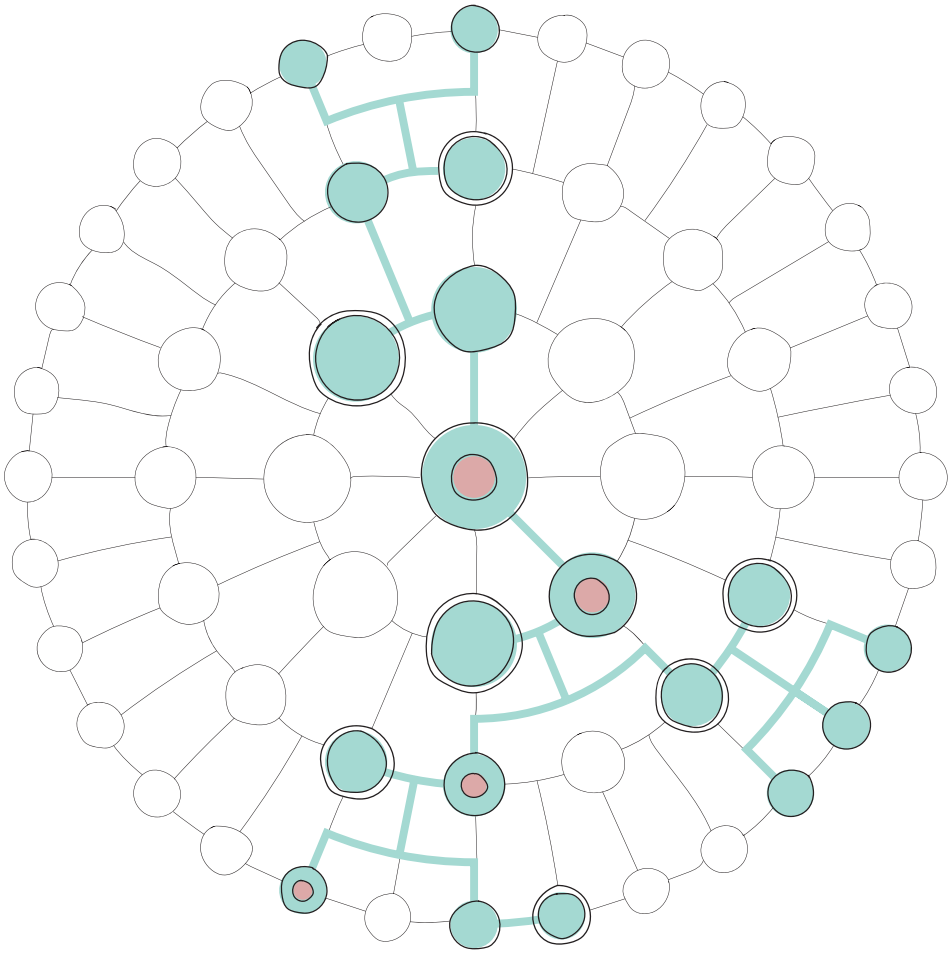
HerediGENE

Physician's booklet



"Your genes speak, we translate."

Genekor

Committed to Biotechnological Innovation

About HerediGENE®

The HerediGENE® test analyzes 52 genes (including *BRCA1* & *BRCA2*) involved in the genetic predisposition to cancer, 21 of which are related to the Homologous Recombination (HR) complex. The content of the analysis covers the most important genes associated with hereditary predisposition to cancer, such as breast, ovarian, colorectal, prostate, pancreatic and other cancers.

The vast majority of individuals who receive a positive finding from the HerediGENE® analysis will receive results for which there are already available guidelines for the individualized clinical management of the subject.

Who should be tested?

The latest guidelines from the American Society of Breast Surgeons suggest that a genetic test should be performed for each case of breast cancer.

Nevertheless, individuals who have a personal and/or family history that meet one or more of the following criteria may be considered as candidates for HerediGENE Assay:

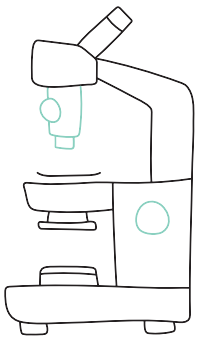
- Early stage of onset of any type of cancer
- Individuals with multiple primary tumors
- Bilateral cancers
- Same type of cancer occurring in close relatives
- Cancer incidence in multiple generations of a family
- Rare tumor occurrence at any age

Hereditary Cancers and NCCN Guidelines

Hereditary cancers	NCCN Guidelines criteria	Heredigene genes
Breast	≤50 y Any age: – Treatment indications – Triple-negative breast cancer – Multiple primary breast cancers – Male breast cancer ASBrS recommendations: Genetic testing should be made available to all patients with a personal history of breast cancer	*ATM, BARD1, BLM, BRCA1, BRCA2* (RRM, RRSO) *BRIP1* (RRSO), *CDH1* (RRM) *CHEK2, NBN, NF1, PALB2* (RRM, RRSO) *PTEN* (RRM, RR Hysterectomy), *RAD50, RAD51C, RAD51D* (RRSO), *STK11* (RRM) *TP53* (RRM)
Ovarian	Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age	*ATM, BARD1, BRCA1,2, BRIP1, EPCAM, MSH1, MSH2, PALB2, RAD51C, RAD51D, SMARCA4, STK11*
Pancreas	All individuals diagnosed with exocrine pancreatic cancer	*APC, ATM, BRCA1,2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, NF1, PALB2, STK11, TP53*
Prostate	By tumor characteristics (any age) – Metastatic – Histology: high- or very-high-risk group	*ATM, ATR, BRCA1,2, CHEK2, FAM175A, GEN1, HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2*
Colon	– Diagnosed <50y – A synchronous or metachronous LS-related cancer regardless of age – 1 first-degree or second-degree relative with an LS-related cancer diagnosed <50y – Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age	*APC, AXIN2, BLM, BMPR1A, CHEK2, EPCAM, GALNT12, MLH1, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, RNF49, RPS20, SMAD4, STK11, TP53*
Gastric	CDH1 criteria Suspicious of Hereditary Cancer Predisposition Syndromes Associated with an Increased Risk for Gastric Cancers (Lynch Syndrome, Juvenile Polyposis Syndrome, Peutz-Jeghers Syndrome, Familial Adenomatous Polyposis)	*APC, BMPR1A, CDH1, NF1, SMAD4, STK11, TP53*

Melanoma	Strong personal or family history of cutaneous melanoma (especially if multiple). Personal history of melanoma and family history of other tumor types (pancreatic, renal and/ or breast cancer, astrocytoma, and/ or mesothelioma) Personal history of uveal melanoma.	*BAP1, BLM, BRCA1,2, CDK4, CDKN2A, MITF, PTEN, TP53*
Endometrial	–Genetic counseling, molecular analysis, and testing for all other MMR abnormalities is recommended. –For those who are MMR-intact/ MSI-stable or those who have not been screened, but who have a strong family history of endometrial and/ or colorectal cancer, genetic counseling and testing is recommended	*EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, STK11*
Endocrine	–Patients with duodenal/pancreatic neuroendocrine tumor at any age –Genetic testing may be a consideration for patients with other combinations of tumors or cancers in the patient and/or their family members	*APC, BAP1, BLM, MEN1, MITF, NF1, PTEN, RET, VHL*

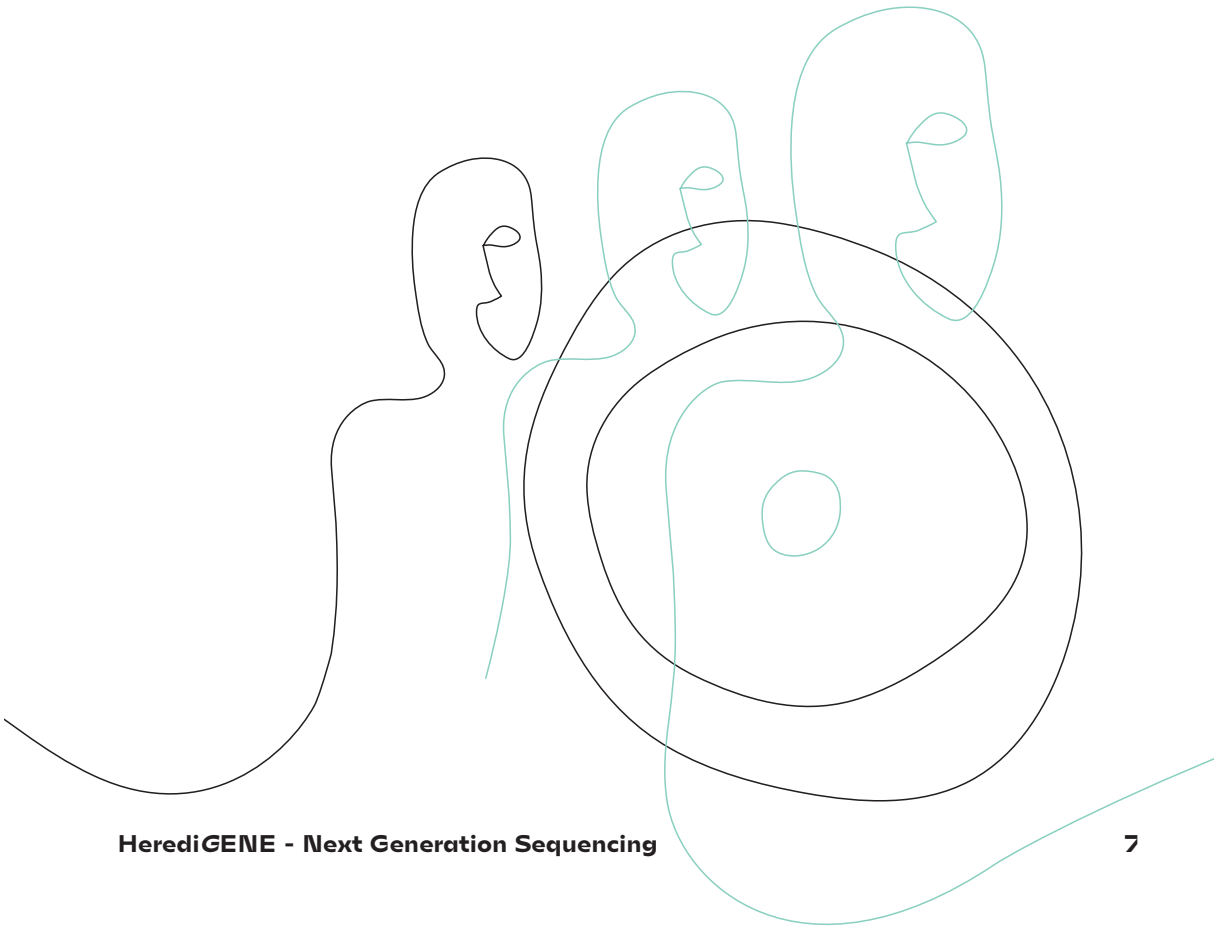
According to International Guidelines each genetic testing procedure should include pre-test counseling and post-test counseling.



Targeted Therapies based on NCCN Guidelines

Cancer types	Treatment implications based on NCCN Guidelines	Targeted therapies
Breast	Adjuvant breast cancer • TNBC -if 1) ≥pT2 or ≥pN1 disease after adjuvant chemotherapy -or 2) residual disease after preoperative chemotherapy • HR-positive, HER2-negative tumors -if 1) ≥4 positive lymph nodes after adjuvant chemotherapy (category 2A) -or 2) residual disease after preoperative therapy and a clinical stage, pathologic stage, estrogen receptor status, and tumor grade (CPS+EG) score ≥3 (category 2A). Metastatic breast cancer Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy (category 1)	Olaparib (g*BRCA*) Olaparib, Talazoparib (g*BRCA*)
Ovarian	Maintenance therapy	Olaparib, Niraparib (g/s*BRCA*)
Pancreas	Metastatic Disease (Maintenance Therapy) • Patients who have response or stable disease after 4–6 months of chemotherapy may undergo maintenance therapy.	Olaparib (g*BRCA*) Rucaparib (g/s *BRCA* or *PALB2*) Useful in Certain Circumstances (off-label)
Prostate	Patients who have an HRR mutation and whose cancer has progressed on prior treatment with androgen receptor-directed therapy regardless of prior docetaxel therapy Patients with mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.	Olaparib (HRR mutations) Rucaparib (g/s *BRCA*)

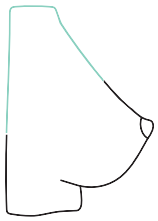
Uterine sarcoma	Consider PARP inhibitors for *BRCA2*- altered uLMS	Olaparib, Rucaparib, Niraparib Off-label
Various cancer types (HRD)	HR genes in Heredigene: *ATM, ATR, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, FAM175A, FANCA, FANCL, FANCM, GEN1, MRE11, NBN, PALB2, PPP2R2A, RAD50, RAD51B, RAD51C, RAD51D*	Sensitivity to poly (ADP ribose) polymerase (PARP) inhibitors Off-label

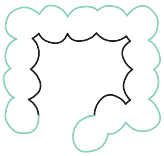


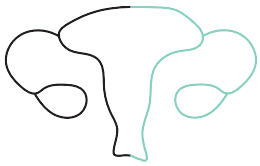
It's a family issue...

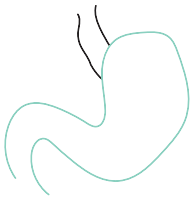
A positive finding in an individual affects the whole family.

Sharing the results with the family members is a matter of high importance. Any at-risk relative must be tested for the same alteration. The possibility that this alteration is passed in the next generation is 50%. In case of a positive result, the physician will suggest the proper management for each case specifically.









In any case, in order to reduce the likelihood of transmitting the risk of inherited cancer syndromes t o a next generation, individuals should discuss available individualized management options with their treating physician, who is now able to manage the patient based on his or her genetics' background and not exclusively from his personal or family history.

Why is HerediGENE® one of the most trusted genetic tests for hereditary cancer?

HerediGENE® Test provides you with:

» The **NGS** analysis of 52 genes, most of which are included in guidelines, where 21 of them are involved in Homologous Recombination

» A **comprehensive analysis:** The assay targets all coding regions of the genes analyzed and 20 base pairs of flanking intronic sequences. Copy number variation (CNV) analysis is also included.

» **Confirmation** of all positive results through alternative methods

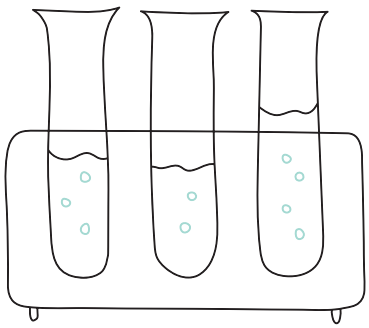
» Constant **updates** according to international guidelines

» An **experienced, dedicated team** with numerous international publications on hereditary cancer

» **Inhouse Bioinformatics** team

» **Genetic Cousneling** from accredited scientists

» **State of the art equipment** for fast and reliable results



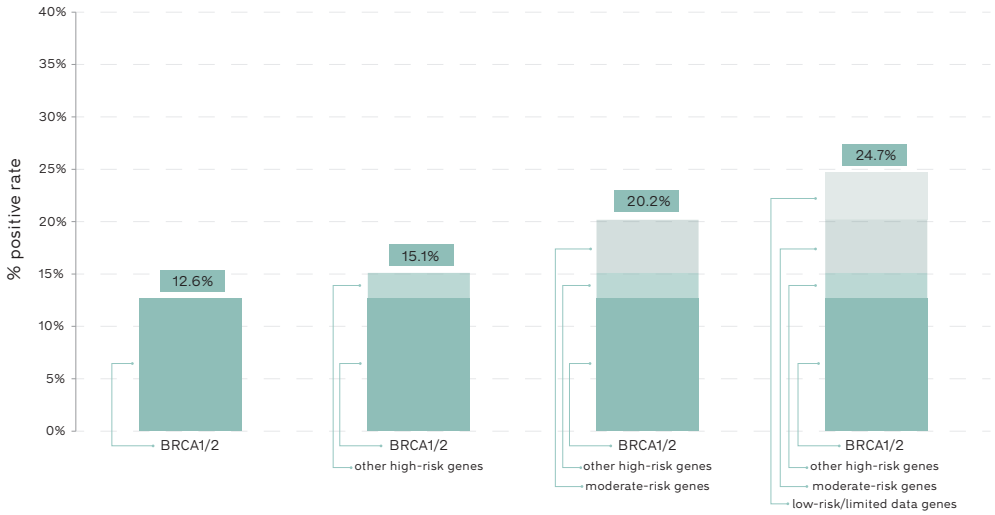
Clinical Utility

The HerediGENE® assay provides valuable information that can be used to reduce the risk of developing cancer.

» It helps physicians to individualize patients' treatment.

» It detects family members who belong to the increased risk category and who can benefit from a personalized risk reduction program.

» It identifies relatives who are not at risk in order to avoid the stress of developing cancer but also to avoid possible unwanted interventions.



Tsaousis G.N., Papadopoulou E, Apessos A, Agiannitopoulos K, Pepe G, Kambouri S, [...] Nasioulas G. (2019) **Analysis of hereditary cancer syndromes by using a panel of genes: Novel and multiple pathogenic mutations.** BMC Cancer. 2019 Jun 3;19(1):535.

International Guidelines For Multi-Gene Testing

International Guidelines for Multigene Panels		
	Selected Patients	All Patients
NCCN®		✓
ASCO®	✓	
American Society of Breast Surgeons (ASBrS)		✓
ESMO	✓	

1. The National Comprehensive Cancer Network. Genetic/ Familiar High Risk Assessment: Breast, Ovarian and Pancreatic (Version 1.2023)

2. Robson, Mark E., et al. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. Journal of Clinical Oncology 33.31 (2015): 3660-3667.

3. Manahan ER, et al. Consensus Guidelines on Genetic Testing for Hereditary Breast Cancer from the American Society of Breast Surgeons. Ann Surg Oncol. 2019;26(10):3025–3031.

4. Paluch-Shimon, S., et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Annals of Oncology 27.suppl_5 (2016): v103-v110.

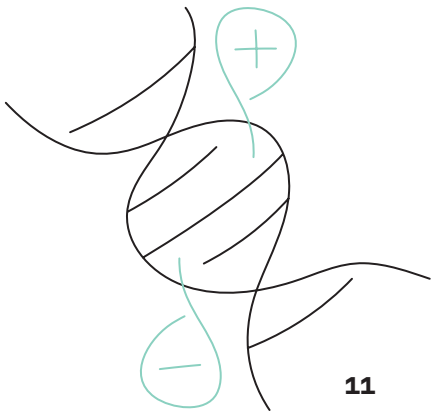
The Scientific Team of Genekor Medical S.A. consists of certified Clinical Geneticists with many years of experience in Cancer Genetics, having taken part in multiple clinical trials and having performed a large number of tests for Hereditary Cancer.

Technical Information

HerediGENE® is designed in order to achieve maximum sensitivity and specificity. Sequencing is performed through the Illumina platform using advanced Next Generation Sequencing (NGS) technology to fully analyze a group of genes associated with inherited cancer syndromes. Analysis of large genomic rearrangements is also included in HerediGENE®.

Sample Requirement
3 Vials of peripheral blood (EDTA) or buccal Swab

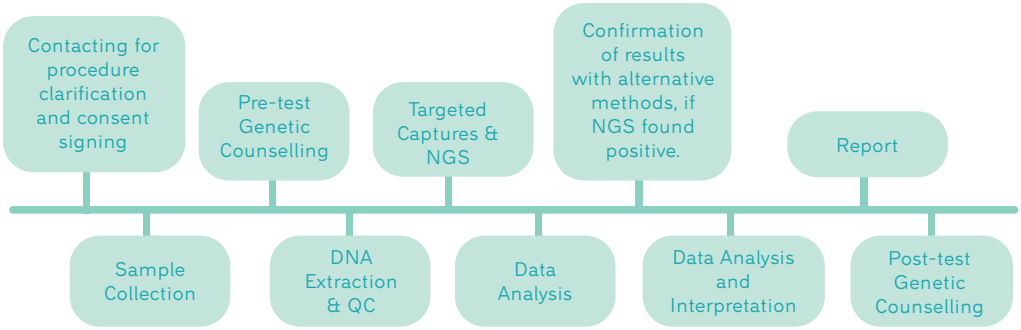
Turnaround Time
20 days (from the day sample arrives to lab)



Colon	Breast	Pancreas	Ovarian	Gastric	Melanoma	Endometrial	Endocrine
APC		*APC*		*APC*			*APC*
	ATM	*ATM*	*ATM*				
AXIN2							
					BAP1		*BAP1*
	BARD1		*BARD1*				
BLM	*BLM*				*BLM*		*BLM*
BMPR1A				*BMPR1A*			
	BRCA1	*BRCA1*	*BRCA1*		*BRCA1*		
	BRCA2	*BRCA2*	*BRCA2*		*BRCA2*		
	BRIP1		*BRIP1*				
	CDH1			*CDH1*			
					CDK4		
		CDKN2A			*CDKN2A*		
CHEK2	*CHEK2*						
EPCAM		*EPCAM*	*EPCAM*			*EPCAM*	
GALNT12							
							MEN1
					MITF		*MITF*
MLH1		*MLH1*	*MLH1*			*MLH1*	
MSH2		*MSH2*	*MSH2*			*MSH2*	
MSH3							
MSH6		*MSH6*				*MSH6*	
MUTYH							
	NBN						
	NF1	*NF1*		*NF1*			*NF1*
NTHL1							
	PALB2	*PALB2*	*PALB2*				
PMS2						*PMS2*	
POLE							
POLD1							
PTEN	*PTEN*				*PTEN*	*PTEN*	*PTEN*
	RAD50						
	RAD51C		*RAD51C*				
	RAD51D		*RAD51D*				
							RET
RNF43							
RPS20							
SMAD4				*SMAD4*			
			SMARCA4				
STK11	*STK11*	*STK11*	*STK11*	*STK11*		*STK11*	
TP53	*TP53*	*TP53*		*TP53*	*TP53*		
							VHL

Prostate	HRD	Associated Syndrome/Condition
		Familial Adenomatous Polyposis
ATM	*ATM*	Ataxia Telangiectasia (recessive)
ATR	*ATR*	
		Polyposis/Oligodontia
	BAP1	
	BARD1	
		Bloom syndrome (recessive)
		Juvenile Polyposis Syndrome
BRCA1	*BRCA1*	Hereditary breast and ovarian cancer
BRCA2	*BRCA2*	Hereditary breast and ovarian cancer, Fanconi anaemia FA-D1 (recessive)
	BRIP1	Fanconi anaemia FA-J (recessive)
		Hereditary diffuse gastric cancer
		Familial Atypical Mole-Malignant Melanoma syndrome (FAMMM)
CHEK2	*CHEK2*	
		Lynch Syndrome
FAM175A	*FAM175A*	
	FANCA	"Fanconi anaemia FA-A (recessive)"
	FANCL	"Fanconi anaemia FA-L (recessive)"
	FANCM	"Fanconi anaemia FA-M (recessive)"
GEN1	*GEN1*	
HOXB13		
		Multiple endocrine neoplasia Type 1
MLH1		Lynch Syndrome / Constitutional mismatch repair deficiency (CMMRD) syndrome (recessive)
	MRE11	Ataxia-telangiectasia-like disorder (recessive)
MSH2		Lynch Syndrome
		Adenomatous Polyposis (recessive)
MSH6		Lynch Syndrome
		MUTYH-associated polyposis
	NBN	Nijmegen breakage syndrome (recessive)
		Neurofibromatosis Type 1
		Adenomatous Polyposis (recessive)
PALB2	*PALB2*	Fanconi anaemia FA-N (recessive)
PMS2		Lynch Syndrome
		Adenomatous Polyposis
		Adenomatous Polyposis
	PPP2R2A	
		Cowden
	RAD50	Nijmegen breakage syndrome like disorder (recessive)
	RAD51B	
	RAD51C	Fanconi anaemia FA-O (recessive)
	RAD51D	Fanconi anaemia (recessive)
		Multiple endocrine neoplasia Type 2
		Serrated polyposis syndrome
		"Juvenile Polyposis/ Hereditary hemorrhagic telangiectasia (HHT)"
		D small cell carcinoma of the ovary hypercalcemic type (SCCOHT), AD rhabdoid tumor predisposition syndrome type 2 (RTPS2)
		Peutz-Jeghers Syndrome
		Li-Fraumeni Syndrome
		von Hippel-Lindau Syndrome

Workflow



Genekor's Validation Studies

» Apessos A, Agiannitopoulos K, Pepe G, Tsaousis GN, [...], Papadopoulou E, Nasioulas G, Georgoulias V. (2022). **Genetic Predisposition to Male Breast Cancer: A Case Series.** In Anticancer Res. 2022 Dec;42(12):5795-5801. doi: 10.21873/anticanres.16086. PMID: 36456130

» Ziogas D., Agiannitopoulos K., Pepe G., Potska K., Tsaousis G, [...] Nasioulas G. (2022). **Cascade genetic testing utilized only in 31% of initial families with pathogenic variants in breast cancer genes.** In ESMO Congress 2022, Paris; Annals of Oncology 33:S1321: Abstract nr 1709P.

» Ozmen V, Caglayan AO, Yararbas K, Ordu C, Aktepe F, Ozmen T, Ilgun AS, Soybir G, Alco G, Tsaousis GN, Papadopoulou E, Agiannitopoulos K, Pepe G, Kampouri S, Nasioulas G, Sezgin E, Soran A. **Importance of multigene panel test in patients with consanguineous marriage and family history of breast cancer.** Oncol Lett. 2022 Apr;23(4):118. doi: 10.3892/ol.2022.13238. Epub 2022 Feb. PMID: 35261632

» Tsaousis GN, Papadopoulou E, Agiannitopoulos K, Pepe G, Tsoulos N, [...] Nasioulas G (2022). **Revisiting the Implications of Positive Germline Testing Results Using Multi-gene Panels in Breast Cancer Patients.** In Cancer Genomics Proteomics. 2022 Jan-Feb;19(1):60-78.

» Agiannitopoulos K, Pepe G, Papadopoulou E, Tsaousis GN, Kampouri S, [...] Nasioulas G (2021). **Clinical Utility of Functional RNA Analysis for the Reclassification of Splicing Gene Variants in Hereditary Cancer.** In Cancer Genomics Proteomics. 2021 May-Jun;18(3):285-294.

» Tsoulos N., Agiannitopoulos K., Pepe G., Papadopoulou E., Tsaousis G. [...] Nasioulas G. (2021). **Different CNVs account for 10.4% of pathogenic variants in 1418 patients referred for hereditary breast cancer testing**. In San Antonio Breast Cancer Symposium (SABCS), San Antonio, Texas, USA; Cancer Res (2022) 82 (4_Supplement): Abstract nr P2-09-10

» Agiannitopoulos K, Papadopoulou E, Tsaousis GN, Pepe G, Kampouri S, [...] Nasioulas G. (2020) **Report of a germline double heterozygote in MSH2 and PALB2.** In Mol Genet Genomic Med. 2020 Oct;8(10):e1242.

» Agiannitopoulos K., Pepe G., Papadopoulou E., Tsaousis G., [...]Nasioulas G. (2020). **Splicing variants in hereditary cancer genes: clinical utility of functional RNA analysis.** In EUROPEAN JOURNAL OF HUMAN GENETICS Conference 2020. EUROPEAN JOURNAL OF HUMAN GENETICS 28 (SUPPL 1), 538-539.

» Agiannitopoulos K., Papadopoulou E., Tsaousis G.N., Pepe G, Kambouri S, Kocdor M.A., Nasioulas G. (2019) **Characterization of the c.793-1G>A splicing variant in CHEK2 gene as pathogenic: a case report** BMC Medical Genetics 20, Article number: 131

» Tsaousis GN, Tsoulos, E. Papadopoulou, K. Agiannitopoulos, G. Pepe, [...] G. Nasioulas. (2019) **Multigene panel testing results for hereditary breast cancer in 1325 individuals: implications for gene selection and considerations for guidelines.** In: ESMO 2019 Congress: Annals of Oncology (2019) 30 (suppl_5): v25-v54.

» Tsoulos N, Apessos A, Agiannitopoulos K, Pepe G, Tsaousis, G., Kambouri S, [...] Nasioulas G. (2017) **Analysis of hereditary cancer syndromes by use of a panel of genes: More answers than questions.** In: 40th San Antonio Breast Cancer Symposium (SABCS), San Antonio, Texas, USA. AACR; Cancer Res 2018;78(4 Suppl):Abstract nr P3-03-03.

» Tsaousis G.N., Papadopoulou E, Apessos A, Agiannitopoulos K, Pepe G, Kambouri S, [...] Nasioulas G. (2019) **Analysis of hereditary cancer syndromes by using a panel of genes: Novel and multiple pathogenic mutations.** BMC Cancer. 2019 Jun 3;19(1):535.

» Tsoulos N, Tsaousis GN, Papadopoulou E, Agiannitopoulos K, Pepe G, Kambouri S, Apessos A, [...] Nasioulas G. (2018) **Analysis of hereditary cancer syndromes by using a panel of genes: Novel and multiple pathogenic mutations.** In: 41th San Antonio Breast Cancer Symposium (SABCS), San Antonio, Texas, USA. AACR; Cancer Res 2019;79(4 Suppl):Abstract nr P4-03-07

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