MEDICOVER
GENETICS

# CATALOGUE
# HEREDITARY CANCER PANELS

Predict&Prevent

Physician Information

# MEDICOVER GENETICS
# ABOUT US

Medicover Genetics was developed as a strategic business area within Medicover, **a network of hospitals and diagnostic laboratories across 10 European markets**. Our purpose is to empower people to use comprehensive and meaningful genetic tests at the forefront of their diagnostic journey, fueled by our vision to place genetics at the core of medical decisions. We want to achieve this by leveraging advancements in genomics to develop relevant diagnostic solutions, supported by professional medical interpretation, to improve people's health and well-being.

Spanning cytogenetic analyses, molecular pathology solutions, the latest in next generation sequencing (NGS) technology and microbiome sequencing, Medicover Genetics offers a **complete in-house and tailor-made portfolio produced in our laboratories in Germany** and offered internationally. Medicover is the sole testing site in Europe for Bionano's Saphyr® technology: the third-generation optical mapping solution which resolves large-scale structural variations currently missed by NGS.

Using a robust diagnostics pipeline, we make **NGS testing and variant discovery efficient**, scalable and accessible by converting NGS data into customized clinical reports in a timely manner, **thereby decreasing turnaround times**.

**Patient support through genetic counselling** is integral to our patient journey and crucial to explain complex findings to them as well as assist physicians as they support their patients. With more than **20 certified genetic counsellors** across our markets, we are able to provide this locally and in the local language.

MEDICOVER GENETICS

## PURPOSE

To empower people to use comprehensive and meaningful genetic tests at the forefront of their diagnostic journey

## VISION

To place genetics at the core of medical decisions

## MISSION

Leverage advancements in genomics to develop relevant diagnostic solutions, supported by professional medical interpretation, to improve people's health and well-being

## VALUES

Humanity | Passion | Innovation | Medical Excellence | Integrity

# MEDICOVER GENETICS
# WHY US

• A network of laboratories and medical institutions makes Medicover Genetics a **leader in genetic testing** in Germany with foundations dating back to 1998

• A clinical team comprised of scientists, physicians and medical geneticists, several with **>20 years of experience** in genetic testing, assuring meaningful and comprehensive genetic tests

• **Up-to-date diagnostic algorithms** and gene panels based on current scientific literature and international guidelines

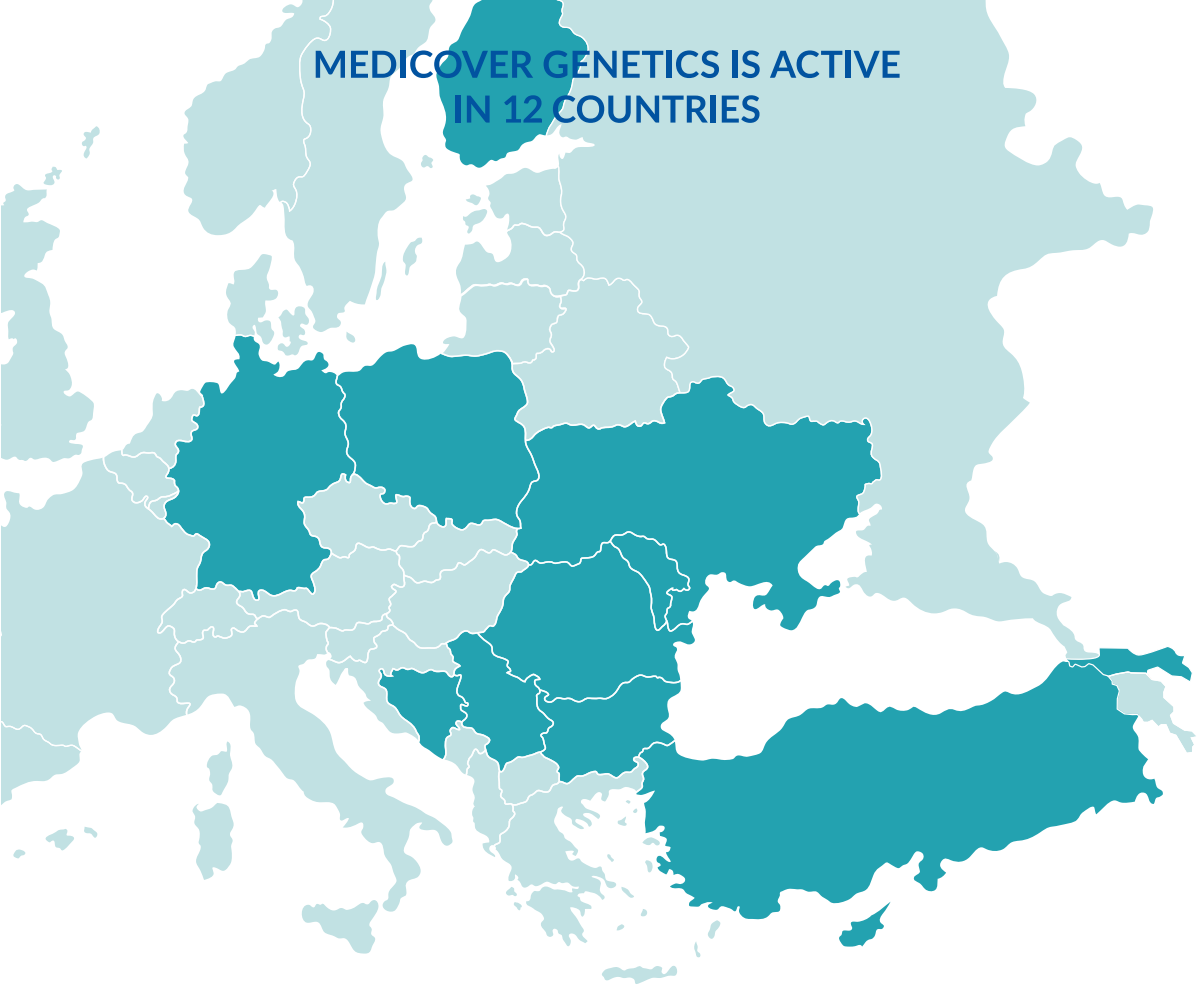
• Expertise in gene variant analysis ensuring "**no variant left behind**"

• Cutting-edge technology in sequencing and laboratory methods allows for **short turnaround times**

• **Quality** assessed by several certified bodies, including EFI, DIN EN ISO 9001, DIN EN ISO15189 accreditation for medical laboratories, DIN EN ISO/IEC 17025 accreditation for testing and calibration laboratories and a generally valid GMP (Good Medical Practice) certificate

• **Data Privacy** is your right and our priority

# MEDICOVER GENETICS IS ACTIVE IN 12 COUNTRIES



BOSNIA-HERZEGOVINA | BULGARIA | CYPRUS | FINLAND | GEORGIA
GERMANY | MOLDOVA | POLAND | ROMANIA | SERBIA | TURKEY | UKRAINE

# MEDICOVER GENETICS
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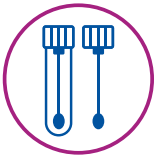
## TECHNICAL INFORMATION

| | |
|---|---|
| Technology | Next generation sequencing, Illumina NovaSeq6000 |
| Gene Coverage & Depth | >95% of the exome yields at least 20X sequence depth with 5bp into flanking introns |
| Single Nucleotide Variant (SNV) Sensitivity | 99.93% |
| Insertions/Deletions (Indel) Detection | Up to 21bp |
| Indel Sensitivity | 95.32% |
| Indel Precision | 94.71% |
| Human Reference Genome | GRCh38 |
| Pathogenic Variant Confirmation | Sanger sequencing (only if quality falls below our criteria) of pathogenic or likely pathogenic variants |
| Variant Classification | According to ACMG guidelines |

## HOW TO ORDER

**STEP 1**
**TEST ORDERED**
Patient visits specialist to find the right test



**STEP 2**
**SAMPLE COLLECTED**
Sample collected at nearest blood drawing point (BDP)

**STEP 3**
**SAMPLE PROCESSED**
Sequencing is performed in Germany

**STEP 4**
**RESULTS DELIVERED**
Report is delivered to you and your patient

## GENETIC COUNSELLING

Genetic counselling by our local Medicover Counsellors is available upon request

## MATERIAL REQUIRED

1 ml EDTA blood sample or 1 Medicover Genetics Buccal Swab Kit

## TURNAROUND TIME

15-25 working days

For complete information about our panels, including technical information and gene list, please visit: https://www.medicover-genetics.com

# HEREDITARY CANCER PANELS OVERVIEW

## BACKGROUND

Cancer is one of the leading causes of death worldwide and hereditary tumor diseases account for about 5-10% of all cancers. If the genetic modification which predisposes the tumor disease is known, it can be directly detected using a patient sample, as all cells of the organism carry the same genetic modification. Carriers are heterozygous and remain asymptomatic until the second intact allele is spontaneously inactivated by another variant ("second hit") ("loss of heterozygosity", LOH). If this occurs in tumor suppressor genes, leads to uncontrolled cell growth and the development of a malignant cell clone. However, spontaneously occurring variants can also lead to the activation of growth factors (protooncogenes), which also leads to uninhibited cell proliferation. In most cases, the risk of developing a tumor during the course of life is very high for carriers of a germline variant. Carriers should be offered frequent screening checks, preventive surgical measures if necessary and psycho-oncological care.

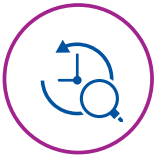
Our comprehensive panel is designed to include "core" genes that are highly associated with the occurrence of hereditary cancer. Additionally, we have expanded our panels to include genes that have been observed in just a few cancer cases.

## TARGET POPULATION

Adults interested in taking the test fall into several categories including:

**Relatives of patients diagnosed with cancer at a young age (>50)**

**Patients diagnosed with cancer who want to know if there is a genetic cause**



**People with a strong family history of cancer**

## SUBPANELS

| | | | |
|---|---|---|---|
| 54 genes Comprehensive Cancer Panel | | 22 genes Fanconi anemia | 7 genes Unspecific tumor syndromes |
| 2 genes Breast & Ovarian BRCA1/2 | 19 genes Breast & Ovarian core | 27 genes Breast & Ovarian extended | 20 genes Gastrointestinal |
| 16 genes Colon, core | 21 genes Colon, extended | 15 genes Pancreas | 14 genes Skin |
| 14 genes Endocrine | 11 genes Kidney | 14 genes Nervous System/ Brain | 11 genes Prostate |

# COMPREHENSIVE HEREDITARY CANCER PANEL

## BACKGROUND

The comprehensive cancer panel analyses **54 genes associated with >30 cancer types spanning 10 organs and systems** including breast, ovary, colon, endocrine system, pancreas, stomach, prostate, skin, kidney and central nervous system/brain. The outcome of the test can be a risk estimation of developing cancer from a genetic cause. If a person has an estimated high cancer risk, certain actions can be taken to reduce the likelihood of developing the cancer such as undergoing routine monitoring. Additionally, family members can be informed and encouraged to get tested.

If a pathogenic variant is identified in one of these genes, the risk of developing one of these syndromes is higher as compared to the average risk in the general population. Conversely, if a pathogenic variant is not identified, this does not preclude the possibility of developing cancer from unknown genetic factors or sporadic causes.

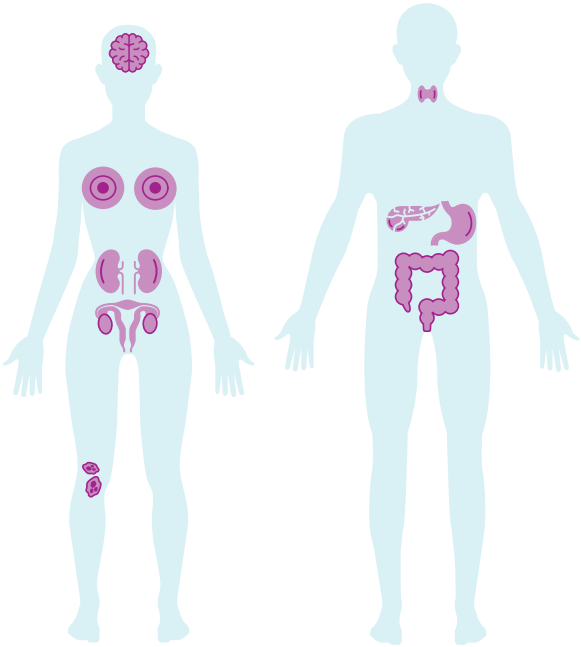
Our genetic counsellors can provide a detailed interpretation of the diagnostic report and advice on preventative measures and surveillance recommendations.

**54 genes**

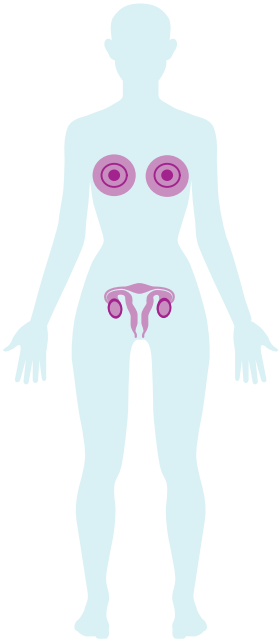
APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CHEK2, DICER1, EPCAM, FH, FLCN, GREM1, MAX, MEN1, MET, MITF, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, POT1, PTCH1, PTEN, RAD51C, RAD51D, RET, RNF43, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, STK11, SUFU, TMEM127, TP53, VHL

# DISORDERS INCLUDED

- Basal Cell Carcinoma Syndrome/Gorlin-Goltz Syndrome
- Birt-Hogg-Dub Syndrome
- Breast Cancer
- Colorectal Cancer
- Constitutional Mismatch Repair Deficiency
- DICER1 Syndrome
- Familial Adenomatous Polyposis
- Fanconi Anemia
- Gastric Cancer
- Hereditary Mixed Polyposis
- Hyperparathyroidism-Jaw Tumor Syndrome
- Juvenile Polyposis Syndrome
- Leiomyomatosis and Renal Cell Cancer
- Li-Fraumeni Syndrome
- Lynch Syndrome
- Medullary Thyroid Carcinoma
- Melanoma
- Multiple Endocrine Neoplasia (MEN) 1
- MEN2
- MEN4
- Neurofibromatosis Type I
- Ovarian Cancer
- Pancreatic Cancer
- Paragangliomas
- Parathyroid Carcinoma
- Peutz-Jeghers Syndrome
- Pheochromocytoma
- PTEN Hamartoma Tumor Syndrome
- Renal Cell Carcinoma
- Sessile Serrated Polyposis Cancer Syndrome
- Tumor Predisposition Syndrome
- Von Hippel-Lindau Syndrome



# BREAST AND OVARIAN CANCERS



## BACKGROUND

With a share of approximately 30% of all cancers, breast cancer is by far the most common tumor in women in Europe. Ovarian cancer accounts for 3.3% of all new cancer cases in female patients and it is estimated that 5-10% of all breast cancers and 10-25% of ovarian cancers are hereditary.

Testing is recommended for people with a high incidence of breast and/or ovarian cancer in their family, or who have a relative diagnosed with breast/ovarian cancer <50 years.

## SUBPANELS

**2 genes**

**BREAST AND OVARIAN CANCER, BRCA1, BRCA2**
BRCA1, BRCA2

**19 genes**

**BREAST AND OVARIAN CANCER, CORE PANEL**
ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MLH1, MLH3, MSH2, MSH3, MSH6, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53

**27 genes**

**BREAST AND OVARIAN CANCER, EXTENDED PANEL**
ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, RECQL, SMARCA4, SMARCB1, STK11, TP53, XRCC2

**1 in 3 cancers in women are either breast or ovarian cancer**

**1 in 4 cases have pathogenic variants in BRCA1/BRCA2**

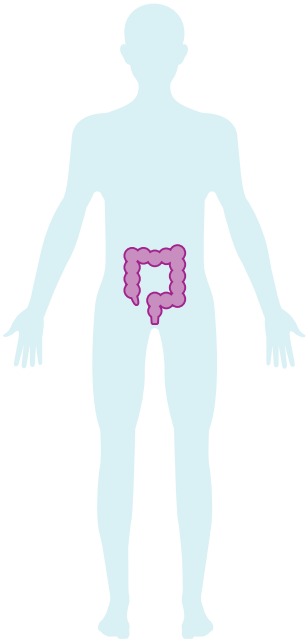
**5% cases have pathogenic variants in other genes**

Pathogenic variants in the *BRCA1* or *BRCA2* genes are detected in about 24% of women to whom one of the target population criteria applies. Pathogenic changes in one of the genes significantly increases the risk of breast and ovarian cancer, but are also associated with a slightly increased risk of other cancers, e.g., pancreatic, prostate and male breast cancer. Carriers are recommended to undergo intensive screening check-ups and, if necessary, preventive measures (e.g., prophylactic mastectomy).

A further 4% of patients who fulfill one of the target population criteria and in whom no *BRCA1/2* variant has been detected are carriers of a genetic modification in the genes *CHEK2* (1.5%), *PALB2* (1.2%) or *RAD51C* (1%). While *CHEK2* and *PALB2* are associated with a moderately increased risk of breast cancer, *RAD51C* variants are associated with an increased risk of ovarian cancer. The prevalence of pathogenic variants in other risk genes (e.g., *ATM*, *BARD1*, *BRIP1*, *CDH1*, *NBN*, *RAD51D*, *TP53*, *PTEN*, *STK11*) is below 1% in each case).

# COLON CANCERS

## BACKGROUND



The third leading case of cancer death, colon cancer accounts for 13% of all adult cancers and is the most diagnosed cancer amongst men, with Europe having one of the highest recorded incidences in the world. The 5-year survival rate for early stage cancers (stages I and II) is around 90%, with a sharp decline in stage IV to 5%. Therefore, early screening and monitoring of persons at-risk of developing cancer can save lives. Up to 10% of colon cancer is caused by a germline variant. Our core panel includes high evidence, actionable genes in several known colon cancer syndromes and the extended panel offers two additional genes that have appeared in just a few cases to date.

## SUBPANELS

**16 genes**

**COLON CANCER, CORE PANEL**
APC, BMPR1A, EPCAM, GREM1, MLH1, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, SMAD4, STK11

**21 genes**

**COLON CANCER, EXTENDED PANEL**
APC, AXIN, BMPR1A, EPCAM, GALNT12, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, RNF43, RPS20, SMAD4, STK11

**3rd leading cause of cancer death**

**13% of all adult cancers**

**Most diagnosed cancer amongst men**

## CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY (CMMRD)/LYNCH SYNDROME

CMMRD is a rare hereditary cancer predisposition syndrome, caused by biallelic mutations in the mismatch repair (MMR) genes: *MLH1*, *MLH2*, *MSH6*, *PMS2*. It appears in childhood or young adulthood and around 200 cases have been documented, resulting in more than 320 various types of abnormal malignancies, some of which include malignancies found within the blood (24%), brain and nervous system (35%), as well as colon and/or rectum carcinomas, and Lynch syndrome related cancers (38%). Lynch syndrome patients develop numerous adenomatous polyps, which clinically presents in a manner similar to familial adenomatous polyposis (FAP) or turcot syndrome (TS).

A suspected diagnosis of CMMRD should be taken into consideration when children and young adults present clinically with one of the following; Lynch syndrome related cancer (colorectal cancer, small intestine cancer, ureteral cancer, endometrial cancer, etc.), family history of CMMRD, children with café au lait spots or other characteristics of neurofibromatosis of idiopathic origin, immunohistochemical staining of MMR proteins in both tumor and normal tissue, tumors in which hypermutation has been detected, brain cancer and leukemia and lymphoma diseases without previous radiation therapy.

## FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

FAP is an autosomal dominant condition characterized by the appearance of multiple (>100 to thousands) colorectal adenomas (polyps). The polyps appear in the second decade of life, and from the age of 35 years about 95% of those affected by classical FAP have polyps with a probability of malignant degeneration of 100%. Therefore, a colectomy is the therapy of choice. In 5-10% of patients there is a deletion or duplication of the *APC* gene.

## MUTYH-ASSOCIATED POLYPOSIS (MAP)

MAP is an attenuated FAP. It is an autosomal recessive condition caused by germline variants in the *MUTYH* gene. MAP should be considered when a colorectal carcinoma is diagnosed at a young age in an individual patient or in siblings whose parents are healthy, or in the presence of a polyposis syndrome without evidence of a pathogenic variant in the *APC* gene.

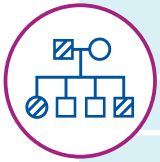
If one pathogenic *APC* variant is detected, annual colonoscopies should begin from the age of 10, and if two pathogenic *MUTYH* variants are detected, the annual procedure should start from about the age of 18. Due to an increased risk of thyroid carcinoma in FAP patients, they should have an annual sonography from the age of 15.

## POLYMERASE PROOFREADING-ASSOCIATED POLYPOSIS (PPAP)

PPAP is an inherited autosomal dominant condition and is caused by pathogenic germline variants in the *POLE* or *POLD1* genes. Heterozygous missense variants in these genes can lead to the development of multiple colorectal adenomas (>100 polyps), the formation of colorectal carcinomas and the development of endometrial carcinomas.

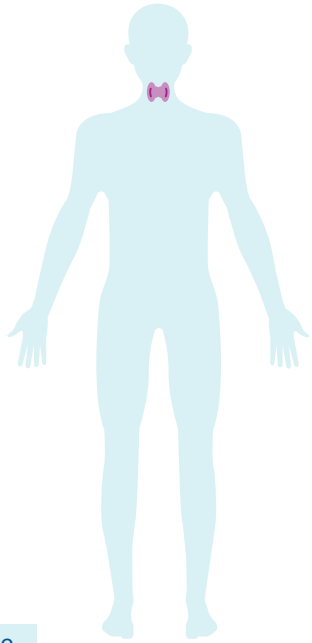
## OTHER SYNDROMES

Hamartomatous polyposis syndromes (HPS), which are sometimes difficult to distinguish from adenomatous syndromes, include juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS) and Cowden syndrome (PTEN hamartoma tumor syndrome, PHTS). All three polyposis syndromes are very rare and follow an autosomal dominant inheritance pattern. Other syndromes in which hamartomatous polyps can also (rarely) manifest are Birt-Hogg-Dubé syndrome (*FLCN* gene), MEN2 syndrome (*RET* gene) and neurofibromatosis type 1 (*NF1* gene).



| | PREVALENCE | INHERITANCE |
|---|---|---|
| FAP | 1:7,000 to 1:22,000 | Autosomal dominant |
| MAP | | Autosomal recessive |
| PPAP | Unknown | Autosomal dominant |

# ENDOCRINE TUMORS



## BACKGROUND

Endocrine cancers are cancers that begin in the hormone-producing glands that make up the endocrine system including the thyroid, adrenal, parathyroid and pituitary glands. Our panel includes genes known to be involved in several endocrine cancer syndromes including: paraganglioma-pheochromocytoma syndrome, CD73-related syndromes and multiple endocrine neoplasia syndromes.

## ENDOCRINE PANEL

**14 genes** AIP, CDC73, CDKN1B, MAX, MEN1, PTEN, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL

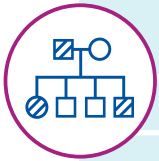
## MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

Multiple endocrine neoplasia (MEN) is a group of syndromes that favor the development of lesions in endocrine organs. A distinction is generally made between the three syndromes MEN1, MEN2 and MEN4, depending on the phenotype and the affected gene.

MEN1 syndrome is associated with the occurrence of parathyroid adenoids (>95% of patients). In addition, adenomas or malignant tumors of the endocrine pancreas, duodenum or the adenohypophysis can be found and less frequently adrenal lesions/ pheochromocytomas or thyroid lesions. MEN1 syndrome is caused by loss-of-function mutations in the *MEN1* gene.

MEN2 syndrome is usually diagnosed with medullary thyroid carcinoma (familial medullary thyroid carcinoma, FMTC). In addition, parathyroid adenomas (about 50% of those affected) and/or pheochromocytomas can be observed (MEN2A). Rarely, other phenotypic manifestations such as Marfanoid habitus, intestinal ganglioneuromatosis and/or mucosal neuroma can be observed (MEN2B, also called MEN3). The various subtypes of MEN2 syndrome are due to gain-of-function mutations in the *RET* gene.

MEN4 syndrome is extremely rare and associated with pathogenic variants in *CDKN1B*. The few patients seen so far have mainly manifested with hyperparathyroidism and/or pituitary adenomas, similar to MEN1 syndrome. In addition, adrenal gland tumors, thyroid tumors, cervical carcinomas, bronchial and gastric carcinomas have been reported in MEN4 patients.



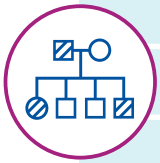
| | PREVALENCE | INHERITANCE |
|---|---|---|
| MEN 1 | 1:30,000 | Autosomal dominant |
| MEN 2 | 1:35,000 | |
| MEN 4 | Unknown | |

## PARAGANGLIOMA-PHEOCHROMOCYTOMA SYNDROME

Paragangliomas (PGL) and pheochromocytomas (PCC) are rare neuroendocrine tumors that arise from paraganglia or the adrenal medulla. Approximately 30% of cases are hereditary and one third of those have pathogenic variants in the *SDHAF2*, *SDHB*, *SDHC*, *SDHD or MAX* genes. Some PGLs secrete catecholamine, which is associated with sudden or persistent high blood pressure and can occur together with headaches, dizziness and/or sweating. These PGLs are often located in the thorax, abdomen or pelvis. Non-secreting PGLs occur more frequently in the head and neck region. These can be asymptomatic or cause impairments in the ear, nose and throat area (e.g., hearing disorders, speech disorders due to tongue paralysis, difficulty swallowing, coughing).

PGL/PCC are associated with other hereditary tumor syndromes such as, neurofibromatosis type 1, von Hippel-Lindau syndrome, or multiple endocrine neoplasia type 2.

Screening medical check-ups are advised for carriers or persons at risk from the age of 10, or at the latest 10 years before the youngest age of disease onset in the family. If a familial pathogenic variant is confirmed, blood relatives and persons at risk can be tested starting at the age of 10.



| | PREVALENCE | INHERITANCE |
|---|---|---|
| PGL | 1:30,000 | Autosomal dominant |
| PCC | 1:35,000 | |

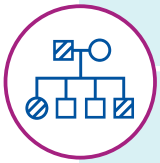
# CDC73-RELATED DISORDERS

Pathogenic variants in *CDC73* predispose patients to several syndromes associated with an increased risk of primary hyperparathyroidism (pHPT), parathyroid adenomas or carcinomas. Pathogenic *CDC73* variants are detected in 20-29% of patients with sporadic parathyroid carcinoma. These are usually functional and manifest themselves in primary hyperparathyroidism, which is usually caused by a parathyroid adenoma, but is also due to parathyroid carcinoma (in about 10-15% of cases).

In addition, (usually non-malignant) fibromas of the upper or lower jaw can be observed in 30-40% of those affected. Renal cysts, renal hamartomas, Wilms tumors or uterine tumors (benign and malignant) are diagnosed in rare cases.

Genetic testing is recommended for patients or relatives of patients with pHPT and fibromas of the upper/lower jaw and other hyperparathyroidism-jaw tumor syndrome (HPT-JT)-associated manifestations or pHPT <45 years of age and cystic, atypical and/or malignant parathyroid histology, or no nuclear expression of parafibromin via immunohistochemical staining.

Various strategies for carriers or persons at risk include; annual monitoring of the calcium serum level from the age of 6 years, periodic ultrasound scans of the parathyroid glands to exclude non-functional parathyroid adenomas/carcinomas, screening for renal cysts and, in female carriers, gynecological examinations for uterine tumors.

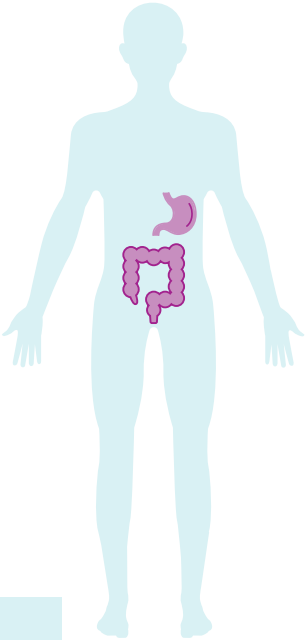


| PREVALENCE | INHERITANCE PATTERN |
|---|---|
| Unknown (200-1,000 cases reported in the literature) | Autosomal dominant |

# GASTROINTESTINAL TUMORS

## BACKGROUND

Gastric cancer is the sixth most common cancer and one of the top causes of cancer deaths in Europe, causing >100,000 deaths per year and affects more males than females. Our panel covers cancers within the gastrointestinal system, including hereditary diffuse gastric cancer (the most common hereditary gastric cancer) and juvenile polyposis syndrome.



## GASTROINTESTINAL PANEL

**20 genes**

APC, BMPR1A, CDH1, CTNNA1, EPCAM, KIT, MLH1, MSH2, MSH6, MUTYH, PDGFRA, PMS2, PTEN, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, STK11

## HEREDITARY DIFFUSE GASTRIC CANCER

Approximately 1-3% of all gastric cancers are hereditary diffuse gastric cancer (HDGC) and 40% of patients have pathogenic variants in *CDH1*. Several characteristics are observed in HDGC patients; familial clustering of the disease, young age of onset (on average 38 years), a carcinoma with signet ring cells or of the diffuse type seen by histopathology and occurrence of a cleft lip/palate.

Carriers of pathogenic *CDH1* variants have a 40-70% (men) and 60-80% (women) risk of developing stomach cancer in their lifetime. Women also have a 40-50% risk of developing lobular breast cancer.

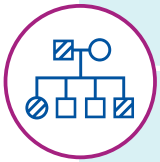
Pathogenic variants in the *CTNNA1* gene were found in a few families that had previously tested negative for *CDH1*. Apart from *CDH1* and *CTNNA1*, no other genes are currently associated with HDGC. Stomach carcinomas can also occur more frequently in HNPCC syndrome, Peutz-Jegher syndrome or FAP syndrome.

Regular endoscopy or chromoendoscopy examinations are recommended for clinically proven HDGC. If a pathogenic *CDH1* variant is detected, a prophylactic gastrectomy is indicated. Women with a *CDH1* germline variant should undergo more intensive breast examinations from the age of 30. Blood relatives and offspring of *CDH1* carriers can be specifically tested for the variants detected in the family after genetic counselling.

**Top leading cause of cancer death**

**Males are more affected than females**

**100,000 deaths per year**



| PREVALENCE | INHERITANCE PATTERN |
|---|---|
| Affects 900,000 people annually | Autosomal dominant |

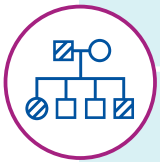
## JUVENILE POLYPOSIS SYNDROME

Juvenile polyposis syndrome (JPS) is a rare disease of the gastrointestinal tract (GI) characterized by the occurrence of juvenile (hamartomatous) polyps (>5 in the colorectal region up to multiple polyps in the entire GI tract). 75% of patients have a positive family history.

Clinically, JPS is considered certain if one of the following criteria is met; patients with numerous (>5) juvenile polyps in the colon/rectum, patients with polyps and positive family history or patients with polyps in the entire GI tract (including stomach and intestine).

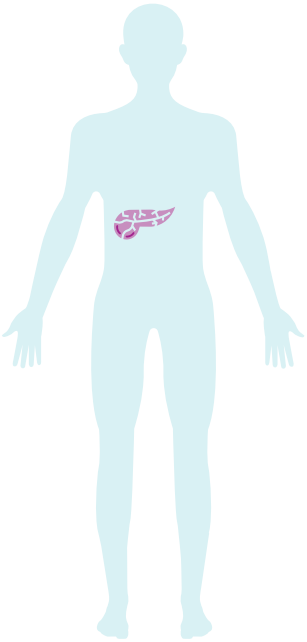
In about 60% of patients the molecular cause is a pathogenic variant in the *SMAD4* gene or the *BMPR1A* gene.

Although most juvenile polyps are benign, 10-50% of patients develop malignant tumors in the gastrointestinal tract (mainly stomach, colon, pancreas). An early diagnosis is important, due to the increased risk of tumors in childhood and adolescence, and regular endoscopic controls should be performed.



| PREVALENCE | INHERITANCE PATTERN |
|---|---|
| 1:16,000 to 1:100,000 | Autosomal dominant |

# PANCREATIC TUMORS



## BACKGROUND

Pancreatic cancers are the fourth leading cause of cancer death in Europe, with about 90,000 deaths annually. The vast majority of cases are pancreatic ductal adenocarcinomas (PDAC). Pancreatic neuroendocrine tumors (PNETs) are neoplasms that occur infrequently and represent 1-2% of all pancreatic cancers. Environmental factors such as alcohol, obesity and smoking contribute to PDAC development, do as old age and family history, with a hereditary component found in 10% of all cases diagnosed.

## PANCREATIC PANEL

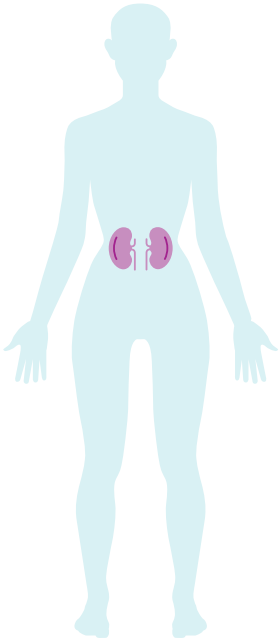
**15 genes** ATM, BRCA1, BRCA2, CDKN1B, CDKN2A, EPCAM, MLH1, MEN1, MSH2, MSH6, PALB2, PMS2, STK11, TP53, VHL

**Lowest survival rate of all cancers in Europe**

**Top 5 leading cause of cancer death**

**100,000 new cases reported each year**

# KIDNEY CANCERS



## BACKGROUND

Kidney cancer is the sixth most common cancer in men and eighth most common cancer in women and approximately 5% of all kidney cancers have a hereditary cause. Only a few genes linked to specific syndromes have been found to increase the chances of developing kidney cancer. Our panel includes genes known to be involved in kidney cancer syndromes including: renal cell cancer and papillary renal cell cancer. Additionally, we included a gene which is related to an extremely rare hereditary kidney disease that often remains undiagnosed.

## KIDNEY PANEL

**11 genes** BAP1, FH, FLCN, MET, PTEN, SDHA, SDHAF2, SDHB, SDHC, SDHD, VHL

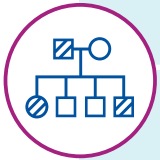
## HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER

Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC) is caused by heterozygous germline variants in the *FH* gene and characterized by the occurrence of cutaneous and/or uterine leiomyomatosis and renal cell carcinoma.

Cutaneous leiomyomas occur in about 76% of patients; uterine leiomyomas are diagnosed in almost all female carriers. The renal cell carcinomas are type 2 papillary carcinomas and have a young manifestation age (~40 years). In rare cases, clear cell renal cell carcinomas or Bellini duct carcinomas are also diagnosed. The risk for carriers of the development of renal cell carcinoma is between 15-30%, although the penetrance and expressivity can be very variable even within a family.

Genetic testing is recommended for patients or relatives of patients with histopathologically-confirmed multiple cutaneous leiomyomas, symptomatic or multiple uterine leiomyomas or type 2 papillary renal cell carcinoma occurring below the age of 40. In addition, the measurement of fumarate hydratase enzyme activity may be helpful, as a 60% reduction in enzyme activity has been found in carriers.

Proposed screening recommendations of at-risk individuals include; examination of the skin with regard to leiomyoma/leimyosarcomas at one to two-year intervals, annual gynecological examinations and annual monitoring of the kidneys.

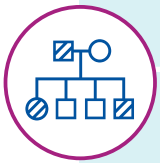


| PREVALENCE | INHERITANCE PATTERN |
| --- | --- |
| 300 families known to date | Autosomal dominant |

## BIRT-HOGG-DUBÉ SYNDROME

Birt-Hogg-Dubé syndrome (BHDS) is a rare hereditary disease that often remains undiagnosed; it is caused by genetic variants that lead to loss-of-function of the *FLCN* gene. BHDS is associated with fibrofolliculomas of the skin, lung cysts and a tendency to spontaneous pneumothorax, as well as renal cell carcinomas which occur in 25% of carriers and have variable histologies. They can be chromophobic or oncocytic, are rarely clear cell or papillary, or they can appear as hybrid tumors. If a hybrid tumor is detected, a BHDS clarification should always be performed.

Currently, there are no defined precautionary screening recommendations for those affected and healthy carriers. An annual MRI examination of the kidneys from the age of 19 has been suggested for carriers and persons at risk. Cigarette smoke and radiation exposure should be avoided, as well as high ambient pressure, which can trigger spontaneous pneumothorax. Since no manifestations before the age of 18 have yet been documented, the American Society of Clinical Oncology recommends predictive genetic testing of persons at risk from the age of 18.



| PREVALENCE | INHERITANCE PATTERN |
|---|---|
| 1:200,000 | Autosomal dominant |

# HEREDITARY PAPILLARY RENAL CELL CANCER

Hereditary papillary renal cell carcinoma (HPRCC) is a predisposition syndrome with increased risk for type 1 papillary renal cell carcinoma, which is often bilateral and multifocal. The carcinomas develop relatively late, between the age of 50 and 70. There is no data on prevalence, and only a few families with HPRCC are currently documented. Other manifestations in connection with HPRCC have not been reported so far.

HPRCC is due to gain-of-function variations in the *MET* proto-oncogene. *MET* encodes a receptor tyrosine kinase that, after ligand binding and dimerization, induces a series of intracellular signaling pathways, thereby promoting cell growth, proliferation and migration. In contrast to most syndromes with an increased predisposition to the development of tumors, genetic changes in *MET* lead to an increase in function, which results in increased kinase activity. However, the development of renal cell carcinomas probably only occurs after spontaneous, somatic duplication of the mutated *MET* allele.

Currently, there are no recommendations for preventive screening measures for carriers and persons at risk. An annual MRI examination of the kidneys has been suggested.

**30 families known to date**

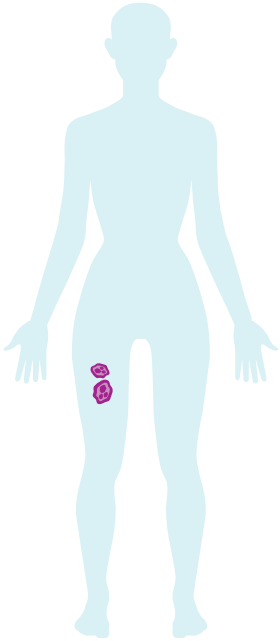
**Caused by gain-of-function in MET gene**


**Carcinomas develop between the ages of 50-70 years**

# SKIN
# TUMORS

## BACKGROUND

Approximately 90,000 new melanoma (skin) cases are diagnosed in Europe each year and around 20,000 lives are claimed. Endogenous factors (high number of pigmentation spots, light skin tone) and high UV radiation exposure are the most important risk factors. Melanoma in a first degree relative increases the risk of developing this cancer and about 5-12% of melanoma cases have a genetic cause.



## SKIN PANEL

**14 genes** BAP1, CDK4, CDKN2A, MITF, MLH1, MSH2, MSH6, NF1, PMS2, POT1, PTCH1, PTCH2, PTEN, SUFU

**90,000 new annual cases**

**20,000 deaths**


**Average age of onset between 30 and 40 years**

## BAP1-RELATED TUMOR PREDISPOSITION SYNDROME

*BAP1* tumor predisposition syndrome is associated with an increased risk of several, rare tumor diseases: Spitz nevus (spindle cell nevus), uveal melanomas, malignant mesotheliomas, cutaneous melanomas, clear cell renal cell carcinomas and basal cell carcinomas. Uveal melanomas show more aggressive disease progression with a higher risk of metastasis. Criteria for clinical diagnosis have not yet been established, but the disease can be suspected in patients who have two or more confirmed BAP1-associated tumors or a tumor and a first or second degree relative with a confirmed BAP1-associated tumor (not basal cell carcinoma and/or cutaneous melanoma due to the high frequency in the general population).

BAP1 tumor predisposition syndrome is caused by pathogenic variants in the *BAP1* gene and is an autosomal dominant inherited condition. Most carriers also have an affected parent, but the occurrence of de novo germline variants or mosaic variants cannot be excluded. So far, only point mutations in *BAP1* have been described, but the occurrence of deletions or duplications of larger gene segments cannot be excluded.

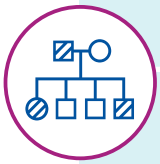
Annual check-ups of the eyes and skin for uveal melanoma or skin lesions are suggested. With regard to renal cell carcinoma, screening examinations can be carried out in accordance with those for von Hippel-Lindau syndrome. If a pathogenic variant has been identified in an affected person, blood relatives can be specifically tested for the variant on request after genetic counselling.

## FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME

Clinically, familial atypical multiple mole and melanoma syndrome (FAMMM) is suspected in patients with numerous nevi (>50), some with atypical features (asymmetric, raised, color variation, variable size) and one or more first or second degree relatives with melanoma.

FAMMM is caused by heterozygous pathogenic variants in the *CDKN2A* gene. However, a pathogenic variant only leads to tumor development after failure of the second intact *CDKN2A* allele due to spontaneous somatic variants. According to studies, about 40% of those affected with FAMMM are carriers of a pathogenic *CDKN2A* variant. The risk for melanoma is reported to be 58-92% until the age of 81. The risk of developing pancreatic carcinoma also appears to be increased and is estimated to be about 17% by the age of 76. In a few families, in which no change in *CDKN2A* could be detected, variants in the genes *CDK4* and *POT1* were identified.

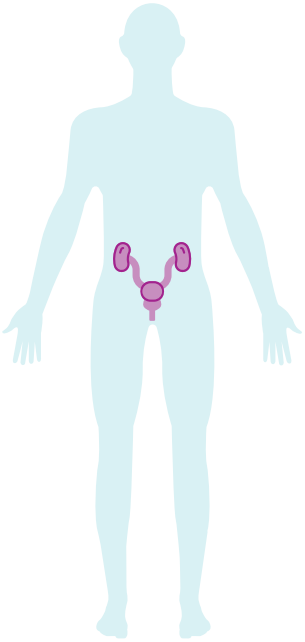
FAMMM carriers and persons at risk (10 years and older) should have regular full body skin examinations and should be encouraged to examine themselves.



| PREVALENCE | INHERITANCE PATTERN |
|---|---|
| 40% of familial cases with melanoma | Autosomal dominant |

# PROSTATE CANCER

## BACKGROUND



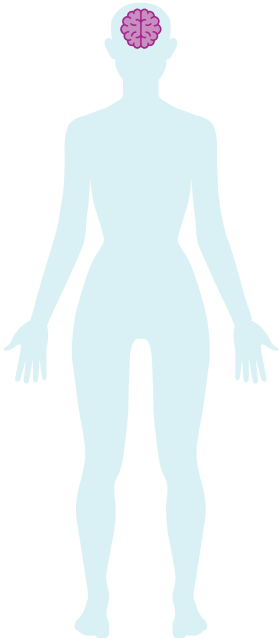
Prostate cancer is a common disease that affects 1 in 7 men from middle age. The severity of the disease varies greatly between individuals, where in some cases, a tumor may grow slowly during a person's lifetime with no negative health impact, while in others, tumors can aggressively metastasize and become life-threatening. A few mutations have been linked to hereditary prostate cancer, and variants in specific genes, such as *BRCA2* or *HOXB13*, correlate with life-threating forms of prostate cancer.

Our panel is designed to test for the occurrence of syndromes that have been associated with the development of prostate cancer, including hereditary breast and ovarian cancer, Li-Fraumeni syndrome and Lynch syndrome.

## PROSTATE PANEL

**11 genes** ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2

# CENTRAL NERVOUS SYSTEM / BRAIN TUMORS



## BACKGROUND

The cause of a brain tumor is generally unknown, but approximately 5% of brain tumors may be associated with a genetic cause. Certain conditions caused by hereditary factors may increase the chances of developing brain tumors, including Li-Fraumeni syndrome, neurofibromatosis, nervoid basal cell carcinoma and von Hippel-Lindau syndrome.

This panel includes high-evidence oncogenic genes, where pathogenic variants lead to hereditary syndromes that are characterized by several tumors across the central nervous system, including the brain. Please see the Endocrine Cancer section for paraganglioma-pheochromocytoma syndrome.

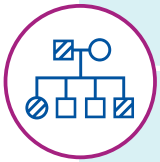
## CENTRAL NERVOUS SYSTEM/BRAIN PANEL

**14 genes** AIP, LZTR1, NF1, NF2, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMARCA4, SMARCB1, SMARCE1, TP53, VHL

# NEUROFIBROMATOSIS 1

Neurofibromatosis type 1 (NF1) is characterized by skin discoloration and tumor growth along nerves in the skin, brain and other organs. Up to 10% of all pathogenic variants in the *NF1* gene are present in the form of somatic mosaics. The highest proportion of mosaics occurs in type 2 microdeletions and atypical microdeletions.

Mosaic neurofibromatosis type 1 (MNF) is caused by a postzygotic genetic modification during embryonic development. Depending on the time of the mutation event and the affected cell population, isolated pigmentation disorders (café au lait spots with or without freckling), neurofibromas or plexiform neurofibromas can develop, each of which often occur unilaterally. If the NF1-characteristic manifestations are restricted to specific body regions, this is also called segmental NF1. The prevalence of mosaic neurofibromatosis is estimated at 1:36,000. In mosaic neurofibromatosis type 1, a genetic change in the *NF1* gene is either not detectable in DNA from peripheral leukocytes or detectable only in small amounts (<5%). For isolated pigmentation disorders, a genetic change can be detected in cultured melanocytes from the affected region. In isolated neurofibromas, a genetic alteration can only be detected in Schwann cells from the corresponding tumor and possibly in the overlying skin.



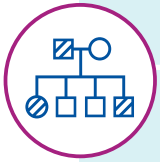
| PREVALENCE | INHERITANCE PATTERN |
|---|---|
| 1:36,000 | Autosomal dominant |

## VON HIPPEL-LINDAU SYNDROME

Von Hippel-Lindau syndrome (VHL syndrome) is a rare hereditary tumor disease which is associated with the development of mostly benign tumors. Affected persons mainly develop hemangiomas or hemangioblastomas in the retina or the central nervous system (CNS). Furthermore, patients are diagnosed with kidney and/or pancreatic cysts, renal cell carcinomas, pheochromocytomas, neuroendocrine tumors (NET) or endolymphatic sac tumors (ELST).

VHL is caused by pathogenic variants in the tumor suppressor gene *VHL*. The *VHL* gene is located on chromosome 3, consists of three exons, and encodes the VHL protein (pVHL), which is part of a protein complex that plays an important role in the regulation of gene expression in response to oxygen.

Germline variants in *VHL* do not lead directly to degeneration. Only after failure of the second intact *VHL* allele caused by spontaneous somatic variants can uncontrolled division and degeneration of the affected cells occur (Knudson's two-hit hypothesis). However, the penetrance of pathogenic *VHL* variants is estimated to be nearly 100% until the age of 65.



| PREVALENCE | INHERITANCE PATTERN |
|---|---|
| 1:50,000 | Autosomal recessive (and in very rare cases, X-linked recessive) |

There are two types of VHL: VHL type I and VHL type II.

**VHL type I** is characterized by the occurrence of hemangiomas in the retina and/or CNS, renal cell carcinomas and/or neuroendocrine tumors. However, the risk for pheochromocytomas is very low. VHL type I is associated with nonsense variants or deletions of larger gene segments. In contrast, **VHL type II** has a very high risk of developing pheochromocytomas, and missense variants are often detected in VHL in affected individuals.

Homozygous or combined heterozygous variants can cause a rare form of familial erythrocytosis (Chuvash polycythemia). Increased erythrocyte numbers and an elevated erythropoietin serum level with normal oxygen content in the tissues are seen clinically in these cases.

If a causative variant is detected, an annual systematic screening program is recommended for carriers consisting of a general clinical examination, an ophthalmological examination and a catecholamine determination, as well as MRI images of the head, spine and abdomen. Children of carriers should be specifically tested for the familial variant before the age of 5, and if the variant is detected, they should participate in the screening program from the age of 5.

**~100% penetrance of VHL variants**

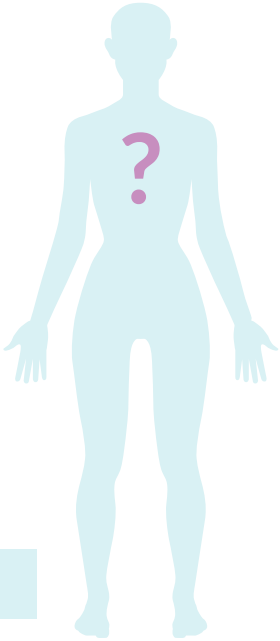
**Can affect other organs including kidney and pancreas**

**10% of VHL patients develop tumors in the inner ear**

# UNSPECIFIC TUMOR SYNDROMES

## BACKGROUND

This panel includes high-evidence oncogenic genes, where pathogenic variants lead to hereditary syndromes that are characterized by several tumors across multiple organs and tissues. Our panel includes a range of syndromes such as Li-Fraumeni syndrome, which is comparatively prevalent, to very rare syndromes such as Peutz-Jeghers Syndrome.




## UNSPECIFIC TUMOR PANEL

**7 genes** BAP1, CDKN1B, DICER1, NF1, PTEN, STK11, TP53

**PTCH1 variants in ~70% of patients**

**SUFU variants in 6% of patients**

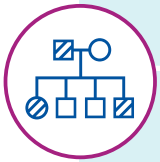
**Predisposition for basic carcinomas**

## LI-FRAUMENI SYNDROME

Li-Fraumeni syndrome (LFS) is a rare familial tumor characterized by the occurrence of multiple tumors (soft tissue sarcomas, osteosarcomas, brain tumors, breast cancer, leukemias, adrenocortical carcinomas). It is caused by germline variants in the tumor suppressor gene *TP53*, and pathogenic germline variants can be detected in up to 80% of families with classical LFS and up to 8% of very young breast cancer patients (<31 years).

The strict classical criteria for diagnosis of LFS are: index patient with sarcoma before the age of 45 and a first degree relative with carcinoma before the age of 45 and other first or second degree relatives with carcinoma before the age of 45 or sarcoma regardless of age of manifestation.

Carriers should perform intensified preventive examinations at specialized centers with regard to LFS-associated tumor diseases. The benefits and risks of radiation diagnostics and therapy should be considered. Blood relatives and offspring of *TP53* variant carriers have an increased risk of being carriers themselves, and they can be specifically tested for the variant detected in the family after a genetic consultation. Predictive testing should be performed early in infancy.



| PREVALENCE | INHERITANCE PATTERN |
|---|---|
| 1:5,000 to 1:20,000 | Autosomal dominant |

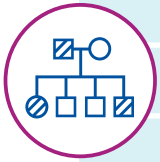
## PTEN HAMARTOMA TUMOR SYNDROME

Phenotypically, PTEN hamartoma tumor syndrome (PHTS) is caused by pathogenic germline variants in the tumor suppressor gene *PTEN* in about 60-80% of patients, and it can be divided into Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome (PS) and Proteus-like syndrome depending on the clinical manifestation.

CS is characterized by the presence of gastrointestinal hamartoma, breast cancer, endometrial carcinoma, follicular thyroid carcinoma, mucocutaneous lesions and macrocephaly (main criteria). In addition, intestinal cancer, lipomas, loss of intelligence, renal cell carcinoma and/or vascular abnormalities (secondary criteria) may occur.

BRRS is characterized by macrocephaly, intestinal hamartomatous polyps, lipomas and genital maculae. The prevalence of BRRS is unknown. The most common manifestations of Proteus syndrome are macrodactyly and hemihypertrophy.

Carriers should undergo intensive preventive examinations such as thyroid sonography and colonoscopy. Female carriers should perform intensive examinations with regards to breast and endometrial carcinomas. A prophylactic hysterectomy can be considered from the age of 40, or 5 years before the earliest age of illness in the family.

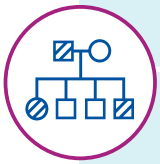


| | PREVALENCE | INHERITANCE |
|---|---|---|
| CS | 1:200,000 | Autosomal dominant |
| BRRS | 1:1,000,000 | |

## DICER1 SYNDROME

DICER1 syndrome is a rare, hereditary predisposition disorder with (moderately) increased risk for the development of certain benign and malignant tumors. It is caused by inactivating variants in the *DICER1* gene and in the few cases reported so far, pleuropulmonary blastomas, multinodular goiter, cystic nephromas, thyroid tumors, rhabdomyosarcoma and Sertoli-Leydig cell tumors of the ovaries have been diagnosed. In addition, pineoblastomas, developmental disorders, lung cysts or macrocephaly can also occur. The tumors mostly occur in children and adolescents. The severity of the tumors is variable, even within a family. In addition, there are indications that the penetrance is not complete, so that it can sometimes be difficult to identify carriers.

The treatment depends on the type of manifestation. As soon as a pathogenic variant has been identified, blood relatives can be specifically tested. However, due to the rarity of the syndrome, there are currently no precautionary screening recommendations for carriers or persons at risk. Annual physical examinations and imagine procedures, that are dependent on the age of the carrier, have been proposed.



| PREVALENCE | INHERITANCE PATTERN |
|---|---|
| Unknown | Autosomal dominant |

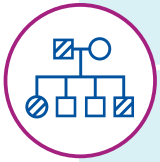
## PEUTZ–JEGHERS SYNDROME

Peutz-Jeghers syndrome (PJS) is a rare disorder with two largely characteristic symptoms:

Hamartomatous polyps in the GI tract (the jejunum has a predisposition to intussusception, obturation and intestinal bleeding, secondary anemia) and pigment spots on lips, mucous membranes, fingers, toes and vulva, occurring mostly in infancy and early childhood.

Patients also have a disposition to gastrointestinal tumors and an increased risk of ovarian, cervical, pancreatic, lung, testicular and breast cancer. Carriers have a cumulative risk of up to 90% of developing an intestinal or extraintestinal tumor during their life.

PJS is caused by pathogenic variants in the *STK11* (*LKB1*) gene. In patients with a clinically confirmed diagnosis and positive family history, the detection rate for point mutations in the *STK11* gene is up to 70%. In patients without a conspicuous family history, causative variants are detected in *STK11* in 20-60% of cases.



| PREVALENCE | INHERITANCE PATTERN |
|---|---|
| 1:50,000 to 1:200,000 | Autosomal dominant |

# NEVOID BASAL CELL CARCINOMA SYNDROME

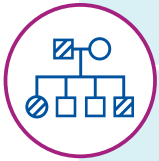
Basal cell nevus syndrome (BCNS), also known as nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin-Goltz syndrome. The most frequent clinical manifestations are multiple basal cell carcinomas (BCC), odontogenic keratocysts of the jaws, hyperkeratosis of the palms of the hands and soles of the feet, skeletal anomalies, ectopic intracranial calcifications and facial dysmorphia. The molecular causes of BCNS are pathogenic variants in the *PTCH1* gene.

Sequencing of all coding exons of the *PTCH1* gene can detect a pathogenic change in 50-85% of patients; in 6-21% of patients, a genomic deletion or duplication in the *PTCH1* gene is present. In 6% of BCNS patients a pathogenic variant in the *SUFU* gene can be identified by sequencing or deletion/duplication analysis. Patients with a pathogenic alteration in the *SUFU* gene have a higher risk of developing medulloblastoma compared to patients with *PTCH1* variants. In individual cases, pathogenic variants in the *PTCH2* gene have also been described in patients with BCNS.

**Caused by mutations in tumor-suppressor genes**

**Incomplete penetration within the same family**

**Multiple organs are affected**



| PREVALENCE | INHERITANCE PATTERN |
|---|---|
| 1:100,000 | Autosomal dominant |

# FANCONI ANEMIA SYNDROME

## BACKGROUND

Fanconi anemia can be caused by one of 22 genes and follows all three inheritance patterns, depending on the affected gene. Fanconi anemia is a clinically and genetically heterogeneous group of diseases that have the following features in common: a pre- and postnatal growth disorder; malformations of the heart, kidneys and skeleton, in particular radial and thumb malformations; pigmentation abnormalities; characteristic facial features and microcephaly of variable severity. Early bone marrow failure with an increased risk of leukemia and solid tumors, is characteristic.

## FANCONI ANEMIA PANEL

**22 genes**

BRCA1, BRCA2, BRIP1, ERCC4, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, MAD2L2, PALB2, RAD51, RAD51C, RFWD3, SLX4, UBE2T, XRCC2

**75% show skeletal malformations, e.g., hypoplastic thumb**

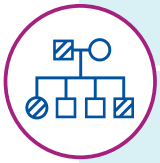
**Patients are susceptible to leukemia and solid tumors**

**40% show abnormal skin pigmentation, e.g., café au lait macules**

This is ultimately caused by a DNA repair defect, which causes increased sensitivity, especially to DNA cross-linking agents, and leads to genomic instability. Accordingly, there is increased chromosomal fragility with mitomycin C or diepoxybutane. More than 20 subtypes with pathogenic genes have been described, whereby more than half of the diseases are due to pathogenic variants in *FANCA*. Inheritance is mostly autosomal recessive, rarely autosomal dominant (*FANCR – RAD51*) or X-linked recessive (*FANCB – FANCB*). There are no strong genotype-phenotype correlations, however the following has been observed in several incidents:

- Two pathogenic variants in *BRCA2* are highly correlated with early-onset malignancies, including acute leukemia and solid tumors, with a probability of 97% by the age of six years.
- Pathogenic variants in *FANCG* may be correlated with a severe form of marrow failure and a higher incidence of leukemia compared to *FANCC*.
- Pathogenic variants in *PALB2* are associated with solid tumors such as medulloblastoma and Wilms tumor.

Regular (annual) screening examinations (bone marrow, interdisciplinary examinations to exclude solid tumors) are recommended for monitoring. Treatment involves the use of oral androgens to increase the number of red blood cells and platelets as well as G-CSF to increase the number of neutrophils. Stem cell transplantation can correct bone marrow deficiency, but not the increased risk of solid tumors.



| PREVALENCE | INHERITANCE PATTERN |
|---|---|
| 1:160,000 | Autosomal dominant, autosomal recessive and X-linked |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