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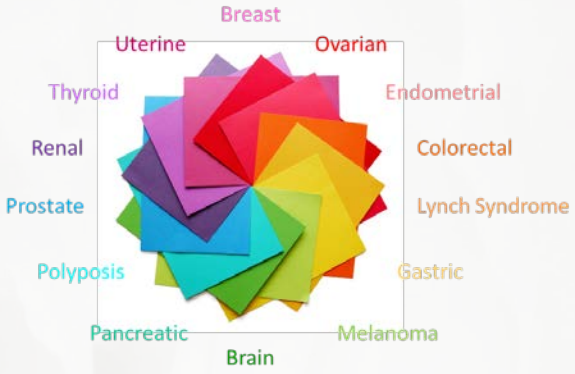
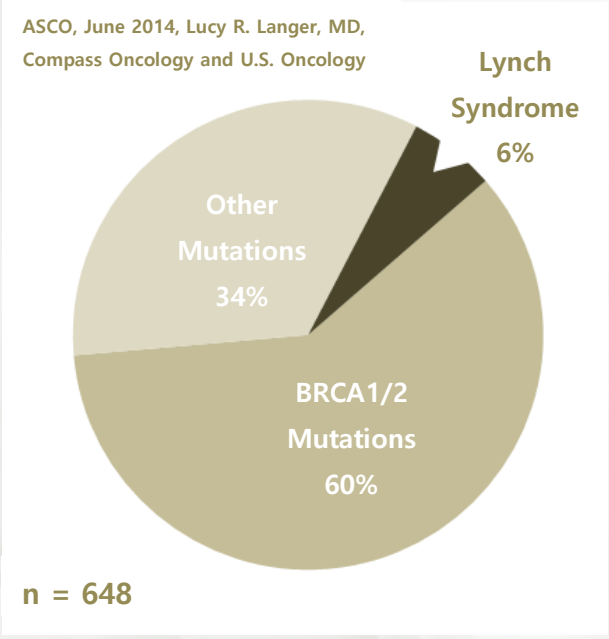
Hereditary Cancer Testing

Hereditary Cancers account for 5-10% of all cancers.
Genetic Testing can aid in diagnosis and identify at-risk patients.

Inherited genetic mutations can increase a person's risk of developing cancer through a variety of mechanisms, depending on the function of the gene. Mutations in genes that control cell growth and the repair of damaged DNA are particularly likely to be associated with increased cancer risk. **The genetic mutations that cause many of the known hereditary cancer syndromes have been identified, and genetic testing can confirm whether a condition is, indeed, the result of an inherited syndrome. Genetic testing is also done to determine whether family members without obvious illness have inherited the same mutation as a family member who is known to carry a cancer-associated mutation.**



Until recently, most testing for cancer genetic risk involved traditional exon-by-exon Sanger sequencing of each candidate gene. For example, individuals susceptible to hereditary cancers were screened based on personal or family history and offered testing for mutations in a single gene or a set of genes associated with a particular syndrome, for example BRCA1 and BRCA2 for hereditary breast and ovarian cancer or mismatch repair genes for Lynch syndrome. In contrast, **the advent of Next Generation Sequencing allows parallel sequencing of millions of short pieces of DNA simultaneously.** Prior to Next Generation Sequencing, genetic testing usually started with the most commonly involved genes and proceeded to less likely genes only when clinical suspicion was very high. However, cancer panels allow testing of all genes in parallel without substantially increasing the cost, leading to a different clinical algorithm in which all known contributing genes can be assayed at first evaluation.



SGO Clinical Practice Statement: Next Generation Cancer Gene Panels Versus Gene by Gene Testing, March 2014

"Advantages of cancer gene panels include decreased cost and improved efficiency of cancer genetic testing by decreasing the time involved, number of patient visits, and number of tests sent. A negative genetic test is more reassuring at eliminating the likelihood of inherited risk when all known genes for that phenotype have been assayed."

"Approximately 15% of all ovarian cancers are attributable to a BRCA1 or BRCA2 mutation. An additional 5-6% of ovarian cancers have gene mutations in other genes including the Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2), and BRIP1, RAD51D, RAD51C, PALB2, BARD1, and TP53".

There are multiple genes other than BRCA1/2, which when abnormal, may elevate an individual's susceptibility to breast cancer and other cancers. Multi-gene testing allows for the identification of 40 to 50 percent more individuals with hereditary cancer gene mutations than is possible testing for BRCA1 and BRCA2 alone. This is a highly cost-effective and time-effective method for the simultaneous evaluation of multiple genes. **Testing more than one gene at a time allows for more information in a designated period of time. Some insurance coverage allows only one genetic testing per lifetime.**

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Otogenetics Hereditary Cancer Panels

- **Comprehensive Inherited Cancer Panel – 39 genes linked to Breast, Ovarian, Endometrial, Colorectal, Lynch Syndrome, Gastric, Melanoma, Pancreatic, Polyposis, Prostate, Renal, Thyroid/Parathyroid, Uterine and other major cancers** APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKn2A, CHEK2, ELAC2, EPCAM, FANCC, HRAS1, MEN1, MET, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, NTRK1, PALB2, PALLD, PMS2, PTCH, PTEN, RAD50, RAD51, RAD51C, RAD51D, RET, SMAD4, STK11, TP53, VHL
- **Comprehensive Inherited Cancer Panel with Confirmation for Lynch Syndrome – 39 Genes**
- **Breast and Ovarian Cancer – 15 genes**
  ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, RAD51C, RET, STK11, TP53, VHL
- **Colorectal, Endometrial and Ovarian Cancer Panel – 12 genes**
  APC, BMPR1A, CDH1, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11

- **Next Generation Sequencing with custom oligonucleotide-based target capture provides robust and clinically actionable data.**
- **Illumina sequencing of the coding regions.**
- **Variant and Copy Number Variations reported using DNAnexus and QCI platforms referencing comprehensive clinical genetic databases.**
- **High depth coverage to detect both common and rare mutations.**
- **Turn Around Time of 2-3 weeks.**
- **Experience in genetic testing over 10 years.**
- **MS and PHD Scientists ensure accuracy of results.**
- **Each report is reviewed and signed off by Board Certified Medical Geneticists.**

American College of Obstetrics & Gynecology, ACOG Recommendations

A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer.

If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing. ACOG Committee Opinion Number 634, June 2015

American College of Medical Genetics & Genomics, ACMG Practice Guidelines

Hereditary breast–ovarian cancer (HBOC) syndrome is caused by mutations in BRCA1 and BRCA2 genes and is characterized by increased risks for early-onset breast, multiple breast primaries, male breast, and epithelial ovarian, Fallopian tube, or primary peritoneal cancers.

Cancers of the pancreas, prostate, and melanoma are more common in individuals with HBOC syndrome.

The pathology of "triple-negative phenotype" breast cancer (estrogen receptor–negative, progesterone receptor–negative, and HER2/neu–negative) has been strongly associated with BRCA1 mutations.

The likelihood of identifying a BRCA1/2 mutation in a woman with ovarian cancer at any age is around 13–18%.

Of males with breast cancer, 15–20% has a BRCA1/2 mutation.

The overall prevalence of BRCA1 mutations is estimated at 1 in 300. BRCA2 mutations are estimated at 1 in 800. Founder mutations in populations e.g., Ashkenazi Jewish, Icelandic, and Mexican Hispanic populations lead to increased mutation prevalence in these populations. doi:10.1038/gim.2014.147

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National Comprehensive Cancer Network, NCCN Guidelines

Genetic testing should be considered for appropriate high-risk individuals where it will impact medical management of the tested individual and/or their at-risk family members.

The probability of a mutation being detected based on these criteria will vary depending family structure.

- Individuals with unknown or limited family history, such as fewer than 2 female first- or second-degree relatives having lived beyond 45 years in either lineage, may have an underestimated probability of familial mutation detection.
- The likelihood of detecting a mutation may be very low in families with a large number of unaffected female relatives.

Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing with current technologies using blood samples due to unreliable test results from contamination by donor DNA. DNA extracted from a fibroblast culture can be used. If not available, then a buccal sample can be considered with understanding of the risk of donor DNA contamination. NCCN, Version 2.2017

Cancer Risk Assessment

Referral for testing should be considered for any individual with a personal history of or first-degree relative with:

- Breast cancer diagnosed at or before age 50
- Triple-negative breast cancer diagnosed at or before age 60
- Two or more primary breast cancers in the same person
- Ovarian, Fallopian tube, or primary peritoneal cancer
- Ashkenazi Jewish ancestry and breast or pancreatic cancer at any age

If more than one family member is affected with cancers associated with particular inherited cancer susceptibility, consider testing:

- A family member with the youngest age at diagnosis, bilateral disease, multiple primary cancers, or other cancers associated with the syndrome.
- If there are no living family members with cancer related to the syndrome in question, then consider testing first- or second-degree family members affected with other cancers thought to be related to the gene in question.
- Testing of unaffected family members when no affected member is available should be considered. The significant limitations of interpretation of test results should be discussed with the patient.
- If no mutation is found, consider other hereditary cancer syndromes associated with breast and ovarian cancer risk for which genetic testing is clinically available.
- Testing family members for Variants of Unknown Significance, VUS should not be used for clinical purposes. Referral to research studies that aim to define the clinical impact of classification of such variants through clinical laboratories or registries.

Male Breast Cancer: Individuals with a family history of three or more cases of breast, ovarian, pancreatic, and/or aggressive prostate cancer (Gleason score ≥7) should also be referred. Note that this should not include families in which all three cases are aggressive prostate cancer.

Risk to Relatives

Advise about possible inherited cancer risk to relatives, their options for risk assessment and management.

Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

Reproductive Options

For patients of reproductive age, options for prenatal diagnosis, assisted reproduction and pre-implantation genetic diagnosis should be discussed.

ACOG, ACMG, NCCN Guidelines

Frequently Used ICD-10 Codes

Breast and Ovarian Cancer		Colorectal Cancer	
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast	Z80.0	Family history of malignant neoplasm of digestive organs
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast	Z83.71	Family history of colonic polyp
D05.11	Intraductal carcinoma in situ of right breast	Z86.010	Personal history of colonic polyps
D05.12	Intraductal carcinoma of in situ of left breast		
Z80.3	Family history of malignant neoplasm of breast	**Other**	
Z80.41	Family history of malignant neoplasm of ovary	C54.1	Malignant neoplasm of endometrium
Z85.3	Personal history of malignant neoplasm of breast	Z80.42	Family history of malignant neoplasm of prostate
Z85.43	Personal history of malignant neoplasm of ovary		

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Interpretation of Test Results – Variant Classification

Variant classification is based on a strict Mendelian perspective and employs the recommended five-tier classification system recommended by the American College of Medical Genetics, ACMG.

A sequence change can be classified as:

Positive - Pathogenic Variant(s) Detected

This result means that a mutation or a genetic change that increases the lifetime chance of developing certain cancers was identified. This variant directly contributes to the risk of developing cancer. Some pathogenic variants may not be fully penetrant. In the case of recessive conditions, a single pathogenic variant may not be sufficient to cause disease on its own. Additional evidence is not expected to alter the classification of this variant. The final report contains detailed risk information specific to the mutation(s). This result does not mean that the patient has cancer or will definitely develop cancer in their lifetime. Follow up with physicians, healthcare providers and genetic counseling is recommended.

Variants(s) Likely to be Pathogenic (VLP) Detected

The result means that a mutation or a genetic change that is likely to increase the lifetime chance of developing certain cancers was identified. However current scientific evidence is insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion of pathogenicity, but we cannot fully rule out the possibility that new evidence may demonstrate that this variant has little or no clinical significance. The final report contains detailed risk information specific to the mutation identified. This result does not mean that the patient has cancer or will definitely develop cancer in their lifetime. Follow up with physicians, healthcare providers and genetic counseling is recommended.

Variant(s) of Unknown Significance (VUS) Detected

Variant(s) of Unknown Significance (VUS) are variants that do not fit into pathogenic, likely pathogenic, or benign classifications according to ACMG and/or other relevant Professional standards, or the criteria for pathogenic or likely pathogenic and benign are contradictory for the variant. There is not enough information at this time to support a more definitive classification of this variant on cancer risk.

Presumed Negative - Likely Benign and/or Benign Variant(s) Detected

The variant identified is not expected to have a major effect on disease; however the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion, but we cannot fully rule out the possibility that new evidence may demonstrate that this variant can contribute to an increased risk.

Negative - No Reportable Variant(s) Detected

The result means that no variant or genetic change known to be associated with or predicted to be associated with, based on current knowledge and test methods, disease(s) was identified. No known pathogenic variant(s) was identified. A benign variant does not cause disease.

Test Inconclusive or Test Failed

Test evaluation was inconclusive. Possible reasons are not enough DNA present in test sample, sample failed quality assurance measures. A new sample submission is recommended.

Gene List									
APC	BRCA1	CDK4	EPCAM	MET	MSH6	NTRK1	PTCH1	RAD51C	STK11
ATM	BRCA2	P16(CDKN2A)	FANCC	MLH1	MUTYH	PALB2	PTEN	RAD51D	TP53
BARD1	BRIP1	CHEK2	HRAS1	MRE11a	NBN	PALLD	RAD50	RET	VHL
BMPR1A	CDH1	ELAC2	MEN1	MSH2	NF1	PMS2	RAD51	SMAD4	

Diseases Covered on the Inherited Cancer Panel		
Cancers	**Syndromes**	**Diseases**
• Breast	• Costello	• Colorectal adenomatous polyposis
• Endometrial	• Cowden	• Familial medullary thyroid cancer
• Ovarian	• Li-Fraumeni	• Familial adenomatous poyposis
• Colorectal	• Lynch	• Fanconi anemia
• Gastric	• Nijmegen breakage	• Hereditary diffuse gastric cancer
• Pancreatic	• Peutz-Jeghers	• Juvenile polyposis
• Prostate	• Von Hippel-Lindau	• Melanoma-pancreatic cancer
• Renal	• Watson	• Multiple endocrine neoplasia type 1 and type 2
• Thyroid/Parathyroid		• Neurofibromatosis type 1
• Melanoma		• Nevoid basal cell carcinoma
• Brain		• Osteosarcoma