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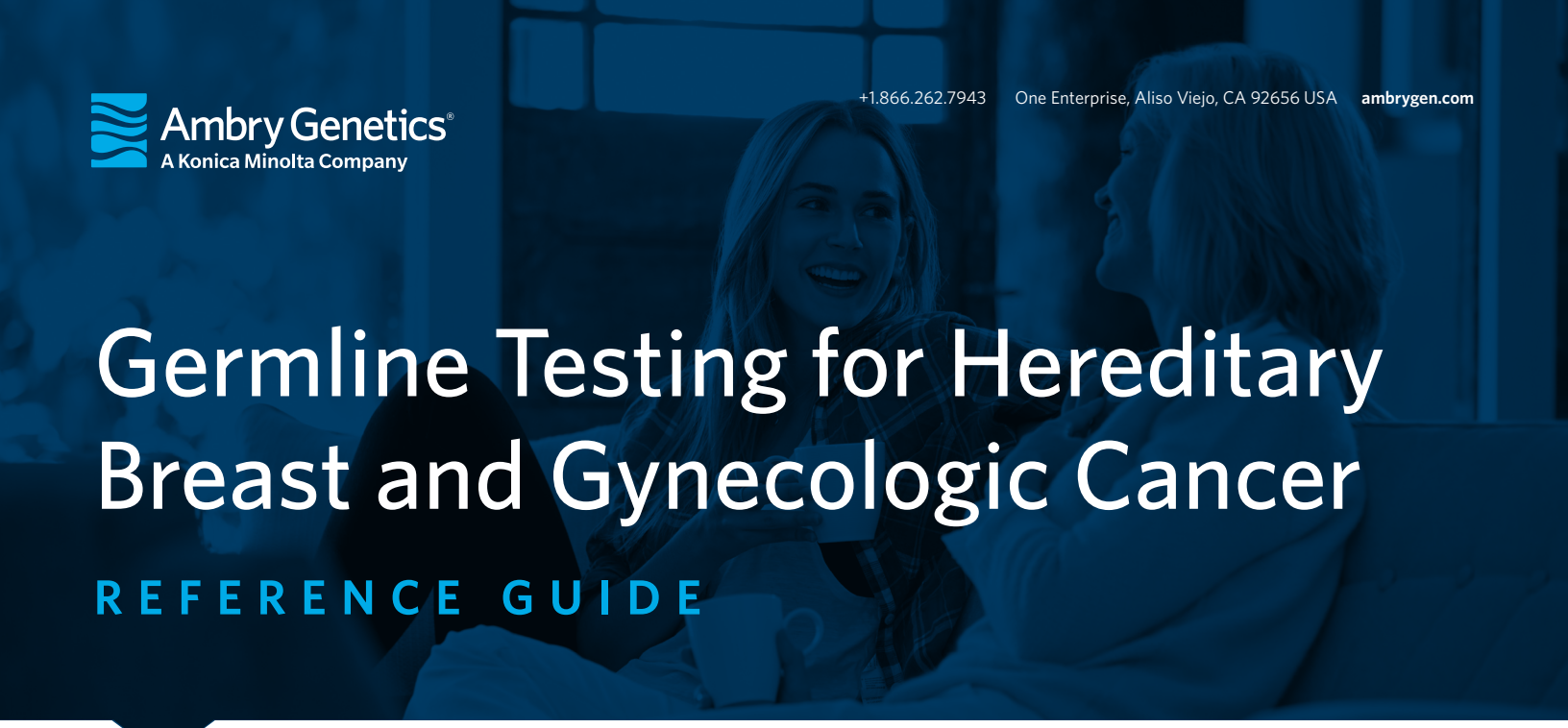


Germline Testing for Hereditary Breast and Gynecologic Cancer

REFERENCE GUIDE

Genetic Testing For Hereditary Breast and Gynecologic Cancer is Recommended By:

- **American Society of Breast Surgeons (ASBrS)[1]**
- **American College of Obstetricians and Gynecologists (ACOG)[2]**
- **Society of Gynecologic Oncology (SGO)[2]**
- **NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®)[3]**

GUIDELINES RECOMMEND GENETIC TESTING IF YOUR PATIENT HAS A PERSONAL OR FAMILY HISTORY OF ANY OF THE FOLLOWING SIGNS* OF HEREDITARY CANCER:

MULTIPLE CANCERS

› 2 or more primary cancers in the same person

› 3 or more cancers on the same side of the family

RARE CANCERS

› Male breast

› Ovarian

› Pancreatic

› Metastatic prostate

EARLY-ONSET CANCERS

› Breast cancer diagnosed before 45

› Triple negative breast cancer before 60

› Uterine cancer diagnosed before 50

ABNORMAL TUMOR SCREENING

› Tumors with microsatellite instability (MSI) or loss of immunohistochemical (IHC) staining

ANCESTRY

› Ashkenazi Jewish with breast cancer

**Adapted from national published guidelines*

PALB2 MUTATION

Case Example

Screening and surgical implications
for patient & family members

IMPACT ON PATIENT MEDICAL MANAGEMENT

› Begin annual mammograms and breast MRIs[3] (starting now instead of at 40)

› Consider risk-reducing mastectomy depending on family history[3]

› Consider risk-reducing salpingo-oophorectomy based on family history[3]

IMPACT ON FAMILY MEMBERS

› Genetic testing recommended for family members[3]

› If positive, medical management of family members may be impacted. For example:

  › Possible increased risk for second primary breast cancer in mother (may consider bilateral mastectomy)

  › Mother may consider risk-reducing salpingo-oophorectomy

31 year-old female

Personal History
No personal history of cancer

Family History
Mother
Breast Cancer (55)

Maternal Aunt
Ovarian Cancer (70)

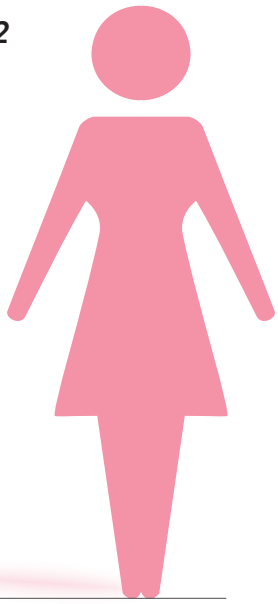
Paternal Grandmother
Breast Cancer (68)

Patient meets *BRCA1/2* genetic testing criteria

Ordered **BRCANext™**

Genetic testing identified a ***PALB2*** mutation

Results Interpretation and Counseling to Inform Medical Management



GENETIC TESTING RESULTS MAY ALSO INFORM TREATMENT RECOMMENDATIONS

› PARP inhibitor therapy for *BRCA1* or *BRCA2* positive patients with ovarian cancer[4-12]

› Immunotherapy for patients with a germline mutation in a mismatch repair gene[13]

HEREDITARY BREAST AND GYNECOLOGIC CANCER TESTING OPTIONS

14-21 DAYS | 36 GENES

CancerNext®

36-gene test covering a range of cancers; NCCN Guidelines® provide recommendations regarding risk management for most genes in the panel[3]

14-21 DAYS | 23 GENES

BRCANext-*Expanded*™

23-gene test for hereditary breast and gynecologic cancers; NCCN Guidelines provide recommendations regarding risk management for most genes in the panel[3]

14-21 DAYS | 18 GENES

BRCANext™

18-gene test for hereditary breast and gynecologic cancers; NCCN Guidelines provide recommendations regarding risk management for **all genes** in the panel[3]

7-10 DAYS | 8 GENES

BRCAplus®

8-gene STAT, breast cancer test; NCCN Guidelines provide recommendations regarding risk management for **all genes** in the panel[3]

Add +RNAinsight® to Find More Mutations, Decrease Variants of Unknown Significance, and Provide More Accurate Results[14-16]

+RNAinsight is Available With Any Hereditary Cancer Panel*

SAMPLE REQUIREMENTS

One kit that includes 1 EDTA tube (DNA) and 1 PAXgene® tube (RNA)

NO IMPACT ON TURNAROUND TIME OR COST

DID YOU KNOW?

Adding RNA genetic testing decreases variants of unknown significance by **5%** and increases diagnostic yield by **7%**[16]

*Exceptions: BRCAplus® and TumorNext® tests

References

1. Manahan ER,*et al.* Ann Surg Oncol. 2019 Oct;26(10):3025-3031. 2. Obstetrics & Gynecology. 2017 Sep;130(3):e110-e126. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. V1.2020. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed June 11, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 4. Banerjee S & Kaye S. Curr Oncol Rep. 2011 Dec;13(6):442-9. 5. Burgess M & Puhalla S. Front Oncol. 2014 Feb 27;4:19. 6. Yamamoto KN *et al.* PLoS One. 2014 Aug 26;9(8): e105724. 7. Moore *et al.* NEJM 2018 Dec 27; 379(26):2495–505. 8. Ledermann, *et al.* Lancet Oncol. 2014;15(8):852-861. 9. Pujade-Lauraine, *et al.* Lancet Oncol. 2017;18:1274-1284. 10. Mirza, *et al.* N Engl J Med. 2016;375:2154-2164. 11. Coleman RL, *et al.* Lancet. 2017 Oct 28;390(10106):1949-1961. 12. Swisher, *et al.* Lancet Oncology 2017;18: 75-87 13. Zhao P, Li *et al.* J Hematol Oncol 2019 May;12:54. 14. Landrith T *et al.* npj Precision Oncology. 2020. 15. Karam *et al.* JAMA Network Open. 2019. 16. Ambry Genetics, internal data on file from first 2,500 cases tested with +RNAinsight.

BREAST AND GYNECOLOGIC GENES AND ASSOCIATED RISKS

BRCAplus
BRCANext
BRCANext-*Expanded*
CancerNext

GENE(S)	ASSOCIATED CANCERS AND RISKS
*ATM**	Breast (2-4 fold), pancreatic, prostate
*BRCA1**	Female breast (57-87%), ovarian (39-40%), pancreatic, melanoma, prostate, male breast
*BRCA2**	Female breast (45-84%), ovarian (11-18%), pancreatic, melanoma, prostate (15%), male breast (>6%)
*CDH1**	Diffuse gastric (67-83%), female lobular breast (39-52%)
*CHEK2**	Breast (2 fold), colorectal, prostate, other
*PALB2**	Breast (33-58%), pancreatic, ovarian, possibly prostate, male breast
*PTEN**	Breast (25-85%), thyroid (10-35%), uterine (5-28%), melanoma (up to 6%), other
*TP53**	Breast, sarcoma, brain, adrenocortical, leukemia, other
*BRIP1**	Ovarian (up to 9%), breast
EPCAM	Colorectal (52-82%), uterine (12-55%), possibly prostate, other
MLH1	Colorectal (52-82%), uterine (25-60%), stomach (6-13%), ovarian (4-12%), prostate (2 fold), other
MSH2	Colorectal (52-82%), uterine (25-60%), stomach (6-13%), ovarian (4-12%), prostate (2 fold), other
MSH6	Colorectal (20-44%), uterine (up to 44%), prostate (2 fold), other
*NBN**	Breast, possibly ovarian, prostate
*NF1**	Female breast (3-5 fold), malignant nerve sheath tumors (8-13%), PGL/PCC (up to 7%), brain, other
*PMS2**	Colorectal (15-20%), uterine (15%), possibly prostate, other
*RAD51C**	Ovarian (5-9%), breast
*RAD51D**	Ovarian (10-12%), breast, prostate
BARD1	Breast, possibly ovarian
DICER1	Pleuropulmonary blastoma, cystic nephroma, ovarian sex-cord tumors, brain, other
RECQL	Breast
SMARCA4	Ovarian (small cell carcinoma, hypercalcemic type), brain, other
*STK11**	GI cancers (up to 57%) breast (up to 45%), pancreatic, other
*APC**	Colorectal (up to 100%), small bowel, stomach, pancreatic, thyroid, other
*AXIN2**	Colorectal
BMPR1A/ SMAD4**	Colorectal (40-50%), stomach (up to 21%)
CDK4	Melanoma (up to 74% by age 50)
*CDKN2A**	Melanoma (28-67%), pancreatic (17-25%)
GREM1	Colorectal
HOXB13	Prostate
*MSH3**	Colorectal
*MUTYH**	Biallelic mutations: colorectal (up to 80%), stomach, duodenal, uterine, Monoallelic mutations: colorectal (up to 2 fold)
*NTHL1**	Colorectal
POLD1/POLE**	Colorectal

* Risk management recommendations are provided in the NCCN Guidelines[3]

+RNAinsight performed for this gene (RNA analysis available only for exons 1-10 for *PMS2*)

MKT-0404_v2 07.22.20

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