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

Susan Hiraki · Erica S. Rinella · Freya Schnabel · Ruth Oratz · Harry Ostrer

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

S. Hiraki (✉) · H. Ostrer
Department of Pathology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Ullmann 819, Bronx, NY 10046, USA
e-mail: susan.hiraki@einstein.yu.edu

E. S. Rinella · F. Schnabel
Department of Surgery, New York University Langone Medical Center, New York, NY, USA

R. Oratz
Department of Medicine, New York University School of Medicine, New York, NY, USA

(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.

Author Susan Hiraki, Author Erica S. Rinella, Author Freya Schnabel, Author Ruth Oratz, and Author Harry Ostrer declare that they have no conflict of interest.

References

Akushevich, I., Kravchenko, J., Akushevich, L., Ukraintseva, S., Arbeev, K., & Yashin, A. (2011). Cancer risk and behavioral factors, comorbidities, and functional status in the US elderly population. *ISRN Oncology, 2011*, 1–9. doi:10.5402/2011/415790.

American Cancer Society recommendations for colorectal cancer early detection. (n.d.). Retrieved April 3, 2013, from http://www.cancer.org/cancer/colonandrectumcancer/moreinformation/colonandrectumcancerearlydetection/colorectal-cancer-early-detection-acs-recommendations

American Cancer Society recommendations for early breast cancer detection in women without breast symptoms. (n.d.). Retrieved April 3, 2013, from http://www.cancer.org/cancer/breastcancer/moreinformation/breastcancerearlydetection/breast-cancer-early-detection-acs-recs

Antoniou, A., Pharoah, P. D. P., Narod, S., Risch, H. A., Eyfjord, J. E., Hopper, J. L., et al. (2003). 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. *American journal of human genetics, 72*(5), 1117–1130. doi:10.1086/375033.

Ataxia-Telangiectasia - GeneReviews™ - NCBI Bookshelf. (n.d.). Retrieved April 8, 2013, from http://www.ncbi.nlm.nih.gov/books/NBK26468/

Balmana, J., Castells, A., Cervantes, A., & On behalf of the ESMO Guidelines Working Group. (2010). Familial colorectal cancer risk: ESMO clinical practice guidelines. *Annals of Oncology, 21*(Supplement 5), v78–v81. doi:10.1093/annonc/mdq169.

Barrow, E., Robinson, L., Alduaij, W., Shenton, A., Clancy, T., Lalloo, F., et al. (2009). Cumulative lifetime incidence of extracolonic cancers in lynch syndrome: a report of 121 families with proven mutations. *Clinical Genetics, 75*(2), 141–149. doi:10.1111/j.1399-0004.2008.01125.x.

Berg, J. S., Khoury, M. J., & Evans, J. P. (2011). Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. *Genetics in Medicine, 13*(6), 499–504. doi:10.1097/GIM.0b013e318220aaba.

Berliner, J. L., Fay, A. M., Cummings, S. A., Burnett, B., & Tillmanns, T. (2013). NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer. *Journal of Genetic Counseling, 22*(2), 155–163. doi:10.1007/s10897-012-9547-1.

Bernstein, J. L., Haile, R. W., Stovall, M., Boice, J. D., Shore, R. E., Langholz, B., et al. (2010). Radiation exposure, the ATM gene, and contralateral breast cancer in the Women's environmental cancer and radiation epidemiology study. *JNCI Journal of the National Cancer Institute, 102*(7), 475–483. doi:10.1093/jnci/djq055.

Birch, J. M., Blair, V., Kelsey, A. M., Evans, D. G., Harris, M., Tricker, K. J., et al. (1998). Cancer phenotype correlates with constitutional TP53 genotype in families with the Li-Fraumeni syndrome. *Oncogene, 17*(9), 1061–1068. doi:10.1038/sj.onc.1202033.

Bisgaard, M. L., Fenger, K., Bülow, S., Niebuhr, E., & Mohr, J. (1994). Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. *Human Mutation, 3*(2), 121–125. doi:10.1002/humu.1380030206.

Boardman, L. A., Thibodeau, S. N., Schaid, D. J., Lindor, N. M., McDonnell, S. K., Burgart, L. J., et al. (1998). Increased risk for cancer in patients with the Peutz-Jeghers syndrome. *Annals of Internal Medicine, 128*(11), 896–899.

Bogdanova, N., Feshchenko, S., Schürmann, P., Waltes, R., Wieland, B., Hillemanns, P., et al. (2008). Nijmegen breakage syndrome mutations and risk of breast cancer. *International Journal of Cancer, 122*(4), 802–806. doi:10.1002/ijc.23168.

Bonadona, V., Bonaïti, B., Olschwang, S., Grandjouan, S., Huiart, L., Longy, M., et al. (2011). Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in lynch syndrome. *JAMA: The Journal of the American Medical Association, 305*(22), 2304–2310. doi:10.1001/jama.2011.743.

BreastNext | Ambry Genetics. (n.d.). Retrieved October 11, 2013, from http://www.ambrygen.com/tests/breastnext

Brosens, L. A. A., van Hattem, A., Hylind, L. M., Iacobuzio-Donahue, C., Romans, K. E., Axilbund, J., et al. (2007). Risk of colorectal cancer in juvenile polyposis. *Gut, 56*(7), 965–967. doi:10.1136/gut.2006.116913.

Brownstein, M. H., Wolf, M., & Bikowski, J. B. (1978). Cowden's disease: a cutaneous marker of breast cancer. *Cancer, 41*(6), 2393–2398.

Burt, R. (2007). Inheritance of colorectal cancer. *Drug Discovery Today: Disease Mechanisms, 4*(4), 293–300. doi:10.1016/j.ddmec.2008.05.004.

Burt, R. W., Bishop, D. T., Lynch, H. T., Rozen, P., & Winawer, S. J. (1990). Risk and surveillance of individuals with heritable factors for colorectal cancer. WHO Collaborating Centre for the Prevention of Colorectal Cancer. *Bulletin of the World Health Organization, 68*(5), 655–665.

Byrnes, G. B., Southey, M. C., & Hopper, J. L. (2008). Are the so-called low penetrance breast cancer genes, ATM, BRIP1, PALB2 and CHEK2, high risk for women with strong family histories? *Breast Cancer Research: BCR, 10*(3), 208. doi:10.1186/bcr2099.

Casadei, S., Norquist, B. M., Walsh, T., Stray, S., Mandell, J. B., Lee, M. K., et al. (2011). Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. *Cancer Research, 71*(6), 2222–2229. doi:10.1158/0008-5472.CAN-10-3958.

Chao, S., Roberts, J. S., Marteau, T. M., Silliman, R., Cupples, L. A., & Green, R. C. (2008). Health behavior changes after genetic risk assessment for Alzheimer disease: the REVEAL study. *Alzheimer Disease and Associated Disorders, 22*(1), 94–97. doi:10.1097/WAD.0b013e31815a9dcc.

Chlebowski, R. T. (2002). Weight loss in breast cancer patient management. *Journal of Clinical Oncology, 20*(4), 1128–1143. doi:10.1200/JCO.20.4.1128.

Cho, M. K., Sankar, P., Wolpe, P. R., & Godmilow, L. (1999). Commercialization ofBRCA1/2 testing: practitioner awareness and use of a new genetic test. *American Journal of Medical Genetics,*

83(3), 157–163. doi:10.1002/(SICI)1096-8628(19990319)83:3<157::AID-AJMG4>3.0.CO;2-G.

Chompret, A., Brugières, L., Ronsin, M., Gardes, M., Dessarps-Freichey, F., Abel, A., et al. (2000). P53 germline mutations in childhood cancers and cancer risk for carrier individuals. *British Journal of Cancer, 82*(12), 1932–1937. doi:10.1054/bjoc.2000.1167.

Collins, V., Halliday, J., Kahler, S., & Williamson, R. (2001). Parents' Experiences with genetic counseling after the birth of a baby with a genetic disorder: an exploratory study. *Journal of Genetic Counseling, 10*(1), 53–72.

ColoNext | Ambry Genetics. (n.d.). Retrieved October 11, 2013, from http://www.ambrygen.com/tests/colonext

Common Cancer Types - National Cancer Institute. (n.d.). Retrieved October 11, 2013, from http://www.cancer.gov/cancertopics/types/commoncancers#1

Comprehensive Cancer Panel - Genetic Testing Company | The DNA Diagnostic Experts | GeneDx. (n.d.). Retrieved September 27, 2013, from http://www.genedx.com/test-catalog/available-tests/comprehensive-cancer-panel/

Couch, F. J., DeShano, M. L., Blackwood, M. A., Calzone, K., Stopfer, J., Campeau, L., et al. (1997). BRCA1 Mutations in women attending clinics that evaluate the risk of breast cancer. *The New England Journal of Medicine, 336*(20), 1409–1415. doi:10.1056/NEJM199705153362002.

Cybulski, C., Wokolorczyk, D., Jakubowska, A., Huzarski, T., Byrski, T., Gronwald, J., et al. (2011). Risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer. *Journal of Clinical Oncology, 29*(28), 3747–3752. doi:10.1200/JCO.2010.34.0778.

Desjardins, S., Joly Beauparlant, C., Labrie, Y., Ouellette, G., BRCAs, I., & Durocher, F. (2009). Variations in the NBN/NBS1 gene and the risk of breast cancer in non-BRCA1/2 French Canadian families with high risk of breast cancer. *BMC Cancer, 9*(1), 181. doi:10.1186/1471-2407-9-181.

Domchek, S. M., Bradbury, A., Garber, J. E., Offit, K., & Robson, M. E. (2013). Multiplex genetic testing for cancer susceptibility: Out on the high wire without a Net? *Journal of Clinical Oncology, 31*(10), 1267–1270. doi:10.1200/JCO.2012.46.9403.

Donnelly, L. S., Watson, M., Moynihan, C., Bancroft, E., Evans, D. G. R., Eeles, R., et al. (2013). Reproductive decision-making in young female carriers of a BRCA mutation. *Human Reproduction (Oxford, England), 28*(4), 1006–1012. doi:10.1093/humrep/des441.

Elias, S., & Annas, G. J. (1994). Generic consent for genetic screening. *The New England Journal of Medicine, 330*(22), 1611–1613. doi:10.1056/NEJM199406023302213.

Fletcher, O., Easton, D., Anderson, K., Gilham, C., Jay, M., & Peto, J. (2004). Lifetime risks of common cancers among retinoblastoma survivors. *JNCI Journal of the National Cancer Institute, 96*(5), 357–363. doi:10.1093/jnci/djh058.

Ford, D., Easton, D. F., Bishop, D. T., Narod, S. A., & Goldgar, D. E. (1994). Risks of cancer in BRCA1-mutation carriers. Breast cancer linkage consortium. *Lancet, 343*(8899), 692–695.

Frank, T. S., Manley, S. A., Olopade, O. I., Cummings, S., Garber, J. E., Bernhardt, B., et al. (1998). Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 16*(7), 2417–2425.

Gail, M. H. (2011). Personalized estimates of breast cancer risk in clinical practice and public health. *Statistics in Medicine, 30*(10), 1090–1104. doi:10.1002/sim.4187.

genetics/BROCA - Lab Med Test Info. (n.d.). Retrieved February 4, 2013, from http://web.labmed.washington.edu/tests/genetics/BROCA

Getting personal. (2008). *Nature*, *455*(7216), 1007. doi:10.1038/4551007a.

Gilpin, C. A., Carson, N., & Hunter, A. G. (2000). A preliminary validation of a family history assessment form to select women at risk for breast or ovarian cancer for referral to a genetics center. *Clinical Genetics, 58*(4), 299–308.

Goldgar, D. E., Easton, D. F., Byrnes, G. B., Spurdle, A. B., Iversen, E. S., & Greenblatt, M. S. (2008). Genetic evidence and integration of various data sources for classifying uncertain variants into a single model. *Human Mutation, 29*(11), 1265–1272. doi:10.1002/humu.20897.

Gooding, H. C., Linnenbringer, E. L., Burack, J., Roberts, J. S., Green, R. C., & Biesecker, B. B. (2006). Genetic susceptibility testing for Alzheimer disease: motivation to obtain information and control as precursors to coping with increased risk. *Patient Education and Counseling, 64*(1–3), 259–267. doi:10.1016/j.pec.2006.03.002.

Green, R. C., Roberts, J. S., Cupples, L. A., Relkin, N. R., Whitehouse, P. J., Brown, T., et al. (2009). Disclosure of APOE genotype for risk of Alzheimer's disease. *The New England Journal of Medicine, 361*(3), 245–254. doi:10.1056/NEJMoa0809578.

Guilford, P., Humar, B., & Blair, V. (2010). Hereditary diffuse gastric cancer: translation of CDH1 germline mutations into clinical practice. *Gastric Cancer: Official Journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association, 13*(1), 1–10. doi:10.1007/s10120-009-0531-x.

Hearle, N., Schumacher, V., Menko, F. H., Olschwang, S., Boardman, L. A., Gille, J. J. P., et al. (2006). Frequency and spectrum of cancers in the peutz-jeghers syndrome. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research, 12*(10), 3209–3215. doi:10.1158/1078-0432.CCR-06-0083.

Heikkinen, K. (2005). RAD50 and NBS1 are breast cancer susceptibility genes associated with genomic instability. *Carcinogenesis, 27*(8), 1593–1599. doi:10.1093/carcin/bgi360.

Heymann, S., Delaloge, S., Rahal, A., Caron, O., Frebourg, T., Barreau, L., et al. (2010). Radio-induced malignancies after breast cancer post-operative radiotherapy in patients with Li- fraumeni syndrome. *Radiation Oncology, 5*(1), 104. doi:10.1186/1748-717X-5-104.

Hopper, J. L., Southey, M. C., Dite, G. S., Jolley, D. J., Giles, G. G., McCredie, M. R., et al. (1999). Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Australian breast cancer family study. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 8*(9), 741–747.

Howe, J. R., Roth, S., Ringold, J. C., Summers, R. W., Järvinen, H. J., Sistonen, P., et al. (1998). Mutations in the SMAD4/DPC4 gene in juvenile polyposis. *Science (New York, N.Y.), 280*(5366), 1086–1088.

Howe, J. R., Sayed, M. G., Ahmed, A. F., Ringold, J., Larsen-Haidle, J., Merg, A., et al. (2004). The prevalence of MADH4 and BMPR1A mutations in juvenile polyposis and absence of BMPR2, BMPR1B, and ACVR1 mutations. *Journal of Medical Genetics, 41*(7), 484–491.

Hsu, H.-M., Wang, H.–. C., Chen, S.-T., Hsu, G.–. C., Shen, C.-Y., & Yu, J.–. C. (2007). Breast Cancer Risk Is Associated with the Genes Encoding the DNA Double-Strand Break Repair Mre11/Rad50/Nbs1 Complex. *Cancer Epidemiology Biomarkers & Prevention, 16*(10), 2024–2032. doi:10.1158/1055-9965.EPI-07-0116.

Hurley, A. C., Harvey, F. R., Roberts, J. S., Wilson-Chase, C., Lloyd, S., Prest, J., et al. (2005). Genetic susceptibility for Alzheimer's disease: why did adult offspring seek testing? *American Journal of Alzheimer's Disease and Other Dementias, 20*(6), 374–381.

Julian-Reynier, C. M., Bouchard, L. J., Evans, D. G., Eisinger, F. A., Foulkes, W. D., Kerr, B., et al. (2001). Women's attitudes toward preventive strategies for hereditary breast or ovarian carcinoma differ from one country to another. *Cancer, 92*(4), 959–968. doi:10.1002/1097-0142(20010815)92:4<959::AID-CNCR1406>3.0.CO;2-V.

Kempers, M. J. E., Kuiper, R. P., Ockeloen, C. W., Chappuis, P. O., Hutter, P., Rahner, N., et al. (2011). Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort

study. *The Lancet Oncology, 12*(1), 49–55. doi:10.1016/S1470-2045(10)70265-5.

Khoury, M. J., Gwinn, M., Yoon, P. W., Dowling, N., Moore, C. A., & Bradley, L. (2007). The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genetics in Medicine, 9*(10), 665–674. doi:10.1097/GIM.0b013e31815699d0

Khoury, M. J., Clauser, S. B., Freedman, A. N., Gillanders, E. M., Glasgow, R. E., Klein, W. M. P., et al. (2011). Population Sciences, Translational Research, and the Opportunities and Challenges for Genomics to Reduce the Burden of Cancer in the 21st Century. *Cancer Epidemiology, Biomarkers & Prevention, 20*(10), 2105–2114. doi:10.1158/1055-9965.EPI-11-0481.

King, M.–. C., Marks, J. H., Mandell, J. B., & New York Breast Cancer Study Group. (2003). Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science (New York, N.Y), 302*(5645), 643–646. doi:10.1126/science.1088759.

Lalloo, F., & Evans, D. G. (2012). Familial Breast Cancer. *Clinical Genetics, 82*(2), 105–114. doi:10.1111/j.1399-0004.2012.01859.x.

Lerman, C., & Croyle, R. (1994). Psychological issues in genetic testing for breast cancer susceptibility. *Archives of Internal Medicine, 154*(6), 609–616.

Li-Fraumeni Syndrome - GeneReviews™ - NCBI Bookshelf. (n.d.). Retrieved April 8, 2013, from http://www.ncbi.nlm.nih.gov/books/NBK1311/

Ligtenberg, M. J. L., Kuiper, R. P., Geurts van Kessel, A., & Hoogerbrugge, N. (2012). EPCAM deletion carriers constitute a unique subgroup of Lynch syndrome patients. *Familial Cancer*. doi:10.1007/s10689-012-9591-x.

Marees, T., Moll, A. C., Imhof, S. M., de Boer, M. R., Ringens, P. J., & van Leeuwen, F. E. (2008). Risk of second malignancies in survivors of retinoblastoma: more than 40 years of follow-up. *Journal of the National Cancer Institute, 100*(24), 1771–1779. doi:10.1093/jnci/djn394.

Martin, S. A., Lord, C. J., & Ashworth, A. (2010). Therapeutic targeting of the DNA mismatch repair pathway. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research, 16*(21), 5107–5113. doi:10.1158/1078-0432.CCR-10-0821.

Masciari, S., Dillon, D. A., Rath, M., Robson, M., Weitzel, J. N., Balmana, J., et al. (2012). Breast cancer phenotype in women with TP53 germline mutations: a Li-Fraumeni syndrome consortium effort. *Breast Cancer Research and Treatment, 133*(3), 1125–1130. doi:10.1007/s10549-012-1993-9.

McBride, C. M., Lipkus, I. M., Jolly, D., & Lyna, P. (2005). Interest in testing for genetic susceptibility to lung cancer among Black college students "at risk" of becoming cigarette smokers. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 14*(12), 2978–2981. doi:10.1158/1055-9965.EPI-05-0269.

Mealiffe, M. E., Stokowski, R. P., Rhees, B. K., Prentice, R. L., Pettinger, M., & Hinds, D. A. (2010). Assessment of Clinical Validity of a Breast Cancer Risk Model Combining Genetic and Clinical Information. *JNCI Journal of the National Cancer Institute, 102*(21), 1618–1627. doi:10.1093/jnci/djq388.

Meijers-Heijboer, H., van den Ouweland, A., Klijn, J., Wasielewski, M., de Snoo, A., Oldenburg, R., et al. (2002). Low-penetrance susceptibility to breast cancer due to CHEK2(*)1100delC in noncarriers of BRCA1 or BRCA2 mutations. *Nature Genetics, 31*(1), 55–59. doi:10.1038/ng879.

Meiser, B., Butow, P., Friedlander, M., Schnieden, V., Gattas, M., Kirk, J., et al. (2000). Intention to undergo prophylactic bilateral mastectomy in women at increased risk of developing hereditary breast cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 18*(11), 2250–2257.

Meldrum, C., Doyle, M. A., & Tothill, R. W. (2011). Next-generation sequencing for cancer diagnostics: a practical perspective. *The Clinical Biochemist Reviews/Australian Association of Clinical Biochemists, 32*(4), 177–195.

Multiplex genetic testing. The Council on Ethical and Judicial Affairs, American Medical Association. (1998). *The Hastings Center Report*, *28*(4), 15–21.

Narod, S. A. (2010). Testing for CHEK2 in the cancer genetics clinic: ready for prime time? *Clinical Genetics, 78*(1), 1–7. doi:10.1111/j.1399-0004.2010.01402.x.

Narod, S. A., Moody, J. R. K., Rosen, B., Fan, I., Risch, A., Sun, P., et al. (2013). Estimating survival rates after ovarian cancer among women tested for BRCA1 and BRCA2 mutations. *Clinical Genetics, 83*(3), 232–237. doi:10.1111/j.1399-0004.2012.01906.x.

Next-gen Cancer Panels | Ambry Genetics. (n.d.). Retrieved February 4, 2013, from http://ambrygen.com/next-gen-cancer-panels

Ng, P. C., Murray, S. S., Levy, S., & Venter, J. C. (2009). An agenda for personalized medicine. *Nature, 461*(7265), 724–726. doi:10.1038/461724a.

Nicolaides, N. C., Papadopoulos, N., Liu, B., Wei, Y. F., Carter, K. C., Ruben, S. M., et al. (1994). Mutations of two PMS homologues in hereditary nonpolyposis colon cancer. *Nature, 371*(6492), 75–80. doi:10.1038/371075a0.

Ormond, K. E., Wheeler, M. T., Hudgins, L., Klein, T. E., Butte, A. J., Altman, R. B., et al. (2010). Challenges in the clinical application of whole-genome sequencing. *The Lancet, 375*(9727), 1749–1751. doi:10.1016/S0140-6736(10)60599-5.

OvaNext | Ambry Genetics. (n.d.). Retrieved October 11, 2013, from http://www.ambrygen.com/tests/ovanext

Peltomäki, P. (2003). Role of DNA mismatch repair defects in the pathogenesis of human cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 21*(6), 1174–1179.

Peltomäki, P., & Vasen, H. F. (1997). Mutations predisposing to hereditary nonpolyposis colorectal cancer: database and results of a collaborative study. The International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer. *Gastroenterology, 113*(4), 1146–1158.

Pennington, K. P., & Swisher, E. M. (2012). Hereditary ovarian cancer: beyond the usual suspects. *Gynecologic Oncology, 124*(2), 347–353. doi:10.1016/j.ygyno.2011.12.415.

Pharoah, P., Guilford, P., Caldas, C., & Theinternationalgastriccancer. (2001). Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology, 121*(6), 1348–1353. doi:10.1053/gast.2001.29611.

Pijpe, A., Andrieu, N., Easton, D. F., Kesminiene, A., Cardis, E., Nogues, C., et al. (2012). Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). *BMJ, 345*(sep06 2), e5660–e5660. doi:10.1136/bmj.e5660.

Rahman, N., & Scott, R. H. (2007). Cancer genes associated with phenotypes in monoallelic and biallelic mutation carriers: new lessons from old players. *Human Molecular Genetics, 16*(Spec No 1), R60–R66. doi:10.1093/hmg/ddm026.

Rennert, G., Lejbkowicz, F., Cohen, I., Pinchev, M., Rennert, H. S., & Barnett-Griness, O. (2012). MutYH mutation carriers have increased breast cancer risk. *Cancer, 118*(8), 1989–1993. doi:10.1002/cncr.26506.

Richards, C. S., Bale, S., Bellissimo, D. B., Das, S., Grody, W. W., Hegde, M. R., et al. (2008). ACMG recommendations for standards for interpretation and reporting of sequence variations: Revisions 2007. *Genetics in Medicine: Official Journal of the American College of Medical Genetics, 10*(4), 294–300. doi:10.1097/GIM.0b013e31816b5cae.

Riley, B. D., Culver, J. O., Skrzynia, C., Senter, L. A., Peters, J. A., Costalas, J. W., et al. (2012). Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. *Journal of Genetic Counseling, 21*(2), 151–161. doi:10.1007/s10897-011-9462-x.

Rinella, E. S., Shao, Y., Yackowski, L., Pramanik, S., Oratz, R., Schnabel, F., et al. (2013). Genetic variants associated with breast cancer risk for Ashkenazi Jewish women with strong family histories but no identifiable BRCA1/2 mutation. *Human Genetics, 132*(5), 523–536. doi:10.1007/s00439-013-1269-4.

Roberts, J. S., LaRusse, S. A., Katzen, H., Whitehouse, P. J., Barber, M., Post, S. G., et al. (2003). Reasons for seeking genetic susceptibility testing among first-degree relatives of people with Alzheimer disease. *Alzheimer Disease and Associated Disorders, 17*(2), 86–93.

Robson, M. E., Storm, C. D., Weitzel, J., Wollins, D. S., & Offit, K. (2010). American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 28*(5), 893–901. doi:10.1200/JCO.2009.27.0660.

Rubinstein, W. S., O'Neill, S. M., Peters, J. A., Rittmeyer, L. J., & Stadler, M. P. (2002). Mathematical modeling for breast cancer risk assessment. State of the art and role in medicine. *Oncology (Williston Park, N.Y), 16*(8), 1082–1094. discussion 1094, 1097–1099.

Rubinstein, W. S., Jiang, H., Dellefave, L., & Rademaker, A. W. (2009). Cost-effectiveness of population-based BRCA1/2 testing and ovarian cancer prevention for Ashkenazi Jews: a call for dialogue. *Genetics in Medicine: Official Journal of the American College of Medical Genetics, 11*(9), 629–639. doi:10.1097/GIM.0b013e3181afd322.

Saadatmand, S., Rutgers, E. J. T., Tollenaar, R. A. E. M., Zonderland, H. M., Ausems, M. G. E. M., Keymeulen, K. B. M. I., et al. (2012). Breast density as indicator for the use of mammography or MRI to screen women with familial risk for breast cancer (FaMRIsc): a multicentre randomized controlled trial. *BMC Cancer, 12*, 440. doi:10.1186/1471-2407-12-440.

Schlich-Bakker, K. J., ten Kroode, H. F. J., & Ausems, M. G. E. M. (2006). A literature review of the psychological impact of genetic testing on breast cancer patients. *Patient Education and Counseling, 62*(1), 13–20. doi:10.1016/j.pec.2005.08.012.

Schwartz, R. S., & D'Andrea, A. D. (2010). Susceptibility Pathways in Fanconi's Anemia and Breast Cancer. *New England Journal of Medicine, 362*(20), 1909–1919. doi:10.1056/NEJMra0809889.

Seal, S., Thompson, D., Renwick, A., Elliott, A., Kelly, P., Barfoot, R., et al. (2006). Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles. *Nature Genetics, 38*(11), 1239–1241. doi:10.1038/ng1902.

Secretary's Advisory Committee on Genetics, Health, and Society. (2006, February). Coverage and Reimbursement of Genetic Tests and Services.

Senter, L., Clendenning, M., Sotamaa, K., Hampel, H., Green, J., Potter, J. D., et al. (2008). The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. *Gastroenterology, 135*(2), 419–428. doi:10.1053/j.gastro.2008.04.026.

Shanley, S., Fung, C., Milliken, J., Leary, J., Barnetson, R., Schnitzler, M., et al. (2009). Breast cancer immunohistochemistry can be useful in triage of some HNPCC families. *Familial Cancer, 8*(3), 251–255. doi:10.1007/s10689-008-9226-4.

Sherman, K. A., Miller, S. M., Shaw, L.-K., Cavanagh, K., & Sheinfeld Gorin, S. (2013). Psychosocial approaches to participation in BRCA1/2 genetic risk assessment among African American women: a systematic review. *Journal of Community Genetics*. doi:10.1007/s12687-013-0164-y.

Sistemas Genómicos - Working areas - Biomedicine - Medical Genetics Unit - Oncology. (n.d.). Retrieved October 31, 2013, from https://www.sistemasgenomicos.com/web_sg/webing/areas-biomedicina-ugm3.php

Stacey, S. N., Sulem, P., Johannsson, O. T., Helgason, A., Gudmundsson, J., Kostic, J. P., et al. (2006). The BARD1 Cys557Ser Variant and Breast Cancer Risk in Iceland. *PLoS Medicine, 3*(7), e217. doi:10.1371/journal.pmed.0030217.

Starink, T. M., van der Veen, J. P., Arwert, F., de Waal, L. P., de Lange, G. G., Gille, J. J., et al. (1986). The Cowden syndrome: a clinical and genetic study in 21 patients. *Clinical genetics, 29*(3), 222–233.

Starita, L. M., & Parvin, J. D. (2006). Substrates of the BRCA1-dependent ubiquitin ligase. *Cancer Biology & Therapy, 5*(2), 137–141.

Supreme Court Invalidates Patents on Breast and Ovarian Cancer Genes | American Civil Liberties Union. (n.d.). Retrieved October 14, 2013, from https://www.aclu.org/womens-rights/supreme-court-invalidates-patents-breast-and-ovarian-cancer-genes

Swan, M. (2010). Multigenic condition risk assessment in direct-to-consumer genomic services. *Genetics in Medicine, 12*(5), 279–288. doi:10.1097/GIM.0b013e3181d5f73b.

Swift, M., Morrell, D., Massey, R. B., & Chase, C. L. (1991). Incidence of cancer in 161 families affected by ataxia-telangiectasia. *The New England Journal of Medicine, 325*(26), 1831–1836. doi:10.1056/NEJM199112263252602.

Tabor, H. K., Stock, J., Brazg, T., McMillin, M. J., Dent, K. M., Yu, J.–. H., et al. (2012). Informed consent for whole genome sequencing: A qualitative analysis of participant expectations and perceptions of risks, benefits, and harms. *American Journal of Medical Genetics Part A, 158A*(6), 1310–1319. doi:10.1002/ajmg.a.35328.

Tan, M.–. H., Mester, J. L., Ngeow, J., Rybicki, L. A., Orloff, M. S., & Eng, C. (2012). Lifetime cancer risks in individuals with germline PTEN mutations. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research, 18*(2), 400–407. doi:10.1158/1078-0432.CCR-11-2283.

Tavtigian, S. V., Greenblatt, M. S., Goldgar, D. E., & Boffetta, P. (2008). Assessing pathogenicity: overview of results from the IARC Unclassified Genetic Variants Working Group. *Human Mutation, 29*(11), 1261–1264. doi:10.1002/humu.20903.

Thompson, D., Duedal, S., Kirner, J., McGuffog, L., Last, J., Reiman, A., et al. (2005). Cancer risks and mortality in heterozygous ATM mutation carriers. *Journal of the National Cancer Institute, 97*(11), 813–822. doi:10.1093/jnci/dji141.

Thorstenson, Y. R., Roxas, A., Kroiss, R., Jenkins, M. A., Yu, K. M., Bachrich, T., et al. (2003). Contributions of ATM mutations to familial breast and ovarian cancer. *Cancer Research, 63*(12), 3325–3333.

Trill, M. D., & Holland, J. (1993). Cross-cultural differences in the care of patients with cancer. *General Hospital Psychiatry, 15*(1), 21–30. doi:10.1016/0163-8343(93)90087-5.

Tumor Syndromes (n.d.). Retrieved February 25th, 2014, from http://www.cegat.de/Tumor-syndromes_l=1_171.html.

Tung, N., & Silver, D. P. (2011). Chek2 DNA damage response pathway and inherited breast cancer risk. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 29*(28), 3813–3815. doi:10.1200/JCO.2011.37.1476.

Vasen, H. F., Stormorken, A., Menko, F. H., Nagengast, F. M., Kleibeuker, J. H., Griffioen, G., et al. (2001). MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: a study of hereditary nonpolyposis colorectal cancer families. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 19*(20), 4074–4080.

Vernarelli, J. A., Roberts, J. S., Hiraki, S., Chen, C. A., Cupples, L. A., & Green, R. C. (2010). Effect of Alzheimer disease genetic risk disclosure on dietary supplement use. *The American Journal of Clinical Nutrition, 91*(5), 1402–1407. doi:10.3945/ajcn.2009.28981.

Walsh, T., Lee, M. K., Casadei, S., Thornton, A. M., Stray, S. M., Pennil, C., et al. (2010). Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel

sequencing. *Proceedings of the National Academy of Sciences of the United States of America, 107*(28), 12629–12633. doi:10.1073/pnas.1007983107.

Wang, Y., Cortez, D., Yazdi, P., Neff, N., Elledge, S. J., & Qin, J. (2000). BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. *Genes & Development, 14*(8), 927–939.

Weischer, M., Bojesen, S. E., Ellervik, C., Tybjaerg-Hansen, A., & Nordestgaard, B. G. (2008). CHEK2*1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 26*(4), 542–548. doi:10.1200/JCO.2007.12.5922.

White, M., & Dorman, S. (2000). Confronting Information Overload. *Journal of School Health, 70*(4), 160–161.

Williams, C., Brunskill, S., Altman, D., Briggs, A., Campbell, H., Clarke, M., et al. (2006). Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy. *Health Technology Assessment (Winchester, England), 10*(34), iii–iv. ix–xi, 1–204.

Wu, X., Platt, J. L., & Cascalho, M. (2003). Dimerization of MLH1 and PMS2 Limits Nuclear Localization of MutL. *Molecular and Cellular Biology, 23*(9), 3320–3328. doi:10.1128/MCB.23.9.3320-3328.2003.

Yasmeen, S., Hubbard, R. A., Romano, P. S., Zhu, W., Geller, B. M., Onega, T., et al. (2012). Risk of advanced-stage breast cancer among older women with comorbidities. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 21*(9), 1510–1519. doi:10.1158/1055-9965.EPI-12-0320.

Zick, C. D., Mathews, C. J., Roberts, J. S., Cook-Deegan, R., Pokorski, R. J., & Green, R. C. (2005). Genetic testing for Alzheimer's disease and its impact on insurance purchasing behavior. *Health Affairs (Project Hope), 24*(2), 483–490. doi:10.1377/hlthaff.24.2.483.

REVIEW ARTICLE

MOLECULAR ORIGINS OF CANCER

Inherited Susceptibility to Common Cancers

William D. Foulkes, M.B., B.S., Ph.D.

From the Program in Cancer Genetics, Departments of Oncology and Human Genetics and Departments of Medicine and Obstetrics and Gynecology, McGill University, Montreal. Address reprint requests to Dr. Foulkes at the Program in Cancer Genetics, Gerald Bronfman Centre for Cancer Research, Department of Oncology, McGill University, 546 Pine Ave. West, Montreal, QC H2W 1S6, Canada, or at william.foulkes@mcgill.ca.

N Engl J Med 2008;359:2143-53.

Rare, large families with multiple cases of early-onset cancer affecting several generations provide clear evidence that inherited factors are important causes of cancer.[1] The range of cancers, the age at onset, and the number of generations affected all suggest familial risk. In this review, I discuss the five cancers in the United States that are associated with the highest number of deaths: lung, breast, colorectal, prostate, and pancreatic cancer.

In the late 1980s and early 1990s, numerous cancer susceptibility genes were identified, including those for breast and colorectal cancer (Glossary and Table 1). These genes confer high relative risks of cancer among carriers (i.e., they are highly penetrant). Thus, they could be detected by linkage analysis, wherein DNA obtained from many members of a family in which there are cases of cancer is collected and analyzed with the use of hundreds of anonymous, highly polymorphic DNA markers that are evenly spread across the genome. Family members are categorized in so-called liability classes, depending on their age and whether or not they have cancer, and a likelihood is assigned to putative gene carriers and noncarriers. With this information, the disease phenotype can be linked to one particular allele of a polymorphic marker, and a logarithm-of-odds (lod) score can be calculated for that allele. A high score (3.0 or higher) indicates a strong chance that the gene is located near the given marker (≥1000:1 in favor), whereas a low score (no higher than –2.0) means the gene is almost certainly not near that DNA marker locus.

Linkage analysis identified mainly tumor-suppressor genes. In hereditary cancer syndromes, one abnormal copy of the gene is inherited in the germ line from either parent, whereas the other copy is inactivated in a somatic cell, typically because of random processes whereby genes, chromosomes, or both are rearranged, deleted, or replaced. As a result, loss of heterozygosity is frequent at the position of the tumor-suppressor gene[2] (Fig. 1), and in a tumor cell there is biallelic inactivation of the gene. Inherited biallelic mutations in tumor-suppressor genes are very rare and often result in a phenotype that differs from the phenotype of a monoallelic mutation (Table 2). In some genes, such as *BRCA1* and *APC*, biallelic truncating mutations are incompatible with intrauterine development and are therefore lethal.

Family history is an important risk factor in almost all cancers, but most familial cancers are not caused by mutations in the rare tumor-suppressor genes described above. Other, lower-risk (less penetrant) genes must be present. Detecting them requires genetic strategies other than linkage analysis, because they do not confer a high enough risk of cancer to cause a noticeable accumulation of cancers in a family.[3] One approach compares the frequency of alleles of genes in cases and controls. Initial case–control studies in cancer genetics used small samples (typically fewer than 500 cases and 500 controls), and relied on existing biologic knowledge as a basis for choosing candidate genes. Initial efforts on this scale were unsuccessful, partly because of the lack of an adequate sample size, but also

Glossary of Selected Genes

AKAP9: A kinase anchor protein 9
APC: Adenomatous polyposis coli
ATM: Ataxia–telangiectasia mutated
BAX: BCL2-associated X
BMPR1A: Bone morphogenetic protein receptor type 1A
BRCA1: Breast-cancer gene 1
BRCA2: Breast-cancer gene 2
BRIP1: *BRCA1*-interacting protein C-terminal helicase 1
CASP8: Caspase 8
CDH1: E-cadherin
CHEK2: Cell-cycle–checkpoint kinase
CHRNA3: Cholinergic receptor nicotinic alpha 3
CHRNA5: Cholinergic receptor nicotinic alpha 5
CHRNB4: Cholinergic receptor nicotinic beta 4
FGFR2: Fibroblast growth factor receptor 2
KLK3: Kallikrein-related peptidase 3
LSP1: Lymphocyte-specific protein 1
MAP3K1: Mitogen-activated protein kinase kinase kinase 1
MLH1: MutL homolog 1
MSH2: MutS homolog 2
MSH6: MutS homolog 6
MSMB: Microseminoprotein, beta
MUTYH: MutY homolog
NBS1: Nijmegen breakage syndrome 1
PALB2: Partner and localizer of *BRCA2*
PARP1: Poly–adenosine diphosphate–ribose polymerase 1
PMS2: Postmeiotic segregation 2
PRSS1: Protease serine 1
PTEN: Phosphatase and tensin homologue
RING: Really interesting new gene
SMAD4, SMAD7: SMAD family members 4 and 7
SPINK1: Serine protease inhibitor Kazal type 1
STK11: Serine-threonine protein kinase 11
TGFBRII: Transforming growth factor beta receptor II
TOX3: Tox high-mobility group box family member 3
TP53: Tumor protein p53
VHL: von Hippel–Lindau

because guessing which genes were relevant proved difficult.[4-6] Recently, large-scale consortia examining thousands of cases and controls have identified 30 or more susceptibility loci for lung, prostate, breast, and colorectal cancer. These genomewide studies test hundreds of thousands of single-nucleotide polymorphisms (SNPs) for their association with cancer cases. The large number of subjects and the huge number of SNPs permit the detection of very small, but highly significant associations between any one SNP and disease.

Genes and loci identified by genomewide association studies bear little resemblance to the candidate genes previously associated with a hereditary risk of cancer[7-27] (Table 1). The biologic relationship of many of these genetic markers to the pathogenesis of a tumor is not yet understood. For instance, one region of chromosome 8q24 harbors several (possibly five) independent loci, each of which is associated with an increased risk of breast, prostate, or colorectal cancer or all of these cancers, but no candidate genes have been identified in this "gene desert."

LUNG CANCER

Lung cancer is mainly attributable to tobacco use, and few large families with multiple cases of lung cancer are suitable for linkage analysis. Even if such families were available, it is not obvious that a single gene with a large effect would account for the cases observed. Nevertheless, one locus on chromosome 6q has been suggested by a traditional linkage study,[28] though no gene has yet been identified. Some tumor-suppressor genes are associated with substantial increases in the risk of lung cancer, and in persons carrying mutations in these genes, tobacco smoking may be particularly dangerous. For example, in families with the Li–Fraumeni syndrome, smokers who carry a *TP53* mutation are at much higher risk for lung cancer than nonsmokers who carry the same mutation,[29] and carriers of *RB1* mutations, which are associated with retinoblastoma, also have a high lifetime risk of lung cancer[30,31] (see the table in the Supplementary Appendix, available with the full text of this article at www.nejm.org). Case reports of lung cancer occurring in the Bloom[32] syndrome and in Werner's[33] syndrome, which are associated with a deficiency of DNA repair and DNA maintenance, respectively, suggest a possible hereditary risk of lung cancer.

Genes linked to the metabolism of tobacco-borne carcinogens have been studied as hereditary risk factors in lung cancer, but they have not been readily linked to risk.[34-37] Individual genes associated with DNA repair,[38,39] inflammation,[40] growth factors,[41] vitamin metabolism,[42] and the cell cycle[43] have also been studied, but the results require confirmation in studies involving large populations. A problem encountered in genetic association studies is the "winner's curse": buyers in sealed-bid auctions tend to overpay because the true value is unknown, and those who most overestimate a commodity's value win the prize.[44]

Table 1. Genes and Loci Implicated in the Inheritance of Common Cancers, According to the Risk among Heterozygotes (Monoallelic Carriers).*

Cancer Site	Relative Risk ≥5.0	Relative Risk ≥1.5 and <5.0	Relative Risk ≥1.01 and <1.5
	Gene (% of Cancers Caused by Mutation in this Gene)	Genes or Loci	
Lung	*RB1* (<0.1), *TP53* (<0.1)	No convincing examples	rs1051730, rs8034191; *CHRNA3*, *CHRNB4*, *CHRNA5* are candidate genes
Breast	*BRCA1* (1–5),† *BRCA2* (1–5),† *TP53* (<0.5), *PTEN* (<0.5), *STK11* (<0.1), *CDH1* (<0.1)	*CHEK2*, *ATM*, *PALB2*, *BRIP1*	*CASP8*,‡ *FGFR2*,§ *MAP3K1*, loci on 8q24, 5p,§ *TOX3*,§ 2q,§ 6q22,¶ *LSP1*
Colon and rectum	*APC* (0.5–1.0), *MLH1* (1–2), *MSH2* (1–2), *MSH6* (<1), *PMS2* (<1)	*APC* (I1307K), *BLM* (*BLM*^{Ash})	*MUTYH*,‖ *CASP8*,‡ 8q24 loci, 8q23 (*EIF3H*), 10p14, 11q23, *CRAC1*, *SMAD7***
Prostate	*BRCA2* (<0.1)	8q24 Loci††	*rs6501455* (and other adjacent loci), *rs721048*, *NBS1*, *EHBP1*, *TCF2*, *CTBP2*, *JAZF1*, *MSMB*, *LMTK2*, *KLK3*, *SLC22A3*‡‡
Pancreas	*BRCA2* (<0.5), *CDKN2A* (<0.1), *STK11* (<0.1), *TP53* (<0.1), *PRSS1* (<0.1), *SPINK1*§§ (<0.1)	*BRCA1*, *MSH2*, *MLH1*	No convincing examples

* In the high-risk category, risk alleles are rare (<0.1% to 0.01%) or very rare (<0.01%). In the moderate-risk category, most risk alleles are very rare and a few risk alleles are common. In the low-risk category, most risk alleles are common (>10%). The population attributable risk percentage is not indicated because it is a misleading number (i.e., it can sum to more than 100%).
† This percentage is closer to 1% in most populations and closer to 5% in the Ashkenazi Jewish population.
‡ Variants in *CASP8* are associated with a decreased risk of breast, colorectal, and other cancers.[8]
§ These loci only contribute to the risk of estrogen-receptor–positive breast cancer.
¶ The effects of this locus appear to be restricted to the Ashkenazi Jewish population.
‖ Biallelic mutations in *MUTYH* result in a distinct syndrome, *MUTYH*-associated polyposis, which is akin to attenuated or classic familial adenomatous polyposis.
** The pooled odds ratio for the association between the *SMAD7* intron 3 SNP rs4939827 and the risk of colorectal cancer is 0.87 (95% confidence interval [CI], 0.80 to 0.95). The rs12953717 is also in intron 3 of *SMAD7* and is associated with an increased risk of colorectal cancer (odds ratio, 1.11; 95% CI, 1.03 to 1.20).
†† The alleles associated with increased risk are remarkably frequent in blacks (approximately 40% of blacks carry one or more of these variants). The allele at rs1447295 is also frequent in this population, but it does not appear to be associated with an increased risk of prostate cancer.
‡‡ Apart from *NBS1*, for all other cases in this group, the named gene is only the most likely candidate to be implicated in prostate cancer. The strength of each candidate varies. *MSMB* encodes a secreted protein. *KLK3* encodes prostate-specific antigen, and therefore it may have nothing to do with prostate-cancer susceptibility itself. *LMTK2* encodes a cyclin-dependent kinase.
§§ Mutations in *STK11* cause Peutz–Jeghers syndrome, whereas *PRSS1* and *SPINK1* mutations are responsible for a sizable fraction of cases of hereditary pancreatitis.

Similarly, the first genetic study to show a significant association is likely to have overestimated the size of the effect,[45] which is one reason for the requirements for several thousand cases and a similar number of controls, with built-in replication, before the candidacy of any low-penetrance gene can be accepted. Recently, the risk of lung cancer has been closely linked to two markers, rs1051730 and rs8034191, which lie within or adjacent to the nicotinic acetylcholine receptor subunit genes *CHRNA3*, *CHRNA5*, and *CHRNB4*.[25-27] These genes are good candidates for low-penetrance, high-frequency lung-cancer susceptibility genes (Table 1). The two SNP markers have a combined odds ratio for lung cancer of approximately 1.30 for the rare allele ($P<1\times10^{-17}$). Notably, the effect of these genes on risk may be independent of any effect they may have on smoking behavior,[27,46] and they may be important determinants of risk in persons with a family history of lung cancer.[47]

BREAST CANCER

Only a small proportion (≤10%) of breast cancers are due to hereditary mutations in single, dominantly acting genes, although models suggest that a larger fraction of so-called sporadic cases of breast cancer might be attributable to the action of multiple genes.[48]

The two most important breast-cancer genes, *BRCA1* and *BRCA2*, confer a risk of breast cancer among carriers that is 10 to 30 times as high as the risk among women in the general population.[49] Other genes with a population frequency and risk profile similar to *BRCA1* or *BRCA2* are

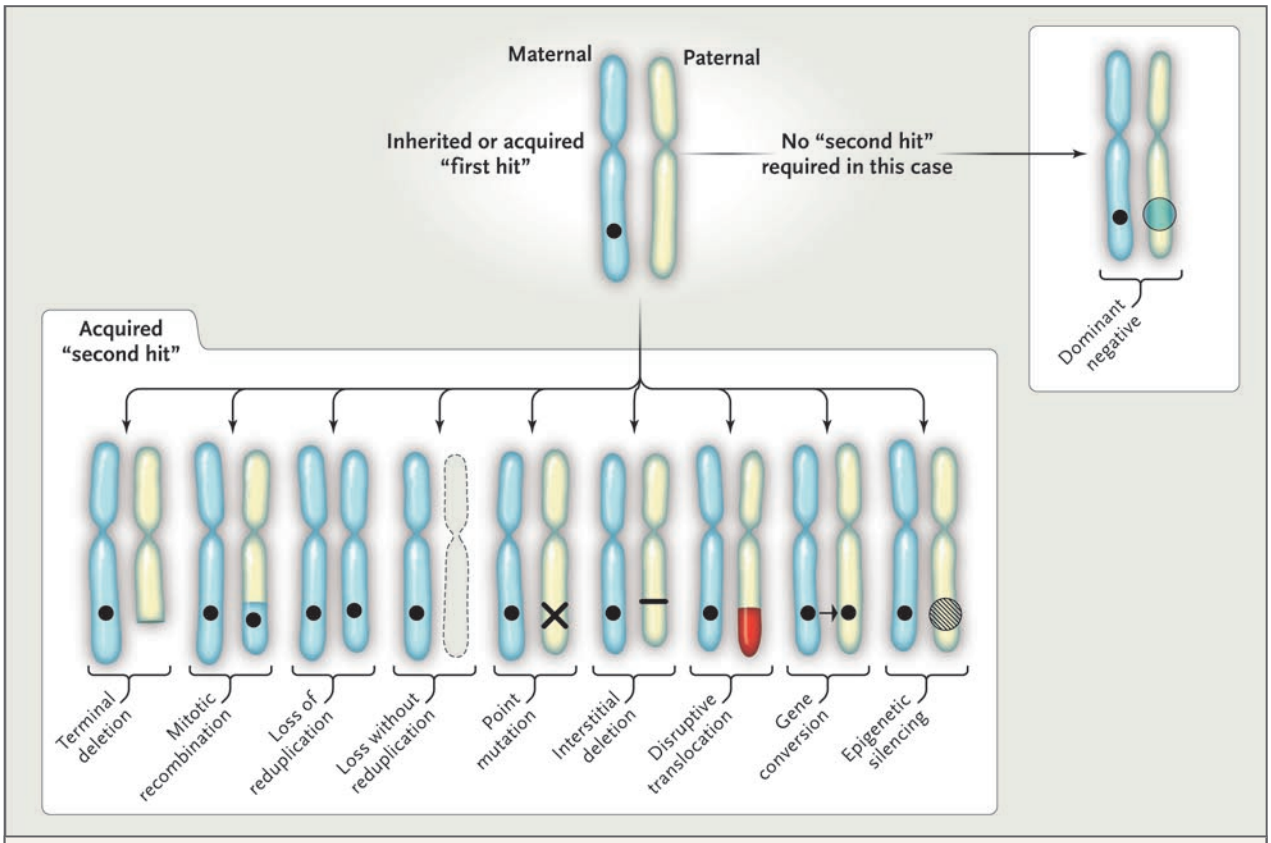

Figure 1. Mechanisms of Loss of Heterozygosity and Inactivation of Wild-Type Tumor-Suppressor Genes.

Mechanisms by which both copies of a gene can be inactivated are shown (bottom). All lead to an absence of wild-type protein. An alternative mechanism is shown (right) whereby the wild-type allele is rendered nonfunctional. Translocations would usually be expected to activate oncogenes or generate new fusion proteins, but they can also be associated with microdeletions. Some mutations can lead to expressed truncated proteins, and these may have dominant negative effects or may be partially functional. With the loss of heterozygosity, the phenotypes are most parsimoniously explained by the absence of the wild-type protein. If two hits occur in the germ line, the phenotype is more severe and is distinct from that seen with monoallelic germ-line mutations.

unlikely to exist.[50] Less frequent mutations associated with a relative risk of breast cancer of 2.0 or greater have been identified (Fig. 2).

Multiple cases of early-onset breast cancer, which typically occurs in women younger than 50 years of age, and a high rate of bilateral breast tumors are characteristic of families with hereditary breast cancer. Serous papillary ovarian carcinoma, which is not described in this review, is a key feature of hereditary breast cancer caused by *BRCA1* mutations, but it is less common in *BRCA2* mutation carriers. Although *BRCA1* and *BRCA2* mutations are rare in most populations (occurring in approximately 1 of 400 persons), they are much more common in the Ashkenazi Jewish population in which 1 of 40 persons carries one of three main disease-causing mutations. Founder mutations exist in other populations as well, and their presence can aid genetic testing.[54] Most pathogenic *BRCA1* or *BRCA2* mutations block protein production from the mutated allele. Missense mutations that interfere with critical regions of the gene, such as the RING finger motif or BRCT region of *BRCA1*[55] or the *PALB2* gene–binding region of *BRCA2*,[56] behave exactly like truncating mutations, whereas most missense mutations remain uncharacterized and hence are variants of unknown significance.[55]

BRCA1-related breast cancers differ from other breast cancers in that they are usually high-grade, aneuploid carcinomas that do not express estrogen receptor, progesterone receptor, or HER2 (hence, they are called "triple negative"), but they often express cytokeratins 5 and 14, vimentin,

Table 2. Distinct Phenotypes in Monoallelic and Biallelic Mutation Carriers.*

Gene	Phenotypic Effect	
	Monoallelic Mutations	Biallelic Mutations
MLH1	Lynch syndrome; cancers of colorectum, endometrium, small bowel, ureter, renal pelvis	CMMR-D syndrome (mainly in children and adolescents); parents may have Lynch syndrome
MSH2	Lynch syndrome; extracolonic cancers are frequent	CMMR-D syndrome (mainly in children and adolescents); parents may have Lynch syndrome
MSH6	Lynch syndrome; endometrial cancer is common, other cancers are less common	CMMR-D syndrome (mainly in children and adolescents); parents may have Lynch syndrome
PMS2	Lynch syndrome; lower risk of colorectal and extracolonic cancers	CMMR-D syndrome (mainly in children and adolescents); cancer in previous generations uncommon
BRCA2	Hereditary breast cancer; ovarian, fallopian-tube, peritoneal, and pancreatic cancer and melanoma	Fanconi's anemia, type D1; early-childhood acute myeloid leukemia; medulloblastoma; Wilms' tumor
PALB2	Breast cancer, can be familial	Fanconi's anemia, type N; early-childhood acute myeloid leukemia; medulloblastoma; Wilms' tumor
BRIP1	Breast cancer, can be familial	Fanconi's anemia, type J; solid tumors
ATM	Breast cancer, can be familial; T-cell leukemia	Ataxia–telangiectasia, childhood and adolescent lymphomas and T-cell leukemia; a wide variety of carcinomas may develop late
VHL	Inherited renal-cell cancer; retinal angiomas, cerebellar hemangioblastomas, endolymphatic sac carcinomas	Polycythemia, thrombosis, vertebral hemangiomas, low blood pressure; endemic in the Chuvashian population of Russia

* CMMR-D denotes constitutional mismatch repair deficiency.

epidermal growth factor receptor (EGFR), and P-cadherin (CDH3). This phenotype is called "basal-like breast cancer."[57] These characteristics make *BRCA1*-related breast cancers difficult to detect by mammography.[58] For this reason, as well as the increased prevalence among mutation carriers, screening for these cancers with magnetic resonance imaging (MRI) is warranted.[59] The risk of contralateral breast cancer among carriers of *BRCA1* and *BRCA2* is substantial (approximately 3% per year),[60] warranting more vigorous breast surveillance with MRI or prophylactic mastectomies.

BRCA1 and BRCA2 are very large proteins with multiple functions, including repair of double-strand breaks in DNA by homologous recombination[61] (see the table in the Supplementary Appendix). This cellular function may be exploited therapeutically with the use of agents that cause DNA strand breaks that require repair through homologous recombination. Compounds such as PARP1 protein inhibitors, which block alternative DNA repair mechanisms (in this case, base excision repair), may have a role in targeting cancers developing in BRCA1 and BRCA2 mutation carriers.

The other high-risk breast-cancer genes (Table 1 and Fig. 2) account for less than 1% of cases of breast cancer. Two rare hereditary cancer syndromes are linked to the risk of breast cancer. Mutations in *PTEN* cause a variety of inherited syndromes, including Cowden's syndrome and the Bannayan–Ruvalcaba–Riley–Smith syndrome.[62] Mutations in *TP53* cause the Li–Fraumeni syndrome, which includes early-onset sarcomas and cancer at any site diagnosed in persons younger than 45 years of age (see the table in the Supplementary Appendix).

A second class of breast-cancer susceptibility alleles includes genes, currently limited to four (*CHEK2*, *ATM*, *BRIP1*, and *PALB2*), which were originally referred to as low-penetrance genes but are now more properly referred to as moderate-risk alleles (Table 1 and Fig. 2). These alleles are rare in most populations, and they confer a risk of breast cancer that is two to three times as high as the risk among persons without these alleles, but the conferred risks may be higher in clinical settings. In selected populations, these alleles may be more clinically important: *CHEK2* 1100delC is carried by approximately 1% of the Dutch and Finnish populations; the S428F mutant of *CHEK2* has a similar frequency in the Ashkenazi Jewish population, as does the found-

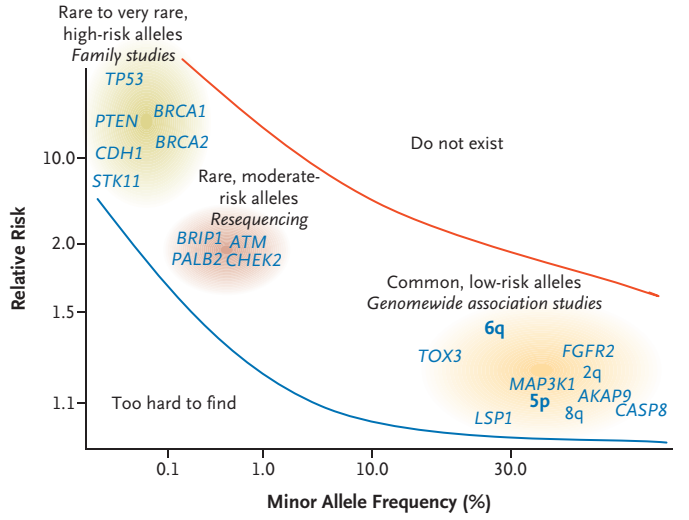

Figure 2. Breast-Cancer Susceptibility Loci and Genes.

All known breast-cancer susceptibility genes are shown between the red and blue lines. No genes are believed to exist above the red line, and no genes have been identified below the blue line. High-risk syndromic genes are highlighted in green. Mutations in serine threosine kinase 11 (*STK11*) cause the Peutz–Jeghers syndrome; in patients with this syndrome, the risk of breast cancer can be as high as 32% by the age of 60 years.[51] Similar or higher risks are seen in association with germ-line mutations in *PTEN* and the E-cadherin gene (*CDH1*). Mutations in *PTEN* are associated with florid bilateral fibrocystic breast disease and a substantially increased risk of breast cancer. Mutations in *CDH1* are associated with an approximate 40% risk of lobular breast cancer[52] and diffuse gastric cancer.[52,53] The moderate-penetrance genes (highlighted in red) have an approximate relative risk of 2.0. There are probably many more genes in this class, but they can be identified only by resequencing candidate genes in affected persons in families with breast cancer. *BRIP1, PALB2,* and *BRCA2* are Fanconi's anemia genes. The common, low-risk genes are shown in orange. SNPs in *FGFR2* and *TOX3,* and those on chromosomes 5p and 2q specifically increase the risk of estrogen-receptor–positive breast cancer.

er mutation IVS2+1G→A in Slavic populations.[63] Founder mutations in *PALB2* occur in persons in Finland and Quebec, Canada.[64,65]

Fanconi's anemia is a rare disease of childhood that is characterized by skeletal defects, skin pigmentation, short stature, and microphthalmia. Among affected children who survive, early-onset acute myeloid leukemia and skin tumors in adulthood are common. In some subtypes of Fanconi's anemia, medulloblastoma and Wilms' tumors occur in infancy or childhood.[66] Remarkably, three breast-cancer genes — *BRCA2, PALB2,* and *BRIP1* — have all been found to be associated with Fanconi's anemia, but only when they are present as biallelic mutations (Table 2 and Fig. 2).

Genomewide association studies have identified a third class of susceptibility genes in 15 to 40% of women with breast cancer[10-13,22] (Table 1). One of these genes, *FGFR2,* encodes a growth factor receptor. The relative risk of breast cancer conferred by these genetic variants is minimal. The clinical usefulness of these findings may be in their suggestion of higher-order gene–gene interactions or multiplicative relationships that could account for a measurable fraction of population risk.

COLORECTAL CANCER

There are three classes of colorectal-cancer susceptibility genes (Table 1). Several of the most important genes — *APC, MUTYH* (familial forms of polyposis), and the Lynch syndrome genes (*MLH1, MSH2, MSH6,* and *PMS2*) — account for less than 5% of all cases of colorectal cancer, but they affect young people disproportionately (see the table in the Supplementary Appendix). Testing for mutations in these genes is recommended in patients with clinicopathological features that are suggestive of these syndromes (Table 2). The underlying defect in the Lynch syndrome is defective mismatch repair. Mismatches between DNA strands that occur naturally, but erroneously, during DNA replication are not repaired because the key genes have become inactivated, usually by two "hits" — one inherited, the other acquired later in life (Fig. 1). This lack of repair results in numerous DNA sequence errors, particularly in runs of tandemly repeated nucleotides such as $(T)_n$ or $(CA)_n$, where n is usually 5 or more. Errors occurring in critical genes such as *BAX* or *TGFBRII* can initiate tumors.[67] Since this mutator phenotype accelerates the rate of carcinogenesis and results in the rapid development of colorectal cancer once polyps have formed,[68] frequent colonoscopic screening in carriers is warranted.[69]

A more severe phenotype results if mutations are inherited on both parental alleles. This has recently been referred to as the constitutional mismatch repair-deficiency syndrome (CMMR-D).[70] It consists of café au lait spots and childhood cancers, particularly leukemia, malignant brain tumors, and gastrointestinal neoplasia (Table 2).

APC causes familial adenomatous polyposis, the most common form of gastrointestinal polyposis. The colorectum in familial adenomatous polyposis is carpeted by hundreds to thousands of polyps (Fig. 3), and extracolonic neoplastic

and non-neoplastic manifestations such as adenocarcinoma of the ampulla of Vater, childhood medulloblastomas and hepatoblastomas, desmoid tumors, and sebaceous cysts are typical.[71] *APC* is a very large gene, and its product has several important functions, particularly with regard to regulation of β-catenin.[72] Although it is considered to be a gatekeeper[73] — a rate-limiting function in carcinogenesis — the APC protein may also have some caretaker functions. The loss of APC can induce chromosomal instability and subsequent aneuploidy, and thus it may cause widespread chromosomal changes[74,75] (see the table in the Supplementary Appendix).

MUTYH is the first base-excision repair gene to be associated with the risk of cancer, and the *MUTYH*-associated polyposis syndrome is inherited as a recessive trait.[76] The risk of colorectal cancer among carriers of biallelic mutations appears to be close to 100% by 60 years of age,[77] although the phenotype is variable, ranging from 10 or more polyps to widespread polyposis with associated colorectal cancer. Limited data suggest that heterozygotes have a slightly increased risk of colorectal cancer.[78,79] The defect in base excision repair, caused by the absence of normally functioning MUTYH, results in a specific target mutation, G-to-C transversion. When these mutations cause loss or inactivation of *APC*, the resulting phenotype resembles familial adenomatous polyposis. Other high-risk polyp-related genes, such as *SMAD4*, *BMPR1A*, and *STK11*, are quite rare.[67]

A missense mutation in *APC* known as I1307K (isoleucine changes to lysine) is associated both with polyps and risk of colorectal cancer that is 1.5 to 2 times as high as the risk among persons without this mutation.[80] The mutation seems to increase the likelihood of DNA replication errors occurring locally because the mutation changes a T to an A (a transversion), resulting in a run of eight adenines in a row. Notably, this allele appears to be largely limited to Ashkenazi Jews, of whom approximately 6% carry this variant.[80,81] Another risk allele that is restricted to the Ashkenazi Jewish population, BLM^{Ash}, has neither the frequency nor the penetrance to be of clinical use.[82] Genomewide association studies confirm that a number of loci, including the chromosome 8q locus previously linked to prostate cancer, are associated with slightly increased risks of colorectal cancer[14-17,23,24,83] (Table 1).

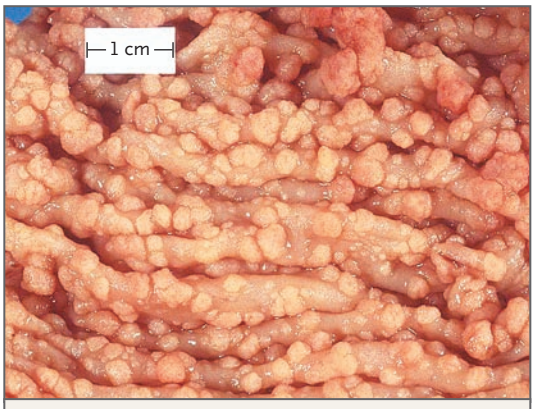

Figure 3. An Operative Section of Colon with Polyps.
A view of a small section of resected colon obtained from a patient with familial adenomatous polyposis is shown. Innumerable polyps are present. Most studies suggest that each polyp contains no fully functioning APC protein. (Image courtesy of Dr. J.R. Jass.)

PROSTATE CANCER

Unraveling the genetics of prostate cancer has been difficult, and no high-risk, prostate-specific genes seem to exist. The closest candidate is *BRCA2*, which confers a risk of prostate cancer that is as much as 20 times the risk in the general population.[84] *BRCA2*-associated prostate cancers are aggressive,[85] suggesting the need for better screening in carriers. *BRCA2* mutations are rare, however, in men with prostate cancer,[84,86,87] and despite considerable collaborative efforts, no prostate-cancer genes have yet been conclusively identified by linkage analysis.[88] Genomewide association studies have identified several new candidate genes and loci.[7,9,18-21] None of these genes are associated with large risks, although some are of considerable interest. The variant near the gene *MSMB* is the most promising because it encodes an immunoglobulin-binding factor that is present in seminal fluid.[19] There are several different risk loci on chromosome 8q24,[89] and some of them are very frequent, especially in blacks, a population with a high prevalence of prostate cancer (Table 1).

PANCREATIC CANCER

Elucidating the genetics of pancreatic cancer has also been difficult, but several genes already described have been implicated in its cause (Table 1). Again, the most important gene is *BRCA2*, which

accounts for approximately 10% of cases of pancreatic cancer in Ashkenazi Jews, and carriers of the *BRCA2* mutation, 6174delT (which is present in approximately 1 of 100 Ashkenazi Jews), have a 7% lifetime risk of pancreatic cancer.[90] Carriers of other *BRCA2* mutations also have a risk of pancreatic cancer that is three to five times the risk among persons without these mutations.[91,92] Patients with *BRCA2*-associated pancreatic cancer may not have a family history of breast or ovarian cancer.[93] The risk of pancreatic carcinoma is also significantly increased among carriers of mutations in *BRCA1*, *MSH2*, *STK11*, and probably both *MLH1* and *TP53*.[67,94,95] The highest risk of pancreatic cancer in association with a mutation in a tumor-suppressor gene is seen among carriers of mutations in *CDKN2A*; among such persons, the standardized incidence ratio may be as high as 52 (4 cases observed and 0.1 case expected in 811 person-years of follow-up).[96] This gene encodes a cell-cycle–dependent kinase inhibitor (see the table in the Supplementary Appendix) that is associated with familial cutaneous malignant melanoma. It is very unusual to find pancreatic-cancer–associated mutations in *CDKN2A* other than in melanoma-prone families.[97]

In rare cases, pancreatic cancer occurs in families with preexisting abnormalities of the pancreas. In some of these cases, the abnormalities lead to chronic pancreatitis, and in these families, pancreatic cancer is up to 50 times as frequent as it is in the general population.[98] Many families with hereditary chronic pancreatitis carry mutations in *PRSS1*[99] or pancreatic *SPINK1*.[100] Case reports have identified one or two families in which the risk of pancreatic cancer among persons with precursor lesions is almost 100%.[101] *PALLD*, which encodes Palladin, appears to be the responsible gene in one family,[102] although its candidacy has been questioned.[103] The gene does not contribute significantly to familial pancreatic-cancer susceptibility.[104-106] Screening by means of endoscopic ultrasonography or endoscopic retrograde cholangiopancreatography (and even preventive pancreatectomy) may be warranted in these exceptional kindreds.[107]

CANCER SUSCEPTIBILITY GENES IN HEALTH AND HEALTH CARE DELIVERY

The identification of high-risk cancer susceptibility genes means that physicians and persons at risk must understand the implications of the risk of genetic cancer; this identification has resulted in the blossoming of cancer genetics as a clinical subspecialty. Genetic counselors and other health specialists with expertise in cancer risk assessment are qualified to offer the kinds of services needed by persons with or at risk for hereditary cancer.

Genetic testing for the highly penetrant genes listed in Table 1 is widely available (see www.genetests.org for a list of testing laboratories). Despite the apparent simplicity of the genetic tests themselves, interpretation, particularly of unclassified variants, can be much more difficult. Such complexities, including genetic sites of low-impact or genetic variants of unknown significance, warrant appropriate pretest and post-test counseling for persons who undergo genetic testing.

Guidelines for deciding which patients should be tested and which tests should be performed are available. As with any test designed to identify risk factors or screen for relatively uncommon events in the general population, genetic tests for cancer present considerable social and ethical challenges. There are complex considerations to take into account before integrating the newer, less penetrant genetic markers into clinical cancer genetics because of the weak penetrance of individual alleles and the limited techniques of early detection and surveillance for certain cancers, including lung and pancreatic lesions. There is concern that direct marketing of genetic tests to the public plays on an often exaggerated fear of cancer.

Following the success of genomewide association studies, new forms of technology are emerging that may offer broader genetic testing to assess the risk of cancer. Grouping low-risk alleles could identify persons at the extremes of risk.[48] However, in most cases, we lack sufficient information on the behavior of these risk panels in the clinical setting. Furthermore, the composition of these panels is likely to change with time as more alleles are detected and advances in computational biology are made. Important practical and ethical questions abound; these include the minimum level of risk associated with a panel of SNPs that would warrant their use. For instance, a change involving twice the risk or less is arguably not meaningful for most persons or societies, but specific populations or persons might feel justified in seeking

genetic testing. It is not clear what thresholds of population-specific allele frequency and age-specific penetrance should trigger widespread consideration of genetic testing.

It is important to ensure that genetic testing, like cancer screening in general, does not become mainly a way for well people to buy reassurance, particularly when some reassurance is false and the findings are lacking in real evidence of benefit.[108] Nevertheless, it would be a great loss if policymakers and the public were to tire of genes and gene-based medicine as a whole, because genetics has shown itself to be an enormously powerful tool in the discovery of new knowledge. If the new discoveries in the inherited basis of the common cancers can be effectively incorporated into other preventive and diagnostic strategies, and moreover, if these strategies can be cheaply and equably delivered, then there is hope of real benefit for the entire population. High-throughput analysis of cancer genomes is revealing previously unrecognized complexity.[109,110] Combined knowledge of inherited and acquired genetic changes is likely to result in significant advances in the prevention, diagnosis, and treatment of the five most common cancers, which are responsible for more than half of all cancer-related deaths in North America.

No potential conflict of interest relevant to this article was reported.

I thank Dr. D.F. Easton for his assistance with the concept for Figure 2.

REFERENCES

1. Lynch HT, Shaw MW, Magnuson CW, Larsen AL, Krush AJ. Hereditary factors in cancer: study of two large midwestern kindreds. Arch Intern Med 1966;117:206-12.
2. Cavenee WK, Dryja TP, Phillips RA, et al. Expression of recessive alleles by chromosomal mechanisms in retinoblastoma. Nature 1983;305:779-84.
3. Risch N, Merikangas K. The future of genetic studies of complex human diseases. Science 1996;273:1516-7.
4. Le Marchand L, Donlon T, Kolonel LN, Henderson BE, Wilkens LR. Estrogen metabolism-related genes and breast cancer risk: the Multiethnic Cohort Study. Cancer Epidemiol Biomarkers Prev 2005;14:1998-2003.
5. Carpenter WR, Robinson WR, Godley PA. Getting over testosterone: postulating a fresh start for etiologic studies of prostate cancer. J Natl Cancer Inst 2008;100:158-9.
6. Haiman CA, Hsu C, de Bakker PI, et al. Comprehensive association testing of common genetic variation in DNA repair pathway genes in relationship with breast cancer risk in multiple populations. Hum Mol Genet 2008;17:825-34.
7. Amundadottir LT, Sulem P, Gudmundsson J, et al. A common variant associated with prostate cancer in European and African populations. Nat Genet 2006;38:652-8.
8. Sun T, Gao Y, Tan W, et al. A six-nucleotide insertion-deletion polymorphism in the CASP8 promoter is associated with susceptibility to multiple cancers. Nat Genet 2007;39:605-13.
9. Gudmundsson J, Sulem P, Steinthorsdottir V, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat Genet 2007;39:977-83.
10. Hunter DJ, Kraft P, Jacobs KB, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet 2007;39:870-4.
11. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007;447:1087-93.
12. Stacey SN, Manolescu A, Sulem P, et al. Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 2007;39:865-9.
13. Frank B, Wiestler M, Kropp S, et al. Association of a common AKAP9 variant with breast cancer risk: a collaborative analysis. J Natl Cancer Inst 2008;100:437-42.
14. Zanke BW, Greenwood CM, Rangrej J, et al. Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24. Nat Genet 2007;39:989-94.
15. Haiman CA, Le Marchand L, Yamamato J, et al. A common genetic risk factor for colorectal and prostate cancer. Nat Genet 2007;39:954-6.
16. Tomlinson I, Webb E, Carvajal-Carmona L, et al. A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24.21. Nat Genet 2007;39:984-8.
17. Broderick P, Carvajal-Carmona L, Pittman AM, et al. A genome-wide association study shows that common alleles of SMAD7 influence colorectal cancer risk. Nat Genet 2007;39:1315-7.
18. Gudmundsson J, Sulem P, Manolescu A, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. Nat Genet 2007;39:631-7.
19. Eeles RA, Kote-Jarai Z, Giles GG, et al. Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet 2008;40:316-21.
20. Thomas G, Jacobs KB, Yeager M, et al. Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet 2008;40:310-5.
21. Gudmundsson J, Sulem P, Rafnar T, et al. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. Nat Genet 2008;40:281-3.
22. Gold B, Kirchhoff T, Stefanov S, et al. Genome-wide association study provides evidence for a breast cancer risk locus at 6q22.33. Proc Natl Acad Sci U S A 2008;105:4340-5.
23. Tenesa A, Farrington SM, Prendergast JG, et al. Genome-wide association scan identifies a colorectal cancer susceptibility locus on 11q23 and replicates risk loci at 8q24 and 18q21. Nat Genet 2008;40:631-7.
24. Tomlinson IP, Webb E, Carvajal-Carmona L, et al. A genome-wide association study identifies colorectal cancer susceptibility loci on chromosomes 10p14 and 8q23.3. Nat Genet 2008;40:623-30.
25. Hung RJ, McKay JD, Gaborieau V, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature 2008;452:633-7.
26. Thorgeirsson TE, Geller F, Sulem P, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature 2008;452:638-42.
27. Amos CI, Wu X, Broderick P, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nat Genet 2008;40:616-22.
28. Bailey-Wilson JE, Amos CI, Pinney SM, et al. A major lung cancer susceptibility locus maps to chromosome 6q23-25. Am J Hum Genet 2004;75:460-74.
29. Hwang SJ, Cheng LS, Lozano G, Amos CI, Gu X, Strong LC. Lung cancer risk in germline p53 mutation carriers: association between an inherited cancer predisposition, cigarette smoking, and cancer risk. Hum Genet 2003;113:238-43.

30. Sanders BM, Jay M, Draper GJ, Roberts EM. Non-ocular cancer in relatives of retinoblastoma patients. Br J Cancer 1989; 60:358-65.
31. Fletcher O, Easton D, Anderson K, Gilham C, Jay M, Peto J. Lifetime risks of common cancers among retinoblastoma survivors. J Natl Cancer Inst 2004;96:357-63.
32. Takemiya M, Shiraishi S, Teramoto T, Miki Y. Bloom's syndrome with porokeratosis of Mibelli and multiple cancers of the skin, lung and colon. Clin Genet 1987; 31:35-44.
33. Yamanaka A, Hirai T, Ohtake Y, Kitagawa M. Lung cancer associated with Werner's syndrome: a case report and review of the literature. Jpn J Clin Oncol 1997;27:415-8.
34. Shaw GL, Falk RT, Frame JN, et al. Genetic polymorphism of CYP2D6 and lung cancer risk. Cancer Epidemiol Biomarkers Prev 1998;7:215-9.
35. Ye Z, Song H, Higgins JP, Pharoah P, Danesh J. Five glutathione s-transferase gene variants in 23,452 cases of lung cancer and 30,397 controls: meta-analysis of 130 studies. PLoS Med 2006;3(4):e91.
36. Raimondi S, Paracchini V, Autrup H, et al. Meta- and pooled analysis of GSTT1 and lung cancer: a HuGE-GSEC review. Am J Epidemiol 2006;164:1027-42.
37. McKay JD, Hashibe M, Hung RJ, et al. Sequence variants of NAT1 and NAT2 and other xenometabolic genes and risk of lung and aerodigestive tract cancers in Central Europe. Cancer Epidemiol Biomarkers Prev 2008;17:141-7.
38. Matakidou A, Eisen T, Fleischmann C, Bridle H, Houlston RS. Evaluation of xeroderma pigmentosum XPA, XPC, XPD, XPF, XPB, XPG and DDB2 genes in familial early-onset lung cancer predisposition. Int J Cancer 2006;119:964-7.
39. Hung RJ, Hall J, Brennan P, Boffetta P. Genetic polymorphisms in the base excision repair pathway and cancer risk: a HuGE review. Am J Epidemiol 2005;162: 925-42.
40. Engels EA, Wu X, Gu J, Dong Q, Liu J, Spitz MR. Systematic evaluation of genetic variants in the inflammation pathway and risk of lung cancer. Cancer Res 2007;67:6520-7.
41. Rudd MF, Webb EL, Matakidou A, et al. Variants in the GH-IGF axis confer susceptibility to lung cancer. Genome Res 2006;16:693-701.
42. Hung RJ, Hashibe M, McKay J, et al. Folate-related genes and the risk of tobacco-related cancers in Central Europe. Carcinogenesis 2007;28:1334-40.
43. Wang W, Spitz MR, Yang H, Lu C, Stewart DJ, Wu X. Genetic variants in cell cycle control pathway confer susceptibility to lung cancer. Clin Cancer Res 2007; 13:5974-81.
44. Bazerman MH, Samuelson WF. I won the auction but I don't want the prize. J Conflict Resolut 1983;27:618-34.
45. Ioannidis JP, Trikalinos TA, Ntzani EE, Contopoulos-Ioannidis DG. Genetic associations in large versus small studies: an empirical assessment. Lancet 2003;361: 567-71.
46. Hung RJ, Baragatti M, Thomas D, et al. Inherited predisposition of lung cancer: a hierarchical modeling approach to DNA repair and cell cycle control pathways. Cancer Epidemiol Biomarkers Prev 2007; 16:2736-44.
47. Liu P, Vikis HG, Wang D, et al. Familial aggregation of common sequence variants on 15q24-25.1 in lung cancer. J Natl Cancer Inst 2008;100:1326-30.
48. Pharoah PD, Antoniou A, Bobrow M, Zimmern RL, Easton DF, Ponder BA. Polygenic susceptibility to breast cancer and implications for prevention. Nat Genet 2002;31:33-6.
49. Antoniou A, Pharoah PD, Narod S, et al. 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; 72:1117-30.
50. Smith P, McGuffog L, Easton DF, et al. A genome wide linkage search for breast cancer susceptibility genes. Genes Chromosomes Cancer 2006;45:646-55.
51. Lim W, Olschwang S, Keller JJ, et al. Relative frequency and morphology of cancers in STK11 mutation carriers. Gastroenterology 2004;126:1788-94.
52. Pharoah PD, Guilford P, Caldas C. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology 2001;121:1348-53.
53. Guilford P, Hopkins J, Harraway J, et al. E-cadherin germline mutations in familial gastric cancer. Nature 1998;392: 402-5.
54. Narod SA, Foulkes WD. BRCA1 and BRCA2: 1994 and beyond. Nat Rev Cancer 2004;4:665-76.
55. Easton DF, Deffenbaugh AM, Pruss D, et al. A systematic genetic assessment of 1,433 sequence variants of unknown clinical significance in the BRCA1 and BRCA2 breast cancer-predisposition genes. Am J Hum Genet 2007;81:873-83.
56. Xia B, Sheng Q, Nakanishi K, et al. Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol Cell 2006;22:719-29.
57. Turner NC, Reis-Filho JS. Basal-like breast cancer and the BRCA1 phenotype. Oncogene 2006;25:5846-53.
58. Tilanus-Linthorst M, Verhoog L, Obdeijn IM, et al. A BRCA1/2 mutation, high breast density and prominent pushing margins of a tumor independently contribute to a frequent false-negative mammography. Int J Cancer 2002;102:91-5.
59. Warner E, Plewes DB, Shumak RS, et al. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. J Clin Oncol 2001;19:3524-31.
60. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328-35.
61. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell 2002;108:171-82.
62. Waite KA, Eng C. Protean PTEN: form and function. Am J Hum Genet 2002;70: 829-44.
63. Nevanlinna H, Bartek J. The CHEK2 gene and inherited breast cancer susceptibility. Oncogene 2006;25:5912-9.
64. Erkko H, Xia B, Nikkilä J, et al. A recurrent mutation in PALB2 in Finnish cancer families. Nature 2007;446:316-9.
65. Foulkes WD, Ghadirian P, Akbari MR, et al. Identification of a novel truncating PALB2 mutation and analysis of its contribution to early-onset breast cancer in French-Canadian women. Breast Cancer Res 2007;9:R83.
66. Tischkowitz MD, Hodgson SV. Fanconi anaemia. J Med Genet 2003;40:1-10.
67. de la Chapelle A. Genetic predisposition to colorectal cancer. Nat Rev Cancer 2004;4:769-80.
68. Kinzler KW, Vogelstein B. Cancer-susceptibility genes: gatekeepers and caretakers. Nature 1997;386:761, 763.
69. Jass JR, Stewart SM. Evolution of hereditary non-polyposis colorectal cancer. Gut 1992;33:783-6.
70. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA 2006;296:1507-17.
71. Wimmer K, Etzler J. Constitutional mismatch repair-deficiency syndrome: have we so far seen only the tip of an iceberg? Hum Genet 2008;124:105-22.
72. Foulkes WD. A tale of four syndromes: familial adenomatous polyposis, Gardner syndrome, attenuated APC and Turcot syndrome. QJM 1995;88:853-63.
73. Fearnhead NS, Britton MP, Bodmer WF. The ABC of APC. Hum Mol Genet 2001;10:721-33.
74. Fodde R, Kuipers J, Rosenberg C, et al. Mutations in the APC tumour suppressor gene cause chromosomal instability. Nat Cell Biol 2001;3:433-8.
75. Kaplan KB, Burds AA, Swedlow JR, Bekir SS, Sorger PK, Näthke IS. A role for the Adenomatous Polyposis Coli protein in chromosome segregation. Nat Cell Biol 2001;3:429-32.
76. Al-Tassan N, Chmiel NH, Maynard J, et al. Inherited variants of MYH associated with somatic G:C→T:A mutations in colorectal tumors. Nat Genet 2002;30:227-32.

77. Farrington SM, Tenesa A, Barnetson R, et al. Germline susceptibility to colorectal cancer due to base-excision repair gene defects. Am J Hum Genet 2005;77:112-9.
78. Croitoru ME, Cleary SP, Berk T, et al. Germline MYH mutations in a clinic-based series of Canadian multiple colorectal adenoma patients. J Surg Oncol 2007; 95:499-506.
79. Webb EL, Rudd MF, Houlston RS. Colorectal cancer risk in monoallelic carriers of MYH variants. Am J Hum Genet 2006;79:768-71.
80. Laken SJ, Petersen GM, Gruber SB, et al. Familial colorectal cancer in Ashkenazim due to a hypermutable tract in APC. Nat Genet 1997;17:79-83.
81. Rozen P, Shomrat R, Strul H, et al. Prevalence of the I1307K APC gene variant in Israeli Jews of differing ethnic origin and risk for colorectal cancer. Gastroenterology 1999;116:54-7.
82. Gruber SB, Ellis NA, Scott KK, et al. BLM heterozygosity and the risk of colorectal cancer. Science 2002;297:2013.
83. Jaeger E, Webb E, Howarth K, et al. Common genetic variants at the CRAC1 (HMPS) locus on chromosome 15q13.3 influence colorectal cancer risk. Nat Genet 2008;40:26-8.
84. Edwards SM, Kote-Jarai Z, Meitz J, et al. Two percent of men with early-onset prostate cancer harbor germline mutations in the BRCA2 gene. Am J Hum Genet 2003;72:1-12.
85. Tryggvadóttir L, Vidarsdóttir L, Thorgeirsson T, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. J Natl Cancer Inst 2007;99:929-35.
86. Agalliu I, Karlins E, Kwon EM, et al. Rare germline mutations in the BRCA2 gene are associated with early-onset prostate cancer. Br J Cancer 2007;97:826-31.
87. Agalliu I, Kwon EM, Zadory D, et al. Germline mutations in the BRCA2 gene and susceptibility to hereditary prostate cancer. Clin Cancer Res 2007;13:839-43.
88. Schaid DJ. The complex genetic epidemiology of prostate cancer. Hum Mol Genet 2004;13(Spec. No 1):R103-R121.
89. Cheng I, Plummer SJ, Jorgenson E, et al. 8q24 and prostate cancer: association with advanced disease and meta-analysis. Eur J Hum Genet 2008;16:496-505.
90. Ozcelik H, Schmocker B, Di Nicola N, et al. BRCA2 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients. Nat Genet 1997;16:17-8.
91. The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 1999;91: 1310-6.
92. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet 2005;42: 711-9.
93. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 2003;95:214-21.
94. Thompson D, Easton DF. Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002;94:1358-65.
95. Birch JM, Alston RD, McNally RJ, et al. Relative frequency and morphology of cancers in carriers of germline TP53 mutations. Oncogene 2001;20:4621-8.
96. Goldstein AM, Struewing JP, Fraser MC, Smith MW, Tucker MA. Prospective risk of cancer in CDKN2A germline mutation carriers. J Med Genet 2004;41:421-4.
97. Bartsch DK, Sina-Frey M, Lang S, et al. CDKN2A germline mutations in familial pancreatic cancer. Ann Surg 2002;236: 730-7.
98. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. J Natl Cancer Inst 1997;89:442-6.
99. Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 1996;14:141-5.
100. Witt H, Luck W, Hennies HC, et al. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. Nat Genet 2000;25:213-6.
101. Evans JP, Burke W, Chen R, et al. Familial pancreatic adenocarcinoma: association with diabetes and early molecular diagnosis. J Med Genet 1995;32:330-5.
102. Pogue-Geile KL, Chen R, Bronner MP, et al. Palladin mutation causes familial pancreatic cancer and suggests a new cancer mechanism. PLoS Med 2006;3(12): e516.
103. Salaria SN, Illei P, Sharma R, et al. Palladin is overexpressed in the non-neoplastic stroma of infiltrating ductal adenocarcinomas of the pancreas, but is only rarely overexpressed in neoplastic cells. Cancer Biol Ther 2007;6:324-8.
104. Zogopoulos G, Rothenmund H, Eppel A, et al. The P239S palladin variant does not account for a significant fraction of hereditary or early onset pancreas cancer. Hum Genet 2007;121:635-7.
105. Klein AP, de Andrade M, Hruban RH, et al. Linkage analysis of chromosome 4 in families with familial pancreatic cancer. Cancer Biol Ther 2007;6:320-3.
106. Slater E, Amrillaeva V, Fendrich V, et al. Palladin mutation causes familial pancreatic cancer: absence in European families. PLoS Med 2007;4(4):e164.
107. Brentnall TA, Bronner MP, Byrd DR, Haggitt RC, Kimmey MB. Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. Ann Intern Med 1999;131:247-55.
108. Hart JT. A few lessons in screening for Gordon Brown. BMJ 2008;336:123.
109. Sjöblom T, Jones S, Wood LD, et al. The consensus coding sequences of human breast and colorectal cancers. Science 2006;314:268-74.
110. Greenman C, Stephens P, Smith R, et al. Patterns of somatic mutation in human cancer genomes. Nature 2007;446: 153-8.