Highlights from the 2018 Joining FORCeS Against Hereditary Cancer Conference

Cancer risks for people with non-BRCA mutations
Jessica Mandell, MS, CGC, University of Washington

About 10% of breast cancers and 20% of ovarian cancers are due to inherited mutations in genes that are associated with these and other cancers. The level of cancer risk associated with each of the following genes may vary between families and even among individuals within a family.

PALB2
The PALB2 gene assists in DNA repair. Women who carry a PALB2 mutation have up to a 58% lifetime risk of breast cancer, and in some families, the ovarian cancer risk is also increased. Men with this mutation also have an increased risk for breast cancer.

CHEK2
The CHEK2 gene regulates cell division and death. Women with a mutation in this gene have a 20-45% lifetime risk of breast cancer; the risk is even greater when there is a family history. Mutations in CHEK2 are more common in people of northern and eastern European ancestries. Among CHEK2 mutations:

- 1100delC is the most common and is associated with ER+ breast cancers.
- S428F is an Ashkenazi Jewish founder mutation that is associated with moderate breast cancer risk.
- I157T is less common and is associated with lower breast cancer risk but increased risk of prostate cancer.
- Men with a CHEK2 mutation likely have increased risk for breast cancer (5%), colon cancer (2-6%), thyroid, kidney, and prostate cancers, as well as sarcoma (cancer of the connective tissue).
- No increased ovarian risk is currently related to mutations in CHEK2.

ATM
ATM assists in DNA repair. About 1% of the general Caucasian population carries a mutation in this gene. Having mutations in both copies of the ATM gene causes ataxia telangiectasia, a recessive musculoskeletal condition in children. Children with ATM have an increased cancer risk, especially for leukemia and lymphoma.

Women who inherit a one mutated copy of the ATM gene have up to a 52% lifetime risk of breast cancer. People (women or men) an inherited ATM mutation should reduce radiation exposure, since
this causes double-stranded DNA breaks. Mammography, however, is currently recommended for ATM mutation carriers—no evidence shows that it should be reduced due to increased risk.

**BARD1**
The BARD1 gene interacts with the BRCA1 gene to help repair DNA damage. In some severely affected families, BARD1 mutations are associated with breast and ovarian cancers.

**CDH1**
The CDH1 gene helps cells stick together. Mutations in CDH1 cause highly diffuse gastric cancer (HDGC) of the stomach wall, accounting for 30-50% of all HDGCs. The lifetime risk of HDGC is 67% for men and 83% for women with a CDH1 mutation. Prophylactic removal of the stomach is recommended for CDH mutation carriers.

Women with CDH1 mutations have up to a 52% lifetime risk of lobular breast cancer. Patients with CDH1 mutations tend to develop HDGC and lobular breast cancer before age 40.

**TP53**
Sometimes called the “guardian of the genome,” TP53 is a tumor suppressor that controls a cell’s life and death. Inherited TP53 mutations cause Li Fraumeni syndrome, which is quite rare and is associated with multiple young onset cancers. Mutation carriers have a very high risk of developing cancer: 50% by age 30 and 90% by age 60. Only about one 1 in 20,000 people carry this mutation.

Mutation carriers have a high risk of developing very early onset breast cancer. Their risk of breast cancer in their teens or 20s is greater than 80%.

**NBN**
The NBN gene is involved in DNA repair. Having mutations in both copies of the NBN gene cause Nijmegen breakage syndrome, a rare condition characterized by high sensitivity to radiation and other agents that can cause breaks in DNA.

Women with an inherited mutation in one copy of NBN have a modest (2 to 3 fold) increase in breast cancer risk compared to women without an NBN mutation.

**BRIP1**
The BRIP1 genes help to unwind DNA for repair. Inherited mutations in this gene have occurred in several breast cancer and ovarian cancer patients in multiple severely affected families. These families have an increased lifetime risk of ovarian cancer (~5-14%) and a moderately increased breast cancer risk, which is currently being reevaluated. Men with BRIP1 mutations have increased risk of prostate cancer.

**RAD51C/D**
RAD51C and RAD51D are part of the RAD gene family which play a role in repairing DNA breaks. Women who have inherited a RAD51C or D mutation have a 10 to 15% increased lifetime risk of ovarian cancer risk (the risk may be higher in RAD51D mutation carriers). Recent studies also suggest
increased risk of breast cancer, especially for RAD51D mutation carriers. Men with either of these mutations may have increased risk for prostate cancer.

**Lynch syndrome**
People with Lynch syndrome are typically at increased risk for colon, uterine, ovarian, and other GI cancers. The risk for developing Lynch syndrome varies, depending on the gene involved—MSH6, MSH2, MLH1, PMS2, or EPCAM.

Because new data suggests that women with a MSH6 or PMS2 mutation have a 2 to 3-fold lifetime risk of breast cancer, breast cancer gene panels are now testing for these genes. New data also shows that mutations in MSH6, MSH2, or MLH1 may increase risk for prostate cancer.

**PTEN**
PTEN is a tumor suppressor gene associated with PTEN Hamartoma Syndrome or PHTS (historically known as Cowden Syndrome or other names). Patients with PHTS may develop cancers and hamartomas (non-cancerous growths) in different areas of the body. Autism and similar features are also associated with PHTS.

People with PTEN mutations have increased lifetime risks of multiple cancers, including female breast (50%) and uterine (28%) cancer, as well as thyroid (10%), colon (9%), kidney (5%), and melanoma. PTEN mutations are also associated with goiters, uterine fibroids, and GI tract polyps.

National Comprehensive Cancer Network (NCCN) guidelines outline recommendations for screening and management for specific gene mutations. Screening often starts at young ages—during a mutation carrier’s 20s or 30s—and may begin 10 years earlier than the youngest diagnosis of a given cancer in the family.