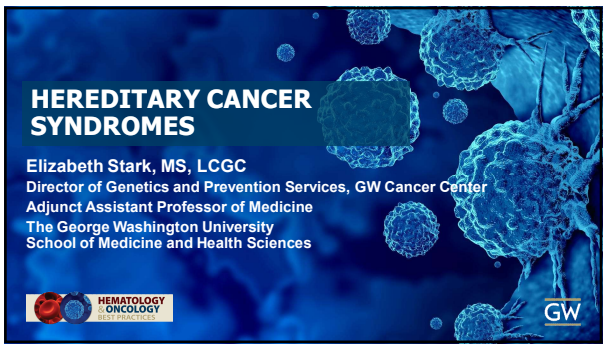


Disclosures

- I am a consultant for Color Genomics.

Learning objectives

1. Recognize key features of common hereditary cancer syndromes
2. Evaluate your patient population for appropriate genetic counseling and testing referrals
3. Identify patients who may benefit from therapeutic agents linked to genetic markers
4. Determine when PRS and RNA testing can add clinical utility

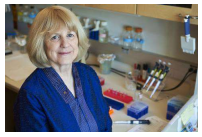
Why is this important

- Targeted Therapeutics
  - Treatment decisions can and should be influenced by genetic testing results
- Prevention
  - Secondary malignancies
  - Cancers in family members

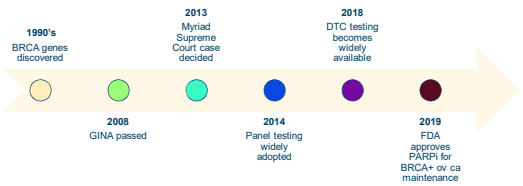
Every breast or ovarian cancer patient with a *BRCA1* or *BRCA2* mutation detected after diagnosis is a missed opportunity to prevent cancer.

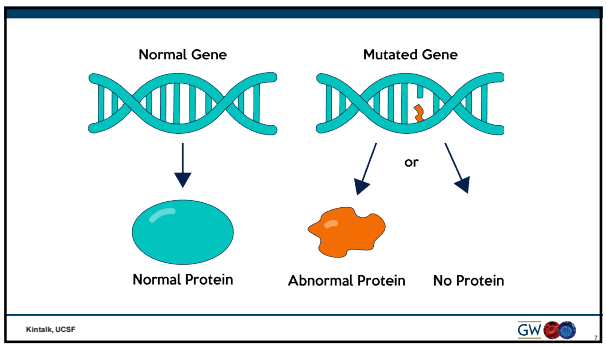
No woman with a mutation in *BRCA1* or *BRCA2* should die of breast or ovarian cancer.

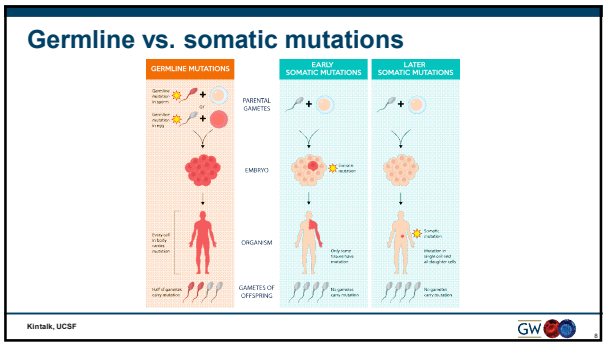
– Dr. Mary-Claire King

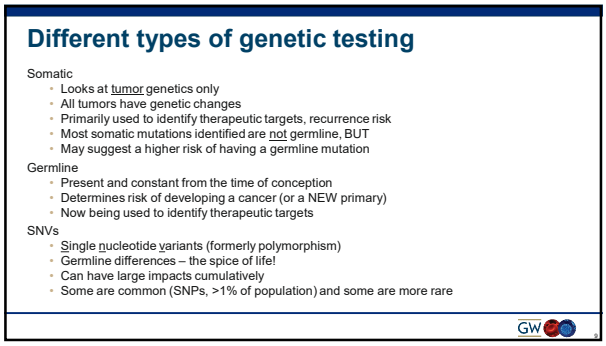


Timeline

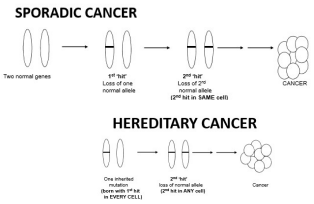








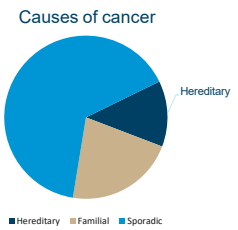
Knudson Two Hit Hypothesis



GW 10

Basic principles of hereditary cancer

- About 15% of cancer is hereditary (higher for rare cancers)
- Autosomal dominant or autosomal recessive inheritance
- Men and women have the same chance to inherit a mutation
- Each child is at risk to inherit the altered gene
- Mutations can be inherited from either parent
- Risk factor – not a diagnosis
- Testing of affected family members is the most informative



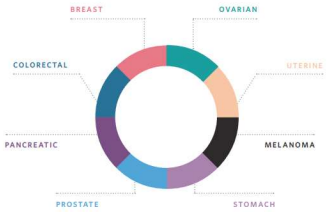
GW 11

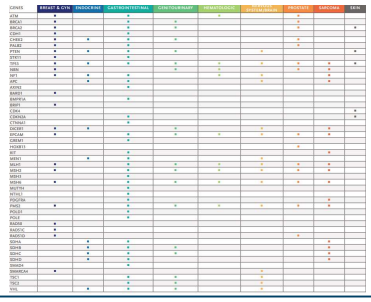
When to suspect a hereditary cancer syndrome

- Cancer in 2 or more family members (same side of family)
- Cancer diagnosis at early age
- Multiple primary tumors in the same individual
- Bilateral or multiple rare cancers
- Constellation of tumors consistent with hereditary cancer syndrome (eg, Lynch)
- Multiple affected generations
- Specific tumor histologies

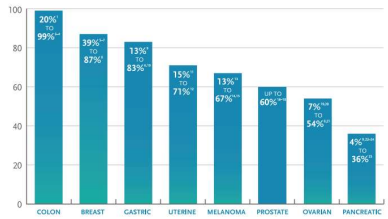
GW 12

What Types of Cancer Can Be Hereditary?





Lifetime Cancer Risk for People with a Genetic Alteration



Results

- Positive
  - Actionable
  - Some modifications for a particularly strong family history
  - Includes Pathogenic and Likely Pathogenic
  - **Follow NCCN guidelines**
- Negative
  - Does not always mean it's not genetic!
  - True negative vs. uninformative negative
  - Includes Benign and Likely Benign. Will not be reported on.
  - **Follow based on family history**
- Variant of Uncertain Significance
  - Vast majority are benign differences
  - Lab needs more time
  - **Follow based on family history**

VUS Follow-up

- Ordering providers are notified as VUSes are reclassified

PROMPT

VUS Rates Falling

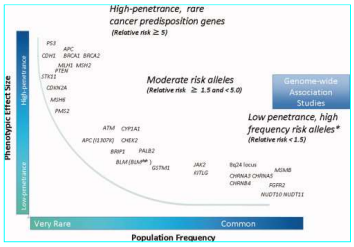
- Introduction of RNA testing is helping to reclassify VUSes, especially splice site variants
  - RNA testing also helping to identify pathogenic intronic variants not typically captured by DNA alone
- Functional modeling harnesses machine learning to combine multiple lines of evidence for better predictions
- If a mutation is found or reclassified, implications are the same.
  - Just another way to identify an underlying familial cancer syndrome
  - Reclassification from pathogenic to VUS or Benign is VERY rare

Where we are now

- Testing is performed the same day
  - Saliva or Blood
- Majority of patients are getting multi-gene panel testing
- Insurance coverage is good, self-pay prices reasonable ($250)
- Results available in 2-3 weeks
  - 7-10 days for some genes
- Cancer genetics is about prevention and targeted therapies

High vs. Moderate Cancer Genes

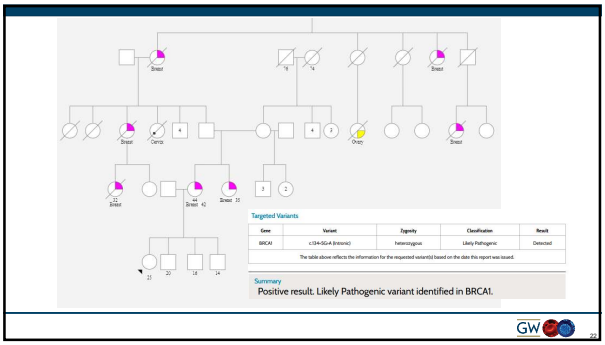
- High Risk Breast
  - *BRCA1*
  - *BRCA2*
  - *TP53*
  - *PALB2*
  - *CDH1*
  - *STK11*
  - *PTEN*
- Moderate Risk Breast
  - *ATM*
  - *CHEK2*
  - *NBN*



Breast Cancer Risk Genes

Gene	Syndrome	Estimated RR(95%CI)	Other Associated Cancers
BRCA1	HBOC	11.4	Ovary, Pancreas, Prostate
BRCA2	HBOC	11.7	Ovary, Pancreas, Prostate, Sarcoma?
TP53	Li-Fraumeni	105 (62-165)	Sarcoma, ACC, CNS, other
PTEN	Cowden	No reliable estimates	Thyroid, Endometrium, Renal, CRC
CDH1	HDGC	6.6 (2.2 – 19.9)	Diffuse gastric
STK11	Peutz-Jeghers	No reliable estimates	Colon, Pancreas, Ovarian sex-cord
PALB2		5.3 (3.0 – 9.4)	Pancreas, ?Ovary
NF1	Neurofibromatosis	2.6 (2.1 – 3.2)	Peripheral nerve sheath, CNS
ATM	Ataxia Telangectasia (AR)	2.8 (2.2 – 3.7)	Pancreas
CHEK2		3.0 (2.6 – 3.5)	CRC, Prostate

Easton DF et al. *N Engl J Med* 2015;372:2243-57



Hereditary Breast and Ovarian Cancer

Study	Breast Cancer Risk (%) (95% CI)		Ovarian Cancer Risk (%) (95% CI)	
	BRCA1	*BRCA2*	*BRCA1*	*BRCA2*
Antoniou et al. (2003) [126]	65 (44–78)[a]	45 (31–56)[a]	39 (18–54)[a]	11 (2.4–19)[a]
Chen et al. (2007) [127]	55 (50–59)[a]	47 (42–51)[a]	39 (34–45)[a]	17 (13–21)[a]
Kuchenbaecker et al. (2017) [128]	72 (65–79)[b]	69 (61–77)[b]	44 (36–53)[b]	17 (11–25)[b]

CI = confidence interval.

[a]Risk estimate calculated up to age 70 years.

[b]Risk estimate calculated up to age 80 years.

https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq

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Cancer Sites [6–8,12,62,169]	*BRCA1*		*BRCA2*	
	Strength of Evidence	Magnitude of Absolute Risk	Strength of Evidence	Magnitude of Absolute Risk
Breast (female)	+++	High	+++	High
Ovary, fallopian tube, peritoneum	+++	High	+++	Moderate
Breast (male)	+	Undefined	+++	Low
Pancreas	++	Very Low	+++	Low
Prostate[a]	+	Undefined	+++	High

https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq

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SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Female Breast Cancer		
Breast awareness • Women should be familiar with their breasts and promptly report changes to their healthcare provider.	18 years old	Periodic and consistent
Clinical Breast Exam	25 years old	Every 6-12 months
Breast Screening:* • Breast MRI with contrast • Mammography with consideration of tomosynthesis	25-29 years old	Individualized
	30-75 years old	Every 12 months
	>75 years old	Individualized
Discuss option of risk-reducing mastectomy	Individualized	N/A
Consider investigational imaging and screening studies, when available in context of a clinical trial	Individualized	Individualized
Consider options for risk reduction agents, such as chemoprevention (i.e. tamoxifen, raloxifene)	Individualized	Individualized
Ovarian Cancer		
Recommend risk-reducing salpingo-oophorectomy (RRSO)**	Typically 35 to 40 years old, and upon completion of child bearing	N/A
If RRSO not elected, transvaginal ultrasound combined with serum CA-125, although of uncertain benefit, may be considered	30-35 years old	Clinician's discretion
Consider investigational imaging and screening studies, when available in the context of a clinical trial	Individualized	Individualized
Consider options for risk reduction agents, such as chemoprevention (i.e. oral contraceptives)	Individualized	Individualized

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SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Male Breast Cancer		
Breast self-exam training and education	35 years old	Periodic and consistent
Clinical breast exam	35 years old	Every 12 months
Prostate Cancer		
Consider prostate cancer screening	40 years old	Clinician's discretion
Melanoma		
General risk management, such as annual full-body skin examination and minimizing UV exposure	Individualized	Annual, or shorter intervals if indicated
Pancreatic Cancer		
For individuals with exocrine pancreatic cancer in >1 first- or second-degree relative on the same side of the family as the identified pathogenic/likely pathogenic germline variant, consider pancreatic cancer screening.*	50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family)	Annually (with consideration of shorter intervals if worrisome abnormalities seen on screening)

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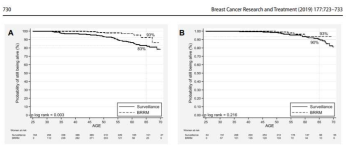
Surveillance vs. Surgery

- 2019 Dutch study demonstrated BRRM was associated with lower mortality than surveillance for *BRCA1* carriers. No difference between the groups noted for *BRCA2* carriers.



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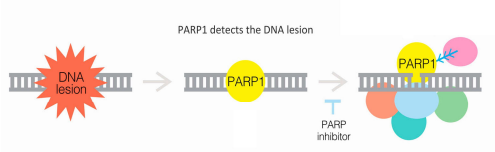
PARP Inhibitors

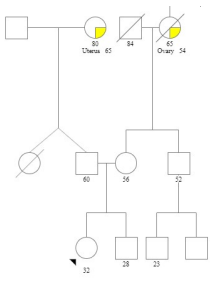
- PARP inhibitors work in part by blocking the ability of PARP proteins to repair damaged DNA, which includes recruiting other DNA repair proteins



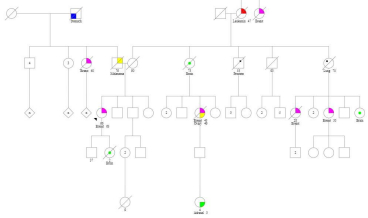
Adapted from Genes. July 2019. https://doi.org/10.3390/genes10080565. CC BY 4.0

PARPi in Breast Cancer

- FDA Approved
  - Metastatic breast cancer
  - *BRCA1* or *BRCA2* positive- germline only
  - HER2-negative
- Clinical Trials
  - Includes other genes (*PALB2, ATM, CHEK2, RAD51, BRIP1, NBN*)
  - Includes somatic *BRCA* mutations



Li-Fraumeni Syndrome



Summary
Positive result. Likely Pathogenic variant identified in TP53.
Variant of Uncertain Significance identified in FH.

TP53 Associated Cancers

Primary Cancers
- Breast cancer
- ACC
- Osteosarcoma
- Brain/CNS
- Leukemia

Also seen
- Lung
- Melanoma
- Thyroid cancer
- GI Tumors
- Kidney
- Gonadal germ cell

Risk is appx 50% by age 30, 90% by age 60. Higher for women than men.

Confirmation of Result

- Becoming standard practice to confirm germline presence of *TP53* through confirmatory testing of a second cell line
  - Can be confirmed on punch biopsy or eyebrow pluck
  - Allele fraction can give a clue (looking for about 50%)
  - Especially important if the case/fam hx doesn't look typical for *TP53*
  - High de novo rate for *TP53*
  - Other possibilities include CHIP, chemo effect, or mosaicism
- LiFT UP Study through DFCI and COH
- Important implications for care of patient and family members

SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Female Breast Cancer		
Breast Awareness • Women should be familiar with their breasts and promptly report changes to their healthcare provider	18 years old	Periodic and consistent
Clinical Breast Exam	20 years old (or at the age of earliest diagnosed breast cancer in the family)	Every 6-12 months
Breast Screening	20-29 years old, or the age of earliest diagnosed breast cancer in the family (if below age 20): MRI or mammogram (MRI preferred over mammogram) 30-75 years old: MRI and mammogram Women treated for breast cancer: MRI and mammogram of remaining breast tissue	Every 12 months
	>75 years old: individualized management	Individualized
Discuss option of risk-reducing mastectomy	Individualized	N/A
Brain Tumors		
Brain MRI as part of whole body MRI (see below, Other Cancers), or a separate exam	Individualized	Every 12 months
Neurologic exam	Individualized	Every 6-12 months
Colorectal and Intestinal Cancer		
Colonoscopy and upper endoscopy	25 years old, or 5 years before earliest known colon cancer in the family (whichever comes first)	Every 2-5 years
Melanoma		
Dermatologic exam	18 years old	Every 12 months

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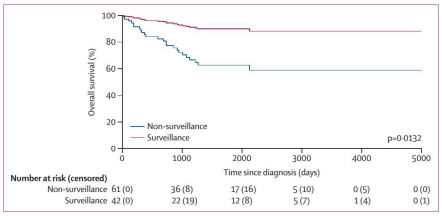
Overall Survival of *TP53* Mutation Carriers in Surveillance and Non-Surveillance Groups



Villani A et al. *Lancet Oncol* 2016;17:1295-1305

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LFS Considerations

- Testing children is appropriate
- Breast cancers are more likely to be triple positive
- Whole body MRI preferred, can do breast, brain separately otherwise
- Radiation sensitivity
  - With breast cancer, radiation therapy should be avoided if possible.
    - Treat the cancer in front of you, even if there is an increased risk of developing a second malignancy

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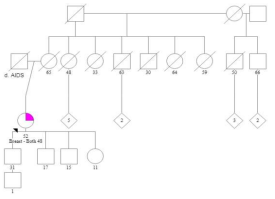
Hereditary Diffuse Gastric Cancer



Summary

Positive result. Pathogenic variant identified in CDH1.

Clinical Summary

- A Pathogenic variant, c.1565+1G>A (Splice donor), was identified in CDH1.
  - The CDH1 gene is associated with autosomal dominant hereditary diffuse gastric cancer (HDGC) syndrome (MedGen UID: 310839), lobular breast cancer (PMID: 11729114, 17545690, 25979631), and possibly an increased risk for colon cancer (PMID: 10072428).
  - This result is consistent with a predisposition to, or diagnosis of, CDH1-related conditions.
  - The estimated lifetime risk of diffuse gastric cancer in individuals with a pathogenic variant in CDH1 is 56–83% for women and 67–80% for men, and the lifetime risk for lobular breast cancer in women is 39%–52%. (PMID: 11729114, 17545690, 20599882, 25979631). Pathogenic variants in CDH1 may also be associated with increased risk for colon cancer (PMID: 10072428). Clinical management guidelines for HDGC syndrome can be found at www.nccn.org.
  - Close relatives (children, siblings, and parents) have up to a 50% chance of being a carrier of this variant. More distant relatives may also be carriers. Parental testing may clarify the inheritance of this variant and may inform recurrence risk and risk for other close relatives. Testing for this variant is available.
- These results should be interpreted within the context of additional laboratory results, family history, and clinical findings. Genetic counseling is recommended to discuss the implications of this result. For access to a network of genetic providers, please contact InvitaeClinicalServices@invitae.com, or visit www.nsgc.org or tags.invitae.com/professional_organizations.asp.

Complete Results

Gene	Variant	Zygosity	Variant Classification
CDH1	c.1565+1G>A (Splice donor)	heterozygous	PATHOGENIC

SCREENING/SURGICAL CONSIDERATIONS	AGE TO START	FREQUENCY
Gastric Cancer[1]		
Prophylactic gastrectomy is recommended. • Baseline endoscopy with multiple random biopsies prior to gastrectomy • Intraoperative frozen sections should be performed to ensure complete removal of gastric tissue • A D2 lymph node dissection is not necessary • Not recommended under 18 years of age, but may be considered for certain patients (i.e. family history of gastric cancer diagnosed under age 25)	Between 18-40 years old	N/A
Patients who elect not to undergo prophylactic gastrectomy should be offered upper endoscopy with multiple random biopsies	Individualized	Every 6-12 months
Female Breast Cancer[2]		
Breast awareness • Women should be familiar with their breasts and promptly report changes to their healthcare provider.	18 years old	Periodic and consistent
Clinical Breast Exam	25 years old	Every 6-12 months
Breast Screening • Mammography with consideration of tomosynthesis • Consider breast MRI with contrast	30 years old	Every 12 months
For consideration of risk-reducing mastectomy , manage based on family history	Individualized	N/A
Consider investigational imaging and screening studies, when available in context of a clinical trial	Individualized	N/A
Consider options for risk reduction agents, such as chemoprevention (i.e. tamoxifen)	Individualized	N/A

NCCN 2.2021 Genetics/Familial High Risk Assessment: Breast, Ovarian, Pancreatic
NCCN 3.2021 Gastric Cancer

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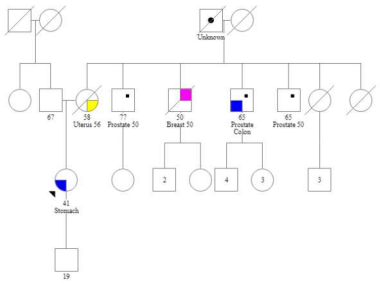

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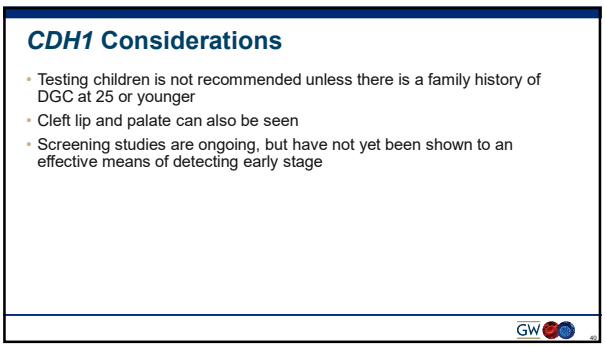
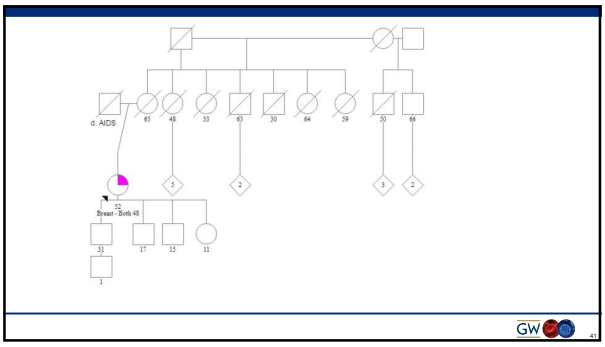
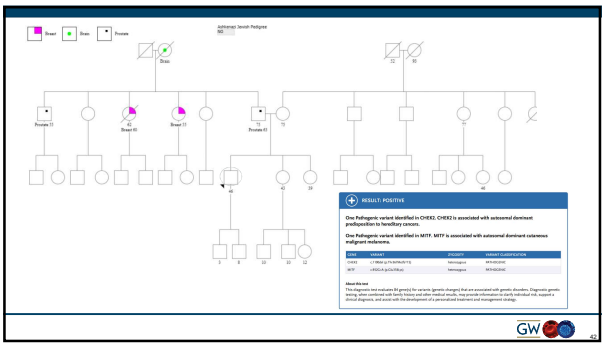
CDH1 Considerations

- Testing children is not recommended unless there is a family history of DGC at 25 or younger
- Cleft lip and palate can also be seen
- Screening studies are ongoing, but have not yet been shown to an effective means of detecting early stage







CHEK2 NCCN Screening Guidelines

SCREENING/SURGICAL CONSIDERATIONS	AGE TO START	FREQUENCY
Female Breast Cancer		
Breast Screening[1] • Mammography with consideration of tomosynthesis • Consider breast MRI with contrast	40 years old, or 5-10 years before the earliest known breast cancer in the family	Every 12 months
For consideration of risk-reducing mastectomy, manage based on family history	Individualized	N/A
Colorectal Cancer[2]		
Colonoscopy *For patients with colorectal cancer, please refer to the surveillance recommendations for post-colorectal cancer resection in the NCCN Guidelines for Colon Cancer and Rectal Cancer.*	For probands unaffected by colorectal cancer with a first degree relative with colorectal cancer, 40 years old or 10 years prior to age of first degree relative's age at colorectal cancer diagnosis For probands unaffected by colorectal cancer and no first degree relative with colorectal cancer, 40 years old	Every 5 years
Prostate Cancer[3]		
No specific screening guidelines exist at this time	N/A	N/A

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Transgender Care

- General recommendations are to start screening mammogram at age 50, and 5-10 years after start of feminizing hormones
- Consider personalization based on strength of family history and personal risk factors
- Absence of data
- www.transcare.ucsf.edu/guidelines

UCSF Transgender Care, Department of Family and Community Medicine, University of California San Francisco. Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People; 2nd edition. Deutsch MB, ed. June 2016.

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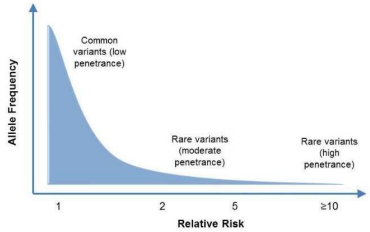
Genetic Architecture of Cancer Risk



https://www.cancer.gov/about-cancer/causes-prevention/genetics/overview-pdq

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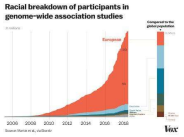
Polygenic Risk Scores

- Use data from GWAS (genome-wide association studies), large scale genetic analyses which focus on uncovering common DNA differences that influence disease and physical traits
- Each variant has modest effect on risk
- Combinations of variants can pose more substantial risk
- Predicts risk in unaffected individuals
- Currently clinically available for breast cancer risk and for *CHEK2* risk stratification for European and Ashkenazi Jewish ancestry

GWAS

- Genome Wide Associate Studies scan the entire genome looking for differences between the control group and the experimental group
- Currently 80% of participants are of European (non Ashkenazi) ancestry
- Better than rate in 2008 (95%!), but really not okay
- Basis for many new advances
- Need information on underrepresented populations: Black, Hispanic, Asian to be truly informative and generalizable
- All of Us Study from NIH hoping to help address this issue



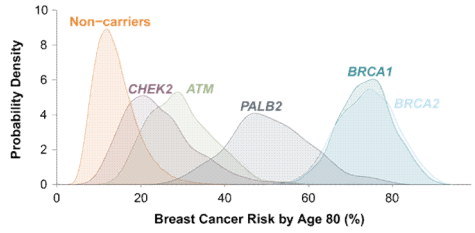
Ancestrally Unbiased PRS

- Efforts to calibrate European derived SNPs to Black/African, Asian and Hispanic ancestral groups are underway

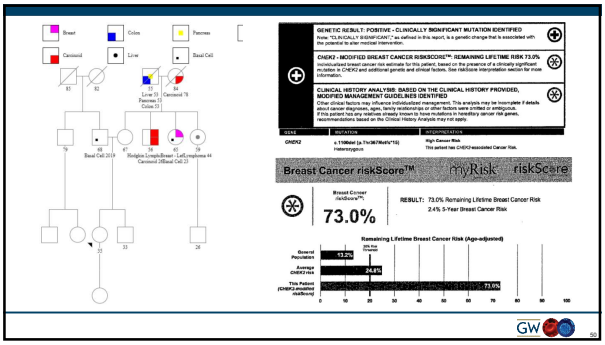
Validation Cohort	Total N	N w/ BC	OR (95% CI)	P-value
All	62,707	15,137	1.41 (1.38-1.44)	2.5×10^{-212}
Asian	1,325	396	1.25 (1.07-1.45)	3.7×10^{-03}
Black/African	6,743	1754	1.23 (1.16- 1.31)	8.5×10^{-11}
Hispanic	5,847	1066	1.35 (1.24-1.46)	1.6×10^{-13}
Mixed Ancestry	2,681	400	1.59 (1.39-1.82)	2.4×10^{-12}
Non-European	14,959	3435	1.29 (1.23- 1.36)	2.5×10^{-25}
White and/or AJ	42,897	10288	1.44 (1.40-1.48)	6.3×10^{-172}

https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.10502

PRS on Mutation Carriers



JAMA Network Open. 2020;3(7):e208501. doi:10.1001/jamanetworkopen.2020.8501



Fanconi Anemia Genes and Breast Cancer Risk

- **High-Risk Genes**
  - *BRCA1* (FANCS)
  - *BRCA2* (FANCD1)
  - *PALB2* (FANCN)
- **Moderate-Risk Genes**
  - *BRIP1* (FANCJ)
  - *FANCD2*
  - *RAD51C* (FANCO)

- 16 genes associated with FA
- 6 have breast cancer risk implications
- Each of these accounts for 3% or less of all pathogenic variants

https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq

Ovarian Cancer

- One of the most heritable cancers, 18% due to a mutation (Norquist, 2016)
  - *BRCA1, BRCA2, BRIP1*, Lynch syndrome, *RAD51C, RAD51D*
    - *PALB2* under investigation
- *BRCA* carriers receive greatest benefit from PARPi
  - Don't forget somatic mutation carriers!
- All epithelial ovarian cancer patients are candidates for genetic testing regardless of age or family history
- WISP trial available for carriers

Gene	Ovarian Cancer Risk	RRSO Rec Age	Other Cancer Risk
ATM	<3%	Manage based on fam hx	Breast, Pancreas
BRIP1	>10%	45-50	Breast (TNBC)
RAD51C	>10%	45-50	Breast (TNBC)
RAD51D	>10%	45-50	
BRCA1	39-58%	35-40	Breast
BRCA2	13-29%	40-45	Breast
MLH1/MSH2	>10%	Individualized	Colon, Uterine
MSH6	>10%	Insufficient data	Colon, Uterine
PMS2	<3%	Insufficient data	Colon, Uterine
PALB2	3-5%	Manage based on fam hx	Breast, Pancreas
STK11	>10% (non epithelial)	Not recommended	Colon, Pancreas, Stomach, Breast

Negative Germline?

- It's not over yet…
  - 3% of breast cancers harbor *BRCA* somatic mutations
  - 7-8% of ovarian cancers harbor *BRCA* somatic mutations

PARPi in Ovarian Cancer

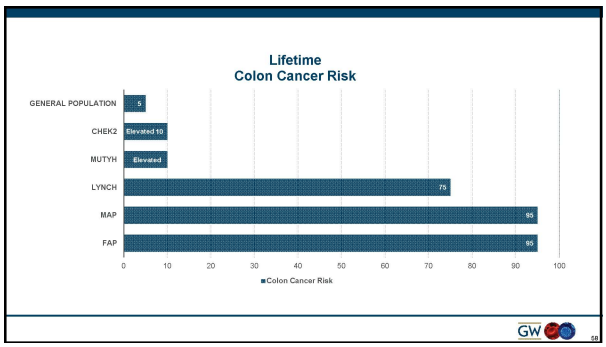
- Stage II-IV
- Approved as first line maintenance for women with a complete or partial response to platinum chemotherapy
- Stronger responses in those who are *BRCA+*

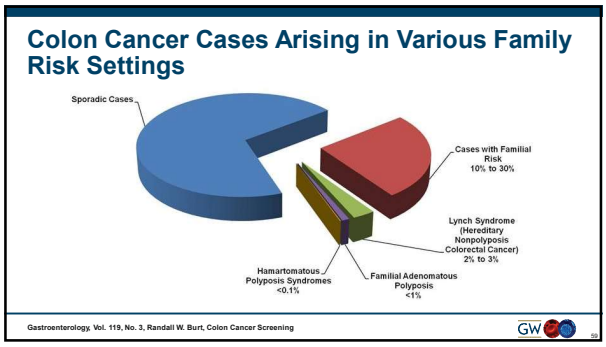
Colorectal Syndromes- Tumor Suppressor Genes

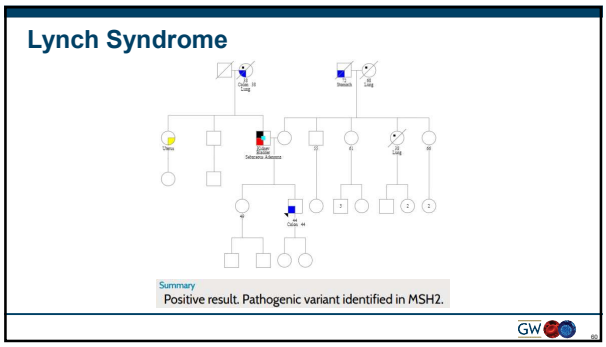
Gene	Syndrome	Inheritance	Predominant Cancer
APC	Familial Adenomatous Polyposis	AD	Colon, Intestinal
TP53	Li-Fraumeni	AD	Multiple (Including colon)
STK11	Peutz-Jeghers	AD	Multiple (Including intestinal)
PTEN	Cowden	AD	Multiple (including intestinal)
BMPR1A	JPS	AD	Gastrointestinal
SMAD4	JPS	AD	Gastrointestinal

Colorectal Cancer Syndromes - MMR Genes

Gene	Syndrome	Inheritance	Predominant Cancer
MLH1, MSH2, MSH6, PMS2	Lynch	AD	Multiple (Including colon, uterine and others)
EPCAM	Lynch	AD	Multiple (including colon, uterine, and others)
MUTYH	MUTYH Associated Polyposis (MAP)	AR	Colon
POLE/POLD1	Oligopolyposis	AD	Colon, endometrial

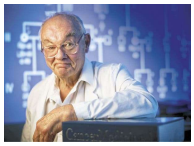






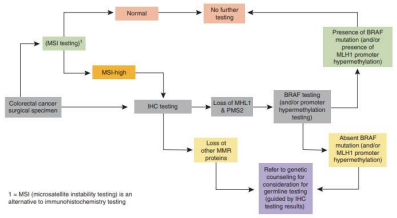
Lynch Syndrome

- AKA: HNPCC
  - Primarily a colon and uterine cancer syndrome
- Genes associated with Lynch Syndrome:
  - *MLH1, MSH2, MSH6, PMS2, EPCAM*
- Most common form of hereditary colon cancer
- Autosomal Dominant inheritance
  - AR inheritance leads to CMMRD
- Standard of care to screen all colon/uterine cancers by MSI or IHC



Dr. Henry Lynch
1928-2019

Guidelines on Genetic Evaluation and Management of Lynch Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer



Lynch Syndrome Cancer Risks Vary By Gene

Cumulative Risk for Diagnosis Through Age 80y

	MLH1	*MSH2/EPCAM*	*MSH6*	*PMS2*
Colorectal	46-61%	33-52%	10-44%	8.7-20%
Endometrial	34-54%	21-57%	16-49%	13-26%
Breast	No data	1.5-12.8%	11.1-12.8%	8.1-12.8%
Ovary	4-20%	8-38%	1-13%	3%
Gastric	5-7%	.2-9%	1-7.9%	Inadequate data
Pancreas	No data	.5-1.6	1.4-1.6%	1-1.6%
Bladder	2-7%	4.4-12.8%	1-8.2%	1-2.4%
Biliary Tract	1.9-3.7%	.02-1.7%	NE	.2-1%
Renal pelvis/ureter	.2-5%	2.2-28%	.7-5.5%	1-3.7%
Small Bowel	.4-11%	1.1-10%	1-4%	.1-.3%
Prostate	04.4-11.6%	3.9-15.9%	2.5-11.6%	4.6-11.6%

NCCN 1.2021 Genetic/Familial High Risk Assessment: Colorectal

Variable Lynch syndrome recommendations

	MLH1	*MSH2/EPCAM*	*MSH6*	*PMS2*
Age to start colonoscopy	20-25	20-25	30-35	30-35
Frequency of colonoscopy	1-2 years	1-2 years	1-2 years	1-2 years
RRSO	Consider RRSO	Consider RRSO	Insufficient evidence	Insufficient evidence

NCCN 1.2021 Genetic/Familial High Risk Assessment: Colorectal

64

CMMRD

- Constitutional Mismatch Repair Deficiency
  - When an individual has biallelic mutations in an MMR gene (AR Inheritance)
- Childhood cancer syndrome
  - 16 fold increased risk in developing cancer
- Heme, CNS, Colon cancers with risks starting at age 1
- Derm features overlapping with NF

65

Polyposis Syndromes

Familial Adenomatous Polyposis (FAP): *APC*

- AD inheritance
- Classic: 100s-1000s of polyps
- Attenuated (AFAP): 10-100 polyps (Avg 30)
- 30% de novo rate for classic
- Upper GI, CHRPE, desmoids, osteomas, thyroid, brain
- APC I1307K = low risk mutation (AJ)

MUTYH Associated Polyposis (MAP): *MUTYH*

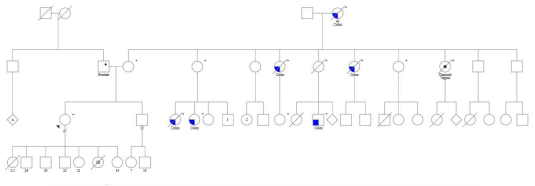
- AR inheritance
- A single mutation slightly increases risk

POLE/POLD1

- AD Inheritance

68

Familial Adenomatous Polyposis



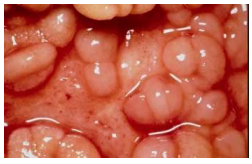
Summary
Positive result. Pathogenic variant identified in APC.

Risks for Extraintestinal Malignancies in FAP

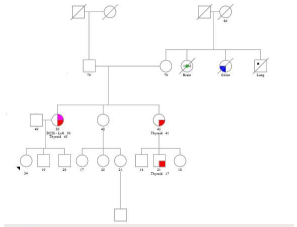
Type of Malignancy	Lifetime Risk
Small bowel: duodenum or periampulla	4-12%
Thyroid: Papillary thyroid cancer	1-2% (higher in women)
CNS: Medulloblastoma	<1%
Liver: Hepatoblastoma	1-2%
Pancreatic Adenocarcinoma	1%
Bile Duct Adenocarcinoma	<1%
Gastric Adenocarcinoma	<1% in Western cultures

FAP Management

- TAC/IRA is recommended for AFAP and TPC/IPAA is recommended for FAP
- If surgery is declined or deferred, yearly c'scope starting at age 10-15.



MEN2/FMTC



Summary
Positive result. Pathogenic variant identified in RET.
Variant of Uncertain Significance identified in MSH3.

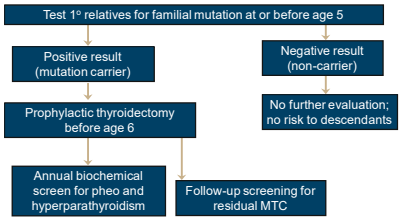
MEN2 Clinical Features

Medullary thyroid cancer

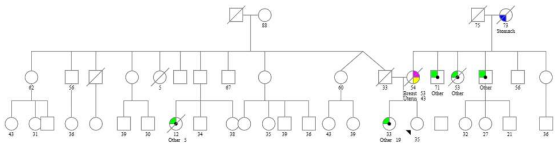
MEN2A
- Pheochromocytoma, PC (50%)
- Parathyroid hyperplasia, HPT (15-30%)

MEN 2B
- Pheochromocytoma (50%)
- Developmental Abnormalities: Ganglioneuromatosis, Mucosal Neuromas, Marfanoid Phenotype

Genetic Testing in MEN 2A or FMTC Families With Known *RET* Mutations



Cowden Syndrome



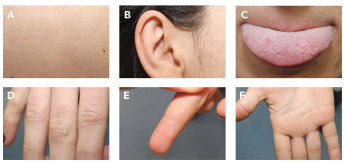
CancerNext-Expanded: Analyses of 49 Genes Associated with Hereditary Cancer

PANEL RESULTS	
PTEN	Pathogenic Mutation: p.R233*
ATM	Variant, Unknown Significance: p.P1354T
MSH2	Variants, Unknown Significance: p.M91T p.N839D

GW 73

PTEN Clinical Features

- Macrocephaly (58cm women, 60cm men)
- Thyroid cancer (papillary or follicular)
- Breast cancer
- Uterine cancer
- GI Polyps (hamartomas)
- Multiple cutaneous lesions
- Oral papillomas
- Autism
- Kidney cancer



GW 74

SCREENING/SURGICAL CONSIDERATIONS*	AGE TO START	FREQUENCY
Female Breast Cancer		
Breast awareness • Women should be familiar with their breasts and promptly report changes to their healthcare provider	18 years old	Periodic and consistent
Clinical Breast Exam	25 years old, or 5-10 years before the earliest known breast cancer in the family (whichever is first)	Every 6-12 months
Breast Screening • Mammography with consideration of tomosynthesis • Breast MRI with contrast	30-35 years old, or 5-10 years before the earliest known breast cancer in the family (whichever is first) Women treated for breast cancer: MRI and mammogram of remaining breast tissue	Every 12 months
Discuss option of risk-reducing mastectomy	>75 years old: individualized management Individualized	Individualized N/A
Endometrial Cancer		
Encourage prompt response to symptoms (e.g., abnormal bleeding)	Individualized	Individualized
Consider random endometrial biopsies and/or ultrasound	30-35 years old	Every 12 months
Discuss option of hysterectomy upon completion of childbearing	Individualized	N/A
Thyroid Cancer		
Comprehensive physical exam, with particular attention to thyroid exam	18 years old, or 5 years before the youngest age of diagnosis of PTEN hamartoma tumor syndrome-related cancer in the family (whichever is first)	Every 12 months
Thyroid ultrasound	Time of PTEN hamartoma tumor syndrome diagnosis	Every 12 months
Colorectal Cancer		
Colonoscopy	35 years old unless symptomatic, or if close relative with colorectal cancer before age 40, then start 5-10 years before the earliest known colorectal cancer in the family	Every 5 years, or more frequently if patient is symptomatic or polyps found
Kidney Cancer		
Renal ultrasound	40 years old	Every 1-2 years
Melanoma		
Dermatologic management	Individualized	Clinician's discretion
Other Cancers		
Psychomotor assessment in children and brain MRI if there are symptoms	In childhood (at diagnosis)	Clinician's discretion

NCCN 1.2021 Genetics/Familial High Risk Assessment: Breast, Ovarian, Pancreatic

GW 75

Prostate Cancer

- Genetic mutation carriers tend to have:
  - Earlier age of diagnosis
  - More aggressive disease
  - Higher likelihood to metastasize
- FDA approval for use of PARPi
  - *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54* metastatic castration-resistant prostate cancer
  - Phase III PROfound trial showed an OS benefit
  - TRITON2 trial showed nearly 45% of men with BRCA2 mutations showed a tumor response
    - In more than half of these men the response lasted at least 6 months

GW 76

199 of 1158 (17.2%) Tulane prostate cancer patients had identifiable mutation in MGPT

ATM	*BRCA1*	*BRCA2*	*CHEK2*	*EPCAM*
HOXB13	*MLH1*	*MSH2*	*MSH6*	*NBN*
PMS2	*TP53*	*PALB2**	*RAD51D**	

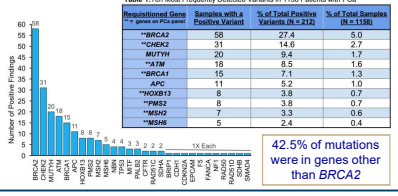


Table 1: Ten Most Frequently Detected Variants in 1158 Patients with PCa

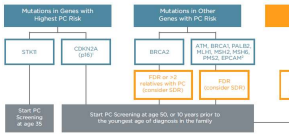
Requisitioned Gene *** = genes on PCa panel	Samples with a Positive Variant	% of Total Positive Variants (N = 212)	% of Total Samples (N = 1158)
BRCA2	58	27.4	5.0
CHEK2	31	14.6	2.7
MUTYH	20	9.4	1.7
ATM	18	8.5	1.6
BRCA1	15	7.1	1.3
APC	11	5.2	1.0
HOXB13	8	3.8	0.7
PMS2	8	3.8	0.7
MSH2	7	3.3	0.6
MSH6	5	2.4	0.4

42.5% of mutations were in genes other than *BRCA2*

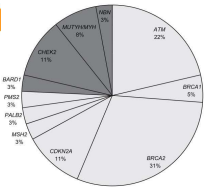
Piper LW et al. ASCO 2017

GW 77

Pancreatic Cancer



Genes	Lifetime PC Risk
STK11	11-36%
CDKN2A	Up to 17%
BRCA2	7% (higher in some families)
MLH1, MSH2, EPCAM	Up to 6%
ATM, BRCA1, PALB2, MSH6, PMS2	Elevated



14% had a mutation identified, 9% did not meet criteria for FPC. Testing should be offered to all with PADC.

Chaffee KR et al. Genet Med 2018;20:119-127
Canto MI, et al. Gut 2013; 62:339-347.
Syngal S, et al. Am J Gastroenterol 2015; 110:223-262

GW 78

NCCN Update for Screening

- MRCP and/or EUS can be considered for:
  - Carriers of ATM, BRCA1, BRCA2, CDKN2A, Lynch syndrome, PALB2, STK11, TP53 with a family history of pancreatic cancer
  - 2 or more first degree relatives with pancreatic cancer, even in absence of a mutation
  - 3 or more first or second degree relatives with pancreatic cancer, even in absence of a mutation

PARPi and Pancreatic Cancer

- FDA Approval:
  - First line maintenance therapy for patients whose disease has not progressed on at leat 16 weeks of platinum based chemotherapy
  - BRCA1 or BRCA2 germline mutation

Syndromes with Melanoma Risk

Gene	Effect on Pigment	Effect on Nevi	Penetrance	Other cancer risks
CDKN2A	No	Yes	High	Panc, Breast, cervical, GI, lymphoma, lung, Wilm's
CDK4	No	Yes	High	Similar to CDKN2A
TERT	No	Yes	High	Renal, bladder, AML, myeloproliferative neoplasms
POT1	No	No	High	Glioma, brain, breast, lung, CLL, endometrial
ACD	No	No	High	Breast, brain, lung, ovarian, cervical, colorectal, prostate, myeloproliferative neoplasms
TERF2IP	No	No	High	Similar to ACD
BAP1	No	Yes	High	Uveal melanoma, mesothelioma, renal, meningioma, paraganglioma
PTEN	Yes	Yes	High	Breast, thyroid, endometrium, colorectal, kidney
MC1R	Yes	No	Medium	None reported
BRCA2	No	No	Medium	Breast, ovarian, prostate, pancreas
MITF	Yes	Yes	Medium	Pancreatic, Renal

RiskHawkes JE et al. *Sem Oncol* 2016;43:591-597

Genetic Testing Referral Criteria: Affected Patients

- All ovarian
- All pancreatic
- Colon or uterine under age 50
- All medullary thyroid
- All pheochromocytoma/ paraganglioma
- All adrenal cortical carcinoma
- Anyone Tested prior to 2014
- Metastatic prostate cancer
- PREMM, BRCAPro, Penn II or other validated model showing a 10% risk for having a mutation

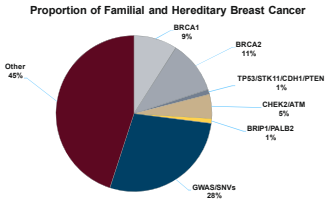
Genetic Testing Referral Criteria: Breast Cancer Patients

- Breast cancer under age 45
- Breast cancer and AJ heritage
- Male breast cancer
- Triple neg breast cancer under age 60
- Bilateral breast cancer under age 50
- Metastatic, Her2- breast cancer
- Anyone Tested prior to 2014
- 2 or more family members with breast cancer at any age
- Family history of ovarian, pancreatic, or metastatic prostate cancer
- Dx <50 and limited or male dominated family structure

Genetic Testing Referral Criteria: Unaffected

- First or second degree relative that meets criteria
  - Per NCCN
  - Not necessarily per insurance!
- Anyone Tested prior to 2014

The changing pie chart



Thank You!

Feel free to email me with any questions or comments.

Elizabeth Stark, MS, LCGC
estark@mfa.gwu.edu