



CANCER GENOMICS

**Comprehensive Hereditary Cancer
Risk Assessment**

722 Weiland Road Rochester NY 14626



INTRODUCTION

Hereditary or “[predisposition](#)” genetic testing looks for specific inherited changes (mutations) in a person’s genetic make-up. Genetic mutations can have harmful, beneficial, neutral, or uncertain impacts on health. Mutations that are harmful may increase a person’s chance, or risk, of developing a disease such as cancer. Overall, inherited mutations are thought to play a role in 5-10% of all cancers. These particular disease states are known as hereditary cancers, and proper genetic testing can be used to determine an individual’s risk.

Cancer is a disorder in which normal control of cell growth is lost—causing abnormal proliferation of the effected cells. Inherited genetic mutations can increase a person’s risk of developing cancer through a variety of mechanisms, depending on the function of the mutated gene. Mutations in genes that control the repair of damaged DNA and cell growth are particularly likely to be associated with an increased risk of cancer.

Some people inherit mutation(s) in the germline, potentially allowing for the cancers associated with the mutation(s) to be passed on. These mutation(s) occur in two classes of cellular genes: oncogenes and tumor suppressor genes.

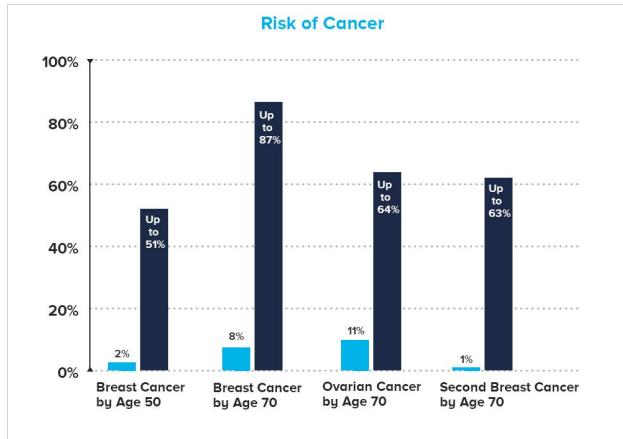
Often, multiple genetic mutations in a single individual are responsible for the development of hereditary cancers.

Cancer can sometimes appear to “[run in families](#)” even if it is not caused by an inherited mutation. For example, a shared environment or lifestyle, such as tobacco use, can cause similar cancers to develop among family members. However, certain patterns, such as the types of cancer that develop, other non-cancer conditions/symptoms that are present, and the ages at which cancers develop, may suggest the cancer is in-fact hereditary in nature and due to inherited genetic mutation(s).

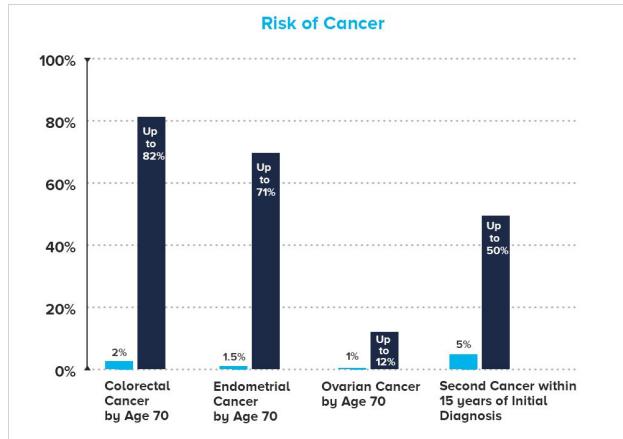
Advancements in gene sequencing technologies have allowed for genetic mutations that cause many hereditary cancers to be well described, and sophisticated mutation screening can confirm whether a cancer is, indeed, the result of an inherited mutation. Genetic testing is also performed to determine whether asymptomatic individuals with family members effected by cancer have inherited the causal genetic mutation.

Approximately 12% of women in the general population will develop breast cancer sometime during their lives. By contrast, according to the most recent estimates, 55 to 65% of women who inherit a harmful BRCA1 gene mutation and 45% of women who inherit a harmful BRCA2 mutation, will develop breast cancer by the age 70. Similarly, 1.3% of women in the general population will develop ovarian cancer sometime during their lives—as opposed to 39% and 11-17% of women with a BRCA1 or BRCA2 mutation present, respectively.

RISK INCREASE OF HEREDITARY BREAST & OVARIAN CANCER, ASSOCIATED WITH BRCA MUTATION



RISK INCREASE OF HEREDITARY COLON & UTERINE CANCER, ASSOCIATED WITH LYNCH MUTATION



EXAMPLES OF COMMON HEREDITARY CANCERS & CANCER SYNDROMES

- ▶ Hereditary Breast and Ovarian Cancer (BRCA1, BRCA2)
- ▶ Colon Cancer (APC, BMPR1A, EPCAM)
- ▶ Uterine Cancer (MLH1, MSH2, EPCAM, MSH6, PMS2)
- ▶ Endometrial Cancer (EPCAM, MLH1, MSH2, MSH6)
- ▶ Lynch Syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM)
- ▶ Cowden Syndrome (PTEN)
- ▶ Li-Fraumeni Syndrome (TP53)



WHO SHOULD GET TESTED

If you suspect that you or someone you know may have an increased risk for cancer, based on factors like abnormal familial cancer history or membership to an at-risk ethnic population (such as Ashkenazi Jewish ancestry), you may want to discuss advanced genomic testing options like our Cancer Genomics with your healthcare provider.

IF ONE OF YOUR FAMILY MEMBERS, HOWEVER DISTANT, HAS BEEN DIAGNOSED WITH CANCER, THERE IS A CHANCE THAT YOU INHERITED A GENE MUTATION THAT NOT ONLY INCREASES YOUR PERSONAL RISK OF DEVELOPING CANCER, BUT MAY ALSO BE PASSED ON TO YOUR OFFSPRING—POTENTIALLY INCREASING THEIR RISK OF DEVELOPING CANCER.

Mutation of the genes known to be associated with an increased risk of developing cancer, like those involved in DNA repair, often result in cancers that appear unique. An individual's familial cancer history may include a number of seemingly distinct cancer cases. This mistakenly leads to the belief that the cancers are un-related, and not caused by a hereditary mutation.

BENEFITS OF TESTING

Those who are carriers of hereditary cancer gene mutations, may be at risk of developing cancer earlier in life, as compared to members of the general population. **The sooner genetic testing is performed, the more likely it is that this increased risk can be managed appropriately.**

Numerous professional practice guidelines describe increasingly stringent monitoring protocol—published specifically for management of patients in which deleterious mutation has been identified. These protocols may suggest the increased use of routine screening tools like mammograms and colonoscopies. Depending on the severity of the identified mutation(s), they may also suggest discussion of more aggressive options like prophylactic surgical intervention. Remember, **your healthcare professional is your most valuable source of information.**

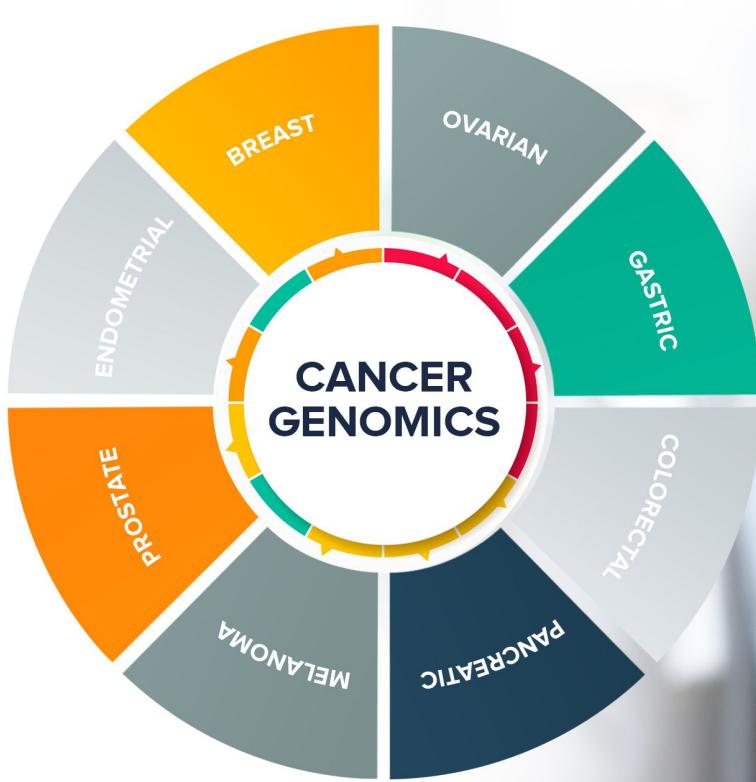
GENES EVALUATED BY CANCER GENOMICS

39 High/Moderate Risk Genes

Breast	ATM BARD1 BMPR1A BRCA1 BRCA2 BRIP1 CDH1 CHEK2 NBN PALB2 PTEN RAD51 RAD51C STK11 TP53
Ovarian	BRCA1 BRCA2 BRIP1 EPCAM MLH1 MSH2 MSH6 PMS2 RAD51C RAD51D STK11 TP53
Endometrial	EPCAM MLH1 MSH2 MSH6 PMS2 PTEN STK11 TP53
Colorectal	APC BMPR1A CDH1 CHEK2 EPCAM MLH1 MSH2 MSH6 MUTYH PMS2 PTEN SMAD4 STK11 TP53
Gastric	APC BMPR1A CDH1 EPCAM MLH1 MSH2 MSH6 PMS2 SMAD4 STK11 TP53
Pancreatic	APC ATM BMPR1A BRCA1 BRCA2 CDK4 CDKn2A EPCAM MLH1 MSH2 MSH6 PALB2 PALLD PMS2 SMAD4 STK11 TP53
Thyroid	HRAS1 MEN1TRK1 RET TP53
Prostate	BRCA1 BRCA2 CHEK2 ELAC2 NBN TP53
Melanoma	BRCA2 CDK4 CDKN2A TP53
Renal	HRAS1 MET TP53 VDL
Brain	TP53 VHL

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





ADDITIONAL HEREDITARY CANCER INFORMATION

BREAST CANCER is the most common cancer in women in developed countries, impacting about 1 in 8 (12.5%) women in their lifetime.¹ The National Cancer Institute (NCI) estimates that approximately **231,840 new cases of female breast cancer and 2,350 new cases of male breast cancer will be diagnosed in the U.S. in 2015.**²

The majority of breast cancers are sporadic, but 5-10% are due to inherited causes. Hereditary breast cancer tends to occur earlier in life than non-inherited sporadic cases, and is more likely to occur in both breasts. The highly penetrant genes, BRCA1 and BRCA2, appear to be responsible for around half of hereditary breast cancer.³⁻⁵ However, additional genes have been discovered that are associated with increased breast cancer risk as well.³⁻⁷ Mutations in the genes included in Cancer Genomics can confer an estimated 20–87% lifetime risk for breast cancer. Some of these genes have also been associated with increased risks for other cancers, such as pancreatic cancer with PALB2.⁸⁻¹²

OVARIAN cancer with BRCA1, BRCA2, RAD51C (and others), and sarcoma with TP53.⁸⁻¹² **OVARIAN CANCER** is the fifth most common cancer among women in developed countries, impacting approximately 1 in 71 (1.4%) women in their lifetime.¹ The NCI estimates that approximately **21,290 new cases of ovarian cancer will be diagnosed and 14,180 ovarian cancer deaths will occur in the U.S. in 2015.**² It is the leading cause of death from gynecologic malignancy, usually characterized by advanced presentation with regional dissemination in the peritoneal cavity. Epithelial ovarian cancer is the most common form, and up to 25% of epithelial cases may be due to inherited gene mutations.^{13,14} BRCA1 and BRCA2 are the most common causes of hereditary ovarian cancer, but several other genes are associated with increased ovarian cancer risk as well.^{11,13,15,16}

COLORECTAL CANCER (CRC) impacts about 1 in 20 (5%) men and women in their lifetime.¹ The NCI estimates that approximately **132,700 new cases will be diagnosed and 49,700 CRC deaths will occur in the U.S. in 2015.**² The majority of CRC is sporadic, but approximately 30% are familial, a subset of which have a strong genetic cause. Lynch syndrome is the most common form of hereditary CRC, but several other genes are associated with increased CRC risk as well.¹⁷

UTERINE CANCER impacts about 1 in 38 (2.6%) women in their lifetime.¹ The NCI estimates that approximately **54,870 new cases of uterine cancer will be diagnosed and 10,170 uterine cancer deaths will occur in the U.S. in 2015.**² Increased risk for uterine cancer has been identified in a number of hereditary cancer syndromes, including Lynch syndrome and Cowden syndrome.

PANCREATIC CANCER impacts about 1 in 65 (1.5%) of men and women in their lifetime.¹ The NCI estimates that approximately **48,960 new cases of pancreatic cancer will be diagnosed in the U.S. in 2015.**² Approximately 95% of pancreatic cancers are pancreatic adenocarcinomas of the exocrine gland (which produces enzymes for food digestion). Neuroendocrine/islet cell tumors of the endocrine gland (a gland that produces insulin and regulates blood sugar) make up the other 5% of pancreatic cancer subtypes. While the majority of pancreatic cancers are sporadic, approximately 5-10% of pancreatic cancer cases are familial, often occurring in families with multiple affected individuals.¹⁸ Multiple genes are associated with increased pancreatic cancer susceptibility.

KIDNEY CANCER impacts about 1 in 60 (1.6%) of men and women in the U.S. in their lifetime and it is the seventh and eighth most common cancer in men and women, respectively.¹ Renal cell carcinoma (RCC) is a complex disease with a diverse spectrum of tumor subtypes, including clear cell or conventional (70-80%), papillary type 1 and type 2 (10-15%), chromophobe (3-5%), and collecting duct (1%).¹⁹ Approximately 3-5% of RCC cases are hereditary²⁰⁻²² and occur as a result of an inherited mutation in one or more genes. Unlike sporadic RCC cases, hereditary RCC is often characterized by earlier disease onset and/or multifocal or bilateral tumors.¹⁹

PARAGANGLIOMAS (PGLs) are often benign, neuroendocrine tumors of the autonomic nervous system originating from the external ganglia. Pheochromocytomas (PCCs) are PGLs that are confined to the adrenal medulla. PGLs are further subdivided into sympathetic and parasympathetic tumors, depending upon their site of origin. Sympathetic PGLs commonly hypersecrete catecholamines and are typically located in the chest, abdomen and pelvis. Parasympathetic PGLs are primarily non-secretory and occur along the nerves in the head, the neck, and the upper mediastinum (termed head and neck PGLs or HNPGLs).^{23,24} The prevalence of PGLs in the U.S. is 1 in 2,500 to 1 in 6,500, although this is likely an underestimate. The average age of diagnosis is between 40-50 years.^{24,25} Approximately 75% of PGL/PCCs are benign; however, morbidity and mortality are associated with high levels of circulating catecholamines, which can lead to hypertension and stroke.^{23,25} Published population studies have found that at least 10-30% individuals with PGL/ PCCs have an inherited germline mutation in one of the known susceptibility genes.

PATIENT PROFILE SHEET

PRODUCT REQUESTED

CGX
 PGX

Patient Id: _____

Green valley Healthcare 722 Weiland Road Rochester NY 14626

PATIENT INFORMATION

First Name: * _____
 Last Name: * _____
 Best Phone #: * _____
 Address: * _____
 City: * _____
 State: * _____
 Zip: * _____
 Date of Birth: * _____
 Gender: * Male Female
 Race/Ethnicity: * _____
 HT/WT : * _____ / _____
 Allergies: _____
 Medicare Claim # * _____

SPECIAL NOTES

A) : _____
 B) : _____
 C) : _____
 D) : _____

PHARMACY

Pharmacy Insurance Name: _____
 ID #: _____
 BIN #: _____
 PCN #: _____
 GROUP #: _____
 History / Reason: _____
 Area(s) of Issue: _____
 Treatments: _____

QUESTIONNAIRE

TYPE*

TYPE

AGE DIAGNOSED

IF DECEASED,

TYPE OF CANCER

MEDICATION LIST

PERSONAL HISTORY:				AGE AT DEATH	* Breast	1. _____
MOTHER:	,				* Ovarian	
FATHER:	,				* Digestive	
DAUGHTER:	,				- Pancreatic	2. _____
SON:	,				- Colon	3. _____
BROTHER:	,				- Rectal	4. _____
SISTER:	,				- Gallbladder	
NEPHEW:	,				- Intestinal	
NIECE:	,				- Stomach	5. _____
UNCLE:	,				- Esophageal	6. _____
AUTN:	,				- Throat	7. _____
MOM'S FATHER:	,				- Liver	8. _____
MOM'S MOTHER:	,				* Lung	9. _____
DAD'S FATHER:	,				- Other Respiratory	10. _____
DAD'S MOTHER:	,				* Genital	11. _____
OTHER :	,				- Cervical	12. _____
OTHER :	,				- Uterine	13. _____
OTHER :	,				- Endometrial	14. _____
					- Other Genital Organs	15. _____
					* Prostate	16. _____
					* Testicular	17. _____
					* Kidney	18. _____
					* Bladder	19. _____
					- Urinary Tract	
					* Leukemia	
					* Lymphatic	
					* Other Organ Systems	

Rep ID: _____



NCCN GENETIC TESTING CRITERIA FOR HEREDITARY BREAST & OVARIAN CANCER SYNDROME

Family history of a known BRCA1 or BRCA2 mutation

Personal history of breast cancer diagnosed at age 45 or younger

Personal history of breast cancer diagnosed at age 50 or younger with one of the following:

- ◆ ≥1 close blood relative(s) with breast cancer at any age
- ◆ An unknown or limited family history
- ◆ Two breast primaries, the first of which was diagnosed at age 50 or younger

Personal history of a triple negative breast cancer diagnosed at age 60 or younger

Personal history of epithelial ovarian, fallopian tube, or primary peritoneal cancer at any age

Personal history of male breast cancer at any age

Personal history of breast cancer at any age with one or more of the following:

- ◆ ≥1 close blood relative(s) with breast cancer diagnosed at age 50 or younger
- ◆ ≥2 close blood relatives with breast cancer at any age
- ◆ ≥1 close blood relative(s) with epithelial ovarian/fallopian tube/primary peritoneal cancer
- ◆ Close male blood relative with breast cancer
- ◆ ≥2 close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age
- ◆ For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) no additional family history may be required*
- ◆ Personal history of pancreatic cancer or prostate cancer (Gleason score ≥7) at any age with ≥2 close blood relatives with breast and/or ovarian and/or pancreatic and/or prostate cancer (Gleason score ≥7) at any age
- ◆ For pancreatic cancer, if Ashkenazi Jewish ancestry, only one additional affected relative is needed
- ◆ Unaffected patient with a first or second-degree relative who meets any of the above criteria
- ◆ Testing unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing

*Testing for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Full sequencing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or other criteria are met.

NCCN TESTING CRITERIA FOR LYNCH SYNDROME (ALSO KNOWN AS HNPCC) & POLYPOSIS SYNDROMES

Criteria for Lynch Syndrome genetic testing

Family history of a known Lynch syndrome mutation (MLH1, MSH2, MSH6, PMS2, EPCAM)

Patient has a cancer on the Lynch syndrome tumor spectrum that demonstrates microsatellite instability (MSI-H) or absence of a mismatch repair protein via immunohistochemistry (IHC)

Patient diagnosed with endometrial cancer at age 50 or younger

Meets Revised Bethesda Guidelines:

- ▶ Patient has a personal history of colorectal cancer AND meets one of the following:
- ▶ Patient diagnosed at age 50 or younger
- ▶ Presence of synchronous or metachronous Lynch syndrome-associated cancers, regardless of age
- ▶ Patient diagnosed at age 60 or younger with a colorectal cancer that demonstrates MSI-high histology (tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern)
- ▶ One or more first-degree relatives with a Lynch syndrome-associated cancer, with one of the cancers being diagnosed at age 50 or younger
- ▶ Two or more first- or second-degree relatives with Lynch syndrome-associated cancers, regardless of age

Meets Amsterdam Criteria:

- ▶ Patient and at least two close relatives who all have or have had a cancer associated with Lynch syndrome AND all of the following criteria must be met:
- ▶ One must be a first-degree relative of the other two;
- ▶ At least two successive generations must be affected;
- ▶ At least one of the cancers should be diagnosed at age 50 or younger;
- ▶ Familial adenomatous polyposis (FAP) should be excluded

Unaffected patient with a close relative who meets any of the above criteria

- ▶ Testing unaffected individuals when no affected family member is available should be considered; significant limitations of interpreting test results should be discussed

Criteria for Adenomatous Polyposis (APC and MUTYH) genetic testing

Family history of a known APC mutation or two (biallelic) MUTYH mutations

Personal history of a total of >10 adenomas

Personal history of a desmoid tumor

Other Polyposis Syndrome Genetic Testing Criteria

Personal or family history of multiple GI hamartomatous polyps or serrated polyps



PHARMACOGENOMICS (PGX Advantage)

PHARMACOGENOMICS (PGX) testing allows a medical provider to identify an individual as a slow, intermediate, fast, or ultra fast metabolizer of over 200 different drugs across 30 different drug classes. Data with respect to a patient's genotype is used to try and maximize drug efficacy while minimizing adverse drug effects and drug interactions.

This test is appropriate for patients who are taking one or more medications, especially those suffering from cardiovascular disease and mental health disorders.

MEDICATION MANAGEMENT CHECKLIST:

PSYCH

BIPOLAR

- ➔ Lithium
- ➔ Abilify
- ➔ Seroquel
- ➔ Clonazepam
- ➔ Latuda
- ➔ Valium
- ➔ Ativan
- ➔ Zyprexa

DEPRESSION

- ➔ Xanax / Alprazolam
- ➔ Zoloft / Cetirizine
- ➔ Celexa / Citalopram
- ➔ Paxil / Paroxetine
- ➔ Cymbalta / Duloxetine
- ➔ Klonopin / Clonazepam
- ➔ Wellbutrin / Bupropion
- ➔ Prozac / Fluoxetine

- ➔ Lexapro / Escitalopram
- ➔ Amitriptyline
- ➔ Viibryd
- ➔ Trazodone

CARDIAC

ANGINA

- ➔ NITROs

HEART ATTACK

- ➔ Just take patients statement that they had a heart attack/myocardial infarction

ATHEROSCLEROSIS (High Cholesterol)

STATINS :

- ➔ Lipitor / Atorvastatin
- ➔ Crestor / Rosuvastatin
- ➔ Zocor / Simvastatin
- ➔ Pravachol / Pravastatin
- ➔ Mevacor / Lovastatin

IRRITANT CONTACT DERMATITIS

(Skin Rash)

Just take patients statement that they had a skin rash at some point

MISCELLANEOUS COMMON DRUG/DISEASE STATES

ACID REFLUX

- ➔ Prilosec / Omeprazole
- ➔ Zantac / Ranitidine
- ➔ Nexium / Esomeprazole

FIBROMYALGIA

- ➔ Neurontin / Gabapentin

DERMATITIS

- ➔ Triamcinolone
- ➔ Clobex
- ➔ Fluocinonide
- ➔ Betamethasone



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