World Journal of Surgical Procedures

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5412/wjsp.v6.i1.13

*World J Surg Proced* 2016 March 28; 6(1): 13-18
ISSN 2219-2832 (online)




# Should multi-gene panel testing replace limited BRCA1/2 testing? A review of genetic testing for hereditary breast and ovarian cancers

Nimmi S Kapoor, Kimberly C Banks

Nimmi S Kapoor, Department of Surgical Oncology, Breastlink, Orange, CA 92868, United States

Kimberly C Banks, Medical Science Liason, Guardant Health, Redwood City, CA 94063, United States

Author contributions: Kapoor NS designed, wrote, and edited this manuscript; Banks KC wrote and edited this manuscript.

Conflict-of-interest statement: Kapoor NS has received honoraria for serving as a speaker for Ambry Genetics and Banks KC was previously employed by Ambry Genetics.



Correspondence to: Nimmi S Kapoor, MD, Director, Department of Surgical Oncology, Breastlink, 230 S. Main Street, Suite 100, Orange, CA 92868,
United States. nimmi.kapoor@breastlink.com
Telephone: +1-714-6193308
Fax: +1-714-5410450

Received: August 22, 2015
Peer-review started: August 23, 2015
First decision: October 27, 2015
Revised: December 12, 2015
Accepted: January 5, 2016
Article in press: January 7, 2016
Published online: March 28, 2016

## Abstract

Clinical testing of patients for hereditary breast and ovarian cancer syndromes began in the mid-1990s with the identification of the *BRCA1* and *BRCA2* genes. Since then, mutations in dozens of other genes have been correlated to increased breast, ovarian, and other cancer risk. The following decades of data collection and patient advocacy allowed for improvements in medical, legal, social, and ethical advances in genetic testing. Technological advances have made it possible to sequence multiple genes at once in a panel to give patients a more thorough evaluation of their personal cancer risk. Panel testing increases the detection of mutations that lead to increased risk of breast, ovarian, and other cancers and can better guide individualized screening measures compared to limited BRCA testing alone. At the same time, multi-gene panel testing is more time-and cost-efficient. While the clinical application of panel testing is in its infancy, many problems arise such as lack of guidelines for management of newly identified gene mutations, high rates of variants of uncertain significance, and limited ability to screen for some cancers. Through on-going concerted efforts of pooled data collection and analysis, it is likely that the benefits of multi-gene panel testing will outweigh the risks in the near future.

**Key words:** Panel testing; Genetic testing; *BRCA*; Breast cancer



**Core tip:** Evaluating multiple genes in a panel test has clear advantages over BRCA1/2 testing including a greater likelihood of identifying patients with actionable pathogenic mutations, improved efficiency over sequential testing, and lower overall cost. At the same time, panel testing comes with limitations; most notably a lack of clear management guidelines for mutations in moderate penetrance genes and limited evidence-based

clinical validity. As more information is gathered on these moderate- and low-penetrance gene mutations, the ability to guide clinical decisions for patients will continue to improve.

Kapoor NS, Banks KC. Should multi-gene panel testing replace limited BRCA1/2 testing? A review of genetic testing for hereditary breast and ovarian cancers. *World J Surg Proced* 2016; 6(1): 13-18 Available from: URL: http://www.wjgnet.com/2219-2832/full/v6/i1/13.htm DOI: http://dx.doi.org/10.5412/wjsp.v6.i1.13

## HISTORICAL CONTEXT

The first hereditary susceptibility gene associated with breast cancer risk was identified in 1994 and called *BRCA1*[1,2]. At that time, there were approximately 182000 cases of breast cancer diagnosed annually in the United States[3] and a growing concern to identify causative factors for a highly prevalent disease. Shortly thereafter in 1995, the *BRCA2* gene was identified and these two genes, *BRCA1* and *BRCA2* (*BRCA1/2*), began to play an important role in evaluating newly diagnosed breast cancer patients and others with high-risk family histories.

Initially, when clinical testing of *BRCA1/2* mutations began in 1996, there were many uncertainties and criticisms: Data to demonstrate outcomes and benefit of proposed management was still being gathered, directive guidelines did not exist, and understanding of the expanding phenotype and variable penetrance was still occurring. The rate of inconclusive results was higher, time to receive results was closer to two months, patient concern about genetic discrimination was much more pronounced, and protective legislation specific to genetic test results was limited. Furthermore, the long-term psychological impact of genetic testing results was yet unknown.

It is now well-documented that germline *BRCA1/2* mutations significantly increase risk for breast, ovarian, and male breast cancer as well as moderately increase risk for prostate and pancreatic cancer[4-6]. Established national guidelines identify which clinical histories warrant *BRCA1/2* genetic testing and how to manage patients who carry *BRCA1/2* mutations, specifically high-risk surveillance and risk-reducing surgical options[7]. *BRCA1/2* genetic testing is now routinely covered by insurance companies in patients with defined clinical histories, the rate of inconclusive results is less than 5%, and results are returned in approximately two weeks. Ultimately, a federal law was passed called Genetic Information Nondiscrimination Act "GINA" of 2008 to prevent medical insurance companies and employers from discriminating against individuals on the basis of their genetic information[8]. Fortunately, initial data has shown that no significant long-term psychological and emotional consequences occur as a result of genetic testing[9].

Many breast surgeons incorporate *BRCA1/2* testing into the initial work-up of newly diagnosed breast cancer patients who meet testing criteria to guide surgical decisions. Family members of affected individuals or other high-risk patients can also be easily referred for cancer genetic counseling for testing and preventive intervention strategies. The high prevalence of *BRCA1/2* mutations among male breast cancer patients and ovarian cancer patients has led to recommendations that any patient with one of these diseases obtain *BRCA1/2* testing[7]. In the last few years, testing criteria have also expanded to include pancreatic cancer and high-grade prostate cancer indications[7].

## RECENT SHIFTS

Of hereditary breast cancers, only 30%-50% is attributed to mutations in *BRCA1* and *BRCA2* genes[10-12]. Over several decades of research, additional genetic mutations in numerous other genes have been implicated in breast and ovarian cancer risk. There are now over 20 genes and hundreds of mutations that have been implicated in the development of breast and/or ovarian cancer (Table 1)[12-14].

Traditionally, testing patients or those at risk for hereditary breast and ovarian cancer risk-began with evaluating *BRCA1/2*. If results were negative, additional testing was offered, often several weeks to months later, only if the patient met certain criteria for additional genetic syndromes. Numerous advances from scientific technology to legislation to public awareness and media, have shifted this testing paradigm.

Technological advances in DNA sequencing have come to what some have termed a "tipping point" in the advancement of genetic evaluation and discovery of new mutations related to hereditary cancer risk[15]. In place of more tedious methods of DNA sequencing using Sanger sequencing techniques, massively parallel DNA sequencing using Next Generation Sequencing (NGS) allows multiple genes to be evaluated at once.

With NGS, came the opportunity to offer panel testing, or evaluating numerous genes at once rather than in sequence. Panel testing decreased the turn-over-time for results while minimizing the cost of the test[10,13]. Even with panel testing, however, there were still restrictions with including *BRCA1/2* testing on a panel due to patents held by the founding company on evaluating these genes for almost 20 years. It was not until a 2013 Supreme Court ruling of Association for Molecular Pathology v. Myriad Genetics that many of these patents that restricted *BRCA1/2* testing became invalidated[16]. Since then, multi-gene panels offered by numerous genetic testing companies were able to include *BRCA1/2* in their panels and offer patients comprehensive testing upfront[17].

Another equally important event that occurred to influence hereditary genetic testing patterns was the public disclosure of the highly acclaimed actress Angelina

**Table 1 List of select genes that can be found on multi-gene panels and associated cancer risks**

| Gene | Cancer risk[1] |
|---|---|
| *ATM* | Breast, pancreatic cancer |
| *BARD1* | Breast |
| *BRCA1* | Breast, ovarian, male breast cancer, melanoma, pancreatic cancer |
| *BRCA2* | Breast, ovarian, male breast cancer, melanoma, pancreatic, prostate cancer |
| *BRIP1* | Breast |
| *CDH1* | Breast, diffuse-type gastric cancer |
| *CHEK2* | Breast, colon, ovarian |
| *EPCAM* | Colorectal, uterine, stomach, ovarian |
| *MLH1* | Colorectal, uterine, stomach, ovarian |
| *MRE11A* | Breast |
| *MSH2* | Colorectal, uterine, ovarian |
| *MSH6* | Colorectal, uterine, stomach, ovarian |
| *MUTYH* | Breast, colorectal, other gastrointestinal sites |
| *NBN* | Breast |
| *NF1* | Breast, peripheral nerve sheath tumors, gliomas, leukemias, pheochromocytomas |
| *PALB2* | Breast, pancreatic cancer |
| *PMS2* | Colorectal, uterine, stomach, ovarian |
| *PTEN* | Breast, thyroid, endometrial cancer |
| *RAD50* | Breast |
| *RAD51C* | Breast, ovarian |
| *RAD51D* | Breast, ovarian |
| *STK11* | Breast, gastrointestinal, ovarian |
| *TP53* | Breast, ovarian, osteosarcomas, brain tumors, colorectal, other gastrointestinal sites |

[1]List of cancer sites is not all-inclusive as additional sites may be pending further clinical validation.

Jolie's *BRCA1* mutation status in 2013. When Jolie explained her decision to choose prophylactic bilateral mastectomy and oophorectomy due to her *BRCA1* mutation, mainstream media brought public awareness to the importance of hereditary genetic testing and as a result, there became a surge in numbers of patients undergoing testing[18]. While numbers referred for testing have more than doubled in some locations, the majority of referrals have been found to be appropriate and for qualified candidates[18].

## NEWER DATA

With this shift in testing, the clinical impact of multi-gene panel testing has become apparent. Prior to inclusion of *BRCA1/2* in panels, LaDuca *et al*[19] evaluated over 2000 patients who underwent multi-gene panel testing with 14-21 genes (excluding *BRCA1/2*) between March 2012 and May 2013. Overall, 8.3% of patients were found to carry pathogenic mutations, ranging from 7.2%-9.6% depending on the number of genes evaluated. Of patients who were deemed to be high risk for hereditary breast and ovarian cancer and underwent a "breast" panel with genes implicated in breast cancer pathogenesis, 10.9% of patients were found to carry pathogenic mutations. The genes found to be mutated most frequently in this cohort of high-risk patients included *PALB2*, *CHEK2*, and *ATM*.

Similarly, Tung *et al*[20] evaluated over 2000 high-risk patients who underwent a NGS multi-gene panel testing with 25 genes including *BRCA1/2*. Of patients who underwent panel testing with *BRCA1/2*, 9.3% were found to carry a *BRCA1/2* mutation and an additional 4.2% of patients carried non-*BRCA* mutations again with the most frequent gene mutations in *PALB2*, *CHEK2*, and *ATM*. Smaller studies have also shown the benefit of panel testing[14,21-23].

We have demonstrated that multi-gene panel testing nearly doubles the pathogenic mutation detection rate in patients with increased risk of hereditary breast and/or ovarian cancer when compared to limited *BRCA1/2* testing alone in a cohort of 966 high-risk patients[21]. Likewise, a French group used their own NGS panel of 27 genes to evaluate 708 high-risk patients and found a 15.4% mutation detection rate[14]. Mutations in *BRCA1/2* accounted for 59% of these genetic alterations in the French study, while 41% were non-*BRCA* genes, again most frequently in *PALB2*, *CHEK2*, and *ATM* genes.

When patients undergo panel testing with multiple genes, there is an increased detection of pathogenic mutations, but there is also increased detection of DNA variants of uncertain significance (VUS). Depending on the number of genes in a panel and the patients who are tested, VUS rates from panel testing have been reported to range from 6.7%-41.7%[19-21]. The VUS rate for any given gene will be highest initially as data starts to accumulate, then will decrease over time[19]. Nonetheless, *BRCA1/2* testing is still associated with a VUS rate of approximately 4%[21].

## BENEFITS

In order for a new testing method to replace an es-

tablished algorithm, a substantial benefit should be possible with limited consequences. There are a number of obvious advantages of multi-gene panel testing over limited *BRCA1/2* testing. Panel testing not only provides patients with more information about their hereditary risk by increasing the detection of pathogenic mutations, but it also identifies actionable mutations for which patients can choose to increase surveillance of high risk cancers, initiate chemoprevention, or even undergo prophylactic surgery to remove a potential at-risk organ site.

Carrying a *BRCA1/2* mutation leads to a lifetime risk of breast cancer up to 85% and a lifetime risk of developing ovarian cancer between 15%-60%[4-6]. Increased surveillance with breast MRI can detect breast cancers at earliest stages for these patients, while prophylactic bilateral mastectomy decreases this risk by over 90% and prophylactic bilateral salpingo-oophorectomy minimizes the risk of both ovarian and breast cancer[24,25]. Similarly, patients with mutations in non-*BRCA* genes that are associated with increased risk of breast cancer, such as *PALB2*, *CHEK2*, and *ATM*, may also benefit from increased screening with breast MRI. Other patients with these non-*BRCA* gene mutations, especially those with a strong family history of breast cancer or who carry particularly penetrant gene mutations may even benefit from prophylactic mastectomies[26-31].

In addition to identifying genes associated with breast and/or ovarian cancer risk, panel testing identifies genes with cancer risk in other organ sites (Table 1). Mutations in the *PTEN* gene, for example, confer a risk of breast, thyroid, and endometrial cancer. Patients with *PTEN* mutations and the related Cowden syndrome are recommended to not only have increased breast cancer surveillance, but annual thyroid ultrasounds and endometrial evaluations as well[7]. On the other hand, *MSH2* mutations are implicated in Lynch syndrome, which is characterized by increased risk of early onset colon, uterine, and ovarian cancers[32]. For these patients, consideration of hysterectomy and oophorectomy and increased frequency of colonoscopies should be included in counseling. Multi-gene panel testing can help direct focused screening in high risk patients and even enable risk-reducing interventions.

Other benefits of panel testing over sequential testing include the ability to test for genes that a patient might not normally be considered for. This is especially true for more rare gene mutations that are typically associated with particular family inheritance patterns or traits such as Li Fraumeni syndrome or Cowden Syndrome[33,34]. With panel testing, these rare mutation carriers can be more readily identified in patients with limited or unknown family history.

Fortunately, NGS allows for multi-gene panel testing to be both efficient and cost-effective[13,23,35]. Rather than thousands of dollars for only *BRCA1/2* testing, dozens of genes can now be sequenced at once for a fraction of the cost.

## LIMITATIONS AND CONCERNS

While panel testing increases the diagnostic yield by up to 50% compared to *BRCA1/2* testing alone, sometimes the pathogenic mutation identified is in a gene for which there is limited data as to the cancer risks and cancer spectrum so patient management recommendations will not be available. National Comprehensive Cancer Network guidelines currently provide detailed recommendations for a handful of well-characterized, highly-penetrant genes (*BRCA1, BRCA2, PTEN, TP53, CDH1,* and *STK11*) and also provide breast and ovarian management considerations for some of the genes commonly identified by panel testing (*ATM, CHEK2*, and *PALB2*)[7]. Detailed recommendations, however, accounting for the other cancer risks associated with these genes and recommendations for management of patients with mutations in less-characterized genes do not yet exist. It is also possible that mutations in moderate/intermediate-risk genes may not entirely explain a personal and/or family history of cancer; the role of gene/gene and gene/environment interactions could influence the manifestation of a gene mutation and/or cause phenocopies in the family (people who do not carry a known familial mutation but develop a cancer associated with the familial gene mutation). In addition, others have argued that there is a lack of clinical validity due to limited data sets that estimate cancer risk for many of the genes found on panels[36]. Clearly larger population and family-based studies will be needed to provide the best risk-estimates for appropriate counseling for the more rare gene mutations. Given this, management recommendations for patients (and their family members) with mutations in less-characterized genes need to take into account what is known about the specific gene as well as the personal and family clinical history[21].

With the identification of cancer risk outside of breast, colon, and ovarian cancer, comes the question of how to screen for and/or prevent rare cancers that associated with specific gene mutations (Table 1). This dilemma is not specific to the "newer" genes included on many panels. Patients with a *BRCA1/2* gene mutation and family history of pancreatic cancer are counseled that they likely have an increased risk for pancreatic cancer, but screening for early-detection of pancreatic cancer is not well-established and only recommended within the scope of a clinical trial[37]. Patients found to carry a *TP53* gene mutation are informed that they have a significantly elevated risk for multiple types of cancers, some of which we have screening modalities and guidelines for but others which do not[7]. On the other hand, patients with a *CDH1* gene mutation can have up to a 70% risk of gastric cancer by age 80 and may be recommended to consider prophylactic total gastrectomy[38]. As with targeted *BRCA1/2* or *TP53* testing, patients undergoing panel testing need to be informed of the benefits, limitations, and possible implications of testing, including limited screening and

prevention options for certain cancers.

Another limitation with panel testing is the higher rate of inconclusive (variant of uncertain significance) results. Similar to the early days of *BRCA1/2* genetic testing when VUS rates were higher, clinicians ordering panels for their patients must be aware of the higher possibility of identifying a VUS and make empiric management recommendations based on the personal and family clinical history when such a result is received[19-22]. An inconclusive result can cause patient (and clinician) anxiety about future cancer risks and potential risk for family members. Patients with VUS results can contribute to research specific to their gene variant and participate in national registries such as the Prospective Registry of Multiplex Testing. Often, however, facilitation of patient participation in such research falls to the managing busy clinician. As additional data is accumulated, VUS results are ultimately re-classified to either benign or deleterious, often years later, and the original ordering clinician receives the reclassification report that they must then act upon.

Lastly, as with any emerging technology, NGS and multi-gene panel tests are currently without established insurance guidelines for payment reimbursement. Without a panel-specific current procedural terminology (CPT) code, billing for panel tests is not as straightforward as *BRCA1/2* or Lynch testing for which gene-specific CPT codes exist. Obtaining authorization for *BRCA1/2* testing is fairly simple, while obtaining authorization for panel testing may require more work from the clinicians' office, although some laboratories will perform insurance authorization services to support the process.

## CONCLUSION

Evaluating patients at risk for hereditary breast and ovarian cancer syndromes has transformed in a short period of time. Mutations in *BRCA1/2* genes are still the most common gene mutations accounting for inherited cancer risk, however numerous other genes have been added to the spectrum of hereditary cancer risk. Evaluating multiple genes in a panel test has clear advantages over *BRCA1/2* testing including a greater likelihood of identifying patients with actionable pathogenic mutations, improved efficiency over sequential testing, and lower overall cost. At the same time, panel testing comes with limitations; most notably a lack of clear management guidelines for mutations in moderate penetrance genes and limited evidence-based clinical validity. As more information is gathered on these moderate- and low-penetrance gene mutations and VUS through national efforts, our ability to guide clinical decisions for our patients will continue to improve. In the interim, thoughtful application of existing guidelines for gene mutations with cancer risk profiles similar to genes with established guidelines can be applied in the management of patients with mutations in some of these newer genes.

## REFERENCES


1 **Miki Y**, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 1994; **266**: 66-71 [PMID: 7545954 DOI: 10.1126/science.7545954]

2 **Friedman LS**, Ostermeyer EA, Szabo CI, Dowd P, Lynch ED, Rowell SE, King MC. Confirmation of BRCA1 by analysis of germline mutations linked to breast and ovarian cancer in ten families. *Nat Genet* 1994; **8**: 399-404 [PMID: 7894493 DOI: 10.1038/ng1294-399]

3 **SEER cancer statistics review 1973-1994.** [accessed 2015 Aug 8]. Available from: URL: http: //seer.cancer.gov/archive/csr/1973_1994/overview.pdf

4 **Struewing JP**, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, Tucker MA. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997; **336**: 1401-1408 [PMID: 9145676 DOI: 10.1056/NEJM199705153362001]

5 **Antoniou A**, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003; **72**: 1117-1130 [PMID: 12677558 DOI: 10.1086/375033]

6 **Ford D**, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Lancet* 1994; **343**: 692-695 [PMID: 7907678 DOI: 10.1016/S0140-6736(94)91578-4]

7 **National Comprehensive Cancer Network.** Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Clinical Practice Guidelines in Oncology. [accessed 2015 Aug 15]. Available from: URL: http://www.nccn.org/professionas/physician_gls/pdf/genetics_screening.pdf

8 **Genetic Information Nondiscrimination Act of 2008.** Available from: URL: http://www.eeoc.gov/laws/statutes/gina.cfm

9 **Lerman C**, Narod S, Schulman K, Hughes C, Gomez-Caminero A, Bonney G, Gold K, Trock B, Main D, Lynch J, Fulmore C, Snyder C, Lemon SJ, Conway T, Tonin P, Lenoir G, Lynch H. BRCA1 testing in families with hereditary breast-ovarian cancer. A prospective study of patient decision making and outcomes. *JAMA* 1996; **275**: 1885-1892 [PMID: 8648868 DOI: 10.1001/jama.1996.03530480027036]

10 **Walsh T**, King MC. Ten genes for inherited breast cancer. *Cancer Cell* 2007; **11**: 103-105 [PMID: 17292821 DOI: 10.1016/j.ccr.2007.01.010]

11 **van der Groep P**, van der Wall E, van Diest PJ. Pathology of hereditary breast cancer. *Cell Oncol* (Dordr) 2011; **34**: 71-88 [PMID: 21336636 DOI: 10.1007/s13402-011-0010-3]

12 **Meindl A**, Ditsch N, Kast K, Rhiem K, Schmutzler RK. Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. *Dtsch Arztebl Int* 2011; **108**: 323-330 [PMID: 21637635 DOI: 10.3238/arztebl.2011.0323]

13 **Walsh T**, Lee MK, Casadei S, Thornton AM, Stray SM, Pennil C, Nord AS, Mandell JB, Swisher EM, King MC. Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. *Proc Natl Acad Sci USA* 2010; **107**: 12629-12633 [PMID: 20616022 DOI: 10.1073/pnas.1007983107]

14 **Castéra L**, Krieger S, Rousselin A, Legros A, Baumann JJ, Bruet O, Brault B, Fouillet R, Goardon N, Letac O, Baert-Desurmont S, Tinat J, Bera O, Dugast C, Berthet P, Polycarpe F, Layet V, Hardouin A, Frébourg T, Vaur D. Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes. *Eur J Hum Genet* 2014; **22**: 1305-1313 [PMID: 24549055 DOI: 10.1038/ejhg.2014.16]

15 **Rainville IR**, Rana HQ. Next-generation sequencing for inherited breast cancer risk: counseling through the complexity. *Curr Oncol Rep* 2014; **16**: 371 [PMID: 24488544 DOI: 10.1007/s11912-013-0371-z]

16 **Association for Molecular Pathology *v.* Myriad Genetics.** Available from: URL: https://www.oyez.org/cases/2012/12-398

17 **Azvolinsky A**. Supreme Court ruling broadens BRCA testing options. *J Natl Cancer Inst* 2013; **105**: 1671-1672 [PMID: 24198329 DOI: 10.1093/jnci/djt342]

18 **Evans DG**, Barwell J, Eccles DM, Collins A, Izatt L, Jacobs C, Donaldson A, Brady AF, Cuthbert A, Harrison R, Thomas S, Howell A, Miedzybrodzka Z, Murray A. The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services. *Breast Cancer Res* 2014; **16**: 442 [PMID: 25510853 DOI: 10.1186/s13058-014-0442-6]

19 **LaDuca H**, Stuenkel AJ, Dolinsky JS, Keiles S, Tandy S, Pesaran T, Chen E, Gau CL, Palmaer E, Shoaepour K, Shah D, Speare V, Gandomi S, Chao E. Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients. *Genet Med* 2014; **16**: 830-837 [PMID: 24763289 DOI: 10.1038/gim.2014.40]

20 **Tung N**, Battelli C, Allen B, Kaldate R, Bhatnagar S, Bowles K, Timms K, Garber JE, Herold C, Ellisen L, Krejdovsky J, DeLeonardis K, Sedgwick K, Soltis K, Roa B, Wenstrup RJ, Hartman AR. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer* 2015; **121**: 25-33 [PMID: 25186627 DOI: 10.1002/cncr.29010]

21 **Kapoor NS**, Curcio LD, Blakemore CA, Bremner AK, McFarland RE, West JG, Banks KC. Multigene Panel Testing Detects Equal Rates of Pathogenic BRCA1/2 Mutations and has a Higher Diagnostic Yield Compared to Limited BRCA1/2 Analysis Alone in Patients at Risk for Hereditary Breast Cancer. *Ann Surg Oncol* 2015; **22**: 3282-3288 [PMID: 26219241 DOI: 10.1245/s10434-015-4754-2]

22 **Kurian AW**, Hare EE, Mills MA, Kingham KE, McPherson L, Whittemore AS, McGuire V, Ladabaum U, Kobayashi Y, Lincoln SE, Cargill M, Ford JM. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol* 2014; **32**: 2001-2009 [PMID: 24733792 DOI: 10.1200/JCO.2013.53.6607]

23 **Yorczyk A**, Robinson LS, Ross TS. Use of panel tests in place of single gene tests in the cancer genetics clinic. *Clin Genet* 2015; **88**: 278-282 [PMID: 25318351 DOI: 10.1111/cge.12488]

24 **Heemskerk-Gerritsen BA**, Brekelmans CT, Menke-Pluymers MB, van Geel AN, Tilanus-Linthorst MM, Bartels CC, Tan M, Meijers-Heijboer HE, Klijn JG, Seynaeve C. Prophylactic mastectomy in BRCA1/2 mutation carriers and women at risk of hereditary breast cancer: long-term experiences at the Rotterdam Family Cancer Clinic. *Ann Surg Oncol* 2007; **14**: 3335-3344 [PMID: 17541692 DOI: 10.1245/s10434-007-9449-x]

25 **Domchek SM**, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, Garber JE, Neuhausen SL, Matloff E, Eeles R, Pichert G, Van t'veer L, Tung N, Weitzel JN, Couch FJ, Rubinstein WS, Ganz PA, Daly MB, Olopade OI, Tomlinson G, Schildkraut J, Blum JL, Rebbeck TR. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA* 2010; **304**: 967-975 [PMID: 20810374 DOI: 10.1001/jama.2010.1237]

26 **Tischkowitz M**, Xia B, Sabbaghian N, Reis-Filho JS, Hamel N, Li G, van Beers EH, Li L, Khalil T, Quenneville LA, Omeroglu A, Poll A, Lepage P, Wong N, Nederlof PM, Ashworth A, Tonin PN, Narod SA, Livingston DM, Foulkes WD. Analysis of PALB2/FANCN-associated breast cancer families. *Proc Natl Acad Sci USA* 2007; **104**: 6788-6793 [PMID: 17420451 DOI: 10.1073/pnas.0701724104]

27 **Rahman N**, Seal S, Thompson D, Kelly P, Renwick A, Elliott A, Reid S, Spanova K, Barfoot R, Chagtai T, Jayatilake H, McGuffog L, Hanks S, Evans DG, Eccles D, Easton DF, Stratton MR. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat Genet* 2007; **39**: 165-167 [PMID: 17200668 DOI: 10.1038/ng1959]

28 **Antoniou AC**, Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J, Lee A, Subramanian D, De Leeneer K, Fostira F, Tomiak E, Neuhausen SL, Teo ZL, Khan S, Aittomäki K, Moilanen JS, Turnbull C, Seal S, Mannermaa A, Kallioniemi A, Lindeman GJ, Buys SS, Andrulis IL, Radice P, Tondini C, Manoukian S, Toland AE, Miron P, Weitzel JN, Domchek SM, Poppe B, Claes KB, Yannoukakos D, Concannon P, Bernstein JL, James PA, Easton DF, Goldgar DE, Hopper JL, Rahman N, Peterlongo P, Nevanlinna H, King MC, Couch FJ, Southey MC, Winqvist R, Foulkes WD, Tischkowitz M. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med* 2014; **371**: 497-506 [PMID: 25099575 DOI: 10.1056/NEJMoa1400382]

29 **Chenevix-Trench G**, Spurdle AB, Gatei M, Kelly H, Marsh A, Chen X, Donn K, Cummings M, Nyholt D, Jenkins MA, Scott C, Pupo GM, Dörk T, Bendix R, Kirk J, Tucker K, McCredie MR, Hopper JL, Sambrook J, Mann GJ, Khanna KK. Dominant negative ATM mutations in breast cancer families. *J Natl Cancer Inst* 2002; **94**: 205-215 [PMID: 11830610 DOI: 10.1093/jnci/94.3.205]

30 **Goldgar DE**, Healey S, Dowty JG, Da Silva L, Chen X, Spurdle AB, Terry MB, Daly MJ, Buys SM, Southey MC, Andrulis I, John EM, Khanna KK, Hopper JL, Oefner PJ, Lakhani S, Chenevix-Trench G. Rare variants in the ATM gene and risk of breast cancer. *Breast Cancer Res* 2011; **13**: R73 [PMID: 21787400 DOI: 10.1186/bcr2919]

31 **Thompson D**, Duedal S, Kirner J, McGuffog L, Last J, Reiman A, Byrd P, Taylor M, Easton DF. Cancer risks and mortality in heterozygous ATM mutation carriers. *J Natl Cancer Inst* 2005; **97**: 813-822 [PMID: 15928302 DOI: 10.1093/jnci/dji141]

32 **NCCN Clinical Practice Guidelines in Oncology.** Genetic/Familial High-Risk Assessment: Colorectal Version 2.2014. [accessed 2015 Aug 15]. Available from: URL: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

33 **Li FP**, Fraumeni JF, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, Miller RW. A cancer family syndrome in twenty-four kindreds. *Cancer Res* 1988; **48**: 5358-5362 [PMID: 3409256]

34 **Lindor NM**, McMaster ML, Lindor CJ, Greene MH. Concise handbook of familial cancer susceptibility syndromes - second edition. *J Natl Cancer Inst Monogr* 2008; **(38)**: 1-93 [PMID: 18559331 DOI: 10.1093/jncimonographs/lgn001]

35 **Domchek SM**, Bradbury A, Garber JE, Offit K, Robson ME. Multiplex genetic testing for cancer susceptibility: out on the high wire without a net? *J Clin Oncol* 2013; **31**: 1267-1270 [PMID: 23460708 DOI: 10.1200/JCO.2012.46.9403]

36 **Easton DF**, Pharoah PD, Antoniou AC, Tischkowitz M, Tavtigian SV, Nathanson KL, Devilee P, Meindl A, Couch FJ, Southey M, Goldgar DE, Evans DG, Chenevix-Trench G, Rahman N, Robson M, Domchek SM, Foulkes WD. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med* 2015; **372**: 2243-2257 [PMID: 26014596 DOI: 10.1056/NEJMsr1501341]

37 **Iqbal J**, Ragone A, Lubinski J, Lynch HT, Moller P, Ghadirian P, Foulkes WD, Armel S, Eisen A, Neuhausen SL, Senter L, Singer CF, Ainsworth P, Kim-Sing C, Tung N, Friedman E, Llacuachaqui M, Ping S, Narod SA. The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. *Br J Cancer* 2012; **107**: 2005-2009 [PMID: 23099806 DOI: 10.1038/bjc.2012.483]

38 **Hansford S**, Kaurah P, Li-Chang H, Woo M, Senz J, Pinheiro H, Schrader KA, Schaeffer DF, Shumansky K, Zogopoulos G, Santos TA, Claro I, Carvalho J, Nielsen C, Padilla S, Lum A, Talhouk A, Baker-Lange K, Richardson S, Lewis I, Lindor NM, Pennell E, MacMillan A, Fernandez B, Keller G, Lynch H, Shah SP, Guilford P, Gallinger S, Corso G, Roviello F, Caldas C, Oliveira C, Pharoah PD, Huntsman DG. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. *JAMA Oncol* 2015; **1**: 23-32 [PMID: 26182300 DOI: 10.1001/jamaoncol.2014.168]


**P- Reviewer**: Butow P, Chung YJ
**S- Editor**: Qi Y **L- Editor**: A **E- Editor**: Jiao XK

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com