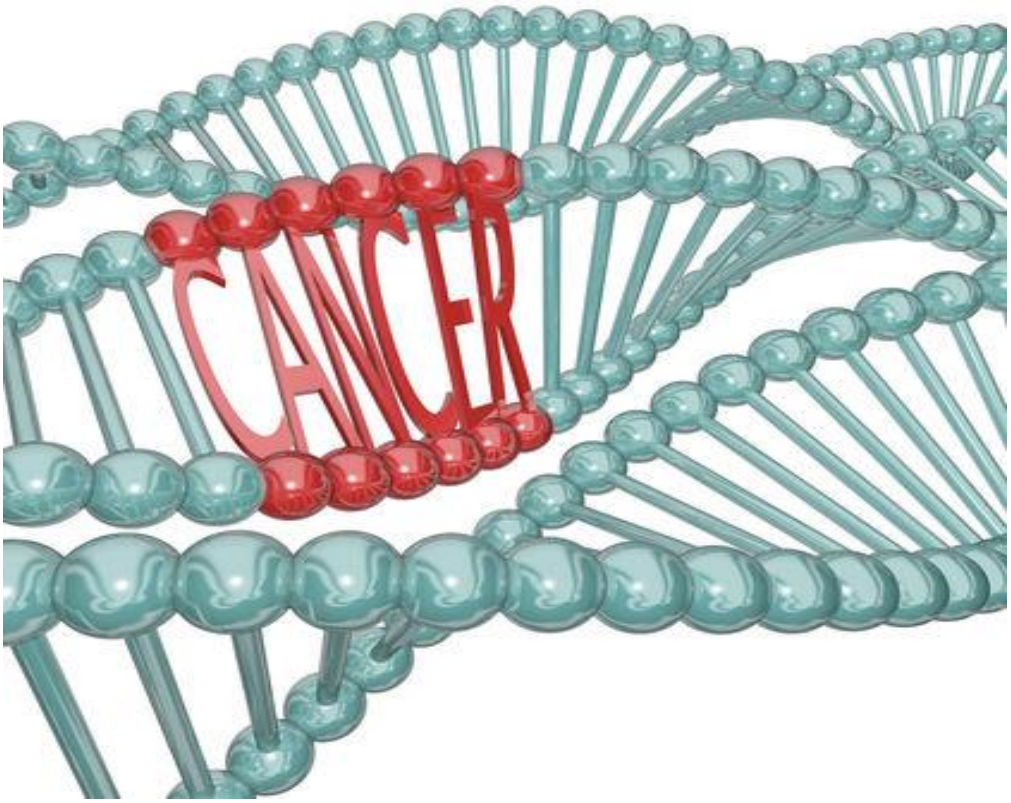
HEREDITARY BREAST CANCER

THE BASICS OF BRCA AND BEYOND



Barbara Haley, M.D., FACP

Division of Hematology Oncology

UT Southwestern Medical Center

Internal Medicine Grand Rounds

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This is to acknowledge that Barbara Haley, M.D. has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Haley will not be discussing off-label uses in her presentation.

Name: **Barbara Haley, M.D.**

Academic Rank: **Professor**

Division: **Hematology Oncology**

Biosketch:
Barbara Haley, M.D., FACP completed here medical school, internal medicine and hematology oncology training at the University of Texas Southwestern Medical Center. In 1999 she joined the faculty and is currently a professor with interest in all aspects of breast cancer care but particularly in clinical trials and investigational drug studies, HER2 and Triple-Negative breast cancer. She is lead investigator for multiple trials at UT Southwestern and holds the Charles Cameron Sprague MD Chair in Clinical Oncology and the Patricia and William L. Watson Award Excellence in Clinical Medicine.

Purpose and Overview:
This presentation is focused on the role of hereditary risk factors in the development of breast cancer and provides insight into proposed mechanisms of carcinogenesis involved in mutational syndromes and current approaches to diagnosis and care.

Educational Objectives:
1. Recognize the increased integration of clinical genetics in the evaluation and care of the breast cancer patient.
2. Describe syndromes associated with increased risk for breast cancer and other organ malignancies.
3. Understand available risk assessment tools and commercially available tests for gene testing.
4. Discuss clinical management of patients with a risk mutation.

CLINICAL CASES

1. 68 year old Caucasian male diagnosed with breast cancer in 2012, treated with bilateral mastectomy, chemotherapy, radiation and tamoxifen. Now has metastatic disease age 72.

2. 46 year old Nigerian female diagnosed with bilateral breast cancer treated with chemotherapy, bilateral mastectomy, radiation and tamoxifen. Family history positive for a sister deceased with breast cancer age 38.

3. 39 year old Ashkenazi Jewish female with unilateral breast cancer, treated with chemotherapy, bilateral mastectomy, and radiation. Family history positive for paternal grandmother with breast cancer in her 30's and death at age 54 due to brain metastasis.. Her father had prostate cancer age 61.

4. 25 year old Afro American female with high grade breast cancer HER2 positive. Treated with chemotherapy, bilateral mastectomies and no radiation. Family history positive for paternal grandmother with stomach cancer age 65.

While these cases have diverse clinical characteristics with respect to patient age, sex and ethnicity, what they all have in common is inheritance of a risk gene for the development of breast cancer. Case 1 is a BRCA2 mutation, Case 2 is a CHEK2 mutation, Case 3 is a BRCA1 mutation and Case 4 is a TP53 Li Fraumeni mutation. These cases represent some of the faces of hereditary breast cancer.

HEREDITARY BREAST CANCER

The most famous spokesperson for HBC is Angelina Jolie who disclosed that she was a BRCA1 mutation carrier and elected bilateral risk reducing mastectomies. Her mother died of ovarian cancer and her maternal aunt died of breast cancer. Her announcement led to a surge in requests for genetic testing and for bilateral mastectomies termed the Angelina Jolie effect. She also pointed out the prohibitive cost of genetic testing in the US in 2013 at greater than $3000 that limited patient access to testing. (1)

HOW COMMON IS HEREDITARY BREAST CANCER?

Breast cancer is a common diagnosis. The American Cancer Society predicts 246,000 new cases of breast cancer in 2016. Approximately 2600 new cases will occur in males.(2) However, HBC is not common and only an estimated 10% of all breast cancer can be attributed to inheritance of a risk gene. The majority of cases of HBC result from a deleterious mutation in one of two susceptibility genes BRCA1 on chromosome 17 q 21 and BRCA2 on chromosome 13 q 12.3. Besides BRCA, there are several other germline gene mutations associated with HBC risk.

HEREDITARY BREAST CANCER

The inherited BCS are divided into gene mutations associated with high risk (5 fold or greater risk) for development of breast cancer, moderate risk (1.5 – 5 fold risk) and a group of other genes that confer increased BC risk but are less well characterized as to penetrance and incidence.(3)

GENE MUTATIONS AND RISK ASSOCIATION

HIGH	MODERATE	OTHER INCREASED
BRCA1	CHEK2	RAD 51 Complex
BRCA2	PALB2	BARD1
TP53	ATM	MRN Complex
PTEN	BRIP1	
STK11		
CDH1		

BREAKING DOWN THE GENE TESTING BARRIER

The BRCA genes were identified in the early 1990's by the work of Dr. Mary Claire King but scientists at Myriad Genetics were the first to clone and sequence the genes and patented both the genes and the gene testing on them. BRCA testing by Myriad Genetics, a commercial company, cost about $4000 thus financially limiting patient access and stifling research by other scientists due to the threat of lawsuits.

This exclusive ownership was tested in the case of the Association for Molecular Pathology et. al. v. Myriad Genetics Inc., et. al. decided June 13, 2013 by the US Supreme Court who ruled "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated but a cDNA is patent eligible because it is not naturally occurring."(4)

The rulings invalidated several key Myriad patents of the BRCA genes. After the ruling, multiple companies offered enhanced testing options at lower cost and included the BRCA genes in their own gene panels combined with other mutations that predispose to breast cancer; thus, widening the landscape of BC risk gene testing. The immediate benefit has been enormous for the patient and for science. Adding to this advance is the development of high throughput technology and next generation sequencing (NGS) that lowered cost and allows multiple genes to be simultaneously evaluated.

SYNDROMES ASSOCIATED WITH HIGH RISK FOR DEVELOPMENT OF BREAST CANCER:

BRCA1, BRCA2, TP53, PTEN, STK11, CDH1

HEREDITARY BREAST AND OVARY CANCER SYNDROME (HBOC)
BRCA1 AND BRCA2

The most common cause of HBC is a germline mutation in either the BRCA1 or BRCA2 gene. The incidence of a BRCA mutation in the general population varies with the population studied and their ethnicity with non-Jewish individuals a 0.02% carrier rate but in the Ashkenazi Jewish population, the carrier rate as high as 2.6% due to ancient founder mutations in one of 3 sites (187delAG, 5385insC and 6174delT). Other founder mutations have been reported in the Dutch, Swedish, French Canadian, Icelandic, German and Spanish populations.(5)

CLINICAL IMPACT OF THE GENE MUTATION

The BRCA1 mutation carrier has a lifetime risk to develop breast cancer of 60-70% and 45-55% risk for BRCA2. This contrasts to the lifetime risk for a female in the general population of 12%. The contralateral breast cancer risk is high up to age 70 and depends on the age of onset of the primary breast malignancy. If under age 40 for the first BRCA1 breast cancer, the contralateral risk is 60% and for BRCA2 is 25%. After age 40, the risk drops but remains high.(6)

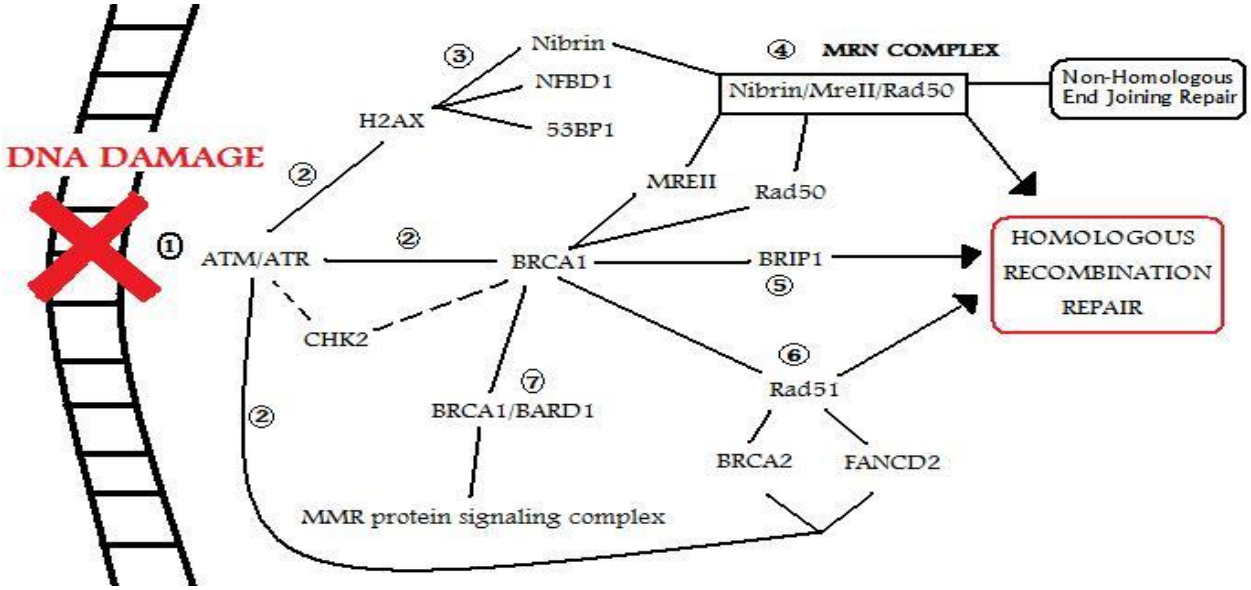
In addition to BC risk, BRCA1 and BRCA2 mutation carriers are at increased risk for epithelial ovarian, fallopian tube and primary peritoneal cancers with BRCA1 carrier risk up to 40% for ovarian cancer and for BRCA2 is 25% and with a 4% risk of primary peritoneal cancer.(7)

HISTOPATHOLOGIC CHARACTERIZATION OF BRCA CANCERS

The histology of BRCA1 cancer is dominated by triple negative disease of high grade often with medullary histology and p53 mutations. BRCA2 cancers lack a characteristic histology and are likely to be ER positive and resemble sporadic breast cancer. BRCA1 tumors often have a basal/myoepithelial phenotype and express basal cytokeratin CK5/6, CK14 and EGFR. BRCA2 tumors more often express ER and PR and CK8 and CK18. With intrinsic subtyping, the BRCA1 tumors are mainly basal like and BRCA2 are ER+ luminal B cancers.(8)

BRCA GENES – THE GENE DEFECT

BRCA1 and BRCA2 function as tumor suppressor genes involved in double strand DNA break repair by homologous recombination (HR). An interaction of at least 13 different tumor suppressor proteins with BRCA1 and 2 create a macromolecular protein complex that directs DNA damage repair and cell cycle checkpoints. BRCA1 and 2 are central constituents of the process.



The primary function of BRCA2 is HR. BRCA1 has additional functions in DNA repair including chromatin remodeling, transcription coupled excision repair and ubiquination combined with BARD1. Cells deficient in BRCA1 or 2 cannot repair DS-DNA breaks by HR resulting in non-homologous end joining by base excision repair (BER) or nucleotide excision repair (NER) which is error prone and leads to genomic instability. Additionally, mutations in other genes involved in the macromolecular protein repair complex may cause genomic instability and increased cancer risk.(9)

DEFECTIVE BRCA GENES – POSSIBLE THERAPEUTIC INTERVENTION

SYNTHETIC LETHALITY AND THE BRCA NETWORK

PARP (poly ADP – ribose polymerase) is a family of proteins responsible for ribosylation in DNA double strand repair. PARP1 and 2 bind to single strand breaks to repair the break. Inhibition of PARP is lethal in a BRCA deficient cell and makes PARP a target of therapy for mutant BRCA cells. This is the concept of synthetic lethality and exploited by Pharma with development of multiple PARP inhibitors including Olaparib (Lynparza) recently approved by the FDA for metastatic BRCA ovarian cancer after failure of 3 lines of therapy and for CRPC prostate cancer associated with BRCA or ATM mutations. It is not yet approved for breast cancer but clinical trials are ongoing.(10), (11) Additionally, drugs that break the DNA strands like platinum compounds can be very effective in killing BRCA deficient cells either as single agents or when combined with PARP inhibitors . This concept is under study for BRCA mutational breast cancers and for breast cancer that has acquired by somatic mutation "BRCA ness" or a defect of DNA repair.

OTHER HEREDITARY SYNDROMES WITH HIGH RISK FOR BREAST CANCER

LI FRAUMENI SYNDROME (TP53 GENE)

TP53 is a tumor suppressor gene located on chromosome 17 and p53 protein bound to DNA plays a critical role in cell cycle control and apoptosis. Mutations are characterized by early onset of aggressive BC (20's or 30's) with median age of 25 years. The cancer may be stromal or epithelial and most are HER2 positive and ER positive. The gene is of low frequency but high penetrance with a lifetime risk of cancer exceeding 90% with BC the most frequent female cancer with BC risk 56% by age 45 and greater than 90% by age 60. Li Fraumeni families have early onset cancers of multiple type including breast, osteosarcoma, brain, adrenocortical cancer and acute leukemia and colon cancer.(12)

PTEN (COWDEN PTEN HAMARTOMA TUMOR SYNDROME)

The PTEN gene (phosphatase and tensin homologue) is located on chromosome 10 and regulates PI3K activity with mutations leading to unregulated cell growth and survival. There is a spectrum of disorders from germline PTEN mutations and Cowden Syndrome is one of these. Cowden Syndrome is characterized by hamartomas a benign tumor located in the skin, mucous membranes, breast, thyroid, endometrium and brain. Clinical manifestations occur before age 30 and breast cancer is the most common cancer with lifetime risk of 50% - 85% and average age of diagnosis in the 30's. Thyroid cancer (follicular or papillary) risk is up to 35% with 28% endometrial, 9% colorectal, 34% renal and 6% melanoma risk. Affected individuals usually have macrocephaly.(13)

PEUTZ-JEGHERS SYNDROM (STK11 GENE)
The STK11 gene located on chromosome 19 is a tumor suppressor gene and negative regulator of the m-TOR pathway. The syndrome is characterized by GI hamartomatous polyps, mucocutaneous pigmentation and increased risk of cancer including breast, colon, stomach, small intestine, pancreas and ovary. The lifetime risk for BC in females ranges up to 50% and is of early onset and the mutation carries an ovary cancer risk of 20%.(14)

HEREDITARY DIFFUSE GASTRIC CANCER (CDH-1 GENE)
The CDH-1 gene encodes for E-cadherin a cell-cell adhesion molecule. There is up to an 80% lifetime risk for diffuse gastric cancer (linitis plastic with signet rings). The lifetime risk for BC is up to 50% with lobular histology. A female with lobular cancer has a 1% chance of carrying a germline CDH-1 mutation but the risk increases with bilaterality or age of diagnosis before age 45.(15)

HEREDITARY BREAST CANCER MODERATE PENETRANCE GENES:
CHEK2, PALB2, ATM, BRIP1

These genes carry a relative risk of causing BC from 1.5 to 5 times normal. The genes have low to moderate penetrance but may be modulated by environmental factors or lifestyle to increase cancer risk. The genes have been identified by their role in cellular pathways and are critical in DNA repair mechanism.(16) 3-5% of patients with HBC have mutations in moderate risk genes.

CHEK2 CHECKPOINT KINASE 2
The CHEK2 gene is involved in DS-DNA repair with the most common mutation 1100delC and is found in patients of northern and eastern European ancestry. The mutation increases BC risk by 2-3 fold and has lifetime risk of 37% with increased risk of bilaterality and risk for male BC. The incidence is 1% of all HBC but up to 5% of BC in patients negative for BRCA1 or 2 testing. The 1100delC mutation also increases risk for colorectal cancer.

PALB2 – BINDING PARTNER AND LOCALIZER OF BRCA2
This gene is involved in HR and DS-DNA repair. It carries a risk for pancreatic cancer, bilateral BC and male BC. The risk for a breast cancer is 15% by age 35 and 35% by age 70. Biallelic mutations of PALB2 cause Fanconi anemia. Mutations are associated with an increased risk of pancreatic cancer.

ATM
This gene plays a central role in DS-DNA repair and homozygous mutations cause ataxia-telangiectasia syndrome with cerebral ataxia, immunodeficiency and increased risk for breast and pancreas cancers, leukemia and lymphoma. This risk for BC may be up to 50% and higher for women younger than age 50 years. Reports suggest that mutations increase susceptibility to both diagnostic and therapeutic radiation and increased cancer risk for biallelic mutation carriers. Heterozygote mutation carriers have a 2 fold increased risk of breast cancer.

BRIP-1
This gene encodes a protein that is the binding partner of BRCA1. Mutations carry a two-fold risk of breast cancer and ovarian cancer.

HEREDITARY BREAST CANCER: LOW PENETRANCE SUSCEPTIBILITY GENES

These are candidate genes identified by genome wide association studies (GWAS) and increase BC risk by about 1.5 but penetrance and incidence is not well defined.(17)

1. **RAD51 and RAD51 Related Genes – RAD51C and RAD51D and XRCC2**
   These are a family of genes involved in DS-DNA repair by HR and interact with BRCA1 and BRCA2. RAD51C and RAD51D mutations are rare and confer increased risk for ovarian cancer.

2. **BARD1**
   This gene interacts with BRCA1 in DS-DNA repair and is reported in 2-3% of BRCA tested negative breast – ovarian cancer families.

3. **MRN Complex (MRE11, RAD50, NBS1)**
   These genes encode for proteins involved in the DS-DNA repair complex and are involved in apoptosis. Mutations have been reported in 2-3% of Finnish BC families but the frequency varies widely.

IDENTIFYING THE PATIENT AT RISK FAMILY AND MEDICAL HISTORY

Every patient history should include a personal and family medical history of malignancy that is periodically updated.

Screening Questions to Ask:

- personal and family history of cancer including 1st and 2nd degree relatives
- type of cancer and age of onset
- maternal or paternal lineage
- ethnic background especially Ashkenazi Jewish or Eastern/Central Europe

Important Additional Key Information

- Multiple primary tumors in the same person
- Multiple blood relatives with same cancer type
- Breast cancer in a male or bilateral breast cancer
- Triple negative BC before age 60
- Epithelial ovarian, tubal or peritoneal cancer
- Endometrial or colorectal cancer

If the data suggests increased risk of a hereditary cancer syndrome then referral to a trained health care provider for further evaluation, counseling, risk assessment and possible testing is recommended. Note that insurers are requiring criteria to approve and pay for gene testing so that a certified health provider trained in genetics must provide detailed family history, template pedigree drawing and signed counseling attestation form for insurance approval and payment.

RISK ASSESSMENT TOOLS

Several models have been developed to estimate lifetime risk for development of cancer and some predict risk of carrying a gene mutation. The models are software programs and include:

- BRCAPRO www4.utsouthwestern.edu/breasthealth/cagene
- BOADICEA www.ccge.medschl.cam.ac.UK/Boadicea
- BCRAT (Gail Model 2) www.cancer.gov/bcrisk tool
- Tyrer Cuzick (IBIS) www.cancertechnology.co.uk/ibis.software-tyrer-cuzick.model
- Myriad PRO BRCA risk calculator www.myriadpro.com/hereditary-cancer-testing

Each model incorporates different risk factors to provide an estimate using an algorithm to determine probability to develop BC and/or mutational carrier probability. Since the majority of HBCS are due to BRCA mutations, most models incorporate that assumption and none predict probability of a moderate or low risk gene mutation.

BRCA Risk Calculator

Answer the following questions to evaluate your patient's risk for a *BRCA1* or *BRCA2* mutation.

- Is the patient male or female? (•) Female ( ) Male
- Is the patient of Ashkenazi Jewish decent? ( ) No (•) Yes
- Has the patient ever been diagnosed with breast cancer? (•) No ( ) Yes
- Has the patient ever been diagnosed with ovarian cancer? (•) No ( ) Yes

Family History

(Includes at least one first or second degree relative.)

- Has anyone in your patient's family been diagnosed with breast cancer under the age of 50?
- ( ) No (•) Yes
- More than 1 relative?
- (•) No ( ) Yes
- Has anyone in your patient's family been diagnosed with ovarian cancer?
- (•) No ( ) Yes
- More than 1 relative?
- (•) No ( ) Yes

Calculated BRCA Mutation Risk: 7.2% Reset

Gene testing is recommended if a mutational probability is greater than 10%. The NCCN publishes testing guidelines used by insurers for coverage determination and payment and are available at www.NCCN.org. Validation and model accuracy varies for different populations with some nationalities not well represented in a model for example Oriental women.

NCCN Selected Criteria for Hereditary Risk Evaluation and Testing

- Female BC before age 50 in one or more relatives or TNBC before age 60
- Two or more primary breast cancers
- Invasive ovarian or fallopian tube or primary peritoneal cancer in patient or one or more relatives
- Male breast cancer
- Ashkenazi Jewish ancestry
- Breast cancer at any age in 2 or more relatives
- Pancreas or prostate at any age in 2 or more relatives

GENETIC TESTING – WHAT TO ORDER

If the personal or family history suggests a single cancer syndrome then testing can be limited to that syndrome but if negative and the history suggests a mutation then multigene panel test is appropriate. Individual genes can be tested separately by Sanger sequencing and is accurate but time consuming and expensive. New high throughput sequencing enables parallel sequencing of multiple genes simultaneously at lower cost and greater efficiency allowing whole genome sequencing and multi panel genes at reduced cost.(13), (14) Academic and commercial labs offer testing that varies in the number and variety of genes tested and in cost. Larger gene panels include BRCA1 and 2, BRCA rearrangement (BART) and genes of high, moderate and low risk. The clinical utility of testing for moderate and low risk genes is unclear as there may be limited to no guideline for risk management.

Selected Genetic Tests for Germline Mutations from Myriad Genetics

1. Comprehensive BRCA Analysis – BRCA1 and BRCA2 –blood or oral rinse
2. BRCA Large Rearrangement – BRCA1 and BRCA2
3. MyRisk - 25 gene panel including BRCA1 and 2 and PALB2 – blood
4. Single Site BRCA Mutation – BRCA 1or 2 – blood
5. Multisite 3 BRCA Analysis - Ashkenazi Jewish founder mutations BRCA1 and BRCA2-187delAG, 5385insC, 6174delT

Selected Genetic Tests for Germline Mutations from Ambry Genetics

1. BRCA1/2 – BRCA 1 and BRCA2 – blood or saliva
2. BRCAplus – BRCA1,BRCA2,CDH1,PTEN,TP53 – blood or saliva
3. BreastNext – 17 gene panel including BRCA1 and BRCA2 – blood or saliva
4. CancerNext – 25 gene panel – blood or saliva
5. Ashkenazi Jewish 3 site founder mutation panel – 187delAG, 5385delC, 6174delT – blood or saliva

INTERPRETATION OF GENETIC TESTING

Gene tests may return as positive for a deleterious mutation or the result may be negative for a deleterious mutation and is a true negative if a person tests negative for a mutation known to be present in other family members with cancer. Testing can be limited to test only for the known family mutation and has low cost but limitations of interpretation. Limited testing may not rule out other causative genes. An uninformative result means no deleterious mutation is identified and the family has no known susceptibility mutations in other family members with cancer.

A variant of unknown significance (VUS) is the report of a gene alteration but the clinical significance is unknown. Some VUS are later classified as deleterious but many are benign polymorphisms that do not affect gene (protein) function and pose no risk for malignancy. Multigene panel tests have higher reported VUS rates. A patient with a VUS should not be managed as if they had a deleterious mutation.(18), (13)

OTHER CAVEATS

Inquire as to the year of previous BRCA testing to see if BART rearrangement testing was done. It was not available until 2006 and 6% of test negative BRCA mutations may be due to a rearrangement in BRCA1 or 2. The interpretation of gene testing can be complicated and a credentialed genetic counselor or health care professional trained in genetics should provide test results and counseling and discuss guidelines and recommendations for surveillance or treatment. Counselors and physician must address the issue of implications for malignancy in other family members and offer guideline recommendations. The psychological impact including depression and anxiety for the patient and family must be recognized and guidance offered. Risk reducing measures such as modification of alcohol intake and obesity, lack of exercise and estrogen progesterone therapy risk discussed. Late term consequences of therapy should be recognized such as the impact on bone and cardiac health, menopausal symptoms such as hot flashes, sweats, vaginal atrophy, diminished libido and altered sexual self-image should be addressed.

HEREDITARY BREAST CANCER PATIENT MANAGEMENT

These guidelines are derived from the latest Version 1 • 2016 of the NCCN guidelines for Hereditary Breast Cancer at NCCN.org

BRCA1 and BRCA2 CARRIERS WITHOUT PERSONAL HISTORY OF CANCER – RECOMMENDATIONS

1. **Screening for Breast Cancer**
    - Age 18 breast self-exam and breast awareness begins
    - Age 25 clinical breast exam every 6 -12 months and annual breast MRI begins
    - Age 30 annual mammograms alternating with annual MRI begins

The sensitivity of screen mammograms is lower in this age group and MRI adds sensitivity and specificity, increases early detection rates and does not carry radiation risk to the breast in patients with abnormal DNA repair mechanism. Breast ultrasound does not add additional benefit to mammogram and MRI.

2. **Screening for Ovarian Cancer**

Every-six-month pelvic exam, ultrasound and CA125 has not been an effective screen. Salpingo-Oophorectomy after age 35 or childbearing completed and by age 40 is recommended.

RCA1 AND BRCA2 CARRIER WITHOUT A PERSONAL HISTORY OF CANCER – TREATMENT

1. **Risk Reducing Chemo Prevention**
   Tamoxifen can be used for risk reduction especially in BRCA2 carriers. Raloxifene can be used for risk reduction but only in post-menopausal women. Aromatase inhibitors also can be used in post-menopausal women. The data on tamoxifen benefit is from the NSABP Prevention Trial, which reduced the risk of BC by 62% in BRCA2 carriers but not BRCA1. This data was based on subset analysis of 8 BRACA1 and 11 BRCA2 carriers in a 288-women subset analysis. There is no data on risk reduction for Raloxifene or aromatase inhibitors in BRCA mutation carriers. There is no data on Tamoxifen chemoprevention in males as overall BC risk is low (BRCA1 is 1-2% and BRCA2 is 6%).

2. **Risk-Reducing Surgery – Bilateral Salpingo-Oophorectomy**
   National guidelines recommend risk-reducing bilateral Salpingo-oophorectomy (BSO) between age 35-40 and once childbearing is completed to reduce the risk of tubal/ovarian/peritoneal cancers by 80-90% and BC by 50%. A newer approach is salpingectomy alone based on data proposing a fallopian tube origin for cancer but this is not standard of care and does not decrease the risk of BC.

3. **Risk-Reducing Surgery – Bilateral Prophylactic Mastectomy**
   Bilateral prophylactic mastectomy decreases the risk of BC by greater than 90% and is offered to BRCA carriers. Total mastectomy is preferred, although bilateral skin-sparing and nipple-sparing mastectomy with immediate reconstruction is now favored. The procedure should be performed by a trained breast surgeon so that glandular tissue is not left behind under the flaps. At prophylactic breast surgery, incidental BC may be found in about 2-3% of cases.(15)

4. **Prophylactic Hysterectomy**
   Hysterectomy is not routinely recommended in BRCA carriers and is not in the guidelines.

BRCA MUTATION CARRIERS WITHOUT MALIGNANCY
CANCER RISK FOR OTHER ORGANS
MALE BRCA CARRIER

<u>Breast Cancer</u>

Surveillance – there is no data on routine screening mammograms. Breast self-exam and clinical exam every 12 months begins age 35.
Chemoprevention – No data on the use of tamoxifen.
Surgical Prevention – No prophylactic surgical options.

Prostate Cancer

Screening – Begins age 40 especially for BRCA2.
Chemoprevention – No data on the use of 5 alpha reductase inhibitors.

Pancreas Cancer

Surveillance – MRI pancreas scan can be done initially but no guidelines as to age to initiate screening or need to repeat. Endoscopic ultrasound and/or MRI cholangiopancreatography is offered if there is family history of pancreas cancer.

MANAGEMENT OF THE BRCA CARRIER WITH CANCER

Female Breast Cancer – Bilateral mastectomy recommended for BRCA1 and 2 patients due to an increased recurrence rate of ipsilateral breast cancer with conservative management and increased contralateral breast cancer risk. Bilateral salpingo-oophorectomy is recommended.

Male Breast Cancer

Mastectomy with axillary sampling recommended. The rate of bilateral mastectomy for males is increasing but has no good evidence as to benefit for survival.

MANAGEMENT OF MUTATION CARRIERS OF OTHER HIGH-RISK AND MODERATE-RISK GENES

P53 LI FRAUMENI

The NCCN has extensive guidelines addressing these patients and are similar to those for HBOC syndrome but are initiated earlier, and screening recommendations for other cancers are also included. Summary guidelines include:

- Age 18 breast awareness begins
- Age 20-25 clinical breast exam every 6-12 months or at the age of the earliest diagnosed BC in the family if below 20 years.
- Age 20-29 annual MRI breast
- Age 30-75 annual MRI and mammogram

Other recommendations include:

- Annual physical exam
- Colonoscopy every 2-5 years starting age 25
- Annual dermatologic exam
- Annual whole body MRI
- Discussion of risk-reducing mastectomy
- Avoid therapeutic radiation if possible

PTEN COWDEN SYNDROME

Breast cancer is the most common cancer in women with Cowden Syndrome, and guidelines are similar to those for HBOC and adjusted to 5-10 years earlier than the earliest known BC in the family. Guidelines include:

- Age 18 breast awareness and self-exam
- Age 25 clinical breast exam every 6-12 months
- Age 30-35 annual mammograms and MRI breast
- Annual endometrial cancer screen
- Annual endometrial biopsy and/or ultrasound
- Age 35 colonoscopy repeated every 5 years
- Annual thyroid ultrasound

Consideration of risk-reducing mastectomy and hysterectomy after completion of childbearing

PATIENTS WITH MODERATE-RISK MUTATION
(CHEK2, PALB2, ATM, BRIP1)

- Age 18 self-exam and awareness
- Age 30 annual screening mammograms and annual screening MRI and clinical breast exam every 6-12 months

Consider risk-reducing bilateral mastectomy if 20% or higher risk of breast cancer, especially PALB2.

CONCLUSION

Mutations in BRCA1 and BRCA2 genes are responsible for the majority of HBC; however, there are important other genes that increase risk of BC and carry an inherent risk to other organs for development of malignancy.

Identifying the patient and family at risk allows for appropriate gene testing, surveillance and risk-reduction measures.

The genetic evaluation, counseling and testing can be complicated, and involvement of trained genetic professionals should be in the care plan. UTSW has a superb Clinical Genetics Department staffed by trained, credentialed counselors who are eager to see and counsel patients and their families. For clinical appointments for genetic evaluation and counseling call 214-645-2563.

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