

Personalis NeXT Dx™ Test

The Personalis NeXT Dx Test provides clinicians with a comprehensive and accurate next-generation sequencing (NGS) based testing solution for solid tumors, to help guide and optimize therapeutic options for patients including enrolling into cancer clinical trials.

The NeXT Dx test is a tumor-normal comprehensive genomic tumor profiling test based on whole exome and transcriptome sequencing. It is intended for profiling a solid tumor's genomic and molecular characteristics using NGS technology to report small nucleotide variants (SNVs), small insertions and deletions (indels), copy number alterations (CNAs), fusions, microsatellite instability (MSI) and exome-wide tumor mutational burden (TMB). Pathogenic and likely pathogenic germline mutations detected in certain cancer-related genes are also reported as incidental findings from sequencing of the matched normal sample. In addition, mutations in genes involved in homologous recombination repair (HRR) are highlighted when identified.

Clinical Report

The Personalis NeXT Dx Test is analytically validated for the detection of SNVs, indels, CNAs, and fusions in ~20,000 genes and MSI and TMB reporting.

- A clinical report includes SNVs, indels and CNAs detected in 401 cancer-related genes, fusions in 284 genes, MSI from 117 loci, exome-wide TMB results based on tumor-normal analysis, and germline small variants (SNVs and indels) identified from 59 cancer-related genes using matched normal tissue (**Figure 1**).
- Based on the tumor's molecular profile, the report delivers relevant therapy recommendations and a custom-generated list of clinical trial matches, including sponsor contact details for trial enrollment.
- We also report clinically important genes, specific to the patient's tumor type, in which no variants were detected.
- We use our Future-Driven™ Personalis NeXT Platform® to provide high accuracy, clinical-grade next generation sequencing and analysis. Each case is reviewed by a team of board-certified molecular geneticists and genetic counselors.
- Test results are provided to clinicians by fax or secure email, and can be accessed via the Personalis Clinical Portal.

All clinically relevant variants available at-a-glance on the first page. Drug indications, potential clinical trials and variant allele fractions in one table

Pathogenic and likely pathogenic germline variants in certain genes are reported as incidental findings

MSI results are reported as High or Stable based on 117 loci

Clinically relevant negatives by tumor type

Genomic Alterations Summary

Gene	Alteration	Drug Associated with Patient's Tumor Type	Drug Associated with Patient's Tumor Type	Clinical Trials	Allele Fraction	Origin
BRCA2	N 173del	None	None	Yes	31.6%	Germline
BRCA1	C 532G	None	None	Yes	13.2%	Somatic
BRCA2	C 532G	None	None	Yes	7.9%	Somatic

Alterations with Clinical Relevance

Gene	Alteration	Clinical Significance	Notes
BRCA2	N 173del	Pathogenic	Pathogenic germline variant for genetic counseling and confirmatory testing in germline tissue.

Other Biomarkers Tested

Biomarker	Result	High Associated with Patient's Tumor Type	High Associated with Patient's Tumor Type	Not Associated with Patient's Tumor Type	Clinical Trials
Mismatchability (MSI)	Positive, High	Yes	Yes	Yes	Yes
Epithelial-mesenchymal transition (EMT)	High	Yes	Yes	Yes	Yes

II. DRUG RESPONSE

DRUGS ASSOCIATED WITH SENSITIVITY - PATIENT'S TUMOR TYPE

Drug	Response to Drug	Alteration	Condition	Other Relevant Information	Line of Therapy	Source
Neoadjuvant Endocrine Therapy	High	BRCA2	BRCA2	Approved for patients with ER-positive, HER2-negative breast cancer who have not received prior endocrine therapy.	Neoadjuvant	FOA/NCCN

DRUGS ASSOCIATED WITH RESISTANCE - PATIENT'S TUMOR TYPE

Drug	Response to Drug	Alteration	Condition	Other Relevant Information	Line of Therapy	Source
Chemotherapy	Low	BRCA2	BRCA2	Not indicated for tumors that harbor somatic BRCA2 mutations.	Neoadjuvant	FOA/NCCN/ASCO/MO

DRUGS ASSOCIATED WITH SENSITIVITY - OTHER TUMOR TYPES

Drug	Response to Drug	Alteration	Condition	Other Relevant Information	Line of Therapy	Source
Endocrine Therapy	High	BRCA2	BRCA2	Indicated for the treatment of postmenopausal women with ER-positive, HER2-negative, progesterone receptor-positive breast cancer.	Neoadjuvant	FOA

III. CLINICAL TRIALS

Trial ID	Trial Title	Phase	Location/Contact
NCT02997276	BRCA2	III	University of California, San Diego, San Diego, California
NCT02997276	BRCA2	III	University of California, San Diego, San Diego, California
NCT02997276	BRCA2	III	University of California, San Diego, San Diego, California

Up-to-date drug sensitivity and resistance recommendations. Sources include FDA, NCCN, and ASCO

Custom-generated list of clinical trial matches

Clickable hyperlinks to trial entry on clinicaltrials.gov

Figure 1: Clinical report example

What Makes Our Test Unique

The Personalis NeXT Dx Test goes beyond typical cancer genomics tests in a few key areas:



1. Personalized Tumor-Normal Approach

More accurately identifies somatic alterations with fewer false positives than a tumor-only approach, while also identifying incidental, cancer-related germline variants*.

*Requires confirmatory germline testing.



2. Future-Driven™ Platform

Comprehensive whole exome and whole transcriptome analytically validated to enable faster integration of new clinically actionable biomarkers as the field of oncology evolves.



3. Sensitive, RNA-Based Fusion Detection

Novel and known fusion detection using RNA sequencing¹ with deeper coverage compared to other transcriptome tests.



4. Leading Technology

Proprietary ACE (Accuracy and Content Enhanced) Technology[®] delivers augmented coverage of ~20,000 genes including difficult-to-sequence regions² missed by conventional methods.



5. Gold-Standard Tumor Mutational Burden

Optimized exome-wide TMB assessment based on matched tumor-normal approach, the gold standard established by the Friends of Cancer Research³.

Test Performance Specifications

Sensitivity	
Single Nucleotide Variants (at mutant allele frequency $\geq 5\%$)	>99%
Small Insertions and Deletions (at mutant allele frequency $\geq 5\%$)	>99%
Copy Number Alterations (at $\geq 30\%$ tumor content)	>99%
Gene Fusions	95%
Positive Predictive Value*	
Single Nucleotide Variants (at mutant allele frequency $\geq 5\%$)	>99%
Small Insertions and Deletions (at mutant allele frequency $\geq 5\%$)	>99%
Copy Number Alterations (at $\geq 30\%$ tumor content)	>99%
Gene Fusions	>99%
Additional Assay Specifications	
Microsatellite Instability (MSI)**	>99% accuracy
Tumor Mutation Burden (TMB)+	94% accuracy (calculated from whole exome by measuring the number of non-synonymous, somatic coding mutations)
Type of Sequencing	DNA and RNA sequencing using whole exome and transcriptome sequencing
Typical Median Depth	
Whole exome (Tumor)	~500x
Boosted region (247 cancer-related genes) (Tumor)	>1500x
Whole exome (blood or saliva as matched normal samples)	~150x
Whole Transcriptome (Tumor)	200M total reads
Sample Types++	Tumor: FFPE Normal: blood or saliva
Regions Analyzed	Coding and relevant non-coding regions of 401 genes
Turn Around Time	About 2 weeks from sample receipt
Test Requisition Form Required	Yes

*Positive predictive value is calculated by comparing variants detected by the NeXT Dx Test to those detected by a validated TSO500 test.

**MSI status is determined by measuring nucleotide repeats from 117 loci.

+TMB is reported as the number of mutations per megabase (mut/Mb) from tumor-normal analysis. Please note that there is currently no standard cut-off to define a high TMB for different tumor types.

++Decalcified bone is not an acceptable specimen. Additionally, specimens collected in New York State are not acceptable at this time.

NeXT Dx Reportable Gene List

Single nucleotide variants, small insertions and deletions, copy number alterations, and gene fusions involving the genes below may be reported in the test.

ABCBI [†]	CAMTA1 [†]	CSF1R [†]	EWSR1 [†]	GATA1 [†]	LIG4	MUTYH [†]	PDGFA	PTPN11 [†]	SDHA*	TMPRSS2 [†]
ABL1 [†]	CBFB [†]	CSF3R [†]	EXO1	GATA2**	LRP1B	MYC [†]	PDGFB [†]	PVRL4 [†]	SDHAF2*	TNFRSF4 [†]
AKAP9 [†]	CBL [†]	CTAG2 [†]	EZH2 [†]	GEN1	MAGEA3 [†]	MYCL	PDGFRA**	RAD21 [†]	SDHB**	TNFRSF8 [†]
AKT1 [†]	CCNA1	CTDNEP1	EZH1 [†]	GLI2 [†]	MAGEA4 [†]	MYCN [†]	PDGFRB [†]	RAD50**	SDHC**	TNFRSF10B
AKT2 [†]	CCNA2	CTLA4 [†]	FAM175A	GNA11 [†]	MAML1	MYD88 [†]	PGR [†]	RAD51 [†]	SDHD**	TP53**
AKT3 [†]	CCNB1	CTNNA1	FAN1	GNAQ [†]	MAP2K1 [†]	MYH11 [†]	PHF1 [†]	RAD51B [†]	SETBP1 [†]	TSC1**
ALK**	CCNB2	CTNNA2	FANCA [†]	GNAS [†]	MAP2K2 [†]	MYOD1 [†]	PIK3CA**	RAD51C**	SETD2	TSC2**
APC**	CCNB3 [†]	CTNNA3	FANCB [†]	GPNMB [†]	MAP2K4 [†]	NAB2 [†]	PIK3CB [†]	RAD51D**	SF3B1 [†]	TYRO3
APOBEC3B	CCND1 [†]	CTNNB1 [†]	FANCC [†]	H3F3A	MAP3K1 [†]	NBN	PIK3CD [†]	RAD52	SHFM1	U2AF1 [†]
AR [†]	CCND2 [†]	CUX1 [†]	FANCD2 [†]	HDAC1	MAPK1 [†]	NCSTN	PIK3CG [†]	RAD54B	SHH [†]	USH2A
ARAF [†]	CCND3 [†]	DDR2 [†]	FANCE [†]	HDAC2	MAPK11	NF1**	PIK3R1 [†]	RAD54L	SLX4 [†]	VEGFA [†]
AREG [†]	CCNE1 [†]	DDX3X	FANCF [†]	HEY1 [†]	MAPK3	NF2**	PIK3R2	RAF1 [†]	SMAD4**	VEGFB [†]
ARID1A [†]	CCNE2	DEK [†]	FANCG [†]	HNF1A [†]	MAX*	NFE2L2 [†]	PML [†]	RARA [†]	SMARCA4 [†]	VEGFC
ARID1B	CD274 [†]	DKK1 [†]	FANCI [†]	HRAS [†]	MBTD1 [†]	NKX2-1 [†]	PMS1	RB1**	SMARCB1 [†]	VGLL2 [†]
ARID2	CD276 [†]	DLL3 [†]	FANCL [†]	HSP90AA1 [†]	MCL1 [†]	NOTCH1 [†]	PMS2**	RBBP8	SMC1A [†]	VHL**
ASXL1 [†]	CD40 [†]	DLL4	FANCM [†]	IDH1 [†]	MCPH1	NOTCH2 [†]	POLD1*	RBM15 [†]	SMC3 [†]	WEE1 [†]
ATM**	CDH1**	DNMT3A [†]	FBXW7 [†]	IDH2 [†]	MDC1	NOTCH3 [†]	POLD2	RECQL4	SMO [†]	WRN
ATR [†]	CDH3 [†]	DOT1L	FCER2 [†]	IGF1R [†]	MDM2 [†]	NOTCH4	POLE**	RELA [†]	SRC [†]	WT1**
ATRX [†]	CDK1	EED	FGF2 [†]	IKBKE	MDM4 [†]	NPAP1	POLQ	RET**	SRSF2 [†]	WWTR1 [†]
AURKA [†]	CDK2	EGFR**	FGF4	IKZF1 [†]	MECOM [†]	NPM1 [†]	PPM1D	RFC1	SS18 [†]	XPO1 [†]
AXL [†]	CDK4**	EIF1AX	FGF19 [†]	IL2RA [†]	MEN1**	NR4A3 [†]	PPP2R1A	RFC2	SSBP1	XRCC1 [†]
BAP1**	CDK6 [†]	EML4 [†]	FGFR1 [†]	JAG1	MERTK	NRAS [†]	PPP2R2A	RFC3	STAG2 [†]	XRCC2
BARD1*	CDK9 [†]	EP300 [†]	FGFR2 [†]	JAK1 [†]	MET**	NRG1 [†]	PRAME [†]	RFC4	STAT3 [†]	XRCC3
BCL2 [†]	CDK12	EPCAM [†]	FGFR3 [†]	JAK2 [†]	MGAM	NTRK1 [†]	PRKACA [†]	RFC5	STAT5B [†]	XRCC4
BCL6 [†]	CDKN1A [†]	EPHA2	FGFR4 [†]	JAK3 [†]	MKL1 [†]	NTRK2 [†]	PRKCA [†]	RHEB	STAT6 [†]	XRCC5
BCOR [†]	CDKN1B**	ERBB2 [†]	FH**	KDM5C	MLH1**	NTRK3 [†]	PRKCB [†]	RICTOR [†]	STK11**	XRCC6
BCORL1 [†]	CDKN2A**	ERBB3 [†]	FIGF	KDM6A [†]	MLH3	NUP214 [†]	PRKCD [†]	ROS1 [†]	SUFU*	YAP1 [†]
BCR [†]	CDKN2B [†]	ERBB4 [†]	FLCN**	KDR [†]	MLL3 [†]	NUTM2A [†]	PRKCE [†]	RPA1	SULT1A1 [†]	YES1 [†]
BLM	CDKN2C	ERCC1	FLT1 [†]	KEAP1	MPL [†]	OTX2	PRKCG [†]	RPA2	SUZ12 [†]	YWHAE [†]
BRAF [†]	CEBPA**	ERCC2	FLT3 [†]	KIT**	MRE11A**	PALB2**	PRKCI [†]	RPA3	SYK [†]	ZMYM3
BRCA1**	CHEK1 [†]	ERCC3	FLT4 [†]	KLB [†]	MS4A1 [†]	PARP1 [†]	PRKCQ [†]	RPA4	TEK	ZRSR2 [†]
BRCA2**	CHEK2**	ERCC4	FOLR1 [†]	KMT2A [†]	MSH2**	PARP2	PRKCZ [†]	RPN1 [†]	TERT**	
BRD4 [†]	CIC [†]	ERCC5	FOXL2 [†]	KMT2C	MSH3	PAX3 [†]	PRKDC	RPTOR	TET2 [†]	
BRIP1**	CREBBP [†]	ERCC6	FOXO1 [†]	KMT2D	MSH6**	PBRM1	PSCA [†]	RTEL1*	TFE3 [†]	
BTK [†]	CRKL [†]	ESR1 [†]	FRK	KRAS [†]	MSLN [†]	PCNA	PTCH1**	RUNX1**	TGFBR1 [†]	
C11orf30	CRLF2 [†]	ESR2 [†]	FUS [†]	LAG3 [†]	MST1R	PDCD1 [†]	PTEN**	RUNX1T1 [†]	TGFBR2 [†]	
CALR [†]	CRTC1 [†]	ETV6**	FYN [†]	LIG3	MTOR [†]	PDCD1LG2 [†]	PTK2 [†]	RYR1	TMEM127*	

* Represents genes in which likely pathogenic/pathogenic germline variants will be reported, in addition to somatic variants, as incidental findings

† Represents fusion genes

References

1. Solomon, J.P. et al. NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. *Mod Pathol* 33, 38-46 (2020).
2. Patwardhan, A. et al. Achieving high-sensitivity for clinical applications using augmented exome sequencing. *Genome Med* 7, 71 (2015).
3. Vega, D.M. et al. Aligning tumor mutational burden (TMB) quantification across diagnostic platforms: phase II of the Friends of Cancer Research TMB Harmonization Project. *Ann Oncol* 32, 1626-1636 (2021).



Personalis, Inc.

1330 O'Brien Drive, Menlo Park, CA 94025

+1 (855) 373-7978

clientservices@personalis.com

Personalis NeXT Dx™ Test: This laboratory developed test (LDT) will be performed in a CLIA/CAP accredited laboratory. The test was developed and its performance characteristics determined by the Personalis Clinical Laboratory. It has not been cleared or approved by the United States Food and Drug Administration (FDA). The Personalis Clinical Laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

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