Ambry Genetics®

Hereditary Cancer Panels Testing Overview

2001
First full gene sequencing of *CFTR*

2010
First commercial NGS panel

2011
First clinical test for whole exome sequencing

2012
First hereditary cancer panels

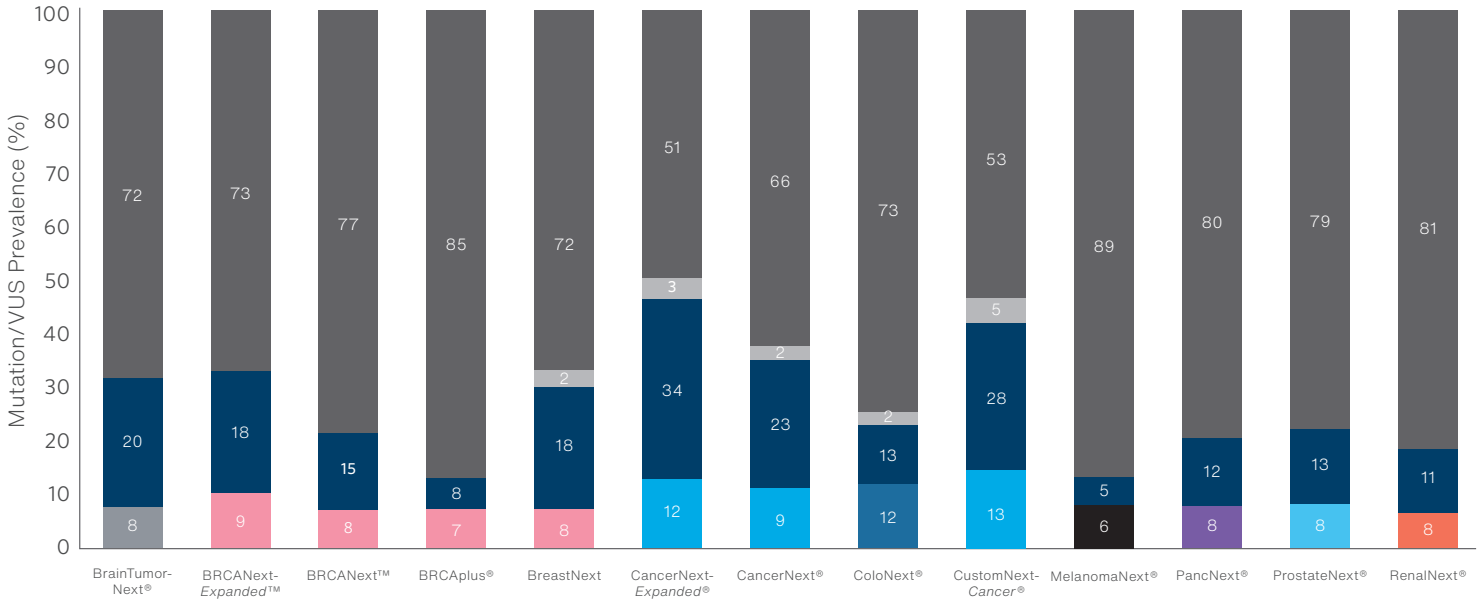
2013
First *BRCA*-related panels

2019
First paired RNA & DNA testing for hereditary cancer (RNAinsight®)

2021
First to offer the most comprehensive coverage (up to 91 genes) for RNA analysis

Hereditary Cancer Panel Experience

UNDERSTANDING DISEASE BETTER THROUGH DATA SHARING AND TRANSPARENCY



Data as of April 2023

Hereditary Cancer Multigene Panels

BRCAplus 8 genes	BRCANext 18 genes	BRCANext-*Expanded* 23 genes	ColoNext 20 genes	ProstateNext 14 genes	PancNext 13 genes	CancerNext 36 genes	BrainTumorNext 29 genes	MelanomaNext 9 genes	RenalNext 20 genes	PGLNext 14 genes	CancerNext-*Exp* 77 genes	CustomNext-*Cancer* up to 91 genes
		BARD1				*BARD1*					*BARD1*	*BARD1*
	BRIP1	*BRIP1*				*BRIP1*					*BRIP1*	*BRIP1*
	NBN	*NBN*		*NBN*		*NBN*	*NBN*				*NBN*	*NBN*
	NF1	*NF1*				*NF1*	*NF1*			*NF1*	*NF1*	*NF1*
	RAD51C	*RAD51C*				*RAD51C*					*RAD51C*	*RAD51C*
	RAD51D	*RAD51D*		*RAD51D*		*RAD51D*					*RAD51D*	*RAD51D*
ATM	*ATM*	*ATM*		*ATM*	*ATM*	*ATM*					*ATM*	*ATM*
PALB2	*PALB2*	*PALB2*		*PALB2*	*PALB2*	*PALB2*					*PALB2*	*PALB2*
			MUTYH			*MUTYH*					*MUTYH*	*MUTYH*
CHEK2	*CHEK2*	*CHEK2*	*CHEK2*	*CHEK2*		*CHEK2*			*CHEK2*		*CHEK2*	*CHEK2*
		STK11	*STK11*		*STK11*	*STK11*					*STK11*	*STK11*
CDH1	*CDH1*	*CDH1*	*CDH1*			*CDH1*					*CDH1*	*CDH1*
BRCA1	*BRCA1*	*BRCA1*		*BRCA1*	*BRCA1*	*BRCA1*					*BRCA1*	*BRCA1*
BRCA2	*BRCA2*	*BRCA2*		*BRCA2*	*BRCA2*	*BRCA2*		*BRCA2*			*BRCA2*	*BRCA2*
PTEN	*PTEN*	*PTEN*	*PTEN*			*PTEN*	*PTEN*	*PTEN*	*PTEN*		*PTEN*	*PTEN*
TP53	*TP53*	*TP53*	*TP53*	*TP53*	*TP53*	*TP53*	*TP53*	*TP53*	*TP53*		*TP53*	*TP53*
	MLH1	*MLH1*	*MLH1*	*MLH1*	*MLH1*	*MLH1*	*MLH1*		*MLH1*		*MLH1*	*MLH1*
	MSH2	*MSH2*	*MSH2*	*MSH2*	*MSH2*	*MSH2*	*MSH2*		*MSH2*		*MSH2*	*MSH2*
	MSH6	*MSH6*	*MSH6*	*MSH6*	*MSH6*	*MSH6*	*MSH6*		*MSH6*		*MSH6*	*MSH6*
	PMS2	*PMS2*	*PMS2*	*PMS2*	*PMS2*	*PMS2*	*PMS2*		*PMS2*		*PMS2*	*PMS2*
	EPCAM	*EPCAM*	*EPCAM*	*EPCAM*	*EPCAM*	*EPCAM*	*EPCAM*		*EPCAM*		*EPCAM*	*EPCAM*
		SMARCA4				*SMARCA4*	*SMARCA4*				*SMARCA4*	*SMARCA4*
			APC		*APC*	*APC*	*APC*				*APC*	*APC*
					CDKN2A	*CDKN2A*	*CDKN2A*	*CDKN2A*			*CDKN2A*	*CDKN2A*
						CDK4		*CDK4*			*CDK4*	*CDK4*
				HOXB13		*HOXB13*					*HOXB13*	*HOXB13*
		DICER1				*DICER1*	*DICER1*				*DICER1*	*DICER1*
			BMPR1A			*BMPR1A*					*BMPR1A*	*BMPR1A*
			SMAD4			*SMAD4*					*SMAD4*	*SMAD4*
			GREM1			*GREM1*					*GREM1*	*GREM1*
			POLD1			*POLD1*					*POLD1*	*POLD1*
			POLE			*POLE*					*POLE*	*POLE*
			AXIN2			*AXIN2*					*AXIN2*	*AXIN2*
			MSH3			*MSH3*					*MSH3*	*MSH3*
			NTHL1			*NTHL1*					*NTHL1*	*NTHL1*
		RECQL				*RECQL*					*RECQL*	*RECQL*
							POT1	*POT1*			*POT1*	*POT1*
								RB1			*RB1*	*RB1*
								BAP1	*BAP1*		*BAP1*	*BAP1*
								MITF	*MITF*		*MITF*	*MITF*
									FLCN		*FLCN*	*FLCN*
									MET		*MET*	*MET*
									FH	*FH*	*FH*	*FH*
									SDHA	*SDHA*	*SDHA*	*SDHA*
									SDHB	*SDHB*	*SDHB*	*SDHB*
									SDHC	*SDHC*	*SDHC*	*SDHC*
									SDHD	*SDHD*	*SDHD*	*SDHD*
										SDHAF2	*SDHAF2*	*SDHAF2*
										MAX	*MAX*	*MAX*
										RET	*RET*	*RET*
										EGLN1	*EGLN1*	*EGLN1*
										KIF1B	*KIF1B*	*KIF1B*
										TMEM127	*TMEM127*	*TMEM127*
							MEN1			*MEN1*	*MEN1*	*MEN1*
							VHL		*VHL*	*VHL*	*VHL*	*VHL*
							TSC1		*TSC1*		*TSC1*	*TSC1*
							TSC2		*TSC2*		*TSC2*	*TSC2*
							AIP				*AIP*	*AIP*
							ALK				*ALK*	*ALK*
							CDKN1B				*CDKN1B*	*CDKN1B*
							NF2				*NF2*	*NF2*
							PHOX2B				*PHOX2B*	*PHOX2B*
							PRKAR1A				*PRKAR1A*	*PRKAR1A*
							PTCH1				*PTCH1*	*PTCH1*
							SMARCB1				*SMARCB1*	*SMARCB1*
							SMARCE1				*SMARCE1*	*SMARCE1*
							SUFU				*SUFU*	*SUFU*
							LZTR1				*LZTR1*	*LZTR1*
											PDGFRA	*PDGFRA*
											XRCC2	*XRCC2*
											BLM	*BLM*
											FANCC	*FANCC*
											GALNT12	*GALNT12*
											CDC73	*CDC73*
											CTNNA1	*CTNNA1*
											EGFR	*EGFR*
											KIT	*KIT*
												Pancreatitis genes**

Most* hereditary cancer multigene panels are compatible with +RNAinsight. The genes listed in each panel can be analyzed for functional RNA data to help classify DNA variants.
See Next Page for Details.

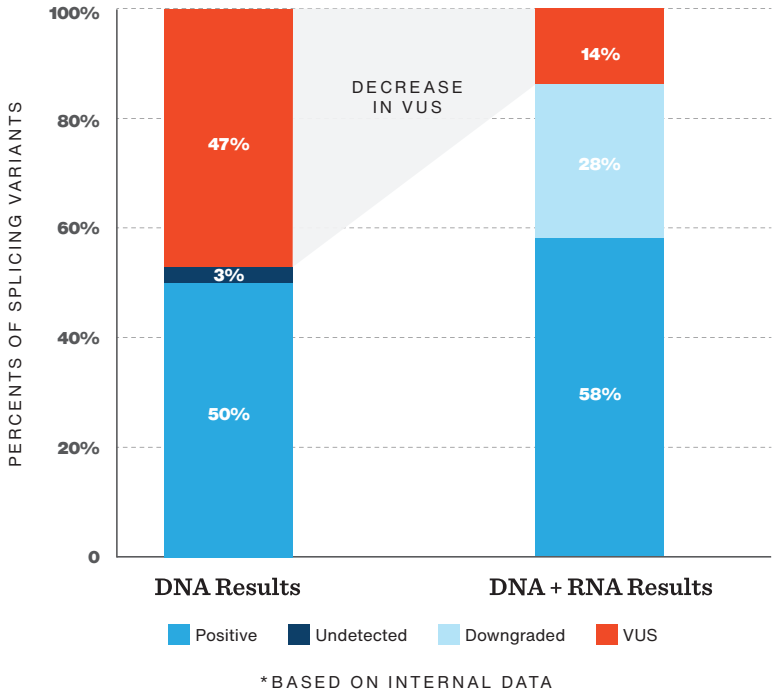
* Not available for STAT testing, BRCAPlus, TumorNext Tests or Pancreatitis panels.
** *CASR, CPA1, CFTR, CTRC, PRSS1, SPINK1*

+RNAinsight®

Paired RNA/DNA genetic testing with +RNAinsight analyzes functional RNA data to help classify DNA variants. It also identifies deep-intronic mutations that are undetected with a DNA-only testing approach. As a result, patients suspected of hereditary cancer can receive a clearer diagnosis and more clinically actionable information.

- Identifies More Positive Results[2]
- Resolves Variants of Unknown Significance[3]
- Increases Diagnostic Yield

Retrospective Study Comparing DNA-Only Results vs DNA/RNA Results



*BASED ON INTERNAL DATA

UP TO 91 Genes

For Maximum Coverage

Analyzes functional RNA data across more genes for better variant classification

>70%

Reclassified Inconclusive[1]

Decreases splicing variants of unknown significance

~1/50

Positive Patients Impacted[1]

Results without +RNAinsight would have been negative or inconclusive

Technical Details +RNAinsight analyzes transcripts for up to 91 genes depending on which Ambry Genetics DNA based Hereditary Cancer Panel it is paired with, and depending on the absence or presence of RNA transcripts expressed in the blood. The results from +RNAinsight are used to provide functional RNA information to further support classification of DNA variants. It is not intended to be used as a stand-alone diagnostic test.

References

1. Horton, C., Cass, A., Conner, B. R., Hoang, L., Zimmermann, H., Abualkheir, N., ... & Karam, R. (2022). Mutational and splicing landscape in a cohort of 43,000 patients tested for hereditary cancer. NPJ Genomic Medicine, 7(1), 49.
2. Landrith, T., Li, B., Cass, A. A., Conner, B. R., LaDuca, H., McKenna, D. B., ... & Karam, R. (2020). Splicing profile by capture RNA-seq identifies pathogenic germline variants in tumor suppressor genes. NPJ precision oncology, 4(1), 4.
3. Karam, R., Conner, B., LaDuca, H., McGoldrick, K., Krempely, K., Richardson, M. E., ... & Chao, E. (2019). Assessment of diagnostic outcomes of RNA genetic testing for hereditary cancer. JAMA Network Open, 2(10), e1913900-e1913900.

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