oncotype MAP™ Pan-Cancer Tissue

Patient Name
Precision Female

Final Report Date
1/1/2099

Pancreatic Adenocarcinoma

Pan-Cancer Tissue

Date of Birth: 00/00/0000
Pan-Cancer Tissue#: OR000000000, PCDx-19-00000
Physician: Dr. Smith
Facility: Cancer Treatment

Case/Specimen ID: AA00-00000 A0
Collection Site: right lung
Collection Date: 00/00/0000
Received for testing: 00/00/0000

Turnaround: 5 business days
Tumor cells: 80%
Specimen size: 24 mm^2
Requirement met: Optimal

3 NCCN/FDA indications

Therapeutic Option	Indicating biomarkers
Entrectinib	ETV6-NTRK3 Fusion
Larotrectinib	ETV6-NTRK3 Fusion
Pembrolizumab	TMB High

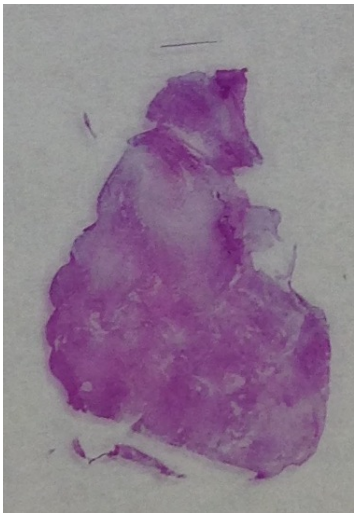
High Interest

Pan cancer	Type specific
TMB: High (10muts/mb)	**KRAS: G12R**
MSI: Stable	PALB2: Wildtype
NTRK fusion: ETV6-NTRK3	
BRCA1: Wildtype	
BRCA2: Wildtype	

1 evidence-based therapy association

Vincristine

Specimen



Tumor cells: 80%
Specimen size: 24 mm^2
Residual tissue: Yes

pancreatic cancer, adenocarcinoma

Gross Description: Xxxxxxxx xxxx Xxtxxxxxx Xxxxtxxx xx 0 Xxxxx xxxxxxx xx 0000-0000 X (xxx XXXx-00-00000) xxxx tx xxxx xxx Xxxxxxxx X&X xxxxx xxxxxxx xx 0000-0000 X (xxx XXXx-00-00000) xxxxtxxxxx xx xxxxxxxxx tx txx xxxxx xxxxx xxtxxxt xxxxx xx txx xxxxxxxxxxxx xxxxxxxx xxtxxxxxx xxxxxt xxtx xxxxxxxx xxxxxxtxxx xxtx xx 0/0/0000. Xxxxx 0000-0000 X xxxx xx xxxxxxxx.

Pathologist has performed a comprehensive review of all records and material submitted.

10 salient genomic findings

Gene	Variant	Quantity	Gene	Variant	Quantity
ATM	K2515*	60%	GATA3	P135Rfs*60	56%
AXL	Amplification	2.53x	KRAS	G12R	41%
CDK4	Amplification	2.38x	MDM2	Amplification	2.65x
CDKN2A	P114_L117del	57%	SMAD4	Loss	0.50x
ETV6-NTRK3	Positive	14%	STK11	c.921-2A>T p.?	61%

26 other genomic findings

Note: this table contains all non-reference alleles found in less than 1% of the population. These may be germline or somatic.

XXXXTX00 x.0000-0X>X
XXXX0 X0000T XXXXX0
X0000X XXX x.0000-0000X>T
XXX0XX X000X
XXXXTX00 X0000
XXX00 Xxxx
XXXXX X0000X
XXX0X0 X0000T
XXX00X x.000+0000X>X
XXX X0000
XXXXXX X0000
XXXXX X0000X
XXXX0 X000
XXX0 Xxxx
XXXX0X Xxxx
XTXX0 x.0000-00000X>X
XTXX X000X
XX000 X000X
XXT T000X XXXX Xxxx
XX X000X XXX0X0
T00 XXT0 X000
XTXX x.0000+00X>X
XXX0 Xxxx
XXX0 X00
XXXX0 X0000X
XXX T000X
XXX0 X000
XXXX0 X00
XXXXXX X00

4 therapies with potential increased benefit

Therapeutic Option	Biomarkers	NCCN/FDA	Level of evidence	References
Entrectinib	ETV6-NTRK3 Fusion	Yes	II-2	4
Larotrectinib	ETV6-NTRK3 Fusion	Yes	II-2	3
Pembrolizumab	TMB High	Yes	II-2	6
Vincristine	ETV6-NTRK3 Fusion		DTT	7

6 therapies with potential reduced benefit

Therapeutic Option	Contraindicating biomarkers	References
Afatinib	KRAS mutation	8
Cetuximab	KRAS mutation	10,2
Erlotinib	KRAS mutation	5,9
Fluorouracil	SMAD4 Loss	1
Gefitinib	KRAS mutation	8
Panitumumab	KRAS mutation	10,2

clinical notes

ATM: Ataxia-telangiectasia mutated (ATM) and ATR (ataxia telangiectasia and Rad3-related protein) are the two key kinases involved in DNA signaling and they have the ability to detect single-strand and double-strand DNA breaks.Pancreatic ductal adenocarcinoma (PDAC) is associated with accumulation of particular oncogenic mutations and recent genetic sequencing studies have identified ATM mutations in PDAC cohorts. Germline mutations in ATM increase Familial Pancreatic Cancer (FPC) susceptibility, and ATM somatic mutations have been identified in resected human pancreatic tumors. ATM deficiency markedly increases the proportion of chromosomal alterations in pancreatic primary tumors and liver metastases. Emerging evidence suggests that deficiency in ATM and reduction of ATR kinase activity may increase sensitivity to PARP inhibition (Pihlak et al. 2017 PMID 29069866)

AXL CNV gain/amplification: The transforming and tumor growth-promoting properties of AXL, a member of the Tyro3, Axl, and Mer (TAM) family of receptor tyrosine kinases (TAMRs), are well recognized. Upregulation of the Axl/Tyro3 receptor family has been found in breast, ovarian and lung tumors.

CDK4 CNV gain/amplification: cyclin-dependent kinase 4 amplification occurs in numerous adult malignancies, including breast carcinoma, lymphoma, melanoma, and sarcoma, most notably in >95% of well-differentiated and dedifferentiated liposarcomas. In addition, CDK4 is also amplified or overexpressed in pediatric tumor types, such as neuroblastoma. Recent development of a new generation of highly selective small molecule inhibitors targeting CDK4/6 has renewed attention to CDK4/6 inhibition. Three orally bioavailable, selective CDK4/6 inhibitors are approved, including abemaciclib, palbociclib, and ribociclib. Emerging evidence from select case reports suggest that CDK4 copy number gain/amplification may be associated with benefit from palbociclib, for example Dickson et al. 2013 PMID: 24795392.

CDKN2A: CDKN2A (p16-INK4a, MTS-1, CDK4I) is a tumor suppressor, which regulates cell cycle progression by inhibiting cyclinD-CDK4 and cyclinD-CDK6 complexes responsible for initiating the G1/S phase transition. CDKN2A disruption can happen by different mechanisms, such as the loss of heterozygosity, homozygous deletion, or promoter silencing. In pancreatic cancer, CDKN2A is one of four major driver genes (KRAS, CDKN2A, TP53, and SMAD4). The incidence of CDKN2A mutations in sporadic pancreatic cancer is impressive, with inactivation occurring in up to 98% of cases. Alterations in CDKN2A appear to be early events in pancreatic tumorigenesis, with emerging clinical evidence for the use of CDKN2A mutations as a prognostic or predictive biomarker (Cicenas et al. 2017 PMID 28452926)

ETV6-NTRK3; The fusion between the ETV6 gene on chromosome 12 and the NTRK3 gene on chromosome 15 was first described in congenital fibrosarcoma in 1998. Since then, ETV6-NTRK3 rearrangements have been found in several other tumor types including acute myeloid leukemia (AML), chronic eosinophilic leukemia (CEL), congenital mesoblastic nephroma, secretory breast carcinoma, and mammary analogue secretory carcinoma of the salivary gland. ETV6, also known as TEL, is a transcription factor from the ETS transcription factor family, which is involved in various oncogenic gene fusions resulting from chromosomal translocations, mostly reported in subtypes of AML. NTRK3 is a transmembrane receptor tyrosine kinase, for which ligand is neurotrophin-3, which is primarily involved in neuronal cellular processes. The rearrangement results in fusion of the SAM domain of ETV6, which is required for dimerization, with the tyrosine kinase domain of NTRK3, such that the transcribed product is a constitutively active tyrosine kinase. NTRK fusions are clinically actionable: first-generation TRK tyrosine kinase inhibitors (larotrectinib or entrectinib) result in histology-agnostic responses in both adult and paediatric patients.

GATA3: The transcription factor GATA binding protein 3 (GATA3) has emerged as a critical regulator of both innate and adaptive immunity. GATA3 belongs to the GATA (GATA-binding protein) family comprised of six members - GATA1 to 6. The immune function of GATA3 is multifaceted and extends beyond controlling Th2 differentiation. GATA3 is important for T cell development, homeostasis, activation, proliferation and effector functions. In addition, GATA3 controls ILC function. With the development of more sophisticated experimental tools, it is expected that additional functions of GATA3 in immune regulation will be unveiled in the future (Wan 2014 PMID: 24786134)

KRAS: A somatic KRAS mutation in exon 2 (codon 12) was identified. Overactive RAS signaling promotes oncogenesis and predicts a lack of response to anti-EGFR therapy. Mutations of KRAS are found in a variety of human malignancies. Oncogenic mutations in RAS genes result in the elevation of cellular active RAS protein levels and increased signal propagation through downstream pathways that drive tumor cell proliferation and survival. These gain-of-function mutations drive over 30% of all human cancers, presenting promising therapeutic potential for RAS inhibitors. Despite efforts, KRAS remains a challenging therapeutic target. RAS remains an elusive drug target despite its well-characterized role in cancer and extensive efforts to develop novel therapeutics targeting RAS-driven cancers. Multiple aspects of RAS structural biology present challenges for the development of small molecule inhibitors, including a lack of deep, druggable pockets, an ultra-high affinity for its guanine nucleotide substrates, and few structural differences between wild-type and oncogenic RAS proteins. A number of anti-cancer drugs that block a multitude of signaling nodes, either upstream or downstream of RAS, have been developed and approved for clinical use by the FDA. However,

clinical notes

these therapies have limited clinical utility for RAS-driven cancers, and often result in the reoccurrence of highly aggressive malignancies. While the progress towards developing clinically effective RAS inhibitors is promising, the therapeutic potential of compounds targeting specific mutants is limited to subsets of RAS-driven cancers. The current understanding of the mechanism of RAS nucleotide exchange presents numerous opportunities for reversible inhibitors (Mattox et al. 2020 PMID: 31878223).

MDM2 CNV gain/amplification: This gene encodes a nuclear-localized E3 ubiquitin ligase. The encoded protein can promote tumor formation by targeting tumor suppressor proteins, such as p53, for proteasomal degradation. This gene is itself transcriptionally-regulated by p53. Overexpression or amplification of this locus is detected in a variety of different cancers [provided by RefSeq, Jun 2013]. Amplification of MDM2 family proteins has been found in patients experiencing hyperprogressive disease under treatment with checkpoint inhibitors such as pembrolizumab, nivolumab and atezolizumab across multiple tumor types (Kato et al. 2018 PMID 28351930). MDM2 amplification has also been implicated in primary resistance to EGFR TKIs in NSCLC (Sun et al. 2020 32611363; Kim et al. 2019 PMID 30391576).

Microsatellite Instability Analysis [MSI] Result Stable (MSS): Cancers are classified as either displaying high-frequency microsatellite instability (MSI-H), low-frequency MSI (MSI-L), or microsatellite stability (MSS) depending on the number of microsatellite loci showing errors. Microsatellite stable cancers (MSS) generally show less immune cell infiltration compared with MSI-H cancers. The greatly increased number of mutation-associated neoantigens resulting from mismatch-repair deficiency appears to be a key mechanism in the observed responsiveness to anti–PD-1 agents such as pembrolizumab (Le et al. 2015; PMID: 26028255).

SMAD4 CNV loss: SMAD4 is involved in the regulation of cell proliferation, differentiation, migration, and apoptosis. Emerging data suggest a putative relationship between SMAD4 and immune evasion and underscore the clinical importance of SMAD4 as a potential prognostic biomarker. In clinical samples, SMAD4 loss has been associated with worse outcomes and correlates with resistance to chemotherapy.

STK11: STK11/LKB1 (serine/threonine kinase 11) is a classic tumor-suppressor gene involved in pancreatic and biliary neoplasia and appears to play a role in the development of both sporadic and familial (PJS) pancreatic and biliary cancers. Inherited mutations in STK11 have been associated with Peutz-Jeghers syndrome. Individuals with Peutz-Jeghers syndome have a very high risk of developing pancreatic cancer. Mutations in the STK11 gene are very rare and account for less than 1% of familial pancreatic cancer.

TMB: Tumor Mutation Burden [TMB] is defined as the total number of DNA mutations per megabase in a tumor sequence. While thresholds for TMB have not been clearly defined for all immunotherapy drugs, and there is at present no consensus for the optimal quantitative or qualitative threshold by cancer type, TMB appears to have an evolving role as a predictive marker for immunotherapy treatment. Overall, a higher TMB is generally associated with longer survival and higher response rates with ICI therapy. While this effect is seen in the majority of cancer types, indicating that TMB underlies fundamental aspects of immune-mediated tumor rejection, the optimal predictive cut-point may vary by histology (Lee et al. 2019 PMID 31361563, Samstein et al 2019 PMID 30643254). For the purpose of TMB stratification, OncotypeMap has adopted the high (≥ 10 mutations per megabase) and low (< 10 mutations per megabase) dichotomy based on the retrospective analysis of TMB in the CheckMate 227 trial, in which NSCLC patients were treated with nivolumab + ipilimumab combination (Hellmann et al. 2018, PMID: 29658845). This cutoff is also the suggested TMB threshold that underlies the recent tissue-agnostic FDA approval for pembrolizumab to treat adult and pediatric patients with unresectable or metastatic solid tumors, who have progressed following prior treatment and who have no satisfactory alternative treatment options.

clinical trials

in tumor type

KRAS mutation	NCT03637491	Avelumab | Binimetinib | Talazoparib

A Study of Avelumab, Binimetinib and Talazoparib in Patients With Locally Advanced or Metastatic RAS-mutant Solid Tumors

multi-indication trials

ATM mutation	NCT02693535	Olaparib

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

ATM mutation	NCT03207347	Niraparib

A Trial of Niraparib in BAP1 and Other DNA Damage Response (DDR) Deficient Neoplasms (UF-STO-ETI-001)

ATM mutation	NCT03718091	M6620

M6620 (VX-970) in Selected Solid Tumors

ATM mutation	NCT03842228	Copanlisib | Durvalumab | Olaparib

Testing the Combination of the Anti-cancer Drugs Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients With Advanced Solid Tumors With Selected Mutations

ATM mutation	NCT04266912	Avelumab;Berzosertib;

Avelumab and M6620 for the Treatment of DDR Deficient Metastatic or Unresectable Solid Tumors

ATM mutation	NCT03682289	ATR Kinase Inhibitor AZD6738;Olaparib;

Phase II Trial of AZD6738 Alone and in Combination With Olaparib

Continued

clinical trials

AXL Amplification	NCT02219711	MGCD516
Phase 1/1b Study of MGCD516 in Patients With Advanced Cancer		
BRAF WT	NCT03114319	TNO155;TNO155 in combination with EGF816 (nazartinib);
Dose Finding Study of TNO155 in Adult Patients With Advanced Solid Tumors		
CDK4 Amplification	NCT02693535	Palbociclib
TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer		
CDK4 Amplification	NCT02896335	Palbociclib
Palbociclib In Progressive Brain Metastases		
CDK4 Amplification	NCT03310879	Abemaciclib
Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6		
CDK4 Amplification	NCT03237390	Gemcitabine I Ribociclib
Ribociclib and Gemcitabine Hydrochloride in Treating Patients With Advanced or Metastatic Solid Tumors		
CDK4 Amplification	NCT04557449	PF-07220060;
Study to Test the Safety and Tolerability of PF-07220060 in Participants With Advance Solid Tumors		
CDKN2A mutation	NCT02693535	Palbociclib
TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer		
ETV6-NTRK3 Fusion	NCT02219711	MGCD516
Phase 1/1b Study of MGCD516 in Patients With Advanced Cancer		
ETV6-NTRK3 Fusion	NCT02568267	Entrectinib
Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions)		
ETV6-NTRK3 Fusion	NCT02576431	LOXO-101
A Study to Test the Effect of the Drug Larotrectinib in Adults and Children With NTRK-fusion Positive Solid Tumors		
ETV6-NTRK3 Fusion	NCT02920996	Merestinib
Merestinib In Non-Small Cell Lung Cancer And Solid Tumors		
ETV6-NTRK3 Fusion	NCT03025360	Larotrectinib
Expanded Access to Provide Larotrectinib for the Treatment of Cancers With a NTRK Gene Fusion		
ETV6-NTRK3 Fusion	NCT03093116	TPX-0005
A Study of Repotrectinib (TPX-0005) in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements		
HRAS WT	NCT03114319	TNO155;TNO155 in combination with EGF816 (nazartinib);
Dose Finding Study of TNO155 in Adult Patients With Advanced Solid Tumors		
KRAS mutation	NCT03637491	Avelumab I Binimetinib I Talazoparib
A Study of Avelumab, Binimetinib and Talazoparib in Patients With Locally Advanced or Metastatic RAS-mutant Solid Tumors		
KRAS mutation	NCT03756818	Paclitaxel I Spleen Tyrosine Kinase Inhibitor TAK-659
TAK-659 and Paclitaxel in Treating Patients With Advanced Solid Tumors		
KRAS mutation	NCT03948763	V941(mRNA-5671/V941
A Study of mRNA-5671/V941 as Monotherapy and in Combination With Pembrolizumab (V941-001)		
KRAS mutation	NCT03989115	RMC-4630;Cobimetinib;Drug: Osimertinib;
Dose-Escalation/Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors and RMC-4630 and Osimertinib in EGFR Positive Locally Advanced/Metastatic NSCLC		
KRAS mutation	NCT04418167	JSI-1187;Dabrafenib;
JSI-1187-01 Monotherapy and in Combination With Dabrafenib for Advanced Solid Tumors With MAPK Pathway Mutations		
KRAS mutation	NCT04145297	Ulixertinib;Hydroxychloroquine;
Ulixertinib (BVD-523) and Hydroxychloroquine in Patients w Advanced MAPK-Mutated Gastrointestinal Adenocarcinomas		
KRAS mutation	NCT03162627	Selumetinib;Olaparib;
Selumetinib and Olaparib in Solid Tumors		
MDM2 Amplification	NCT03449381	BI 907828
This Study Aims to Find the Best Dose of BI 907828 in Patients With Different Types of Advanced Cancer (Solid Tumors)		

Continued

clinical trials

MSI Stable	NCT03711058	Copanlisib | Nivolumab
Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer		
NRAS WT	NCT03114319	TNO155;TNO155 in combination with EGF816 (nazartinib);
Dose Finding Study of TNO155 in Adult Patients With Advanced Solid Tumors		
NTRK3 (TrkC) Fusion	NCT02219711	MGCD516
Phase 1/1b Study of MGCD516 in Patients With Advanced Cancer		
NTRK3 (TrkC) Fusion	NCT02568267	Entrectinib
Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions)		
NTRK3 (TrkC) Fusion	NCT02576431	LOXO-101
A Study to Test the Effect of the Drug Larotrectinib in Adults and Children With NTRK-fusion Positive Solid Tumors		
NTRK3 (TrkC) Fusion	NCT02920996	Merestinib
Merestinib In Non-Small Cell Lung Cancer And Solid Tumors		
NTRK3 (TrkC) Fusion	NCT03025360	Larotrectinib
Expanded Access to Provide Larotrectinib for the Treatment of Cancers With a NTRK Gene Fusion		
NTRK3 (TrkC) Fusion	NCT03093116	TPX-0005
A Study of Repotrectinib (TPX-0005) in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements		
NTRK3 (TrkC) Fusion	NCT03215511	LOXO-195
A Study to Test the Safety of the Investigational Drug Selitrectinib in Children and Adults That May Treat Cancer		
NTRK3 (TrkC) Fusion	NCT03834961	Larotrectinib
Larotrectinib in Treating Patients With Previously Untreated TRK Fusion Solid Tumors and TRK Fusion Relapsed Acute Leukemia		
PTPN11 WT	NCT03114319	TNO155;TNO155 in combination with EGF816 (nazartinib);
Dose Finding Study of TNO155 in Adult Patients With Advanced Solid Tumors		
STK11 mutation	NCT03872427	Glutaminase Inhibitor CB-839
Testing Whether Cancers With Specific Mutations Respond Better to Glutaminase Inhibitor, Telaglenastat Hydrochloride, Anti-Cancer Treatment, BeGIN Study		
TMB High	NCT02693535	Pembrolizumab or Nivolumab + Ipilimumab
TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer		
TMB High	NCT03911557	Durvalumab | Tremelimumab
Durvalumab and Tremelimumab Combination in Somatically Hypermutated Recurrent Solid Tumors		
TP53 WT	NCT01877382	DS-3032
A Phase 1 Multiple Ascending Dose Study of Milademetan in Subjects With Advanced Solid Tumors or Lymphomas		
TP53 WT	NCT03449381	BI 907828
This Study Aims to Find the Best Dose of BI 907828 in Patients With Different Types of Advanced Cancer (Solid Tumors)		
TP53 WT	NCT03560882	Atorvastatin
A Pilot Trial of Atorvastatin in Tumor Protein 53 (p53) -Mutant and p53 Wild-Type Malignancies		
TP53 WT	NCT03725436	MDM2/MDMX Inhibitor ALRN-6924 | Paclitaxel
ALRN-6924 and Paclitaxel in Treating Patients With Advanced, Metastatic, or Unresectable Solid Tumors		

genes negative for small variants

ABCB1	ABCC1	ABCC2	ABL1	ACVR1	ACVR1B	ACVR2A	ACVR2B	ACVRL1	ADAMTS1
ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9	ADAMTSL1	AKT1	AKT2	AKT3	ALK	AMER1
APC	APLNR	AR	ARAF	AREG	ARID1A	ARID1B	ARID2	ATR	ATRX
AURKA	AURKB	AXIN1	AXL	B2M	BAP1	BARD1	BCOR	BMP6	BMPR1A
BMPR1B	BNIP3	BRAF	BRCA1	BRCA2	BRIP1	BTK	BUB1B	CALR	CBL
CCND1	CCND2	CCND3	CCNE1	CD274	CDA	CDC73	CDH1	CDK12	CDK4
CDK6	CHEK1	CHEK2	CHFR	CHKA	CIC	CREBBP	CSF1R	CTLA4	CTNNB1
CYP19A1	CYP1A1	CYP2D6	CYP3A4	CYSLTR2	dCK	DDR2	DICER1	DNMT3A	EGFR
EMSY	EP300	EPCAM	EPHA5	EPHA7	ERBB2	ERBB3	ERBB4	ERCC1	ERCC2
ERCC3	ERRFI1	ESR1	ESR2	EWSR1	EZH2	FAM175A	FANCA	FANCC	FANCD2
FANCE	FANCF	FANCG	FANCM	FAT1	FBXW7	FCGR2A	FGD4	FGF3	FGF4

Continued

genes negative for small variants

FGFR1	FGFR2	FGFR3	FGFR4	FLT3	FLT4	FOXL2	FUBP1	GAS6	GLI1
GNA11	GNAQ	GNAS	GSTP1	HAMP	HDAC2	HGF	HNF1A	HRAS	HSD3B1
IDH1	IDH2	IGF1R	IKZF1	IL6R	JAK1	JAK2	JAK3	KDM5C	KDM6A
KDR	KEAP1	KIT	MAF	MAP2K1	MAP2K2	MAP3K1	MAPK1	MAPK3	MAPKAPK5
MDM2	MDM4	MED12	MEN1	MET	MGMT	MLH1	MPL	MRE11A	MSH2
MSH6	MTHFR	MTOR	MUTYH	MYC	MYCN	MYOD1	NBN	NF1	NF2
NFE2L2	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS	NTRK1	NTRK2	NTRK3	PALB2
PBRM1	PDCD1LG2	PDGFRA	PDGFRB	PIK3CA	PIK3CB	PIK3CD	PIK3CG	PIK3R1	PIM1
PLCB4	PLCG1	PMS2	POLD1	POLE	PPP2R1A	PTCH1	PTEN	PTPN11	RAD50
RAD51C	RAD51D	RAF1	RB1	RBM10	RECQL	RET	RHEB	RICTOR	RIT1
RNF43	ROS1	RPTOR	RRM1	SDHB	SDHC	SETD2	SF3B1	SMAD1	SMAD2
SMAD4	SMAD5	SMAD9	SMARCA4	SMARCB1	SMO	SOCS1	SPOP	STAG2	STAT3
STAT5A	STAT5B	SUFU	TERT-p	TGFB1	TGFB2	TGFB3	TGFBR1	TGFBR2	TNFAIP3
TNK1	TOP2A	TP53	TSC1	TSC2	TSHR	TYMS	VEGFA	VHL	WT1
XRCC1	YES1								

genes negative for fusions and structural variants

RET	ALK	BRAF	EGFR	FGFR1	FGFR2	FGFR3	MET	ROS1	NTRK1
NTRK2									

genes negative for copy number variants (amplifications)

ABCB1	ABCC1	ABCC2	ABL1	ACVR1	ACVR1B	ACVR2A	ACVR2B	ACVRL1	ADAMTS1
ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9	ADAMTSL1	AKT1	AKT2	AKT3	ALK	AMER1
APC	APLNR	AR	ARAF	AREG	ARID1A	ARID1B	ARID2	ATM	ATR
ATRX	AURKA	AURKB	AXIN1	B2M	BAP1	BARD1	BCOR	BMP6	BMPR1A
BMPR1B	BNIP3	BRAF	BRCA1	BRCA2	BRIP1	BTK	BUB1B	CALR	CBL
CCND1	CCND2	CCND3	CCNE1	CD274	CDA	CDC73	CDH1	CDK12	CDK6
CDKN2A	CHEK1	CHEK2	CHFR	CHKA	CIC	CREBBP	CSF1R	CTLA4	CTNNB1
CYP19A1	CYP1A1	CYP2D6	CYP3A4	CYSLTR2	dCK	DDR2	DICER1	DNMT3A	EGFR
EMSY	EP300	EPCAM	EPHA5	EPHA7	ERBB2	ERBB3	ERBB4	ERCC1	ERCC2
ERCC3	ERRFI1	ESR1	ESR2	EWSR1	EZH2	FAM175A	FANCA	FANCC	FANCD2
FANCE	FANCF	FANCG	FANCM	FAT1	FBXW7	FCGR2A	FGD4	FGF3	FGF4
FGFR1	FGFR2	FGFR3	FGFR4	FLT3	FLT4	FOXL2	FUBP1	GAS6	GATA3
GLI1	GNA11	GNAQ	GNAS	GSTP1	HAMP	HDAC2	HGF	HNF1A	HRAS
HSD3B1	IDH1	IDH2	IGF1R	IKZF1	IL6R	JAK1	JAK2	JAK3	KDM5C
KDM6A	KDR	KEAP1	KIT	KRAS	MAF	MAP2K1	MAP2K2	MAP3K1	MAPK1
MAPK3	MAPKAPK5	MDM4	MED12	MEN1	MET	MGMT	MLH1	MPL	MRE11A
MSH2	MSH6	MTHFR	MTOR	MUTYH	MYC	MYCN	MYOD1	NBN	NF1
NF2	NFE2L2	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS	NTRK1	NTRK2	NTRK3
PALB2	PBRM1	PDCD1LG2	PDGFRA	PDGFRB	PIK3CA	PIK3CB	PIK3CD	PIK3CG	PIK3R1
PIM1	PLCB4	PLCG1	PMS2	POLD1	POLE	PPP2R1A	PTCH1	PTEN	PTPN11
RAD50	RAD51C	RAD51D	RAF1	RB1	RBM10	RECQL	RET	RHEB	RICTOR
RIT1	RNF43	ROS1	RPTOR	RRM1	SDHB	SDHC	SETD2	SF3B1	SMAD1
SMAD2	SMAD5	SMAD9	SMARCA4	SMARCB1	SMO	SOCS1	SPOP	STAG2	STAT3
STAT5A	STAT5B	STK11	SUFU	TERT-p	TGFB1	TGFB2	TGFB3	TGFBR1	TGFBR2
TNFAIP3	TNK1	TOP2A	TP53	TSC1	TSC2	TSHR	TYMS	VEGFA	VHL
WT1	XRCC1	YES1							

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Performance

Biomarker	Sensitivity	Specificity
SNVs, Indels ≥ 7.5%:	>99%	>99%
SNVs, Indels ≥ 5%:	>97%	>99%
CNV:	>90%	>99%
Fusions:	>91%	>99%
IHC:	>94%	>94%

Limitations: Mutation calls may not be available from some regions due to pseudogenes or sequence context. Select IHCs may not be run if already performed within the last six months unless indicated in the notes section.

These tests were developed and the performance characteristics determined by Exact Sciences. NGS is performed by Exact Sciences on genomic DNA extracted from a formalin fixed paraffin-embedded tumor. **Immunohistochemistry: Detection:** IHC testing is done on formalin fixed, paraffin-embedded tissue (FFPE) utilizing the detection method of avidin-biotin free polymer is employed according to an optimized protocol. **Scoring:** HER2 testing meets the 2013 ASCO-CAP HER2 testing guidelines in breast cancer and results are reported using the ASCO/CAP scoring criteria as defined in the references below. For ER and PR, historical cutoffs for all non-breast tissues are followed. The following are antibody clones for each test: HER2 - CB11, ER - SP1, PR - PgR636. Note that these assays have not been validated on decalcified specimens. Controls: External controls are reviewed on all stains for appropriate positive and negative immunoreactivity and found to be satisfactory. If HER2 by FISH is run, it is currently performed and interpreted by PhenoPath at 551 N. 34th St., Seattle, WA 98103. If RNA Fusion testing is run, it is currently performed by PathGroup - Molecular Pathology Accessioning at 658 Grassmere Park, Suite 101, Nashville, TN 37211.

Pan-Cancer Tissue tests were developed and their performance characteristics determined by Exact Sciences. These tests have not been cleared or approved by the U.S. Food and Drug Administration. These tests are used for clinical purposes to guide patient care under the responsibility of the physician.

1. Wolff et al. (2013) J Clin Oncol. 31:3997-4013.
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Professional Component of IHC results performed by Integrated Pathology located at 9150 W. Indian School Road, Building 6, Suite 122, Phoenix, Arizona 85037.

Clinical trials

The clinical trials information provided with the potential biomarker were compiled from www.clinicaltrials.gov a service provided by the U.S. NIH. The presentation is for informational purposes only and may not include all relevant trials. Health care providers should employ their clinical judgment in interpreting this information for individual patients. Specific enrollment criteria for each clinical trial should be carefully reviewed as additional inclusion criteria may apply and the biomarker may be associated with contraindications or exclusion criteria. The attending physician may need to contact the clinical trial administrator to ensure the patient is a possible candidate for admission to a particular clinical trial.

NCCN compendium

This report includes information about therapeutic agents that appear to be associated with clinical benefit based on NCCN Compendium guidelines, relevance of tumor lineage, level of publishing evidence and strength of biomarker expression, as available, as reviewed and assessed by Exact Sciences. The agents are not ranked in order of potential or predicted efficacy. The finding of a biomarker expression does not necessarily indicate effectiveness or lack thereof. The agents identified may or may not be suitable for use with a particular patient and the report does not guarantee or suggest that any particular agent will be effective with the treatment of any particular condition.

Reimbursement and acknowledgment

Exact Sciences makes no representations or guarantee that an insurer, third party payor, or healthcare provider, whether private or governmental, will provide payment or reimbursement for the cost of tests performed. By accessing this report you agree that the analysis and associated report is owned by Exact Sciences and that you only have a limited right to use the information to potentially assist with the clinical treatment of the associated patient.

Pan-Cancer Tissue panel core components

Unless fewer tests are ordered on the requisition, every Pan-Cancer Tissue test run interrogates a wide panel of targets including the following clinically actionable genes for specific therapeutic interventions. Pan-Cancer Tissue tests are not intended to displace other specific standard of care tests for other gene targets. The BRCA1 and BRCA2 component is not intended to diagnose or identify a hereditary condition, and mutations detected may be somatic or germline in origin and are to be used primarily for individualized therapeutic purposes while appropriate genetic counseling and testing may be advisable.

Levels of evidence

U.S. Preventive Services Task Force Level of Evidence Rankings are summarized from: American journal of preventive medicine (2001), 20(3 Suppl), 21-35. Level of evidence doesn't necessarily indicate greater potential utility.

Level 1: Evidence from at least one properly designed randomized controlled trial.
Level II-1: Evidence from well-designed controlled trials without randomization.
Level II-2: Evidence from well-designed cohort or case- control analytic studies, preferably from more than one center or research group.
Level II-3: Evidence from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
Level III: Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.
Different Tumor Type (DTT): Alteration in biomarker present, however published evidence of biomarker utility was in a tumor type different from patient's tumor type.

No warranty or guarantee

This report does not make any promise or guarantee that a particular drug or treatment regimen will be effective or helpful in the treatment of disease in any patient. This report also makes no promise or guarantee that a drug with a potential clinical benefit will in fact provide a clinical benefit or that a drug with potential lack of clinical benefit will in fact provide no clinical benefit. Exact Sciences expressly disclaims and makes no representation or warranties whatsoever relating, directly or indirectly, to this review of evidence or identified scientific literature, the conclusions drawn from it or any of the information set forth in this report that is derived from such review, including information and conclusions relating to therapeutic agents that are included or omitted from this report.

This assay has not been validated on decalcified tissues. Results should be interpreted with caution given the possibility of false negative results on decalcified specimens.

Treatment decisions

Treatment Decisions Reside with Treating Physician and Patient. The selection of any treatment or potential treatment suggested by a biomarker resides within the discretion and judgment of the treating physician and patient. Decisions on patient care should be based on the independent medical judgment of the treating physician based upon all available clinical information, according to the applicable standard of care and should not be based solely on the tests and information contained in this report.