Genetic Companion Testing in Oncology

The Importance of Genetic Counseling and Testing For Hereditary Cancer Syndromes

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About Me





Importance of Diagnosis of Hereditary Cancer Syndromes





Enhanced Surveillance

Treatment Options



Cascade Testing



https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

The Problem

- 2023 Study: 1.4 million cancer patients from 2013-2019 in Georgia & California
- 6.8% of cancer patients received germline genetic testing
- Highest rates

Kurian et al 2017 & 2019, 2023

Childers et al 2017 Farmer et al 2021

Armstrong et al 2015

- 50% males breast cancer
- 28% ovarian cancer

Low rates of genetic testing 'a missed opportunity' to reduce cancer burden

Nick Paul Taylor Jun 5, 2023

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Latest in Molecular Diagnostics

Illumina names new CEO SEPTEMBER 8, 2023



Actome outlines sequencing expansion plans as EU funding kicks.. SEPTEMBER 7, 2023

SPONSORED At-home or Lab-based STI



TEXAS

More breakthroughs. More victories."

https://www.labpulse.com/diagnostic-technologies/molecular-diagnostics/article/15539929/low-rates-of-genetic-testing-a-missed-opportunity-to-reduce-cancer-burden

Why is this happening?





Source: NSGC PSS 2022

TX Oncology Solution: The GREAT Program

1. CGCs train TXO Providers to offer Genetic Evaluations & Testing in office

2. Build & Expand Genetics Services within the TXO Virtual Care Clinic

3. Other Novel Options?

Improved Access to Genetic Services

> TEXAS ONCOLOGY More breakthroughs. More victories:

https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.27_suppl.123 https://ascopubs.org/doi/pdf/10.1200/EDBK_238937?role=tab

How is it going?





BRCA1/2 Testing Rates by Indication



https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.16_suppl.e22533

We Still Have Work to Do!



All Cancer is Genetic, but Most Cancer is NOT Inherited





Cancer Type	Prevalence of Pathogenic or Likely Pathogenic Variants
Epithelial Ovarian Cancer	18.1-23.6%
Metastatic Prostate Caner	11.8%
Colon Cancer	9.9%
Breast Cancer	9.3%
Pancreatic Cancer	3.8-8.4%
All Solid Tumors	12.5%



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7326311/pdf/nihms-1595967.pdf https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7600058/

Hereditary Breast & Ovarian Cancer Syndrome





BRCA1 & BRCA2
1 in 190 people
Critical for HRR pathway



- L. Manickam et al 2018
- 2. Ferla et al 2007
- 3. Image credit: Myriad Genetics

Lynch Syndrome





Can't Stop at BRCA or Lynch Anymore!



Ovarian Cancer Risk Genes BRIP1 MLH1 MSH2 EPCAM MSH6BRCA1 BRCA1 BRCA2 PALB2 CAD51C RAD51C RAD51C BRCA1 BRCA1 BRCA2 PALB2 CDH1 ATM RAD51C RAD51C BARD1 NF1Breast Cancer Cancer Risk Genes MLH1 MSH2 CHEK2 TP53 PTEN STK11Colon Cancer Risk Genes APC MLH1 MSH2 BRCA2 PALB2 PALB2 DH1 BRCA1 BRCA1 BRCA1 BRCA2 PALB2 CDH1 ATM RAD51C RAD51D BARD1 NF1Colon Cancer Risk Genes APC MLH1 MSH2 BRCA2 PALB2 PALB2 PALB2 DH1 ATM RAD51C RAD51D BARD1 NF1Colon Cancer Risk Genes APC MSH2 BRCA1 BRCA2 PALB2 PALB2 PALB2 DH1 BRCA1 BRCA1 BRCA1 BRCA2 PALB2 DH1 BRCA2 BRCA1 BRCA1 BRCA2 PALB2 DH1 BRCA2 BRCA1 BRCA2 PALB2 DH1 BRCA2 BRCA1 BRCA2 DH1 BRCA2 BRCA1 BRCA2 <th>5</th>	5
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www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

Who Needs Genetic Counseling and Testing?

Red Flags for Hereditary Cancer





www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

Slam Dunk Referrals



- Breast Cancer
 - □50 or younger
 - Triple negative
 - Metastatic
 - □ Male breast cancer
- Epithelial ovarian cancer
- Pancreatic cancer
- Metastatic, high risk, very high-risk prostate cancer
- Colon Cancer
- Ampullary Cancer

- WHEN IN DOUBT REFER!
 Endometrial under 51
 Any Lynch cancer under 51
 10+ adenomatous colon polyps (cumulative)
- Renal under age 47
- Medullary Thyroid Cancer
- Paraganglioma or Pheochromocytoma
- Ashkenazi Jewish Ancestry
- Tumors with abnormal MSI/IHC (deficient MMR)
- Somatic mutations in a known hereditary cancer gene



Things to Remember

Family History

- Maternal & Paternal
- 1st, 2nd and 3rd degree
- ANY cancer
- Relationship, type of cancer, age at diagnosis

Meeting Criteria ≠ Testing

- Person in front of you may not be BEST person to test
- When possible, test family member with cancer (person most likely to be positive)
- However, sometimes reasonable to test unaffected relatives

Not Meeting Criteria ≠ NO Testing

- Criteria continue to evolve
- Ok to test outside of criteria if informed consent obtained
- Self-pay cost \$250



What Happens at a Genetics Visit?

Anatomy of a Genetic Evaluation





Genetic testing is NOT one size fits all!

There are 77k genetic tests currently listed in the NIH Genetic Testing Registry. 10 tests added DAILY





What cancers are in my patient/their family?

What genes need to be included (or not)?

How quickly do I need this information?

What is the cost or will insurance cover?

What does this lab offer me that others don't?

What are the logistics for each lab?





Management Based on Variant Classification



Management based <u>ONLY</u> on personal/family history

- Resist managing based on test results alone
- Negative results do not eliminate the possibility of a hereditary cancer predisposition syndrome in the family
 - e.g., the person tested may not have inherited the familial variant
- Consider testing other at-risk family members
- Familial VUS testing should not be offered outside of research or VUS resolution studies through the laboratory

- Cancer risks increased over general population
 - Management based on NCCN or consensus guidelines and family history
- Identify at-risk relatives who would benefit from genetic testing & help facilitate cascade testing
- Management may include:
 - Increased Surveillance
 - Surgery
 - Chemoprevention
 - Treatment Options (Ex: PARP inhibitors)



https://www.genome.gov/sites/default/files/media/files/2020-04/Guide_to_Interpreting_Genomic_Reports_Toolkit.pdf

Is a Genetic Evaluation REALLY **Needed?**

Cautionary Tale – Choosing the right test



Unnecessary Surgeries?



• Unaffected 46 yo

- Maternal aunt w. breast at 50
- Lifetime risk of breast cancer 12%
- CDH1 VUS

FINAL RESULTS SUMMARY



Negative

No known pathogenic or likely pathogenic variants were detected.

Genes analyzed on this panel

APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GALNT12, GREM1, HOXB13, MEN1, MTF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, HAD51C, RAD51D, RNF43, RPS20, SMADK, STK11, TP53, VHL

ADDITIONAL FINDINGS VARIANTS OF UNCERTAIN SIGNIFICANCE (NUS)

Variants of uncertain significance (VUS) are common and the American CoBege of Medical Genetics and Generative (ACMG) states that a VUS should NOT be used in clinical decision making. A VUS means that a change in the DNA was detected, but there is not enough information to determine whether or not the change increases the risk of cancer. Many VUS represent normal human variation, Medical management should be based on the patient's personal and/or femily history.

Genv	Variant	Zygosity	Classification
GDH1	c.854C>T (p.T285))	heterozygous	VUS

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DATE OF OPERATION: 12/30/2022.

PREOPERATIVE DIAGNOSES:

- 1 Bilatoral fibrocyctic mactenathy (fibrocyctic disease of bilateral breast).
- 2. Genetic predisposition to malignancy by genetic testing.

POSTOPERATIVE DIAGNOSES:

- 1. Bilateral fibrocystic mastopathy (fibrocystic disease of bilateral breast).
- 2. Genetic predisposition to malignancy by genetic testing.

PROCEDURE:

Bilateral mastectomy, simple.

CLINICAL RESUME:

Please see admission note for past medical history, admission physical examination, laboratory, and radiographic data.

PRESENTING HISTORY:

She presented to the hospital for elective bilateral mastectomy secondary to farme or conservative measures for severe intractable fibrocystic disease of the breasts and + genetic testing indicating a possible increased risk of developing breast cancer.



Is Genetic Counseling/Evaluation REALLY necessary?



Benefits

- Improved patient knowledge & understanding
- Improved satisfaction
- Better outcomes

Genetic Testing w/o Counseling

- Wrong test is ordered or recommended
- Wasted healthcare dollars
- Results misinterpreted
- Inappropriate/inadequate lack of counseling and/or consent
- Inappropriate use of DTC testing





But My Patient Already Had Somatic Testing?

When Worlds Collide



Germline Somatic TRÉATMENT PARP **Inhibitors BRCA1 BRCA1** Somatic Pathogenic **Germline Pathogenic** Variant Variant

TEXAS

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62-year-old with TNBC. Her oncologist already ordered a large somatic panel using one of the commercially available products. The results are negative. The patient reports no significant family history of cancer.



⁵²⁵³⁶⁵¹⁸ Myriad myRisk™ myRisk	Hereditary Cancer Update Test Genetic Result	CONFIDENTIAL	Sr	YRIAD NYRisk [™] Powered by Wision [™]
RECEIVING HEALT	HCARE PROVIDER	SPECIMEN Specimen Type: Draw Date: Accession Date: Report Date:	Biood 2016 2016 2016	PATIENT Name: Date of Birth: Patient ID: Gender: Female Accession #: Requisition #:
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Tumor & Germline Testing Differ





Normal Somatic Genetic Testing ≠ Normal Germline Testing





Lincoln et al 2020

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75-year-old man with metastatic NSCLC has NGS testing.

A BRCA2 variant is found in his lung cancer. His chart indicates his paternal grandmother had breast cancer in her 70's.

WWYD?







Germline testing is indicated; refer for a genetic evaluation. Confirmation testing found *BRCA2* variant to be germline

Only 31% of cancer patients w. a somatic BRCA1/2 mutation had germline confirmation if they did NOT meet traditional testing criteria.

ORDERING PF	IYSICIAN: Theodora Ross, MD	SPECIMEN Specimen Type: Draw Date: Accession Date: Report Date:	Blood 2018 2018 2018	PATIENT Name: Date of Birth: Patient ID: Gender: Accession #: Requisition #:		
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TEXASTONCOLOGY



Is this *BRCA2* variant germline?



70 yo, fhx of hepatobiliary cancer (mom)

Myriad myRisk [®] Hereditary Cancer Update To myRisk Genetic Res	est ult	myRisk Provension
RECEIVING HEALTHCARE PROVIDER	SPECIMEN Specimen Type: Oraw Date: Accession Date: Report Date:	PATIENT Name: Date of Birth Patient ID: Gender: Accession # Requisition 4
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ADDITIONAL FINDINGS: NO VARIANT(S) OF Details About Non-Clinically Significant Variants, individuals risk of cancer or other diseases. When id Polymophisms) and benign variants (Polymorphism increased cancer risk, Present evidence does not su- management beyond what is indicated by the persor Variant Classification: Myriad's myVision ^{TW} Variant cases, healthcare providers may be contacted for m evidence about a variant is identified and determined made available to the healthcare provider through ar	UNCERTAIN SIGNIFICANCE (VUS) All individuals carry DNA changes (i.e., tentified, variants of uncertain significance s) are not reported and available data ind ggest that non-clinically significant varian hal and family history and any other clinic it Classification Program performs ongoing one clinical information or to arrange famil to result in clinical significance and man n amended report.	IDENTIFIED variants), and most variants do not increase an a (VUS) are reported. Likely benign variants (Favor licete that these variants most lively do not cause at findings be used to modify patient medical alty significant findings. g evaluations of variant classifications. In certain ly testing to aid in variant classification. When new agement change, that information will automatically be

GENES ANALYZED

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

APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM (large rearrangement only), MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RADSIC, RAD51D, SMAD4, STK11, TP53. Sequencing was performed for select regions of POLE and POLD1, Indication for Testing: It is our understanding that this individual was identified for testing due to a personal or family history suggestive of a hereditary predisposition for cancer.

Associated Cancer Risks and Clinical Management: Piease see the "myRisk Management 'Tool' associated with this report for a summary of cancer risk and professional society medical management guidelines that may be useful in developing a plan for this patient based on test results and reported personal/family history, if applicable. Testing of other family members may assist in the interpretation of this patient's test result.

Analysis Description: The Technical Specifications summary (https://www.myriadpro. comidocuments-and-forms/technical-specifications/) describes the analysis, method,

Cheat Sheet: Somatic Variants that Warrant Germline Confirmation



Germline testing indicated, regardless of age and tumor type:

- ATM
- BRCA1
- BRCA2
- BRIP1
- CHEK2
- *MLH1MSH2*
- MSH2
- PMS2
- PALB2

- RAD51C
- RAD51D
- RET
- SDHA
- SDHAF2SDHB
- SDHC
- SDHD
- *TSC2*

Germline testing indicated if MMR abnormality detected in ANY tumor type:

- MSI-high tumors
- Abnormal IHC: Absent staining of ANY of the Mismatch Repair genes
 - *MLH1*
 - MSH2
 - MSH6
 - PMS2

For the following genes, see specific details for when germline testing is indicated:

- *APC*: only if patient is under age 30 (any tumor type)
- *BAP1*: in uveal melanoma, mesothelioma, melanoma, or renal tumors
- FH: in renal tumors
- FLCN: in renal tumors
- *MUTYH*: if two variants are detected (any tumor type)
- *NF1*: in breast patients under age 30, or patients with gliomas or nerve sheath tumors
- POLE: in colon cancers
- *RB1*: only if patient is under 30 (any tumor type)
- *TP53*: if seen in any breast cancer tumor or sarcoma or a NON-BRAIN tumor under 30
- VHL: if seen in any NON-RENAL tumor

Take Home Points





Cancer Genetic Resources

Online Resources

- NCCN <u>www.nccn.org</u>
- GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1116/
- Familial Cancer Database
 <u>http://www.familialcancerdatabase.nl/</u>
- Genetic Testing Registry <u>http://www.ncbi.nlm.nih.gov/gtr/</u>
- Ask2Me <u>www.ask2me.org</u>
- JAX (Free genetics education): <u>https://www.jax.org/</u>
- ASCO (genetics education): <u>https://education.asco.org/product-details/principles-of-genetics-and-genomics</u>

Texas Oncology GREAT Program

- Multiple sites of service across state by multiple providers
- <u>http://www.texasoncology.com/services-and-</u> <u>treatments/genetic-risk-evaluation-and-testing</u>

Online Patient Resources

- Sharsheret <u>https://sharsheret.org/</u>
- FORCE <u>http://www.facingourrisk.org/index.php</u>
- HCC Takes Guts <u>www.hcctakesguts.org</u>
- UTSW Patient Fact Sheets
 <u>https://utswmed.org/conditions-treatments/genetics-and-hereditary-cancers/hereditary-cancer-syndromes/</u>
- Mass General Patient Fact Sheets
 <u>https://www.massgeneral.org/cancer-center/treatments-and-services/cancer-genetics/fact-sheets</u>

Find a Genetic Counselor

- <u>www.nsgc.org</u>
- https://www.tsgc.org/

Questions?

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