Pan-Cancer Tissue

Date of Birth:	00/00/0000	Case/Specimen ID:	AA00-00000 A0	Turnaround:	3 business days
Pan-Cancer Tissue#:	OR000000000, PCDx-19-00000	Collection Site:	Right lateral base	Tumor cells:	70%
Physician:	Dr. Smith	Collection Date:	00/00/0000	Specimen size:	180 mm^2
Facility:	Some Cancer Treatment Center	Received for testing:	00/00/0000	Requirement met:	Optimal

2 NCCN/FDA indications

Therapeutic Option	Indicating biomarkers
Olaparib	BRCA2 mutation
Rucaparib	BRCA2 mutation

High Interest

Pan cancer	Type specific
TMB: Low (4muts/mb)	AR CNV: Not Changed
MSI: Stable	AR: Wildtype
NTRK fusion: Negative	ATM: Wildtype
BRCA1: Wildtype	BARD1: Wildtype
BRCA2: K1286del	BRIP1: Wildtype
PD-L1 (22C3) Tumor IHC: Negative	CDK12: Wildtype
PD-L1 (22C3) TILs IHC: Negative	CHEK1: Wildtype
	CHEK2: Wildtype
	FANCA: Wildtype
	PALB2: Wildtype
	RAD51C: Wildtype
	RAD51D: Wildtype
	AR IHC: Positive

10 evidence-based therapy associations

Abiraterone	Bicalutamide	Docetaxel
Enzalutamide	Flutamide	Medroxyprogesterone
Niraparib	Paclitaxel	Talazoparib
Vinorelbine		

Specimen

Prostate adenocarcinoma

Tumor cells: 70%
Specimen size: 180 mm^2
Residual tissue: No

Gross Description: Xxxxxxxx xxxx Xxtxxxxxx - Xxxxxxxx Xxtxxxxxx xx 0 Xxxxx xxxxxxx xx X00-00000 X0 (xxx XXXx-00-00000) xxxx tx xxxx xxx Xxxxxxxx X&X xxxxx xxxxxxx xx X00-00000 X0 (xxx XXXx-00-00000) xxxxtxxxxx xx xxxxxxxxx tx txx xxxxx xxxxx xxtxxxt xxxxx xx txx xxxxxxxxxxx xxxxxxxx xxtxxxxxx xxxxxt xxtx xxxxxxxx xxxxxxtxxx xxtx xx 0/00/0000. Xxxxx X00-00000 X0 xxxx xx xxxxxxxx.

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

4 IHCs

AR	3+	100%	Positive
PD-L1 (22C3) TILs	N/A	0%	Negative
PD-L1 (22C3) Tumor	N/A	0%	Negative
PTEN	2+	100%	Positive
TUBB3	N/A	0%	Negative

3 salient genomic findings

Gene	Variant	Quantity	Gene	Variant	Quantity
BRCA2	K1286del	40%	TP53	S183*	24%
SPOP	K129E	14%			

Genes with indeterminate findings: STAT5A

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

12 therapies with potential increased benefit

Therapeutic Option	Biomarkers	NCCN/FDA	Level of evidence	References
Abiraterone	AR +		II-3	6
	SPOP mutation		II-3	4
Bicalutamide	AR +		II-3	8
Docetaxel	TUBB3 -		II-3	13
Enzalutamide	AR +		II-3	7
Flutamide	AR +		II-3	8
Medroxyprogesterone	AR +		DTT	5,3
Niraparib	BRCA2 mutation		DTT	12
Olaparib	BRCA2 mutation	Yes	I	9,11,15
Paclitaxel	TUBB3 -		DTT	14
Rucaparib	BRCA2 mutation	Yes	II-2	1,2
Talazoparib	BRCA2 mutation		DTT	10
Vinorelbine	TUBB3 -		DTT	14

clinical notes

AR expression in Prostate Cancer: Androgens acting through the androgen receptor (AR), are required for prostate development and normal prostate function and AR remains important in the development and progression of prostate cancer. Histological analysis of primary and metastatic prostate cancer indicates that AR is expressed throughout prostate cancer progression and in hormone refractory cancer. Although AR expression is heterogeneous within tumor foci, the absence of completely AR-negative hormone refractory tumors suggests that lack of AR expression does not confer a selective advantage to cancer survival or growth. Similarly, the majority of prostate cancers at all stages of progression express a wild-type AR, although AR mutations are found to occur more frequently with increasing tumor grade and stage (Heinlein & Chang 2004 PMID 15082523). Collectively, these data show the necessity for full-length AR in all stages of prostate cancer and illustrate the importance of continued targeting of AR in advanced prostate cancer. AR antagonists have had a major impact on the treatment of metastatic castration-resistant prostate cancer (CRPC). However, even with the advent of AR antagonist therapies, patients continue to develop resistance, and new strategies to combat continued AR signalling are needed.

BRCA2: BRCA2 is a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair, thereby playing a role in genome stability. BRCA germline mutations increase the risk of developing breast and ovarian cancer; somatic mutations are highest in CRC (7.5%), NSCLC (4.0%), prostate cancer (2.7%) and pancreatic (1.8%) cancers - with somatic mutations also identified in breast 91.7% and ovarian cancer (3.0%) (Jain et al. 2016; PMID: 27283171). Tumor BRCA testing will detect somatic (isolated to the tumor) and germline (inherited) BRCA1/2 mutations and can help inform PARP inhibitor treatment decision making. The identified BRCA mutation in this specimen is a pathogenic alteration in the neoplastic cell population. At present, the primary indication for PARPi is focused on deleterious gBRCA although somatic BRCA mutations have likewise shown benefit from PARP inhibition.

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).

PD-L1 (22C3) TILs: Expression on tumor-infiltrating lymphocytes (TILs) is determined by evaluating the percentage of PD-L1 expressing tumor-infiltrating immune cells of any intensity. The scoring system divides the results into three groups: those with ≥50% of tumor cells showing any level of positivity (high), those with <50% of tumor cells but ≥1% of tumor cells positive (low), and those with <1% positive (negative). Please note that for PD-L1 (22C3) TILs, the referenced studies utilize a prototype immunohistochemical assay with a proprietary antibody and cutoff.

PD-L1 (22C3) tumor negative: PD-L1 expression is determined by identifying the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. The scoring system divides the results into three groups: those with ≥50% of tumor cells showing any level of positivity (high), those with <50% of tumor cells but ≥1% of tumor cells positive (low), and those with <1% positive (negative). Per the medical literature, there is a strong positive association between PD-L1 expression and response to immune checkpoint inhibitors. However, several studies have revealed that favorable long-term outcomes can be achieved in patients that are PD-L1 negative and this benefit is observable across multiple tumor types and histologies (for example, Patel & Kurzrock 2015, PMID 25695955). A recent meta-analysis (Shen and Zhao 2018, PMID 30201790) that included 2000 patients that were PD-L1 negative, revealed that PD-1 or PD-L1 inhibitors were associated with prolonged overall survival in patients that were PD-L1 negative. The favorable overall survival achieved in this patient group is likely due the biological function of the PD-1 or PD-L1 pathway itself and the complicated interaction between cancer cells and the immune system.

SPOP: SPOP, or Speckle-type POZ protein, plays a role in regulating androgen receptor signaling. SPOP mutations were identified in 6–13% of primary prostate adenocarcinomas and 14.5% of metastatic prostate cancers, suggesting that SPOP mutation is an early event. SPOP mutations are also frequently found in a subtype of prostate cancer associated with a high genomic rearrangement frequency (Barbieri et al., 2012 PMID: 22610119). Upon SPOP mutation in prostate cancer, impaired ubiquitination of its substrates can lead to enhanced AR signaling and cell proliferation. Both AR and AR coactivators are substrates deregulated by SPOP mutation, providing a possible explanation for the associated increase in AR activity seen in this subtype of prostate cancers.

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, the Paradigm PCDx™ test 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.

TP53: Compared with other epithelial tumors, TP53 mutation is relatively infrequent in prostate cancer, with the prevalence hovering around 7% of contemporary surgical cohorts such as the TCGA cohort, with an additional 1% or so of tumors harboring homozygous deletions involving TP53. It has been proposed that the low rate of TP53 alteration in prostate cancer may be a reflection of the generally lower mutational burden seen in this tumor type compared with other carcinomas (TCGA 2015 PMID 26544944). Although TP53 aberrations are relatively rare in primary tumors, there is a 5-fold increase in alterations in CRPC TP53 mutations are among the most highly enriched genomic alterations among castrate-resistant prostate cancers (CRPC) compared with primary tumors and recent preclinical data suggests that TP53 inactivation may cooperate with other alterations to confer lineage plasticity and androgen independence in the prostate

clinical notes

(Robinson et al. 2015 PMID 26000489).

TUBB3: Class III beta-tubulin (βIII-tubulin, also known as TUBB3) is a microtubule protein, normally expressed in cells of neuronal origin. Its expression has been reported in various other tumor types. In the classical view, TUBB3 expression and drug resistance have been linked, and together they have been associated with a perturbation in microtubule dynamics such as aberrant protein folding of tubulins due to mutation and/or dysfunction of tubulin-specific chaperons. The association between TUBB3 and chemoresistance may derive from its role during development, as TUBB3 is expressed during mesenchymal dedifferentiation. It is also associated with histologically high-grade malignancies, cell dedifferentiation, anaplastic transformation, and acquisition of progenitor- or stem cell–like phenotypic properties, a hallmark of cancer stem cells, which are often chemotherapy-resistant. TUBB3 is therefore of clinical relevance as overexpression has been linked to poor response to microtubule-targeting anti-cancer drugs, specifically taxane- or vinca-alkaloid-containing regimens (Person et al. 2017 PMID: 29022485). High expression of TUBB3 correlates with low response rates to these agents and in addition to being prognostically relevant (reduced survival in patients with overexpression).

clinical trials

in tumor type

AR +	NCT03531827	Enzalutamide | CRLX101

Combining CRLX101, a Nanoparticle Camptothecin, With Enzalutamide in People With Progressive Metastatic Castration Resistant Prostate Cancer Following Prior Enzalutamide Treatment

AR +	NCT03532217	Prostvac-V | Nivolumab | Ipilimumab | Neoantigen DNA vaccine

Neoantigen DNA Vaccine in Combination With Nivolumab/Ipilimumab and PROSTVAC in Metastatic Hormone-Sensitive Prostate Cancer

AR +	NCT03543189	Nivolumab | Radiation | Androgen Deprivation Therapy

Combination of Nivolumab Immunotherapy With Radiation Therapy and Androgen Deprivation Therapy

AR +	NCT03709550	Decitabine | Enzalutamide

Enzalutamide and Decitabine in Treating Patients With Metastatic Castration Resistant Prostate Cancer

AR +	NCT03821792	Abiraterone | Apalutamide | Prednisone

Abiraterone Acetate, Prednisone, and Apalutamide in Treating Patients With Hormone-Naive Metastatic Prostate Cancer

BRCA2 mutation	NCT02203513	LY2606368

A Phase II Single Arm Pilot Study of the Chk1/2 Inhibitor (LY2606368) in BRCA1/2 Mutation Associated Breast or Ovarian Cancer, Triple Negative Breast Cancer, High Grade Serous Ovarian Cancer, and Metastatic Castrate-Resistant Prostate Cancer

BRCA2 mutation	NCT02598895	Carboplatin | Docetaxel |

Docetaxel and Carboplatin in Treating Patients With Metastatic, Castration Resistant Prostate Cancer Containing Inactivated Genes in the BRCA 1/2 Pathway

BRCA2 mutation	NCT02952534	Rucaparib

A Study of Rucaparib in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency

BRCA2 mutation	NCT03442556	Carboplatin | Docetaxel | Rucaparib

Docetaxel, Carboplatin, and Rucaparib Camsylate in Treating Patients With Metastatic Castration Resistant Prostate Cancer With Homologous Recombination DNA Repair Deficiency

BRCA2 mutation	NCT03570476	Olaparib

Olaparib Before Surgery in Treating Participants With Localized Prostate Cancer

BRCA2 mutation	NCT03732820	Olaparib | Abiraterone

Study on Olaparib Plus Abiraterone as First-line Therapy in Men With Metastatic Castration-resistant Prostate Cancer

PDL1:Tumor -	NCT03637543	Nivolumab

Nivolumab in Patients With High-Risk Biochemically Recurrent Prostate Cancer

multi-indication trials

BRCA2 mutation	NCT01434316	Dinaciclib | Veliparib | Carboplatin

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

BRCA2 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

BRCA2 mutation	NCT02873975	LY2606368

A Study of LY2606368 (Prexasertib) in Patients With Solid Tumors With Replicative Stress or Homologous Repair Deficiency

BRCA2 mutation	NCT03565991	Avelumab | Talazoparib

Javelin BRCA/ATM: Avelumab Plus Talazoparib in Patients With BRCA or ATM Mutant Solid Tumors

clinical trials

BRCA2 mutation	NCT03718091	M6620
M6620 (VX-970) in Selected Solid Tumors		
BRCA2 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		
BRCA2 mutation	NCT04030559	Niraparib;Niraparib Tosylate Monohydrate;
Niraparib Before Surgery in Treating Patients With High Risk Localized Prostate Cancer and DNA Damage Response Defects		
BRCA2 mutation	NCT04038502	Carboplatin;Docetaxel;
BRcA Deficient Prostate Cancer Treated With Carboplatin or Docetaxel		
BRCA2 mutation	NCT04266912	Avelumab;Berzosertib;
Avelumab and M6620 for the Treatment of DDR Deficient Metastatic or Unresectable Solid Tumors		
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		
RAS WT, BRAF WT	NCT02693535	Cetuximab
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		
TP53 mutation	NCT02576444	AZD2281 | AZD5363 | AZD1775 | AZD2014
OLAParib COmbinations		
TP53 mutation	NCT02935907	APG-115
APG-115 in Patients With Advanced Solid Tumors or Lymphomas		
TP53 mutation	NCT03560882	Atorvastatin
A Pilot Trial of Atorvastatin in Tumor Protein 53 (p53) -Mutant and p53 Wild-Type Malignancies		

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	ATM	ATR
ATRX	AURKA	AURKB	AXIN1	AXL	B2M	BAP1	BARD1	BCOR	BMP6
BMPR1A	BMPR1B	BNIP3	BRAF	BRCA1	BRIP1	BTK	BUB1B	CALR	CBL
CCND1	CCND2	CCND3	CCNE1	CD274	CDA	CDC73	CDH1	CDK12	CDK4
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	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
STAG2	STAT3	STAT5A	STAT5B	STK11	SUFU	TERT-p	TGFB1	TGFB2	TGFB3
TGFBR1	TGFBR2	TNFAIP3	TNK1	TOP2A	TSC1	TSC2	TSHR	TYMS	VEGFA
VHL	WT1	XRCC1	YES1						

genes negative for fusions and structural variants

ALK	BRAF	EGFR	FGFR1	FGFR2	FGFR3	MET	RET	ROS1	NTRK1
NTRK2	ETV6-NTRK3								

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	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	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	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	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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IHC thresholds

Biomarker	Negative	Not Significant	Positive
AR	≤1+ or ≤10%	Not applicable	≥1+ and ≥10%
PD-L1 (22C3) TILs	NA and 0%	Not applicable	≥1+ and ≥50%
PD-L1 (22C3) Tumor	NA and 0%	Not applicable	≥1+ and ≥50%
PTEN	≤1+ or <10%	Not applicable	≥1+ and ≥10%
TUBB3	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%

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. Path read at 1820 W Calle de Pompas Phoenix, AZ 85085 CLIA #: 03D2125615

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.
2. Hammond et al. (2010) Arch Pathol Lab Med. 134:48-72.
3. Tse, et al. (2011) J Clin Oncol. 29:4168-4174.

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.