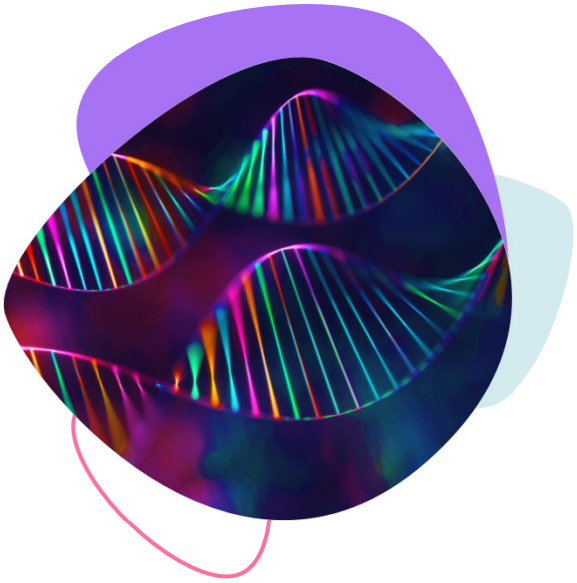
Somatic vs. Germline Mutations



Their Differences and Importance in Cancer Care

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Disclosures

- No financial disclosures.

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Objectives

1st Describe the difference between “somatic” and “germline” mutations

2nd Identify when a somatic mutation may be indicative of a germline mutation

3rd Recognize how both somatic and germline mutations can have implications for patients and their cancer treatment plans

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“What does ‘somatic’ or ‘germline’ mean?”

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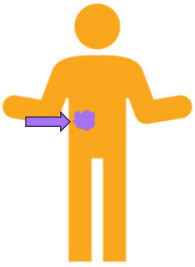
Germline: DNA that represents the DNA you are born with, in all your cells, that can be passed down offspring

Somatic: DNA that represents the tumor's DNA, often acquired changes, <u>not</u> passed down to offspring



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"How do I know if a genetic variant is somatic or germline?"

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Gene(s) Altered

Germline

More likely to be germline

BRCA1/2
MSH2/6
PALB2
RAD51C/D
Founder mutations

Somatic

More likely to be somatic

APC	CDKN2A	EGFR
MEN1	NF1/2	PTEN
RB1	RET	STK11
TP53	TSC1	VHL

Meric-Bernstam et al., 2016; Lincoln et al., 2020

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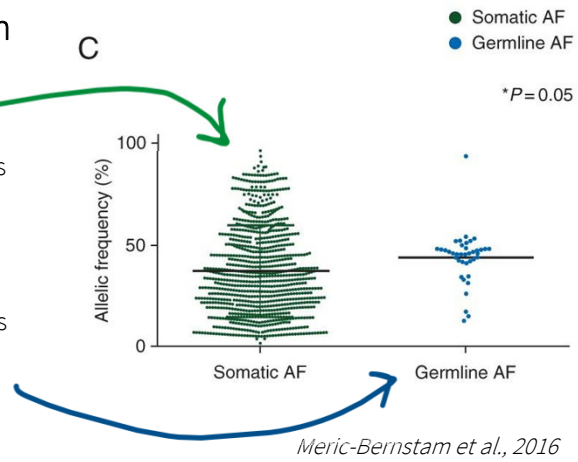
Variant Allele Frequency (VAF)

- VAF = % of cells with that mutation
  - Somatic = ~33.4%
    - Range = 1.2% - 96.5%
    - Influenced by proportion of tumor cells in the sample
  - Germline = close to 50%
    - Range = 13% – 93.9%
    - Anywhere from 20% - 60% is suspicious and often warrants a referral



Meric-Bernstam et al., 2016

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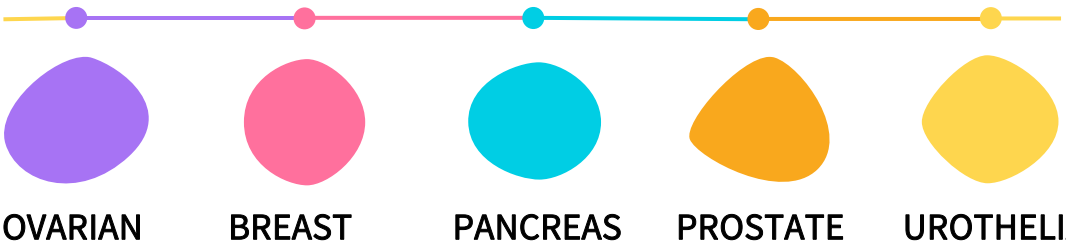
Cancer Type



Lincoln et al., 2020; Yap et al., 2022

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How does germline or somatic testing impact the patient?

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Cancer Treatment

- Targeted Therapies
  - Somatic testing helps to identify patients that would respond to targeted therapy
  - Molecular targets can provide improved outcomes
- Clinical Trials
  - Somatic and germline testing helps to identify patients that are eligible for certain clinical trials
- Surgical Options
  - Germline testing helps to identify patients that may be candidates for a different surgery if they have a hereditary cancer syndrome that places them at a high risk to develop cancer again

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Impact for Family Members

Germline

Often inherited and can be passed down

- 50% chance for first-degree relatives to test positive
- Impacts their cancer risks and screening recommendations
- May impact family planning options

Somatic

Not inherited/passed down

- No testing needed for relatives

Meric-Bernstam et al., 2016; Lincoln et al., 2020

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Case Examples

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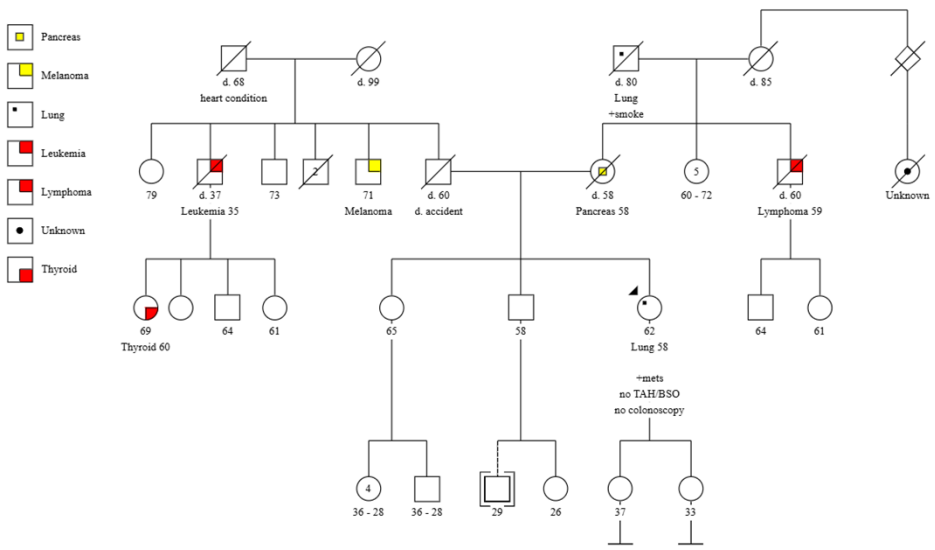
Metastatic Lung Cancer



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Tumor Results

Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

KEY ✓ Approved in indication ◌ Approved in other indication ⊗ Lack of response

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 4)	% cfDNA or Amplification
BRAF V600E	✓ Dabrafenib + trametinib ◌ Binimetinib, Cobimetinib, Dabrafenib, Encorafenib+binimetinib, Trametinib, Vemurafenib, Vemurafenib+cobimetinib	Yes	0.3%
BRCA2 R3128*	◌ Olaparib, Talazoparib	Yes	48.8%

Variants of Uncertain Clinical Significance
PIK3CA K711N (0.1%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Comments
The BRCA2 R3128* (c.9382C>T) alteration was detected in this patient's sample at an allele fraction suspicious for germline origin. This variant may lead to the loss of functional protein, and similar variants have been associated with hereditary predisposition to cancer. As Guardant360 is neither intended nor validated for the reporting or interpretation of germline variants, we cannot confirm the germline vs. somatic origin of this finding and recommend verification with an assay validated for germline testing if this potential incidental finding is of clinical interest.

somatic

suspicious for germline

Uncertain, low %

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Case Examples – Germline Results

BRCA1/2 Analyses with CustomNext-Cancer® +RNAinsight®

RESULTS

BRCA2 Pathogenic Mutation: p.R3128*

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **p.R3128* (c.9382C>T)** pathogenic mutation in the *BRCA2* gene.
- This result is consistent with a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome.
- **Risk estimate**: increased lifetime risks for female breast cancer (45-69%), ovarian cancer (13-29%), male breast cancer (1.8-7.1%), pancreatic cancer (5-10%) and prostate cancer (19-61%); increased risk for melanoma.
- The expression and severity of disease for this individual cannot be predicted.
- Genetic testing for pathogenic mutations in family members can be helpful in identifying at-risk individuals.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

No additional pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected. Genes Analyzed (83 total): ***AIP, ALK, APC, ATM, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CHEK2, DICER1, FANCC, FH, FLCN, GALNT12, KIF1B, LZTR1, MAX, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PHOX2B, PMS2, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RECQL, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL*** **and** ***XRCC2*** **(sequencing and deletion/duplication);** ***AXIN2, CASR, CFTR, CPA1, CTNNA1, CTRC, EGFR, EGLN1, HOXB13, KIT, MITF, MSH3, PDGFRA, POLD1, POLE, PRSS1*** **and** ***SPINK1*** **(sequencing only);** ***EPCAM*** **and** ***GREM1*** **(deletion/duplication only)**. RNA data is routinely analyzed for use in variant interpretation for all genes.

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Treatment

Somatic *BRCA2* mutation

- PARP inhibitor therapy candidate (Olaparib and talazoparib)
- Clinical trial eligibility

Germline *BRCA2* mutation

- **Breast Cancer (Female):** 55-69% lifetime risk –discussion about risk-reducing mastectomies
- **Breast Cancer (Males):** 1.8-7.1%
- **Ovarian Cancer:** 13-29% - discussion about surgical removal of ovaries
- **Pancreatic Cancer**: 5-10% - eligible for pancreas cancer screening
- **Prostate Cancer**: 19-61% for males
- **Melanoma**: Increased – discussion about annual derm

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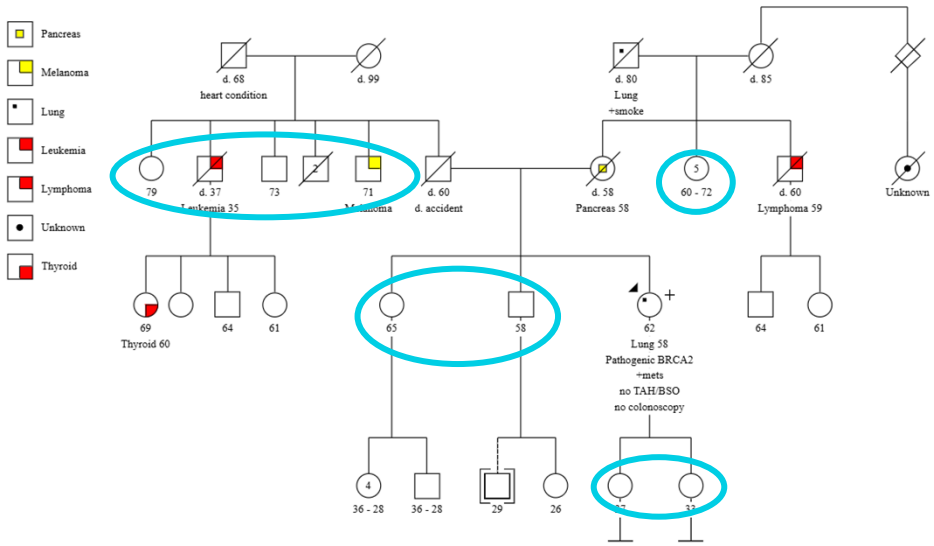
Testing Relatives



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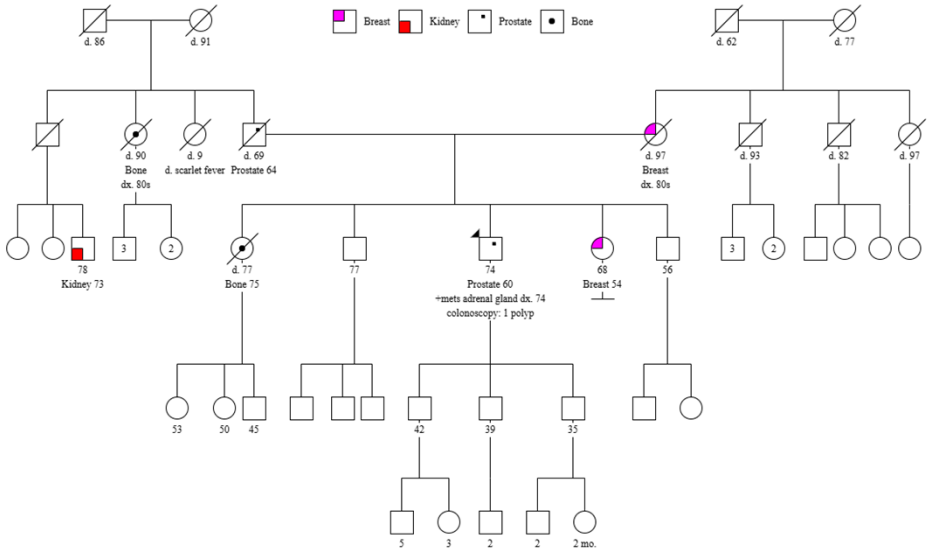
Metastatic Prostate Cancer



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Tumor Results

Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
ATM	Seq	DNA-Tumor	Pathogenic Variant Exon 36 | p.E1822fs	BENEFIT	talazoparib + enzalutamide olaparib	Level 2

Genes Tested with Pathogenic or Likely Pathogenic Alterations

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
AR	Seq	RNA-Tumor	V7 Detected	-	3	-	-
ATM	Seq	DNA-Tumor	Pathogenic Variant	p.E1822fs	36	c.5465_5490del26	18
ETV5	Seq	RNA-Tumor	Pathogenic Fusion	EP300-ETV5	6	-	-
MCL1	CNA-Seq	DNA-Tumor	Amplified	-	-	-	-

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
CHEK2	DNA-Tumor	Variant of Uncertain Significance	p.D438N	12	c.1312G>A	49	NM_007194.3

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Case Examples – Germline Results

BRCA1/2 Analyses with CancerNext-Expanded®: Analyses of Genes Associated with Hereditary Cancer (76 genes)

RESULTS

CHEK2 Variant, Unknown Significance: p.D438N

SUMMARY

Variant of Unknown Significance Detected

INTERPRETATION

- **No known clinically actionable alterations were detected.**
- One variant of unknown significance was detected in the *CHEK2* gene.
- **Risk Estimate:** should be based on clinical and family history, as the clinical significance of this result is unknown.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

This individual is heterozygous for the p.D438N (c.1312G>A) variant of unknown significance in the *CHEK2* gene, which may or may not contribute to this individual's clinical history. Refer to the supplementary pages for additional information on this variant. No additional pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected. Genes Analyzed (76 total): ***AIP, ALK, APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CEBPA, CHEK2, DICER1, ETV6, FH, FLCN, GATA2, LZTR1, MAX, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NF1, NF2, NTHL1, PALB2, PHOX2B, PMS2, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL*** and ***WT1*** **(sequencing and deletion/duplication);** ***AXIN2, CTNNA1, DDX41, EGFR, HOXB13, KIT, MBD4, MITF, MSH3, PDGFRA, POLD1*** and ***POLE*** **(sequencing only);** ***EPCAM*** and ***GREM1*** **(deletion/duplication only).**

- *CHEK2*– not on our gene list
- Pers hx of prostate ca and fam hx of breast ca – fits with *CHEK2* gene
- Classified as "uncertain" by another germline lab

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Treatment

Somatic *ATM* mutation

- PARP inhibitor therapy: Talozoparib + enzalutamide or olaparib

Germline *CHEK2* VUS

- No management changes based on variant of uncertain significance

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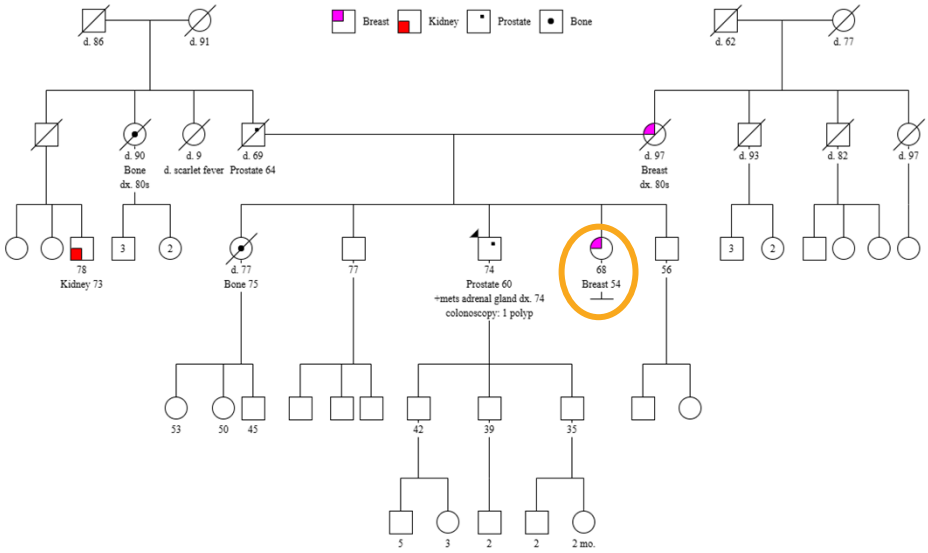
Testing Relatives



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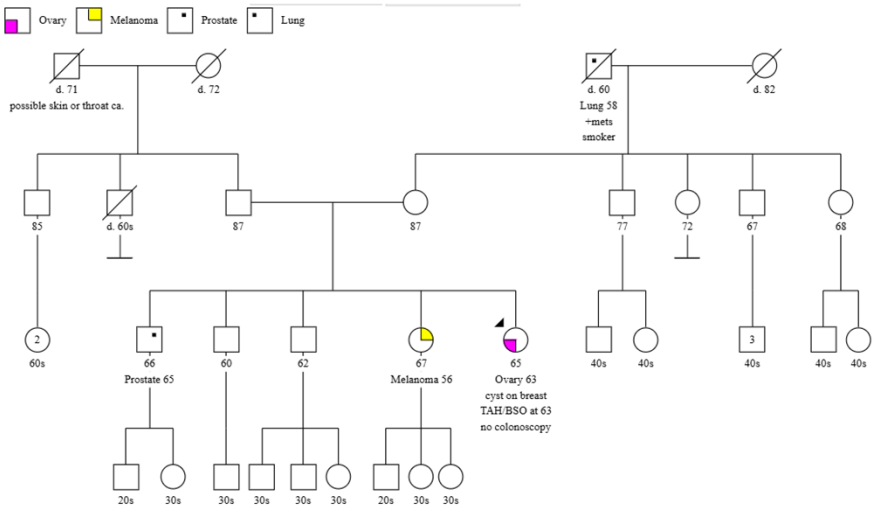
Ovarian Cancer



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Tumor Results

Tumor Mutation *BRCA1/BRCA2* Status: **POSITIVE FOR A CLINICALLY SIGNIFICANT MUTATION**

GENE	CLINICALLY SIGNIFICANT MUTATION(S)	INTERPRETATION
BRCA1	c.5333-1G>A	Suspected Deleterious

NOTE: This result represents findings from all analyzable regions. It may or may not reflect the germline status of this individual. Follow-up germline testing may be appropriate. In addition, the variants listed above may not be present in all tumor cells.

TABLE 1: Companion diagnostic indications

Tumor Type	Biomarker	Therapy
Ovarian Cancer	Myriad HRD, defined as: • deleterious or suspected deleterious mutations in *BRCA1* and *BRCA2* genes and/or • positive Genomic Instability Score	Lynparza® (olaparib)‡

‡ Refer to the drug label for HRD definition for olaparib monotherapy or combination therapy.

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Case Examples – Germline Results

GENETIC RESULT: NEGATIVE - NO CLINICALLY SIGNIFICANT MUTATION IDENTIFIED

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

ADDITIONAL INFORMATION

Genes Analyzed: Unless otherwise noted sequencing and large rearrangement analyses were performed on the following genes:

BRCA1, BRCA2

GENETIC RESULT: POSITIVE - CLINICALLY SIGNIFICANT MUTATION IDENTIFIED

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

CLINICAL HISTORY ANALYSIS: BASED ON THE CLINICAL HISTORY PROVIDED, MODIFIED MEDICAL MANAGEMENT GUIDELINES IDENTIFIED

Other clinical factors may influence individualized management. This analysis may be incomplete if details about cancer diagnoses, ages, family relationships or other factors were omitted or ambiguous. If this patient also has a clinically significant mutation, the recommendations based on the clinical history analysis should be considered in light of the possibility that this mutation explains all or some of the cancer history in the family.

GENE	MUTATION	INTERPRETATION
ATM	c.103C>T (p.Arg35*) Heterozygous	High Risk This patient has *ATM*-associated cancer risk.

DETAILS ABOUT: *ATM* c.103C>T (p.Arg35*): NM_000051.3

Functional Significance: Deleterious - Abnormal Protein Production and/or Function

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Treatment

Somatic *BRCA1* mutation

- PARP inhibitor therapy candidate (olaparib)

Germline *ATM* mutation

- **Breast Cancer:** 21-24% lifetime risk - Qualifies for high-risk breast screening
- **Ovarian Cancer:** 2-3%
- **Pancreatic Cancer:** 5-10% - eligible for discussion of pancreas cancer screening
- **Colorectal Cancer:** 5-10%
- **Prostate Cancer:** Increased for males

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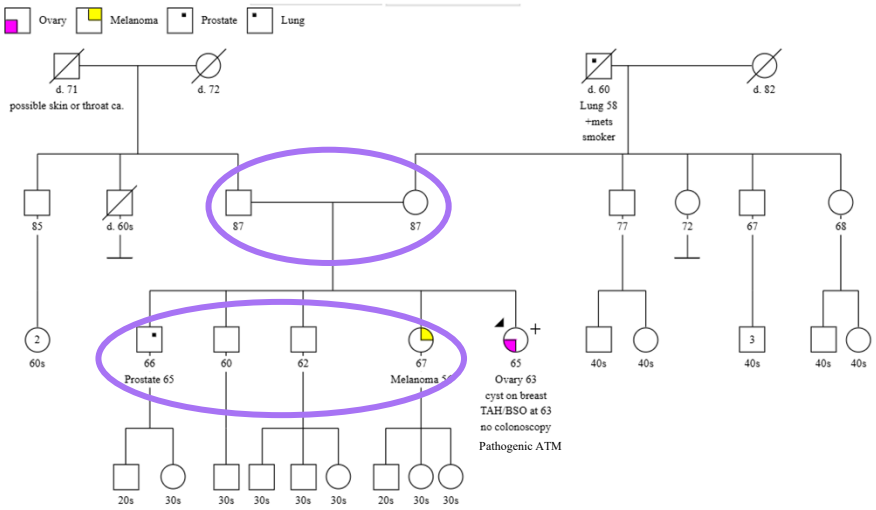
Testing Relatives



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Takeaways

1. Somatic = tumor DNA vs. Germline = all cells/born with DNA
2. The gene, VAF, and cancer type can all be clues to know if a somatic mutation is indicative of a germline one
3. Both somatic and germline testing play a role in cancer treatment
4. Never hesitate to reach out to your genetic counselor with questions! ☺

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References

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Thank you!

Questions?

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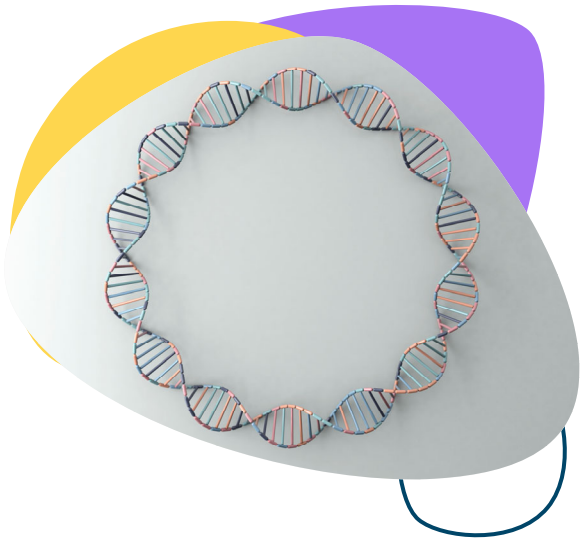

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