Ambry Genetics®

Hereditary Cancer Panels Testing Overview

2001
- First full gene sequencing of *CFTR*

2011
- First clinical test for whole exome sequencing

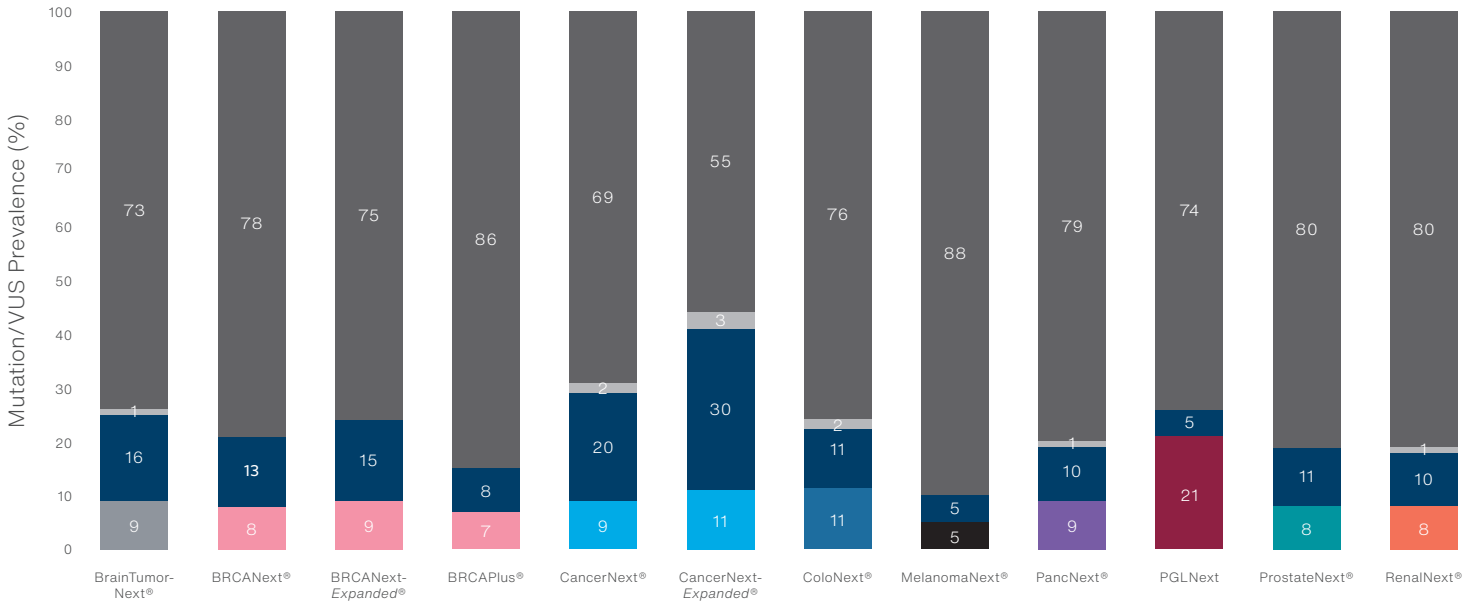
2013
- First *BRCA*-related panels

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
- First to systematically use CRISPR/MAVE for clinical variant interpretation

Hereditary Cancer Panel Experience

UNDERSTANDING DISEASE BETTER THROUGH DATA SHARING AND TRANSPARENCY



Annual data as of June 2023

Hereditary Cancer Multigene Panels

BRCAPlus 13 genes	BRCANext 19 genes	BRCANext-*Expanded* 21 genes	ColoNext 20 genes	ProstateNext 14 genes	PancNext 13 genes	CancerNext 34 genes	BrainTumorNext 29 genes	MelanomaNext 9 genes	RenalNext 20 genes	PGLNext 14 genes	CancerNext-*Exp* 71 genes	CustomNext-*Cancer* up to 91 genes
				NBN			NBN					NBN
	BRIP1	BRIP1				BRIP1					BRIP1	BRIP1
RAD51D	RAD51D	RAD51D		RAD51D		RAD51D					RAD51D	RAD51D
ATM	ATM	ATM		ATM	ATM	ATM					ATM	ATM
PALB2	PALB2	PALB2		PALB2	PALB2	PALB2					PALB2	PALB2
NF1	NF1	NF1				NF1	NF1			NF1	NF1	NF1
BARD1	BARD1	BARD1				BARD1					BARD1	BARD1
RAD51C	RAD51C	RAD51C				RAD51C					RAD51C	RAD51C
CDH1	CDH1	CDH1	CDH1			CDH1					CDH1	CDH1
STK11	STK11	STK11	STK11		STK11	STK11					STK11	STK11
CHEK2	CHEK2	CHEK2	CHEK2	CHEK2		CHEK2			CHEK2		CHEK2	CHEK2
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
		DICER1				DICER1	DICER1				DICER1	DICER1
			APC		APC	APC	APC				APC	APC
					CDKN2A	CDKN2A	CDKN2A	CDKN2A			CDKN2A	CDKN2A
				HOXB13		HOXB13					HOXB13	HOXB13
			MUTYH			MUTYH					MUTYH	MUTYH
			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
						CDK4		CDK4			CDK4	CDK4
							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
											CDC73	CDC73
											CTNNA1	CTNNA1
											EGFR	EGFR
											KIT	KIT
												XRCC2
												BLM
												FANCC
												GALNT12
												RECQL
												Pancreatitis genes**
												Additional 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.

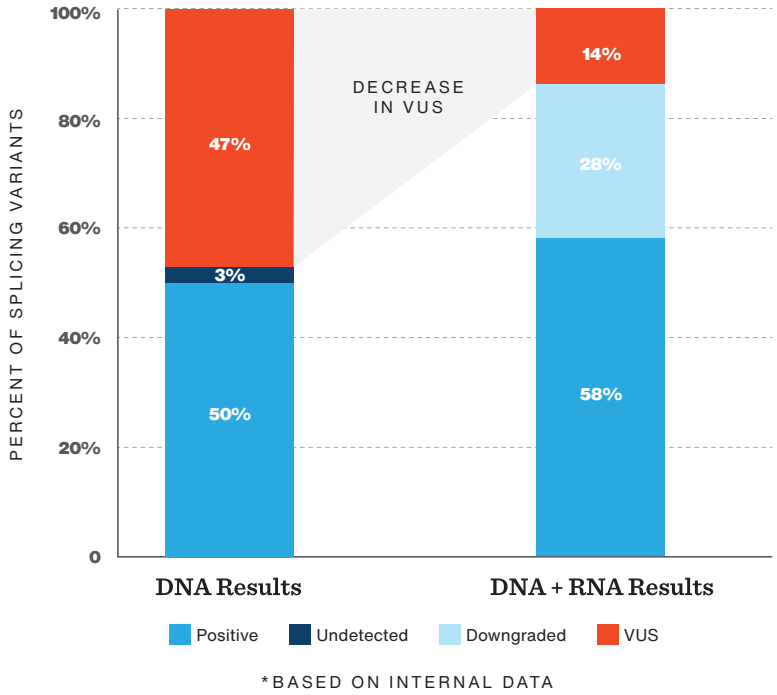
* Not available for STAT testing, BRCAPlus or Pancreatitis panels.
** *CASR, CPA1, CFTR, CTRC, PRSS1, SPINK1*
\+ *Additional genes with limited evidence: FAM175A,MLH3,MRE11A, PALLD, RAD50, RINT1, RPS20, TERT*

+RNAinsight®

Paired DNA/RNA genetic testing with +RNAinsight analyzes functional RNA data to help classify DNA variants. It also identifies deep-intronic mutations that may go undetected with a DNA only or reflexive RNA testing approach. This novel functional evidence is especially important in non-White populations that have been underrepresented in research and clinical testing. As a result, diagnostic yield is higher and variant of uncertain significance rate is lower, providing clarity for patients and healthcare providers.[1]

- Identifies More Positive Results[1,3]
- Resolves Variants of Unknown Significance[1,4]
- Reduces Evidence Gaps in Non-White Populations[1]

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 from Inconclusive[2]

Decreases splicing variants of unknown significance

~1/50

Positive Patients Impacted[2]

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., Hoang, L., Zimmermann, H., Young, C., Grzybowski, J., Durda, K., Vuong, H., Burks, D., Cass, A., LaDuca, H., Richardson, M. E., Harrison, S., Chao, E. C., & Karam, R. (2023) Diagnostic outcomes of concurrent DNA and RNA sequencing in individuals undergoing hereditary cancer testing. JAMA Oncology. https://doi.org/10.1001/jamaoncol.2023.5586
2. 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.
3. 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.
4. 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.

One Enterprise, Aliso Viejo, CA 92656 USA Toll Free +1.866.262.7943 Fax +1.949.900.5501 **ambrygen.com**

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