

Paradigm Cancer Diagnostic (PCDx)

Date of Birth:

PCDx Case#:

Physician:

Facility:

Case/Specimen ID:

Collection Site:

Collection Date:

Received for testing:

Turnaround: 4 business days

Tumor cells: 100%

Specimen size: 360 mm²

Requirement met: Optimal

4 actionable genomic findings

ARID1A G191del
EGFR E746_A750del
KDR L912
TP53 T125K

Pertinent Negatives: ALK Mutation, BRAF Mutation, KRAS Mutation, MET CNV,
MYC CNV

10 IHC results

hENT1 Negative
TRKpan Negative
PDL1:Tumor Low
PDL1:TILs Low
MLH1 Positive

MSH2 Positive
MSH6 Positive
PMS2 Positive
ALK Negative
ROS1 Negative

Immunotherapy

tumor mutation burden: Low (5 muts/mb)

MMR: Proficient

PD-L1: Low

11 therapies with potential increased benefit

Afatinib*	NCCN	EGFR
Atezolizumab*	NCCN	PDL1:TILs, PDL1:Tumor
Durvalumab	NCCN	PDL1:TILs, PDL1:Tumor
Erlotinib*	NCCN	EGFR
Gefitinib*	NCCN	EGFR
Nivolumab*	NCCN	PDL1:Tumor
Osimertinib*	NCCN	EGFR
Pembrolizumab*	NCCN	PDL1:Tumor
Pembrolizumab	NCCN	PDL1:Tumor
+ Carboplatin		
+ Pemetrexed*		
Nivolumab		PDL1:Tumor
+ Ipilimumab*		
Avelumab		PDL1:Tumor

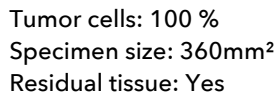
1 therapy with potential reduced benefit

Gemcitabine hENT1

* Indicates associations supported by the highest level of evidence

For additional information or to set up an interactive online account please contact your sales representative or call 1-844.232.4719

10 IHC results



Lung adenocarcinoma.

Gross Description: Received from is 1 Block labeled as (and PCDx-) used to make one Paradigm H&E slide labeled as (and PCDx-) identified as belonging to the above named patient based on the accompanying surgical pathology report with specimen collection date of Block will be analyzed.

hENT1	1+	50%	Negative
TRKpan	N/A	0%	Negative
PDL1:Tumor	N/A	10%	Low
PDL1:TILs	2+	10%	Low
MLH1	3+	100%	Positive
MSH2	3+	100%	Positive
MSH6	3+	100%	Positive
PMS2	3+	100%	Positive
ALK	N/A	0%	Negative
ROS1	N/A	0%	Negative

4 actionable genomic findings

Gene	Variant
ARID1A	G191del
EGFR	E746_A750del

Gene	Variant
KDR	L912
TP53	T125K

Genes with indeterminate findings: AREG, PMS2

31 genomic findings of unknown significance

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



11 therapies with potential increased benefit

Therapeutic Option	On NCCN	Indicating biomarkers	Level of evidence	References
Afatinib	Yes	EGFR Mutated	I	17
Atezolizumab	Yes	PDL1:TILs Low PDL1:Tumor Low	I I	5, 6 5, 6
Avelumab		PDL1:Tumor Low	DTT	9
Durvalumab	Yes	PDL1:TILs Low PDL1:Tumor Low	DTT II-3	7, 8 13
Erlotinib	Yes	EGFR Mutated	I	15
Gefitinib	Yes	EGFR Mutated	I	16
Nivolumab	Yes	PDL1:Tumor Low	II-2	4
Nivolumab + Ipilimumab		PDL1:Tumor Low	II-2	10
Osimertinib	Yes	EGFR Mutated	I	18
Pembrolizumab	Yes	PDL1:Tumor Low	I	2, 3
Pembrolizumab + Carboplatin + Pemetrexed	Yes	PDL1:Tumor Low	I	14

1 therapy with potential reduced benefit

Therapeutic Option	Contraindicating biomarkers	References
Gemcitabine	hENT1 Negative	1

clinical notes

The results for gene expression (mRNA) will be reported out in an addendum.

An EGFR exon 19 deletion was detected. The EGFR E746_A750del mutation arises from the deletion c.2235_2249delGGAATTAAGAGAAGC in exon 19, resulting in an in-frame deletion of five amino acids from position 746 to 750 (glutamic acid, leucine, arginine, glutamic acid, and alanine). In lung cancer, there is a clear association between the presence of Exon 19 deletions and high response rates to certain tyrosine kinase inhibitors.

Cetuximab is on Compendium for NSCLC. However, the NCCN specifies that cetuximab may be considered in combination with afatinib as subsequent therapy for metastatic disease in patients with a known sensitizing EGFR mutation who are T790M negative, have progressed on EGFR tyrosine kinase inhibitor therapy, and have multiple symptomatic systemic lesions.

PD-L1 (22C3) expression is determined by using a Tumor Proportion Score (TPS), which is 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 $\geq 50\%$ of tumor cells showing any level of positivity (high), those with $< 50\%$ of tumor cells but $\geq 1\%$ of tumor cells positive (low), and those with $< 1\%$ positive (negative). A minimum of 100 viable tumor cells must be present in the PD-L1 stained slide for the specimen to be considered adequate for PD-L1 evaluation. Pembrolizumab (KEYTRUDA) is indicated for the treatment of: (1) Patients with metastatic NSCLC whose tumors have high PD-L1 expression [TPS $\geq 50\%$] with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC. (2) Patients with metastatic NSCLC whose tumors express PD-L1 [TPS $\geq 1\%$], with disease progression on or after platinum-containing chemotherapy. The predictive value of the PD-L1 clone 22C3 for nivolumab, atezolizumab, avelumab or durvalumab is currently unclear.

PD-L1 (22C3) expression on TILs is determined by evaluating 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 $\geq 50\%$ of tumor cells showing any level of positivity (high), those with $< 50\%$ of tumor cells but $\geq 1\%$ 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.

Tumors are classified as pMMR (proficient Mismatch Repair) if no loss in the MMR proteins is detected. Tumors without mutations in the mismatch repair genes generally do not show the elevated mutation rates or higher number of potential mutation-associated neoantigens that characterize the dMMR phenotype. Mutation-associated neoantigen recognition is an important component of the endogenous antitumor immune response and tumors with a high number of actual mutation-associated neoantigens are more likely to stimulate the immune system to react against the tumor (Le et al. 2015/PMID: 26028255; Le et al. 2017/PMID:28596308).

Tumor Mutation Burden (TMB) - TMB is defined as the total number of DNA mutations per megabase in a tumor sequence. Low TMB refers to a cutoff off less than 7 mutations per megabase. High TMB (≥ 14 mutations per megabase) appears to have an evolving role as a predictive marker for immunotherapy treatment in various cancers.

Select Genomic Alteration: HER2 (ERBB2) C236W is located on exon 6 of the EERBB2 gene. C236W is currently deemed a Variant of Uncertain Significance (VUS). HER2 (ERBB2) c.1157C>A p.A386D lies within the extracellular domain of the Erbb2 (Her2) protein. A386D has not been characterized in the scientific literature and therefore, its effect on Erbb2 (Her2) protein function is unknown.

clinical trials
in tumor type

EGFR	NCT01306045	AZD 1775 MK-2206 Lapatinib Erlotinib sunitinib
Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies		
EGFR	NCT01553942	Afatinib Cisplatin Pemetrexed
Afatinib With CT and RT for EGFR-Mutant NSCLC		
EGFR	NCT01859026	MEK162 Erlotinib
A Phase I/IB Trial of MEK162 in Combination With Erlotinib in NSCLC Harboring KRAS or EGFR Mutation		
KRAS	NCT02047344	Antroquinonol
Efficacy, Safety and Pharmacokinetics Study of Antroquinonol to Treat NSCLC		
EGFR	NCT02143466	AZD9291 + MEDI4736 AZD9291 + AZD6094 AZD9291 + selumetinib
AZD9291 in Combination With Ascending Doses of Novel Therapeutics		
PDL1:Tumor	NCT02273375	MEDI4736 Placebo
Double Blind Placebo Controlled Study of Adjuvant MEDI4736 In Completely Resected NSCLC		
KDR	NCT02299141	Nintedanib
Nintedanib in Molecularly Selected Patients With Advanced Non-Small Cell Lung Cancer		
EGFR	NCT02314364	SBRT with protons or photons
A Trial of Integrating SBRT With Targeted Therapy in Stage IV Oncogene-driven NSCLC		
EGFR	NCT02323126	EGF816 INC280 Nivolumab
Study of Efficacy and Safety of Nivolumab in Combination With EGF816 and of Nivolumab in Combination With INC280 in Patients With Previously Treated Non-small Cell Lung Cancer		
EGFR	NCT02364609	Afatinib Pembrolizumab
Pembrolizumab and Afatinib in Patients With Non-small Cell Lung Cancer With Resistance to Erlotinib		
EGFR	NCT02411448	Ramucirumab Placebo Erlotinib
A Study of Ramucirumab (LY3009806) in Combination With Erlotinib in Participants With EGFR Mutation-Positive Metastatic NSCLC		
EGFR	NCT02424617	Erlotinib BGB324
A Study of BGB324 in Combination With Erlotinib in Patients With Non-Small Cell Lung Cancer		
EGFR	NCT02438722	Afatinib Capecitabine
S1403, Afatinib Dimaleate With or Without Cetuximab in Treating Patients With Newly Diagnosed Stage IV or Recurrent, EGFR Mutation Positive Non-small Cell Lung Cancer		
EGFR	NCT02448251	AC0010MA
Safety, Pharmacokinetic and Preliminary Efficacy Study of AC0010MA in Advanced Non Small Cell Lung Cancer		
EGFR	NCT02496663	EGFR Inhibitor AZD9291 Necitumumab
EGFR Inhibitor AZD9291 and Necitumumab in Treating Patients With EGFR-Positive Stage IV or Recurrent Non-small Cell Lung Cancer Who Have Progressed on a Previous EGFR Tyrosine Kinase Inhibitor		
EGFR	NCT02511106	AZD9291 Placebo AZD9291
AZD9291 Versus Placebo in Patients With Stage IB-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy		
EGFR	NCT02520778	EGFR Inhibitor AZD9291 Navitoclax
EGFR Inhibitor AZD9291 and Navitoclax in Treating Patients With EGFR-Positive Previously Treated Advanced or Metastatic Non-small Cell Lung Cancer		
PDL1:Tumor	NCT02576574	Avelumab Platinum-based Doublet
Avelumab in First-line Non-Small Cell Lung Cancer (JAVELIN Lung 100)		
PDL1:Tumor	NCT02595944	Nivolumab
Nivolumab After Surgery and Chemotherapy in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer		
PDL1:Tumor	NCT02655822	CPI-444 CPI-444 + Atezolizumab
Phase 1/1b Study to Evaluate the Safety and Tolerability of CPI-444 Alone and in Combination With Atezolizumab in Advanced Cancers		
ERBB2	NCT02675829	Ado-Trastuzumab emtansine
Trial of Ado-Trastuzumab Emtansine for Patients With HER2 Amplified or Mutant Cancers		
PDL1:Tumor	NCT02716038	MPDL3280A Carboplatin Nab-Paclitaxel
Neoadjuvant MPDL3280A, Nab-paclitaxel and Carboplatin (MAC) in NSCLC		
EGFR	NCT02716116	AP32788
A Trial of AP32788 in Non-Small Cell Lung Cancer		
EGFR	NCT02759835	Osimertinib
Local Ablative Therapy for Treatment of Oligoprogressive, EGFR-Mutated, Non-Small Cell Lung Cancer After Treatment With Osimertinib		
KDR	NCT02795156	Regorafenib
Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations		

clinical trials - continued

EGFR	NCT02803203	Osimertinib Bevacizumab
Osimertinib and Bevacizumab as Treatment for EGFR-mutant Lung Cancers		
EGFR	NCT02864251	Nivolumab Ipilimumab Pemetrexed Cisplatin Carboplatin
A Study of Nivolumab + Chemotherapy or Nivolumab + Ipilimumab Versus Chemotherapy in Patients With EGFR Mutation, T790M Negative NSCLC Who Have Failed 1L EGFR TKI Therapy		
PDL1:Tumor	NCT02888743	Durvalumab Radiation Tremelimumab
Durvalumab and Tremelimumab With or Without High or Low-Dose Radiation Therapy in Treating Patients With Metastatic Colorectal or Non-small Cell Lung Cancer		
EGFR	NCT02917993	INCB039110 Osimertinib
An Open-Label Phase 1/2 Study of INCB039110 in Combination With Osimertinib in Subjects With Non-Small Cell Lung Cancer		
EGFR	NCT03256136	Carboplatin Nivolumab Pemetrexed Ipilimumab
Nivolumab in Combination With Chemotherapy, or Nivolumab in Combination With Ipilimumab, in Advanced EGFR-Mutant or ALK-Rearranged NSCLC		
EGFR	NCT03292133	EGF816 Gefitinib
A Study of EGF816 and Gefitinib in TKI-naïve EGFR-mutant Non-Small Cell Lung Cancer		
PDL1:Tumor	NCT03330405	Avelumab Talazoparib Avelumab Talazoparib
Javelin Parp Medley: Avelumab Plus Talazoparib In Locally Advanced Or Metastatic Solid Tumors		
EGFR	NCT03333343	EGF816 trametinib ribociclib LXH254 INC280 gefitinib
Study of EGF816 in Combination With Selected Targeted Agents in EGFR-mutant NSCLC		
PDL1:Tumor	NCT03353675	TG4010 Chemotherapy Nivolumab
A Study Evaluating the Efficacy and the Safety of First-line Chemotherapy Combined With TG4010 and Nivolumab in Patients With Advanced Non-squamous Non-Small Cell Lung Cancer (NSCLC)		
EGFR	NCT03446417	ZN-e4
A Study of ZN-e4 in Subjects With Epidermal Growth Factor Receptor Mutated Non-Small Cell Lung Cancer		
PDL1:Tumor	NCT03455556	Anetumab Ravtansine Atezolizumab
Anetumab Ravtansine and Atezolizumab in Treating Participants With Advanced Non-small Cell Lung Cancer		
EGFR	NCT03455829	G1T38 Osimertinib
G1T38, a CDK 4/6 Inhibitor, in Combination With Osimertinib in EGFR-Mutant Non-Small Cell Lung Cancer		
PDL1:Tumor	NCT03523702	PembroRT ChemoRT
The Selective Personalized Radio-Immunotherapy for Locally Advanced NSCLC Trial.		
PDL1:Tumor	NCT03546361	CCL21-gene modified dendritic cells Pembrolizumab
Intratumoral Administration of CCL21-gene Modified Dendritic Cell With Intravenous Pembrolizumab for Advanced NSCLC		
PDL1:Tumor	NCT03563716	Atezolizumab MTIG7192A Placebo
A Study of MTIG7192A in Combination With Atezolizumab in Chemotherapy-Naïve Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer		
PDL1:Tumor	NCT03583086	VEGFR/PDGFR Dual Kinase Inhibitor X-82 Nivolumab
H I/II Eval Safety & Prelim Activity Nivolumab Comb W/Vorolanib Pts W/Refractory Thoracic Tumors		
PDL1:Tumor	NCT03631706	M7824 Pembrolizumab
M7824 Versus Pembrolizumab as a First-line (1L) Treatment in Participants With Programmed Death-ligand 1 (PD-L1) Expressing Advanced Non-small Cell Lung Cancer (NSCLC)		

multi-indication trials

ERBB2	NCT01953926	Neratinib
An Open-label, Phase 2 Study of Neratinib in Patients With Solid Tumors With Somatic Human Epidermal Growth Factor Receptor (EGFR, HER2, HER3) Mutations or EGFR Gene Amplification		
ERBB2	NCT02091141	Trastuzumab plus Pertuzumab
A Study Evaluating Herceptin/Perjeta, Tarceva, Zelboraf, and Erivedge Treatment Targeted Against Certain Mutations in Cancer Patients		
EGFR	NCT02451553	Afatinib Capecitabine
Afatinib Dimaleate and Capecitabine in Treating Patients With Advanced Refractory Solid Tumors, Pancreatic Cancer or Biliary Cancer		
PDL1:Tumor	NCT02460224	LAG525 PDR001
Safety and Efficacy of LAG525 Single Agent and in Combination With PDR001 in Patients With Advanced Malignancies		
ARID1A	NCT02576444	AZD2281 AZD5363 AZD1775 AZD2014
OLAParib Combinations		
PDL1:Tumor	NCT02608268	MBG453 PDR001
Safety and Efficacy of MBG453 as Single Agent and in Combination With PDR001 in Patients With Advanced Malignancies		
PDL1:Tumor	NCT02614456	Interferon-gamma and Nivolumab
Combination of Interferon-gamma and Nivolumab for Advanced Solid Tumors		
KDR	NCT02693535	Axitinib, Sunitinib, Regorafenib
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		

clinical trials - continued

TP53	NCT02935907	APG-115
APG-115 in Patients With Advanced Solid Tumors or Lymphomas		
EGFR	NCT03065387	Neratinib Everolimus Palbociclib Trametinib
Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/Amplification or HER3/4 Mutation		
ARID1A	NCT03207347	Niraparib
A Trial of Niraparib in BAP1 and Other DNA Double-Strand Break Repair Deficient Neoplasms (UF-STO-ETI-001)		
ARID1A	NCT03297424	PLX2853
A Study of PLX2853 in Advanced Malignancies.		
PDL1:Tumor	NCT03474640	TAB001, Recombinant Humanized anti-PD-1 Monoclonal Antibody
Safety, Tolerability and Pharmacokinetics of an Anti-PD-1 Monoclonal Antibody in Subjects With Advanced Malignancies		
TP53	NCT03560882	Atorvastatin
A Pilot Trial of Atorvastatin in Tumor Protein 53 (p53) -Mutant and p53 Wild-Type Malignancies		

genes negative for small variants

ABCB1	ATR	CDA	DICER1	FANCE	GNAS	MDM4	NTRK1	RAD51D	STAT3
ABCC1	ATRX	CDC73	DNMT3A	FANCF	GSTP1	MEN1	NTRK2	RAF1	STK11
ABCC2	AURKA	CDH1	EMSY	FANCG	GSTT1	MET	NTRK3	RB1	SUFU
ADAMTS1	AURKB	CDK4	EP300	FANCM	HGF	MGMT	PALB2	RECQL1	TERT
ADAMTS16	AXIN1	CDK6	EPCAM	FAT1	HNF1A	MLH1	PBRM1	RET	TGFBR2
ADAMTS18	AXL	CDK12	EPHA5	FBXW7	HRAS	MRE11A	PDCD1LG2	RHEB	TNFAIP3
ADAMTS6	B2M	CHEK1	EPHA7	FCGR2A	HSD3B1	MSH2	PDGFRA	RICTOR	TOP2A
ADAMTS9	BAP1	CHEK2	ERBB3	FGD4	IDH1	MSH6	PDGFRB	RIT1	TYMS
ADAMTSL1	BARD1	CHFR	ERBB4	FGF3	IDH2	MTHFR	PIK3CA	RNF43	TSC1
AKT1	BCOR	CHKA	ERCC1	FGF4	IGF1R	MUTYH	PIK3CB	RPTOR	TSHR
AKT2	BNIP3	CIC	ERCC2	FGFR1	IKZF1	MYC	PIK3CG	RRM1	VEGFA
AKT3	BRAF	CREBBP	ERCC3	FGFR2	JAK3	MYCN	PIK3R1	SDHB	VHL
ALK	BRCA1	CSF1R	ERRF1	FGFR4	KDM5C	MYOD1	PLCB4	SDHC	WT1
AMER1	BRCA2	CTLA4	ESR1	FLT3	KIT	NBN	PLCG1	SETD2	YES1
APC	BRIP1	CTNNB1	ESR2	FLT4	KRAS	NF1	POLD1	SF3B1	XRCC1
APLN	BTK	CYP2D6	EWSR1	FOXL2	MAP2K1	NF2	POLE	SMAD2	
AR	BUB1B	CYP3A4	EZH2	FUBP1	MAP3K1	NFE2L2	PPP2R1A	SMAD4	
ARAF	CBL	CYP19A1	FAM175A	GATA3	MAPKAPK5	NOTCH1	PTEN	SMO	
ARID1B	CCND2	CYSLTR2	FANCA	GLI1	MAPK1	NOTCH2	PTPN11	SOCS1	
ARID2	CCND3	dCK	FANCC	GNA11	MAPK3	NPM1	RAD50	SPOP	
ATM	CCNE1	DDR2	FANCD2	GNAQ	MDM2	NRAS	RAD51C	STAG2	

genes negative for copy number variants (amplifications)

ABCB1	ATR	CDC73	EGFR	FANCM	HNF1A	MDM4	NTRK1	RAD51D	STAG2
ABCC1	ATRX	CDH1	EMSY	FAT1	HRAS	MED12	NTRK2	RAF1	STAT3
ABCC2	AURKA	CDK4	EP300	FBXW7	HSD3B1	MEN1	NTRK3	RB1	STK11
ADAMTS1	AURKB	CDK6	EPCAM	FCGR2A	IDH1	MET	PALB2	RBM10	SUFU
ADAMTS16	AXIN1	CDK12	EPHA5	FGD4	IDH2	MGMT	PBRM1	RECQL1	TERT
ADAMTS18	AXL	CDKN2A	EPHA7	FGF3	IGF1R	MLH1	PDCD1LG2	RET	TGFBR2
ADAMTS6	B2M	CHEK1	ERBB2	FGF4	IKZF1	MRE11A	PDGFRA	RHEB	TNFAIP3
ADAMTS9	BAP1	CHEK2	ERBB3	FGFR1	JAK1	MSH2	PDGFRB	RICTOR	TOP2A
ADAMTSL1	BARD1	CHFR	ERBB4	FGFR2	JAK2	MSH6	PIK3CA	RIT1	TP53
AKT1	BCOR	CHKA	ERCC1	FGFR3	JAK3	MTHFR	PIK3CB	RNF43	TYMS
AKT2	BNIP3	CIC	ERCC2	FGFR4	KDM5C	MTOR	PIK3CD	ROS1	TSC1
AKT3	BRAF	CREBBP	ERCC3	FLT3	KDM6A	MUTYH	PIK3CG	RPTOR	TSC2
ALK	BRCA1	CSF1R	ERRF1	FLT4	KDR	MYC	PIK3R1	RRM1	TSHR
AMER1	BRCA2	CTLA4	ESR1	FOXL2	KEAP1	MYCN	PLCB4	SDHB	VEGFA
APC	BRIP1	CTNNB1	ESR2	FUBP1	KIT	MYOD1	PLCG1	SDHC	VHL
APLNR	BTK	CYP1A1	EWSR1	GATA3	KRAS	NBN	PMS2	SETD2	WT1
AR	BUB1B	CYP2D6	EZH2	GLI1	MAF	NF1	POLD1	SF3B1	YES1
ARAF	CBL	CYP3A4	FAM175A	GNA11	MAP2K1	NF2	POLE	SMAD2	XRCC1
ARID1B	CCND1	CYP19A1	FANCA	GNAQ	MAP2K2	NFE2L2	PPP2R1A	SMAD4	
ARID2	CCND2	CYSLTR2	FANCC	GNAS	MAP3K1	NOTCH1	PTCH1	SMARCA4	
ATM	CCND3	dCK	FANCD2	GSTP1	MAPKAPK5	NOTCH2	PTEN	SMARCB1	
ATR	CCNE1	DDR2	FANCE	GSTT1	MAPK1	NOTCH3	PTPN11	SMO	
ATRX	CD274	DICER1	FANCF	HDAC2	MAPK3	NPM1	RAD50	SOCS1	
AURKA	CDA	DNMT3A	FANCG	HGF	MDM2	NRAS	RAD51C	SPOP	

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IHC thresholds

Biomarker	Negative	Not Significant	Positive
ALK	2+ or <5%	Not applicable	≥2+ and ≥5%
AR	≤1+ or ≤10%	Not applicable	≥1+ and >10%
CAIX	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%
ER	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%
hENT1	≤2+ or <50%	Not applicable	≥2+ and ≥50%
HER2	≤2+ and ≤10%	Equivocal = 2+ in ≤100% or 3+ in ≤10%	≥3+ and ≥10%
IDO	≤1+ or <10%	Not applicable	≥1+ and ≥10%
MET	≤1+ or <10%	Not applicable	≥1+ and ≥10%
MGMT	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%
MLH1	≤1+ and <1%	Not applicable	≥1+ and ≥1%
MSH2	≤1+ and <1%	Not applicable	≥1+ and ≥1%
MSH6	≤1+ and <1%	Not applicable	≥1+ and ≥1%
PD1:TILs	≤1+ or <10%	Not applicable	≥1+ and ≥10%
PD1:Tumor	≤1+ or <10%	Not applicable	≥1+ and ≥10%
PD-L1:TILs	NA and 0%	Not applicable	≥1+ and ≥50%
PD-L1:Tumor	NA and 0%	Not applicable	≥1+ and ≥50%
PMS2	≤1+ and <1%	Not applicable	≥1+ and ≥1%
PR (PGR)	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%
PTEN	≤1+ or <10%	Not applicable	≥1+ and ≥10%
RET	≤1+ or <10%	Not applicable	≥1+ and ≥10%
ROS1	2+ or <5%	Not applicable	≥2+ and ≥5%
TOP1	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%
TP	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%
TRKpan	≤1+ or <10%	Not applicable	≥1+ and ≥10%
TS	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%
TUBB3	≤1+ and ≤10%	1+ in 11-100% or 2+/3+/4+ in 1-29%	≥2+ and ≥30%

Performance

Biomarker	Sensitivity	Specificity
SNV, ins, del up to 40bp: ≥7.5% allele frequency	>99%	>99%
≥5.0% allele frequency	>97%	>99%
Tumor mutation burden	>85%	>92%
Amplifications >5 fold	>90%	>99%
Immunohistochemistry	>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 Paradigm. NGS is performed by Paradigm on genomic DNA and RNA 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 – EP3, 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 ROS1 by FISH is run, it is currently performed and interpreted by PhenoPath at 551 N. 34th St., Seattle, WA 98103. If MSI testing is run it is currently performed by MLabs at 1500 E. Medical Center Drive, Ann Arbor, MI 48109. Fusion testing may be performed by PathGroup – Molecular Pathology Accessioning at 658 Grassmere Park, Suite 101, Nashville, TN 37211. Fusion testing may be performed by PathGroup – Molecular Pathology Accessioning at 658 Grassmere Park, Suite 101, Nashville, TN 37211. The tests have neither been cleared nor approved by the U.S. Food and Drug Administration (FDA). However, the FDA has determined that such clearance or approval is not necessary. Paradigm is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing. The Laboratory Director is Bradly Clark, MD.

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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 Paradigm. 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

Paradigm 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 Paradigm and that you only have a limited right to use the information to potentially assist with the clinical treatment of the associated patient.

PCDx panel core components

Unless fewer tests are ordered on the requisition, every PCDx test run interrogates a wide panel of targets including the following clinically actionable genes for specific therapeutic interventions. PCDx is 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. Paradigm 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.

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.

Evidence-based Medicine:
(electronic signature)

Immunohistochemistry Review:
Pathologist
(electronic signature)

Approval of NGS results:
(electronic signature)