مركـــز الخليـــج الدولـــي لـــلأورام
Gulf International Cancer Center

Epidemiology of BRCA Mutation
&
The Pre-existing Guidelines for BRCA

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Declaration

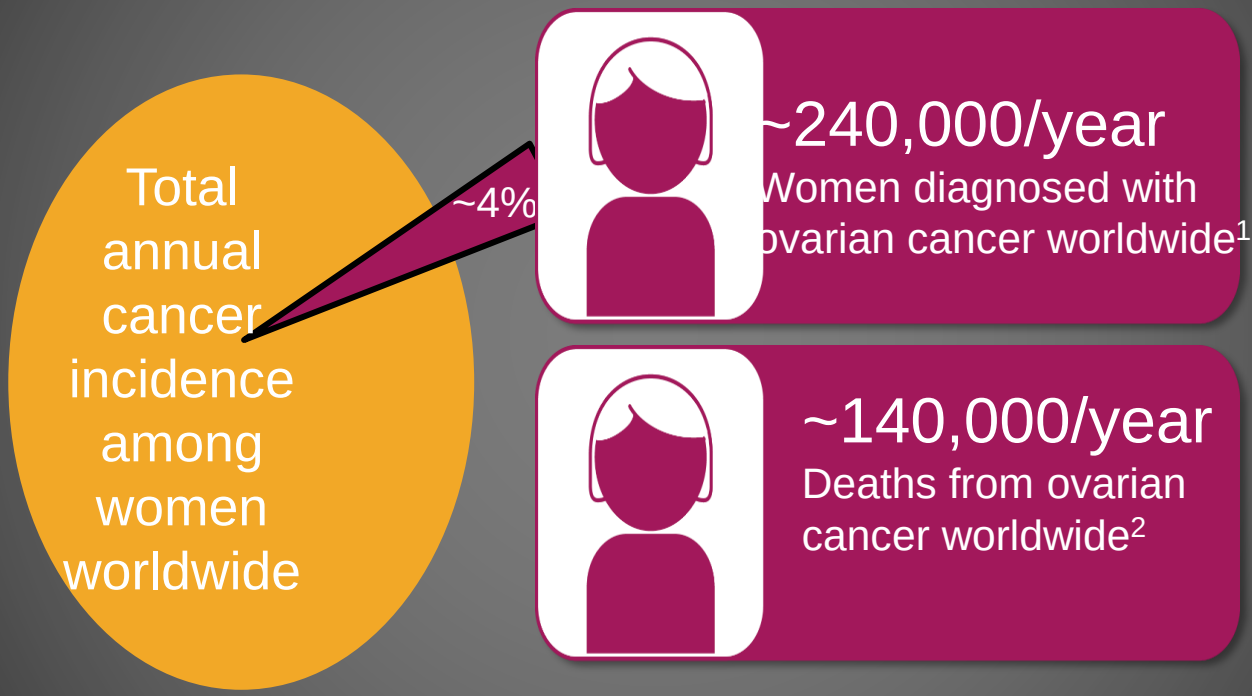
Presenter has no conflict of interest to declare.

بسم الله الرحمن الرحيم

Presentation objectives

- Epidemiology.
- How risky is BRCA?
- What is BRCA?
- How to test for?
- Results expected.
- Guidelines.

• Ovarian cancer incidence and mortality rate



• 1. GLOBOCAN, 2012. http://globocan.iarc.fr/Pages/fact_sheets_population.aspx; 2. Romero I, *et al.* *Endocrinology* 2012;153:1593–602.

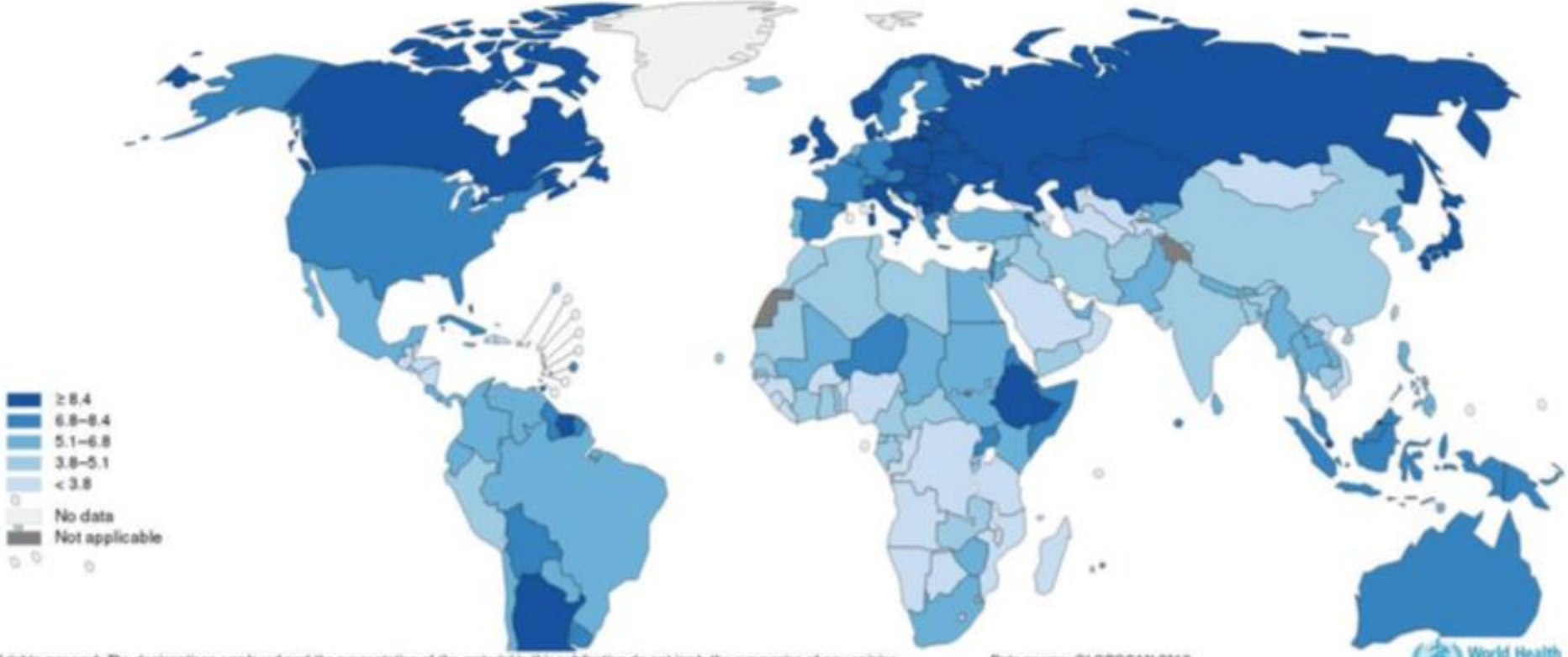
• A regional perspective on ovarian cancer

In the USA ovarian cancer accounts for about 3% of all female cancers and approximately 5% of cancer deaths among women[1]

Outside the USA, Northern Europe has the highest incidence of ovarian cancer and mortality[2]

• 1. Jemal A, *et al. CA Cancer J* 2010;60:277–300; 2. Cramer DW. *Hematol Oncol Clin North Am* 2012;26:1–12.

Estimated age-standardized rates (World) of incident cases, ovarian cancer, worldwide in 2012



Data source: GLOBOCAN 2012
Map production: IARC (http://gco.iarc.fr/today)
World Health Organization

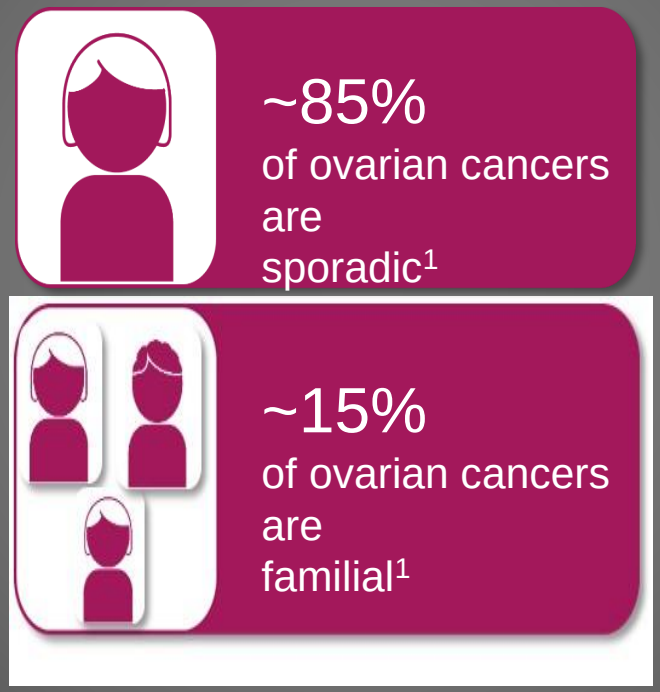
Countries with Highest Rates of Ovarian Cancer

Ovarian cancer rates

Serbia had the highest rate of ovarian cancer in 2018, followed by Brunei.

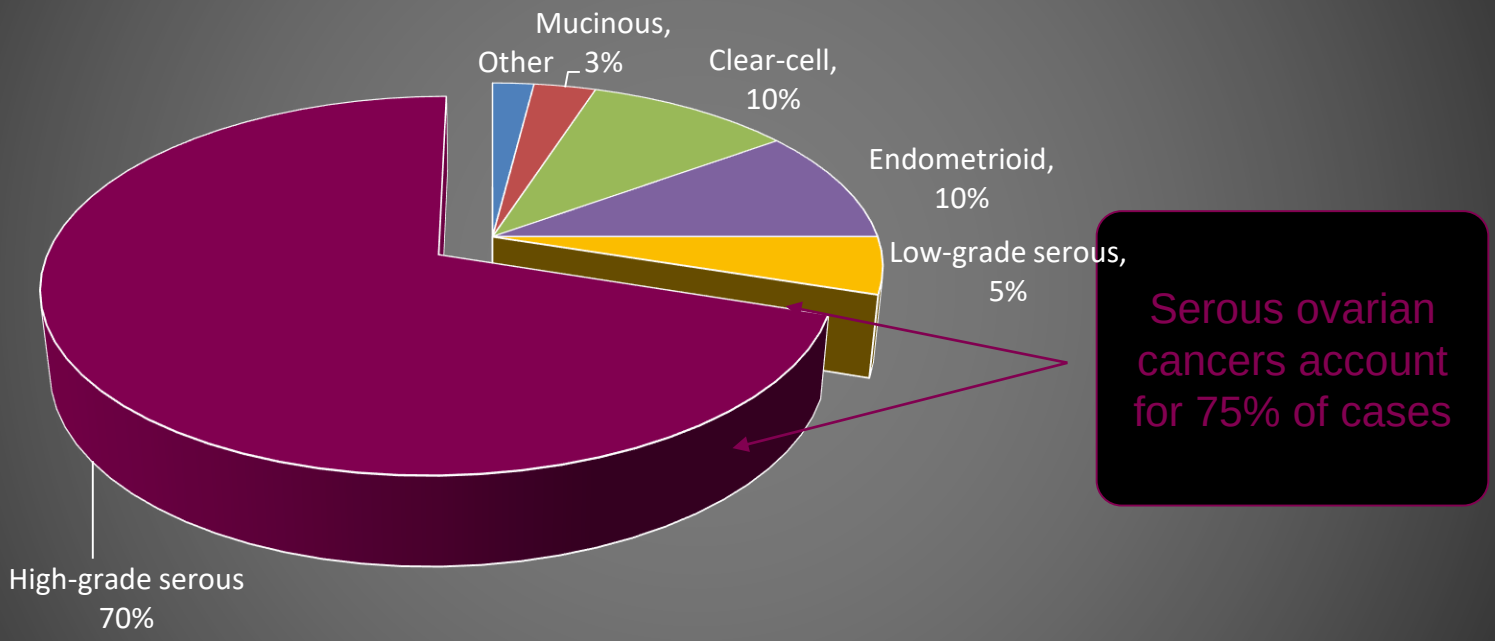
Rank	Country	Age-standardised rate per 100,000
1	Serbia	16.6
2	Brunei	16.0
3	Belarus	15.4
4	Poland	14.7
5	Latvia	14.3
6	Hungary	13.2
7	Ukraine	12.3
8=	Fiji	12.2
8=	Lithuania	12.2
10	Croatia	12.1
11	Slovakia	11.6
12	Ireland	11.4
13=	Moldova	11.1
13=	Russia	11.1

• Sporadic and familial ovarian cancer



• 1. Romero I, *et al. Endocrinology* 2012;153:1593–602.

• Frequency of ovarian cancer types



Prat J.. Ann Oncol 2012; 23(10): 111-117.

• Increased cancer risk associated with *BRCA* mutations

Among the general female population, the lifetime risk for developing breast cancer is 12.3%[1], and for ovarian cancer 1.3%[2]

Lifetime risk for both cancers is substantially increased among women harbouring mutations in *BRCA1* or *BRCA2*[3]

Lifetime risk for developing cancer			
	General female population	Women harbouring BRCA1 mutation[3]	Women harbouring BRCA2 mutation[3]
Breast	12.3%[1]	65% (95% CI 44-78)	45% (95% CI 31-56)
Ovarian	1.3%[2]	39% (95% CI 18-54)	11% (95% CI 2.4-19)

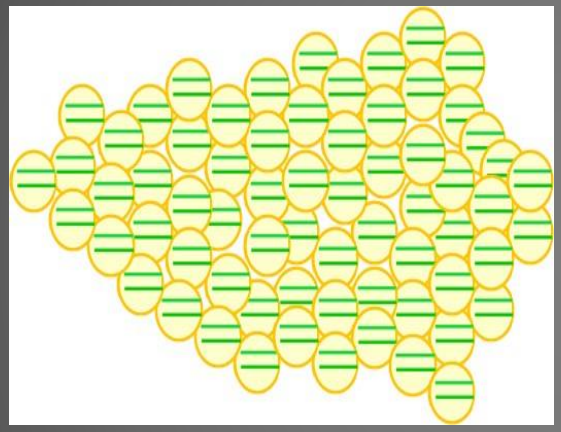
• 1. SEER Stat Fact Sheets: Breast cancer. http://seer.cancer.gov/statfacts/html/breast.html 2. SEER Stat Fact Sheets: Ovary Cancer. http://seer.cancer.gov/statfacts/html/ovary.html 3. Balmaña J, *et al. Ann Oncol* 2011;22(Suppl. 6):vi31–vi34

• Germline and somatic *BRCA* mutations

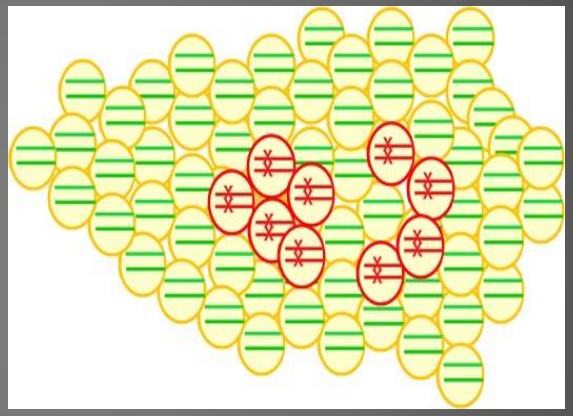
Germline mutations[1]
Mutations described as germline are replicated in every cell of the body. This reflects their origin in the DNA within germinal cells (eggs or sperm) and the resulting transmission to progeny at conception. Inherited (germline) *BRCA* mutations account for the majority of familial ovarian cancer.[2]

Somatic mutations[3]
Somatic mutations can arise in any cell other than a germinal cell.
BRCA mutations described as somatic are those that occur in the *BRCA* genes within tumour cells. Somatic mutations are non-heritable.

- Tumour specific somatic mutation in women without germline *BRCA* mutation

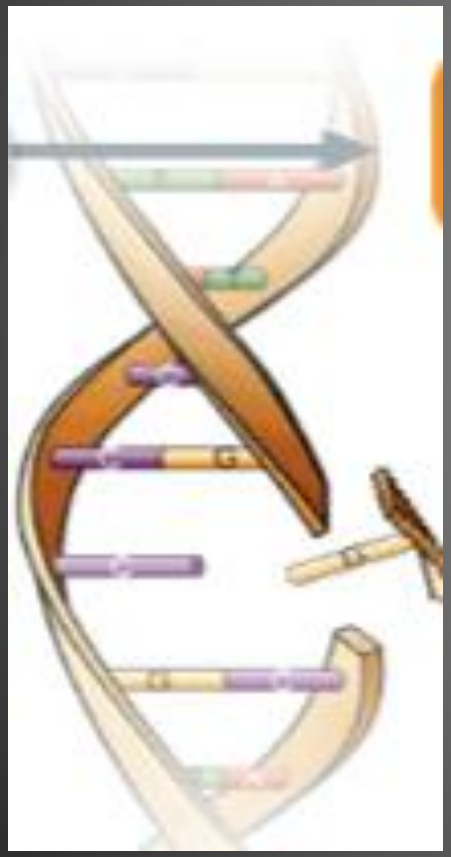


All body cells wild type



Mutation in tumor cells only

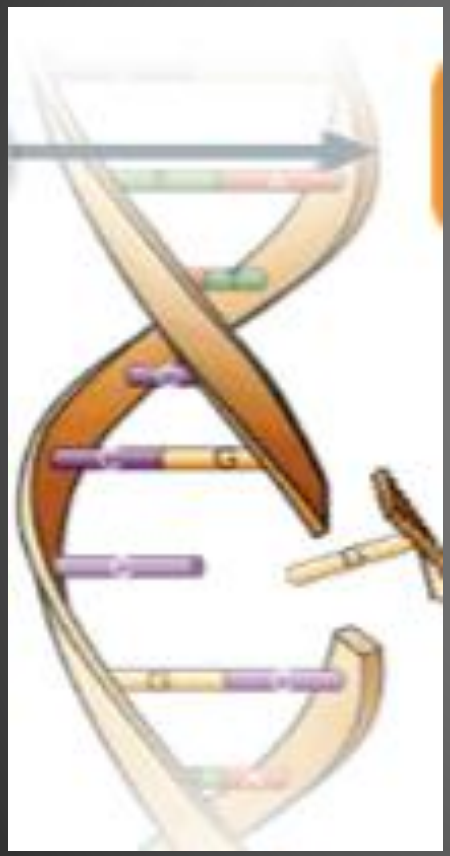
Normal BRCA in cell



BRCA-1
BRCA-2

Courtesy of Aladdin Maarraoui

What is PARP: In a normal cell?

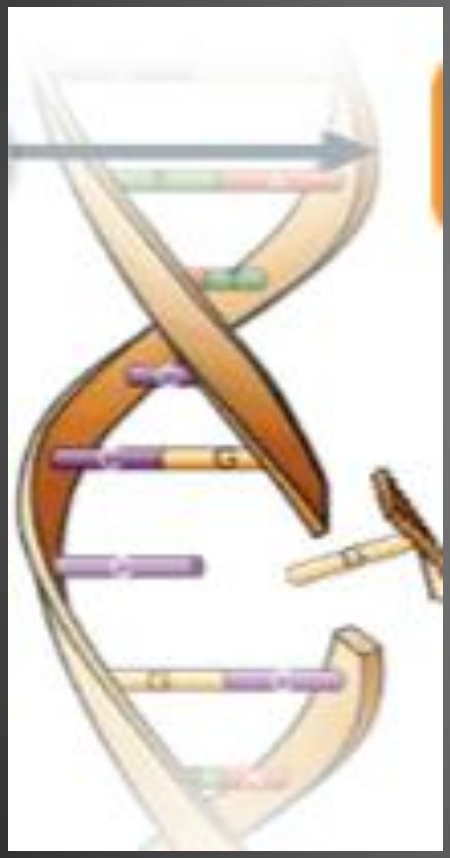


BRCA-1
BRCA-2

PARP

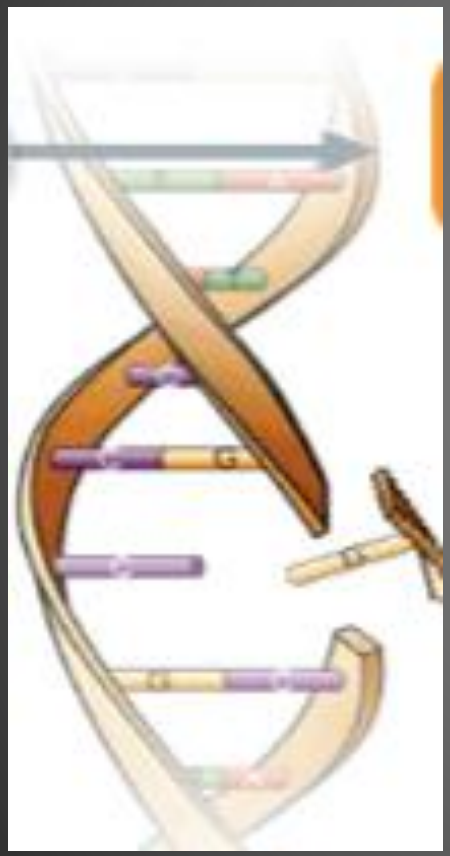
Courtesy of Aladdin Maarraoui

In BRCA there is only 1 Repair Tool



PARP

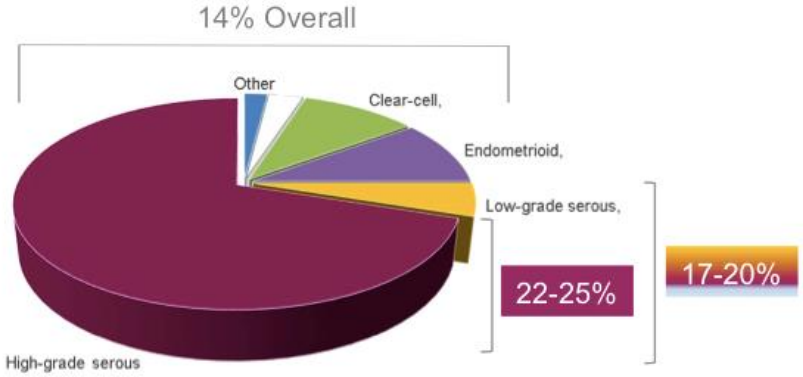
In a BRCA cell, PARP Inhibitor will prevent DNA repair and leads to Apoptosis



X

The prevalence of germline *BRCA* mutations in women with ovarian cancer

- Germline *BRCA* mutations have been reported in 14% of women with non-mucinous ovarian cancer [1]
- The prevalence of *BRCA* mutations was higher among women with serous ovarian cancer (17–20% overall and **~22–25% in high-grade serous ovarian cancer)** [1,2]



1. Alsop K, *et al. J Clin Oncol* 2012;30:2654-63; 2. Schrader KA, *et al. Obstet Gynecol* 2012;120:235–40.

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however, a study has reported that over time, buccal epithelial cells are replaced by donor-derived cells in allogeneic HSCT recipients.[48,49] Therefore, genetic testing using buccal swab samples may be limited given this known risk of donor DNA contamination.

The genetic testing strategy is greatly facilitated when a pathogenic or likely pathogenic variant has already been identified in another family member. In that case, the genetic testing laboratory can limit the search for pathogenic or likely pathogenic variants in additional family members to the same location in the gene. In most cases, an individual testing negative for a known familial pathogenic or likely pathogenic variant predisposing to breast cancer can be followed with routine breast screening. Individuals who meet testing criteria but do not undergo gene testing should be followed as if a pathogenic or likely pathogenic variant (ie, *BRCA1/2*, *PTEN*, or *TP53* pathogenic or likely pathogenic variant) is present, if they have a close family member who is a known carrier of the pathogenic or likely pathogenic variant.

For the majority of families in whom presence of a pathogenic or likely pathogenic variant is unknown, it is best to consider testing an affected family member first, especially a family member with early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood for a positive test result. Unless the affected individual is a member of an ethnic group for which particular founder pathogenic or likely pathogenic variants are known, comprehensive genetic testing (ie, full sequencing of the genes and detection of large gene rearrangements) should be performed by commercial or academic laboratories that are clinically approved or validated.

For individuals with family histories consistent with a pattern of hereditary breast and/or ovarian cancer on both the maternal and paternal sides, the possibility of a second pathogenic or likely pathogenic variant in the family should be considered, and full sequencing may be indicated, even if a variant has already been identified in a relative.

In the situation of an unaffected individual with a significant family history, the testing of the unaffected individual (or of unaffected family members) should only be considered when no affected family member is available for testing. In such cases, the unaffected individual or unaffected close relative with the highest likelihood of testing positive for the pathogenic or likely pathogenic variant should be tested. A negative test result in such cases, however, is considered indeterminate (see Table 2) and does not provide the same level of information as when there is a known pathogenic or likely pathogenic variant in the family. Thus, one should be mindful that when testing unaffected individuals (in the absence of having tested affected family members), significant limitations may exist in interpreting the test results, and testing multiple family members may be indicated.

In the case of *BRCA*-related breast/ovarian cancer, if no family member with breast or ovarian cancer is living, consideration can be given to testing first- or second-degree family members affected with cancers thought to be related to the pathogenic or likely pathogenic variant in question (eg, prostate or pancreatic cancer). Importantly, the significant limitations of interpreting testing results for an unaffected individual should be discussed prior to testing.

Reports regarding germline findings that may impact medical management should come from laboratories that are certified by the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA), with some U.S. states (eg, New York) having additional reporting requirements. Certain large genomic rearrangements are not detectable by a primary sequencing assay, thereby necessitating supplementary testing in some cases.[50-53] For example, there are tests that detect rare, large cancer-associated rearrangements of DNA in the

In 2019, I tested more patients for BRCA that what I ever did

- 55 hereditary cancer panel cost dropped to 550 Euro =2,270 Dirham. Last year it was 1850 Euro=7,500 Dirham.
- Full gene sequencing with Large GENOMIC Rearrangements LGR dropped to 1,000 $.

Colon	Breast	Pancreas	Ovarian	Gastric	Melanoma	Endometrial	Endocrine	Prostate
APC							APC	
	ATM	ATM						ATM
	BARD1		BARD1					
BMPR1A								
	BRCA1	BRCA1	BRCA1					BRCA1
	BRCA2	BRCA2	BRCA2					BRCA2
	BRIP1		BRIP1					BRIP1
	CDH1			CDH1				
					CDK4			
		CDKN2A			CDKN2A			
	CHEK2							CHECK2
EPCAM			EPCAM			EPCAM		EPCAM
	FANCA	FANCA		FANCA		FANCA		FANCA
	FANCM	FANCM						
								HOXB13
		MEN1					MEN1	
MLH1		MLH1	MLH1			MLH1		MLH1
	MRE11A							MRE11A
MSH2		MSH2	MSH2			MSH2		MSH2
MSH6		(MSH6)	MSH6			MSH6		MSH6
MUTYH	MUTYH							
	NBN							NBN
	NF1							
	PALB2	PALB2						PALB2
PMS2						PMS2		PMS2
POLE								
POLD1								
	PTEN				PTEN			
	RAD50							
	RAD51C		RAD51C					
	RAD51D		RAD51D					
							RET	
SMAD4								
	STK11	STK11						
	TP53		TP53		TP53			TP53
							VHL	

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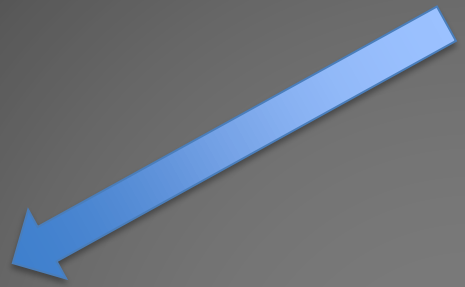
- 55 hereditary cancer panel cost dropped to 550 Euro =2,270 Dirham. Last year it was 1850 Euro=7,500 Dirham.
- Full gene sequencing dropped to 1,000$.
- Some pharmaceutical companies are offering free testing.

Result comes as



Pathogenic
Mutation

Result comes as

Pathogenic Mutation

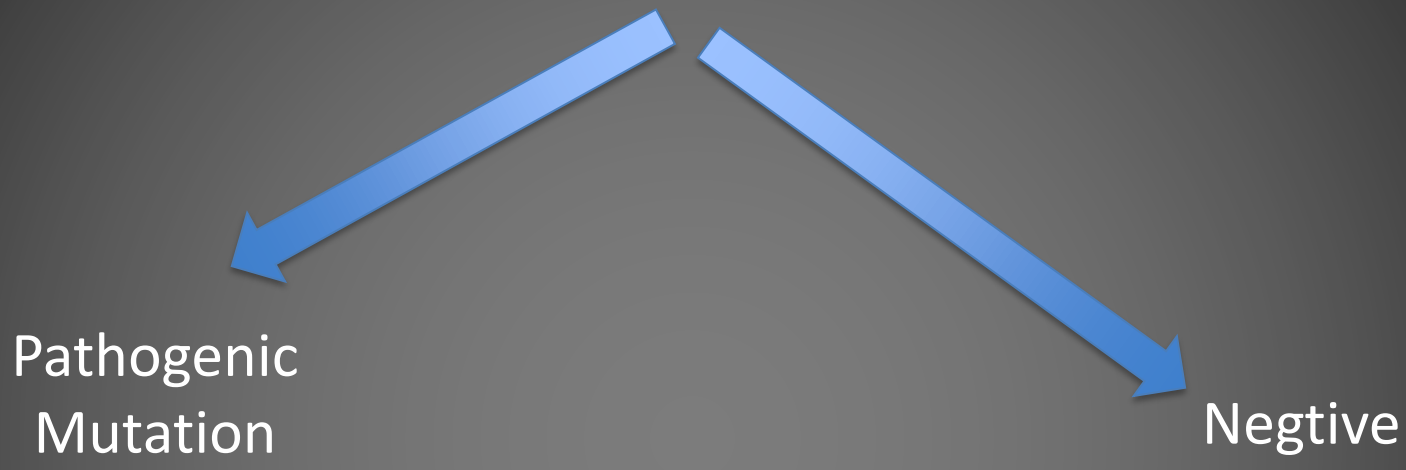
RESULT: POSITIVE

THE CLINICALLY SIGNIFICANT VARIANT WAS IDENTIFIED IN THE GENE.

Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

ADDITIONAL FINDINGS: No Variant(s) of Uncertain Significance (VUS) identified

Result comes as



PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- Cancer risk assessment and genetic counseling is highly recommended when genetic testing is offered (ie, pre-test counseling) and after results are disclosed (ie, post-test counseling).[1-5] A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in the counseling of patients.

• Pre-test counseling includes: ‣ Collection of a comprehensive family history ◊ Note that when assessing family history, close blood relatives include first-, second-, and third-degree relatives on each side of the family (See BR/OV-B) ‣ Evaluation of a patient's cancer risk ‣ Generating a differential diagnosis and educating the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity ‣ Preparing the patient for possible outcomes of testing including positive (pathogenic, likely pathogenic), negative, and uncertain findings and obtaining informed consent	• Post-test counseling includes discussions of: ‣ Results along with their significance and impact and recommended medical management options ‣ Interpretation of results in context of personal and family history of cancer ‣ Informing and testing at-risk family members ‣ Available resources such as disease-specific support groups and research studies

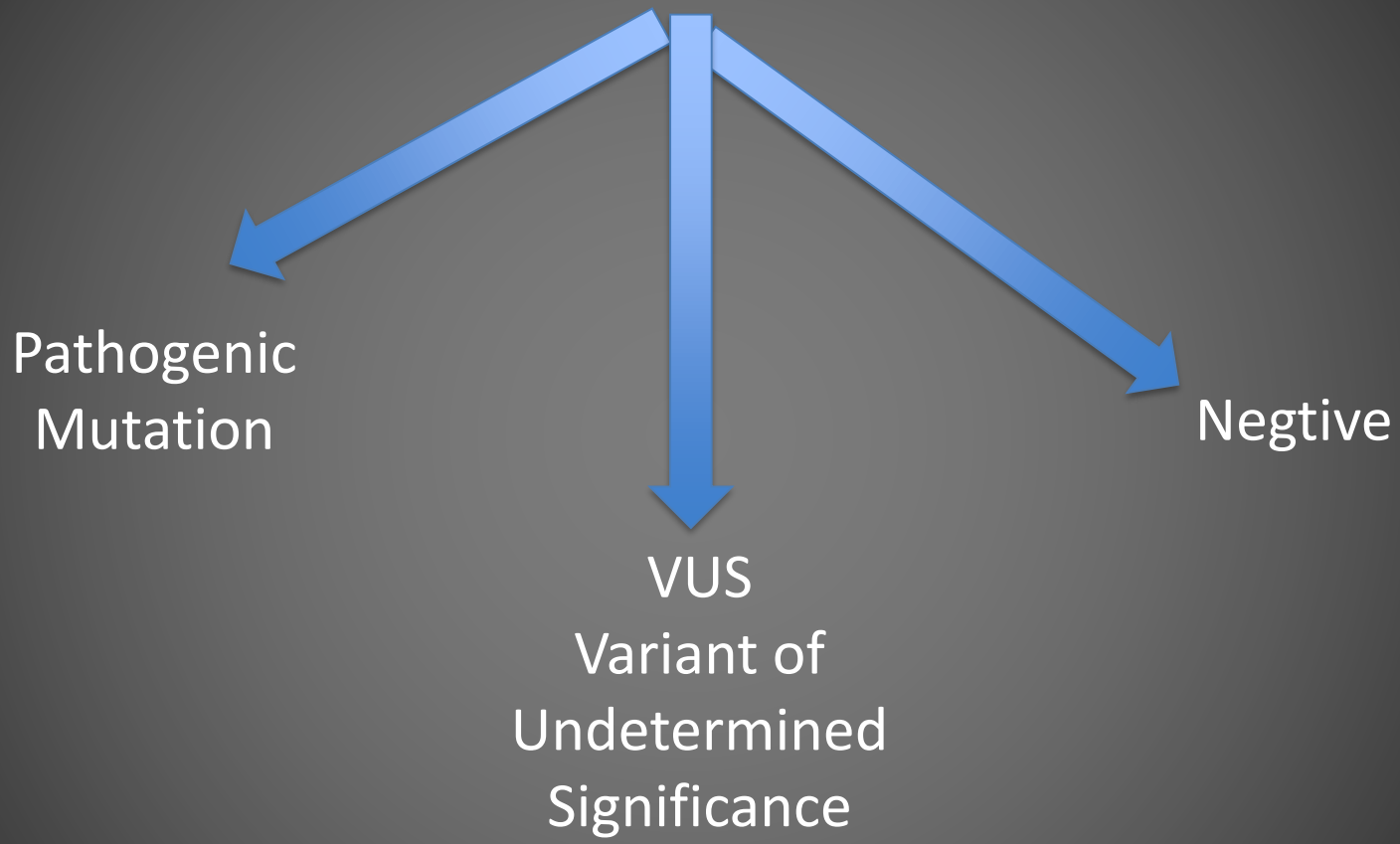
Genetic Testing Considerations

- Testing should be considered in appropriate high-risk individuals where it will impact the medical management of the tested individuals and/or their at-risk family members. It should be performed in a setting in which it can be adequately interpreted.[1]
- The probability of pathogenic/likely pathogenic variant detection associated with these criteria will vary based on family structure. Individuals with unknown or limited family history/structure, such as fewer than 2 female first- or second-degree relatives having lived beyond age 45 in either lineage, may have an underestimated probability of familial pathogenic/likely pathogenic variant detection. The estimated likelihood of pathogenic/likely pathogenic variant detection may be very low in families with a large number of unaffected female relatives.
- Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to unreliable test results from contamination by donor DNA until other technologies are available. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.
- Comprehensive genetic testing includes full sequencing and testing for large genomic rearrangements. It is encouraged that testing be done in commercial or academic labs that are clinically approved and validated. See BR/OV-A 3 of 3.
- In children <18 y, genetic testing is generally not recommended when results would not impact medical management.[6]
- Likely pathogenic variants are often treated similarly to pathogenic variants.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

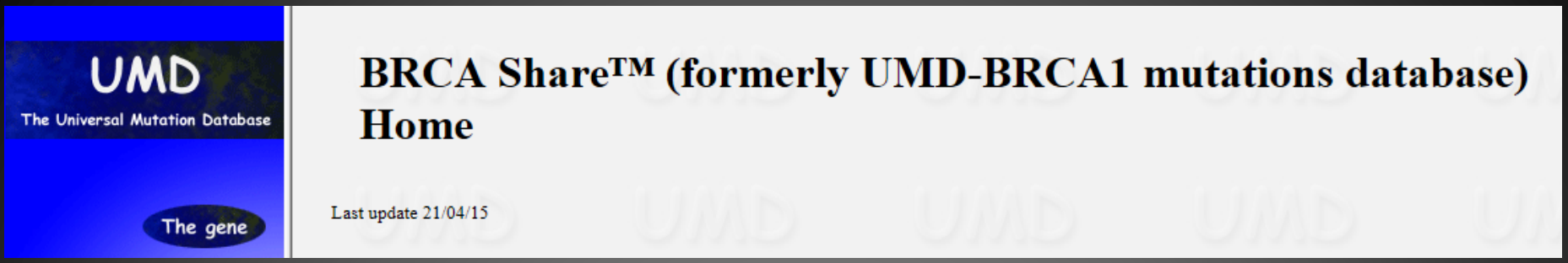
Result comes as



Novel versus VUS?

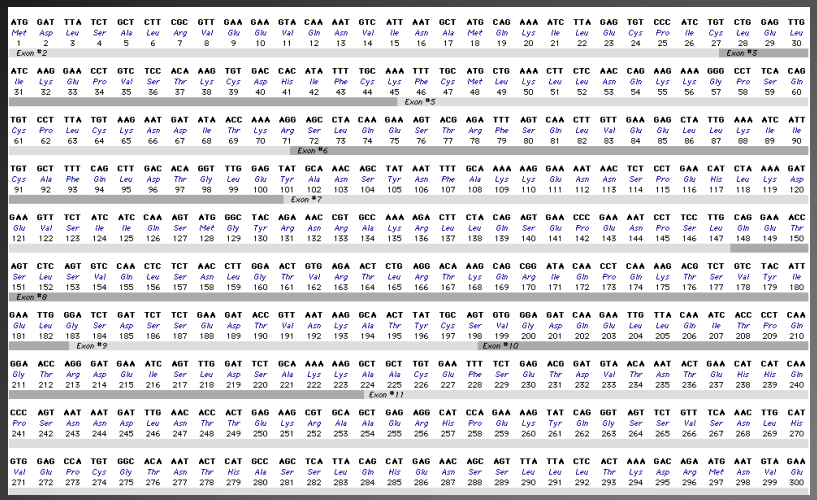
c.1608 deletion in BRCA-1

- In exon 10 of the BRCA1 gene. This variant was not previously described by the Exome Sequencing Project and has not been yet reported in the UMD database.



BRCA Share was launched on April 21st 2015

- BRCA Share is a novel gene data share initiative that provides scientists and commercial laboratory organizations around the world with open access to BRCA1 and BRCA2 genetic data. The program's goal is to accelerate research on BRCA gene mutations, particularly variants of uncertain significance, to improve the ability of clinical laboratory diagnostics to predict which individuals are at risk of developing these cancers.



ATG GAT TTA TCT GCT CTT CGC GTT GAA GAA GTA CAA AAT GTC ATT AAT GCT ATG CAG AAA ATC TTA GAG TGT CCC ATC TGT CTG GAG TTG
Met Asp Leu Ser Ala Leu Arg Val Glu Glu Val Gln Asn Val Ile Asn Ala Met Gln Lys Ile Leu Glu Cys Pro Ile Cys Leu Glu Leu
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

Exon #2 Exon #3

ATC AAG GAA CCT GTC TCC ACA AAG TGT GAC CAC ATA TTT TGC AAA TTT TGC ATG CTG AAA CTT CTC AAC CAG AAG AAA GGG CCT TCA CAG
Ile Lys Glu Pro Val Ser Thr Lys Cys Asp His Ile Phe Cys Lys Phe Cys Met Leu Lys Leu Leu Asn Gln Lys Lys Gly Pro Ser Gln
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

Exon #5

TGT CCT TTA TGT AAG AAT GAT ATA ACC AAA AGG AGC CTA CAA GAA AGT ACG AGA TTT AGT CAA CTT GTT GAA GAG CTA TTG AAA ATC ATT
Cys Pro Leu Cys Lys Asn Asp Ile Thr Lys Arg Ser Leu Gln Glu Ser Thr Arg Phe Ser Gln Leu Val Glu Glu Leu Leu Lys Ile Ile
61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90

Exon #6

TGT GCT TTT CAG CTT GAC ACA GGT TTG GAG TAT GCA AAC AGC TAT AAT TTT GCA AAA AAG GAA AAT AAC TCT CCT GAA CAT CTA AAA GAT
Cys Ala Phe Gln Leu Asp Thr Gly Leu Glu Tyr Ala Asn Ser Tyr Asn Phe Ala Lys Lys Glu Asn Asn Ser Pro Glu His Leu Lys Asp
91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120

Exon #7

GAA GTT TCT ATC ATC CAA AGT ATG GGC TAC AGA AAC CGT GCC AAA AGA CTT CTA CAG AGT GAA CCC GAA AAT CCT TCC TTG CAG GAA ACC
Glu Val Ser Ile Ile Gln Ser Met Gly Tyr Arg Asn Arg Ala Lys Arg Leu Leu Gln Ser Glu Pro Glu Asn Pro Ser Leu Gln Glu Thr
121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150

AGT CTC AGT GTC CAA CTC TCT AAC CTT GGA ACT GTG AGA ACT CTG AGG ACA AAG CAG CGG ATA CAA CCT CAA AAG ACG TCT GTC TAC ATT
Ser Leu Ser Val Gln Leu Ser Asn Leu Gly Thr Val Arg Thr Leu Arg Thr Lys Gln Arg Ile Gln Pro Gln Lys Thr Ser Val Tyr Ile
151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180

Exon #8

GAA TTG GGA TCT GAT TCT TCT GAA GAT ACC GTT AAT AAG GCA ACT TAT TGC AGT GTG GGA GAT CAA GAA TTG TTA CAA ATC ACC CCT CAA
Glu Leu Gly Ser Asp Ser Ser Glu Asp Thr Val Asn Lys Ala Thr Tyr Cys Ser Val Gly Asp Gln Glu Leu Leu Gln Ile Thr Pro Gln
181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210

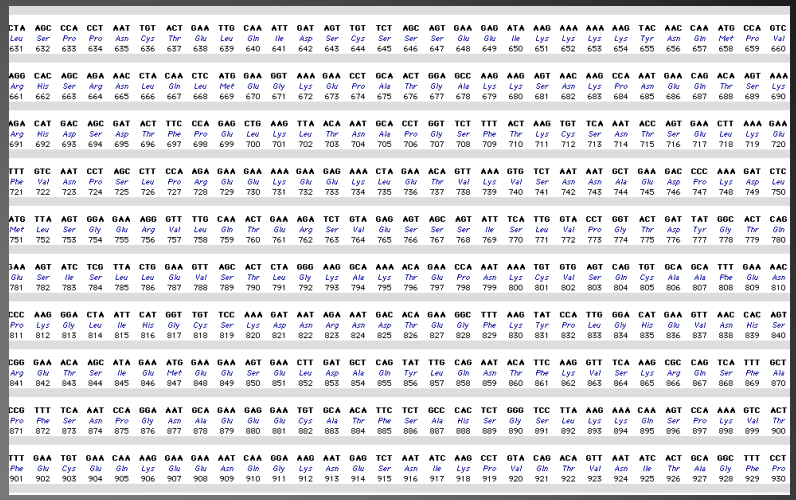
Exon #9 Exon #10

GGA ACC AGG GAT GAA ATC AGT TTG GAT TCT GCA AAA AAG GCT GCT TGT GAA TTT TCT GAG ACG GAT GTA ACA AAT ACT GAA CAT CAT CAA
Gly Thr Arg Asp Glu Ile Ser Leu Asp Ser Ala Lys Lys Ala Ala Cys Glu Phe Ser Glu Thr Asp Val Thr Asn Thr Glu His His Gln
211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240

Exon #11

CCC AGT AAT AAT GAT TTG AAC ACC ACT GAG AAG CGT GCA GCT GAG AGG CAT CCA GAA AAG TAT CAG GGT AGT TCT GTT TCA AAC TTG CAT
Pro Ser Asn Asn Asp Leu Asn Thr Thr Glu Lys Arg Ala Ala Glu Arg His Pro Glu Lys Tyr Gln Gly Ser Ser Val Ser Asn Leu His
241 242 243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270

GTG GAG CCA TGT GGC ACA AAT ACT CAT GCC AGC TCA TTA CAG CAT GAG AAC AGC AGT TTA TTA CTC ACT AAA GAC AGA ATG AAT GTA GAA
Val Glu Pro Cys Gly Thr Asn Thr His Ala Ser Ser Leu Gln His Glu Asn Ser Ser Leu Leu Leu Thr Lys Asp Arg Met Asn Val Glu
271 272 273 274 275 276 277 278 279 280 281 282 283 284 285 286 287 288 289 290 291 292 293 294 295 296 297 298 299 300



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Leu Ser Pro Pro Asn Cys Thr Glu Leu Gln Ile Asp Ser Cys Ser Ser Ser Glu Glu Ile Lys Lys Lys Lys Tyr Asn Gln Met Pro Val
631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657 658 659 660

AGG CAC AGC AGA AAC CTA CAA CTC ATG GAA GGT AAA GAA CCT GCA ACT GGA GCC AAG AAG AGT AAC AAG CCA AAT GAA CAG ACA AGT AAA
Arg His Ser Arg Asn Leu Gln Leu Met Glu Gly Lys Glu Pro Ala Thr Gly Ala Lys Lys Ser Asn Lys Pro Asn Glu Gln Thr Ser Lys
661 662 663 664 665 666 667 668 669 670 671 672 673 674 675 676 677 678 679 680 681 682 683 684 685 686 687 688 689 690

AGA CAT GAC AGC GAT ACT TTC CCA GAG CTG AAG TTA ACA AAT GCA CCT GGT TCT TTT ACT AAG TGT TCA AAT ACC AGT GAA CTT AAA GAA
Arg His Asp Ser Asp Thr Phe Pro Glu Leu Lys Leu Thr Asn Ala Pro Gly Ser Phe Thr Lys Cys Ser Asn Thr Ser Glu Leu Lys Glu
691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720

TTT GTC AAT CCT AGC CTT CCA AGA GAA GAA AAA GAA GAG AAA CTA GAA ACA GTT AAA GTG TCT AAT AAT GCT GAA GAC CCC AAA GAT CTC
Phe Val Asn Pro Ser Leu Pro Arg Glu Glu Lys Glu Glu Lys Leu Glu Thr Val Lys Val Ser Asn Asn Ala Glu Asp Pro Lys Asp Leu
721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750

ATG TTA AGT GGA GAA AGG GTT TTG CAA ACT GAA AGA TCT GTA GAG AGT AGC AGT ATT TCA TTG GTA CCT GGT ACT GAT TAT GGC ACT CAG
Met Leu Ser Gly Glu Arg Val Leu Gln Thr Glu Arg Ser Val Glu Ser Ser Ser Ile Ser Leu Val Pro Gly Thr Asp Tyr Gly Thr Gln
751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780

AAA AGT ATC TCG TTA CTG GAA GTT AGC ACT CTA GGG AAG GCA AAA ACA GAA CCA AAT AAA TGT GTG AGT CAG TGT GCA GCA TTT GAA AAC
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781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800 801 802 803 804 805 806 807 808 809 810

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Pro Lys Gly Leu Ile His Gly Cys Ser Lys Asp Asn Arg Asn Asp Thr Glu Gly Phe Lys Tyr Pro Leu Gly His Glu Val Asn His Ser
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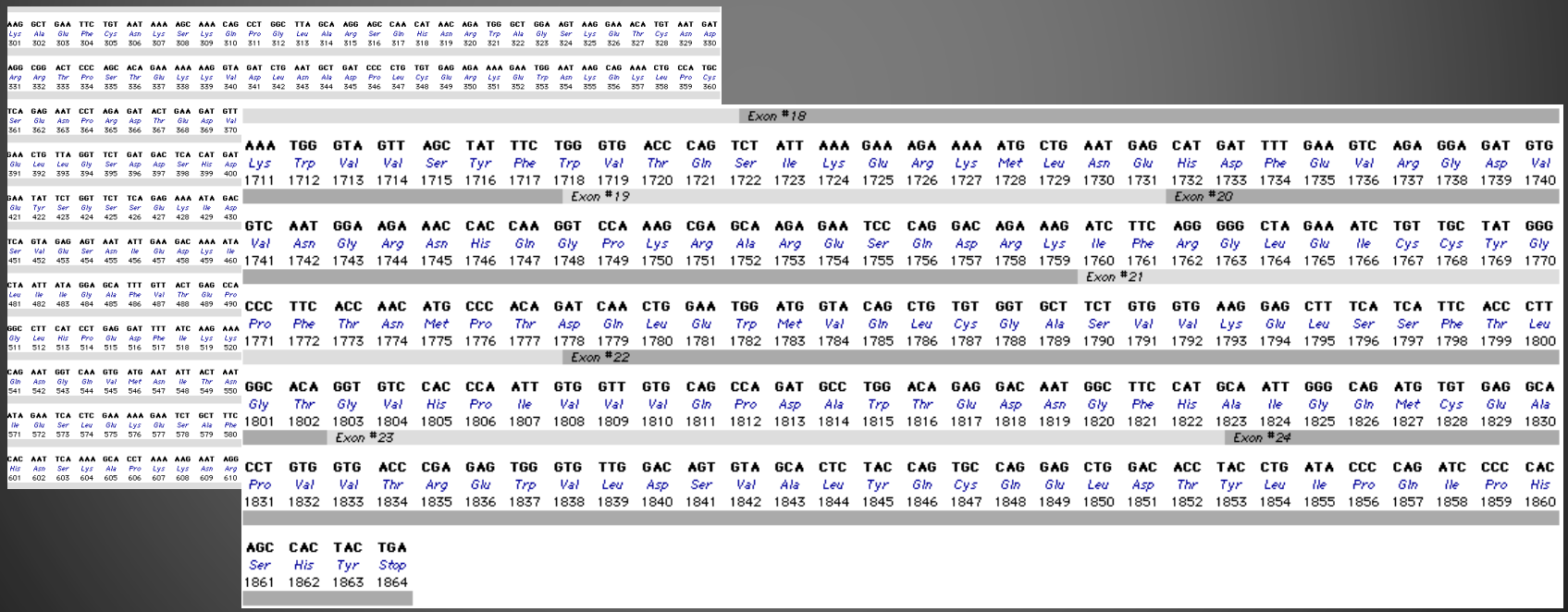

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His Asn Ser Lys Ala Pro Lys Lys Asn Arg
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Exon #18

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1711 1712 1713 1714 1715 1716 1717 1718 1719 1720 1721 1722 1723 1724 1725 1726 1727 1728 1729 1730 1731 1732 1733 1734 1735 1736 1737 1738 1739 1740

Exon #19 Exon #20

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Exon #21

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Exon #22

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Exon #23 Exon #24

CCT GTG GTG ACC CGA GAG TGG GTG TTG GAC AGT GTA GCA CTC TAC CAG TGC CAG GAG CTG GAC ACC TAC CTG ATA CCC CAG ATC CCC CAC
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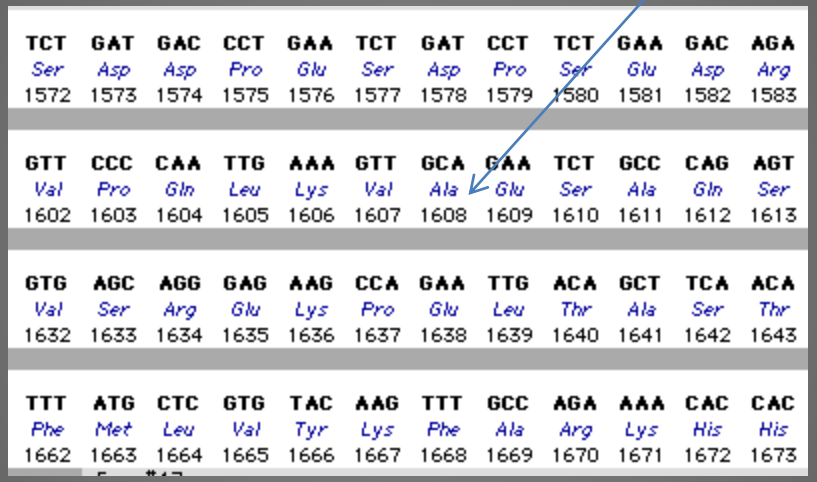
AGC CAC TAC TGA
Ser His Tyr Stop
1861 1862 1863 1864



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1572	1573	1574	1575	1576	1577	1578	1579	1580	1581	1582	1583
GTT	**CCC**	**CAA**	**TTG**	**AAA**	**GTT**	**GCA**	**GAA**	**TCT**	**GCC**	**CAG**	**AGT**
Val	*Pro*	*Gln*	*Leu*	*Lys*	*Val*	*Ala*	*Glu*	*Ser*	*Ala*	*Gln*	*Ser*
1602	1603	1604	1605	1606	1607	1608	1609	1610	1611	1612	1613
GTG	**AGC**	**AGG**	**GAG**	**AAG**	**CCA**	**GAA**	**TTG**	**ACA**	**GCT**	**TCA**	**ACA**
Val	*Ser*	*Arg*	*Glu*	*Lys*	*Pro*	*Glu*	*Leu*	*Thr*	*Ala*	*Ser*	*Thr*
1632	1633	1634	1635	1636	1637	1638	1639	1640	1641	1642	1643
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Phe	*Met*	*Leu*	*Val*	*Tyr*	*Lys*	*Phe*	*Ala*	*Arg*	*Lys*	*His*	*His*
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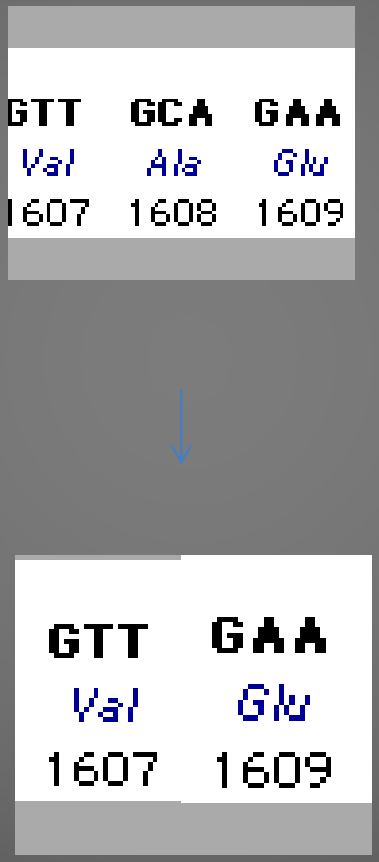
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Val Ala Glu
1607 1608 1609
GTT GAA
Val Glu
1607 1609

Patient DNA

GTT	GAA
Val	Glu
1607	1609

GTT	GCA	GAA
Val	Ala	Glu
1607	1608	1609

NCCN Guidelines 2019

The common question:
Am I Eligible for BRCA testing?

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Breast and/or Ovarian Cancer Genetic Assessment

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CRITERIA FOR FURTHER GENETIC RISK EVALUATION[a]

- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene within the family, including such variants found on research testing[b]
- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene found on tumor testing (See BR/OV-A 3 of 3)
- An individual diagnosed at any age with any of the following:
  - Ovarian cancer[c]
  - Pancreatic cancer
  - Metastatic prostate cancer[d]
  - Breast cancer or high-grade (Gleason score ≥7) prostate cancer and of Ashkenazi Jewish ancestry
- An individual with a breast cancer diagnosis meeting any of the following:
  - Breast cancer diagnosed age ≤50 y
  - Triple-negative (ER-, PR-, HER2-) breast cancer diagnosed age ≤60 y
  - Two breast cancer primaries[e]
  - Breast cancer at any age, and
    - ≥1 close blood relative[f] with:
      - breast cancer age ≤50 y; or
      - invasive ovarian cancer[c]; or
      - male breast cancer; or
      - pancreatic cancer; or
      - high-grade (Gleason score ≥7) or metastatic prostate cancer[d]
    - ≥2 close blood relatives[f] with breast cancer at any age

- An individual who does not meet the above criteria but has a first- or second-degree relative with any of the following:[g]
  - Breast cancer ≤45 y
  - Ovarian[b] cancer
  - Male breast cancer
  - Pancreatic cancer
  - Metastatic prostate cancer[d]
  - ≥2 breast cancer primaries in a single individual
  - ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 y
- An individual with a personal and/or family history on the same side of the family of three or more of the following (especially if diagnosed age ≤50 y; can include multiple primary cancers in same individual):[g]
  - breast cancer, sarcoma, adrenocortical carcinoma, brain tumor, leukemia (see LIFR-1),
  - colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations,[h] macrocephaly, or hamartomatous polyps of gastrointestinal (GI) tract (see COWD-1),
  - lobular breast cancer, diffuse gastric cancer (see CDH1 guidelines, GENE-2),
  - breast cancer, gastrointestinal cancer or hamartomatous polyps, ovarian sex chord tumors, pancreatic cancer, testicular sertoli cell tumors, or childhood skin pigmentation (see STK11 guidelines, GENE-4)

The common question:
Am I Eligible for BRCA testing?

National Comprehensive Cancer Network®

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CRITERIA FOR FURTHER GENETIC RISK EVALUATION[a]

- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene within the family, including such variants found on research testing[b]
- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene found on tumor testing (See BR/OV-A 3 of 3)
- An individual diagnosed at any age with any of the following:
  - Ovarian cancer[c]
  - Pancreatic cancer
  - Metastatic prostate cancer[d]
  - Breast cancer or high-grade (Gleason score ≥7) prostate cancer and of Ashkenazi Jewish ancestry
- An individual with a breast cancer diagnosis meeting any of the following:
  - Breast cancer diagnosed age ≤50 y
  - Triple-negative (ER-, PR-, HER2-) breast cancer diagnosed age ≤60 y
  - Two breast cancer primaries[e]
  - Breast cancer at any age, and
    - ≥1 close blood relative[f] with:
      - breast cancer age ≤50 y; or
      - invasive ovarian cancer[c]; or
      - male breast cancer; or
      - pancreatic cancer; or
      - high-grade (Gleason score ≥7) or metastatic prostate cancer[d]
    - ≥2 close blood relatives[f] with breast cancer at any age

- An individual who does not meet the above criteria but has a first- or second-degree relative with any of the following:[g]
  - Breast cancer ≤45 y
  - Ovarian[b] cancer
  - Male breast cancer
  - Pancreatic cancer
  - Metastatic prostate cancer[d]
  - ≥2 breast cancer primaries in a single individual
  - ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 y
- An individual with a personal and/or family history on the same side of the family of three or more of the following (especially if diagnosed age ≤50 y; can include multiple primary cancers in same individual):[g]
  - breast cancer, sarcoma, adrenocortical carcinoma, brain tumor, leukemia (see LIFR-1),
  - colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations,[h] macrocephaly, or hamartomatous polyps of gastrointestinal (GI) tract (see COWD-1),
  - lobular breast cancer, diffuse gastric cancer (see CDH1 guidelines, GENE-2),
  - breast cancer, gastrointestinal cancer or hamartomatous polyps, ovarian sex chord tumors, pancreatic cancer, testicular sertoli cell tumors, or childhood skin pigmentation (see STK11 guidelines, GENE-4)

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BRCA-Related Breast and/or Ovarian Cancer Syndrome

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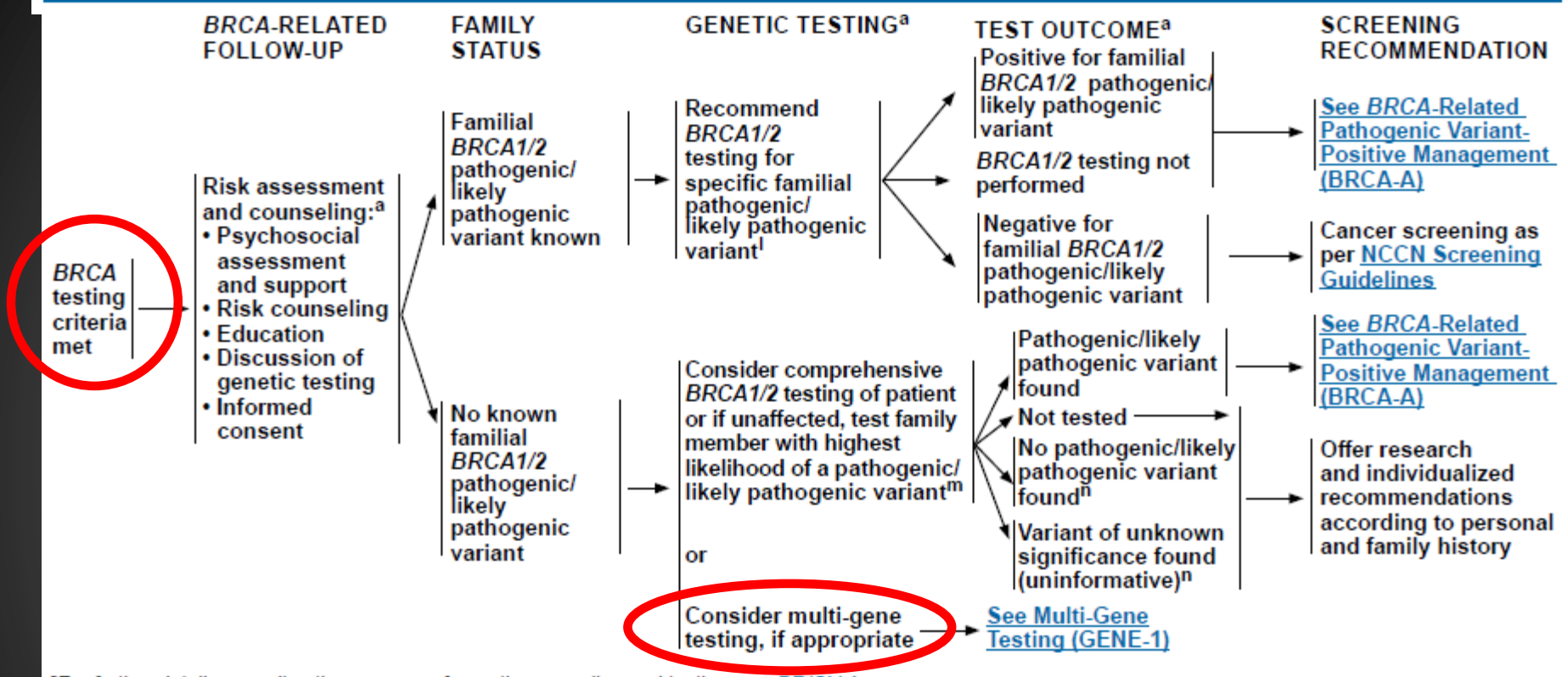

[a]For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.

[l]If of Ashkenazi Jewish descent, in addition to the specific familial pathogenic/likely pathogenic variant, test for all three founder pathogenic/likely pathogenic variants. Additional testing may be indicated if there is also a significant family history of cancer on the side of the family without the known pathogenic/likely pathogenic variant.

[m]For both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial pathogenic/likely pathogenic variant, first test for the three common pathogenic variants. Then, if negative for the three pathogenic/likely pathogenic variants and ancestry also includes non-Ashkenazi Jewish relatives or other *BRCA*-related criteria are met, consider comprehensive genetic testing. For both affected and unaffected individuals who are non-Ashkenazi Jewish and who have no known familial pathogenic/likely pathogenic variants, comprehensive genetic testing is the approach, if done.

[n]If no pathogenic/likely pathogenic variant is found, consider testing another family member with next highest likelihood of having a pathogenic/likely pathogenic variant and/or other hereditary breast/ovarian cancer syndromes such as Li-Fraumeni (LIFR-1) and/or Cowden syndrome (COWD-1) or multi-gene testing (GENE-1). For additional information on other genetic pathogenic/likely pathogenic variants associated with breast/ovarian cancer risk for which genetic testing is clinically available, see GENE-2.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BRCA1/BRCA2 and Other Genes are recommended

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Genetic/Familial High-Risk Assessment: Breast and Ovarian

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BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Potential increase in ovarian cancer risk, with insufficient evidence for recommendation of RRSO**	Unknown or insufficient evidence for pancreas or prostate cancer
	Comments: Insufficient evidence to recommend against radiation therapy. Counsel for risk of autosomal recessive condition in offspring.		
BARD1	**Potential increase in breast cancer risk, with insufficient evidence for management recommendations**	**Unknown or insufficient evidence for ovarian cancer risk**	N/A
BRCA1	**Increased risk of breast cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Increased risk of ovarian cancer** • See *BRCA* Pathogenic Variant-Positive Management	Prostate cancer • See *BRCA* Pathogenic Variant-Positive Management
BRCA2	**Increased risk of breast cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Increased risk of ovarian cancer** • See *BRCA* Pathogenic Variant-Positive Management	Pancreas, Prostate, Melanoma • See *BRCA* Pathogenic Variant-Positive Management
BRIP1	**Unknown or insufficient evidence**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *BRIP1* appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
CDH1	**Increased risk of lobular breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 30 y[f,g] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	Diffuse gastric cancer • See NCCN Guidelines for Gastric Cancer: Principles of Genetic Risk Assessment for Gastric Cancer

RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Footnotes on GENE-5

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BRCA1/BRCA2 and Other Genes are recommended

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BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a-d]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
CHEK2	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 40 y[f,g] • RRM: Evidence insufficient, manage based o family history	**No increased risk of ovarian cancer**	Colon • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
	Comments: Risk data are based only on frameshift pathogenic/likely pathogenic variants. The risks for most missense variants are unclear but for some pathogenic/likely pathogenic variants, such as Ile157Thr, the risk for breast cancer appears to be lower. Management should be based on best estimates of cancer risk for the specific pathogenic/likely pathogenic variant.		
MSH2, MLH1, MSH6, PMS2, EPCAM	**Unknown or insufficient evidence for breast cancer risk[g]** • Manage based on family history	**Increased risk of ovarian cancer** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	**Colon, Uterine, Others** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
NBN	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 40 y[f,g] • RRM: Evidence insufficient, manage based o family history	**Unknown or insufficient evidence for ovarian cancer risk**	Unknown or insufficient evidence
	Comments: Management recommendations are based on data derived from the 657del5 Slavic truncating pathogenic/likely pathogenic variant. Although risks for other pathogenic/likely pathogenic variants have not been established it is prudent to manage patients with other truncating pathogenic/likely pathogenic variants similarly to those with 657del5. Counsel for risk of autosomal recessive condition in children.		
NF1	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis starting at age 30 y and consider breast MRI with contrast from ages 30–50 y[f,g] • RRM: Evidence insufficient, manage based o family history	**No increased risk of ovarian cancer**	• Malignant peripheral nerve sheath tumors, GIST, others • Recommend referral to *NF1* specialist for evaluation and management
	Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Screening recommendations only apply to individuals with a clinical diagnosis of NF. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.		

RRM: Risk-reducing mastectomy

Footnotes on GENE-5

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

BRCA1/BRCA2 and Other Genes are recommended

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BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a-d]

The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
PALB2	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Unknown or insufficient evidence for ovarian cancer risk**	Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal rece sive condition in offspring.		
PTEN	**Increased risk of breast cancer** • See Cowden Syndrome Management	**No increased risk of ovarian cancer**	See Cowden Syndrome Management
RAD51C	**Unknown or insufficient evidence for breast cancer risk**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Counsel for risk of autosomal rece sive condition in offspring. Based on estimates fro available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants *RAD51C* appears to be sufficient to justify consi eration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age f this procedure. Based on the current, limited evi ence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific fam y history of an earlier onset ovarian cancer.		
RAD51D	**Unknown or insufficient evidence for breast cancer risk**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carrie s of pathogenic/likely pathogenic variants in *RAD51D* appears to be sufficient to justify consideration of RRSO The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around a e 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
STK11	**Increased risk of breast cancer** • Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal • RRM: Evidence insufficient, manage based on family history	**Increased risk of non-epithelial ovarian cancer** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
TP53	**Increased risk of breast cancer** • See Li-Fraumeni Syndrome Management	**No increased risk of ovarian cancer**	See Li-Fraumeni Syndrome Management

Footnotes on GENE-5

RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

WOMEN

- Breast awareness[1] starting at age 18 y.
- Clinical breast exam, every 6–12 mo,[2] starting at age 25 y.
- Breast screening[3,4]
  - Age 25–29 y, annual breast MRI[5] screening with contrast[6] (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
  - Age 30–75 y, annual mammogram with consideration of tomosynthesis and breast MRI[5] screening with contrast.
  - Age >75 y, management should be considered on an individual basis.
  - For women with a *BRCA* pathogenic/likely pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram and breast MRI should continue as described above.
- Discuss option of risk-reducing mastectomy
  - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
- Recommend risk-reducing salpingo-oophorectomy (RRSO), typically between 35 and 40 y, and upon completion of child bearing. Because ovarian cancer onset in patients with *BRCA2* pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with *BRCA1* pathogenic/likely pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 y in patients with *BRCA2* pathogenic/likely pathogenic variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery. See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer - Principles of Surgery.
  - Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone replacement therapy, and related medical issues.
  - Salpingectomy alone is not the standard of care for risk reduction, although clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy likely reduces the risk of developing breast cancer but the magnitude is uncertain and may be gene-specific.
- Limited data suggest that there may be a slightly increased risk of serous uterine cancer among women with a *BRCA1* pathogenic/likely pathogenic variant. The clinical significance of these findings is unclear. Further evaluation of the risk of serous uterine cancer in the *BRCA* population needs to be undertaken. The provider and patient should discuss the risks and benefits of concurrent hysterectomy at the time of RRSO for women with a *BRCA1* pathogenic/likely pathogenic variant prior to surgery.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.
- For those patients who have not elected RRSO, transvaginal ultrasound combined with serum CA-125 for ovarian cancer screening, although of uncertain benefit, may be considered at the clinician's discretion starting at age 30–35 y.
- Consider risk reduction agents as options for breast and ovarian cancer, including discussing risks and benefits (See Discussion for details). (See NCCN Guidelines for Breast Cancer Risk Reduction).
- Consider investigational imaging and screening studies, when available (eg, novel imaging technologies, more frequent screening intervals) in the context of a clinical trial.

Footnotes on next page (BRCA-A 2 of 2)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

Thanks