Cancer Genetics in the Primary Care Setting

Greta Henry, MS, CGC
Certified Genetic Counselor
Allina Health Cancer Institute

Bonnie Hatten, MS, CGC
Certified Genetic Counselor
Allina Health Cancer Institute

Allina Health

1

Disclosure

- We have no conflicts of interest in relation to this program or presentation.

2

Objectives

1. Review genetic factors in cancer risk
2. Outline which patients to refer
3. Discuss the utility of genetic counseling
4. Acknowledge other ways that patients may encounter genetic concepts or obtain their genetic data

3

Who are Genetic Counselors

Allina Health

4

Genetic Counselors

- Master's level training in medical genetics and psychosocial counseling.
- Meet with individuals or families before and after genetic testing.
- All specialized in **oncology**, prenatal, cardiology, pediatrics, neurology, ophthalmology, and psychiatry, among others.
- Non-clinical roles in research, education, industry, marketing, public health

Allina Health 5

5

Cancer Genetics

Allina Health

6

Cell Cycle Regulation

- DNA repair genes
  - Fix errors made during DNA replication
  - Inactivation leads to cancer development
  - Ex: *MLH1, MSH2, MSH6, PMS2*
- Tumor suppressor genes
  - Negatively regulate the growth of cells
  - Inactivation leads to cancer development
  - Ex: *BRCA1/2*
- Oncogenes
  - Play roles in cell cycle regulation
  - Activation leads to cancer development
  - Ex: *RET*

labs.wsu.edu

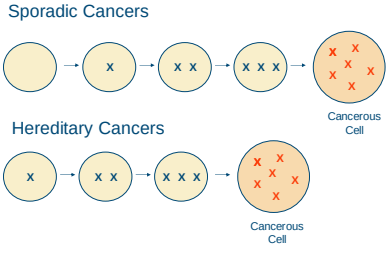
Allina Health 7

7

Hereditary Cancer Assessment

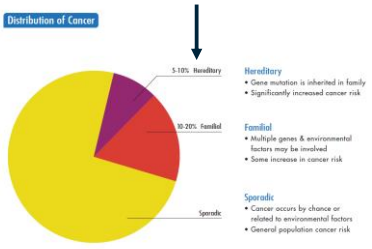
Allina Health

8



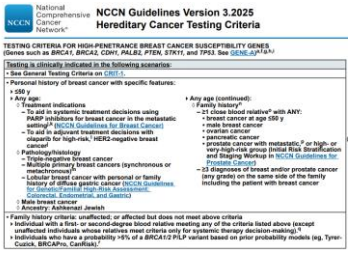
Allina Health 9

9



Hereditary Cancer Red Flags

Genetic Testing Criteria for Breast Cancer Genes



Genetic Testing Criteria for Colorectal Cancer Genes

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

NCCN Guidelines Index
Table of Contents
Discussion

CRITERIA FOR TESTING FOR LYNCH SYNDROME

Testing is clinically indicated in the following scenarios:	
• Known LS PV in the family • Personal history of a LS-related cancer (CRC, EC, or other) and any of the following: ▸ Diagnosed <50 y ▸ A synchronous or metachronous LS-related cancer regardless of age ▸ 1 first-degree or second-degree relative with an LS-related cancer diagnosed <50 y ▸ ≥2 first-degree or second-degree relatives with an LS-related cancer regardless of age • Family history of any of the following: ▸ ≥1 first-degree relative with a CRC or EC diagnosed <50 y ▸ ≥1 first-degree relative with a CRC or EC and a synchronous or metachronous LS-related cancer regardless of age ▸ ≥2 first-degree or second-degree relatives with LS-related cancers including ≥1 diagnosed <50 y ▸ ≥3 first-degree or second-degree relatives with LS-related cancers regardless of age • Increased model-predicted risk for LS ▸ An individual with a ≥5% risk of having an MMR gene PV based on predictive models (ie, $PREMM_5$, MMRpro, MMRpredict) ◦ Individuals with a personal history of CRC and/or EC with a $PREMM_5$ score of ≥2.5% should be considered for MGPT. ◦ For individuals without a personal history of CRC and/or EC, some data have suggested using a $PREMM_5$ score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity.	Strategies for Testing for LS (LS-1)
• Personal history of CRC, EC, or of other tumor with MMR deficiency determined by polymerase chain reaction (PCR), next-generation sequencing (NGS), or IHC diagnosed at any age • Personal history of a P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline	Additional tumor-based testing (LS-A) OR Germline MGPT for LS and other hereditary cancer syndromes Strategies for Testing for LS (LS-1)

Testing may be considered in the following scenarios:
• Personal history of CRC or EC at age ≥50 y and any of the following (category 2B): ▸ untested for MMR deficiency status in tumor ▸ absence of MMR deficiency in tumor See Rationale, pros, and cons of multigene panel testing for Lynch syndrome and other cancer risk genes (HRS-A)

Allina Health NCCN 3.2024 13

13

Genetic Counseling

Allina Health

14

Appointment Structure

Initial Appointment

- Risk assessment of personal and family histories
- Education about basic genetics, inheritance, and hereditary cancer syndromes
- Explanation of testing process and insurance coverage
- Informed consent (if testing)
- Cancer risks and risk management recommendations if no test or if negative test

Results call

- Interpretation of results based on personal and family histories, stressing limitations of negative result
- Screening and risk management recommendations
- Psychosocial support
- Cascade testing for family members

Allina Health

15

Genetic Information Nondiscrimination Act of 2008 (GINA)

Allina Health

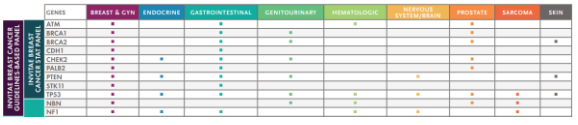
Myriad Genetics

16

16

Genetic Testing

- DNA sequencing and deletion/duplication analysis of genes related to inherited cancer syndromes
- Multi-gene panels are commonly used to test for multiple genes at once



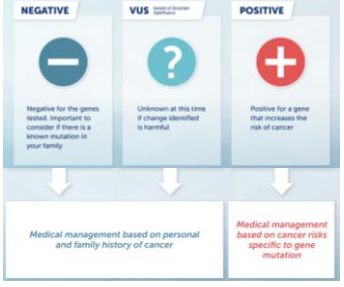
Invitae

Allina Health

17

17

Potential Results of Genetic Testing



Allina Health

Myriad Genetics

18

18

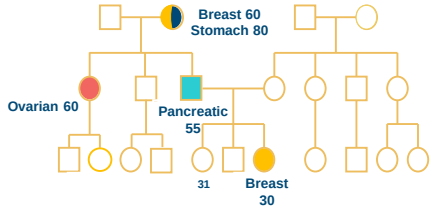
Case Examples

2 case examples within one family

Allina Health

19

Family History Evaluation



Allina Health

20

20

Case 1: Affected with Pancreatic

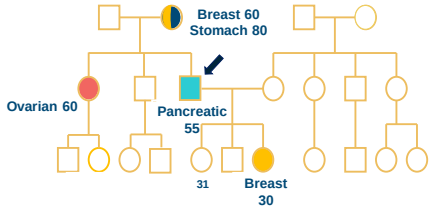
- 55 yo male
- Presented to the ER with unintentional weight loss and abdominal pain
- Diagnosed with metastatic adenocarcinoma of the pancreas
- Port placed and is about to begin chemotherapy

Allina Health

21

21

Family History Evaluation



Allina Health 22

22

Genetic Testing Result: BRCA2 mutation

RESULT: POSITIVE

One Pathogenic variant identified in BRCA2. BRCA2 is associated with autosomal dominant hereditary breast and ovarian cancer syndrome and autosomal recessive Fanconi anemia.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
BRCA2	c.3744_3747del (p.Ser1248Argfs*10)	heterozygous	PATHOGENIC

Allina Health 23

23

BRCA2 considerations for treatment

- Consider PARP inhibitors
  - PARP inhibitors are a type of targeted cancer drug
  - PARP (poly-ADP-ribose polymerase) is an enzyme that helps damaged cells repair themselves.
  - PARP inhibitors stop the PARP from doing its repair work in cancer cells and the cell dies.
  - Cancer cells with BRCA mutations already have a poor repair system.
  - So blocking PARP can take advantage of this fact by further inhibiting cell repair in these mutation cells.

Allina Health 24

24

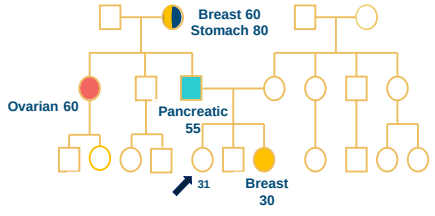
Case 2: Family History of Breast

Allina Health

25

25

Family History Evaluation



Allina Health

26

26

Family history of breast cancer

- Referral often placed by PCP or OBGYN (GCs can self-refer)
- Scheduled in a “routine” or “ASAP”
- Genetic testing discussion, best to test affected, can test unaffected, but limitations
- Risk modeling
- Counsel regarding screening implications, future risk reduction, and familial risk

Allina Health

27

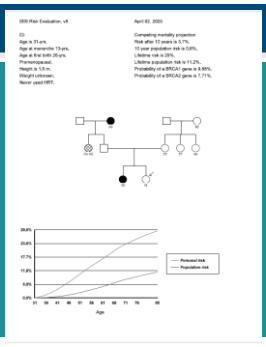
27

Risk modeling

- IBIS risk model
  - Personal history (menarche, menopause, breast density, HRT, age at first child, etc)
  - Family history
  - Genetic test results if done
- Qualify for high-risk screening if risk greater than 20%. High-Risk screening includes MRI/mammogram yearly alternating every 6 months, can be done at High-Risk Program

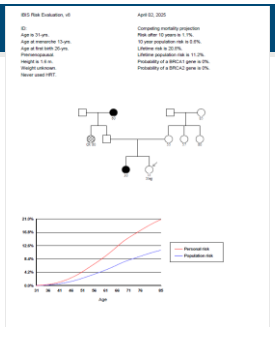
Risk Model #1

- No genetic testing
- Risk 29%
- Qualifies for high-risk screening



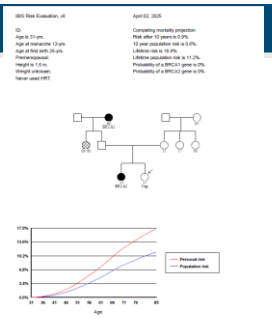
Risk Model #2

- Additional information
- Negative genetic test for patient
- Risk 20.8%
- Qualifies for high-risk screening



Risk Model #3

- Even more information
- Positive test results for affected relatives
- Negative result for patient
- Risk 16.9%
- Does NOT qualify for high-risk screening



Allina Health 31

31

Does testing, BRCA2 mutation found

- With a positive genetic result, risk and management based on mutation-specific data
- No risk modeling done

RESULT: POSITIVE

One Pathogenic variant identified in BRCA2. BRCA2 is associated with autosomal dominant hereditary breast and ovarian cancer syndrome and autosomal recessive Fanconi anemia.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
BRCA2	c.3744_3747del (p.Ser1248Argfs*10)	heterozygous	PATHOGENIC

Allina Health 32

32

NCCN guidelines for BRCA2 female

BRCA2		
Cancer risk	**Associated cancer management**	**Age to begin management**
Breast cancer 55-70% in females	Annual breast MRI and clinical exam Annual mammogram (alternating with MRI) Discuss option of risk-reducing bilateral mastectomy	Age 25 Age 30
Ovarian cancer 13-29%	Surgery to remove ovaries and fallopian tubes, consider hysterectomy	Age 40-45
Pancreatic cancer 5-10%	Annual screening only recommended with family history of pancreatic cancer, consider if no family history of pancreatic cancer	Age 50 (or 10 years younger than relative)

Allina Health NCCN 33

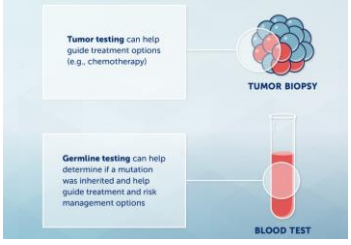
33

Other Sources of Genetic Results

Allina Health

34

Germline vs Somatic



Allina Health

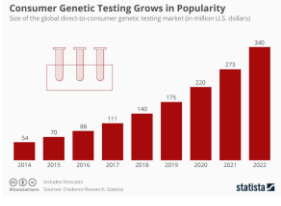
Myriad Genetics

35

35

Direct to Consumer Tests

- **Who:**
  - AncestryDNA, FamilyTreeDNA, etc.
- **What:**
  - Tests for a selection of SNPs, think of these like flags or markers (lost key analogy)
  - Related to inherited conditions, health risks, drug responses, inherited traits, ancestry
  - Can link to family members who also did testing
- **Limitations**
  - Most risks are multifactorial
  - Clinician involvement not required
  - Unexpected results (APOE-4, 44-site BRCA1/2)
  - Overly reassured by results (44-site *BRCA1/2*)
  - Privacy concerns
  - Eurocentric data



Allina Health

36

36

Population-based screening

What:

- Build genetic databases for research
- Same tech as clinical testing, more limited gene panels reported out
- Can provide non-comprehensive genetic screening to patients upon request
  - Familial hypercholesterolemia (FH), hereditary breast and ovarian cancer (HBOC), and Lynch syndrome
  - Some with pharmacogenomic results reported

Who:

- Tapestry Study at Mayo Clinic
- Helix Study at HealthPartners
- All of Us Research Program at NIH

Limitations:

- Patients may require more comprehensive testing

Allina Health 37

37

Cell-free DNA (cfDNA) cancer screening

- **Who:**
  - Galleri
- **What:**
  - Screening test and does not diagnose cancer
  - Looks for a unique "fingerprint" of cancer by analyzing methylation patterns of cell-free DNA
  - If detected, the test predicts the most likely origin of the cancer signal, to help guide the diagnostic workup
  - Not yet FDA approved or offered by GC
- **Limitations**
  - Low sensitivity in early-stage cancers
  - Potential for false positives and negatives
  - Challenges in distinguishing cancer-derived DNA from background noise
  - Cost

Galleri® Multi-cancer early detection

Allina Health https://www.galleri.com/ 38

38

Summary

- Genetic testing for hereditary cancer is a complex, ever-evolving field
- Identifying a hereditary cause for cancer in a family can aid prevention/screening for the patient and family members
- Different types of genetic tests have different applications
- Genetic counselors are here to help!

Allina Health 39

39

References

The American Society of Breast Surgeons

Cybulski, Cezary et al. "Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis." *The Lancet. Oncology* vol. 16,6 (2015): 638-44. doi:10.1016/S1470-2045(15)70142-7

Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers. *JAMA.* 2017;317(23):2402–2416. doi:10.1001/jama.2017.711

National Comprehensive Cancer Network

Reiner, Anne S et al. "Breast Cancer Family History and Contralateral Breast Cancer Risk in Young Women: An Update From the Women's Environmental Cancer and Radiation Epidemiology Study." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* vol. 36,15 (2018): 1513-1520. doi:10.1200/JCO.2017.77.3424

Song, Honglin et al. "Population-based targeted sequencing of 54 candidate genes identifies *PALB2* as a susceptibility gene for high-grade serous ovarian cancer." *Journal of medical genetics* vol. 58,5 (2021): 305-313. doi:10.1136/jmedgenet-2019-106739

Yang, Xin et al. "Cancer Risks Associated With Germline *PALB2* Pathogenic Variants: An International Study of 524 Families." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* vol. 38,7 (2020): 674-685. doi:10.1200/JCO.19.01907

40

Thank You!

greta.henry@allina.com
bonnie.a.hatten@allina.com

41