# Clinician Considerations: Perspectives for High-Risk Patient Management

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# Disclosure/Conflict of Interest

The following have nothing to disclose:

- Amanda Bond, PA-C, MPAS
- Molly Johnson, MSN, AOCNP-BC

The following has disclosed a relevant financial relationship:

- Rachael Schmidt, DNP, FNP, AOCNP
  Research: Daiichi-Sankyo Company, Limited

# Agenda

CLINICAL CONSIDERATIONS

GUIDELINE UPDATES

CASE PRESENTATIONS WITH DISCUSSION

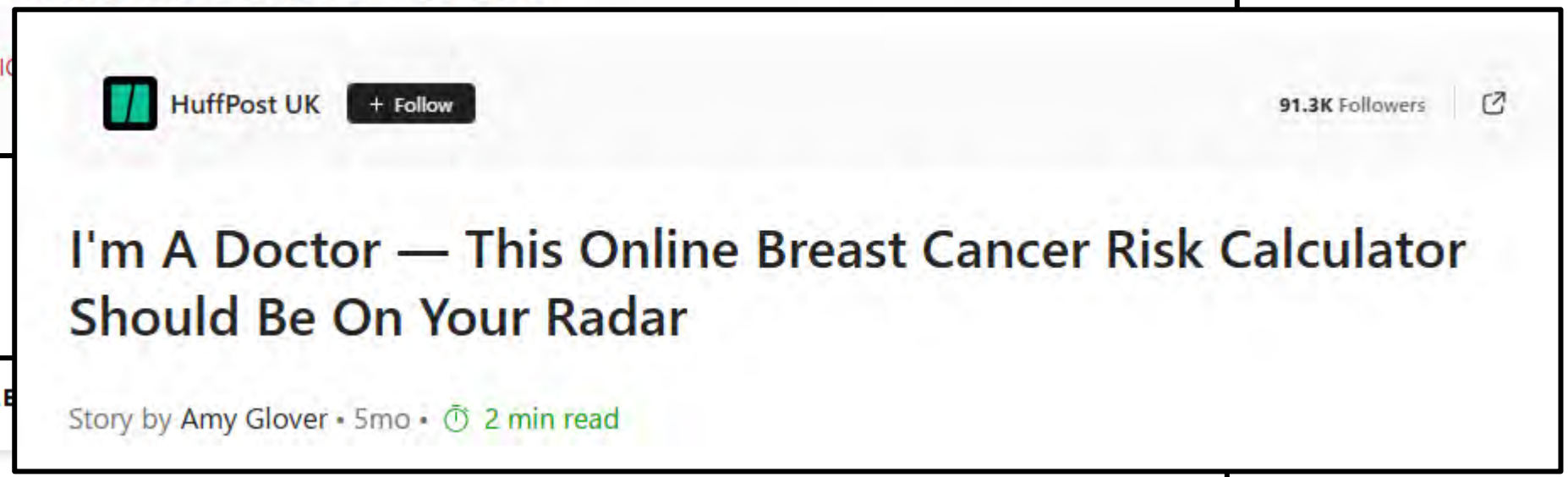

Forbes

LEADERSHIP

# Screening Saves Lives: Working Together To Promote Early Cancer Detection

By American Cancer Society, BRANDVOI

Apr 14, 2025, 09:14am EDT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# I'm A Doctor — This Online Breast Cancer Risk Calculator Should Be On Your Radar

Story by Amy Glover • 5mo • 2 min read


People ENTERTAINMENT CRIME

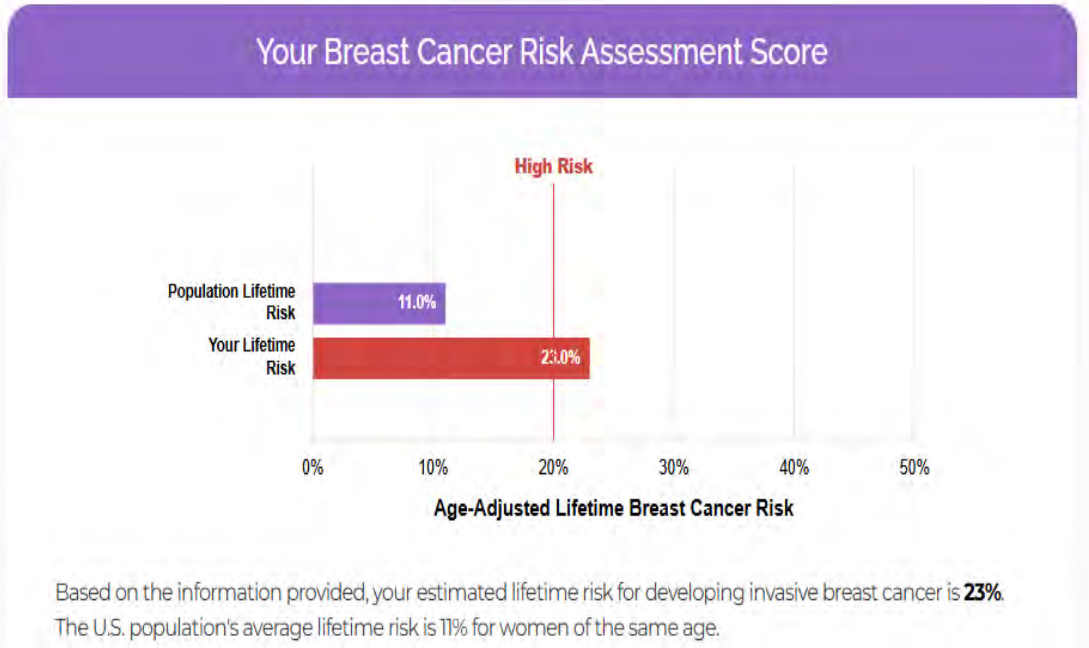
LIFESTYLE > HEALTH > CELEBRITY HEALTH

# What Olivia Munn's Doctor Wants You to Know About Your Breast Cancer Risk Assessment Score (Exclusive)

# TC Considerations

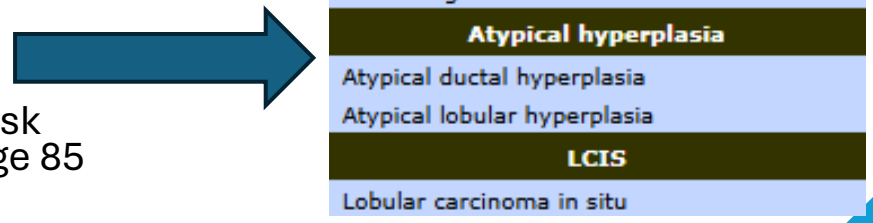
What is the Tyrer-Cuzick Model?

- Incorporates personal, familial, and hormonal factors
- Estimates 10-year and remaining lifetime breast cancer risk
- Used to determine eligibility for:
  - High-risk screening (MRI)
  - Risk-reducing medications
  - Genetic counseling referrals
- Why does TC score change when calculated by different providers/platforms? Potential for "user error"...



# Limitations of Tyrer-Cuzick (TC)

- Does not incorporate moderate penetrance breast cancer genes (ATM, PALB2, CHEK2, etc)
- May overestimate risk with atypical hyperplasia/LCIS and dense breast tissue
- May not perform well with "true negative"
- “User errors”
  - if unaffected family members are not entered in the risk model, it can lead to an overestimation of risk
  - does not account for competing mortality in the risk assessment unless selected by the user
  - Selecting incorrect benign breast risk category
- May not be as helpful to qualify older women for high-risk screening with MRI because it gives remaining risk to age 85 (not total lifetime risk)
- Developed based on data primarily in non-Hispanic White women; may overestimate risk in Hispanic women, especially if not US born.



# Common Discussions with Patients

# Borderline High Risk

- Clinical judgment becomes essential:
  - Dense breast tissue
  - Family history
  - Additional risk factors not captured in the model
  - Insurance/financial toxicity
  - Important to discuss uncertainties and tailor recommendations

# Risk-Benefit Discussion Framework

**Benefits of MRI screening:**

- Higher sensitivity, especially in dense breasts
- Can detect cancers missed by mammography

**Risks/downsides:**

- False positives, unnecessary biopsies
- Cost/insurance coverage
- Patient anxiety
- Contrast agent (gadolinium) exposure

**Why this conversation matters:**

- Helps patients make informed, values-based decisions
- Builds trust and engagement in long-term screening plans

# “What’s new in the guidelines?”

Genetic/Familial High-Risk Assessment V.2025

# Chek2
## Colorectal, Endometrial, Gastric (Aug 2024)

- The panel now suggests there is **no increased risk for colon cancer**
- The recommendation is to follow general population screening for all Chek2 with no Family History CRC or Hx of colon polyps

**Attenuated Breast Cancer Risk** – Pathogenic Missense Variants
- Ile157Thr & Ser428Phe (Added Version 1.2025)
  - High Risk breast screening with MRI, is not recommended.


***CHEK2***

Hanson H, Astiazaran-Symonds E, Amendola LM, et al. Management of individuals with germline pathogenic/likely pathogenic variants in CHEK2: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2023;25:100870.

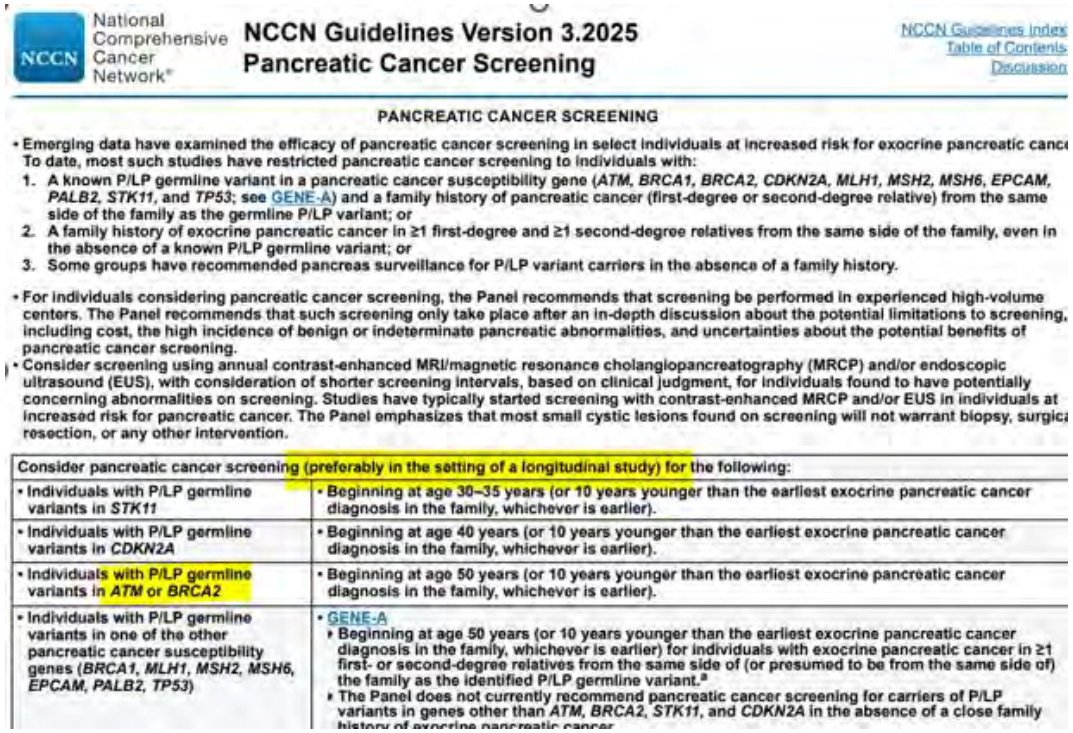
Bychkovsky BL, Agaoglu NB, Horton C, et al. Differences in cancer phenotypes among frequent CHEK2 variants and implications for clinical care-checking CHEK2. JAMA Oncol 2022;8:1598-1606.

Mundt E, Mabey B, Rainville I, et al. Breast and colorectal cancer risks among over 6,000 CHEK2 pathogenic variant carriers: A comparison of missense versus truncating variants. Cancer Genet 2023;278-279:84-90.

Ma X, Zhang B, Zheng W. Genetic variants associated with colorectal-cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. Gut 2014;63:326-336.

Katona BW, Yang YX. Colorectal cancer risk associated with the CHEK2 1100delC variant. Eur J Cancer 2017;83:103-105.

# **BRCA2 & ATM**
# Breast Ovarian Pancreas (Sept 2024)



National Comprehensive Cancer Network®

**NCCN Guidelines Version 3.2025**
**Pancreatic Cancer Screening**

NCCN Guidelines Index
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Discussion

**PANCREATIC CANCER SCREENING**

- Emerging data have examined the efficacy of pancreatic cancer screening in select individuals at increased risk for exocrine pancreatic cancer. To date, most such studies have restricted pancreatic cancer screening to individuals with:
  1. A known P/LP germline variant in a pancreatic cancer susceptibility gene (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11,* and *TP53*; see GENE-A) and a family history of pancreatic cancer (first-degree or second-degree relative) from the same side of the family as the germline P/LP variant; or
  2. A family history of exocrine pancreatic cancer in ≥1 first-degree and ≥1 second-degree relatives from the same side of the family, even in the absence of a known P/LP germline variant; or
  3. Some groups have recommended pancreas surveillance for P/LP variant carriers in the absence of a family history.
- For individuals considering pancreatic cancer screening, the Panel recommends that screening be performed in experienced high-volume centers. The Panel recommends that such screening only take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of benign or indeterminate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening.
- Consider screening using annual contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS), with consideration of shorter screening intervals, based on clinical judgment, for individuals found to have potentially concerning abnormalities on screening. Studies have typically started screening with contrast-enhanced MRCP and/or EUS in individuals at increased risk for pancreatic cancer. The Panel emphasizes that most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention.

| Consider pancreatic cancer screening (preferably in the setting of a longitudinal study) for the following: | |
|---|---|
| • Individuals with P/LP germline variants in *STK11* | • Beginning at age 30–35 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier). |
| • Individuals with P/LP germline variants in *CDKN2A* | • Beginning at age 40 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier). |
| • Individuals with P/LP germline variants in *ATM* or *BRCA2* | • Beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier). |
| • Individuals with P/LP germline variants in one of the other pancreatic cancer susceptibility genes (*BRCA1, MLH1, MSH2, MSH6, EPCAM, PALB2, TP53*) | • GENE-A<br>▸ Beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relatives from the same side of (or presumed to be from the same side of) the family as the identified P/LP germline variant.[a]<br>▸ The Panel does not currently recommend pancreatic cancer screening for carriers of P/LP variants in genes other than *ATM, BRCA2, STK11,* and *CDKN2A* in the absence of a close family history of exocrine pancreatic cancer |

- **BRCA2**
  - All qualify Pancreas Ca screening at 50
- **ATM**
  - All qualify Pancreas Ca screening at 50
  - CRC added, manage based on FH
- BRCA1, MSH2, MLH1, MSH6, EPCAM, PALB2, TP53
  - FH still required to qualify

Goggins M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer: updated 2:51:22 PM. NCCN Guidelines Version 3.2025 Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut **2020**;69:7-17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31672839.

# ctDNA – Multi Cancer Early Detection Hereditary Risk Population

- ctDNA, detected by mutation profile, copy number changes, altered methylation patterns, fragmentation, size alterations, or other approaches, has application for disease monitoring as well as early detection. For individuals at increased hereditary risk for cancer, use of pre-symptomatic ctDNA cancer detection assays should only be offered in the setting of prospective clinical trials, because the sensitivity, false-positive rates, and positive predictive value of ctDNA tests for early-stage disease, which are needed to derive clinical utility and determine clinical validity, are not fully defined.[15-18] The psychological impact of ctDNA testing remains unknown. For these reasons, ctDNA should not be used, outside of the clinical trial setting, to replace well-established methods of cancer screening (eg, mammography).

# What's coming?

| Gene | Breast Cancer[b] | Epithelial Ovarian Cancer[b] | Pancreatic Cancer,[11-20] Prostate Cancer, and Other Cancer Risks |
|---|---|---|---|
| *ATM* | Primary breast cancer<br>• Absolute risk: 21%–24%[3,4]<br>• Management:<br>▸ Screening: Annual mammogram at age 40 y and consider breast MRI with and without contrast starting at age 30–35 y[c,d,e,f]<br>▸ Risk reduction: Evidence insufficient for risk-reducing mastectomy (RRM); manage based on family history<br>• Strength of evidence of association with cancer: Strong<br>Contralateral breast cancer<br>• 10-year cumulative risk: 4%[g,5]<br>• Strength of evidence of association with cancer: Limited | • Absolute risk: 2%–3%[8-10]<br>• Management:<br>▸ Risk reduction: Evidence insufficient for risk-reducing salpingo oophorectomy (RRSO); manage based on family history<br>• Strength of evidence of association with cancer: Strong | Pancreatic cancer<br>• Absolute risk: ~5%–10%[h,21]<br>• Management: Screening, see PANC-A.<br>• Strength of evidence of association with cancer: Strong<br>Prostate cancer<br>• Emerging evidence for association with increased risk.[22] Consider prostate cancer screening starting at age 40 (NCCN Guidelines for Prostate Cancer Early Detection)<br>Colorectal cancer<br>• NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric |
| | Comments: Heterozygous *ATM* P/LP variants should not lead to a recommendation to avoid RT at this time. *ATM* missense c.7271T>G variant is a higher penetrance allele (60% by age 80 y; Goldgar DE, et al. Breast Cancer Res 2011;13:R73; Hall MJ, et al. Cancer Prev Res (Phila) 2021;14:433-440; Southey MC, et al. J Med Genet 2016;53:800-811). See GENE-B for reproductive implications/recessive disease. | | |

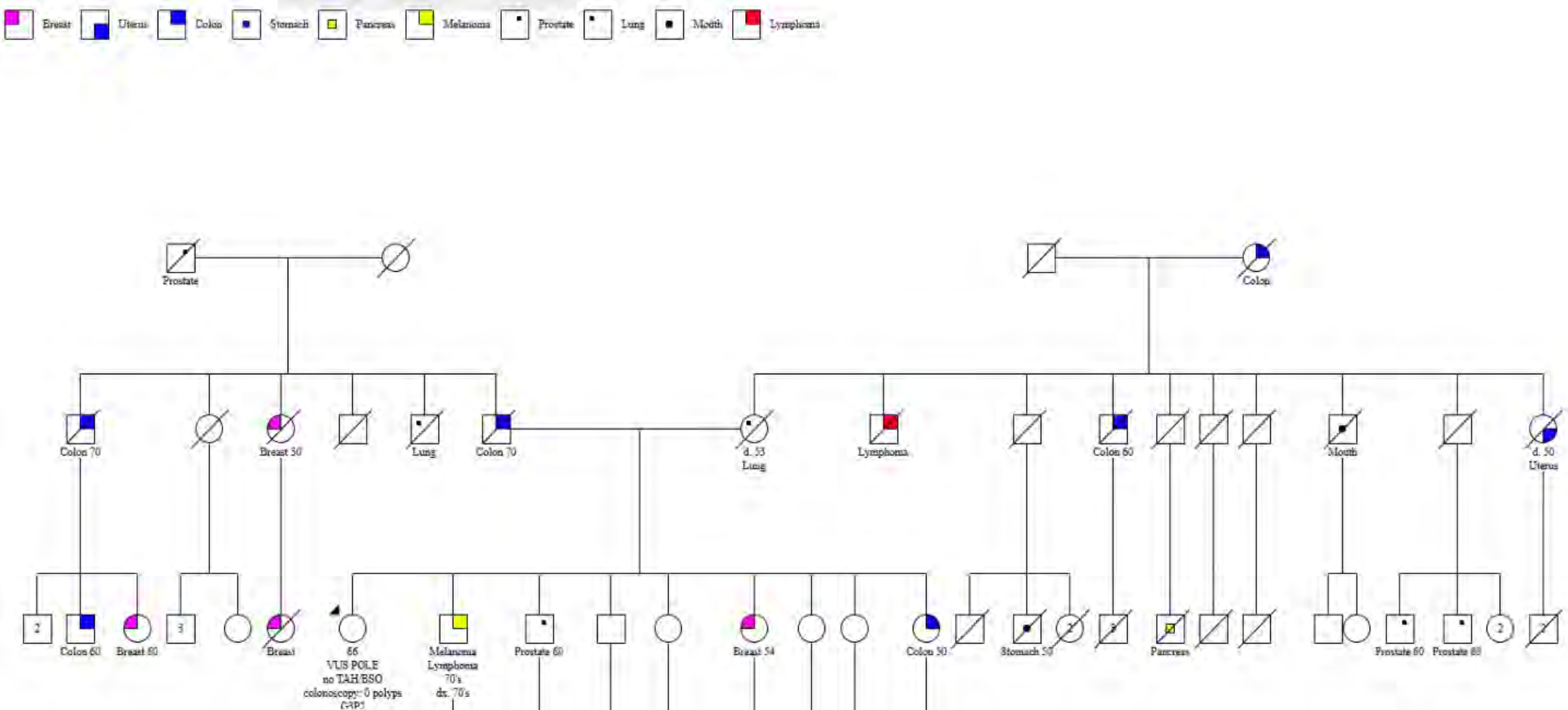
- High penetrance missense ATM c.7271T>G
- No recommendation for management changes yet

# What's coming?

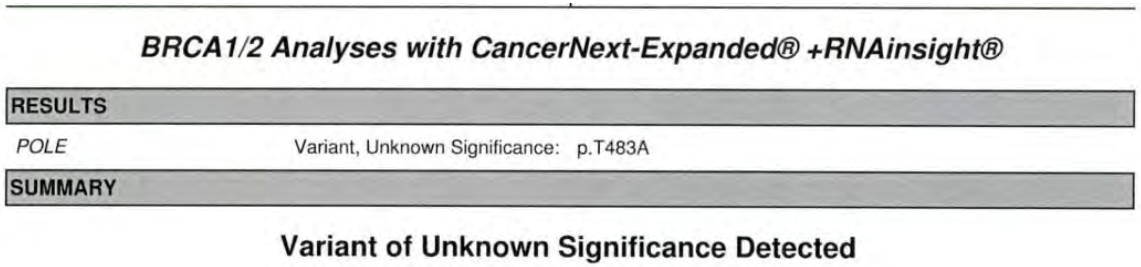
| Gene | Breast Cancer[b] | Epithelial Ovarian Cancer[b] | Pancreatic Cancer,[11-20] Prostate Cancer, and Other Cancer Risks |
|---|---|---|---|
| *BRCA1* | Primary breast cancer<br>• Absolute risk: 60%–72%[23,24]<br>• Management: See *BRCA* Pathogenic Variant-Positive Management<br>• Strength of evidence of association with cancer: Very strong<br>Contralateral breast cancer[i,j]<br>• 20-year cumulative risk: 30%–40%[5,25]<br>• 15-year cumulative risk in premenopausal women: >20%[5,25]<br>• Strength of evidence of association with cancer: Strong<br>Male breast cancer<br>• Absolute risk: 0.2%–1.2% by age 70 y[26,27]<br>• Management: See *BRCA* Pathogenic Variant-Positive Management<br>• Strength of evidence of association with cancer: Strong | • Absolute risk: 39%–58%[29]<br>• Management: See *BRCA* Pathogenic Variant-Positive Management<br>• Strength of evidence of association with cancer: Very strong | Pancreatic cancer<br>• Absolute risk: ≤5%[27]<br>• Management: Screen P/LP variant carriers with a family history of pancreatic cancer, see PANC-A.<br>• Strength of evidence of association with cancer: Strong<br>Prostate cancer<br>• Absolute risk: 7%–26%[30]<br>• Management: See *BRCA* Pathogenic Variant-Positive Management |
| | Comment: See GENE-B for reproductive implications/recessive disease. The risk for breast cancer appears to be lower for the *BRCA1* R1699Q variant (24% by age 70 y) (Spurdle AB, et al. J Med Genet 2012;49:525-532). Screening should be individualized based on personal and family history. | | |

- BRCA1 Low risk Variant
- No recommendation for management changes

# Case 1


Breast
Uterus
Colon
Stomach
Pancreas
Melanoma
Prostate
Lung
Mouth
Lymphoma
Prostate
Colon
Colon 70
Breast 50
Lung
Colon 70
d. 53
Lung
Lymphoma
Colon 60
Mouth
d. 50
Uterus
2
Colon 60
Breast 60
3
Breast
66
VUS POLE
no TAH/BSO
colonoscopy: 0 polyps
Melanoma
Lymphoma
70's
dx. 70's
Prostate 60
Breast 54
Colon 50
Stomach 50
Pancreas
Prostate 60
Prostate 60
2

# Do not base clinical recommendations on a genetic result alone



*BRCA1/2 Analyses with CancerNext-Expanded® +RNAinsight®*

**RESULTS**

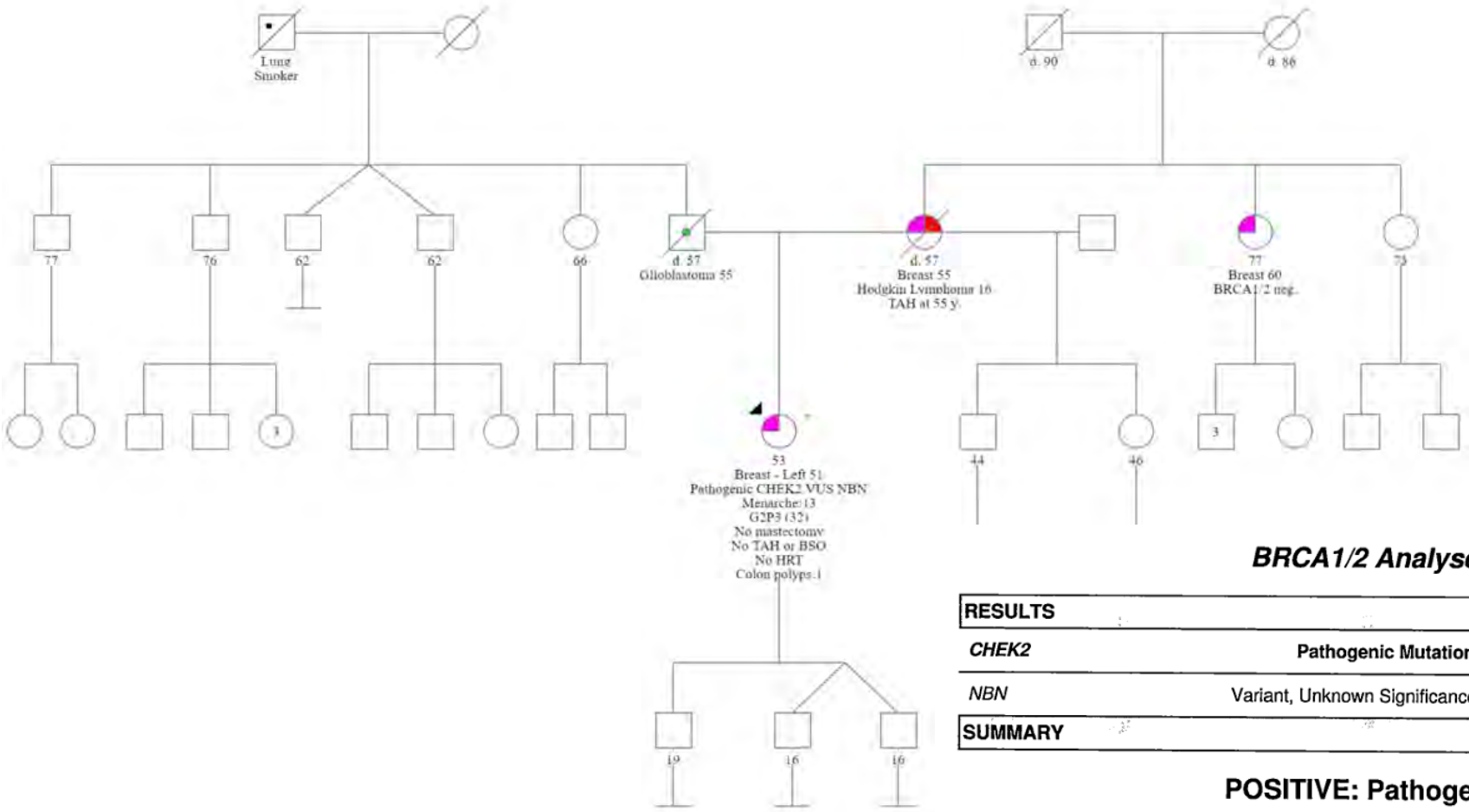
*POLE* Variant, Unknown Significance: p.T483A

**SUMMARY**

**Variant of Unknown Significance Detected**

- **Risk assessment still matters!!**
  - **A VUS doesn't rule out increased cancer risk.**
    - Patients with a strong personal or family history may still meet clinical criteria for high-risk screening.
  - **Family history is critical.**
    - In this case, the patient has a family history consistent with **familial colon cancer**, which independently indicates increased risk.
  - **Follow clinical guidelines for familial risk.**
    - For familial colorectal cancer (e.g., first-degree relative with CRC), colonoscopy is recommended starting at **age 40 or 10 years before the earliest diagnosis** in the family, with repeat screening every **5 years**.

# Case 2 (2023)




***BRCA1/2 Analyses with CancerNext®***

| RESULTS | | |
|---|---|---|
| *CHEK2* | **Pathogenic Mutation:** | **c.1100delC** |
| *NBN* | Variant, Unknown Significance: | p.R43* |
| **SUMMARY** | | |

**POSITIVE: Pathogenic Mutation Detected**

# Present day (2 years later)

- Updated guidelines no longer support high-risk colon screening based on evolving evidence and no family history of colon cancer.

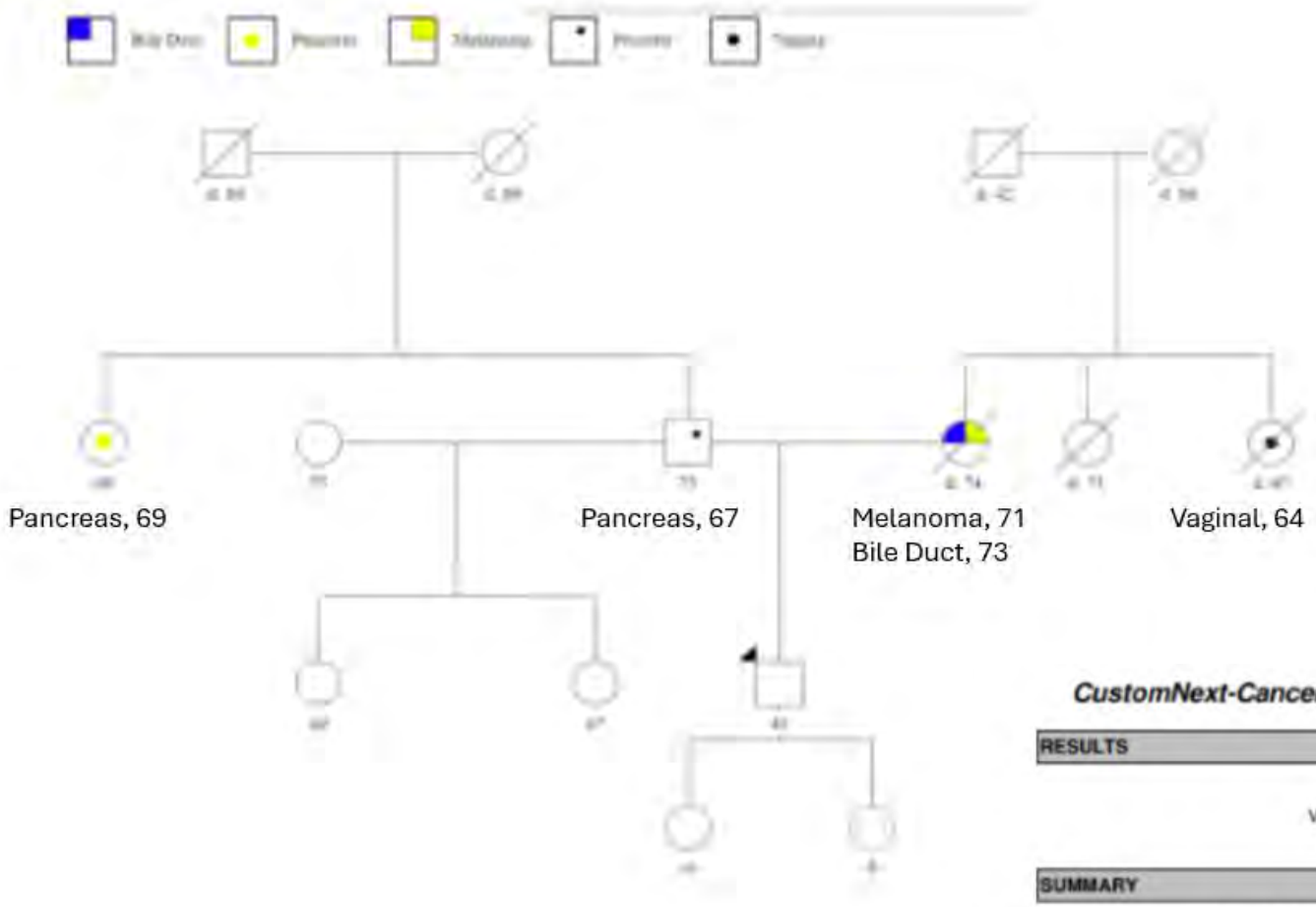
**Challenges:**

- Patient anxiety and distrust
- Emotional attachment to routine
- Difficult understanding evolving science
- Provider discomfort

**Counseling Considerations:**

- Normal evolution of evidence
- Reinforce the patient's risk
- Validate emotions
- Focus on what is still being monitored
- Continued screening options (will insurance continue to pay?)
- Continued re-evaluation

# Case 3 (2022)




***CustomNext-Cancer® +RNAinsight®: Analyses of Selected Hereditary Cancer Genes***

**RESULTS**

Pathogenic Mutation(s): None Detected
Variant(s) of Unknown Significance: None Detected
Gross Deletion(s)/Duplication(s): None Detected

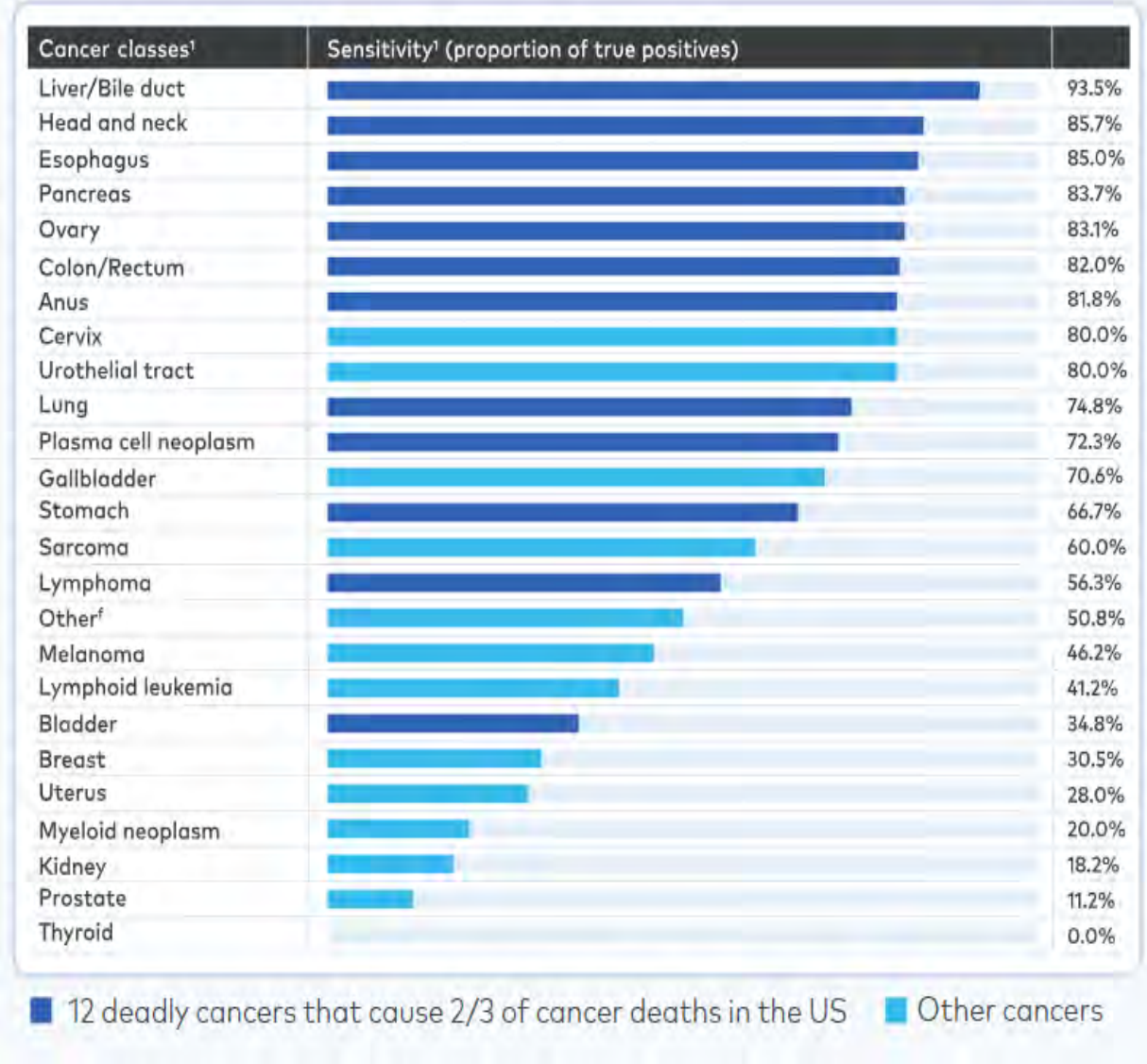
**SUMMARY**

**NEGATIVE: No Clinically Significant Variants Detected**

# Present day (3 years from last visit)

Patient returns to clinic expressing ongoing concern about his cancer risk. He recently heard about the Multi-Cancer Early Detection (MCED) tests and is considering it for peace of mind.

- Discuss Specificity vs Sensitivity
- Insurance coverage
- It is not a replacement test for other cancer screenings



# Questions?