IntelligeneCG℠
Cancer Genomics

Kansas Biosciences Authority
10900 S Clay Blair Blvd, Suite 1400
Olathe, KS - 66061

www.intelligene-cg.com
info@intelligene-cg.com

Phone: 913 258 2300

Report Guideline

IntelligeneCG℠
Cancer Genomics

Understand the results:

Your Hereditary Cancer genetic test can yield 3 possible results: **Negative, Positive,** or **Variant of Uncertain Significance (VUS)**.

Explanations of the possible results:

Negative Report - Some individuals have known harmless changes in their genome (DNA). These changes are normal variations that make us all a bit different from one another and are also called polymorphisms. These changes are classified as likely benign or benign variants and will result in a negative report. If no mutations are detected then the report will also be negative.

Positive Report - Other individuals have a genetic change that has been reported as harmful. These changes may increase your risk to develop certain diseases or cancers. These changes are reported as harmful because they have previously and repeatedly been found to be associated with certain medical problems such as a specific type of cancer. These changes are classified as pathogenic or likely pathogenic mutations and will result in a positive report. In these cases, it may be recommended that other family members be tested for this mutation

VUS (Variant of Uncertain Significance) - Some genetic changes cannot be categorized as potentially disease causing or harmless at this time because there currently isn't enough data or information known about the variant. These variants will likely be re-classified into one of the other categories (likely benign, benign, likely pathogenic or pathogenic) as additional information is obtained. Once the variant has been re-classified, IntelligeneCG will update the information in the report and notify the ordering provider so that the patient can be contacted. Therefore, it is very important to stay in contact with the provider who orders genetic testing..

I have a Negative Report. What that does mean?

A negative report means that the laboratory did not find a mutation or variant in any of the genes tested that are potentially disease causing or are of unknown significance. For the individuals tested that have not been diagnosed with cancer (screening/predictive testing), a negative test result means that the individual is at low or average risk of developing the specific type of cancer or cancers in question in comparison to the general population. You should continue to follow your doctor's recommendations for cancer screening and medical care.

For men or women that have been diagnosed with cancer, testing negative means that there may be other non-genetic factors that caused the cancer, in which case, the individual's children and direct family members are not at higher risk for cancer than the general population. Alternatively, there may be a mutation or variant in a gene that was not tested. Approximately, 10% to 15% of cancers are caused by hereditary factors. You should continue to follow your doctor's recommendations for cancer treatment and medical care

My report has a Variant of Unknown Significance (VUS), what does that mean?

A VUS is a variation in a genetic sequence (DNA) whose association with disease risk is unknown. It is also called an unclassified variant, variant of uncertain significance, and variant of unknown significance. In other words, it is an alteration in the gene sequence with unknown consequences on the function of the gene product (protein) or on the association to disease. A VUS is neither good nor bad in terms of the tested individual's future health, and as any other results, the individual's medical management and possible further genetic testing should be based on the individual's personal medical history and on the their family's medical history, not on the VUS result. Classification of variants can change as new information and data becomes available, so it is important to stay in touch with the provider that ordered the test and with the laboratory to see if the VUS has been re-classified.

I have a Positive report. What does that mean?

A positive test result means that the laboratory found a specific genetic alteration (or mutation) that is associated with an increased risk of developing (or having) a hereditary cancer syndrome. A positive test result may:

- Confirm a hereditary cancer syndrome diagnosis;
- Indicate an increased risk of developing certain cancer(s) in the future;

Summary of Medical Management (age to begin)[34]

Management could include any of the following. Please refer to published guidelines for complete management recomendations.

mammography and breast MRI (25), colonoscopy and upper endoscopy (late teens), CT or MRI enterography (8-10), pancreatic surveillance (EUS/MRCP) and/or other clinical trials for screening (30-35), pelvic exam/pap smear/transvaginal ultrasound (18-20), testicular exams (10)[2,3]

mammography and breast MRI (35), endoscopy with biopsy (16), gastrectomy (20),

colonoscopy and upper endoscopy (15), monitor for rectal bleeding and/or anemia[2,6]

colonoscopy and upper endoscopy (15), monitor for rectal bleeding and/or anemia[2,6] brain MRI, contrast echocardiogram, and chest CT may be recommended[7]

mammography and breast MRI (30),[8,10] male breast screening,[1,10] pancreatic surveillance (EUS/MRCP) and/or other clinical trials for screening[3,11]

mammography and breast MRI (30),[8,12] individualized colorectal screening,[13,25] prostate screening (40),[9,14,24]

mammography and breast MRI (30),[8,15] pancreatic surveillance (EUS/MRCP), and/or other clinical trials for screening[3,16]

individualized breast and prostate screening/rik reduction,[8,17] prostate screening (40)[9,18,24]

individualized breast and screening/rik reduction,[1,8,19]

Information listed in this table is subject to change per guideline updates.

14. Cybulski C, et al. A large germline deletion in the CHEK2 kinase gene is associated with an increased risk of prostate cancer. J Med Genet. 2006 43:863-6. PMID17085682.
15. Thonpson D, et al. Cancer risks and mortality in heterozygous ATM mutation carriers. J Natl Cancer Inst. 2005 97:813-22. PMID: 15928302. 16. Roberts NJ, et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov.2012 2:41-6. PMID: 22585167.
17. Steffen J, et al. Germline mutations 657del5 of the NBS1 gene contributes significantly to the incidence of breast cancer in Central Poland. Int J Cancer. 2006 119:472-5. PMID: 16770759.
18. Cybulski C, et al. An inherited NBN mutation is associated with poor prognosis prostate cancer. Br J Cancer. 2013 108:461-8. PMID: 23149842.
19. De Brakeleer S, et al. Cancer predisposing missense and protein truncating BARD1 mutations in non-BRCA1 or BRCA2 breast cancer families. Hum Mutat. 2010 31:E1175-85. PMID: 20077502.
20. Seal S, et al. Breast Cancer Susceptibility Collaboration (UK). Truncating mutations in the Fanconi Anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles. Nat Genet. 2006 38:1239-41. PMID 17033622.
21. Rafnar T, et al. Mutations in BRP1 confers high risk of ovarian cancer. Nat Genet. 2011 43:1104-7. PMID: 21964575.
22. Society of Gynecologic Oncology Clinical Practice Statement: Next Generation Cancer Panels versus Gene by Gene Testing. March 2014.
23. Society of Gynecologic Oncology Clinical Practice Statement: Genetic Testing for Ovarian Cancer. March 2014.
24. Carter HB, et al. American Urological Association. Early Detection of Prostate cancer: AUA Guideline. 2013.
25. Provenzale D, et al. NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening. V 1.2014. May 19.
26. Tung N et al. Prevalence of gene mutations among hereditary breast and ovarian cancer patients using a 25-gene panel. San Antonio Breast cancer Symposium 2013
27. Yurgelun MB, et al. Multi -gene panel testing in patients suspected to have Lynch syndrome. ASCO 2014.
28. Robson ME, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. J Clin Oncol. 2010 28:893-901. PMID: 20065170.

Clinical Management Guideline

Gene	Maximun Lifetime Cancer Risk in %								
	Breast	Ovarian	Colorrectal	Endometrial	Melanoma	Pancreatic	Gastric	Prostate	Other Cancers
STK11	● 50	● 21	● 39	● 9		● 36	● 29		● 17
CDH1	● 52		○ PE				● 80		
BMPR1A			● 50			○ R,E	● 21		○ R,E
SMAD4			● 50			○ R,E	● 21		○ HHT
PALB2	● 40					○ E			
CHEK2	● 48		○ 9.5					○ 44	
ATM	● 52					○ E			
NBN	○ 30							○ I	
BARD1	○ E								
BRIP1	○ 20	● 8.3							
RAD51C	○ PE	○ 6.5							
RAD51D		○ 7							

E = Elevated Risk **P** = Possibly Elevated Risk **R,E** = Rare but Elevated Risk **EYA** = Elevated Risk, Young Age of Diagnosis
I = Increased Risk **HHT** = Hereditary Hemorrhagic Telangiectasia ● High Risk ○ Elevated Risk

1. Daly M, et al. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment Breast and Ovarian. V 1.2014. February 28.
2. Provenzale D, et al. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment Colorectal V 2.2014. May 19.
3. Canto MI, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013 62:339-47. PMID: 23135763.
4. Kefford RF, et al. Counseling and DNA testing for individuals perceived to be genetically predisposed to melanoma: A consensus statement of the Melanoma Genetics Consortium. J Clin Oncol. 1999 17:3245-51. PMID: 10506626.
5. Coit DG, et al. NCCN Clinical Practice Guidelines in Oncology: Melanoma. V 4.2014. April 22.
6. Larsen Haldle J, Howe JR. Juvenile Polyposis Syndrome. In: Pagon RA, et al., editors. Gene Reviews. 2011
7. McDonald J, et al. Hereditary hemorrhagic telangiectasia: an overview of diagnosis, management, and pathogenesis. Genet Med. 2011 13:607-16. PMID: 21546842.
8. Bevers TB, et al. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Screening and Diagnosis. V 2.2013. July 3.
9. Carrol PR, et al. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection. V 1.2014. March 10.
10. Casadei S, et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. Cancer Res. 2011 71:2222-9. PMID: 21285249.
11. Slater EP, et al. PALB2 mutations in European familial pancreatic cancer families. Clin Genet. 2010 78:490-4 PMID: 20412113.
12. Weischer M, et al. CHEK2 1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. J Clin Oncol. 2012 30:4308-16. PMID: 23109706.
13. Xiang HP, et al. Meta-analysis of CHEK2 1100delC variant and colorectal cancer susceptibility. Eur J Cancer. 2011 47:2546-51. PMID: 21807500

- Show that someone carries a particular genetic change that does not increase their own risk of cancer but that may increase the risk in their children if they also inherit an altered copy from their other parent (that is, if the child inherits two copies of the abnormal gene, one from their mother and one from their father);
- Suggest a need for further testing;
- Provide important information that can help other family members make decisions about their own health care.

Risk management decisions are very personal, and the best option depends on many factors. For those individuals that have not been diagnosed with a hereditary cancer syndrome, screening tests, such as mammograms or colonoscopies, typically begin earlier than the general population and are often more frequently performed. It is important the tested individual discusses their options with their doctor. Knowing about the genetic mutation earlier will allow the doctor to modify the standard of care for that patient and design an effective personalized health management plan to avoid the onset of the disease, treat the disease more effectively and/or reduce the severity of treatment side effects.

What is genetic counseling and do I need it?

Genetic testing can reveal information not only about the person being tested but also about that person's relatives. The presence of a harmful genetic mutation in one family member makes it more likely that other blood relatives may also carry the same mutation. A conversation with a genetic counselor will help patients and their family members to better understand the complicated choices they may face.
A genetic counselor is a healthcare professional trained in genetics that can help an individual and their family members to understand their test results and what the impact on their health management may be.
Genetic counseling is strongly recommended before and after a genetic test. A genetic counselor will usually conduct risk assessments based on a detailed review of the individual's personal and family medical history. Genetic counseling will also include discussions about issues such as:

- Whether genetic testing is appropriate and which specific test(s) might be indicated;
- The medical implications of a positive or a negative test result;
- The possibility that a test result might not be informative—that is, that the information may not be useful in making health care decisions;
- The psychological risks and benefits of learning one's genetic test results;
- The risk that other family members may also have this mutation and/or the risk of passing a genetic mutation (if one is present in a parent) to children.

How do I get genetic counseling at IntelligeneCG?

IntelligeneCG laboratory offers the patients who get tested through our laboratory up to two consultations with a Genetic Counselor, one pre- and one post-test, at no charge. The topics discussed with the counselor may include the possible test results the patient can expect, which family members should consider genetic testing and what the patient's genetic test results mean. IntelligeneCG also has professionals available to help an ordering provider decide which patients may be good candidates for genetic testing and which of the genetic tests we provide may be appropriate for each of those patients. **Contact us at (913) 258-2300 to schedule a genetic counseling appointment or discuss our available test options.**

What shall I do after I get tested at IntelligeneCG?

Once the test is performed, you might consider:

- Scheduling an appointment with your doctor or the healthcare provider that ordered the test to obtain a copy of your report;
- Discussing the results with your doctor or healthcare provider. They will assist in the development of a health management plan;
- Scheduling a consultation with a genetic counselor. Call IntelligeneCG at (913) 258-2300 to schedule an appointment with our genetic counseling team;
- Calling IntelligeneCG laboratory at at (913)258-2300 once an year, if your results include a VUS, to obtain an updated copy of your report if any change on the VUS classification occurred.
- Consulting your healthcare provider and/or doctor to update your management plan as new information on cancer management becomes available.

Clinical Management Guideline

Gene	Maximun Lifetime Cancer Risk in %								
	Breast	Ovarian	Colorrectal	Endometrial	Melanoma	Pancreatic	Gastric	Prostate	Other Cancers
BRCA1	● 87	● 44				○ E		○ 16	
BRCA2	● 84	● 27			○ E	● 7		○ 20	
MLH1		● 12	● 82	● 60		○ 6	● 13		● 9
MSH2		● 12	● 82	● 60		○ 6	● 13		● 9
MSH6		○ E	● 69	● 71		○ E	○ E		○ E
PMS2		○ E	● 20	● 15		○ E	○ E		○ E
EPCAM		● 12	● 82	● 60		○ 6	● 13		● 9
APC			● 99			○ PE	○ E		● 12
MUTYH *(2 copies)*			● 100						● 5
CDKN2A *(p16INK40)*					● 76	● 17			
CDKN2A *(p14ARF)*					● 76	○ E			
CDK4					● 76	○ E			
TP53	● EYA	○ EYA	○ EYA	○ EYA	○ EYA	○ EYA	○ EYA	○ EYA	● EYA
PTEN	● 85		● 16	● 28	● 6				● 38

E = Elevated Risk **P =** Possibly Elevated Risk **R,E =** Rare but Elevated Risk **EYA =** Elevated Risk, Young Age of Diagnosis
I = Increased Risk **HHT =** Hereditary Hemorrhagic Telangiectasia ● High Risk ○ Elevated Risk

Summary of Medical Management (age to begin)[34]

Management could include any of the following. Please refer to published guidelines for complete management recomendations.

breast awareness (18), clinical exams (25), breast MRI (25), mammogram (30), mastectomy, salpingo-oophorectomy (35-40), male breast surveillance (35), CA-125 and transvaginal ultrasound (30), breast/ovarian chemoprevention, prostate screening (40)[1]

pancreatic surveillance endoscopic ultrasound/magnetic resonance cholangiopancreatography (EUS/MRCP) and/or other clinical trials for screening, consider whole-body skin exams (BRCA2 only) [1]

colonoscopy (20-25, or 25-30 for MSH6/PMS2), hysterectomy, salpingo-oophorectomy, endometrial sampling, CA-125 and transvaginal ultrasound, EGD (30-35), urinalysis (25-30)[2] (excluding PMS2 & MSH) pancreatic surveillance (EUS/MRCP) and/or other clinical trials for screening[3]

colonoscopy/sigmoidoscopy (10-15), colectomy, chemoprevention, upper endoscopy and MRI/CT (25-30), thyroid exam/ultrasound (late teens) abdominal palpation[2]

colonoscopy (25-30), colectomy, chemoprevention, upper endoscopy (30-35)[2]

skin protection, skin exams (10),[4,5] pancreatic surveillance (EUS/MRCP) and/or other clinical trial screening [3]

skin protection, skin exams (10),[4,5]

breast awareness (18), clinical exams (20), breast MRI (20) mammography (30), mastectomy, colonoscopy (25), skin exams, physical/neurological exams, individualized additional other organ-targeted surveillance[1]

breast awareness (18), clinical exams (20), breast MRI (30-35) mammography (30-35), mastectomy, endometrial biopsy/ultrasound (30-35), hysterectomy, thyroid ultrasound (18), colonoscopy (35), renal ultrasound (40)[1]

Information listed in this table is subject to change per guideline updates.