Molecular Testing Options for Clinically Relevant Homologous Recombination Repair (HRR) Mutations

MULTIGENE TESTING FOR HEREDITARY FORMS OF CANCER HAS RAPIDLY ALTERED THE CLINICAL APPROACH TO TESTING AT-RISK PATIENTS AND THEIR FAMILIES[1]

Often based on NGS technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes[1]

GENES ASSOCIATED WITH HEREDITARY BREAST AND OVARIAN CANCER[1,a,b]
ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53

METASTATIC BREAST CANCER WORKUP[2]	
Subpopulation	**Gene/Biomarker**
HER2 negative (HR positive or TNBC)	Germline *BRCA1* or *BRCA2* mutation (strongly recommended)
TNBC and considering therapy with atezolizumab plus nab-paclitaxel	PD-L1 on tumor-infiltrating immune cells
HR positive/HER2 negative and considering therapy with alpelisib	*PIK3CA* mutation (tumor- or plasma-based testing)

ADVANCED OVARIAN CANCER WORKUP[3]	
Subpopulation	**Gene/Biomarker**
All patients with histologically confirmed advanced ovarian cancer, fallopian tube cancer, or primary peritoneal cancer	*BRCA1* or *BRCA2* mutation (recommended)
	Germline and/or somatic *BRCA1* or *BRCA2* mutation status may inform maintenance therapy
Recurrent disease	Tumor testing to include at least *BRCA1/2* and microsatellite instability or DNA mismatch repair. Evaluation of HRD can be considered

METASTATIC PANCREATIC CANCER WORKUP	
Subpopulation	**Gene/Biomarker**
All patients with confirmed pancreatic cancer	Consider germline *BRCA1* or *BRCA2* mutation testing[1]
Locally advanced or metastatic pancreatic cancer	Tumor testing, which may include *BRCA1* or *BRCA2* and microsatellite instability or DNA mismatch repair [4,c]

[a]This table is only a summary of the molecular markers that may be included as part of a panel test. Please review the full guideline documents to determine which patients should receive testing. [b]Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome.[1] When >1 gene can explain an inherited cancer syndrome, then multigene testing may be more efficient and/or cost-effective.[1]
[c]Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Check NCCN guidelines regularly for updates.

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MULTIPLE MULTIGENE TESTS ARE AVAILABLE TO IDENTIFY CLINICALLY RELEVANT HRR PATHWAY MUTATIONS

Available tests and fundamental parameters may influence test selection. Please note that the list of tests below does not represent a comprehensive list of testing options.

Laboratory	Test Name	Testing Method	Genes	Turnaround Time	Sample Requirement	Contact Information
Ambry	CancerNext®[5,6]	Sanger, NGS Large rearrangement analysis	34 genes	14-21 days	Blood[b] Adult: 3-5 cc Saliva	Direct any questions regarding these tests to customer service at 949.900.5500.
	GYNplus®[6,7]	Sanger, NGS	13 genes: *BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, RAD51C, RAD51D, TP53*	14-21 days	Blood[b] Adult: 3-5 cc Saliva	
	OvaNext®[6,8]	Sanger, NGS Large rearrangement analysis	25 genes	14-21 days	Blood[b] Adult: 3-5 cc Saliva	
	TumorNext-BRCA[6,9]	Sanger, NGS Large rearrangement analysis	2 genes: *BRCA1, BRCA2*[a]	21-28 days	Blood[b] Adult: 3-5 cc Saliva	
	TumorNext-HRD[6,9]	Sanger, NGS Large rearrangement analysis	11 genes: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, MRE11A, NBN, PALB2, RAD51C, RAD51D*[a]	21-28 days	Blood[b] Adult: 3-5 cc Saliva FFPE tissue (block preferred)	
Caris	Molecular Intelligence® Comprehensive Tumor Profiling[10-12]	Sanger, NGS, IHC Large rearrangement analysis, MSI	592 genes	8-14 days	FFPE tissue	Direct any questions regarding this test to customer service at 866.771.8946.
Foundation Medicine	FoundationOne® CDx[13,14,c]	NGS MSI, TMB	324 genes	<14 days	FFPE tissue (block + 1 H&E slide OR 10 unstained slides + 1 H&E slide)	Direct any questions regarding these tests to customer service at 888.988.3639.
	FoundationOne® Liquid[15]	NGS MSI	70 genes	<14 days	Plasma (2 tubes of whole blood: 8.5 mL per tube)	
GenPath/ GeneDx	Breast cancer management panel[16]	NGS Large rearrangement analysis	9 genes: *BRCA1, BRCA2, CDH1, PALB2, PTEN, TP53, ATM, CHEK2, NBN*[a]	14 days	Blood (2-5 mL) Saliva	Direct any questions regarding these tests to customer service at 888.729.1206.
	Breast/gyn cancer panel[17]	NGS, PCR Large rearrangement analysis	23 genes	14 days	Blood (2-5 mL) Saliva	
Invitae	*BRCA1* and *BRCA2* STAT panel[18,19]	Sanger, NGS	2 genes: *BRCA1, BRCA2*[a]	5-12 days	Blood (preferred) 3 mL Saliva	Direct any questions regarding these tests to customer service at 800.436.3037.
	Breast and gyn cancers panel[18,20]	Sanger, NGS	23-37 genes	10-21 days	Blood (preferred) 3 mL Saliva, or DNA	
	Breast cancer guidelines-based panel[18,21]	Sanger, NGS	11-12 genes: *ATM, BRCA1, BRCA2, CDH1, CHEK2, NBN, NF1, PALB2, PTEN, STK11, TP53 ± BARD1*[a]	10-21 days	Blood (preferred) 3 mL Saliva, or DNA	
	Common hereditary cancers panel[18,22]	Sanger, NGS	47 genes	10-21 days	Blood (preferred) 3 mL Saliva	
	Multi-cancer panel[18,23]	Sanger, NGS	84 genes	10-21 days	Blood (preferred) 3 mL Saliva	
Myriad	BRACAnalysis CDx®[24-26,c]	Sanger and PCR Large rearrangement analysis	2 genes: *BRCA1, BRCA2*[a]	<14 days	Blood (7 mL)	Direct any questions regarding these tests to customer service at 800.469.7423.
	myChoice® HRD[27-29]	Sanger, NGS Large rearrangement analysis, TAI, LST, LOH	2 genes: *BRCA1, BRCA2*[a]	14-21 days	FFPE tissue (block OR 5-11 unstained slides)	
	myRisk®[30-33]	NGS Large rearrangement analysis	35 genes	7-14 days	Blood Saliva	
Tempus	Tempus xT[34-36]	NGS	596 genes	14-21 days	Blood (8 mL) Saliva FFPE tissue (block + 1 H&E slide OR 10 unstained slides + 1 H&E slide)	Direct any questions regarding this test to customer service at 800.739.4137.

[a]List of genes is limited to *BRCA* and other HRR pathway mutations.

[b]NGS panels and clinical exome sequencing require 6-10 cc (adult blood) and 5 cc (pediatric blood).

[c]FDA-approved test.

Blood or saliva specimen testing provides germline results. FFPE tissue testing provides combined germline and somatic results but cannot distinguish between them.[37-39]
Plasma testing may detect circulating tumor DNA.[40]

Abbreviations

ATM, ATM serine/threonine kinase; ***BARD1,*** BRCA1associated RING domain 1; ***BRCA,*** breast cancer susceptibility gene; ***BRCA1,*** breast cancer susceptibility gene 1; ***BRCA2,*** breast cancer susceptibility gene 2; ***BRCA1/2***, breast cancer susceptibility gene 1 and/or 2; ***BRIP1,*** BRCA1-interacting protein C-terminal helicase 1; ***CDH1,*** cadherin 1; **CDx,** companion diagnostic; ***CHEK2,*** checkpoint kinase 2; **CPT,** current procedural terminology; ***EPCAM,*** epithelial cell adhesion molecule; **FDA,** US Food and Drug Administration; **FFPE,** formalin-fixed, paraffin-embedded; **gyn,** gynecologic; **H&E,** hematoxylin and eosin; ***HER2,*** human epidermal growth factor receptor 2; **HR,** hormone receptor; **HRD,** homologous recombination deficiency; **HRR,** homologous recombination repair; **IHC,** immunohistochemistry; **LOH,** loss of heterozygosity; **LST,** large-scale state transitions; ***MLH1,*** mutL homolog 1; ***MSH2,*** mutS homolog 2; ***MSH6,*** mutS homolog 6; **MSI,** microsatellite instability; ***NBN,*** nibrin; **NCCN,** National Comprehensive Cancer Network; ***NF1,*** neurofibromin 1; **NGS,** next-generation sequencing; ***PALB2,*** partner and localizer of *BRCA2*; **PD-L1,** programmed death-ligand 1; ***PIK3CA,*** phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; ***PMS2,*** PMS1 homolog 2, mismatch repair system component; ***PTEN,*** phosphatase and tensin homolog; ***RAD51C,*** RAD51 paralog C; ***RAD51D,*** RAD51 paralog D; ***STK11,*** serine/threonine kinase 11; **TAI,** telomeric allelic imbalance; **TMB,** tumor mutational burden; **TNBC,** triple-negative breast cancer; ***TP53,*** tumor protein p53.

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1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian. V.3.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed September 20, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V.3.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed September 20, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer. V.2.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed September 20, 2019. 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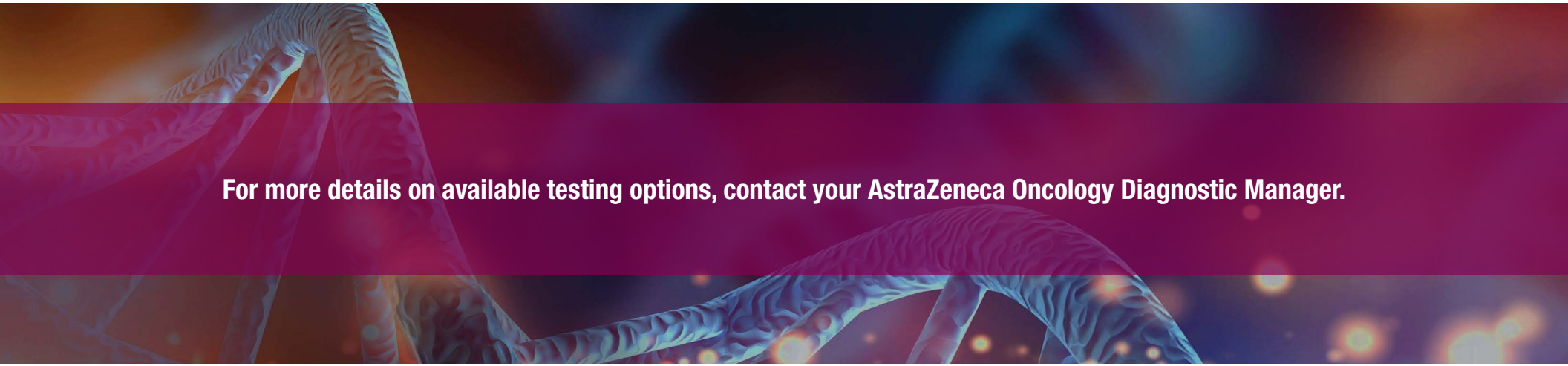

For more details on available testing options, contact your AstraZeneca Oncology Diagnostic Manager.

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