for their largest cancer gene panel (Ambry Lab 2013). Genetic counselors should share this information with patients so that they understand that while NGS panels may have a good detection rate, they also have a greater VUS rate.

Medical Management Recommendations

Many gene panels include testing for conditions with variable penetrance, although the optimal medical management of carriers of low to moderately penetrant conditions is not typically well-defined. In many cases, medical management guidelines do not exist and the appropriate clinical response remains unclear. Data regarding cancer risks may not be available for all genes being tested, and risk estimates may be especially difficult for patients who carry variants and/or mutations in multiple genes. In some cases, appropriate medical management will be based on a patient's personal and family history more so than genetic test results. However, genetic test results may still be beneficial for excluding a diagnosis (in the case of a negative result) or allowing targeted testing for family members (in the case of a positive result). It is possible that more information will be discovered about the phenotype and cancer risks related to each syndrome as more patients are tested and a larger pool of patients with hereditary cancer syndromes are identified. In much the same way that testing criteria and medical management guidelines have evolved for families at high risk for hereditary breast and ovarian cancer syndrome, it is plausible that management guidelines for cancer syndromes with incomplete penetrance will be developed in the future.

Table 1 Choosing a laboratory for NGS cancer panels

What technology is used	▪ Platform of the testing
	▪ Depth of coverage
	▪ Presence of deletion/duplication assay
Which genes are included	▪ Number of genes (Larger panels may not be of any more benefit to the patient)
	▪ A cancer site-specific test (e.g. breast cancer susceptibility) versus a pan-cancer test (all cancer susceptibility)
	▪ The proportion of genes that are considered "medically actionable", meaning mutated genes will lead to a change in medical management that is supported by guidelines
	▪ Option to exclude results per patient request
What is the cost of testing/Insurance coverage	▪ List price
	▪ Billing options (e.g. insurance vs. institutional billing)
	▪ "In network" or "out of network"
	▪ Medicare or Medicaid billing options
	▪ Financial assistance or payment plans for uninsured patients
	▪ Presence of a patient "cap" to control patient expense
	▪ Requirements for letters of medical necessity
What is the Turn-Around-Time (TAT)	▪ TAT for insurance preauthorization (if offered) and testing
	▪ TAT for panels vs. single genes
	▪ Importance of TAT may be dictated by whether or not a patient is using the information to make an immediate management decision (e.g. surgery for recent diagnosis)
Variants of Unknown Significance (VUS) rate	▪ VUS rate for the panel under consideration
	▪ How conservative is the laboratory in calling out a mutation versus VUS versus benign polymorphism
	▪ VUS reclassification process (Does the laboratory offer free VUS testing to affected family members? How are ordering providers notified when reclassifications occur?)
	▪ Supplementary data provided by the laboratory regarding the variant (e.g. cosegregation data, data from in silico models, population frequency, review of the literature, etc.)
	▪ Patient's level of anxiety about a VUS result (which may dictate the importance you place on a laboratory's VUS rate)
How reliable is the laboratory	▪ Past experience with the laboratory for other cancer susceptibility genetic testing
	▪ Laboratory's experience with NGS technology
	▪ Laboratory's experience with the gene(s) of interest (e.g. lab may be able to better classify missense mutations, etc.)
	▪ Accuracy of result interpretation
Ease of laboratory use	▪ Insurance pre-verification process
	▪ Reliable communication
	▪ Sample submission process (workload to order a test)
	▪ Readability of test report
	▪ Availability and reliability of online reporting system
	▪ Access to genetics professionals

Breaking Down the Panels: Gene Stratification

Obtaining informed consent for concurrent testing of multiple genes requires that genetics professionals modify their discussions with patients regarding the potential cancer risks and the associated implications to medical management. We propose dividing the genes on each panel into three categories that vary by degree of cancer risk and availability of management guidelines, with the aim to improve patient understanding of the range of information that can derive from a Cancer Panel genetic test.

Category 1: Genes that, when mutated, confer high cancer risks, with published management guidelines for those with mutations.

This category includes genes for which there is a substantial amount of peer-reviewed literature to support the clinical significance of a mutation. Mutations in these genes are associated with significant lifetime cancer risks (often 50 % or greater) and generally, there are published guidelines that direct healthcare professionals on how to manage individuals with these associated cancer risks. Many genes in this category, such as the *BRCA1/BRCA2* and mismatch repair genes, have been analyzed for years via single syndrome testing, primarily when family history risk assessment has raised concern for the associated syndrome. However, this category also includes genes in which prior testing uptake was relatively low, often due to the rarity of mutations in such genes. An example of this is the *TP53* gene. *TP53* mutations are thought to occur in 1 in 20,000 individuals (Gonzalez et al. 2009) and are associated with Li Fraumeni syndrome (LFS) (Chompret et al. 2000; Nichols et al. 2001). The component cancers of LFS (i.e. cancers that defined this syndrome when diagnostic criteria were first published) include female breast cancer, soft-tissue sarcomas, osteosarcomas, brain tumors, leukemia, and adrenal cortical cancers (Li et al. 1988); however, the list of cancers that have been reported with increased frequency with this syndrome is extensive (Birch et al. 2001; Kleihues et al. 1997). There are established management guidelines for patients with this syndrome (e.g. National Comprehensive Cancer Network guidelines), as well as published screening protocols that are currently under investigation but show promise of increasing early cancer detection for patients with LFS (National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, "Genetic/Familial High-Risk Assessment: Breast and Ovarian," 2013; Villani et al. 2011). The *TP53* gene is on nearly all of the cancer gene panels. Genes that fit within this category and that are available on current cancer panels include the aforementioned TP53 gene, as well as the genes listed in Table 2.

Category 2: Genes that when mutated, confer moderate cancer risks, with no management guidelines for those with mutations.

This category includes genes for which there is peer-reviewed literature to support the clinical significance of a mutation and often, clinical testing has been available for years. However, these genes are less likely to have been ordered routinely given that mutations in such genes are associated with more moderate cancer risks and no well-established management guidelines exist. An example of a gene in this category includes *PALB2*. *PALB2* mutations are associated with a 2.3–3.4 fold increased risk of breast cancer (Casadei et al. 2011; Rahman et al. 2007). *PALB2* mutations have also been documented in familial pancreatic cancer families (Jones et al. 2009). In addition, familial breast cancer patients (breast cancer patients with ≥2 family members with breast cancer) with *PALB2* mutations are six times more likely to have a family history of pancreatic cancer than familial breast cancer patients without such mutations (Casadei et al. 2011). Despite this apparent association, the degree of pancreatic cancer risk has yet to be fully elucidated. There is still a question as to whether *PALB2* mutations may contribute to increases in other cancer risks, such as prostate or ovarian cancer (Casadei et al. 2011; Erkko et al. 2007). While one can use clinical judgment to guide medical management for *PALB2* mutation carriers (e.g. add breast MRIs to a woman's annual screening regimen), there are no guidelines to indicate when to begin such screening or to assist with requesting insurance coverage for high-risk screening. Genes that fit within this category include the aforementioned *PALB2* gene, as well as the genes listed in Table 2.

Category 3: Genes that, when mutated, are known to be prevalent within a certain cancer patient population,

Table 2 Three categories of genes found on NGS cancer panels

	Syndrome penetrance (Cancer risk)	Understanding of phenotype	Management guidelines	Examples of genes
Mutations found in Category 1	High	Good to Excellent	Published guidelines likely to exist, screening or prevention for many of associated cancer risks exist, mutation likely to change management	*APC, BMPR1A BRCA1, BRCA2, CDH1, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11, TP53*
Mutations found in Category 2	Moderate	Fair to Good	Guidelines unlikely to be published, screening may exist for associated cancer risks, mutation may or may not change management	*ATM, CHEK2,PALB2*
Mutations found in Category 3	Unknown	Poor	Guidelines do not exist, difficult to make recommendations and therefore unlikely to change management	*BARD1, BRIP1, MRE11, NBN, NBS1, RAD50, RAD51C, RAD51D*

however the degree of cancer risk and tumor spectrum are not well understood, with no management guidelines for those with mutations.

This category includes genes in which clinical testing was generally not available prior to the availability of cancer panels, likely given limited data regarding the implications of such gene mutations. It is not that these genes do not or will not have clinical relevance—they may. However, our present understanding of the implications of mutations in these genes is still in development, and mutations in these genes may not be immediately clinically relevant (i.e. would not change a patient's medical management). An example of a gene in this category includes *BRIP1*. While *BRIP1* mutations have been found to be more prevalent in individuals with familial breast cancer compared to controls (Seal et al. 2006), other studies have failed to show an association (Frank et al. 2007; Lewis et al. 2005). There is more recent data to show a significantly elevated ovarian cancer risk with *BRIP1* mutations (Rafnar et al. 2011), although this finding has yet to be replicated. Also, it appears that even if the elevated risk is real, *BRIP1* mutations account for <1 % of ovarian cancers (Walsh et al. 2011). While it is likely that *BRIP1* mutations play some role in cancer predisposition, more research is necessary to understand that role and the clinical implications. Genes that fit within this category include the aforementioned *BRIP1* gene, as well as the genes listed in Table 2.

Adopting Next Generation Genetic Counseling

As discussed, there are no clear guidelines on when to order NGS cancer panels. The American College of Medical Genetics (ACMG) has developed a position statement for whole exome and genome sequencing ("Points to consider in the clinical application of genomic sequencing," 2012) that can be adapted to apply to NGS cancer panels and be used by genetic counselors to guide their cancer risk assessments (Table 3). Most pediatric genetic panel testing is guided by this ACMG statement. The National Comprehensive Cancer Network (NCCN) addressed the use of gene panels in their 2013 Guidelines for Risk Assessment (National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, "Genetic/Familial High-Risk Assessment: Breast and Ovarian," 2013). The authors of the NCCN guidelines indicated that cancer gene panels could be considered after highly penetrant syndromes have been ruled out and there is still reason to believe the family history is suggestive of a hereditary cancer syndrome. Genetic counselors and health professionals can use these early guidelines to determine when to consider counseling for NGS cancer panels. In the future, guidelines for NGC cancer panels may be developed by a professional organization. For example, the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) developed a consensus statement on genetic testing for channelopathies and cardiomyopathies (Ackerman et al. 2011). This consensus statement is used by cardiovascular genetic counselors to guide NGS panel testing. Both the ACMG and NCCN recommend that genetic counseling should be performed by a cancer genetic professional (National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, "Genetic/Familial High-Risk Assessment: Breast and Ovarian," 2013; Pletcher et al. 2007).

Table 3 ACMG indications for diagnostic testing using NGS

WGS/WES should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:

- The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis.
- A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach.
- A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.

Importance of Informed Consent

When genetic counseling for highly penetrant cancer syndromes was first performed, there were concerns about the lack of knowledge of the cancer risks associated with each syndrome, what early detection and/or risk-reducing options would be available for patients with mutations, and whether patients would experience significant anxiety upon learning they carried a mutation. As an increasing number of individuals with hereditary cancer syndromes were identified, the knowledge of highly penetrant cancer syndromes increased, improving our ability to create effective clinical guidelines for management.

Studies have shown that individuals receiving mutation-positive results describe an increase in anxiety, but that anxiety often returns to baseline with the passage of time (Halbert et al. 2011; Hamilton et al. 2009). Organizations like the NCCN, American Society of Clinical Oncology, and the U.S. Preventive Services Task Force, have acknowledged the research that shows the benefits of genetic counseling and testing for hereditary cancer syndromes; they have written guidelines and recommendations for cancer predisposition testing, all of which include pretest counseling as part of the informed consent process (National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, "Genetic/Familial High-Risk Assessment: Breast and Ovarian," 2013; Robson et al. 2010; U.S. Preventive Services Task Force 2014).

While existing genetic counseling models encourage in-depth discussion of the syndrome to be tested, these models do not address testing multiple syndromes, simultaneously (Domchek et al. 2013). The pre-test genetic counseling model will need to involve a discussion of the range of information that could be learned via a cancer panel, as well as the increased risk of discovering unanticipated results and VUS's. Along with the progress of genetic testing technology, genetic counseling will also have to shift and adapt to ensure patients are educated about the unique benefits and risks of NGS genetic panel testing in order to facilitate informed consent.

Suggested Genetic Counseling Techniques

Traditionally, cancer genetic counseling has evaluated a patient's risk based on personal and family history of cancer, ages of diagnosis, and other phenotypic features. Genetic counselors have used their expert knowledge to choose which genes to test and then counseled the patient about the cancer risks and management options for mutations in those specific genes. Genes that are unlikely to be mutated are not analyzed in this model. This approach to genetic counseling is more specific and targeted than genetic counseling for panel genetic tests. However, this approach can lead to serial testing of multiple genes, which can be expensive and time consuming for the patient if a clear hereditary cancer syndrome is not apparent. In the case where a NGS cancer panel may best serve the patient's quality of care as an initial test, genetic counselors will need to update the depth of information which they provide the patient.

While adapting the amount of information shared with the patient, it is important to maintain patient autonomy and the ability to make an informed decision. Genetic counselors must educate patients about the implications of all the genes included in an NGS panel. A suggestion to help present this information in a timely and effective manner is to group the genes into the aforementioned three categories (Table 2). This technique could help patients understand that mutations in different genes are associated with different levels of risks for cancer, and not all results have clear management guidelines.

It may also be helpful to group the cancers associated with each panel test. The genetic counselor could then broadly describe how the increased cancer risk for each organ may/could be managed. For example, some genes on the breast panels would put a patient at risk for breast and pancreatic cancer; the genetic counselor would explain increased breast cancer surveillance options and then explain the limited screening options for pancreatic cancer. Patients should know a deleterious mutation could mean a risk for multiple sites of cancer and understand the degree to which surveillance and management strategies exist and are efficacious for each site of cancer.

As noted earlier, it is important that patients understand the chance of a VUS result and the limitations of such results. Genetic counselors should consider sharing the VUS rate reported by the elected laboratory when considering NGS panels. Patients should understand that VUS's will not be treated as deleterious nor causative of a cancer predisposition.

Documenting Genetic Testing

There are multiple NGS cancer panels with varying sets of genes, and more genes may be added to these panels as our knowledge about cancer susceptibility improves. While many genetic counselors document the type of genetic testing ordered, it will become more important to document which genes were tested for each patient and which lab was used. It will also be helpful to document the testing platform, depth of coverage, and presence of a deletion/duplication assay. As part of post-test genetic counseling, genetic counselors should continue to inform patients that updated testing may be available for them in the future. The protocol for patients to be notified of such updates (e.g. who has the responsibility to follow-up to discuss advances in testing options) should be clear.

Conclusion

While NGS-based technology, including gene panels, is available and use of this technology is increasing, our understanding of how best to counsel patients for whom we recommend this testing is still evolving. It is essential that future research focus on the outcomes of using this technology, with hope to limit the potential for harm and to maximize the benefit to the patient (Domchek et al. 2013). This was the approach used to develop counseling models for highly penetrant cancer syndromes such as hereditary breast and ovarian cancer syndrome and Lynch syndrome. Collaborative epidemiologic work will also be necessary to gather information about genes included in the NGS panels; this will help provide more substantial information about each gene's associated tumor spectrums and cancer risks, which will lead to the development of appropriate clinical management (Offit 2011).

Conflict of Interest Heather Fecteau MS, CGC, Kristen Vogel MS, CGC, Kristen Hanson MS, CGC, and Shannon Morrill-Cornelius MS, CGC declare that they have no conflict of interest.

Human and Animal Rights No animal or human studies were carried out by the authors for this article.

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