Current Trends and New Directions in Hereditary Breast Cancer

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January 10, 2015
Current Trends and New Directions in Hereditary Breast Cancer

Objectives:

- Identify criteria for hereditary assessment in patients with breast cancer.
- Learn criteria for screening and treatment of high risk individuals.
- Establish criteria for panel testing evolving classification of variance.
- Determine therapeutic implications of genetic testing and new clinical trials.
Testing Criteria

- A personal history of breast, colon, uterine or other cancer at age < 50
- Triple Negative Breast Cancer <60
- Multiple Breast Cancers in Person or Family
- A personal and/or family history of ovarian cancer
- A personal history of multiple cancers such as ovarian and breast cancer
- Clusters of specific cancer (breast, ovarian, colon) in 3 generations in the family
- Ashkenazi Jewish ancestry (applies to BRCA1 and BRCA2 only)
- Personal or family history of male breast cancer
- Other uncommon cancer(such as sarcoma, childhood cancers and cancer with uncommon tumor pathology)
- Any unusual physical findings (skin, head-size, polyp types etc.)
2014 NCCN Guidelines: Expansion of Multigene Testing Section

- Overview of multi–gene testing
- Points in favor:
  - Increase likelihood of mutation detection
  - Reduce number of uninformative families
  - Potential for cost- and time-effectiveness
- May reveal >1 pathogenic mutation
- Limitations:
  - Technical limitations
  - Clinical limitations
  - Clinical actionability is key
- General Recommendations:
  - Provider
  - Laboratory
Any woman who has a personal history of early-onset breast cancer and does not have an identifiable BRCA1 or BRCA2 mutation. A woman who is diagnosed with breast cancer before age 30 years and is not found to have a pathogenic BRCA mutation has an estimated 4% – 8% likelihood of having a TP53 mutation [Gonzalez et al 2009b, Mouchawar et al 2010, McCuaig et al 2012].

Women with breast cancer diagnosed between ages 30 and 39 years may also have a small increased risk of having a TP53 mutation [Lee et al 2012].

The likelihood of a TP53 mutation in women with early-onset breast cancer is further increased if any of the following are also present:

- A personal history of a breast tumor that is positive for estrogen, progesterone, and/or Her2/neu markers [Masciari et al 2012, Melhem-Bertrandt et al 2012]
- A personal history of an additional LFS related cancer [Tinat et al 2009]
Single Gene Sequencing—the old way

Personal history of breast cancer and or family history of breast cancer:

Previous testing BRCA 1 & 2 (Myriad) and no mutation detected?

??? Review Case

NO: Myriad for BRCA testing

Large rearrangement performed?

No? order BART

Yes, and no mutation detected

Breast Cancer dx. less than age 35?

TP53 (Li-Fraumeni)

Yes, and no mutation detected?

Consider research studies, family studies
Panels currently offered by Ambry Genetics, Myriad, GeneDx, Invitae, Emory, University of Washington, University of Washington and more laboratories expected to offer similar products.

Panels are offered specific to cancer site (all breast cancer genes, colon cancer genes etc) or may be customized “a la carte”.
## Genetic Test Summary

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# Next-gen Cancer Panels

Hereditary breast, ovarian, and colorectal cancer

- BreastNext
- OvaNext
- ColoNext
- CancerNext
- PancNext
- RenalNext
- PGLNEx
- Comprehensive sequence and deletion/duplication testing

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Traditional Sequencing vs. Next Generation Sequencing
Other familial risk factors (genes, environment)

BRCA1

BRCA2

25%

CHEK2
PALB2
BARD1
BRIP1
RAD50
RAD51C
MRE11A

ATM
NBN
PTEN
TP53
STK11
CDH1
MUTYH

20%
# Breast Cancer Genetics and High-Risk Assessment

## Genes predisposing to breast cancer

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- 25% of cancers are accounted for by genetic risks due to the above genes based on newer studies
High Risk Genes
NCCN Guidelines apply

Versus

low to moderate risk genes without current NCCN guidelines
Facts About Hereditary Genes

- 15% of all breast cancer patients have one first degree relative with breast cancer
- Two decades since BRCA–1 and BRCA–2 have been tested
- One million individuals have now been tested and pathogenic mutations account for 30% of high risk breast cancer families
- 15% of breast cancer is familial risk
Emerging Data Confirms This Dilemma Across Multiple Patient Presentations

In 1,781 Patients with Breast Cancer
- 68% BRCA1/2
- 32% Other

32% of pathogenic mutations identified with Myriad myRisk™ were outside of BRCA1 and BRCA2


In 1,260 Patients Suspicious for Lynch Syndrome (LS)
- 73% LS genes
- 27% Other

27% of pathogenic mutations identified with Myriad myRisk™ were outside of the genes associated with Lynch syndrome

Multi-gene panel testing in patients suspected to have Lynch syndrome. Matthew B. Yurgelun et al. Presented at ASCO June 2014

In 648 Patients with Ovarian Cancer
- 60% BRCA1/2
- 34% Other
- 6% LS

34% of pathogenic mutations identified with Myriad myRisk™ were outside of BRCA1/2 and the genes associated with LS

Prevalence in Mutations in a Panel of Breast Cancer Susceptibility Genes in Patients With Early Breast Cancer

**Background:**

- Approximately 5–10% of breast cancers are attributable to single inherited gene mutations
- Clinical testing for germline variation in multiple cancer susceptibility genes is available using massively paralleled sequencing
- However, data is needed on the spectrum of mutations and variants of uncertain significance in defined patient populations

**Methods:**

- 277 BRCA–1 and 2 negative patients with early onset breast cancer were studied for 19 cancer susceptibility genes

Maxwell et al. ASCO 2014, Abstract 1510.
Results:

- Exploring synonymous variants, 60% of patients were identified to have at least one rare variant
- 28 patients (10%) were found to have a pathogenic mutation or likely deleterious variant of uncertain significance
- 7 patients (2.5% overall) were found to have class 4/5 variants

Conclusions:

- These data showed that massively paralleled sequencing identifies the portable variants in known cancer susceptibility genes in 30% of patients with early onset breast cancer
- However, only rare (2.5%) have definitely actionable mutations given current clinical guidelines
- Large scale cooperative group studies are therefore needed to determine the clinical utility of multiplex panel testing in early onset breast cancer

Maxwell et al. ASCO 2014, Abstract 1510.
Background:

- Prior to next generation sequencing technology, genetic testing for hereditary cancer risk was gene and syndrome specific.
- Fox Chase Cancer Center began offering patients a 25-gene panel utilizing NGS. This was started in September 2013.
- This panel included BRCA-1 and 2 and other high to moderate-risk genes for breast, colon, and other cancers.
- Utilization of this panel test compared to syndrome specific testing has not been assessed in a clinical setting.

Methods:

- Patients were offered a choice between syndrome specific testing and a 25-gene panel from Myriad genetics.
- 152 tests ordered from September 2013 to January 2014. Results were available for 144 patients.
- All tested patients met NCCN criteria for genetic testing or were deemed appropriate for testing after assessment by a certified genetics counselor.
Clinical Experience Hereditary Cancer Testing by 25-Gene Panel

Results:

- 144 test results available; 87 had 25-gene panel testing
- 26 had syndrome specific testing for BRCA-1 and 2
- 31 had tolerated testing (Ashkenazi panel, single site, or deletion duplication analysis)
- In the BRCA-1 and 2 test group, a deleterious mutation was found in 3 out of 26 (of note, 12 out of 26 patients declined the 25-gene panel)
- From 87 patients in the 25-gene panel:
  - 8 had clinically positive results for deleterious gene mutation of which 3 were unanticipated test results that influenced clinical management (ATM, APC, RAD51D)
    - All 8 individuals were affected with cancer
  - We found a high rate of variance of unknown significance (33%), as well as a high rate of monoallelic deleterious mutations MYH (5.7%)

Conclusions:

- Multigene panel testing is now available for patients seeking genetic identification of an inherited predisposition to cancer
- The experience here indicated that such a multigene panel may yield results that would not otherwise be discovered through syndrome specific testing
  - May provide additional clinical guidance
  - Results can have uncertain clinical impact given the high VUS rate, as well as other findings
  - Monoallelic MYH for which there is no clear clinical management was also present

Impact of 25-gene Panel and Integrated Risk Management Tool on Medical Management in Hereditary Cancer Syndrome Evaluation

Background:
- Identification of patients with hereditary cancer syndromes such as breast and ovarian cancer or Lynch syndrome leads to profound clinical management changes
- Using next generation sequencing more comprehensive gene panels with greater sensitivity have been developed
- However, most patients still receive a negative test result
- Integrating personal and family cancer history identified during the screening process with the genetic test results can also redefine management recommendations

Methods:
- Patients identified using criteria for HBOC or Lynch syndrome were testing using 25 hereditary cancer panel
- Recommendations from testing incorporated the genetic test result and the personalized cancer risk and management tool (CRMT) based on patients' personal and family history and professional guidelines
- Healthcare providers were surveyed for their management advice to the patient for four cancers, breast, ovarian, endometrial, and colon, before and after testing
- Pre-test surveys were received from 100,414 patients at the time of data analysis
- Data was reported from matched pre and post test survey pairs for a preliminary 100 patients to be updated upon presentation

Impact of 25-gene Panel and Integrated Risk Management Tool on Medical Management in Hereditary Cancer Syndrome Evaluation

Results:

- 48% of patients had a diagnosis of breast, ovarian, colon, endometrial, pancreatic, melanoma, stomach, and prostate cancer
- 3% had a history of other cancers
- 49% had no personal history of cancer
- 65% of patients met NCCN guidelines for HBOC
- 10% met guidelines for Lynch syndrome
- 18% met guidelines for both syndromes
- Overall, HCTs used the genetic test result with the CRMT to guide their management decisions in 91% of cases
- After testing, 25% of patients received a change in management decision
- 60% of patients with a positive result and 23% of patients with a negative result
- Of the management changes:
  - 72% were in surveillance; 16% chemoprevention; 20% surgery; and 28% other

Conclusions:

Integrating expanded genetic panel testing with the personalized cancer care and management tool assists HCPs in providing tailored cancer risk management in both genetic positive and negative populations
## Founder Mutations Occur in All Populations

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<td>● 6-kb duplication of exon 13</td>
<td>● 6503delITT</td>
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<td>● 4184del4</td>
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<td>Dutch (Netherlands)</td>
<td>● 2804delIAA ● Large deletions of exons 13 &amp; 22</td>
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<td>Chinese</td>
<td>● 1081delG</td>
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<tr>
<td>Russian</td>
<td>● 5382insC ● 4153delA</td>
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<td>African A.</td>
<td>● 1832del5 ● 5296del4</td>
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<tr>
<td>Hispanic</td>
<td>● 185delAG ● deletion exons 9-12</td>
<td>● 3492insT</td>
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</tbody>
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Background:

- Previous studies have shown that the prevalence of BRCA mutation among young triple negative patients is elevated.
- Current guidelines recommend that women under 60 with triple negative breast cancer be referred for genetic testing.
- Different studies in Mexico have shown an early onset of breast cancer and a high prevalence of triple negative breast cancer would suggest that BRCA mutations may account for a higher population of breast cancer in this population.
- There is limited information regarding BRCA mutation prevalence mainly due to lack of access to clinical BRCA gene analysis in Mexico.

Methods:

- The purpose of the study was to analyze BRCA mutation in young Mexican triple negative patients using a panel of 114 current BRCA mutations found in women of Hispanic ancestry.
- Mexican women diagnosed with triple negative breast cancer at or before age 50 were prospectively recruited from the NCI in Mexico City.
- Patients were screened by Hispanic and by PCR for the Mexican founder BRCA-1 ex9-12del large gene rearrangement.
Founder Effect and the High Prevalence of BRACA-1 Mutations Among Young Mexican Triple-Negative Breast Cancer Patients

Results:

- 190 consecutive triple negative breast cancer cases were studied.
- Median age of diagnosis was 42 years of age.
- 69% were younger than 45.
- Majority of the patients presented with locally advanced disease.
- BRCA mutation was detected in 43 out of 190 patients (23%).
- 45% of breast cancer mutation carriers had a family history of breast and ovarian cancer.

Conclusions:

- There is remarkable prevalence of BRCA–1 mutations among young triple negative patients in the Mexican population.
- This is the first documented Mexican founded mutation, BRCA–1 ex9–12del, as the most frequent BRCA mutation and is likely responsible for a significant burden of disease in women from South Mexico.
- Hispanican can be completed within 72 hours, at a modest cost of $20 U.S. per sample and implementation among women of Mexican ancestry could reduce overall genotyping cost and increase access to cancer prevention among under–served women in Mexico and the U.S.

T.L.

- Hx: 53 year old with Breast CA
- Age at Dx: 47
- Family Hx: Father had lung and liver CA
- Genetic Dx: MUTYH 1187G>A
Pedigree:
M.B.

- Hx: 76 Caucasian female with ovarian CA with abdominal/peritoneal mets
- Age at Dx: 73
- Family Hx: Aunt had female CA at age 56, one of first cousins had breast CA at age 60, sister had esophageal CA
- Genetic Dx: MUTYH 1187G>A
M.B.
Hx: 59 year old female with Breast CA with L supraclavicular and L axillary mets and involvement of brachial plexus
Age at Dx: 44
Family Hx: No breast or ovarian CA
Genetic Dx: MUTYH 1438G>T, also VUS ATM (3449G>C) and VUS PMS2 (1801T>C)
A.P.
MUTYH

- MUTYH–associated polyposis (MAP), caused by bi–allelic mutations in MUTYH, is characterized by a greatly increased lifetime risk of colorectal cancer (CRC) (43% to almost 100% in the absence of timely surveillance). Although typically associated with ten to a few hundred colonic adenomatous polyps that are evident at a mean age of about 50 years, colonic cancer develops in some individuals with bi–allelic MUTYH mutations in the absence of polyposis. Duodenal adenomas are found in 17%–25% of individuals with MAP; the lifetime risk of duodenal cancer is about 4%. Also noted are a modestly increased risk for rather late–onset malignancies of the ovary, bladder, and skin, and some evidence for an increased risk for breast and endometrial cancer. More recently, thyroid abnormalities (multinodular goiter, single nodules, and papillary thyroid cancer) have been reported in some studies. Some affected individuals develop sebaceous gland tumors.

- Risk for heterozygous carriers of MUTYH still to be defined
Hx: 71 year old Middle Eastern female diagnosed with metastatic colon cancer, initially diagnosed in 2004 with colon cancer and metastasis to liver.
- Right colon with poorly differentiated adenocarcinoma
- 6 of 19 lymph nodes show metastatic carcinoma (N2)

Age at Dx: 61

Family Hx: Colon, pancreatic, prostate and lung cancers met criteria for Lynch testing only. Patient had family history of Breast Cancer, two paternal aunts with post-menopausal diagnosis, but did not meet criteria for BRCA testing

Genetic Dx: Deleterious BRCA1, 4096 + G > A
J.B. (Colon)

- Referred by: Dr. Srinivasiah
- 54-year-old Caucasian female diagnosed in 2013 with colon cancer, adenocarcinoma Grade 2, MO Stage III-B, total of 3 lymph nodes involved in metastatic carcinoma
- No evidence of mismatch repair per IHC, family history of CRC mildly suggestive of Lynch
- Personal history of colon cancer and family history of colon and melanoma
On 12/18/2013 she was tested with myRisk Panel
- Deleterious BRCA1, 2457del (p. Asp821Ilefs*25)
Multigene Panel Testing in Patients Suspected to Have Lynch Syndrome

Background:
- Multigene panels are increasingly used for assessing hereditary cancer risk due to their ability to analyze numerous cancer susceptibility genes in parallel
- Our aim was to study the outcomes in multigene panel testing in patients undergoing clinical testing for Lynch syndrome

Methods:
- The study cohort was 1260 consecutive patients with a history of Lynch syndrome, associated cancers and/or polyps, who had undergone clinical genetic testing for Lynch syndrome in a commercial lab
- Genomic DNA mutations were identified using a 25-gene hereditary panel by PCR and Next-Gen sequencing
- Germline sequence variations and large gene arrangements were classified for pathogenicity
- The patient’s personal and family histories of cancer were obtained from test request forms submitted with clinical Lynch syndrome testing

Multigene Panel Testing in Patients Suspected to Have Lynch Syndrome

Results:

- Panel testing found greater than 1 pathogenic mutation in 160 out of 1260 patients (13%).
- Greater than 1% variant of uncertain significance, 552 out of 1260.
- Of the 160 mutation carriers 160 mutations (73%) were seen in 5 of the Lynch syndrome genes.
- 48 (30%) had a mutation in one of the non-Lynch syndrome genes which included 15 (31%) BRCA-1 and BRCA-2.
- 10 (21%) were in genes underlying other hereditary colorectal cancer syndromes (APC, MUTYH, PTEN, STK11).
- 23 (48%) with other susceptibility genes (ATM, BRD1, BRIT1, CHEK2, MBN, PALB2, and Rad51C).
- Based on their personal family histories a large majority of patients met NCCN criteria for Lynch syndrome testing, but not for HPOC testing.

Conclusions:

- In this large cohort of patients suspected to have Lynch syndrome 30% of the mutation carries identified by panel testing had non-Lynch syndrome cancer susceptibility gene mutations.
Evaluation of Breast Cancer Incidence in Lynch Syndrome Patients

Background:
- The current literature is divided as to whether or not breast cancer is a feature of Lynch syndrome.
- The aim of this analysis was to investigate the prevalence of breast cancer in patients with mutations in individual mismatch repair genes that cause Lynch syndrome.

Methods:
- A retrospective review of patients' personal and family history was performed on patients with Lynch syndrome causing mutations.
- All patients that underwent full sequencing and/or large gene rearrangement testing for mutations MLH1, MSH2, MSH6, PMS2 or EPCAM at Myriad Genetics Lab between 2006 and 2013 were included.
- Patients were excluded if they only had single slide testing for a known Lynch syndrome mutation or they were known to have a mutation in BRCA-1 or 2.
- A Pearson Chi-square test was performed to determine if the prevalence of breast cancer was significantly different among individual MMR genes.
Evaluation of Breast Cancer Incidence in Lynch Syndrome Patients

Results:
- A total of 5638 patients with Lynch syndrome causing gene mutations were identified and the proportion of patients with breast cancer was calculated for each gene.
- A Chi-Square test shows that at least one of these proportions is statistically significantly different from the others.
- The percentage of confidence intervals of patients with breast cancer by gene are:
  - 5.9% for MSH6; 4% for PMS2; 3.7% for MSH2; 3.9% for MLH1; 1.8% for EpCAM

Conclusions:
- The confidence interval for the proportion of MSH6 carriers with breast cancer does not overlap those of MLH1 and MSH2.
- Our results suggest that a personal history of breast cancer is more prevalent in MSH6 mutation carriers than in Lynch syndrome patients with mutations in other MMR genes. This may explain some of the confusion surrounding the inclusion of breast cancer as a Lynch syndrome associated cancer rather than taking an approach of accepting or rejecting that breast cancer is associated with Lynch syndrome as a whole. It may be more appropriate to define breast cancer risk by specific MMR gene or a broader panel of genes.

J.T.

- Hx: 43 year old female with Breast CA and papillary CA of thyroid
- Age at Dx: 42
- Family Hx: paternal aunt had cervical CA, other paternal aunts had unknown female CA, PGF in his 70’s had unknown CA, maternal side of family with skin CA, PGGGF also had CA
- Genetic Dx: CHEK2 +
L.B.

- Hx: First breast CA @ age 46 in 2006, ER+ PR- DCIS. Second primary @ age 53 in 2013, ER/PR + HER2–Ductal.
- Age at Dx: 46
- Family Hx: Family history of pancreatic, prostate, myeloid leukemia, osteosarcoma, ovarian and lung cancers
- Genetic Dx: CHEK2 +
On 5/2/2014 she was tested with MyRisk Panel; deleterious CHECK2, heterozygous 1100 del C
**BRCA1**
- Encodes a protein kinase required for DNA damage and replication check points
- Connects Tp53 response to DNA breaks

**BRCA2**

**TP53**

**Li–Fraumeni Syndrome**
- May increase breast cancer risk by two-fold
- Bilateral Breast Cancer, somewhat later onset
- Male Breast Cancer
- Ovarian Cancer
- Prostate Cancer
- Thyroid Cancer
- Colorectal Cancer

**CHEK2**

Clinical Features:
- May increase breast cancer risk by two-fold
- Bilateral Breast Cancer, somewhat later onset
- Male Breast Cancer
- Ovarian Cancer
- Prostate Cancer
- Thyroid Cancer
- Colorectal Cancer

**Li–Fraumeni Associated Cancers**

- CHEK2
- BRCA1
- BRCA2

Chek2 binds and Regulates BRCA1
Heterozygosities associated with breast, prostate and colorectal cancer
This hypothesis was tested in the general population
9,231 individuals were followed for 34 years
1,101 patients with breast cancer and 4,665 controls were followed
In this prospective study CHEK2 heterozygosity – hazard ratios compared to control:
A. Breast cancer 3.2
B. Prostate cancer 2.3
C. Colorectal cancer 1.6
This suggests a three-fold increase in breast cancer
Development of Breast Tumors in CHEK2, N/NBS1 and BLM Mutation Carriers Does Not Commonly Involve Somatic Inactivation of Wild–Type Allele

Methods:
- 32 tumors obtained from 30 patients with non-BRCA-1 and 2 breast cancer associated germline mutations were assessed
- 25 had single mutations (7 BLM, 15 CHEK-2, and 3 NBN/NBS1 and 5 were double mutation carriers)

Conclusions:
- Tumor specific loss of the wild type allele is not characteristic for breast cancer arising in CHEK2, N/NBS1, and BLM mutation carriers.
- Rarity of second hit inactivation of the involved gene in CHEK-2 demonstrates their substantial biologic difference from BRCA-1 and 2 driven cancers and makes them poorly suitable for cisplatin and PARP inhibitors

CHEK2 gene provides instructions for making checkpoint kinase 2.
It is a tumor suppressive gene on the long arm of chromosome 22.
Moderate increased risk of breast cancer in European population (2–3 fold) (20%–40%)
The lesion of single DNA building block at 1100 in the CHEK2 gene.
1100delC leads to abnormality in nonfunctional version of CDK2 protein.
Closely associated with Li–Fraumeni syndrome (TP53).
Other cancers that it predisposes to are lung, colon, prostate, kidney, thyroid, ovarian, brain tumors and osteosarcoma.

Bibliography: Breast Cancer Treatment 2014
415 patients with breast cancer, 50 years or younger, were studied.

Choice of chemo without knowing mutation status was done.

19 BRCA-1 patients (4.6%) and 8 CHEK2 patients (1.9%) were studied.

BRCA-1 mutation carriers had pathologic CR more than non-carriers, 31.9% vs 11.9%. This effect was limited to anthracyclin containing regimens.

CHEK2 mutation carriers had poor response compared to non-carriers, 50% vs 85% with no pathologic complete responders, particularly poorer without taxanes. This suggests distinct sensitivity.

Bibliography: Breast Cancer Treatment 2014
Patients and Methods:

- 25,572 white women with invasive breast cancer were genotyped for CHEK2 1100delC and observed for 20 years. Median followup was 6.6 years.

Data analyzed:

- Early death.
- Breast cancer specific death by ER status.
- Risk of second breast cancer after first breast cancer were analyzed.
CHEK2 – 1100delC heterozygositites associated with early death, breast cancer specific death and risk of second breast cancer in women with first breast cancer

Results:

- CHEK2 1100delC heterozygosity was found in 459 patients (1.8%).
- Early death heterozygous (1.43%) vs non-carriers for a P value 0.004).
- Breast cancer specific death for heterozygous was 1.63 vs non-carriers for a P value of less than 0.001.
- Second cancer was 2.77 for heterozygous vs 1 for non-carriers.
  - 3.52 for heterozygous (ER positive) vs non-carriers.

Conclusions:

- In women with ER positive breast cancer, CHEK2 1100delC heterozygosity was associated with 1.4 fold early death, 1.6 fold cancer specific death, and 3.5 fold second cancers.

Bibliography: JCO December 10, 2014
B.S.

- Hx: 67 year old with Colon CA, Duke’s B2
- Age at Dx: 51
- Family Hx: Father died of Lung CA, uncle died of unknown CA, mother diagnosed with breast CA at age 50, MGM diagnosed with breast cancer at age 46
- Genetic Dx: BRIP1: Deletion (exon8), also VUS MSH2(1070A>C)
B.S.
BRIP1, PALB2, RAD51C mutation analysis reveals the relative importance as genetics susceptibility factors for breast cancer

Bibliography: Breast Cancer Treatment 2014
BRIP1, PALB2, RAD51C

- BRIP1, PALB2 and RAD51C were sequenced from mutations as a result of previously being associated with breast cancer due to the role in double stranded break repair pathway and their close association with BRCA–1 and 2.

- This study confirmed a small but substantial portion of inherited breast cancer in PALB2 but not in RAD51C.
Breast Cancer Risk With Mutations in PALB2

Background:
- Germline loss of function mutations in PALB2 are known to confer a predisposition to breast cancer.
- However, the lifetime risk of breast cancer that is conferred by such mutations remains unknown.

Methods:
- Breast cancer risk was analyzed among 362 members. Of 154 families who had deleterious truncated, splice or deletion mutations in PALB2.
- The eight specific breast cancer risks for mutation carriers was estimated with the use of a modified segregation analysis approach that allowed for the affects of PALB2 genotype and residual familial aggregation.

Breast Cancer Risk With Mutations in PALB2

Results:

• The risk of breast cancer for female PALB2 carriers as compared with the general population was 8-9 times as high among those younger than 40 years of age.
  - 6-8 times higher for women ages 40-60
  - 5 times as high among those older than 60
• Estimated cumulative risk of breast cancer among female mutation carriers was 14% by 50 years of age and 35% by 70 years of age.
• Breast cancer risk was significantly influenced by birth control and by other familial risk factors.
• Absolute breast cancer risk for PALB2 female mutation carriers by 70 years of age ranged from 33% for those with no family history of breast cancer to 58% for those with two or more first-degree relatives with breast cancer at 50 years of age.

Conclusions:

• Loss of function mutations in PALB2 are an important cause of hereditary breast cancer.
  • With respect both to the frequency of cancer predisposing mutations and to the risk association with them.
• Our data suggest the breast cancer risk for PALB2 mutation carriers may overlap with that for BRCA-2 mutation carriers.

The gene PALB2 is a tumor suppressor gene that has been identified as a pancreatic cancer susceptibility gene. It interacts with BRCA2 to repair damaged DNA and help maintain the rate of cell growth and division.

PALB2 Genetic Testing may be considered for those with familial pancreatic cancer and those with familial breast cancer who tested negative for BRCA1 and BRCA2 mutations.

PALB2 mutations were found in 10 of 923 (1.1%) individuals with BRCA1 and BRCA2 mutation negative familial breast cancer, compared to none of 1084 (0%) controls (P = .0004). One of the ten families with a PALB2 mutation included a case of male breast cancer, raising the possibility that male breast cancer is included in the spectrum of PALB2 mutations in families with hereditary breast cancer. A Finnish PALB2 founder mutation (c.1592delT) has been reported to confer a 40% risk of breast cancer to age 70 years, and is associated with a high incidence (54%) of triple-negative disease and lower survival.
The frequency of mutation in 17 genes including BRCA–1 and 2 in a cohort of triple negative breast cancer were studied.

They were not selected based on family history or breast or ovarian cancer.

PATIENT METHODS:

- Triple negative breast cancer 1824 patients.
- Unselected for family history of breast or ovarian cancer were recruited through 12 studies.
- Germline DNA was sequenced to identify mutations.
RESULTS:

- Deleterious mutations were identified in 14.6% of all patients.
- 11.2% – had BRCA mutations.
- BRCA-1 – 8.5%
- BRCA-2 – 2.7%
- 3.7% abnormalities were seen in other genes.
  - PALB2 (1.2%)
  - BARD1
  - RAD51D
  - RAD51C
  - BRIP1 (0.3–0.5%)
- Those with mutations were diagnosed at earlier age and had higher grade tumors.
CONCLUSIONS:

- Even in patients without family history, triple negative patients should be considered for germline testing.
- Exceeding 10% risk of carrying the gene especially in patients less than 40 years of age.
- Other predisposing genetic mutations were identified in these patients.
- Better cancer risk estimates are needed to test their relatives.
PALB2 has been shown to be associated with high lifetime risk of breast cancer (moderate penetrance).

No mutations in CHEK2, CDH1, STK11 suggesting that syndromic predisposing genes are rarely involved in predisposition to triple negative breast cancer.

The appropriate application of non–BRCA–1 and 2 breast cancer susceptibility genes to patient care is not yet established.

Bibliography: JCO, December 1, 2014
P.R. (Breast)

- 42-year-old Asian-Indian female diagnosed with infiltrating ductal carcinoma, ER/PR+ this year
- No past medical history
- No cancer in family, only asthma and Crohn’s disease
- BARD1, variant uncertain significance, 1694 G > A
Multiple mutations have been identified in the BRCA-1 and 2 that inactivate corresponding proteins and increase risk of cancer.

VUS including missense, intrinsic and small in-frame insertions/deletions types of variants have been observed.

Using proprietary data they can be reclassified, which can only be done by big companies such as Myriad/GeneDX.

ClinVar data have been posting results to reclassify variants.

Factors included are:

- Functional impact of variants are based on amino acid conservation and structure.
- ENIGMA uses evidenced based networks that include evolutionary sequence, conservation of protein, and tumor pathology.
- May be complicated by homophobic mutations.
62-year-old male with a history of no major medical problems other than fluctuating blood pressure

Presented with a mass in the left breast measuring 3 x 3 cm on exam (T2 NX MX). The lump in the left breast was found by his girlfriend.

Patient underwent a biopsy of the breast mass.

Consistent with infiltrating ductal carcinoma, ER/PR-positive, HER2-negative, and axillary node negative
• Deleterious BRCA1, 3653delC
## Triple Negative Breast Cancer Subtypes
**GeparSixto; Role of BRCA**

### Addition of Carboplatin to NACT in TNBC

<table>
<thead>
<tr>
<th>Strata</th>
<th>pCR Control</th>
<th>pCR + Cb</th>
<th>Δ</th>
<th>OR</th>
<th>p</th>
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<td>No risk factor</td>
<td>34.5%</td>
<td>46.0%</td>
<td>11.5%</td>
<td>1.61</td>
<td>0.13</td>
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<tr>
<td>+FH w/o mutation</td>
<td>30.8%</td>
<td>57.5%</td>
<td>26.7%</td>
<td>3.04</td>
<td>0.02</td>
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<tr>
<td>BRCA or RAD mut</td>
<td>43.5%</td>
<td>66.7%</td>
<td>23.2%</td>
<td>2.60</td>
<td>0.13</td>
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</table>

- Impact of +FH without identified mutation suggests unidentified genes or multigenic factors.
- BRCA analysis of CALGB 40603 patients underway

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Von Minckwitz et al, ASCO 2014, Abstract 1005
<table>
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<tr>
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<th>No Carbo (n=212)</th>
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<th>Bev effect</th>
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<td>39%</td>
<td>49%</td>
<td>44%</td>
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<td><strong>Bev</strong> (n=215)</td>
<td>43%</td>
<td>60%</td>
<td>52%</td>
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<tr>
<td><strong>Carbo effect</strong></td>
<td>41%</td>
<td>54%</td>
<td>Carbo/Bev Interaction p=0.43</td>
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</table>

Correlative studies and BRCA analysis of CALGB 40603 patients underway
TBCRC009: Study Design

Eligibility

- Triple negative by local assessment
- Archived tissue from the primary or metastatic biopsy
- RECIST 1.0 measurable disease
- ECOG PS ≤ 2
- ≤1 Prior chemotherapy mBC
- No prior treatment with platinum
Efficacy: Response by BRCA1/2 Status

<table>
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<th>BRCA1/2 Status</th>
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<th>% (95% CI)</th>
<th>p</th>
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<tr>
<td>BRCA1/2-Carrier</td>
<td>6 (6 PR)</td>
<td>54.5% (23.4-83.3)</td>
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<td>BRCA1/2- WT</td>
<td>13 (10 PR, 3 CR)</td>
<td>19.7% (10.9-31.3)</td>
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<tr>
<td>BRCA1/2-Unk</td>
<td>3 (3 PR )</td>
<td>33.3% (19.1-48.5)</td>
<td></td>
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</table>
BRCA1/2 germline mutation does not predict longer PFS or OS.

A. Progression Free Survival
- Median PFS, Mo: 2.9

B. Overall Survival
- Median OS, Mo: 11.0

C. BRCA Mut vs BRCA WT
- Median PFS, Mo: 3.3 vs 2.8
- P=0.92
- HR 1.03 (0.53-2.00)

D. BRCA Mut vs BRCA WT
- Median OS, Mo: 13.7 vs 10.9
- P=0.58
- HR 1.22 (0.53-2.00)
Triple Negative Breast Cancer
Platinum After Neoadjuvant Therapy

HCRN BRE09-146\(^1\)

- Randomized 128 TNBC with residual disease after NACT (RCB 2-3 or MP 0-2) to cisplatin 75 mg/m\(^2\) q3wks x 4 +/- rucaparib IV d1-3 q3wks x 4 then PO weekly x 24 wks

- Primary endpoint - DFS at 2 yrs - pending

- At 1 year, DFS is identical +/- rucaparib (83%)

- However
  - 0/8 BRCA carriers assigned to cisplatin + rucaparib have recurred
The goal of the study is to create a confidential registry and biologic repository to:

- Define the underlying predisposition to cancer (genetic and/or environmental)
- Learn more about susceptibility to cancer.
- Genes will be tested now and in the future.
Features of *gBRCA1* and *gBRCA2* Breast Cancer

- Often high grade

- *BRCA1*-associated tumors are:
  - 70% Triple Negative
  - 20% ER+, PR+, HER2 negative
  - 10% HER2 positive

- *BRCA2*-associated tumors are:
  - 70% ER+, PR+, HER2 negative
  - 20% Triple Negative
  - 10% HER2 positive

Should Treatment of Breast Cancer Patients with *gBRCA1/2* Mutations be Different?

1. Bilateral mastectomies often elected over breast conservation to reduce the risk of second cancers.

2. Bilateral salpingo-oophorectomy to:
   - Reduce ovarian cancer risk.
   - Treat hormone receptor positive breast cancers in premenopausal women.
   - Reduce the risk of second breast cancers in women who do not have bilateral mastectomies.

3. Should systemic therapy be different for *BRCA1/2* related tumors? Platinums? PARP inhibitors?
BRCA1 and Differential Chemo-Sensitivity

- BRCA1 cell line was killed more effectively by platinum than by doxorubicin or paclitaxel.

- Platinum is a DNA-cross linking agent and causes the kind of double strand breaks in DNA that BRCA1 is necessary to repair.

Response to Neoadjuvant Cisplatin in BRCA1+ Breast Cancer Patients

10 women with BRCA1 mutations
4 cycles CDDP 75 mg/m² q 21d
Trial is ongoing

<table>
<thead>
<tr>
<th>Response</th>
<th>No.</th>
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<tr>
<td>Clinical Complete Response</td>
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<td>90</td>
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<tr>
<td>Clinical Partial Response</td>
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<td>10</td>
</tr>
<tr>
<td>Pathologic CR</td>
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<td>90</td>
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<tr>
<td>Pathologic PR</td>
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<tr>
<td>Residual Disease in the Breast</td>
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<td>0</td>
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<tr>
<td>Number Positive Nodes</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td>1-3</td>
<td>1</td>
<td>10</td>
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</table>

ASCO Result: 18/25 or 72% pathCR

Remarkable pCR rate and increased interest in DNA-cross-linking chemotherapies.
Double-strand and Single-strand Break Repair with Poly (ADP-ribose) Polymerase Inhibitors (PARPis)
Principle of Synthetic Lethality

(a) DNA damage
- Normal cells
  - Pathway A
  - Pathway B
  - Repaired by pathway A
  - Cell survival
- Cancer cells
  - Pathway A
  - Pathway B
  - Repaired compensated by pathway B
  - Cell survival

(b) DNA damage
- Normal cells
  - Pathway A
  - Pathway B
  - Repaired by pathway A
  - Cell survival
- Cancer cells
  - Pathway A
  - Pathway B
  - Inhibition of pathway B
  - Not repaired
  - Cell death

BRCA1<sup>−/−</sup> and BRCA2<sup>−/−</sup> Cells are Extremely Sensitive to PARP Inhibition

No difference in sensitivity between heterozygous and wild-type BRCA cells

Targeted inhibition → selective and less toxic therapy

Olaparib
Orally Active PARP Inhibitor

- A phase I trial\(^1\) identified olaparib 400 mg bid as the maximum tolerated dose with a signal of efficacy in BRCA-mutated ovarian cancer\(^2\)

- Most common toxicities: CTCAE grade 1 and 2 nausea and fatigue

- Significant PARP inhibition and response at olaparib doses 100 – 400 mg bid

---

Olaparib in Patients with $gBRCA1$ and/or $gBRCA2$ Mutations and Metastatic Breast Cancer

Phase II multicenter trial

Women with germline $BRCA1/2$ mutation and metastatic breast cancers who had $\geq 1$ prior therapy

Olaparib 400 mg or 100 mg po BID x 28 day cycles

PI: Andrew Tutt, MD
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 400 mg bid (n=27)</th>
<th>Olaparib 100 mg bid (n=27)</th>
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<tr>
<td><strong>ECOG status, n</strong></td>
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<tr>
<td>0/1/2</td>
<td>12/13/2</td>
<td>16/10/1</td>
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<td><strong>Prior chemotherapy regimens</strong></td>
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<td>Median (range)</td>
<td>3 (1–5)</td>
<td>3 (2–4)</td>
</tr>
<tr>
<td>Taxane and anthracycline, n (%)</td>
<td>25 (96)</td>
<td>19 (70)</td>
</tr>
<tr>
<td>Taxane/anthracycline/capecitabine, n (%)</td>
<td>10 (37)</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Platinum, n (%)</td>
<td>6 (22)</td>
<td>8 (30)</td>
</tr>
<tr>
<td><strong>Hormonal status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple negative</td>
<td>13/26 (50)</td>
<td>16/25 (64)</td>
</tr>
<tr>
<td>ER+ HER2–</td>
<td>11/27 (41)</td>
<td>4/26 (15)</td>
</tr>
<tr>
<td>ER+ HER2+</td>
<td>1/27 (4)</td>
<td>4/26 (15)</td>
</tr>
<tr>
<td>ER- HER2+</td>
<td>1/27 (4)</td>
<td>1/26 (4)</td>
</tr>
</tbody>
</table>
**Efficacy of Olaparib in *gBRCA1/2* Mutation Associated Metastatic Breast Cancer**

<table>
<thead>
<tr>
<th>ITT cohort</th>
<th>Olaparib 400 mg bid (n=27)</th>
<th>Olaparib 100 mg bid (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate, n (%)</td>
<td>11 (41)*</td>
<td>6 (22)*</td>
</tr>
<tr>
<td>Complete Response, n (%)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response, n (%)</td>
<td>10 (37)</td>
<td>6 (22)</td>
</tr>
</tbody>
</table>

*An additional 1 patient in the 400 mg cohort and 3 patients in the 100 mg cohort had unconfirmed responses*
Response to Olaparib

BRCA1 carrier
ER, PR, HER2 neg
3rd line Rx for mets

Olaparib 400 mg bid cohort

Increasing tumor shrinkage
Single Agent Olaparib in Metastatic Breast and Ovarian Cancer +/- BRCA Mutations

TNBC: No responses if BRCA1/2 WT
Ovarian: Responses in BRCA1/2+ and WT

NSABP B-55/BIG 6-13
OlympiA
Schema

Post **neoadjuvant** *gBRCA* TNBC,
  - Non-Path CR pts
Assumptions:
  - Control arm 3 year EFS ~ 60%

Randomize 1:1
*Double blind*
*N=1320*

Post **adjuvant** *gBRCA* TNBC,
  - Node positive disease (any tumour size) OR
  - Node negative, primary > 2 cm
Assumptions:
  - Control arm 3 year EFS ~ 75%

Olaparib
300 mg bid
12 month duration

Placebo
12 month duration
OlympiA
Major Eligibility Criteria

- Completed at least 6 cycles neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or both
- Allow prior platinum administered as potentially curative treatment for previous cancer (e.g., ovarian) or as adjuvant or neoadjuvant treatment for breast cancer
- No persistent toxicities $\geq$ CTCAE grade 2 caused by previous cancer therapy, excluding alopecia and grade 2 peripheral neuropathy
Completed at least 6 cycles neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or both

Allow prior platinum administered as potentially curative treatment for previous cancer (e.g., ovarian) or as adjuvant or neoadjuvant treatment for breast cancer

No persistent toxicities $\geq$ CTCAE grade 2 caused by previous cancer therapy, excluding alopecia and grade 2 peripheral neuropathy
M12–914:

A Phase 3 Randomized, Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the PARP Inhibitor Veliparib (ABT–888) in HER2 Negative Metastatic or Locally Advanced Unresectable BRCA Associated Breast Cancer
M12-914 Overall Study Design

Patient Population
- Women or men ≥18 years
- Locally advanced or metastatic HER2-breast cancer
- \(gBRCA1\) or \(gBRCA2\)
- No more than 2 prior lines of DNA-damaging therapy
- No prior PARP-I
- Stable CNS metastases

Endpoints
Primary Endpoint
Progression Free Survival
Additional Endpoints
OS
CBR
ORR
PFS2
Duration of Response

Randomization 2:1
- Pac / Carbo / Veliparib* (N = 180)
- Pac / Carbo / Placebo* (N = 90)

* If carbo and paclitaxel are discontinued for toxicity, veliparib/placebo will be continued as a single agent

Stratification Factors for Randomization:
- ER and/or PR positive vs. ER and PR negative
- Prior platinum therapy (yes vs. no)
- CNS metastases (yes vs. no)
Based on our 20-year experience working with families with cancer predisposing mutations in BRCA–1 and BRCA–2, it is time to offer genetic testing of these genes to every woman!
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