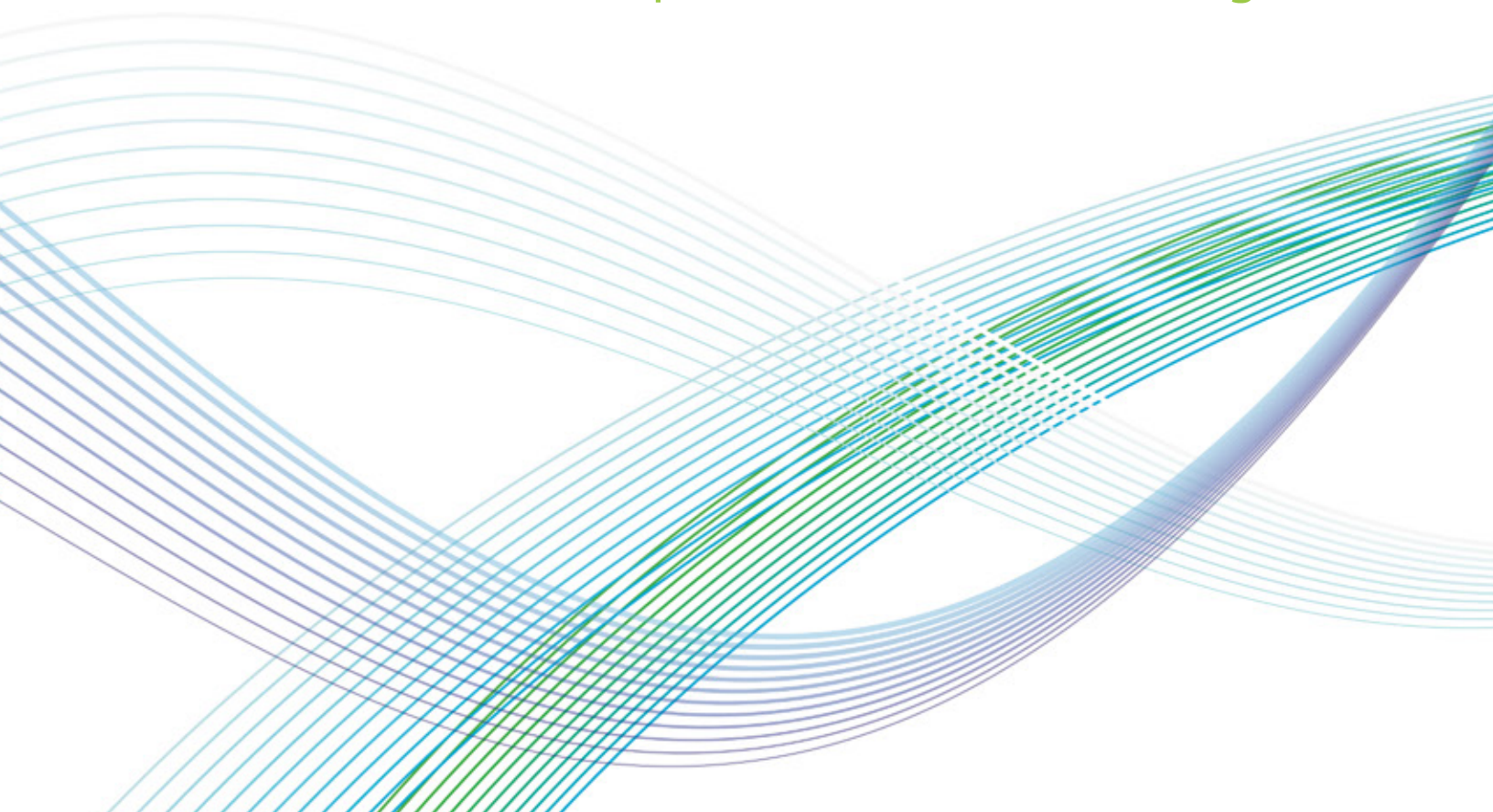


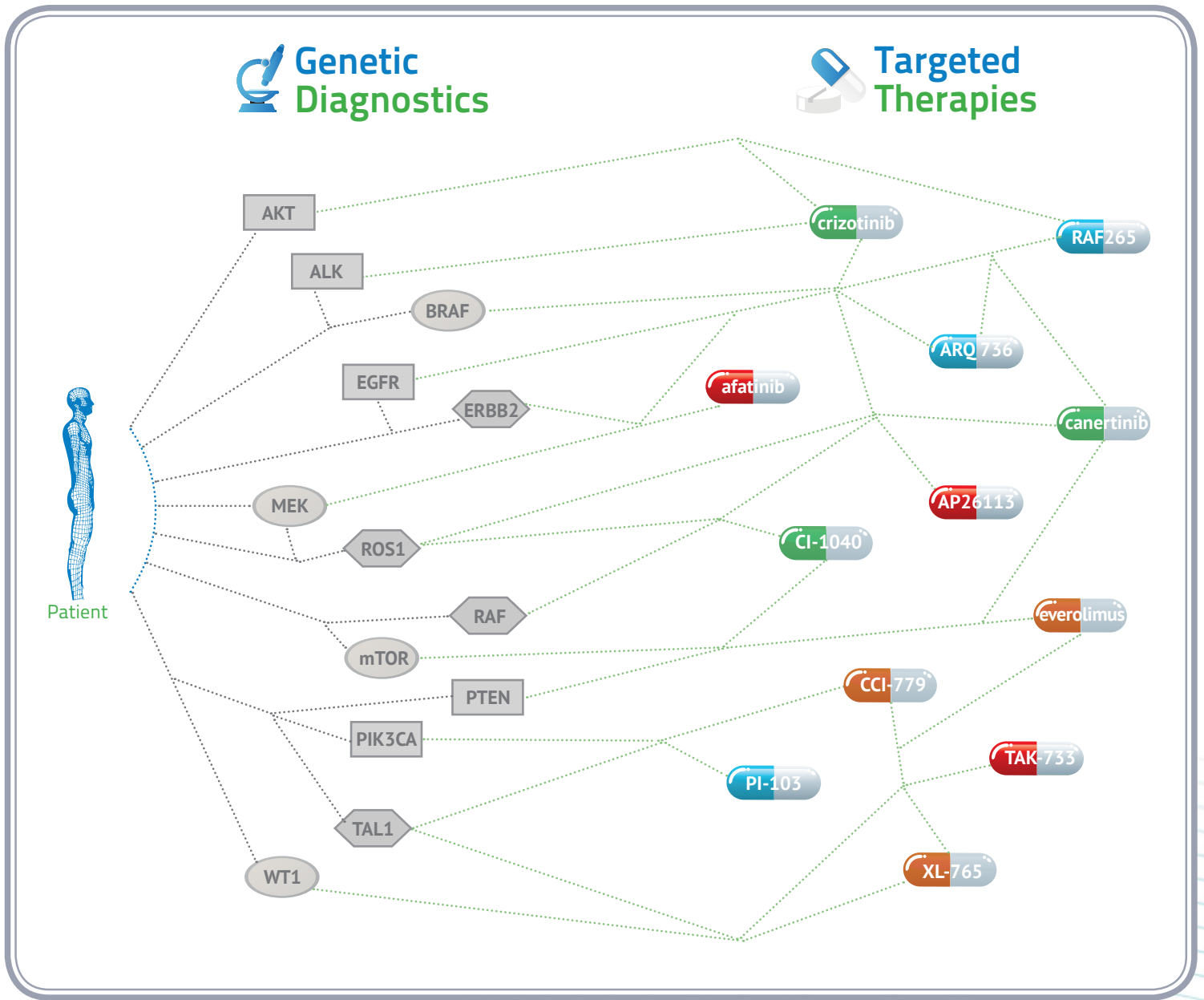


# SmartGen™

Comprehensive Genetic Diagnostics



# The Precision Medicine Challenge



**Note:** The graphics above are intended to demonstrate the complexity of matching diagnostics and subsequent targeted therapies to a patient's individual clinical situation. They are NOT intended to suggest or direct neither the selection of the proper diagnostic tests, nor to advise or serve as a reference to any associated therapy.

# Yale

The challenges surrounding the diagnosis & prognosis of cancer, and the subsequent decisions on selecting the therapeutic path, are becoming increasingly complex. One thing is clear – the treatment of cancer is no longer a one-size-fits-all approach, but rather the selection of therapy pathways carefully tailored to the patient's unique situation.

# Baylor

The field of advanced molecular testing, and the advent of next-generation-sequencing, brings with it increasingly complex diagnostic alternatives. These rapidly developing diagnostic tools evaluate dozens-to-hundreds of genes, across various technology platforms, using a variety of amplification, enrichment, analysis and bioinformatics tools to arrive at the results. Similarly, there is no single test that is suitable for all cancer patients.

# Harvard

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**SmartGen™** is a combination of academically-based diagnostic tools that were developed utilizing the expertise of faculty at world-leading academic institutions such as Baylor College of Medicine, Harvard, and Yale Medical School. Precipio's **SmartGen™** offers the most robust and advanced suite of diagnostic tools available.

# Table of Tests

Cancer Panels	Genes	Specimen Type	DNA*	Test Methodology	TAT
NGS-421 Comprehensive Cancer Panel	421	Paraffin Block Tumor >50% Tissue	400ng DNA	Whole Exon sequencing by NGS	7-10 days
NGS-409 Comprehensive Cancer Panel	409	Paraffin Block Tumor >50% Tissue	40ng DNA	Whole Exon sequencing by NGS	7-10 days
NGS-50 Solid tumor Cancer Panel	50	Paraffin Block Tumor >30% Tissue	10ng DNA	Hotspot Mutation Sequencing by NGS	10-14 days
NGS-48 Leukemia/MDS/MPN Cancer Panel	48	Peripheral Blood (Purple Top Tube); Bone Marrow Aspirate (Purple Top Tube); Bone Marrow Clot Section	20ng DNA	Hotspot Mutation Sequencing by NGS	10-14 days
TP - Tumor Profiling Cancer Panel	12	Paraffin Block; Fine needle biopsy; aspirate; Cell block; Cytology fluid	10ng DNA	TaqMan Array PCR +/- Laser Capture Microdissection	10-14 days

\* DNA minimum requirements

Hereditary Panels	Genes	Specimen Type	Test Methodology	TAT
NGS-47 Comprehensive Cancer Panel	47	Blood (EDTA Purple top)	Full Gene Sequencing by NGS and Deletion/Duplication Analysis	10-12 weeks
NGS-20 Breast/Ovarian Cancer Panel	20	Blood (EDTA Purple top)	Full Gene Sequencing by NGS and Deletion/Duplication Analysis	10-12 weeks
NGS-7HR Breast High-Risk Cancer Panel	7	Blood (EDTA Purple top)	Full Gene Sequencing by NGS and Deletion/Duplication Analysis	3 - 4 weeks
NGS-18 GI/Colorectal Cancer Panel	18	Blood (EDTA Purple top)	Full Gene Sequencing by NGS and Deletion/Duplication Analysis	10-12 weeks
NGS-11HR Colorectal High-Risk Cancer Panel	11	Blood (EDTA Purple top)	Full Gene Sequencing by NGS and Deletion/Duplication Analysis	6 - 8 weeks
NGS-17 Brain/CNS/PNS Cancer Panel	17	Blood (EDTA Purple top)	Full Gene Sequencing by NGS and Deletion/Duplication Analysis	8-10 weeks
NGS-14 Endocrine Cancer Panel	14	Blood (EDTA Purple top)	Full Gene Sequencing by NGS and Deletion/Duplication Analysis	10-12 weeks
NGS-11 Renal Cancer Panel	11	Blood (EDTA Purple top)	Full Gene Sequencing by NGS and Deletion/Duplication Analysis	8-10 weeks
NGS-9 Pheochromocytoma; Paraganglioma Cancer Panel	9	Blood (EDTA Purple top)	Full Gene Sequencing by NGS and Deletion/Duplication Analysis	8-10 weeks

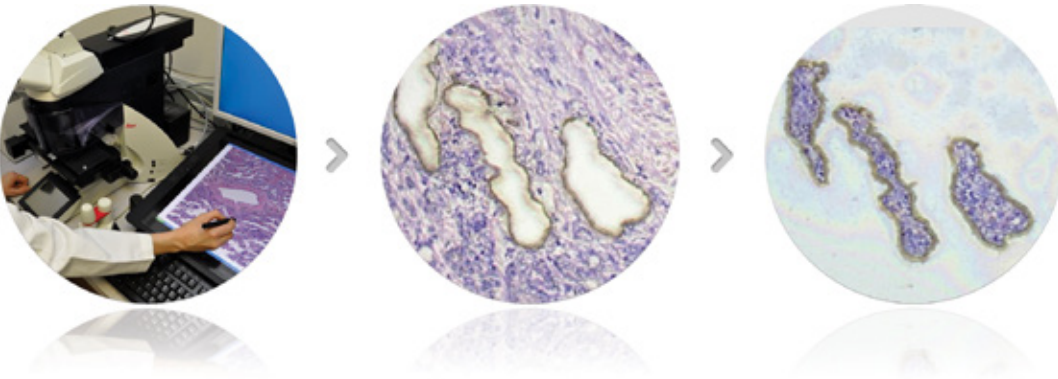
Whole Exome Sequencing	Genes	Specimen Type*	Shipping*	TAT
Germline Whole Exome	~ 22,000	Blood – min 10cc EDTA (purple top)	Express ship at room temperature in an insulated container. Do not heat or freeze. Sample must arrive within 48 hrs.	15 weeks
Cancer Whole Exome	~ 22,000	Fresh/Frozen Tumor tissue: 200 mg (0.5-1.0 cm <sup>3</sup> ) Fresh tissue snap frozen at -20°C. Store at -20°C.	Express ship on frozen on dry iced in an insulated container. Do not allow to thaw.	15 weeks
		Blood – min 10cc EDTA (purple top)	Express ship at room temperature in an insulated container. Do not heat or freeze. Sample must arrive within 48 hrs.	

\* Please contact our lab to discuss specimen and shipping logistics prior to ordering these tests.

**Omnia™** Utilizing the expertise of prominent faculty from premier academic institutions, we will provide you with the guidance and support to select the appropriate test for your patient. Our **Omnia™** option provides each patient case a review of your patient's clinical situation, to arrive at a recommendation for the appropriate test.

# Laser-Capture Micro-Dissection

Laser-capture micro-dissection is a specimen preparation technique conducted by highly trained pathologists, to selectively extract tumor cells (as opposed to non-tumor cells) for the analysis of the relevant nucleic acids. This enables testing on very limited sample sizes, and decreases the risk of diluting the sample with normal or benign DNA that can yield inconclusive or false negative results.



As always, the academic expertise is coupled with Precipio's high level of service you have come to expect from us. Our easy-to-use requisitions; reliable logistics; rapid turnaround time; and digital report delivery via our [iLabConnect™](#) system, brings the world's leading academic-based diagnostics, to your fingertips, to support you in giving your patients the care they deserve.

## Sample SmartGen™ Report

**Precipio** Smart-Gen™ **Yale CANCER CENTER**  
A Comprehensive Cancer Center Designed for the Patient Cancer Service

**SMARTGEN - TUMOR NEXT GENERATION SEQUENCING REPORT**

**A Patient Name:** John A. Doe **B Case No:** S011-000036-GS  
**C DOB/Gender:** 01/01/1940 95y-m Female **D Collected:** 05/09/10 00:00  
**E Received:** 05/13/11 13:14  
**F Reported:** 05/09/11 09:47  
**G Provider:** Jane Doe, MD **H Accession No:** 123456  
**I Account:** Hematology/Oncology Associates-05080013 **J Report Status:** Final  
**K Phone:** 355-655-6555 **L Fax:** 355-655-6555  
**M Copy:** See Smith, MD **N Variant Status:** Detected

**Clinical Information:** Typical sarcoma - right hip bone biopsy. Pathology: Monophasic spindle cell sarcoma with S11 management by IGH. Estimated malignant cell fraction >90%.

**Received Information:** 1 Tumor Block Specimen analyzed: X10-12345 Tests ordered: Onco

**RESULTS**

**EMBODDED TISSUE (X10-12345): EPYNOVIAL SARCOMA, RIGHT HIP BONE BIOPSY!**  
VARIANTS DETECTED IN TUMOR TISSUE AND NOT FOUND IN THE PATIENT'S BLOOD (SEE SUMMARY).

**SUMMARY**

Two potentially "actionable" mutations were detected in a high percentage of cells within this patient's tumor: one mutation in *PTEN* and one in *BCL2*. Drugs trials relevant to both of these genes, or the pathway they regulate, have been conducted with at least some benefits observed. However, computer programs predict that the *BCL2* mutation should significantly affect protein function, and may therefore be of no clinical consequence. Only functional studies of these specific mutations can determine the important points. Furthermore, drug trials involving alterations of *BCL2* have been directed only at overexpression of the gene, and not mutations within the gene, as found in this case. Whether there is also overexpression of *BCL2* or the mutation detected represents the equivalent of overexpression is not assessed by the present analysis.

**DRUG TREATMENT CORRELATED TO FINDINGS**

Drugs Associated with Clinical Benefit:

- rituximab
- AP-133, ARI-061, ARI-198

**RELEVANT CLINICAL TRIALS SPECIFIC TO MUTATIONAL ANALYSIS**

See summary section above.

**Disclaimer:** The information provided in the drug treatment and clinical trial section is gathered from various information sources available to the public, and are intended for the physician's convenience. These sources are intended for informational purposes only and are not intended to be used as a substitute for professional medical advice or a patient's medical history. Please do not rely on this information for the purpose of making a clinical decision, and this information may not reflect the most current information available. Please discuss all relevant and related findings with the physician and/or the patient's care team. Any physician reviewing this report should conduct their own independent research prior to making any course of action.

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Actionable Diagnosis

Drug Responsiveness Analysis

Clinical Trials Information

## SmartGen™ Whole Exon (409/421) Gene Cancer Panels

A	ABL1	BRIP1	DDIT3	FGFR1	IKZF1	MCL1	NTRK3	RALGDS	T	TAF1
	ABL2	BTK	DDR1	FGFR2	IL2	MDM2	NUMA1	RARA		TAF1L
	ACVR1B	BUB1B	DDR2	FGFR3	IL21R	MDM4	NUP214	RASA1		TAL1
	ACVR2A	C11orf30	DEK	FGFR4	IL6ST	MED12	NUP93	RB1		TBX22
	ADAMTS20	CARD11	DICER1	FH	IL7R	MEF2B	NUP98	RECQL4		TCF12
	AFF1	CASC5	DNMT3A	FLCN	ING4	MEN1	PAK3	REL		TCF3
	AFF3	CASP8	DOT1L	FLI1	INHBA	MET	PALB2	RET		TCF7L1
	AKAP9	CBFB	DPYD	FLT1	IRF4	MITF	PARP1	RHOH		TCF7L2
	AKT1	CBL	DST	FLT3	IRS2	MLH1	PAX3	RICTOR		TCL1A
	AKT2	CCND1	EDNRB	FLT4	ITGA9	MLL	PAX5	RNASEL		TET1
	AKT3	CCND2	EGFR	FN1	ITGA10	MLL2	PAX7	RNF2		TET2
	ALK	CCND3	EML4	FOXA1	ITGB2	MLL3	PAX8	RNF213		TFE3
	AMER1	CCNE1	EP300	FOXL2	ITGB3	MLLT10	PBRM1	RNF43		TGFB2
	APC	CD79A	EP400	FOXO1	JAK1	MMP2	PBX1	ROS1		TGM7
	AR	CD79B	EPHA3	FOXO3	JAK2	MN1	PDE4DIP	RPS6KA2		THBS1
	ARAF	CDC73	EPHA5	FOXP1	JAK3	MPL	PDGFB	RPTOR		TIMP3
	ARFRP1	CDH1	EPHA7	FOXP4	JUN	MRE11A	PDGFRA	RRM1		TLR4
	ARID1A	CDH2	EPHB1	FZR1	KAT6A	MSH2	PDGFRB	RUNX1		TLX1
	ARID2	CDH5	EPHB4	G6PD	KAT6B	MSH6	PDK1	RUNX1T1		TNFAIP3
	ARNT	CDH11	EPHB6	GATA1	KDMSA	MST1R	PER1	SAMD9		TNFRSF14
	ASCL4	CDH20	ERBB2	GATA2	KDM5C	MYTOR	PGAP3	SBDS		TNK2
	ASXL1	CDK4	ERBB3	GATA3	KDM6A	MTR	PHOX2B	SDHA		TOP1
	ATF1	CDK6	ERBB4	GDNF	KDR	MTRR	PIK3C2B	SDHB		TP53
	ATM	CDKB	ERCC1	GID4	KEAP1	MUC1	PIK3CA	SDHC		TP63
	ATR	CDK12	ERCC2	GNA11	KIAA1804	MUC16	PIK3CB	SDHD		TPR
	ATRX	CDKN1B	ERCC3	GNA13	KIT	MUTYH	PIK3CD	SETD2		TRIM24
	AURKA	CDKN2A	ERCC4	GNAQ	KLF5	MYB	PIK3CG	SEPT9		TRIM33
	AURKB	CDKN2B	ERCC5	GNA5	KLF6	MYC	PIK3R1	SF3B1		TRIP11
	AURKC	CDKN2C	ERG	GPC6	KLHL6	MYCL1	PIK3R2	SGK1		TRRAP
	AXIN2	CEBPA	ESR1	GPR124	KRAS	MYCN	PIK3R3	SH2D1A		TSC1
	AXL	CHEK1	ETS1	GRIK3	LAMP1	MYD88	PIM1	SLIT2		TSC2
B	BAI3	CHEK2	ETV1	GRIN2A	LCK	MYH11	PKHD1	SMAD2		TSHR
	BAP1	CIC	ETV4	GRM8	LIFR	MYH9	PLAG1	SMAD4		TYK2
	BARD1	CKS1B	EXT1	GSK3B	LPHN3	NBN	PLCG1	SMARCA4	U	UBR5
	BCL10	CMPK1	EXT2	GUCY1A2	LPP	NCOA1	PLEKHG5	SMARCB1		UGT1A1
	BCL11A	COL1A1	EZH2	HCAR1	LRP1B	NCOA2	PML	SMO		USP9X
	BCL11B	CRBN	FAM123B	HCN1	LTF	NCOA4	PMS1	SMUG1	V	VHL
	BCL2	CREB1	FAM46C	HGF	LTN1	NF1	PMS2	SOC51	W	WAS
	BCL2L1	CREBBP	FANCA	HIF1A	M	MAF	NF2	POT1		WBSCR17
	BCL2L2	CRKL	FANCC	HLF	MAFB	NFE2L2	POU5F1	SOX11		WHSC1
	BCL3	CRLF2	FANCD2	HNF1A	MAGEA1	NFKB1	PPARG	SOX2		WISP3
	BCL6	CRTC1	FANCE	HNF4A	MAG1	NFKB2	PPP2R1A	SOX9		WRN
	BCL9	CSF1R	FANCF	HOOK3	MALT1	NFKBIA	PRDM1	SPEN		WT1
	BCOR	CSMD3	FANCG	HRS	MAML2	NIN	PRKAR1A	SPOP	X	XPA
	BCORL1	CTCF	FANCL	HSP90AA1	MAP2K1	NKX2-1	PRKDC	SRC		XPC
	BCR	CTNNA1	FAS	HSP90AB1	MAP2K2	NLRP1	PSIP1	SSX1		XPO1
	BIRC2	CTNNA2	FBXW7	ICK	MAP2K4	NOTCH1	PTCH1	STAG2		XRCC2
	BIRC3	CTNNB1	FGF10	IDH1	MAP3K1	NOTCH2	PTEN	STAT3	Z	ZNF384
	BIRC5	CYLD	FGF14	IDH2	MAP3K7	NOTCH4	PTGS2	STAT4		ZNF521
	BLM	CYP2C19	FGF19	IGF1R	MAPK1	NPM1	PTPN11	STK11		
	BLNK	CYP2D6	FGF23	IGF2	MAPK8	NRAS	PTPRD	STK36		
	BMPR1A	DAXX	FGF3	IGF2R	MARK1	NSD1	PTPRT	SUFU		
	BRAF	DCC	FGF4	IKBK	MARK4	NTRK1	R	RAD50		
	BRD3	DDB2	FGF6	IKBKE	MBD1	NTRK2	RAF1	SYK		
								SYNE1		

- Gene appearing in BOTH the 409 and 421 panels
- Gene appearing in the 409 panel ONLY
- Gene appearing in the 421 panel ONLY

## SmartGen™ Hotspot Mutation Panels

### NGS-50

Comprehensive Solid Tumor  
Gene Cancer Panel

ABL1	EGFR	GNA11	KRAS	PTPN11
AKT1	ERBB2	GNAQ	MET	RB1
ALK	ERBB4	HNF1A	MLH1	RET
APC	EZH2	HRAS	MPL	SMAD4
ATM	FBXW7	IDH1	NOTCH1	SMARCB1
BRAF	FGFR1	IDH2	NPM1	SMO
CDH1	FGFR2	JAK2	NRAS	SRC
CDKN2A	FGFR3	JAK3	PDGFRA	STK11
CSF1R	FLT3	KDR	PIK3CA	TP53
CTNNB1	GNAS	KIT	PTEN	VHL

### NGS-48

Comprehensive  
Leukemia/MDS/MPN  
Gene Cancer Panel

ABL1	CSF1R	FBXW7	IL7R	NRAS	SF3B1
ASXL1	CTCF	FLT3	JAK2	PAX5	SRSF2
BRAF	DNM2	GATA1	JAK3	PDGFRA	SUZ12
CBL	DNMT3A	HRAS	KIT	PHF6	TAL1
CDKN2A	EED	IDH1	KRAS	PTEN	TET2
CEBPA	EP300	IDH2	MPL	PTPN11	TP53
CREBBP	ETV6	IKZF1	NOTCH1	RELN	U2AF1
CRLF2	EZH2	IKZF3	NPM1	RUNX1	WT1

### NGS-47

Hereditary Comprehensive  
Cancer Panel

ALK	CDH1	MAX	NF1	PTEN	SMAD4
APC	CDKN1C	MEN1	NF2	RAD51C	STK11
ATM	CDKN2A	MET	PALB2	RAD51D	SUFU
BMPR1A	CHEK2	MLH1	PHOX2B	RET	TMEM127
BRCA1	EPCAM	MSH2	PMS1	SDHAF2	TP53
BRCA2	FH	MSH6	PMS2	SDHB	VHL
BRIP1	FLCN	MUTYH	PRKAR1A	SDHC	WT1
CDC73	GPC3	NBN	PTCH1	SDHD	

### NGS-20

Hereditary Breast/Ovarian  
Cancer Panel

■ **NGS-7HR** High Risk Cancer Panel

ATM	CDH1	MSH2	PALB2	RAD51C
BRCA1	CHEK2	MSH6	PMS1	RAD51D
BRCA2	EPCAM	MUTYH	PMS2	SKT11
BRIP1	MLH1	NBN	PTEN	TP53

### NGS-18

GI/Colorectal  
Cancer Panel

■ **NGS-11HR** High Risk Cancer Panel

APC	CDH1	MLH1	PMS1	SKT11
BMPR1A	CDKN2A	MSH2	PMS2	TP53
BRCA1	CHEK2	MSH6	PTEN	
BRCA2	EPCAM	MUTYH	SMAD4	

### NGS-17

Hereditary Brain/CNS/PNS  
Cancer Panel

ALK	MLH1	NF1	PMS2	VHL
APC	MSH2	NF2	PTCH1	
ATM	MSH6	PALB2	SUFU	
MEN1	NBN	PHOX2B	TP53	

### NGS-14

Hereditary Endocrine  
Cancer Panel

CDC73	PRKAR1A	SDHB	TP53
MAX	PTEN	SDHC	VHL
MEN1	RET	SDHD	
NF1	SDHAF2	TMEM127	

### NGS-11

Hereditary Renal Cancer Panel

CDKN1C	MET	SDHD
FH	PALB2	VHL
FLCN	PTEN	WT1
GPC3	SDHB	

### NGS-9

Hereditary Pheochromocytoma/  
Paraganglioma Cancer Panel

MAX	SDHB	VHL
NF1	SDHC	
RET	SDHD	
SDHAF2	TMEM127	

## SmartGen™ Taqman Actionable Therapy Panel

### TP-12

Taqman Array Actionable  
Cancer Panel

AKT1	EGFR	KRAS	NRAS
BRAF	ERBB2	MEK1	PIK3CA

\* For NSCLC, Reflex to ALK & ROS1 rearrangement by FISH



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