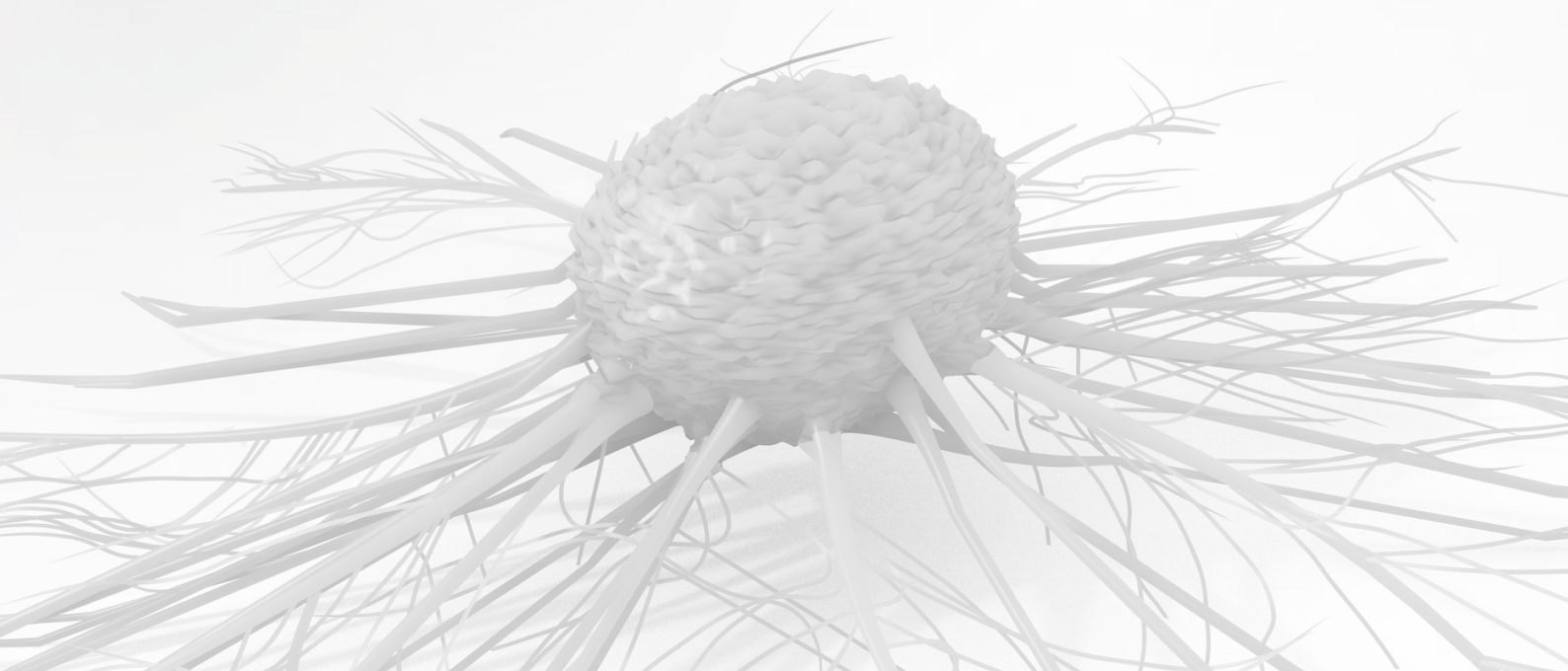
CENTOGENE

THE RARE DISEASE COMPANY



CentoCancer™

Strive for the most complete information

CENTOGENE offers CentoCancer™ - a specially designed cancer-risk-related panel, created for all patients with a positive family history of cancer.

Dear colleague,

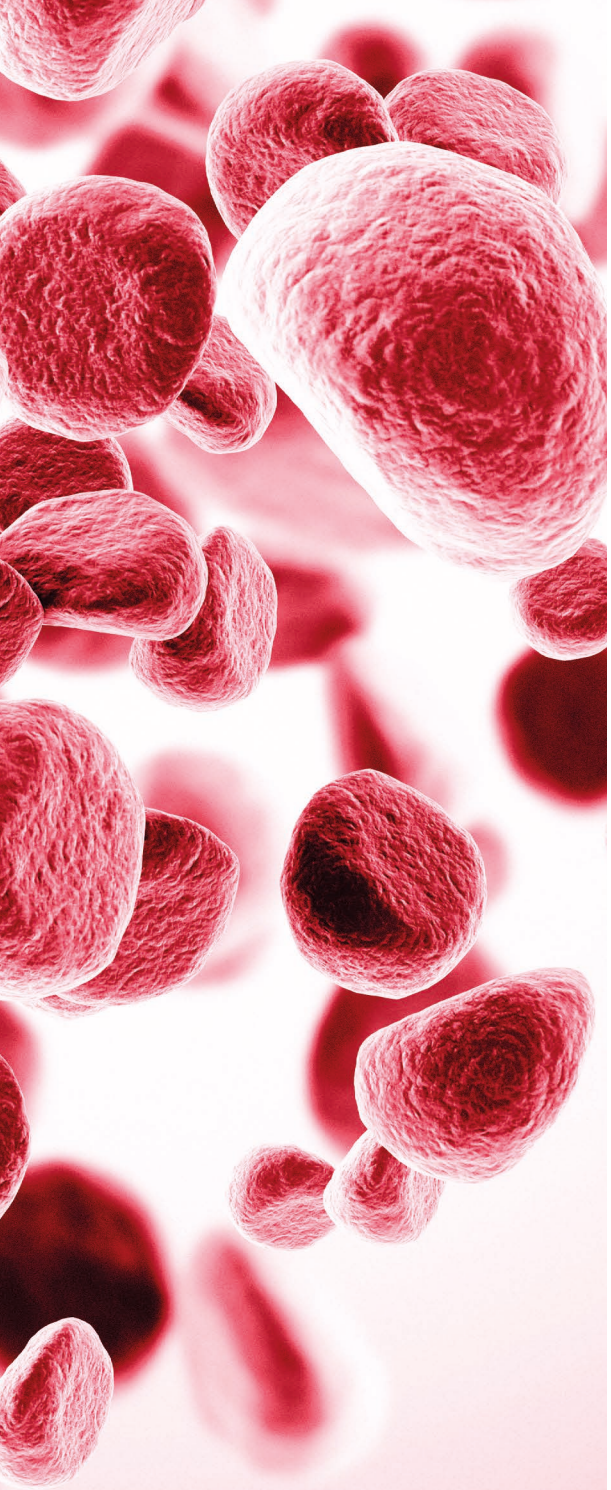
The correct profiling of mutations in cancer genes represents a fundamental step in the diagnosis and treatment of these malignancies. Certain mutations result in increased risk for hereditary cancer, and lead to development of breast, ovarian, colon, gastric, renal or other cancers.

BRCA1 and BRCA2 mutations are the most common causes of hereditary breast and ovarian cancers, but other genes are also associated with hereditary malignancies. For example mutations in genes involved in the repair of double-stranded DNA breaks, such as ATM, BRIP1, CHEK2, PALB2 and RAD51D, represent further mechanisms of hereditary carcinogenesis.

CENTOGENE is a global leader in the diagnosis of hereditary disorders testified by multiple accreditations like ISO, CAP, CLIA. Our experience combined with our scientific expertise and medical competence allows the application of state-of-the-art technologies and the development of a unique, multi-ethnic mutation database, CentoMD®. We would like to offer you a complete answer to achieve the best possible therapeutic approach for your patients.

CENTOGENE offers CentoCancer™ - a specific and sensitive panel with highly penetrant cancer genes.

Prof. Arndt Rolfs, MD
Chief Executive Officer



Introduction

CENTOGENE´s CentoCancer™ is a 31-gene panel that identifies an elevated risk of significant hereditary cancers, including breast, ovarian, gastric, colon, endometrial, prostate, pancreatic, renal, liver, and skin cancer.

CentoCancer™ addresses people with an identified cancer where the type of cancer or the family history warrant an extended NGS panel analysis, or those who have no family history, no positive anamnesis and would like to know their risk of inherited cancer.

CentoCancer™ includes some of the most relevant genes such as: APC, ATM, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, NBN, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, and TP53. To have an overview of all genes included in the panel, see next page.

Each gene in CentoCancer™ has been carefully selected based on its risk potential in the development of one of the following cancers: **breast, ovarian, colorectal, gastric, bowel, endometrial, pancreatic, melanoma, renal, and prostate cancer.**

CentoCancer™ genes

APC, ATM, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, NBN, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53

NGS bidirectional sequencing is used for all genes in the panel, including 100% coding region (all exons), exon/intron boundaries +/-10bp, with validation for every genetic variant detected.

Who should consider CentoCancer™ for genetic testing?

- Affected individuals with an increased risk of hereditary cancer indicated by family history, multifocal tumor development, or early onset.
- Non-affected individuals with a positive family history.

Hereditary cancers

Breast cancer

Breast cancer is the most common form of cancer affecting women, with an estimated lifetime risk of ~12.5% to develop a tumor. In women, deaths resulting from cancer are caused primarily by lung cancer with breast cancer as the 2nd leading cause of fatality. Roughly one in every eight[8] women will find out they have breast cancer at some point in their lifteimes[1,2]. Mutations in the BRCA1 and BRCA2 genes account for the majority of mutations that increase the risk of these cancers. In addition to these two genes, mutations in several others genes can also convey significant increases in risk of developing malignancies in other hereditary cancer syndromes.

Breast cancer risk is associated with a number of risk factors, including female gender, age, caucasian ethnicity, excess weight and increased height, hormone therapy after menopause, radiation therapy, early menarche, late menopause, no or late first birth, alcohol consumption, benign breast conditions, exposure to certain environmental substances (organ chlorines, tobacco). However, the strongest risk factor known today is a genetic predisposition due to changes in genes associated with breast cancer. Breast cancers cluster in affected families and 5-8% percent[1,2,4] are associated with inherited gene mutations. These cancers are described as hereditary breast cancers and tend to develop earlier in life than do sporadic cases, and new primary tumors are more likely to develop in both breasts.

An estimated 5-10% of all breast cancers are directly attributable to inherited gene mutations, most often to mutations in the BRCA1 or BRCA2 genes[1,2,4]. Mutations in the genes ATM, TP53, CHEK2, PTEN, CDH1, and STK11 also increase the risk of breast cancer, but these are much rarer and do not increase the risk as much as the BRCA genes. All of these genes are tumor-suppressor genes that in one way or another inhibit cell proliferation. Because generally one copy of a tumor-suppressor gene is sufficient to control cell proliferation, both alleles of a tumor-suppressor gene must be lost or inactivated in order to promote tumor development. An inherited mutation in a predisposed tumor suppressor gene can initiate by chance a genetic alteration of the so far unaffected allele. A loss of both gene copies is the first step in tumor development.

Ovarian cancer

Ovarian cancer is the fifth most common cancer among women in developed countries, affecting approximately 1 in 71 (1.4%)[2] women in their lifetimes. 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.

BRCA1 and BRCA2 are the most common causes of hereditary ovarian cancer, but several other genes are associated with an increased ovarian cancer risk as well.

Colorectal cancer

Colorectal cancer (CRC) affects about 1 in 20 (5%)[17] men and women in their lifetimes. The majority of CRC cases are 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 additional cancer syndromes are also associated with increased CRC risk, such as familial adenomatous polyposis (FAP), MYH associated polyposis (MAP), and juvenile polyposis syndrome (JPS).

Lynch syndrome is also called hereditary non polyposis colon cancer (HNPCC). It is caused by faults in the MLH1, MSH2, MSH6, and PMS2 genes. Lynch syndrome is rare, accounting for between 2 and 5 of every 100 bowel cancers (2-5%)[17]. Between 70-90% of people with Lynch syndrome[17] develop bowel cancer. Most bowel cancers occur under the age of 50. People with Lynch syndrome also have an increased risk of developing other cancers, including womb and ovarian cancer in women. Other cancers that Lynch syndrome may cause include stomach, small bowel, and gallbladder.

FAP is caused by a fault in the APC gene. It is a rare disease that causes 1 in 100 bowel cancers (1%)[17]. Mutations in the APC gene can cause hundreds of non cancerous (benign) growths called polyps to develop in the bowel at a young age. Over time, these polyps can develop into cancer. The average age of bowel cancer in people with FAP is 35 years[17]. MAP is caused by faults in the MYH gene. It is much rarer than FAP and is caused by homozygous mutations in the MYH gene. People with MAP develop polyps and are likely to develop bowel cancer before the age of 50[17].

Juvenile Polyposis Syndrome (JPS) is linked to the BMPR1A and SMAD4 genes. A mutation in one of these genes can cause polyps in the stomach and small bowel. An increased number of polyps leads to an increased risk of developing bowel cancer.

Bowel cancer

Bowel cancer affects ~5% of people worldwide during their lifetimes. Roughly 1 in 20 cases of bowel cancer (5%)[17] occur in people who have other family members with bowel cancer.

Uterine cancer

Uterine cancer affects about 1 in 38 (2.6%)[19] women in their lifetimes. An increased risk of uterine cancer has been identified in a number of hereditary cancer syndromes, including Lynch syndrome and Cowden syndrome.

Pancreatic cancer

Researchers estimate that around 1-2%[7] of the population will develop pancreatic cancer at some point in their lifetimes. Pancreatic cancer is caused by germline mutations in about 10 in 100 cases (10%)[6]. Cancer of the pancreas can also develop as part of one of the family cancer syndromes when different types of cancer occur in the same family. Mutations in other genes included in CentoCancer™ can increase the risk of other types of cancer as well as pancreatic cancer.

Prostate cancer

Prostate cancer is the most common cancer in men and it is most common over the age of 70[5,6]. Scientists have found a number of genes that increase the risk of prostate cancer, including BRCA1, BRCA2.

Melanoma

Melanoma is a type of cancer that usually occurs in the skin. The main cause of melanoma is too much exposure to ultraviolet light, from sunlight or from artificial sources such as sun beds. About 1 in 10 people (10%)[60] who have melanoma have a strong family history of the disease. People with a family history of melanoma are at increased risk.

Renal cancer

Renal cancer affects the kidneys and is most common in older persons with a positive family history. There are a number of inherited conditions that increase the risk of developing renal cancer, including Birt-Hogg-Dube (BHD) syndrome caused by mutations in the FLCN gene, von Hippel-Lindau disease caused by mutations in the VHL gene, and others.

Liver cancer

Liver cancer, also called hepatoma, is the most common form of liver tumor in adults caused by mutations in several genes. It is more frequent in people affected with chronic liver diseases.

Increased risk of hereditary cancers

Carriers of inherited pathogenic variants in some cancer associated genes have an increased risk of developing tumors in other tissues. The affected tissues and the lifetime risk of developing cancer in these tissues is dependent on the affected gene. For pathogenic variants in BRCA1, the risk of developing breast cancer is estimated to be 51% up to age 50 and 87% to age 80. In addition, BRCA1 carriers have a 23% increased risk of developing ovarian cancer by age 50 and a 44% risk by age 80[46]. There is also an increased risk of pancreatic cancer, and male carriers have an increased risk of breast and prostate cancer. In comparison, carriers of pathogenic STK11 variants have a 45-50% risk of breast cancer and 18-21% of ovarian cancer until the age of 80, but additionally also have an increased risk of colorectal, gastric, endometrial, small bowel, testicular cervical, and lung cancers[47,48]. The identification of a pathogenic variant in a specific gene can therefore be associated with a risk of cancer of other tissues which may not be noticed, and surveillance and treatment programs should also be tailored with regard to an affected cancer gene.

Screening Options

Early detection of hereditary cancer significantly prolongs survival and offers many opportunities for early treatment or management. In addition to the cancer prevention programs generally recommended, people with an increased risk due to inherited mutations in cancer genes should be offered additional programs according to guidelines regarding the risks for breast and other tumors.

Risk reduction

Patients with a significantly increased cancer risk due to an inherited variant should be informed about the possibilities of individual risk reduction. Toxic substances should be avoided and an optimal therapeutic approach, including possible surgical preventive measures, can be discussed.

APC

Gene name: Adenomatous polyposis coli gene (APC), also known as deleted in polyposis 2.5 (DP2.5)

OMIM gene: 611731

Associated syndromes:

- Adenomatous polyposis coli (OMIM: 175100) (autosomal dominant): Characterized by predisposition to cancer and development of hundreds to thousands of adenomatous polyps of the colon and rectum (familial adenomatous polyposis, FAP). Gardner syndrome is a variant of FAP in which desmoid tumors, osteomas, and other neoplasms occur together with multiple adenomas of the colon and rectum.

- Desmoid disease (OMIM: 135290) (autosomal dominant): Extraintestinal manifestation of FAP resulting from abnormal growth of connective tissue that are locally aggressive.

Protein:

The APC protein has multiple cellular functions and interactions, including roles in signal transduction in the Wnt-signaling pathway, mediation of intercellular adhesion, stabilization of the cytoskeleton, and possibly regulation of the cell cycle and apoptosis. The APC protein associates with beta-catenin and regulates genes expression, promoting proliferation and differentiation of cells.

Cancer type	General population	Cancer risk for APC mutation carriers
Female breast cancer	Lifetime risk: 5-10%[1,2]	For age >60: increased[17]
Colorectal cancer	Lifetime risk: 5-6%[17] For age men<30 years: 0.07-0.96% For age <40 years: 0.26-2% For age <50 years: 0.67-3.27% For age <60 years: 1.22-4.04% For age <70 years: 1.87-3.30% For age women<30 years: 0.07-0.79% For age <40 years: 023-1.53% For age <50 years: 0.51-2.59% For age <60 years: 0.86-3.46% For age <70 years: 1.46-2.88%	For age <21 years: 7%[17,27,32] For age <45 years: 87% For age <50 years: 93%
Gastric cancer	Lifetime risk: 1–3%[22] 1.49% men 0.74% women	For age >20 years: 4/14[17,27,32] For age >30 years: 7/33 For age >40 years: 9/25 For age >40 years: 6/28
Hepatoblastoma	Lifetime risk: >5%[17,38]	For age 0-3 years: 1-1.6%[17,27,32] For codons 216-1524: 12/31 For codons 457-1309: 3/31 For codons 141-1230: 7/31 For codons Exon 8-1751: 9/31

Percentages are average values. For specific mutations these values might be different.

ATM

Gene name: Ataxia-teleangiectasia mutate gene (ATM)

OMIM gene: 607585

Associated syndromes:

- Ataxia-telangiectasia (OMIM: 208900) (autosomal recessive): Characterized by cerebellar ataxia, telangiectasia, immune defects, and a predisposition to develop malignancy.
- Susceptibility to breast cancer (OMIM number 114480) (autosomal dominant): Associated with an increased risk for the development of breast cancer.

Protein:

The ATM protein is an ATM serine/threonine kinase, enzyme located primarily in the nucleus of cells, where it helps controlling the rate of cell growth and division. This protein also plays an important role in the normal development and activity of several body systems, including the nervous system and the immune system. Additional functions of ATM protein are tumor suppression, DNA repair, maintaining genetic stability and other functions that are disrupted in cancerogenesis.

Several proteins have been shown to interact with ATM. ATM can directly phosphorylate and activate TP53, thereby triggering the various TP53-dependent signaling pathways. ATM also interacts with the protein product of the c-Abl proto-oncogene, an important participant in many signaling pathways.

In addition to interaction with c-Abl, ATM also forms the tri-molecular complex between ATM, c-Abl and the RAD51 protein, involved in strand break repair and DNA recombination. β-adaptin was recently identified as an ATM-interacting protein. This protein is involved in clathrin-mediated endocytosis of receptors and its interaction with ATM confirms the role of ATM in the vesicle and/or protein transport.

Cancer type	General population	Cancer risk for ATM mutation carriers
Female breast cancer	Lifetime risk: 5-10%[1,2]	Lifetime risk: 2.37%[38] For age > 50 years: 4.94%[38]
Pancreatic cancer	Lifetime risk: 1.31%[7]	Lifetime risk: 2.41%[38]

Percentages are average values. For specific mutations these values might be different.

BARD1

Gene name: BRCA1-associated RING domain type 1 (BARD1)

OMIM gene: 601593

Associated syndromes:

- Susceptibility to breast cancer (OMIM: 114480) (autosomal dominant): Associated with an increased risk for the development of breast cancer

Protein:

BARD1 protein is a partner protein of BRCA1 and it binds to the N-terminal region. In addition to its ability to bind BRCA1 in vivo and in vitro, it shares homology with the 2 most conserved regions of BRCA1: the N-terminal RING motif and the C-terminal BRCT domain. Through these regions, BARD1 regulates cell growth, produces tumor suppressor genes and dominant protooncogenes.

Cancer type	General population	Cancer risk for BARD1 mutation carriers
Female breast cancer	Lifetime risk: 5-10%[1,2]	Elevated risk[45]

Percentages are average values. For specific mutations these values might be different.

BLM/RECQL3

Gene name: BLM gene, also known as RECQL3

OMIM gene: 604610

Associated syndromes:

- Bloom syndrome (OMIM: 210900) (autosomal recessive): Characterized by proportionate pre- and postnatal growth deficiency; sun-sensitive, telangiectatic, hypo- and hyperpigmented skin; predisposition to malignancy; and chromosomal instability.

Protein:

The BLM gene encodes DNA helicase 2 protein, also known as RECQ protein-like 3, a member of the RecF recombination pathway. BLM regulates recombination proficiency and resistance to UV, and it has DNA-dependent ATPase, DNA helicase, and 3-prime-to-5-prime single-stranded DNA translocation activities. As a result of the lack of functional BLM protein, the frequency of sister chromatid exchange is about 10 times higher than average. Approximately 1% of individuals of Ashkenazi Jewish descent carry a blmAsh mutation (c.2207_2212delinsTAGATTC)[57].

Cancer type	General population	Cancer risk for BLM/RECQL3 mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[58] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years:16.83-21.23%	Increasing with age[58]
Colorectal cancer	Lifetime risk: 5-6%[17] For age (men)<30 years: 0.07-0.96% For age <40 years: 0.26-2% For age <50 years: 0.67-3.27% For age <60 years: 1.22-4.04% For age <70 years: 1.87-3.30% For age (women)<30 years: 0.07-0.79% For age <40 years: 023-1.53% For age <50 years: 0.51-2.59% For age <60 years: 0.86-3.46% For age <70 years: 1.46-2.88%	Increased risk
Lymphoma	Lifetime risk: 3.68%[17]	Increased risk
Acute myelogenous leukemia	Lifetime risk: 10.75%[17]	Increased risk

Percentages are average values. For specific mutations these values might be different.

BMPR1A

Gene name: Bone morphogenetic protein receptor type 1A (BMPR1A), also known as ALK3

OMIM gene: 601299

Associated syndromes:

- Juvenile polyposis syndrome (infantile form) (OMIM: 174900) (autosomal dominant): Characterized by predisposition to hamartomatous polyps in the gastrointestinal tract, specifically in the stomach, small intestine, colon, and rectum. Approximately 20% of individuals with JPS have pathogenic variants in BMPR1A; approximately 20% have pathogenic variants in SMAD4.

- Hereditary mixed polyposis syndrome 2 (OMIM: 610069) (autosomal dominant): characterized by atypical juvenile polyps, colonic adenomas, and colorectal carcinomas.

Protein:

Bone morphogenetic protein receptor type 1A is a member of transmembrane serine/threonine kinase family, closely associated with activin receptors and TGF-beta pathway known to regulate cell proliferation and growth.

Cancer type	General population	Cancer risk for BMPR1A mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[58] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	For age >60: increased[58]
Colorectal cancer	Lifetime risk: 5-6%[17, 27] For age (man) <30 years: 0.07-0.96% For age <40 years: 0.26-2% For age <50 years: 0.67-3.27% For age <60 years: 1.22-4.04% For age <70 years: 1.87-3.30% For age (woman) <30 years: 0.07-0.79% For age <40 years: 023-1.53% For age <50 years: 0.51-2.59% For age <60 years: 0.86-3.46% For age <70 years: 1.46-2.88%	For age <42 years: 20%-25%[58] For age <80 years: 40%-50%
Gastric cancer	Lifetime risk: 1–3%[32] 1.49% man 0.74% woman	For age >80 years: up to 21%[32, 58]
Pancreatic cancer	Lifetime risk: 1-2%[7,12]	For age >80 years: elevated risk[58]
Bowel cancer	Lifetime risk: 0.2-1%[17, 25] 7.14% men 5.26% women	For age >80 years: elevated risk[58]

Percentages are average values. For specific mutations these values might be different.

BRCA1

Gene name: Breast cancer gene 1 (BRCA1)

OMIM gene: 113705

Associated syndromes:

- Familial breast-ovarian cancer type 1, BROVCA1 (OMIM: 604370) (autosomal dominant): Associated with an increased risk for the development of breast and ovarian cancer.
- Susceptibility to pancreatic cancer (OMIM: 614320): Associated with an increased risk for the development of pancreatic cancer.

Protein:

BRCA1 gene encodes the BRCA1 protein that acts as tumor suppressor and prevents cells from growing and dividing in an uncontrolled way. BRCA1 protein is involved in repairing breaks in DNA that arise by chance but also can be caused by natural and medical radiation or other environmental exposures. Many of the known breast cancer genes interact with BRCA1 or are involved in the same pathway. Its association with ATM and CHEK2 regulates cell cycle progression, whilst its association with RAD51C has a direct impact on the repair of double strand DNA breaks by homologous recombination.

BRCA1 interactions with the delete 'phosphor' protein BRIP1 is also implicated in DNA repair mechanisms and cell cycle checkpoint control. PALB2 directly interacts with BRCA1and BRCA2 and is believed to be involved in the homologue recombination repair process.

Patients with metastatic breast cancer and documented BRCA1 mutations have shown good results with PARP inhibitor treatment. Currently several phase 3 studies are on their way and there are high expectations for an FDA approval of PARP inhibitors for breast cancer treatment similar to the approved treatment of BRCA1/2 positive ovarian cancer in 2014. An inclusion of PARP inhibitors in adjuvant and neoadjuvant treatment of BRCA1/2 positive breast cancer patients is currently tested in Phase 2 trials.[1]

Cancer type	General population	Cancer risk for BRCA1 mutation carriers
Breast cancer	Lifetime risk: 5-10% [1,2]	For age <30 years: 3.2%[1] For age <40 years: 19%[1] For age <50 years: 50.8%[1] For age <60 years: 54%[1] For age <70 years: 85%[1]
Ovarian cancer	Lifetime risk: 5-15%[3,14]	For age <30 years: 0.17%[1] For age <40 years: 0.61%[1] For age <50 years: 22.7%[1] For age <60 years: 29.8%[1] For age <70 years: 63.3%[1]
Male breast cancer	Lifetime risk: up to 0.1%[4]	Lifetime risk: 1.2%[4]
Prostate cancer	Lifetime risk: 4.6%[4]	For age 40-69 years: 11%[6]
Pancreatic cancer	Lifetime risk: 1.31%[7]	For age <70 years in males: 2.1%[9] For age <70 years in females: 1.5%[9]

Percentages are average values. For specific mutations these values might be different.

Additional information:

For BRCA1, different founder mutations have been identified for which mutation specific risk estimations are also available. Two examples are the Ashkenazi founder BRCA1 mutations 185delAG (also known as c.68_69delAG) and 5382insC (also known as c.5266dupC) with a risk of breast cancer by age 70 years of 64% and 67%, respectively. Another common mutation is c.3016_3019del4 (known as c.3135del4) found in 8% of the BRCA1 mutation families of European origin[49].

BRCA2

Gene name: Breast cancer gene 2 (BRCA2), also known as FANCD1 gene

OMIM gene: 600185

Associated syndromes:

- Familial breast-ovarian cancer type 2 (OMIM: 612555) (autosomal dominant): Associated with an increased risk for the development of breast and ovarian cancer.
- Fanconi anemia, complementation group D1 (OMIM: 605724) (autosomal recessive): Fanconi anemia (FA) is characterized by physical abnormalities, a 90% cumulative incidence of bone marrow failure, an increased incidence of hematologic malignancies (10%-30%) and non-hematologic malignancies (25-30%).
- Pancreatic cancer (OMIM: 613347) (autosomal dominant): Associated with an increased risk for the development of pancreatic cancer.
- Prostate cancer (OMIM: 176807) (autosomal dominant): Associated with an increased risk for the development of prostate cancer.
- Wilms tumor (OMIM: 194070) (autosomal dominant): Associated with an increased risk for the development of Wilms tumor.
- Glioblastoma type 3 (OMIM: 613029) (autosomal dominant): Associated with an increased risk for the development of gliomas.
- Susceptibility to breast male cancer (OMIM: 114480) (autosomal dominant): Associated with an increased risk for the development of breast cancer in men.
- Medulloblastoma (OMIM: 155255) (autosomal dominant): Associated with an increased risk for the development of medulloblastomas.

Additional information:

There have been several founder mutations identified. In individuals of Ashkenazi Jewish heritage c.5946delT accounts for 1.52% of all mutations and it causes the average risk of breast cancer by the age of 70 years to be of 43%[51]. The corresponding value for ovarian cancer lifetime risk is 20% in mutation carriers[52].

Protein:

Breast cancer early onset type 2 (BRCA2)

The BRCA2 gene encodes the BRCA2 protein, which acts as tumor suppressor and is involved in DNA repair. It is localized within cellular nucleus where it interacts with many partner proteins and participates in the repair of the DNA breaks. By helping to repair DNA, the BRCA2 protein plays a critical role in maintaining the stability of a cell's genetic information. Researchers suspect that the BRCA2 protein has additional functions within cells, as a regulator of cytokinesis, which is the step in cell division when the fluid surrounding the nucleus (the cytoplasm) divides to form two separate cells.

Cancer type	General population	Cancer risk for BRCA2 mutation carriers
Female breast cancer	Lifetime risk: 5-10%[2]	For age 20-29 years: 0%[11] For age 30-39 years: 11,4%[11] For age 40-49 years: 41.4%[11] For age 50-59 years: 15.2%[11] For age >60 years: 16.2%[11]
Ovarian cancer	Lifetime risk: 5-15%[3,14]	For age 20-29 years: 0%[11] For age 30-39 years: 1.7%[11] For age 40-70 years: 15.2%[11] For age >70 years: 11.2%[11]
Male breast cancer	Lifetime risk: up to 0.1%[4,9]	For age up to 70 years: 6.8%[4 8,10] For age up to 70 years: 5-10%[4,8,10]
Prostate cancer	Lifetime risk: 4.6%[5]	Lifetime risk: 19.9%[6] For age up to 70 years in males: 2.1%[9]
Pancreatic cancer	Lifetime risk: 1.31%[7]	For age up to 70 years in females: 1.5%[9]

Percentages are average values. For specific mutations these values might be different.

BRIP1

Gene name: BRCA1-interacting protein (BRIP1), also known as BACH1, FANCJ and DOG1

OMIM gene: 605882

Associated syndromes:

- Breast cancer, early-onset (OMIM: 114480) (autosomal dominant): Associated with an increased risk for the development of breast cancer.
- Fanconi anemia, complementation group J (OMIM: 609054) (autosomal recessive): Characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure and a high predisposition to cancer. The cellular hallmark of FA is hypersensitivity to DNA crosslinking agents and high frequency of chromosomal aberrations pointing to a defect in DNA repair.

Protein:

BRCA1 interacting protein 1 (BRIP1) is a member of the helicase family and interacts with the BRCT repeats of BRCA1. The bound complex is important in the normal double-strand break repair. DNA-dependent ATPase and 5′ to 3′ DNA helicase activity of BRIP1 are required for the maintenance of chromosomal stability. This protein is involved in late stages of Fanconi anemia pathway, after FANCD2 ubiquitination.

Cancer type	General population	Cancer risk for BRIP1 mutation carriers
Female breast cancer	Lifetime risk: 5-10%[1,2]	Lifetime risk: 3.4%[41]
Ovarian cancer	Lifetime risk: 5-15%[3,14]	For age >80 years: 8.3%[40]

Percentages are average values. For specific mutations these values might be different.

CDH1

Gene name: Cadherin 1 (CDH1), also known as E-cadherin (ECAD), Uvomorulin (UVO), Liver cell adhesion molecule (LCAM)

OMIM gene: 192090

Associated syndromes:

- Gastric cancer, familial diffuse, with or without cleft lip and/or palate (OMIM: 137215) (autosomal dominant): Associated with an increased risk for the development of hereditary diffuse gastric cancer (HDGC).
- Breast cancer, lobular (OMIM: 114480) (autosomal dominant): Associated with an increased risk for the development of breast cancer.
- Susceptibility to prostate cancer (OMIM: 176807) (autosomal dominant): Associated with an increased risk for the development of prostate cancer.

Protein:

Cadherin 1 is a calcium ion-dependent cell adhesion molecule found within the membrane of epithelial cells. Cadherins regulate cell adhesion and form organized tissues. Cadherin 1 is believed to act as a tumor suppressor protein by forming cell-cell contacts and preventing cells from growing and dividing in an uncontrolled way.

Cancer type	General population	Cancer risk for CDH1 mutation carriers
Female breast cancer	Lifetime risk: 5-10%[1,2]	For age >30 years: 0%[30] For age >40 years: 3%[30] For age >50 years: 10%[30] For age >60 years: 19%[30] For age >70 years: 29%[30] For age >80 years: 39%[30]
Gastric cancer	Lifetime risk: 1–3%[22]	For age >30 years: 4%/4% (m/f)[30] For age >40 years: 9%/21% (m/f)[30] For age >50 years: 21%/46%(m/f)[30] For age >60 years: 43%/64%(m/f)[30] For age >70 years: 52%/71%(m/f)[30] For age >80 years: 67%/83%(m/f)[30]
Colorectal cancer	Lifetime risk: 6%[17]	Lifetime risk: ~1%[30]

Percentages are average values. For specific mutations these values might be different.

CDK4

Gene name: Cyclin-dependant kinase 4 (CDK4)
OMIM gene: 123829

Associated syndromes:

- Cutaneous malignant melanoma 3 (CMM3), Melanoma cancer syndrome (MCS) (OMIM: 609048) (autosomal dominant): Malignant melanoma is a neoplasm of pigment-producing cells called melanocytes that occurs most often in the skin, but may also occur in the eyes, ears, gastrointestinal tract, leptomeninges, and oral and genital mucous membranes.

Protein:

Cyclin-dependent kinase 4 is a protein-serine kinase involved in the cell cycle. CDK4 regulates G1-S phase of cell proliferation thus influencing tumorogenesis when mutated.

Cancer type	General population	Cancer risk for CDK4 mutation carriers
Female breast cancer	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67% For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Not determined
Pancreatic cancer	Lifetime risk for all hereditary cancers: 2-3%[7] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	For age >75: elevated risk[60]
Melanoma	Lifetime risk: 0.3-1.6%[60]	For age > 50: 14-50%[60] For age > 80: 28-76%

Percentages are average values. For specific mutations these values might be different.

CDKN2A

Gene name: Cyclin dependent kinase inhibitor 2A (CDKN2A)
OMIM gene: 600160

Associated syndromes:

- Cutaneous malignant melanoma 2 (OMIM: 155601) (autosomal dominant): A neoplasm of pigment-producing cells called melanocytes that occurs most often in the skin, but may also occur in the eyes, ears, gastrointestinal tract, leptomeninges, and oral and genital mucous membranes.

- Melanoma and neural system tumor syndrome (OMIM: 155755) (autosomal dominant): An extremely rare tumor association characterized by dual predisposition to melanoma and neural system tumors, reported in less than 20 affected families reported to date.

- Pancreatic cancer/melanoma syndrome OMIM: (606719) (autosomal dominant): An inherited cancer predisposition syndrome in which mutation carriers have an increased risk of developing malignant melanoma and/or pancreatic cancer. Mutation carriers within families may develop either or both types of cancer.

Protein:

Cyclin-dependent kinase inhibitor 2A encodes proteins p16(INK4a) and the p14(ARF), which both function as tumor suppressors and help regulate cell cycle, cell division, and self-destruction (apoptosis).

Cancer type	General population	Cancer risk for CDKN2A mutation carriers
Female breast cancer	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Not determined
Pancreatic cancer	Lifetime risk for all hereditary cancers: 2%-3%[7] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	For age > 75: elevated risk[60]
Melanoma	Lifetime risk: 0.3-1.6%[60]	For age > 50: 14-50%[60] For age > 80: 28-76%

Percentages are average values. For specific mutations these values might be different

CHEK2

Gene name: Checkpoint kinase type 2, homolog of Pombe (CHEK2), known as homolog of cervisiae RAD53, CDS1 homolog of Pombe

OMIM gene: 604373

Associated syndromes:

- Li-Fraumeni syndrome type2 (OMIM: 609265) (autosomal dominant): Li-Fraumeni syndrome (LFS) is characterized by an increased risk for a variety of tumor types. The most common types are soft tissue sarcomas and osteosarcomas, breast cancer, brain tumors, leukemia, and adrenocortical carcinoma.
- Susceptibility to breast cancer (OMIM: 114480) (autosomal dominant): Associated with an increased risk for the development of breast cancer.
- Susceptibility to prostate cancer, familial (OMIM: 176807) (autosomal dominant): Associated with an increased risk for the development of prostate cancer.

Protein:

Checkpoint kinase type 2 is an enzyme that is activated in response to DNA damage and is involved in cell cycle arrest. CHEK2 interacts with several other proteins, including tumor protein 53 and BRCA1, to regulate DNA repair, cellular survival or self-destruction by apoptosis.

Cancer type	General population	Cancer risk for CHEK2 mutation carriers
Female breast cancer	Lifetime risk: 5-10%[1,2]	Lifetime risk for c.1100delC female carriers: 4.8%[36,37]
Prostate cancer	Lifetime risk: 4.6%[5]	Lifetime risk >80 years: 24-44%[35]
Colorectal cancer	Lifetime risk: 6%[17]	Lifetime risk >80 years: 7,2-9.5%[37]
Male breast cancer	Lifetime risk: 0.1%[4,9]	Lifetime risk >80 years: 0.4-1%[36]

Percentages are average values. For specific mutations these values might be different.

Additional information:

The c.1100delC founder mutation is most commonly seen among individuals of Eastern European descent, Netherlands and Denmark.

Two additional founder mutations, IVS2+1G>A and c.5395del have the highest occurrence in populations of Eastern European descent.[56]

EPCAM

Gene name: Epithelial cellular adhesion molecule (EPCAM) also known as tumor-associated calcium signal transducer 1 (TACSTD1)

OMIM gene: 185535

Associated syndromes:

- Hereditary nonpolyposis colorectal cancer type, e.g. Lynch syndrome (OMIM: 613244) (autosomal recessive): An inherited disorder that increases the risk of many types of cancer, particularly colorectal cancer.

- Congenital diarrhea with tufting enteropathy 5 (OMIM: 613217) (autosomal recessive): A rare inherited intractable diarrhea of infancy characterized by villous atrophy and absence of inflammation, with intestinal epithelial cell dysplasia manifesting as focal epithelial tufts in the duodenum and jejunum.

Protein:

The EPCAM gene encodes epithelial cell adhesion molecule protein, expressed only in epithelial cells. The protein plays a role in regulation of cell adhesion and it is involved in cell proliferation and differentiation processes.

Cancer type	General population cancer risk	Cancer risk for EPCAM mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Not determined
Colorectal cancer	Lifetime risk: 5-6%[17] For age (man)<30 years: 0.07-0.96%[17] For age <40 years: 0.26-2% For age <50 years: 0.67-3.27% For age <60 years: 1.22-4.04% For age <70 years: 1.87-3.30% For age (women) <30 years: 0.07-0.79% For age <40 years: 023-1.53% For age <50 years: 0.51-2.59% For age <60 years: 0.86-3.46% For age <70 years: 1.46-2.88%	For age >70: 52%-82%[17]
Gastric cancer	Lifetime risk: 1%–3%[22] 1.49% men 0.74% women	For age >70: 6%-13%[26]
Bowel cancer	Lifetime risk: 0.2%-1%[17,25] 7.14% men 5.26% women	For age >70: 3%-6%[26]
Pancreatic cancer	Lifetime risk for all hereditary cancers: 2-3%[7] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	For age >70: 3%-6%[26,27]
Liver cancer	Lifetime risk: >5%[7]	For age >70:1.4%-4%[27]
Endometrial cancer	Lifetime risk: 2.4-2.7%[1,2,25]	For age >70: 1%-4%[17,19]
Ovarian cancer	Lifetime risk: 5-15%[3,14] Lifetime risk: 0.7%[1,2]	For age >70: 4%-12%[19]

Percentages are average values. For specific mutations these values might be different.

FH

Gene name: Fumarase, Fumaraze hydroxylase (FH)

OMIM gene: 602216

Associated syndromes:

- Leiomyomatosis and renal cell cancer (OMIM: 606812) (autosomal recessive): Characterized by predisposition to benign leiomyomas of the skin and the uterus, renal cell carcinoma (RCC), and uterine leiomyosarcoma (ULMS).

- Fumarase deficiency (OMIM: 150800) (autosomal dominant): severe autosomal recessive metabolic disorder characterized by early-onset hypotonia, profound psychomotor retardation, and brain abnormalities, such as agenesis of the corpus callosum, gyral defects, and ventriculomegaly. Many patients show neonatal distress, metabolic acidosis, and/or encephalopathy

Protein:

An enzymatic component of the tricarboxylic acid, or Krebs, cycle. It catalyzes the conversion of fumarate to malate and is involved in fundamental cellular energy production. FH is also a tumor suppressor.

Cancer type	General population	Cancer risk for FH mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Not determined
Hereditary leiomyomatosis and renal cell cancer	Lifetime risk: <70 years [61]	For age 15–29: 3/34[61] For age 30–44: 5/34 For age 45-59: 5/34 For age 50-74: 15/34
Breast cancer	Lifetime risk: 5-10%[1,2]	For age 60-74: 4/22[61]
Renal cell carcinoma	Lifetime risk: ~1%[16,17] Lifetime risk: 1.9% men Lifetime risk: 1.14% women	For age 60-74: 12/22[61]
Uterine leiomyosarcoma	Lifetime risk: 2,43-2.7% women[61]	For age 60-74: 5/22[61]

Percentages are average values. For specific mutations these values might be different.

FLCN

Gene name: Folliculin (FLCN)
OMIM gene: 607273

Associated syndromes:

- Birt-Hogg-Dube syndrome (OMIM: 135150) (Autosomal dominant): characterized clinically by skin fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax, and renal cancer. Individuals with BHDS are at a sevenfold increased risk of renal tumors that are typically bilateral and multifocal and are usually slow growing; median age of tumor diagnosis is 48 years. The most common renal tumors are a hybrid of oncocytoma and chromophobe histologic cell types (so-called oncocytic hybrid tumor) and chromophobe histologic cell types.

- Pneumothorax, primary spontaneous (OMIM: 173600) (Autosomal dominant): Birt-Hogg-Dube syndrome (BHD; 135150) is an allelic disorder characterized by spontaneous pneumothorax, as well as fibrofolliculomas of the skin and increased risk of renal and colonic tumors. Gunji et al. (2007) suggested that isolated primary spontaneous pneumothorax associated with FLCN mutations may be part of the clinical spectrum of BHD, showing incomplete disease penetrance.

Protein:

The FLCN gene encodes folliculin, a protein that regulates AMP-activated protein kinase (AMPK) and activation of the mTOR signaling pathway. It is hypothesized that FLCN inhibits tumorigenesis by preventing AMPK-dependent signaling pathways activation and subsequent metabolic transformation. A mutation deletion (c.1285delC) in the FLCN gene was identified in 27/51 (53%)[62] of families with BHDS.

Cancer type	General population	Cancer risk for FLCN mutation carriers
All hreditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Not determined
Renal cancer	Lifetime risk: ~1%[16, 17] Lifetime risk: 1.9% men Lifetime risk: 1.14% women	For age >48: 7-fold risk[62]

Percentages are average values. For specific mutations these values might be different.

MLH1

Gene name: MutL, homologue of E.Coli 1 (MLH1)
OMIM gene: 602216

Associated syndromes:

- Colorectal cancer, hereditary nonpolyposis, type 2 (OMIM: 609310) (autosomal recessive): An inherited disorder that increases the risk of many types of cancer, particularly colorectal cancer.
- Mismatch repair cancer syndrome (OMIM: 276300) (autosomal recessive): A rare childhood cancer predisposition syndrome with 4 main tumor types: hematologic malignancies, brain/central nervous system tumors, colorectal tumors, and multiple intestinal polyps, as well as other malignancies including embryonic tumors and rhabdomyosarcoma.
- Muir-Torre syndrome (OMIM: 158320) (autosomal dominant): A part of the Lynch cancer family syndrome, the association of sebaceous skin tumors with internal malignancy.

Protein:

The MLH1 gene encodes a protein mutL homolog 1, a member of mismatch repair family. In a complex with PMS2, MLH1 acts as a DNA repair factor during DNA replication.

Cancer type	General population cancer risk	Cancer risk for MLH1 mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Not determined
Colorectal cancer	Lifetime risk: 5-6%[17] For age (men) <30 years: 0.07-0.96% For age <40 years: 0.26-2% For age <50 years: 0.67-3.27% For age <60 years: 1.22-4.04% For age <70 years: 1.87-3.30% For age (women) <30 years: 0.07-0.79% For age <40 years: 023-1.53% For age <50 years: 0.51-2.59% For age <60 years: 0.86-3.46% For age <70 years: 1.46-2.88%	For age >70: 52%-82%[63]
Gastric cancer	Lifetime risk: 1–3%[22] 1.49% men 0.74% women	For age >70: 6%-13%[63]
Bowel cancer	Lifetime risk: 0.2-1%[17,25] 7.14% men 5.26% women	For age >70: 3%-6%[63]
Endometrial cancer	Lifetime risk: 2.4-2.7% [25]	For age >70: 25%-60%[63]
Liver cancer	Lifetime risk: >5%[7]	For age >70: 1.4%-4%[63]
Ovarian cancer	Lifetime risk: 5-15%[3, 14]	For age >70: 4%-12%[63]
Renal cancer	Lifetime risk: ~1%[16,17] Lifetime risk: 1.9% men Lifetime risk: 1.14% women	For age >70: 1%-4%[63]
CNS	Lifetime risk: >2%[6]	For age >70: 1%-3%[63]

Percentages are average values. For specific mutations these values might be different.

MSH2

Gene name: MutS homologue of e.Coli 2 (MSH2)
OMIM gene: 609309

Associated syndromes:

- Colorectal cancer, hereditary nonpolyposis, type 1 (OMIM: 120435) (autosomal dominant): An inherited disorder that increases the risk of many types of cancer, particularly colorectal cancer.
- Mismatch repair cancer syndrome (OMIM: 276300) (autosomal recessive): A rare childhood cancer predisposition syndrome with 4 main tumor types: hematologic malignancies, brain/central nervous system tumors, colorectal tumors, and multiple intestinal polyps, as well as other malignancies including embryonic tumors and rhabdomyosarcoma.
- Muir-Torre syndrome (OMIM: 158320) (autosomal dominant): Part of the Lynch cancer family syndrome, the association of sebaceous skin tumors with internal malignancy.

Protein:

The MSH2 gene encodes a protein mutS homolog 2, a member of mismatch repair family (MMR). In a complex with other members of MMR family, MSH2 acts as a DNA repair factor during DNA replication.

Cancer type	General population cancer risk	Cancer risk for MSH2 mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Not determined
Colorectal cancer	Lifetime risk: 5-6%[17] For age (men) <30 years: 0.07-0.96% For age <40 years: 0.26-2% For age <50 years: 0.67-3.27% For age <60 years: 1.22-4.04% For age <70 years: 1.87-3.30% For age (women) <30 years: 0.07-0.79% For age <40 years: 023-1.53% For age <50 years: 0.51-2.59% For age <60 years: 0.86-3.46% For age <70 years: 1.46-2.88%	For age >70: 52-82%[63]
Gastric cancer	Lifetime risk: 1–3%[22] 1.49% men 0.74% women	For age >70: 6-13%[63]
Bowel cancer	Lifetime risk: 0.2-1%[17,25] 7.14% men 5.26% women	For age >70: 3-6%[63]
Endometrial cancer	Lifetime risk: 2.4-2.7%[25]	For age >70: 25-60%[63]
Liver cancer	Lifetime risk: >5%[7]	For age >70: 1.4-4%[63]
Ovarian cancer	Lifetime risk: 5-15%[3, 14]	For age >70: 4-12%[63]
Renal cancer	Lifetime risk: 1.9% men Lifetime risk: 1.14% women	For age >70: 4-12%[63]
CNS	Lifetime risk: 5-15%[3, 14] Lifetime risk: 0.7%	For age >70: 4-12%[63]

Percentages are average values. For specific mutations these values might be different.

MSH6

Gene name: MutS homolog of E.Coli 6 (MSH6)
OMIM gene: 600678

Associated syndromes:

- Colorectal cancer, hereditary nonpolyposis, type 5 (OMIM: 614350) (autosomal dominant): An inherited disorder that increases the risk of many types of cancer, particularly colorectal cancer.
- Mismatch repair cancer syndrome (OMIM: 276300) (autosomal recessive): A rare childhood cancer predisposition syndrome with 4 main tumor types: hematologic malignancies, brain/central nervous system tumors, colorectal tumors, and multiple intestinal polyps, as well as other malignancies including embryonic tumors and rhabdomyosarcoma.
- Endometrial cancer, familial (OMIM: 608089) (autosomal dominant): Also referred to as corpus uterine cancer or corpus cancer, it is the most common female genital cancer in the developing world, with adenocarcinoma of the endometrium the most common type. Approximately 20% of endometrial cancers demonstrate microsatellite instability, a reflection of mutations in mismatch repair genes.

Protein:

The MSH6 gene encodes a protein mutS homolog 6, a member of mismatch repair family (MMR). In a complex with other members of MMR family, MSH2 acts as a DNA repair factor during DNA replication.

Cancer type	General population cancer risk	Cancer risk for MSH6 mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Not determined
Colorectal cancer	Lifetime risk: 5-6%[17] For age (men) <30 years: 0.07-0.96% For age <40 years: 0.26-2% For age <50 years: 0.67-3.27% For age <60 years: 1.22-4.04% For age <70 years: 1.87-3.30% For age (women) <30 years: 0.07-0.79% For age <40 years: 023-1.53% For age <50 years: 0.51-2.59% For age <60 years: 0.86-3.46% For age <70 years: 1.46-2.88%	For age >70: 22-69% men For age >70: 10-30% women
Gastric cancer	Lifetime risk: 1–3%[22] 1.49% men 0.74% women	For age >70: Elevated risk
Bowel cancer	Lifetime risk: 0.2-1%[17,25] 7.14% men 5.26% women	For age >70: Elevated risk
Endometrial cancer	Lifetime risk: 2.4-2.7%[25]	For age >70: 16-71%
Liver cancer	Lifetime risk: >5%[7]	For age >70: 1.4-4%
Ovarian cancer	Lifetime risk: 5-15%[3,14]	For age >70: Elevated risk
Renal cancer	Lifetime risk: ~1%[16,17] Lifetime risk: 1.9% men Lifetime risk: 1.14% women	For age >70: Elevated risk
CNS	Lifetime risk: >2%[3,14]	For age >70: Elevated risk

Percentages are average values. For specific mutations these values might be different.

MUTYH

Gene name: MutY E. COLI, homolog (MUTYH), also known as MYH
OMIM gene: 604933

Associated syndromes:

- Multiple colorectal adenoma (OMIM: 608456) (autosomal recessive, somatic mutations): Characterized by adult-onset of multiple colorectal adenomas and adenomatous polyposis. Affected individuals have a greatly increased lifetime risk of colorectal cancer (43-100%).[63]

Protein:

The MUTYH gene encodes mutY DNA glycosylase involved in DNA repair. MUTYH plays a key role in base excision repair-mediated removal of 8-oxoG:A mismatches. Most reported mutations in this gene cause production of a nonfunctional or low-functioning glycosylase enzyme. The two most common mutations in Caucasians, accounting for about 75-80% of mutant alleles, are Y165C (or Tyr165Cys) and G382D (or Gly382Asp).[63]

Cancer type	General population cancer risk	Cancer risk for MUTYH mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	For age >60: increased
Colorectal cancer	Lifetime risk: 5-6%[17] For age (men) <30 years: 0.07-0.96% For age (men) <40 years: 0.26-2% For age (men) <50 years: 0.67-3.27% For age (men) <60 years: 1.22-4.04% For age (men) <70 years: 1.87-3.30% For age (women) <30 years: 0.07-0.79% For age (women) <40 years: 023-1.53% For age (women) <50 years: 0.51-2.59% For age (women) <60 years: 0.86-3.46% For age (women) <70 years: 1.46-2.88%	For age >70: 6.39 men[63] For age > 4.42 women
Gastric cancer	Lifetime risk: 1–3%[22] 1.49% men 0.74% women	For age >70: 1.81 men[63] For age > 70: 0.69 women
Bowel cancer	Lifetime risk: 0.2-1%[17, 25] 7.14% men 5.26% women	For age >80 years: 5%[63]
Female breast cancer	Lifetime risk: 5-10%[1, 2]	For age >80: 6.7% for variant G396D[63]
Liver cancer	Lifetime risk: 0.95% men Lifetime risk: 0.51% women[7] Lifetime risk: >5% Lifetime risk: 0.89%	For age >70: 0.75% men[63] For age >70: 0.27% women
Endometrial cancer	Lifetime risk: 2.4-2.7%[25]	For age >70: 3.94%[63]

Percentages are average values. For specific mutations these values might be different.

NBN

Gene name: Nibrin gene (NBN), also known as p95 protein of the MRE11/ RAD50 complex, NBS1 gene

OMIM gene: 602667

Associated syndromes:

- Nijmegen breakage syndrome (OMIM: 251260) (autosomal recessive): Characterized by microcephaly, growth retardation, immunodeficiency, and predisposition to cancer.
- Aplastic anemia (OMIM: 609135) (autosomal dominant): Aplastic anemia only, no additional symptoms of NBS.
- Leukemia, acute lymphoblastic (OMIM: 613065) (autosomal dominant): Acute lymphoblastic leukemia (ALL) only, no additional symptoms of NBS.

Protein:

NBN gene provides instructions for making the protein nibrin which is involved in several critical cellular functions, including the repair of damaged DNA. Nibrin interacts with two other proteins, MRE11A and RAD50, creating a larger protein complex.

This complex regulates DNA repair. Repairing DNA prevents cells from accumulating genetic damage that may cause them to die or to divide uncontrollably.

Cancer type	General population	Cancer risk for NBN mutation carriers
Female breast cancer	Lifetime risk: 5%-10% [1,2]	For all ages: 3.13%[44] For mutation 657del5 carriers[44] For age >40 years: 8.36%[44] For age >50 years: 4.27%[44] For age >80 years: 2.63%[43]
Prostate cancer	Lifetime risk: 4.6%[5]	Lifetime risk: 9%[42]

Percentages are average values. For specific mutations these values might be different.

Additional information:

Much of what is reported about NBS is based on individuals who are homozygous for the single most common Eastern European pathogenic variant, 657_661del5.[56]

NTHL1

Gene name: Endonuclease III-like 1 (NTHL1)
OMIM gene: 602656

Associated syndromes:

- Familial adenomatous polyposis 3 (OMIM: 616415) (autosomal recessive): Cancer predisposition syndrome characterized by the development of multiple colonic adenomas, often with progression to colorectal cancer. Carcinomas affecting other tissues may also occur, and these carcinomas tend to develop in middle age or late adulthood.

Protein:

The NTHL1 gene encodes endonuclease that initiate DNA base excision repair of oxidized ring saturated pyrimidine residues, thus influencing the primary repair pathway for the repair of oxidative DNA damage.

Cancer type	General population cancer risk	Cancer risk for NTHL1 mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Not determined
Colorectal cancer	Lifetime risk: 5-6%[17] For age (men) <30 years: 0.07-0.96% For age <40 years: 0.26-2% For age <50 years: 0.67-3.27% For age <60 years: 1.22-4.04% For age <70 years: 1.87-3.30% For age (women) <30 years: 0.07-0.79% For age <40 years: 023-1.53% For age <50 years: 0.51-2.59% For age <60 years: 0.86-3.46% For age <70 years: 1.46-2.88%	Increased risk[58]
Endometrial cancer	Lifetime risk: 2.4-2.7%[25]	Increased risk[58]

Percentages are average values. For specific mutations these values might be different.

PALB2

Gene name: Partner and localizer of BRCA2 (PALB2), FANCN

OMIM gene: 610355

Associated syndromes:

- Fanconi anemia, complementation group N (OMIM: 610832) (autosomal recessive): Characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. The cellular hallmark of FA is hypersensitivity to DNA crosslinking agents and high frequency of chromosomal aberrations pointing to a defect in DNA repair.
- Susceptibility to breast cancer (OMIM: 114480) (autosomal dominant): Associated with an increased risk for the development of breast cancer.
- Susceptibility to pancreatic cancer type 3 (OMIM: 613348) (autosomal dominant): Associated with an increased risk for the development of pancreatic cancer.

Protein:

PALB2 binds to and co-localizes with BRCA2 in the nucleus and most likely permits the stable intranuclear localization and accumulation of BRCA2. PALB2 also plays a critical role in homologous recombination DNA repair through its ability to recruit BRCA2 and RAD51 genes at DNA breaks. Furthermore, PALB2 serves as the molecular scaffold in the formation of the BRCA1-PALB2-BRCA2 complex which is essential for homologous DNA recombination.

Cancer type	General population	Cancer risk for PALB2 mutation carriers
Female breast cancer	Lifetime risk: 5%-10%[1,2]	For age >46 years: 3.4%[33] For age >55 years: 7.8%[33] For age >85 years: 11.6%[33]
Pancreatic cancer	Lifetime risk: 1.31%[7]	Elevated[34]
Male breast cancer	Lifetime risk: 0.1%[4,9]	For age >60 years: 1–2%[33]

Percentages are average values. For specific mutations these values might be different.

Additional information:

Several founder PALB2 mutations have been identified: c.2323C>T in the French Canadian population[52], c.1592delT in the Finnish population[53] and c.3113G>A in Australian populations.[54]

PMS2

Gene name: Postmeiotic segregation increased, S. Cerevisiae, 2 (PMS2), also known as mismatch repair gene PMSL2

OMIM gene: 600259

Associated syndromes:

- Colorectal cancer, hereditary nonpolyposis, type 1 (OMIM: 120435) (autosomal dominant): An inherited disorder that increases the risk of many types of cancer, particularly colorectal cancer.
- Mismatch repair cancer syndrome (OMIM: 276300) (autosomal recessive): A rare childhood cancer predisposition syndrome with 4 main tumor types: hematologic malignancies, brain/central nervous system tumors, colorectal tumors, and multiple intestinal polyps, as well as other malignancies including embryonic tumors and rhabdomyosarcoma.

Protein:

The MSH2 gene encodes a protein mutS homolog 2, a member of mismatch repair family (MMR). In a complex with other members of MMR family, MSH2 acts as a DNA repair factor during DNA replication.

Cancer type	General population cancer risk	Cancer risk for PMS2 mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Not determined
Colorectal cancer	Lifetime risk: 5-6% For age (men) <30 years: 0.07-0.96% For age <40 years: 0.26-2% For age <50 years: 0.67-3.27% For age <60 years: 1.22-4.04% For age <70 years: 1.87-3.30% For age (women) <30 years: 0.07-0.79% For age <40 years: 023-1.53% For age <50 years: 0.51-2.59% For age <60 years: 0.86-3.46% For age <70 years: 1.46-2.88%	For age >70: Up to 20%[63]
Gastric cancer	Lifetime risk: 1–3%[22] 1.49% men 0.74% women	For age >70: Elevated risk[63]
Small bowel cancer	Lifetime risk: 0.2%-1%[17, 25] 7.14% men 5.26% women	For age >70: Elevated risk[63]
Endometrial cancer	Lifetime risk: 2.4-2.7%[25]	For age >70: Up to 15%[63]
Liver cancer	Lifetime risk: >5%[7]	For age >70: Elevated risk[63]
Ovarian cancer	Lifetime risk: 5-15%[3, 14]	For age >70: Elevated risk[63]
Renal cancer	Lifetime risk: ~1%[16, 17] Lifetime risk: 1.9% men Lifetime risk: 1.14% women	For age >70: Elevated risk[63]
CNS	Lifetime risk: >2%[3,14]	For age >70: Elevated risk[63]

Percentages are average values. For specific mutations these values might be different.

POLD1

Gene name: DNA polymerase delta 1 (POLD1)
OMIM gene: 174761

Associated syndromes:

- Susceptibility to colorectal cancer (OMIM: 612591) (autosomal dominant): An inherited heterogeneous disease/predisposition to colorectal cancer. It is caused by changes in different molecular pathogenic pathways, such as chromosomal instability, CpG island methylator phenotype, and microsatellite instability.

- Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (OMIM: 615381) (Autosomal dominant): A systemic disorder characterized by prominent loss of subcutaneous fat, characteristic facial appearance, and metabolic abnormalities including insulin resistance and diabetes mellitus.

Protein:

DNA polymerase delta has both 3´and 5´exonuclease activity and plays a critical role in DNA replication and repair. Also involved in completing Okazaki fragments initiated by the DNA polymerase alpha/primase complex.

Cancer type	General population cancer risk	Cancer risk for POLD1 mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Increasing with age[1,2]
Colorectal cancer	Lifetime risk: 5-6%[17] For age (men) <30 years: 0.07-0.96% For age <40 years: 0.26-2% For age <50 years: 0.67-3.27% For age <60 years: 1.22-4.04% For age <70 years: 1.87-3.30% For age (women) <30 years: 0.07-0.79% For age <40 years: 023-1.53% For age <50 years: 0.51-2.59% For age <60 years: 0.86-3.46% For age <70 years: 1.46-2.88%	Increased risk[17]

Percentages are average values. For specific mutations these values might be different.

POLE

Gene name: DNA polymerase epsilon (POLE)
OMIM gene: 174762

Associated syndromes:

- Susceptibility to colorectal cancer (OMIM: 615083) (autosomal dominant): An inherited heterogeneous disease/predisposition to colorectal cancer. It is caused by changes in different molecular pathogenic pathways, such as chromosomal instability, CpG island methylator phenotype, and microsatellite instability.
- FILS syndrome (OMIM: 615139) (Autosomal dominant): A very rare inherited disease characterized by facial dysmorphism, imunodeficiency, livedo, and short stature (FILS).

Protein:

DNA polymerase epsilon has both 3´and 5´exonuclease activity and plays a critical role in DNA replication and repair.

Cancer type	General population cancer risk	Cancer risk for POLE mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Increasing with age[17]
Colorectal cancer	Lifetime risk: 5-6%[17] For age (man) <30 years: 0.07-0.96% For age <40 years: 0.26-2% For age <50 years: 0.67-3.27% For age <60 years: 1.22-4.04% For age <70 years: 1.87-3.30% For age (woman) <30 years: 0.07-0.79% For age <40 years: 023-1.53% For age <50 years: 0.51-2.59% For age <60 years: 0.86-3.46% For age <70 years: 1.46-2.88%	Increased risk[17]

Percentages are average values. For specific mutations these values might be different.

PTEN

Gene name: Phosphatase and Tensin homolog (PTEN), also known as PTEN1 and MMAC1

OMIM gene: 601728

Associated syndromes:

- Cowden syndrome 1 (OMIM: 158350) (autosomal dominant): Associated with the development of multiple hamartomas and a high risk of benign and malignant tumors of the thyroid, breast, and endometrium and most probably also renal cell carcinoma and colorectal carcinoma.
- Bannayan-Riley-Ruvalcaba syndrome (OMIM: 153480) (autosomal dominant): Characterized by macrocephaly, intestinal polyposis, lipomas, and pigmented macules of the glans penis.
- Macrocephaly/autism syndrome (OMIM: 605309) (autosomal dominant): Characterized by macrocephaly and autism.
- VATER association with macrocephaly and ventriculomegaly (OMIM: 276950) (autosomal recessive): Characterized by macrocephaly, ventriculomegaly, tracheoesophageal fistula and limb defects.
- Susceptibility to Glioma type 2 (OMIM: 613028) Associated with an increased risk of the development of gliomas.
- Meningioma (OMIM: 607174) (autosomal dominant): Associated with an increased risk of the development of meningiomas
- Prostate cancer, somatic (OMIM: 176807) (autosomal dominant): Associated with an increased risk of the development of prostate cancer.

Protein:

The PTEN gene encodes a protein tyrosine phosphatase with homology to tensin, a ubiquitously expressed tumor suppressor and phosphatase that antagonizes the PI3K signaling pathway through its lipid phosphatase activity and negatively regulates the MAPK pathway through its protein phosphatase activity.

Cancer type	General population	Cancer risk for PTEN mutation carriers
All cancers	Lifetime risk for all tumors, ages and both sexes: 6.3%[12] Lifetime risk for all cancers: 9.9%[16]	For age 20-29 years: 9%[18] For age 30-39 years: 18%[18] For age 40-49 years: 35%[18] For age 50-59 years: 63%[18] For age 60-69 years: 78%[18] For age >70: 89%[18]
Female breast cancer	Lifetime risk: 5-10%[1, 2]	For age 20-29 years: 0%[17] For age 30-39 years: 4%[17] For age 40-49 years: 19%[17] For age 50-59 years: 53%[17] For age 60-69 years: 73%[17] For age >70: 81%[17]
Ovarian cancer	Lifetime risk: 5-15%[3, 14]	Low[19]
Endometrial cancer	Lifetime risk: 3%[17]	For age 20-29 years: 1%[17] For age 30-39 years: 1%[17] For age 40-49 years: 1%[17] For age 50-59 years: 9%[17] For age 60-69 years: 19%[17] For age >70: 19%[17]
Thyroid cancer	Lifetime risk: 1%[17]	For age 20-29 years: 4%[17] For age 30-39 years: 5%[17] For age 40-49 years: 9%[17] For age 50-59 years: 17%[17] For age 60-69 years: 21%[17] For age >70: 21%[17]
Colorectal cancer	Lifetime risk: 6%[17]	For age 20-49 years: 0% For age 50-59 years: 3%[11] For age 60-69 years: 13%[11] For age >70: 16%
Renal cancer	Lifetime risk: ~1%[16,17]	For age 20-29 years: 0%[17] For age 30-39 years: 1%[17] For age 40-49 years: 1%[17] For age 50-59 years: 3%[17] For age 60-69 years: 7%[17] For age >70: 15%[17]
Melanoma	Lifetime risk:1.1%[16]	Lifetime risk: 8.5%[16]

Percentages are average values. For specific mutations these values might be different.

RAD51C

Gene name: RAD51C, Homolog of S. Cervisiae

OMIM gene: 602774

Associated syndromes:

- Fanconi anemia, complementation group O (OMIM: 613390) (autosomal recessive): Characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. The cellular hallmark of FA is hypersensitivity to DNA crosslinking agents and high frequency of chromosomal aberrations pointing to a defect in DNA repair.
- Susceptibility to breast-ovarian cancer, familial, (OMIM: 613399) (autosomal dominant): Associated with an increased risk of the development of breast cancer.

Protein:

RAD51 paralog C, encoded by RAD51C, is a member of the RAD51 family and it is involved in homologous recombination and DNA repair. It has an early function in DNA repair in facilitating phosphorylat on of the checkpoint kinase CHEK2 and thereby transduction of the damage signal, leading to cell cycle arrest and homologous recombination activation. RAD51C also protects RAD51 from ubiquitin-mediated degradation, that is enhanced following DNA damage. It also plays a role in regulating mitochondrial DNA copy number under conditions of oxidative stress in the presence of RAD51 and XRCC3. RAD51C contributes to DNA cross-link resistance, sister chromatid cohesion and genomic stability and it is involved in maintaining centrosome number in mitosis.

Cancer type	General population	Cancer risk for RAD51C mutation carriers
Female breast cancer	Lifetime risk: 5-10%[1,2]	Lifetime risk: 1%[39]
Ovarian cancer	Lifetime risk: 5-15%[3,14]	Lifetime risk: 9%[39]

Percentages are average values. For specific mutations these values might be different.

RAD51D

Gene name: RAD51 homolog of S. Cervisiae D (RAD51D) or RAD51 paralog D

OMIM gene: 602954

Associated syndromes:

- Susceptibility to familial breast-ovarian cancer 4, BROVCA4 (OMIM: 614291) (autosomal dominant): Associated with familial predisposition to cancer of the breast and ovaries, characterized by early age of onset (often before age 50), increased chance of bilateral cancers, frequent occurrence of breast cancer among men, and increased incidence of tumors of other specific organs (prostate).

Protein:

The RAD51D gene encodes a member of RAD51 protein family, which is known to be involved in the homologous recombination and repair of DNA. RAD51D binds to single-stranded DNA and has DNA-dependent ATPase activity. It is also involved in telomere maintenance.

Cancer type	General population	Cancer risk for RAD51D mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Not determined
Ovarian cancer	Lifetime risk: 5-15%[3, 14]	For age >70: 1.32-6.3%[14] For age >80: 10%[14]

Percentages are average values. For specific mutations these values might be different.

SMAD4

Gene name: SMAD family member 4, previously known as MADH4
OMIM gene: 600993

Associated syndromes:

- Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (OMIM: 175050) (autosomal dominant): includes the features of both the juvenile polyposis syndrome (JPS) and hereditary hemorrhagic telangiectasia (HHT), characterized by hamartomatous polyps, vascular dysplasia, telangiectases and arteriovenous malformations of the lungs, liver, brain, and gastrointestinal tract, and increased risk of gastrointestinal cancer.

- Myhre syndrome (OMIM: 139210) (autosomal dominant): Characterized by mental retardation, dysmorphic facial features, including microcephaly, midface hypoplasia, short stature and deafness.

- Pancreatic cancer (OMIM; 260350) (autosomal dominant, somatic mutations): Characterized by one of the highest mortality rates of all cancers, with a 5-year relative survival rate of less than 5%.[27]

- Polyposis, juvenile intestinal 3 (OMIM. 174900) (autosomal dominant): Characterized by predisposition to hamartomatous polyps in the gastrointestinal tract, specifically in the stomach, small intestine, colon, and rectum. SMAD4 mutations account for about 20% of JPS cases.[14, 27]

Protein:

The SMAD4 gene encodes a protein involved in signal transduction of the transforming growth factor-beta superfamily and bone morphogenic proteins by mediating transcriptional activation of target genes. SMAD4 serves both as a transcription factor and as a tumor suppressor, regulating cell proliferation and growth. Most pathogenic variants are unique, but three have been reported in multiple unrelated families: c.1244_1247delACAG, c.1162C>T, and p.Arg361Cys.[14]

Cancer type	General population cancer risk	Cancer risk for SMAD4 mutation carriers
All hereditary cancers	Lifetime risk for all hereditary cancers: 2-3%[1,2] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	Not determined
Colorectal cancer	Lifetime risk: 5-6%[17] For age (men) <30 years: 0.07-0.96% For age <40 years: 0.26-2% For age <50 years: 0.67-3.27% For age <60 years: 1.22-4.04% For age <70 years: 1.87-3.30% For age (women) <30 years: 0.07-0.79% For age <40 years: 023-1.53% For age <50 years: 0.51-2.59% For age <60 years: 0.86-3.46% For age <70 years: 1.46-2.88%	For age >42: 20-25% For age >80: 40-50%[27]
Gastric cancer	Lifetime risk: 1–3%[22] 1.49% men 0.74% women	For age >80: up to 21%[22,27]
Bowel cancer	Lifetime risk: 0.2-1%[17,25] 7.14% men 5.26% women	For age >80: elevated risk (rare)[17,27]
Pancreatic cancer	Lifetime risk for all hereditary cancers: 2-3%[7] For age <10 years: 0.17-0.79% For age <20 years: 0.18-1.67 For age <30 years: 0.45-4.13% For age <40 years: 1.06-9.85% For age <50 years: 6.57-31% For age <60 years: 13.09-38.2% For age <70 years: 17.85-31.59% For age <80 years: 16.83-21.23%	For age >80: elevated risk (rare)[7,27]

Percentages are average values. For specific mutations these values might be different.

STK11

Gene name: Serine Threonine Protein Kinase 11 (STK11), also known as LKB1

OMIM gene: 602216

Associated syndromes:

- Peutz-Jeghers syndrome (OMIM: 175200) (autosomal dominant): Characterized by melanocytic macules of the lips, buccal mucosa, and digits, multile gastrointestinal hamartomatous polyps, and an increased risk for various neoplasms.
- Pancreatic cancer (OMIM: 260350) (autosomal dominant): Associated with an increased risk for the development of pancreatic cancer.

Protein:

STK11 gene encodes serine/threonine kinase that regulates energy metabolism and cell polarity. This enzyme is a tumor suppressor, which means that it helps to keep the cells from growing and dividing too fast or in an uncontrolled way.

STK11 enzyme helps certain types of cells to orient themselves correctly within tissues (polarization) and assists in determining the amount of energy a cell uses. It also promotes programmed cell death known as apoptosis.

Cancer type	General population	Cancer risk for STK11 mutation carriers
Overall cancers in individuals with clinical symptoms of PJS	Lifetime risk: 10-70%[18]	For age <20 years: 1%[20] For age >40 years: 19%[20] For age >60 years: 63%[20] For age >70 years: 81%[20]
Colorectal cancer	Lifetime risk: 6%[17]	For age >40 years: 3%[21] For age >50 years: 5%[21] For age >60 years: 15%[21] For age >70 years: 39%[21]
Pancreatic cancer	Lifetime risk: 1.31%[7]	For age >50 years: 5%[21] For age >60 years: 17%[21]
Female breast cancer	Lifetime risk: 5-10%[1, 2]	For age >40 years: 8%[21] For age >60 years: 31%[21]
Gastric cancer	Lifetime risk: 1–3%[22]	For age >30 years: 1%[21] For age >40 years: 9%[21] For age >50 years: 15%[21] For age >60 years: 33%[21]
Bowel cancer	Lifetime risk: <1%[17,25]	For age >30 years: 1%[21] For age >40 years: 9%[21] For age >50 years: 15%[21] For age >60 years: 33%[21]
Ovarian cancer	Lifetime risk: 5-15%[3,14]	For age >30 years: 1%[21] For age >60 years: 18%[21]
Endometrial cancer	Lifetime risk: 3%[17]	Risk for age 15-64 years: 9-16%[26]
Cervical cancer	Lifetime risk: 1.8-2.3%[24]	Lifetime risk: 5.2%[21] For age >30 years: 1%[12] For age >60 years: 18%[21]
Lung cancer	Risk up to age 68: 1.7%[23]	Lifetime risk for men: 13%[21] Lifetime risk for women: 1%[21]

Percentages are average values. For specific mutations these values might be different.

TP53

Gene name: Tumor protein 53 (TP53), also known as P53

OMIM gene: 191170

Associated syndromes:

- Li-Fraumeni syndrome (OMIM: 151623) (autosomal dominant): Characterized by an increased risk for a variety of tumor types. The most common types are soft tissue sarcomas and osteo sarcomas, breast cancer, brain tumors, leukemia, and adrenocortical carcinoma.
- Nasopharyngeal carcinoma (OMIM: 607107) (autosomal dominant): Associated with a increased risk for the development of nasopharyngeal carcinoma (NPC).
- Osteosarcoma (OMIM: 259500) (autosomal dominant): Associated with an increased risk for the development of osteosarcomas.
- Adrenal cortical carcinoma (OMIM: 202300) (autosomal dominant): Associated with an increased risk for the development of adrenocortical carcinoma (ADCC).
- Breast cancer (OMIM: 114480) (autosomal dominant): Associated with an increased risk for the development of breast cancer.
- Choroid plexus papilloma (OMIM: 260500) (autosomal dominant) Associated with an increased risk for the development of choroid plexus tumors ranging from benign choroid plexus papillomas (CPPs) to malignant choroid carcinomas (CPCs).
- Colorectal cancer (OMIM: 114500) (autosomal dominant): Associated with an increased risk for the development of colorectal cancer.
- Hepatocellular carcinoma (OMIM: 114550) (autosomal dominant): Associated with an increased risk for the development of hepatocellular carcinoma.

- Pancreatic cancer (OMIM: 260350) (autosomal dominant): Associated with an increased risk for the development of pancreatic cancer.
- Basal cell carcinoma type 7 (OMIM: 614740) (autosomal dominant): Associated with an increased risk for the development of basal cell carcinoma (BCC7).
- Susceptibility to Glioma type 1 (OMIM: 137800) (autosomal dominant): Associated with an increased risk for the development of gliomas.

Protein:

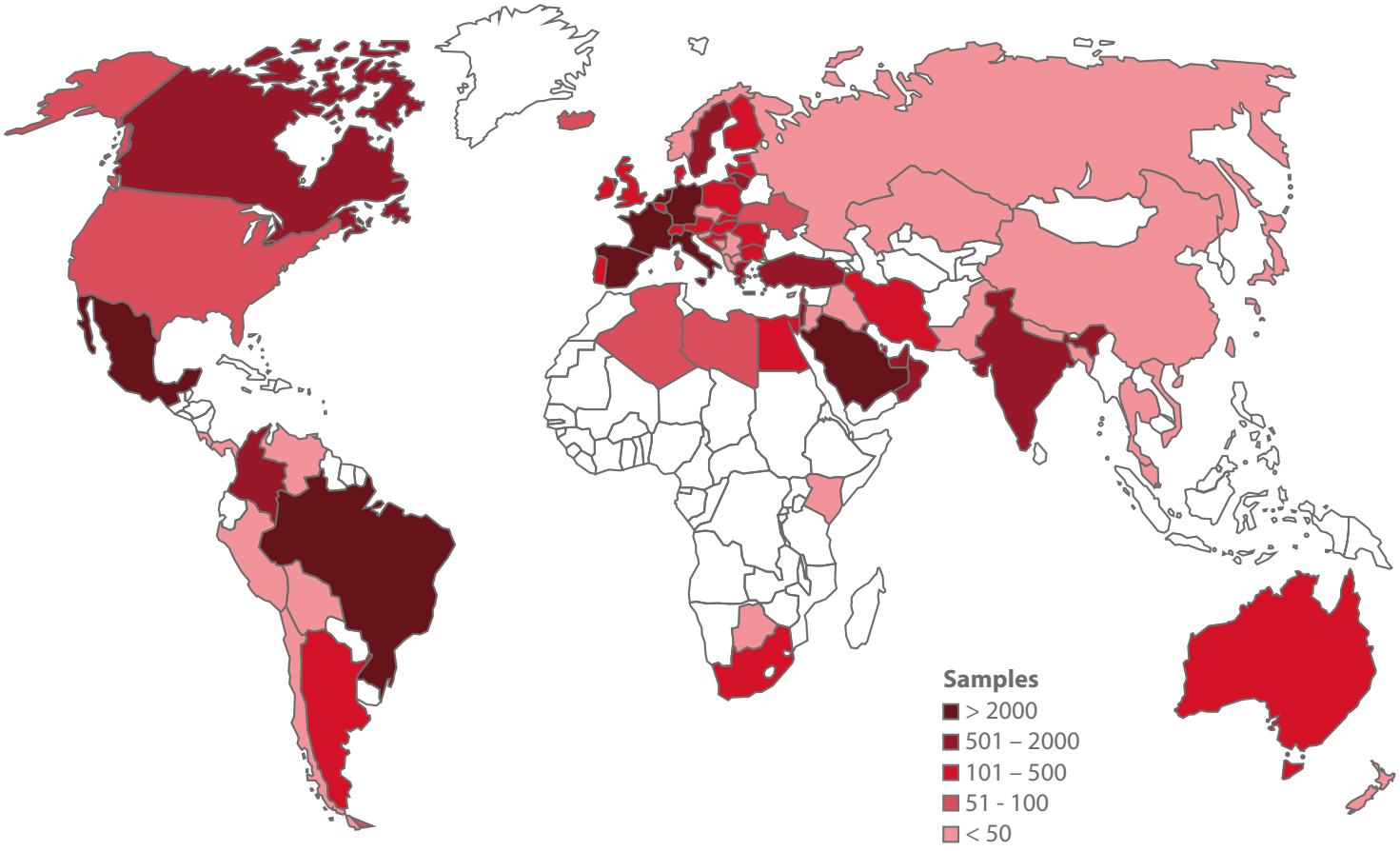
Tumor protein p53: TP53 is a nuclear protein that acts as a regulator of DNA activity, depending on the level of DNA damage. When the DNA in a cell becomes damaged by toxic agents, TP53 plays a critical role in determining whether the DNA will be repaired or the damaged cell will undergo self-destruction, i.e. apoptosis.

If the DNA can be repaired, p53 activates other genes, working as a transcriptional factor, and subsequently leads to DNA repair. If the DNA damages are numerous, TP53 regulates other sets of genes which keep cells with mutated DNA from dividing and lead to subsequent apoptosis and tumor prevention.

Cancer type	General population	Cancer risk for TP53 mutation carriers
All cancers	Lifetime risk for all tumors, ages and both sexes: 6.3%[1,2]	For age 0-15 women: 12%[12] For age 0-15 men: 19%[12] For age 16-45, women: 82%[12] For age 16-45, men: 27%[12] For age >45, women: 100%[12] For age >45, men: 54%[12]
Female breast cancer	Lifetime risk: 17%[13]	For age <30 years: 2-3%[13] For age >70 years: 31.2%[13]
Ovarian cancer	Lifetime risk: 5%-15%[3,14]	Lifetime risk: 50%[14]
Male breast cancer	Lifetime risk: 0.001%[4]	Lifetime risk 4.2%[15]
Soft tissue sarcoma	Lifetime risk: <1%[27]	Lifetime risk: 11%[12]
Osteosarcoma	Lifetime risk: <1%[29]	Lifetime risk: 15.8%[12]
Brain tumor	Lifetime risk: 2%[28]	Lifetime risk: 9%[12]
Adrenocortical carcinoma (ACC)	Lifetime risk: 1-2%[12]	Lifetime risk: 50%[16]

Percentages are average values. For specific mutations these values might be different.

Countries sending samples to CENTOGENE



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