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Genomic Biomarkers for Breast Cancer Risk

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Abstract

Clinical risk assessment for cancer predisposition includes a three-generation pedigree and physical examination to identify inherited syndromes. Additionally genetic and genomic biomarkers may identify individuals with a constitutional basis for their disease that may not be evident clinically. Genomic biomarker testing may detect molecular variations in single genes, panels of genes, or entire genomes. The strength of evidence for the association of a genomic biomarker with disease risk may be weak or strong. The factors contributing to clinical validity and utility of genomic biomarkers include functional laboratory analyses and genetic epidemiologic evidence. Genomic biomarkers may be further classified as low, moderate or highly penetrant based on the likelihood of disease. Genomic biomarkers for breast cancer are comprised of rare highly penetrant mutations of genes such as *BRCA1* or *BRCA2*, moderately penetrant mutations of genes such as *CHEK2*, as well as more common genomic variants, including single nucleotide polymorphisms, associated with modest effect sizes. When applied in the context of appropriate counseling and interpretation, identification of genomic biomarkers of inherited risk for breast cancer may decrease morbidity and mortality, allow for definitive prevention through assisted reproduction, and serve as a guide to targeted therapy.

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Keywords

Genetics; Genomics; Breast oncology; Biomarkers; Prophylactic; Chemoprevention; Genetic counseling; Genetic testing; BRCA

As inherited variation in DNA sequence has been shown to correlate with future disease risk, genomic tests constitute objective “biomarkers” of an individual’s susceptibility to cancer [1]. A family history of breast cancer has long been thought to indicate the presence of inherited genetic events that predispose to this disease. Although familial breast cancer has been recognized since the nineteenth century, the detailed medical description of inherited breast (and ovarian cancer) in families took place in the 1970s [2, 3]. Subsequently, up to 15 % of patients diagnosed with invasive breast cancer were shown to have at least one first-degree female relative (mother, sister, or daughter) with the disease. Testing for genetic biomarkers of risk has evolved over the past two decades to complement family history and physical findings. The most notable of these genetic biomarkers emerged from genetic analysis of families affected by multiple cases of early-onset (50 years of age) breast cancer, leading to the discovery of the breast cancer susceptibility genes, *BRCA1* and *BRCA2* [4–6]. The genetic mapping of *BRCA1* strongly suggested an inherited risk of breast cancer resulting from genetic alterations located on chromosome 17q21 [7]. The subsequent discovery of *BRCA1,* and later *BRCA2* [8, 9]*,* initiated widespread interest in hereditary breast cancer. These discoveries also galvanized resource allocation to investigators exploring translation of this information to improve clinical care for those with breast cancer susceptibility. In the late 1990s, mutations in *BRCA1/2* were established as the main contributors to familial breast cancer, and population specific frequencies of mutations in these genes were compiled [10–14]. In the 10 years following, the clinical utility and the benefits of clinical genetic biomarkers became evident, as genetic testing led to individualized risk reduction strategies including preventive surgeries, chemoprophylaxis and targeted therapies [15, 16].

Although genetic tests for cancer risk constitute “biomarkers” in a general sense, these genomic markers are distinct from non-genetic biomarkers in that they reflect the impact of modifiers of penetrance, population-specific differences in allele frequencies, and influence of gene-environment interactions. As genomic testing continues to evolve, biomarkers of various strength and significance are being routinely detected and gene-gene and gene-environment interactions are beginning to emerge [17–22]. Understanding the functional significance of genomic alterations is conceptually critical in assessing the potential utility of genetic variants as biomarkers. The type of alteration and the location of an aberration in a gene, i.e., a synonymous missense variant, a nonsense missense variant, a deletion/duplication, a translocation, or an inversion, all bear on the assessment of a gene test as a “biomarker” of inherited cancer risk. Thus, understanding the type of genetic change is as important as the fact that the gene is altered.

Novel biomarkers are being revealed by next generation sequencing and tend to be associated with low and moderate penetrance genomic loci [23]. As more is known, algorithms will be required to weigh multiple biomarkers simultaneously and hence allow

clinicians to most informatively provide recommendations pertaining to risk reduction surgeries, surveillance guidelines, family planning, apply novel therapies, and modify and dose-adjust existing therapies.

Genetics in Breast Cancer Predisposition

Although the ease of testing for different genetic biomarkers is appealing in the "information age," the ability to contextualize this information remains a challenge. Statements from the American Society of Clinical Oncology (ASCO) have stressed the process of offering predictive genetic testing and the elements pertaining to medical, social, and psychological consequences of positive, negative and yet to be determined results. Provided here is an updated algorithm of the contents of informed consent for genomic testing for inherited genetic changes (Table 1).

Genetic testing for mutations in *BRCA1, BRCA2,* and other breast cancer susceptibility genes has served as a model for the integration of genomics into the practice of personalized medicine, with proven efficacy required for enhanced screening and prevention strategies, and as markers for targeted therapy. The rapid pace of molecular sequencing still requires due diligence to assure that the basic tenets of genetic counseling are fulfilled. Historically, a clinical genetics visit entails rapport building, a detailed account of the family history in the form of a pedigree, documentation of medical history, a physical exam with specific focus on the presence or absence of syndrome stigmata (e.g. macrocephaly or skin findings which may be manifestations of alterations in specific breast cancer genes), review of genetic concepts, discussion of options for screening and early detection, an opportunity for questions, a link to supporting services and a plan for follow up. In cases whereby a genetic visit indicates testing, the basic elements of informed counseling remain the standard of care [24], although these may increasingly be conveyed and communicated in on-line via video conferencing as well as in-person contexts. In an era of increasing somatic genetic analysis of breast and other tumors for the purposes of "targeting" therapies, it will be important to distinguish whether the primary purpose of genomic analysis is to determine inherited susceptibilities, or whether this information may emerge as a secondary byproduct of tumor genomic analysis (Fig. 1).

The current number of individuals having been tested for mutations in *BRCA1/2* exceeds one million. Pathogenic mutations appear to account for ~ 30 % of high-risk breast cancer families and explain ~ 15 % of the breast cancer familial relative risk (the ratio of the risk of disease for a relative of an affected individual to that for the general population) (Fig. 1) [4–6, 25]. Contextualizing disease risk of inherited mutations and sequence variants in *BRCA1/2* can be complex, since the pathogenicity of sequence variants is uncertain, and requires annotation and curation using existing databases (e.g. the Breast Cancer Information Core; www.research.nhgri.nih.gov/bic).

Syndromes of Breast Cancer Predisposition

Hereditary Breast and Ovarian Syndrome

BRCA1 and *BRCA2* are the predominant breast cancer susceptibility genes. Pre-test probability for *BRCA2* testing is higher for families with male and female breast cancer and for *BRCA1* testing in families with both breast and ovarian cancer [26]. 18,000 cases of breast cancer annually are associated with an obvious hereditary predisposition. Detection of breast cancer leads to a cure rate of more than 90 % if detected at an early stage. All told more than 200,000 breast cancer survivors in the United States developed their primary cancers as a result of a constitutional (inherited) predisposition, highlighting the importance and rationale for genetic testing [27]. Estimates range from one in 150 to one in 800 individuals in the population who are genetically predisposed to developing breast cancer and in certain ethnic groups these estimates are as high as 1 in 40 [28, 29]. A woman carrying a mutation in *BRCA1* has a lifetime breast cancer risk as high as 70 % by age 70 by epidemiologic analysis [29, 30–32]. In select families with a high frequency of early onset of breast or ovarian cancer risk, estimates further increase to as high as 90 % lifetime breast cancer risk [33].

Highly Penetrant Breast Cancer Genes

BRCA1 and BRCA2—The *BRCA1 and BRCA2* genes function in DNA damage response and homologous recombination [34]. *BRCA1* is a large gene located on chromosome 17 and is made up of 24 exons, 22 of which are coding and two of which are non-coding. *BRCA2* spans greater than 70,000 bases and the gene is comprised of 27 exons (genenames.org).

Premature truncations of the BRCA1 and BRCA2 proteins by nonsense or frame-shift alterations are the predominant genomic aberrations underlying susceptibility. Variants of uncertain significance were initially observed in up to a quarter of patients, however the frequency of these predominantly missense variants of unknown significance (VUS) dropped to between 2 and 5 % as large databases of genetic variants and “high-risk” kindreds were created [35, 36]. With the uptake of commercial testing by new laboratories, and the expansion of testing criteria beyond “high-risk” kindreds, this percentage of VUS may again increase [37].

Over 2000 distinct rare variants, in the form of intronic changes, missense mutations, and small in-frame insertions and deletions, have been reported in *BRCA1* and *BRCA2* (Breast Cancer Information Core; www.research.nhgri.nih.gov/bic). The main domains of *BRCA1,* which are critical for DNA repair activity, are located in the RING finger and BRCT domains. In *BRCA2*, highly penetrant, pathogenic missense mutations reside mainly in the DNA binding domain [38, 39]. Large genomic rearrangements or structural variations occur in *BRCA1* (14 % of mutations) and *BRCA2* (2.6 % of mutations). A reason for the relative increase in structural variations in *BRCA1* compared to *BRCA2* results from the large number of Alu repeats in the genomic region containing the *BRCA1* gene [40].

Population specific or “founder” mutations in *BRCA1/2* have been described. Some of the most common founder mutations occur in individuals of Ashkenazi (eastern European) Jewish ancestry, including two mutations in *BRCA1* (185delG and 5382insC) and one

mutation in *BRCA2* (6174delT) [41–43]. A small number of patients in the Ashkenazi population with breast cancer have non-founder mutations in *BRCA1/2* (5 % of all mutations) and thus reflex full gene sequencing may be required if founder mutations are non-revealing [42, 43]. The Ashkenazi Jewish founder mutations are the best studied and described; 3 % of individuals in this population carry a founder mutation. Other examples of *BRCA1* founder mutations are reported in the Dutch and Hispanic populations. Again for these populations, targeted sequencing for specific *BRCA1/2* mutations is advised before reflex to full gene testing in cases of a negative result. Carriers ascertained from population studies demonstrate a lower penetrance of disease in comparison to those identified through kindred based studies, which is not surprising as a striking overt phenotype in the families prompted initial study.

Including follow up recommendations for screening and prevention for *BRCA1* mutation carriers remains as a standard of care given a ~ 57 % probability of developing breast cancer and a 40 % chance of developing ovarian cancer by age 70. *BRCA2* mutation carriers are estimated to have a 49 % chance of breast cancer and an 18 % chance of ovarian cancer [44]. Contributing factors to the development of cancer include environment, modifying genomic alterations and the specific type of constitutional aberration in *BRCA1/2.* Statistical evidence has emerged suggesting genotype-phenotype correlations with regard to ovarian cancer risk. The early literature correlated the location of mutations in *BRCA1/2* with specific phenotypes and gleaned that nonsense and frameshift mutations located in the central regions of either coding sequence, termed ovarian cancer cluster regions (OCCR), were associated with a greater risk of ovarian cancer than similar mutations in the proximal and distal regions of each gene [45, 46]. Among the greater than 22,000 *BRCA1/2* mutation carriers enrolled in Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) group, the relative increases in ovarian cancer and decreases in breast cancer risk for mutations in the central region of each gene and higher risk of breast cancer for mutations in the 5′ and 3′ regions of each gene have been observed. Further variability in risk is also partly explained by common genetic modifiers of breast and ovarian cancer risk in *BRCA1/2* mutation carriers that have been identified through genome-wide association studies [19, 47–51]. [55, 117] (Fig. 2).

The genomic location of a patient's *BRCA1/2* mutation and the risk from modifier genes suggests that the *BRCA1* mutation carriers in the highest risk category may have an 81 % or greater chance of breast cancer and a 63 % or greater chance of ovarian cancer by age 80, whereas *BRCA2* mutation carriers at greatest risk may have more than an 83 % chance of breast cancer by age 80 [19, 52]. In conjunction with other variables modifying risk in *BRCA1/2* mutation carriers, these emerging biomarker data on mutation location and modifier genes offer the potential for more precise risk estimates. It is also possible that such biomarkers may correlate with disease behavior. As breast cancer patients with *BRCA1* mutations tend to have tumors that display features of more aggressive disease [53–56], genomic biomarkers of risk may also impact on the phenotype (e.g. estrogen receptor status) of hereditary disease.

As alluded to previously, VUS, including missense, intronic, and small in-frame insertion/deletion variants, continue to pose clinical challenges in terms of interpreting test results.

Although one large testing company has classified many *BRCA1/2* variants as neutral or pathogenic using data collected over years, that data have thus far not been placed into public access. Thus, laboratories now entering the clinical sequencing space have had challenges classifying variants encountered during testing. In an effort to improve the classification process for variants in all genes now offered as part of clinic genetic testing, the Clinvar (www.ncbi.nlm.nih.gov/clinvar) database has been curating variants and attempting to capture clinical information, efforts pioneered for BRCA1/2 by the international Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) Consortium (see below). In 2014, the Global Alliance announced a demonstration project to create an international database of *BRCA1/2* variants. These steps are crucial to allow the most accurate interpretation of these genetic biomarkers for inherited risk. In the absence of these definitive databases, evaluation of VUS has often relied on in-silico models or animal models that predict the functional impact of variants on the basis of amino acid conservation and/or structure or try equate the human disease to a different species that is not a direct homologue to humans.

To provide algorithms to the interpretation of variants of uncertain significance, expert and evidence-based committees focused on the development of quantitative risk prediction methods. One such effort is ENIGMA, which has substantially improved assessment of the pathogenicity of VUS [57]. The following elements are assessed for each variant: conservation, family history, tumor pathology, and the effects of RNA splicing [39, 57–59]. This effort also estimates the probability of pathogenicity for each variant using combined evolutionary sequence conservation (Align-GVGD) [39, 59–61], and has resulted in classification of many *BRCA1/2* VUS as pathogenic or of neutral/low effect [59]. Due to the lack of statistical power for rare variants or individual VUS, high throughput quantitative cell-based *in vitro* assays have been developed to evaluate the effect of variants on established functions of the BRCA1 and BRCA2 proteins, with known controls of normal and pathogenic mutations as controls to asses sensitivity and specificity for VUS [39] or variant specific biomarker.

A special challenge in interpreting gene variants is the example of hypomorphic mutations, which retain some protein activity. Insights are being gained for some specific variants, i.e. the p. Arg1699Gln (R1699Q) missense mutation in the BRCT domain of *BRCA1* that abrogates the repression of microRNA-155 [62] and is associated with a cumulative risk of breast cancer of 24 % by age 70 [57], and the well-known polymorphic stop codon in *BRCA2*, p.Lys3326X, which is associated with only a modest increase in breast cancer risk [odds ratio (*OR*) = 1.26] [63] and appears to have little clinical relevance. As more moderate risk variants or biomarkers in breast cancer predisposition genes are detected and clinically validated, personalized surveillance and prophylaxis measures may be developed.

Impact on Clinical Management for *BRCA1 and BRCA2* Mutation Carriers— Genetic testing informs both medical decisions and family planning. While evidence-based medicine continues to evolve, *BRCA* mutation carriers should undergo a triple assessment for breast surveillance, including self-examination, clinician examination and mammography/Magnetic resonance imaging (MRI) [64–66].

Mammography is of limited sensitivity in *BRCA* mutation carriers; in one study 29 % of new tumors were missed by mammography [16]. This limitation may be due to higher breast density in younger women and as hereditary breast cancers are often more rapidly growing "triple negative" tumors (negative for estrogen and progesterone receptors and lacking HER2/*neu* overexpression or amplification) [67]. It is strongly recommended that women at hereditary risk begin annual mammography/MRI screening at age 25 (http://www.nccn.org/professionals/physician_gls/pdf/f_guidlines.asp#breast_risk) [68]. MRI detects twice as many breast cancers in *BRCA1/2* mutation carriers as mammography or sonography [16], and is considered the standard of care. Alternatively, risk reducing mastectomy (RRM) decreases the risk of breast cancer by at least 90 % in *BRCA1/2* mutation carriers [69, 70], but only 36 % of women in the United States and 22 % in Canada choose to undergo this surgery [71]. In contrast, risk-reducing salpingo-oophorectomy (RRSO) has become the standard of care for all women with *BRCA1/2* mutations because ovarian cancer screening methods using serum markers and imaging are ineffective [72, 73]. RRSO has been shown to reduce the risk of *BRCA*-associated gynecologic cancer by 80–96 % [15, 69, 74] and to reduce the risk of breast cancer by ~ 50 %, most likely through the induction of premature menopause [15, 69, 75]. Most significantly, RRSO reduces overall mortality of women with *BRCA1/2* mutations by 60 % [76]. This reduction in mortality occurs despite the 0.2 % annual risk of cancer of the peritoneal lining around the ovaries and fallopian tubes, which remains as these tissues cannot be surgically removed by RRSO [74]. Genetic testing for *BRCA1/2* mutations and RRSO provided an early example of the deployment of 'personalized' prevention through genetics [16, 77].

Data pertaining to chemoprevention based on inherited biomarkers such as *BRCA1/2* are limited. Efficacy of tamoxifen for *BRCA1/2* mutations carriers was conducted as a sub-analysis as part of the 13,388 women enrolled in the National Surgical Adjuvant Breast and Bowel Project Prevention Trial (NSABP-P1). In this study, 19 *BRCA1/2* mutation carriers were identified among 288 that developed breast cancer, with risk ratios for developing breast cancer with tamoxifen estimated to be 1.67 (95 % confidence interval (CI): 0.32–10.7) for *BRCA1* mutation carriers and 0.38 (95 % CI: 0.06–1.56) for *BRCA2* mutation carriers [78]. In a larger study of 2464 mutation carriers, tamoxifen use after a first breast cancer was associated with a reduced risk of contralateral breast cancer [79]. More refined chemoprevention options for women with mutations in *BRCA1/2* may evolve. In patients with no mutations in *BRCA1/2*, other selective estrogen receptor modulators and aromatase inhibitors have been shown to prevent breast cancer,(http://www.nccn.org/professionals/physician_gls/pdf/f_guidlines.asp#breast_risk). Some data have also begun to emerge suggesting that modulators of RANKL signaling may be a target for chemoprevention [80].

Ovarian cancer chemoprevention studies have produced somewhat conflicting results bearing on benefits for *BRCA* mutation carriers [81–83], although most believe that oral contraception does decrease risk of hereditary as well as sporadic ovarian cancer. In that regard, treatment and standard of care for *BRCA1/2* mutation carriers must address ovarian cancer detection and prevention. Given the unproven methods of screening and the high mortality at time of diagnosis associated with ovarian cancer, definitive counseling and recommendations for prophylactic removal of ovaries after childbearing are standards of care for *BRCA1/2* mutation carriers or for women with two or more first degree relatives

with ovarian cancers in the family (http://www.nccn.org/professionals/physician_gls/pdf/f_guidlines.asp#breast_risk). [15, 69, 84–88].

Finally, the identification of mutated genes as biomarkers has led to therapeutic applications. *In vitro* and *in vivo* experiments and clinical trials have shown that platinum chemotherapy is effective against *BRCA1* (and, by analogy, *BRCA2*) mutant tumors, in part because platinum generates interstrand cross-links that can only be adequately repaired by *BRCA1*- and *BRCA2*-dependent homologous recombination DNA repair [89]. A new class of drugs that inhibit poly(ADP-ribose) polymerase (PARP), an enzyme involved in base excision repair [90, 91] shows antitumor activity in the background *of BRCA*-associated defects in homologous recombination-mediated DNA repair [92]. Clinical trials have explored the efficacy of PARP inhibitors in the treatment of *BRCA1/2* mutant breast, ovarian, pancreatic, prostate, and other cancers, and one such compound was recently licensed for use in the U.S. for patients with previously treated *BRCA* mutant ovarian tumors [93]. Not all *BRCA* mutation carriers respond to these agents; mutations in the N-terminal BARD1 binding domain of *BRCA1,* such as the relatively common p.Cys61Gly (C61G), may not confer hypersensitivity to PARP ihibitors [94, 95]. Acquired resistance to PARP inhibitors has been associated with multiple mechanisms, including drug metabolism and efflux, post-transcriptional alterations of *BRCA1/2*, secondary mutations that restore the homologous recombination activity of *BRCA1/2*, and accumulation of somatic genetic alterations that counteract the sensitivity associated with *BRCA1/2* mutations [95–97]. Whether combination therapies can overcome these complications remains to be determined.

Other Highly Penetrant Breast Cancer Predisposing Genes

TP53 and CDH1—Compared to *BRCA1/2* mutations, *TP53* mutations are rare. However when testing for *BRCA1/2* is non-revealing or determined not causative, testing of *TP53* may be warranted in cases with a strong family history of cancer and negative *BRCA1/2* testing. Li-Fraumeni syndrome (LFS) is a multi-cancer predisposing syndrome driven by genomic alterations in the *TP53* gene. *TP53* encodes the tumor suppressor protein p.TP53. Patients with *TP53* mutations have an increased risk of breast cancer [98]. In determining the importance to variants detected by next generation sequencing similar steps taken by ENIGMA's efforts in assessing the *BRCA* genes are required. The International Association Cancer Research (IARC) hosts the *TP53* locus specific database. The database curates frequency of variants, if the variant has been detected in the germline, been found in the tumor, seen in a cell line, segregation information of the variants and functional prediction of the genomic variant on protein function. National guidelines for patients with Li-Fraumeni Syndrome support *TP53* testing concurrently for women ≤35 years of age or as a follow-up test after negative *BRCA1/2* testing (http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf).

For carriers of *TP53* mutations, it seems reasonable to consider adding annual MRI starting at age 20–25 years of age or based on earliest age of onset in the family. When patients are found to harbor a *TP53* mutation, there is some laboratory based evidence that radiation exposure may be deleterious, although this remains incompletely documented. Ongoing trials are testing other approaches such as whole body MRI, PET, and other focused

screening; patients should discuss approaches to novel screening and technology with their providers [99].

Reports of germline *CDH1* mutations emerged in patients with hereditary diffuse gastric cancer in the late 1990s [100–104] and it was soon observed that these families also included individuals with lobular breast cancer. In screening of over 400 cases of breast cancer, three patients were found to harbor germline mutations in *CDH1*. Families with multi-generations affected with gastric cancer have a 30 % chance of harboring a mutation in E-Cadherin *(CDH1),* and 70 % of carriers of mutations in this gene develop gastric cancer. In addition to the diffuse gastric cancer risk individuals with *CDH1* mutations also have approximately a 40–50 % risk of lobular cancer of the breast (http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf).

While no formal testing recommendations are established for patients with *CDH1* mutations and breast cancer, Petridis et al. recently proposed *CDH1* mutation screening should be considered in patients with bilateral lobular carcinoma *in situ* with or without invasive lobular breast cancer and with or without a family history. Gastrectomy for patients with *CDH1* mutations is routinely advised. However, the identification of families with *CDH1* mutations through multi-gene panel testing and no family history of gastric cancer are proving difficult to counsel, as the risk of gastric cancer in those patients is unknown. Patients are also presented options regarding mastectomy given the frequency of breast cancer in these patients or cumulative risk for breast cancer for females by age 75 years is 52 % [104].

PTEN/STK11—The majority of patients that undergo inherited genetic testing do not have overt physical manifestations of a syndrome. However, a few constitutional syndromes with overt phenotypes and genetic testing or “biomarkers” do have an increased risk of breast cancer such as Cowden syndrome/Bannayan-Riley-Ruvalcaba syndrome/*PTEN* hamartoma tumor syndrome (PHTS), and Peutz-Jeghers syndrome [105–107]. Major criteria to assess in diagnosing female patients suspected of having Cowden syndrome include breast cancer, endometrial cancer, follicular thyroid cancer, multiple gastrointestinal hamartomas or ganglioneuromas, macrocephaly (> 97 %), and mucocutaneous lesions (trichilemmoma, palmoplantar keratosis, extensive mucosal papillomatosis or verrucous facial papules). Minor criteria include autism spectrum disorder, colon cancer, ≥three esophageal glycogenic acanthosis, lipomas, intellectual disability, papillary or follicular variant of thyroid cancer, thyroid structural lesions, renal cell carcinoma, single gastrointestinal hamartoma or ganglioneuroma, testicular lipomatosis, and vascular anomalies. Individuals with a family member with a known mutation, patients with autism and macrocephaly, two or more biopsy proven trichilemmomas, two or more major criteria where one has to equal macrocephaly, three major criteria without macrocephaly or one major and three minor criteria and four minor criteria [108]. Screening for patients with Cowden is as per National Comprehensive Cancer Network (NCCN) guidelines; breast MRI is part of this strategy and preventive surgeries can also be considered (http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf) (Table 1).

STK11—Peutz-Jeghers syndrome (PJS) is an autosomal dominant cancer predisposition syndrome with clinical characteristics of mucocutaneous pigmentation and gastrointestinal polyps. Patients with PJS are at increased risk of colon cancer, breast cancer, ovarian (mucinous tumors and sex cord tumors with annular tubules) [109–112]. Most mutations are small deletions/insertions or single base substitutions resulting in aberrant protein function with loss of kinase activity. In the analysis of greater than 400 patients, and close to 300 of these individuals with known *STK11* mutations, the cancer risk for the development of breast cancer was 50 % by age 60 [113, 114]. However, in the largest study to date of PJS patients no differences in breast cancer risk have been found [113, 114] but the absolute numbers of kindreds with this syndrome collected for study is still small.

The major phenotype of PJS is gastrointestinal polyps. Patients require frequent endoscopic surveillance with polypectomy, which decreases the rate of intussusception and potential bowel loss. Patients with PJS should be counseled required the high rate of breast cancer and the benefits of prophylactic mastectomy and bilateral salpingo-oophorectomy after the age of 35 to prevent malignancy. In addition to monitoring of the gastrointestinal tract, routine screening of the breast (e.g. mammography and possibly MRI) should be standard of care for individuals with PJS. In addition, patients should be offered investigational pancreatic cancer screening (e.g. magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound) starting at an early age, as well as small bowel visualization, and pelvic exam with consideration of transvaginal ultrasound (although unproven, to address ovarian cancer risk) and annual physical exam [113, 114].

Moderate Penetrance Breast Cancer Genes or Biomarkers: CHEK2, ATM, PALB2, BRIP1, RAD51C, RAD51D, BARD1

There are no standardized guidelines for the management of other cancer risks or for the relatives of carriers with moderate penetrance gene mutations; screening recommendation should be established based on the patient's personal and family histories.

CHEK2—*CHEK2* normally functions by preventing cellular entry into mitosis when DNA is damaged. In 2000, Lee et al. reported that *CHEK2* function in DNA damage by phosphorylating *BRCA1* [115]. Further experiments revealed *CHEK2* and *BRCA1* interaction is necessary for *BRCA1* to restore the survival after DNA damage. Heterozygous mutations were initially reported in a LFS-like family, suggesting CHEK2 serves as a tumor suppressor and mutations predispose individuals to cancer [116]. Subsequently mutations were shown to be associated with a moderate risk of breast cancer, rather having any association with LFS. Population studies have aimed to determine the role of *CHEK2* in patients without an identifiable mutation in *BRCA1/2* but a suggestive family history [117]. The truncating mutation *CHEK2**1100delC affecting kinase activity was revealed in 1.1 % of healthy individuals compared to 5.1 % coming from over 700 families with breast cancer (male and female breast cancers both included) and negative *BRCA1/2* testing. These data suggest a greater than a two-fold increase of breast cancer risk in females and 10-fold increase in men with the *CHEK2**1100delC. As a means to assess for additional mutations in *BRCA* negative families with breast cancer, Shutte et al. assessed 89 kindreds with three or more individuals with breast cancer and did not find other appreciable site specific

variation in *CHEK2* [118]. Although studies are still in progress, it appears that the detection of a *CHEK2* deleterious mutation in the setting of a strong family history of breast cancer may warrant clinical use of this biomarker in the pre-symptomatic assessment for screening. Whether the absolute level of *CHEK2*-associated risk meets threshold for MRI screening can be determined on an individualized basis, taking into account population derived as well as family history data.

ATM—*ATM* is a gene encoding a protein that allows for the efficient repair of DNA. *ATM* when altered manifests phenotypes from bi-allelic and arguably mono-allelic genomic alterations. Individuals with two mutations or bi-allelic or homozygous mutations develop severe disease of the immune system and are predisposed to developing leukemia and lymphoma, called Ataxia-Telangiectasia (A-T). Various degrees of evidence support or refute individuals harboring a single mutation in the *ATM* gene as having an increased risk of developing breast cancer, stomach, ovarian, pancreatic, or lung cancer [119–122, 123]. Approximately 1 % of the population is heterozygous for mutations in the *ATM* gene.

Mutant specific evidence for *ATM* p.S49C and p.F858L in association with increased breast cancer susceptibility show an odds ratio of 1.44 combining data from an American and Polish study [124]. When mutations that have been identified specifically in patients with *ATM* have been studied in mono-allelic carriers the estimated relative risk for familial breast cancer was = 2.37. The data are based on the evaluation of individuals from 443 familial breast cancer kindreds [120, 125–127]. Breast cancer-associated *ATM* mutations tend to be missense mutations whereas missense mutations are uncommon in individuals with A-T, even in the same host population [121].

Individuals who are carriers for *ATM* gene mutations should be aware that they might be sensitive to radiation, although the magnitude of this radiation sensitivity requires further study. There are no *ATM* mutation specific sets of recommendations for therapy, treatment, or tailored management options [128–131]. No definitive evidence has emerged regarding increased risk of mammograms in *ATM* mutation carriers, however, MRIs and ultrasound remain an important screening strategy. Annual breast MRI screening is recommended for women with a lifetime risk for breast cancer of 20–25 % or greater and it is generally recommended that MRI be used in conjunction with mammogram.

Regarding prevention, prophylactic mastectomy has not been evaluated extensively in individuals who are carriers for *ATM* gene mutations. There is no evidence concerning the effectiveness of chemoprevention in the *ATM* gene carrier population, although there is also no evidence that it will not be as effective as in the general population.

PALB2—*PALB2* is a gene encoding a necessary protein of the Fanconi complex and is also known as the partner and localizer of BRCA2 and FANCN. PALB2 interacts with the BRCA2 protein and work together to correct and fix DNA breaks. PALB2, as it helps control the rate of cell growth and division, is a tumor suppressor (http://ghr.nlm.nih.gov/gene/PALB2). Moreover, by limiting mistakes in DNA repair, *PALB2* aids in maintaining the stability of genetic information.

Literature is emerging in regards to the contribution of germline mutations of *PALB2* and hereditary breast cancer. Approximately a dozen mutations have been identified in *PALB2* and familial breast cancer. Mutations in *PALB2* are estimated to lead to a two-fold increase in breast cancer risk. In 2007, investigators sequenced the *PALB2* gene in close to 1000 individuals with breast cancer who were negative for *BRCA1/2* mutations [132]. Ten out of 923 harbored *PALB2* mutations conferring a 2.3-fold higher risk of breast cancer. The Q775X variant was identified in 1/50 high-risk women or 2/356 breast cancer cases and not present in any of > 6000 controls [133]. Assessing 559 women with contralateral disease and 565 women with unilateral disease as controls, fine truncating pathogenic mutations were identified. A study of Australian and New Zealand women who were negative for *BRCA1/2* mutations underwent *PALB2* testing and 26 out of 747 women were detected having *PALB2* genomic alterations. Two women harbored nonsense mutations and two frameshift mutations. Investigators concluded that ~ 1.5 % of Australasian women in families with multiple members affected with breast cancer segregate *PALB2* mutations in their families.

Recent studies analyzing the risk of breast cancer in > 150 families assessing truncating, splicing or deletions in *PALB2* and family history estimated the risk of breast cancer for female carriers compared to the general population was eight to nine times as high among women younger than 40, six to eight times as high among those 40–60 years of age and five times as high for those females older than 60 years of age [134]. The estimated cumulative risk of breast cancer among female mutations carriers was 35 % by age 70 and the absolute risk ranged from 33 to 58 % depending on the extent of family history [134]. The investigators of this study concluded the breast cancer risk from *PALB2* potentially overlap with that for *BRCA2* mutation carriers and that loss of function mutations account for roughly 2.4 % of familial aggregation of breast cancer [134]. These data would support the role for MRI breast screening in this genetically defined population.

BRIP1—*BRIP1,* or alternatively named *FANCJ,* similar to *PALB2* manifests disease in both the heterozygous and homozygous state. *BRIP1* is also known as the *BRCA* interacting helicase. Patients with constitutional bi-allelic mutations in these two genes are notable for a Fanconi anemia phenotype. One study suggests that constitutional heterozygous carriers have a relative risk of breast cancer of 2.0 [135], however further validation studies need to be done.

RAD51C and RAD51D—Nonsense, frameshift, splice and non-functional missense mutations have been described in *RAD51C*, however the evidence that they are a driver of familial breast cancer is limited [136, 137]. Evidence of *RAD51C* mutations in familial ovarian cancer is greater than familial breast cancer [137, 138]. In a cohort of familial breast and ovarian cancer cases a distinct difference was noted between ovarian and breast cancer i.e., data revealed a relative risk of 5.88 in mutation carriers for ovarian cancer and 0.91 for breast cancer [139].

Loveday et al. also demonstrated a similar risk ratio for patients harboring mutations in *RAD51D*. Regarding therapeutics, the group showed that cells deficient in RAD51D are sensitive to treatment with a PARP inhibitor, suggesting a possible therapeutic approach for *RAD51D* mutant patients with a family history of breast and predominantly ovarian cancer.

BARD1—In Finnish families with breast and/or ovarian cancer, 5.6 % of individuals were detected to have a cys557-to-ser substitution (C557S) in the *BARD1* gene compared to healthy controls (5.6 vs. 1.4 %, $p = 0.005$) [140]. The highest prevalence of C557S was detected in a subgroup of 94 patients with breast cancer whose family history did not include ovarian cancer (7.4 vs 1.4 %, $p = 0.001$). The C557S mutation is located in a region of *BARD1* needed for induction of apoptosis and possibly also transcriptional regulation. The investigators concluded that C557S may be a breast cancer-predisposing allele.

Low Penetrant Polygenes

Other single nucleotide variations or single nucleotide polymorphisms have been detected conferring a moderate to low penetrant breast cancer genes or biomarkers [23] (Fig. 2). Genome-wide association studies (GWAS) have identified common genetic variants in 76 loci associated with small increases in the risk of breast cancer (Fig. 1) [63, 141]. However, most of these variants have weak effects on risk (OR < 1.10) [63]. Little is known about the relevance of these risk factors to the different molecular subtypes of breast cancer, although three of these loci (*MDM4*, 19p13.1, and *TERT-CLPTM1L* rs10069690) are exclusive to triple-negative breast cancer [142–145] and *BRCA1*-associated breast cancer [19]. Although the identification of causal variants and mechanism of action for most remain unclear, some variants are near known genes such as *BRCA2, TGFBR2, MYC*, and *TET2* [63]. One mechanism of action of common variants is on gene transcription, as evidenced by the 11q31.1 locus and Cyclin D1 expression via a transcriptional enhancer and a silencer of the *CCND1* gene [146], and FGFR2 expression via induction of FOXA1, ER*a*, and E2F1 binding to enhancers [142].

The clinical utility of these common variants as a paradigm of polygenic risk assessment for human cancer remains a work in progress [144–146]; breast cancer–associated common variants combined with traditional breast cancer risk markers had minimal impact on risk prediction models [147] or discriminatory accuracy [148]. A polygenic risk score calculated as the sum of the ORs for each allele, correlated with risk of early onset breast cancer ($OR = 3.37$, $P = 0.03$) [148] and other such studies are now under way [145], with the goal of leading to better identification of women who will benefit from enhanced screening and intervention [22].

New Paradigms for Genomic Biomarkers of Risk

Two decades of molecular biologic and genetic epidemiologic research have resulted in tests for inherited genomic variants as useful biomarkers for breast cancer risk. Tests for highly penetrant (high-risk) genetic mutations have been incorporated into clinical practice. Currently, “panel” tests for large numbers of genes, including some of unclear clinical utility, are commercially available. A pressing challenge posed by these developments is the interpretation and actionability of the large number of variants and “low penetrance” mutations discovered. To address this challenge, in 2014, the Prospective Registry of Multiplex Testing (PROMPT) began as an academic-commercial-and patient-centered initiative, and readers are encouraged to access it at https://connect.patientcrossroads.org. Such longitudinal studies would also add to the evidence base for targeted screening and prevention in genetically defined high-risk cohorts. Other federal initiatives are underway to

catalogue and interpret the emerging array of genomic biomarkers of inherited cancer risk, which will only increase as screening of entire exomes and genomes becomes more feasible.

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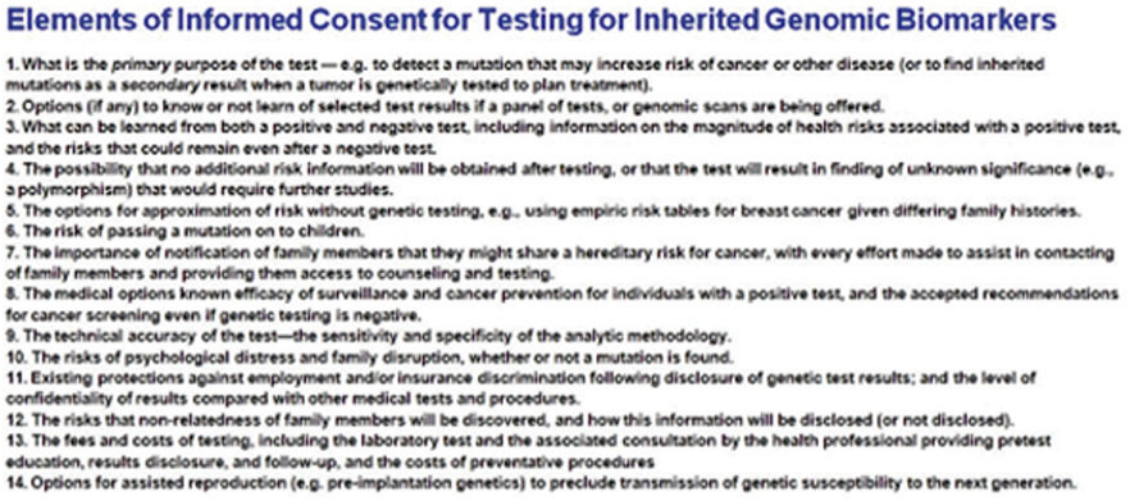

Fig. 1.
Elements of informed consent

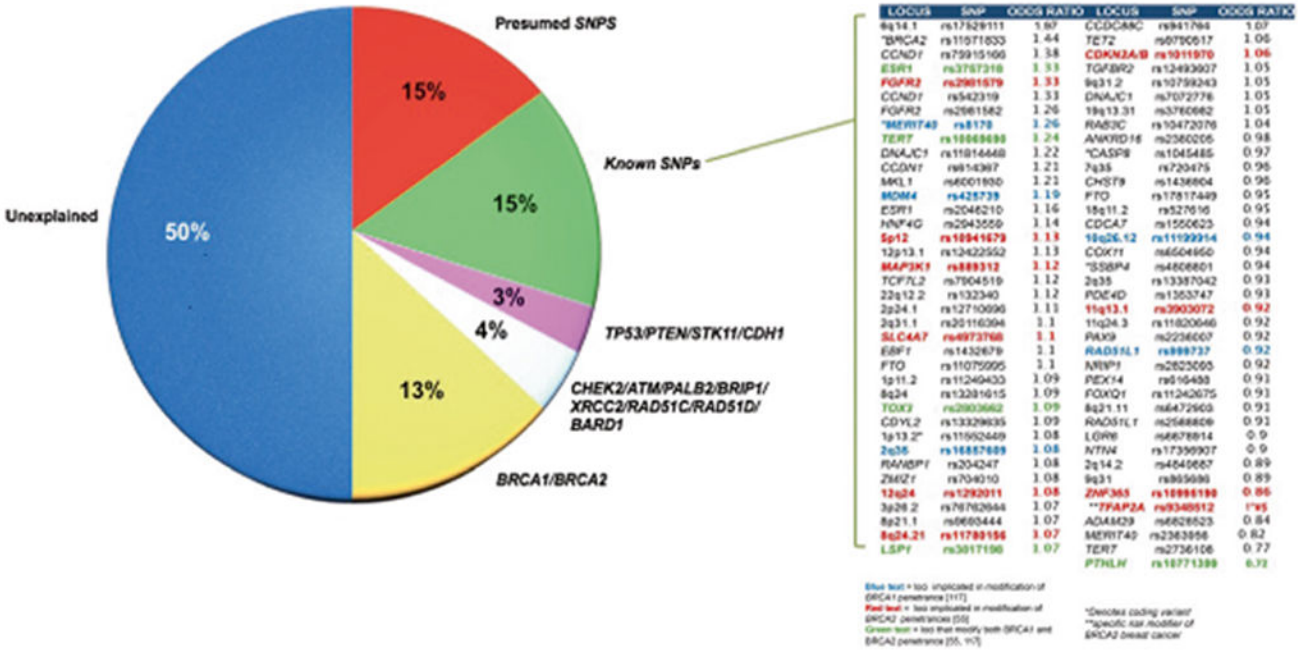

Fig. 2.
Breast cancer biomarkers

Table 1

HUGO Gene ID, inheritance pattern, clinical manifestations and context dependent guidelines for highly penetrant breast cancer predisposition syndromes

Characterization of breast cancer predisposition syndromes						
Gene	**Syndrome**	**Inheritance**	**Overt stigmata**	**General surveillance**	**Context specific risk reduction considerations**	**Penetrance**
BRCA1/BRCA2	Hereditary breast and ovarian	AD	No	Exam, Imaging (MRI, mammography)	Chemoprevention with tamoxifen, Mastectomy, TAH/BSO	High
TP53	Li Fraumeni	AD	No	Biochemical and endocrine testing, MRI whole body	+/− Mastectomy	High
PTEN	Cowden	AD	Yes	Clinical exam, MRI, colonoscopy, skin exams	+/− Mastectomy	High
STK11	Peutz-Jeghers	AD	Yes	Clinical exam, mammography, colonoscopy, skin exam	Polypectomy, Mastectomy, TAH/BSO	High
CDH1	Familial gastric cancer	AD	No	Colonoscopy, esophogealduodenaloscopy, mammography, MRI	Gastrectomy	High

AD autosomal dominant, *MRI* magnetic resonance imaging, *TAH/BSO* total abdominal hysterectomy bilateral salpingo-oophorectomy