HOW ONCOGENETICS PREDICTS & EDUCATES

Promoters of advanced oncogenetics open online training and multimedia raise awareness on multidisciplinary assessment of patients and their families at risk of hereditary or familial cancer
Ref. no. 2018-1-RO01-KA202-049189

Hereditary predisposition panel analysis :

- Opportunities provided by genetic testing is now an unquestionably principal role in today's patient care. The emergence of next generation DNA sequencing (NGS) techniques has brought paradigm shift in gene diagnostics. The launching of high-throughput next generation sequencing platforms has fundamentally changed the clinical practice. Genetic tests are becoming more prominent and the diagnostic power of results is increasingly important. Numerous diseases have complex multifactorial etiology, therefore a cost-effective sequencing of multigene panels. Using next generation technology, in addition to providing a more reliable diagnosis, we can reveal the pathogenetic background of hereditary syndromes in more details, highlight disease-modifying gene variants, and find new therapeutic targets as well.

- The following gene panels can be used in familiar hereditary cancer syndromes:
  - -colorectal
  - -breast
  - -endocrine

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Hereditary Colorectal Cancer Gene Panel

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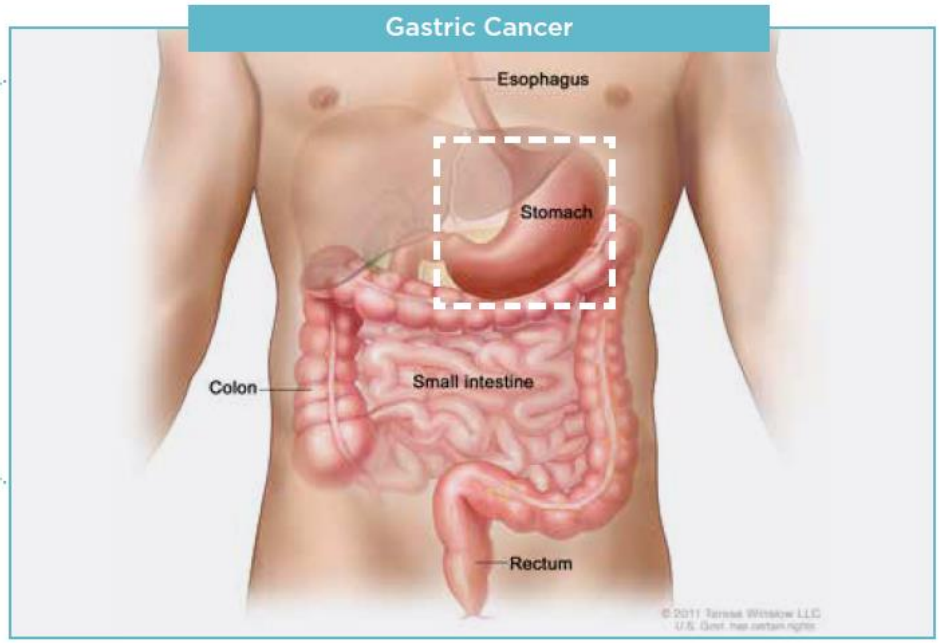
Hereditary Colorectal Cancer Gene Panel

- This genetic test is ideal for patients with a clinical suspicion of an inherited susceptibility to gastric-or colorectal cancer.
- Hereditary colorectal cancer (HCC) occurs when a person has a genetic change (mutation) that causes their cells to be more likely to become cancerous. **About 5%** of cases are inherited (hereditary colorectal cancer), while most are not. The mutation can be passed through generations in a family. Hereditary colorectal cancer is most commonly inherited in an autosomal dominant way. For dominant conditions, having only one copy of a gene mutation is enough to cause symptoms. In the case of HCC, having one mutation leads to an increased risk for cancer. If a person has a mutation in one gene for HCC, **there is a 50%** risk that each of their children will inherit this mutation.



- Identification of various genetic alterations causing an inherited susceptibility to gastric-or colorectal cancer can help doctors and healthcare practioners in the diagnosis, prognosis and thearapy of the diseases and the detection of the family members with elevated cancer risk.

- The hereditary colorectal cancer panel covers classical genes associated with Peutz-Jeghers syndrome, Cowden syndrome, colorectal cancer, APC-related attenuated familial adenomatous polyposis, Lynch syndrome, MUTYHrelated attenuated familial adenomatous polyposis, generalized juvenile polyposis/juvenile polyposis coli and familial adenomatous polyposis

Gene mutations and hareditary cancer syndromes causing cancers of the digestive system :

Hereditary colorectal cancer:

- **Lynch Syndrome,** also known as Hereditary Non-polyposis Colorectal Cancer (HNPCC), is caused by a mutation in a gene whose job is to repair the DNA damage that normally occurs as cells grow and divide ***(MSH1, MLH2, MSH6, PMS2 és EPCAM)***.. About 1 in 30 cases of colorectal cancer are linked to this condition. People with Lynch syndrome have up to an **80% risk** to develop colon cancer by age 70 years. They are also at an increased risk for many other types of cancers, such as endometrial, gastric, and prostate. In the case of gastric cancer the risk is **13%.**

- **Familial Adenomatous Polyposis** (FAP) is primarily caused by germline mutations in the ***APC*** gene mutations. People with FAP develop hundreds of benign growths (polyps) in their intestines and rectum. Because these polyps can become cancerous, the chance someone with FAP will eventually develop colorectal cancer is near **100%**. With such a high risk for cancer, screening by colonoscopy may be started in childhood, and preventative surgery to remove the colon is common. The prevalence of FAP is 1/10.000 , **0,5-1%** of colorectal cancers**.**

- Other rarer CRC predisposition syndromes include **MUTYH**-associated polyposis (MAP). The phenotype in MAP resembles that in FAP, but patients tend to develop fewer polyps (5-100) and are diagnosed at an older age. MAP is caused by biallelic germline mutations in the ***MUTYH*** gene.

- **A Peutz-Jeghers syndrome (PJS)** is characterized by intestinal hamartomatous polyps and mucocutaneous pigmentation. The polyps in PJS are most commonly located in the small bowel but may also occur anywhere along the gastrointestinal tract. Patients have an increased risk of developing extraintestinal cancers. PJS is caused by germline mutations in the ***STK11*** gene. The prevalence of PJS is approximately 1 in 200 000.

- **Juvenile polyposis (JPS):** The features in JPS are multiple hamartomatous polyps in the colon and rectum and an increased risk of colon, gastric, small intestine, and pancreatic cancers. The causative genes of JPS are ***SMAD4 and BMPR1A***. The prevalence is estimated at 1:100 000.

- **Cowden syndrome** is characterized by multiple hamartomatous tumors that most commonly appear on the skin, intestine, breast and thyroid gland. Patients have a particularly high risk of breast and thyroid cancers. Germline mutations in ***PTEN*** have been described **in 80%** of Cowden syndrome patients

- Germline mutations in ***POLE, POLD1*** and ***GREM1*** have been associated with hereditary CRC predisposition (PMID: 23263490, 26493165).*).*

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Hereditary gastointestinal cancers:

- **Hereditary Diffuse Gastric Cancer (HDGC)** is an autosomal dominant cancer syndrome that is characterised by a high prevalence of diffuse gastric cancer and lobular breast cancer. It is largely caused by inactivating germline mutations in the tumour suppressor gene *CDH1 (***1-3%** of the hereditary gastric cancers), although pathogenic variants in *CTNNA1* occur in a minority of HDGC families. The disease manifest under 40 years and tumor develops in **80%** of the *CDH1* mutations carrier under 80 years. Mutations in *CDH1* gene elevates the risk of lobular breast cancer by **39-52%.**

- **Gastrointestinal stromal tumors (GISTs)** are the most common mesenchymal tumors of the GI tract, with a wide spectrum of clinical behaviors that span from indolent and curable disorders to highly malignant diseases that metastasize and become lethal. GISTs have been reported to occur in association with cutaneous lesions and other manifestations that may mimic neurofibromatosis (***NF1*** gene) and other diseases. Despite their rarity, GISTs have recently received considerable attention because of the clinical efficacy of molecularly targeted therapy with the selective tyrosine kinase inhibitor, imatinib mesylate (ST1571; Gleevec; Novartis, East Hanover, NJ). Acquired mutations in the *KIT* proto-oncogene have been found to be involved in the pathogenesis of GISTs, and germline ***KIT*** mutations have been identified in rare kindreds with multiple occurrences of GIST among blood relatives.

- **Carney Stratakis syndrome** is an association of familial paraganglioma and gastric stromal sarcoma and it is considered to be a distinct condition from Carney triad as it is dominantly inherited and not associated with pulmonary chondroma. It is caused by the hereditary mutations of ***SDHB, SDHC and SDHD*** *(PMID: 17667967) genes.*

List of genes in Colorectal gene panel:

Basic gene panel: 21 genes

APC	ATM	BLM	BMPR1A	BRCA1	BRCA2	CDH1	CDKN2A	CHEK2	EPCAM	MLH1	MSH2
MSH6	MUTYH	PALB2	PMS2	PTEN	SMAD4	STK11	TP53	VHL			

Complementary gene panel: 17 genes

BUB1B	FANCC	GREM1	KIT*	MEN1	NF1	PDGFRA	POLE	SDHA	SDHB	SDHC	SDHD*
SMARCB1	TGFBR2	TMEM127	TSC1	TSC2	*Sequencing of the whole gene except: KIT: exon 5, 9, 11, 13, 14, 17, 19 és 21; SDHD: exon1.						

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- Known cancer-risk gene mutation in the family
- Colorectal or endometrial cancer diagnosed before age 50 years
- Diagnosis of colorectal cancer and more than 10 adenomas
- Diagnosis of colorectal cancer with a pathology evaluation that suggests Lynch syndrome
- Multiple family members with colorectal, endometrial, or thyroid cancer, polyposis, hepatoblastoma, or an eye finding called CHRPE (congenital retinal pigment epithelial hypertrophy)

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Hereditary breast and gynecological cancer panel

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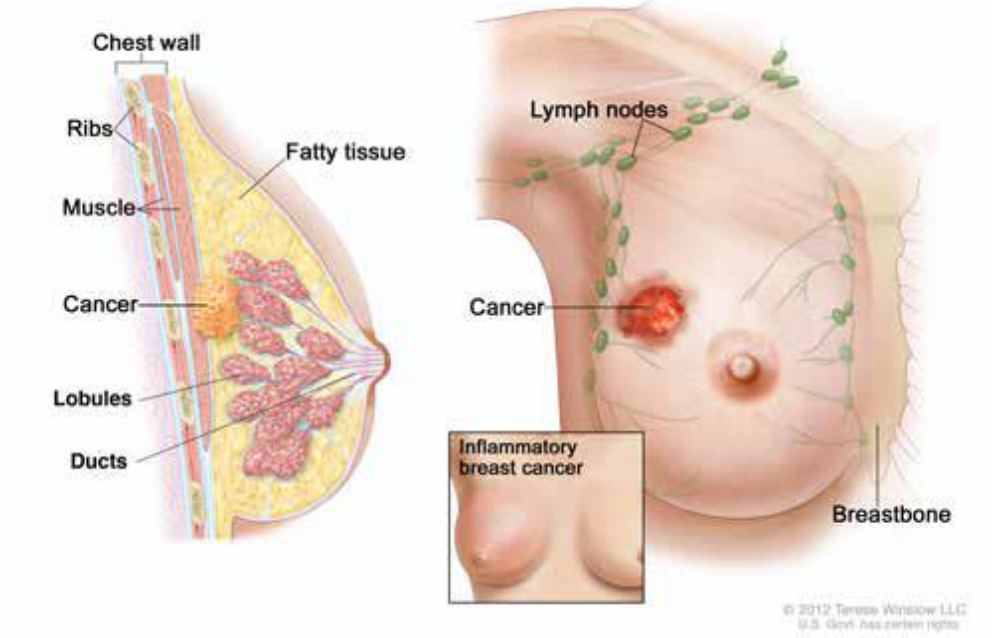
Hereditary breast and gynecological cancer panel

- This genetic test is ideal for patients with a clinical suspicion of an inherited susceptibility to breast-,ovarian or other gynecological cancers.

- Breast cancer is the most common cancer in women. Gynecological cancers are originating in the female reproductive organs and include cervical, ovarian, uterine, vaginal, and vulvar cancers.

- Breast and gynecological cancers are usually sporadic but 5-10% of the disease onset is caused by pathogenic mutations in cancer susceptibility genes. Inheritance pattern of these genetic cancer predisposition conditions is autosomal dominant. If a person has a mutation in one gene for these cancers, **there is a 50%** risk that each of their children will inherit this mutation.



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- **Breast cancer** is the most common cancer in women. Hereditary breast and ovarian cancer syndrome is caused by the mutations in ***BRCA1*** and ***BRCA2*** genes. Carriers of pathogenic mutations in *BRCA1* and *BRCA2* have an increased risk of breast cancer; **55-88%** to develop breast cancer by age 75 years and **26-48%** risk to develop ovarian cancer.

- **Lynch Syndrome,** also known as Hereditary Non-polyposis Colorectal Cancer (HNPCC), is caused by a mutation in a gene whose job is to repair the DNA damage that normally occurs as cells grow and divide ***(MSH1, MLH2, MSH6, PMS2 és EPCAM).*** People with Lynch syndrome have up to an **15 % risk** to develop ovarian and **40-60%** to develop endometrial cancer.

- **Cowden syndrome (CS)** People with Cowden syndrome often have large heads (macrocephaly) and are at an increased risk for different types of benign and malignant tumors, including endometrial, thyroid, and breast cancer. CS is caused by a mutation in the PTEN gene. The lifetime risk for breast cancer in women with Cowden syndrome can be as high as 85% and 28% risk for endometrial cancer.

- **Li-Fraumeni syndrome** is caused by a mutation in the TP53 gene. People with LFS have up to a 78% lifetime risk for cancer. Many kinds of cancer can occur in LFS, and more than one type can arise in a single person. It is important to diagnose LFS, because exposure to radiation therapy raises the cancer risk even further. LFS is a dominant condition, in that having only one mutation in the TP53gene is enough to cause the syndrome

- Li-Fraumeni syndrome (*TP53*), Cowden syndrome (*PTEN*) and Peutz-Jegherssyndrome (*STK11*) increase the likelihood of having an inherited predisposition to breast and gynecological cancer. Mutations in DNA repair genes, *RAD51C*, *RAD51D*, and *BRIP1*, have shown clear evidence of an association with ovarian cancer. Certain,most often protein truncating variants in *PALB2*, *CHEK2* and *ATM* have been shown to confer a moderate risk of breast cancer..

- **The Breast and Ovarian Cancer Gene Panel** contains the majority of genes, the mutations of these genes elevate the risk of hereditary gynaecological cancers.

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List of the genes in the Breast and ovarian cancer panel

Basic gene panel: 23 genes

ATM	BARD1	BLM	BRCA1	BRCA2	BRIP1	CDH1	CHEK2	EPCAM	MLH1	MRE11A	MSH2
MSH6	MUTYH	NBN	PALB2	PMS2	PTEN	RAD50	RAD51C	RAD51D	STK11	TP53	

Complementary gene panel : 11 genes

AKT1	ERCC2	FANCD2	FH	NF1	POLE	RB1	SDHB	SDHD*	SMARCA4	XRCC2

Who might need genetic testing for hereditary breast cancer

- Breast cancer diagnosed before age 50 years
- Known cancer-risk gene mutation in the family
- Triple negative (ER-, PR-, HER2-) breast cancer before age 60 years
- Two primary breast cancers in a single individual
- Breast cancer and either ovarian or pancreatic cancer in a single individual
- Ovarian cancer
- Male breast cancer
- Ashkenazi Jewish ancestry
- A family history of 3 or more individuals with breast, pancreatic, prostate, melanoma, or other cancers, especially if early onset or if multiple cancers occurred in a single individual

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Pancreatic and other endocrine tumors syndromes Gene Panel

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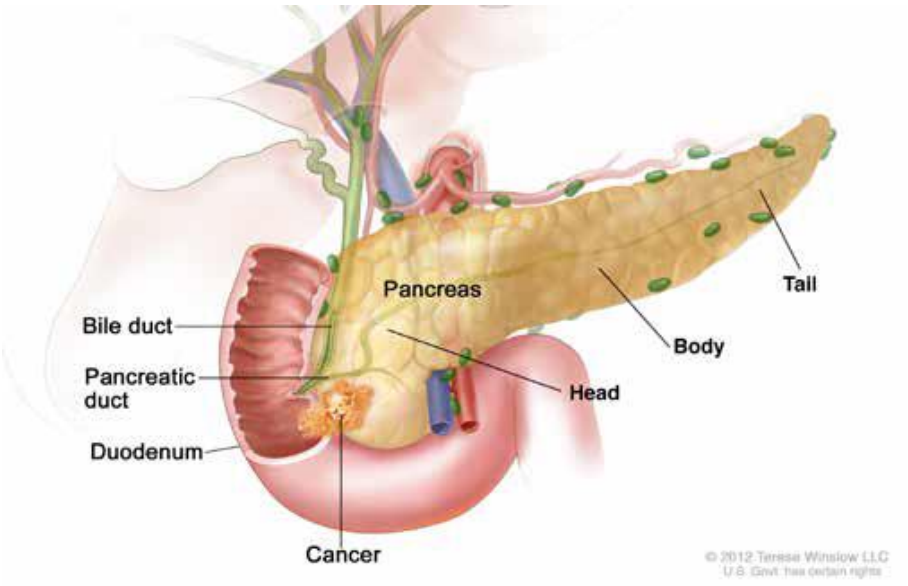
Pancreatic and other endocrine tumors syndromes Gene Panel:

- This genetic test is ideal for patients with a clinical suspicion of an inherited susceptibility to pancreatic , thyroid or other endocrine cancer.
- Hereditary endocrine tumor syndromes result in overproduction of hormones, cause growth of tumors in endocrine glands and increase the lifetime risk of developing metastatic diseases, such as gastrointestinal and pancreatic carcinomas.
- Pancreatic ductal carcinoma makes up the vast majority (90%) of all pancreatic neoplasms and remains a disease with very poor prognosis and high morbidity. Familial aggregation has been recognized in approximately **10%** of pancreatic cancers.



Information obtained from candidate gene testing may potentially be helpful in guiding clinical management in the future. Also, if an inherited susceptibility is found, patient's family members can be tested to help define their risk.

The Pancreatic –and other endocrine tumors syndromes Gene Panel can detect the most common mutations associated with a potential risk of hereditary pancreatic or other endocrine cancer.

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Genetic conditions that cause tumors of the endocrine glands :

- Genetic conditions that cause tumors of the endocrine glands include rare inherited syndromes such as multiple endocrine neoplasias ***(MEN1, RET, CDKN1B)***, familial medullary thyroid carcinoma ***(RET)***, familial isolated pituitary adenoma ***(AIP),*** Carney complex ***(PRKAR1A),*** Hirschsprung disease ***(RET),*** and Von Hippel-Lindau disease ***(VHL***).

- Genetic conditions that cause increased thyroid cancer risk include syndromes such as familial adenomatous polyposis ***(APC),*** Li-Fraumeni syndrome ***(TP53),*** multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma ***(RET),*** Cowden syndrome ***(PTEN),*** Carney complex **(PRKAR1A)** and ***DICER1*** syndrome ***(DICER1).***

Hereditary pancreatic cancer :

- Hereditary pancreatic cancer syndromes are conditions that impact other areas of an individual's body in addition to increasing their risk for pancreatic cancer. A syndrome can be inherited in a dominant, de novo, or recessive manner. Some examples of hereditary pancreatic cancer syndromes are listed below.

- **Peutz-Jegher Syndrome (PJS**) PJS is associated with a combination of unusual pigmentation on the face, inside the mouth, and on the fingers in childhood, gastrointestinal polyps (especially in the small intestine), and an increased risk for cancer. For pancreatic cancer, the risk is estimated at between **11% and 36%.** Individuals with PJS have a mutation in the ***STK11*** gene. The condition is dominant, so the risk to pass on the mutation is 50% with each pregnancy**.**

- **Lynch syndrome** also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is caused by a mutation in of five genes whose jobs are to repair the DNA damage that normally occurs as cells grow and divide. The condition shows dominant inheritance. People with Lynch syndrome have up to a **3.7%** risk for pancreatic cancer and an 80% risk to develop colon cancer by age 70 years. They are also at an increased risk for many other types of cancers, such as endometrial, gastric, and prostate

- **Hereditary Breast and Ovarian Cancer (HBOC)** Two genes, named BRCA1 and BRCA2, are common causes of dominant hereditary breast cancer. Mutations in these two genes are also associated with a significant risk for breast cancer, as well as ovarian and prostate cancer. A mutation in BRCA2 also confers a higher risk for breast cancer in men, and melanoma for both men and women. Individuals with BRCA2 mutations have approximately 17-19% risk for pancreatic cancer.

- **Familial Atypical Multiple Mole Melanoma (FAMMM)** Individuals with FAMMM have a higher risk for pancreatic cancer, can have many atypical moles, and are more likely to develop melanoma. FAMMM is caused by mutations in the ***CDKNA gene***, which is inherited in a dominant way.

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Hereditary thyroid cancer syndromes :

Hereditary thyroid cancer syndromes are conditions that impact other areas of an individual's body in addition to increasing the risk for thyroid cancer. A syndrome can be inherited in a dominant, de novo, or recessive manner. Several examples are listed below:

- **Li-Fraumeni syndrome (LFS)** Li-Fraumeni syndrome is caused by a mutation in the ***TP53*** gene. People with LFS have up to **a 78%** lifetime risk for cancer. Many kinds of cancer can occur in LFS, and more than one type can arise in a single person. Non-medullary thyroid cancer has been reported in some families affected by Li-Fraumeni syndrome. It is important to diagnose LFS, because exposure to radiation therapy raises the cancer risk even further.

- **Cowden syndrome (CS)** People with Cowden syndrome often have large heads (macrocephaly) and are at an increased risk for different types of benign and malignant tumors, including endometrial, thyroid, and breast cancer. CS is caused by a mutation in the PTEN gene. The lifetime risk for thyroid cancer in women with

  Cowden sndrome is approximately **35%.**

- **Multiple Endocrine Neoplasia Type 2 (MEN2)** Dominant mutations in the RET gene cause MEN2. People with this condition are at a higher risk to develop pheochromocytomas and medullary carcinoma of the thyroid, as well as parathyroid disease. The risk for medullary thyroid carcinoma in people with a ***RET*** mutation approaches **100%**. For MEN2, knowing the specific mutation in a person can help determine the type of MEN2 they have, along with their type's specific risks and related health problems.

Hereditary paraganglioma-pheochromocytomas :

Hereditary paraganglioma-pheochromocytomas (PGL/PCC) are rare Neuroendocrine tumors represented by paragangliomas (occurring in any paraganglia from the skull base to the pelvic floor) and pheochromocytomas (adrenal medullary paragangliomas; see this term).Hereditary PGL/PCCs represent 30% of all PGL/PCC, for which prevalence is around 1/500,000 for PCC and 1/1,000,000 for PGL.

- **Hereditary paraganglioma -pheochromocytoma** syndrome is caused by different mutations of six genes ***(F1, RET, SDHB, SDHD, VHL és FH)****, but the number of the disease causing genes will grow in the future.* The lifetime risk of the mutation carriers for PGL/PCC syndrome is **86** % The risk depends on the type of the gene or the detected mutation. The detection of the mutation provide information on the prognosis of the disease.
- Multiple Endocrine Neoplasia Type 2M
- **Multiple Endocrine Neoplasia Type 2a (MEN2a)**MEN2a is a genetic mutation of the RET protooncogene which increases a patient's risk for developing medullary thyroid cancer, hyperparathyroidism and pheochromocytoma (50%)
- **Multiple Endocrine Neoplasia Type 2b (MEN2b)**
  MEN2b is also a genetic mutation of the RET protooncogene which increases a patient's risk for developing medullary thyroid cancer at a very young age, pheochromocytoma and mucosal neuromas of the lips, tongue and eyelids.
- **von Hippel-Lindau (VHL)** von Hippel-Lindau disease is a familial disorder caused by a genetic mutation ***VHL gene***. Patients with this mutation have increased risk of developing pheochromocytomas, central nervous system hemangioblastomas - inner ear tumors, kidney tumors, pancreatic neuroendocrine tumors and retinal tumors.

The Pancreatic –and other endocrine tumors syndromes Gene Panel can detect the most common mutations associated with a potential risk of hereditary pancreatic or other endocrine cancer.

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List of genes of Pancreatic and other endocrine tumors syndromes Gene Panel

Basic gene panel: 20 genes

APC	ATM	BMPR1A	BRCA1	BRCA2	CDK4	CDKN2A	CHEK2	EPCAM	MLH1	MSH2	MSH6
PALB2	PMS2	PRSS1	PTEN	SMAD4	STK11	TP53	VHL				

Complementary gene panels: 21 genes

BUB1B	CDC73	CDKN1B	FANCC	FH	HNF1A	MAX	MEN1	MET*	NF1	PRKAR1A	RET
SDHA	SDHAF2	SDHB	SDHC	SDHD*	TMEM127	TSC1	TSC2	WRN	* Sequencing of the whole gene except MET: exon2, 14-21; SDHD: exon1.		

Who might need genetic testing?

- Known cancer-risk gene mutation in the family
- Personal or family history of melanoma, multiple atypical moles, or unusual skin spots in childhood
- Family history of pancreatic cancer in multiple individuals
- Male breast cancer, female bilateral breast cancer, or endometrial cancer
- Breast or colon cancer that occurs below the age of 50 years
- A combination of slow growth, limb anomalies, and bone marrow failure, possibly with leukemia or lymphoma
- A family history of multiple individuals with breast, thyroid, endocrine, pancreatic, prostate, kidney, or other cancers, especially if early onset or if multiple cancers occurred in a single individual.
- Personal or family history of one or more endocrine tumors (medullary thyroid cancer, pheochromocytoma, parathyroid adenoma/hyperplasia) with or without mucosal neuromas and/or a tall/thin body type (marfanoid)
- Personal or family history of a sarcoma diagnosed before age 45 years
- More than one family member with a brain tumor or cancer (neuroblastoma, schwannoma, meningioma, astrocytoma,medulloblastoma, etc.)
- History of a tumor and macrocephaly (large head size)
- Personal or family history of colon polyposis or colorectal cancer under the age of 50 years
- A family history of multiple individuals with breast, pancreatic, prostate, gastric, kidney, or other cancers, especially if early onset or if multiple cancers occurred in a single individual

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