Hereditary Breast and Ovarian Cancers: Risk Management Recommendations

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National Comprehensive Cancer Network®

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Objectives

① Identify genes associated with Hereditary Breast/Ovarian Cancer, including new and emerging genes

② Summarize risk management recommendations for Hereditary Breast/Ovarian Cancer

③ Be familiar with genetic testing strategies and limitations of interpreting a negative test result.

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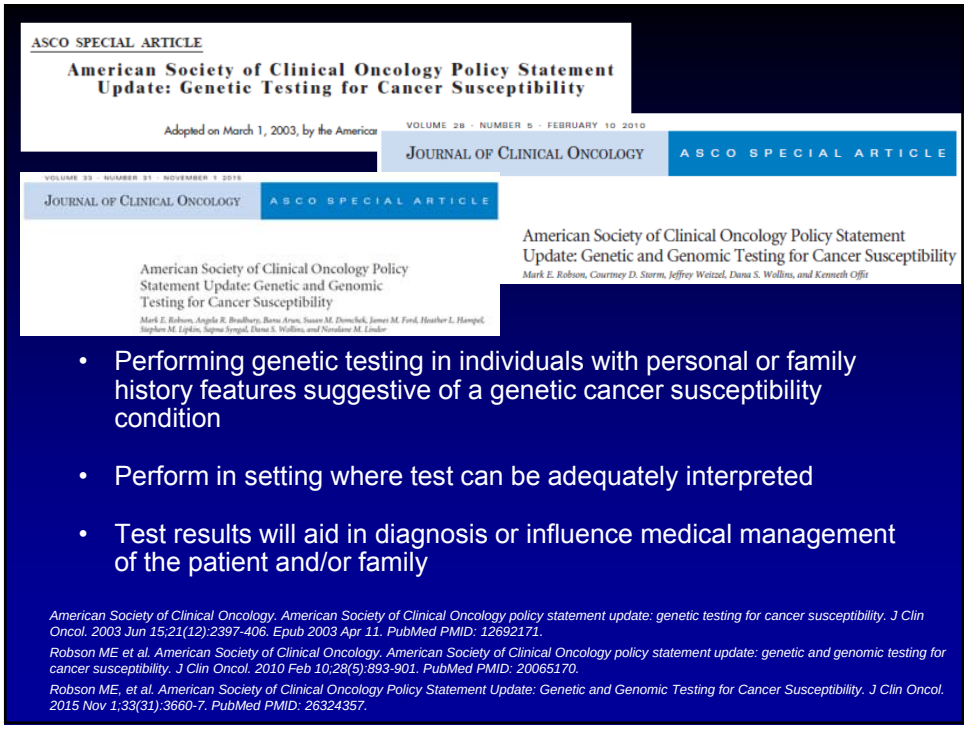

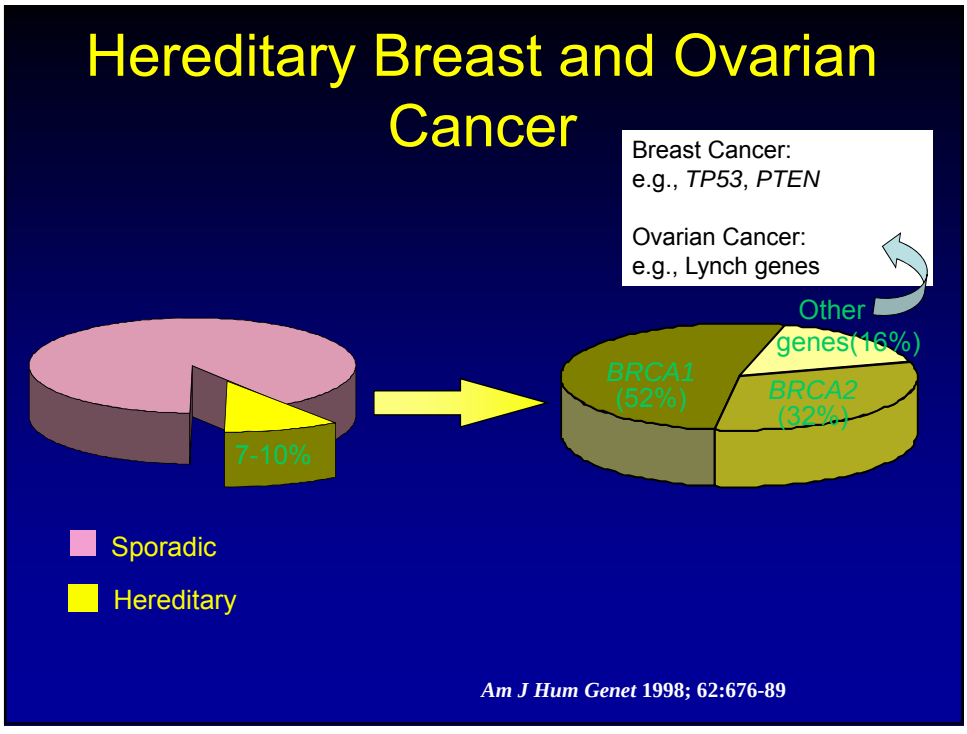

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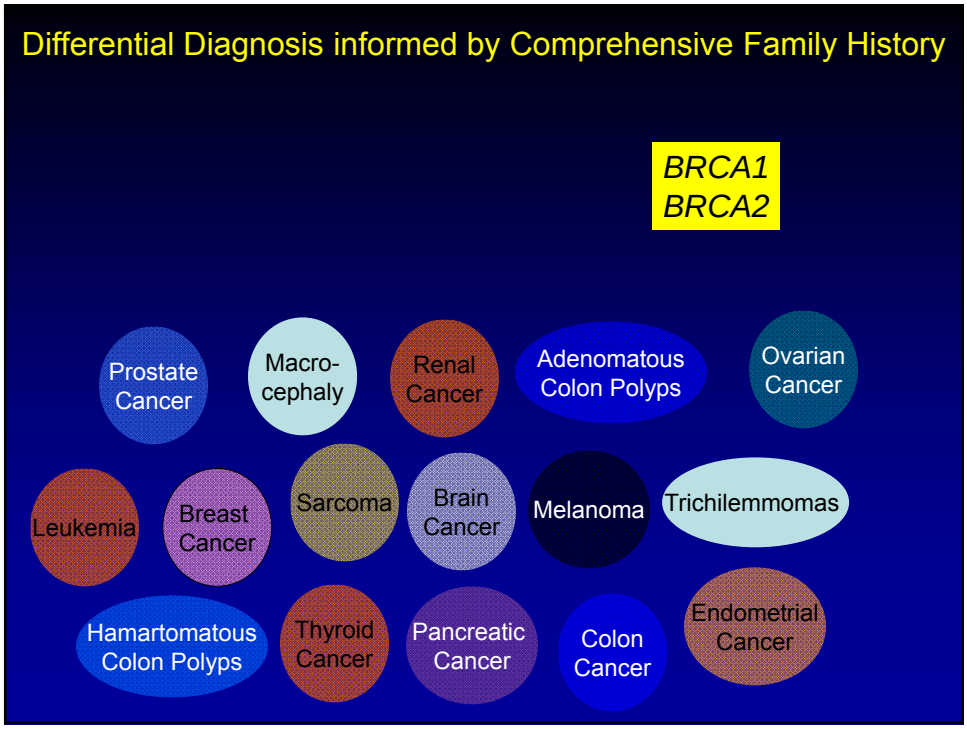

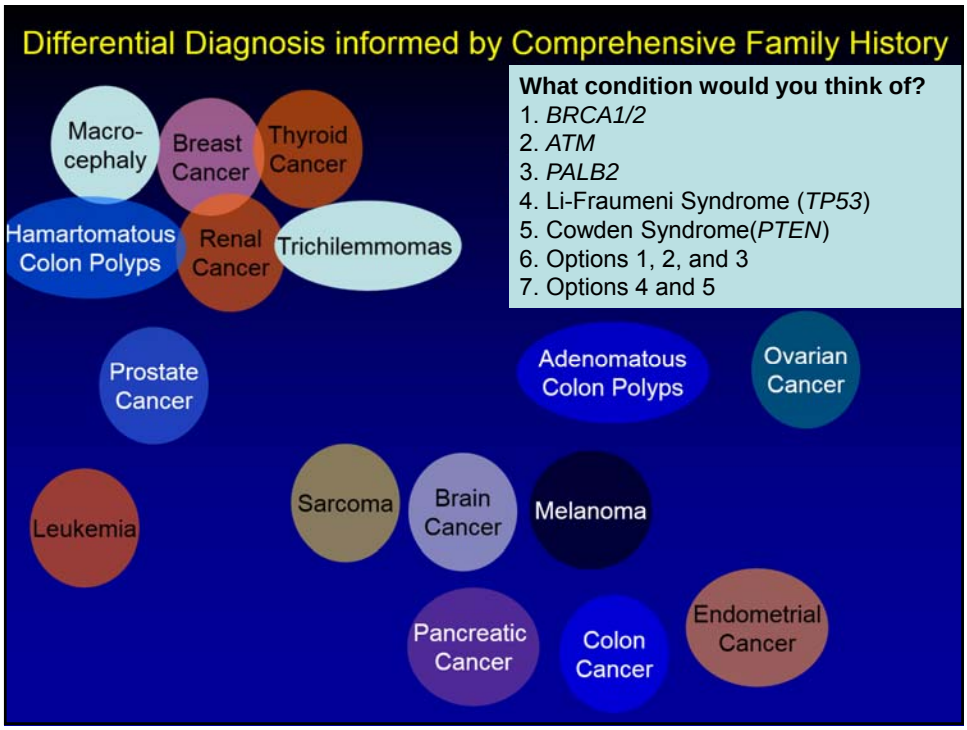

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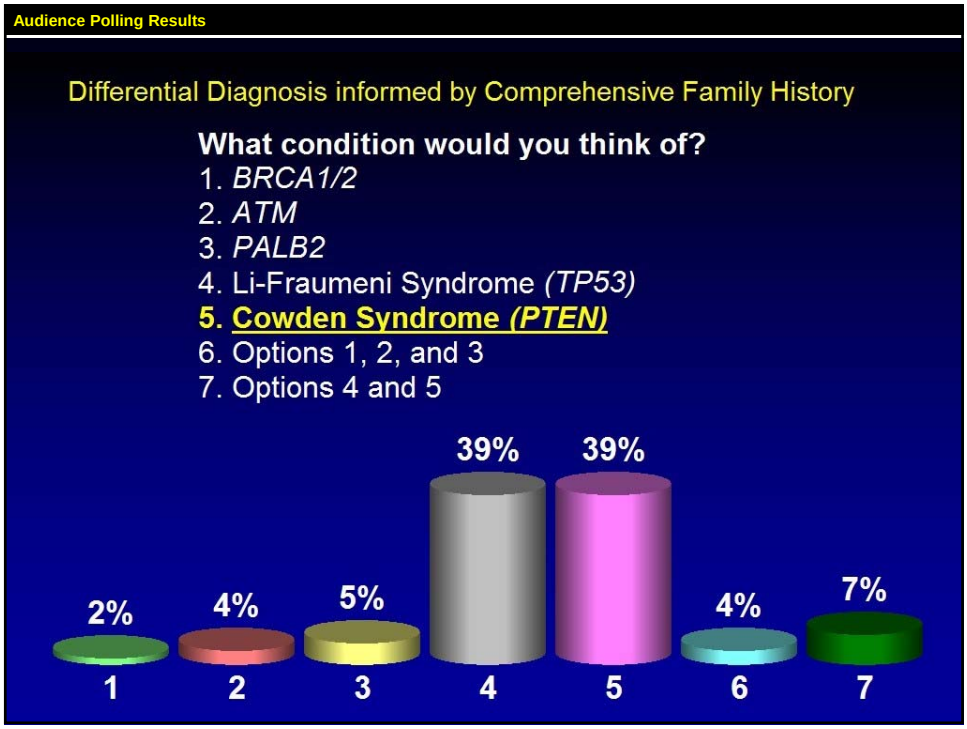

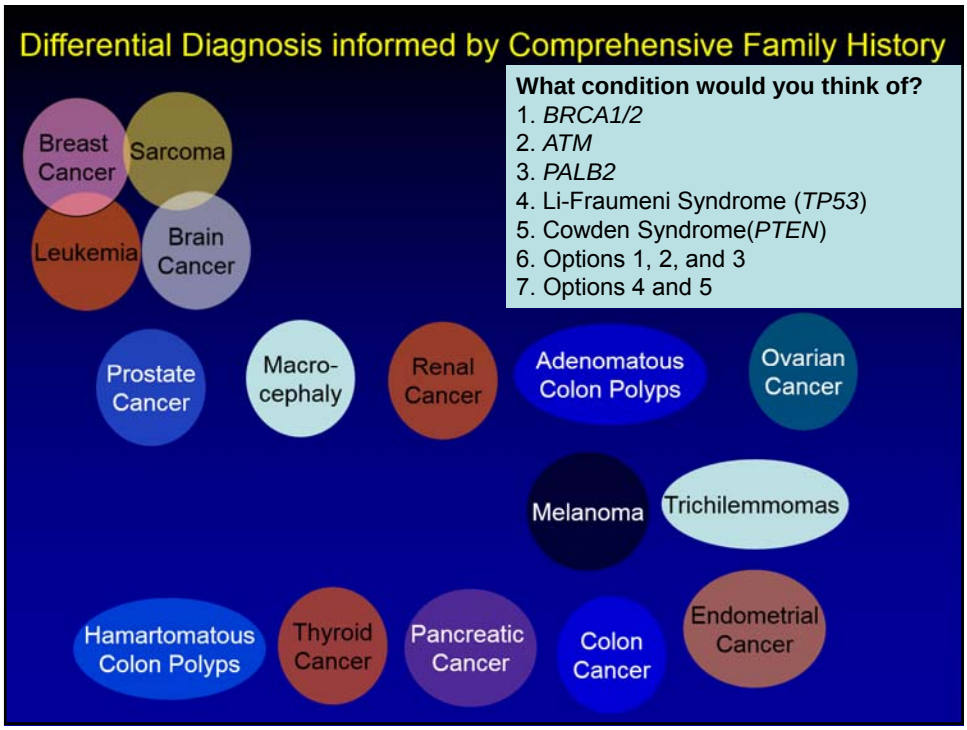

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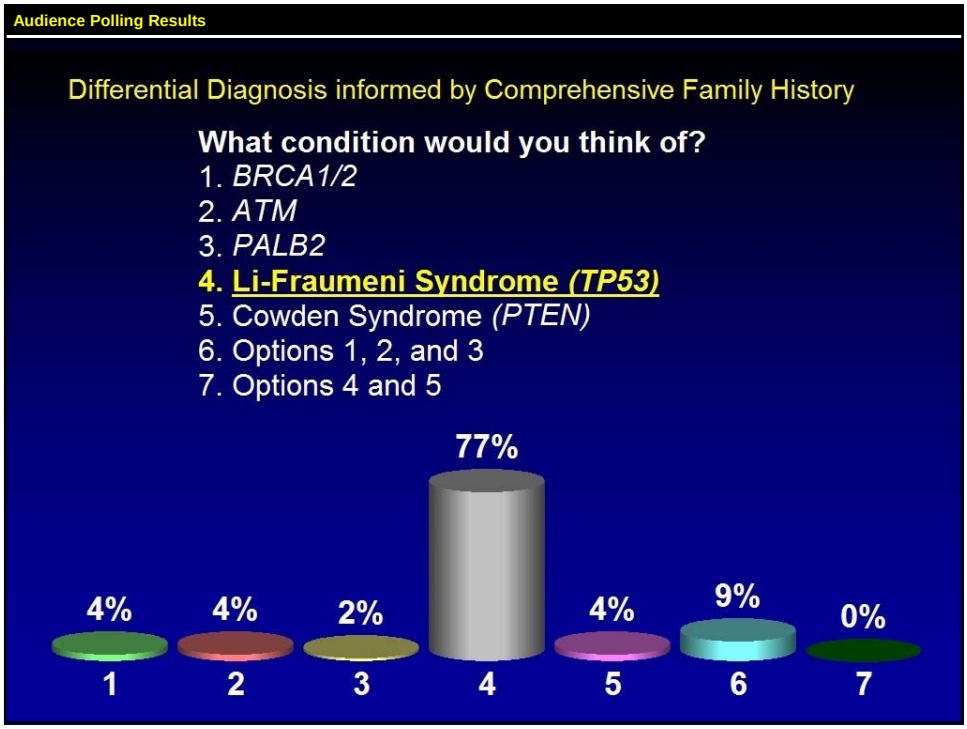

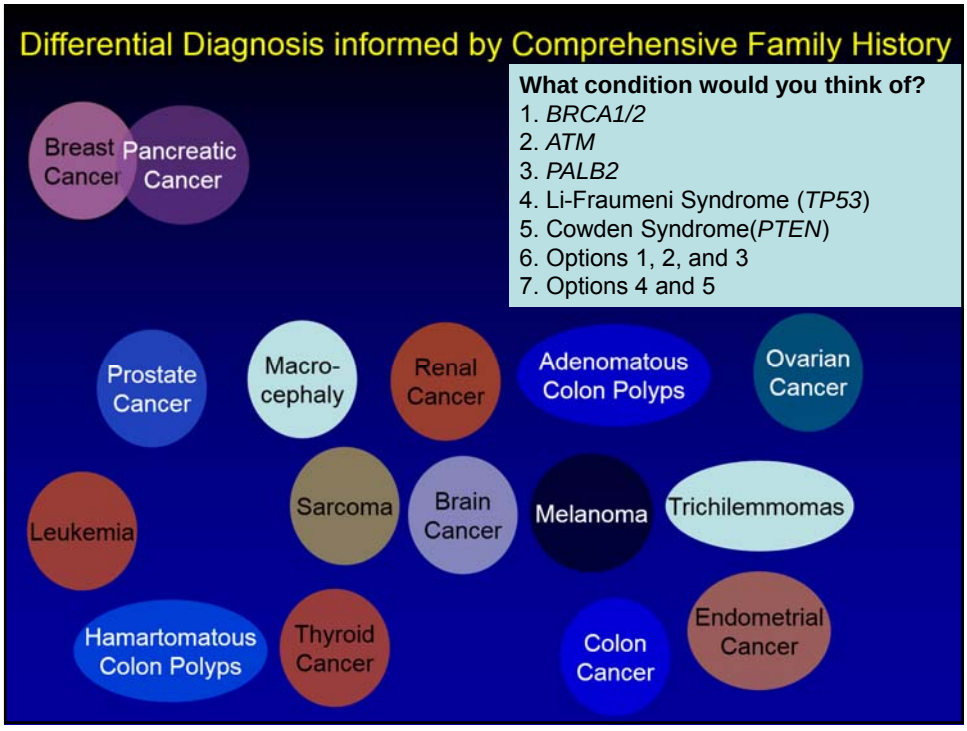

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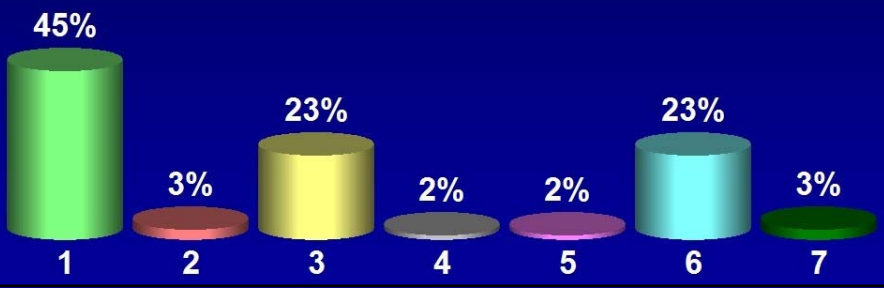
Audience Polling Results

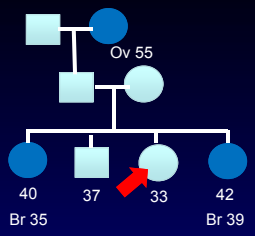
Differential Diagnosis informed by Comprehensive Family History

What condition would you think of?

1. *BRCA1/2*
2. *ATM*
3. *PALB2*
4. Li-Fraumeni Syndrome *(TP53)*
5. Cowden Syndrome *(PTEN)*
6. **Options 1, 2, and 3**
7. Options 4 and 5



Considerations when testing



You perform *BRCA* testing on an unaffected 33 year old woman with two sisters diagnosed with breast cancer <50 and a paternal grandmother with ovarian cancer. Her *BRCA* results return as no mutation detected.

How do you advise the family?

1. She is at general population risk for breast and ovarian cancer
2. There is no *BRCA* mutation present in the family
3. Testing her sisters with breast cancer would help to interpret her negative test result
4. Testing her unaffected brother would help to interpret her negative test result
5. Options 1 and 2 above

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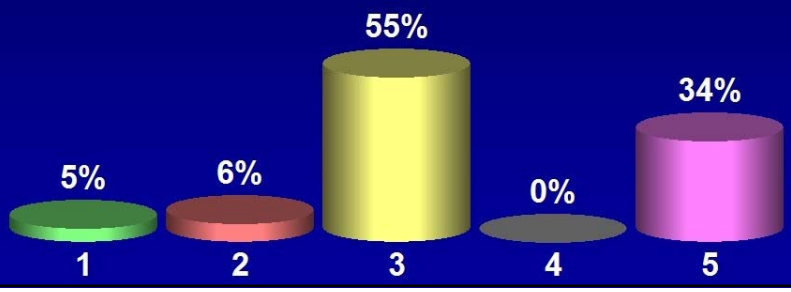
Audience Polling Results

Considerations when testing

How do you advise the family?

1. She is at general population risk for breast and ovarian cancer
2. There is no BRCA mutation present in the family
3. **Testing her sisters with breast cancer would help to interpret her negative test result**
4. Testing her unaffected brother would help to interpret her negative test result
5. Options 1 and 2 above

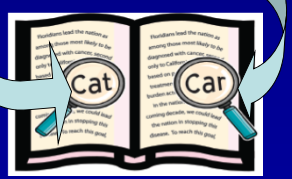


Interpretation of Genetic Test Results

True Negatives

Uninformatives

"No mutation detected" (negatives)	"Deleterious mutation" (positives)	"Variant of Uncertain Significance" (VUS)
◆ Chance that cancer was due to a *BRCA* gene change goes down. ◆ There may still be a chance that cancer "runs in your family."	◆ Increased cancer risk.	◆ Cancer risk not completely known.
the cat ate the rat	the car ate the rat	the cat ate one rat



Genes: set of encyclopedias…

Mutations: 'spelling mistakes'

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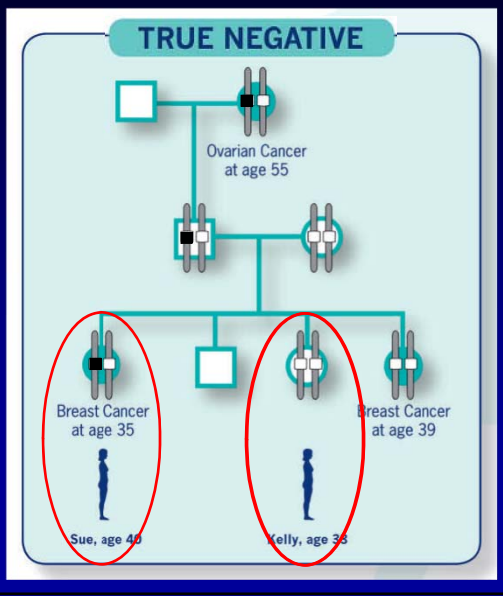
Concept of 'best testable' Uninformative versus True Negative



Anna and Irene

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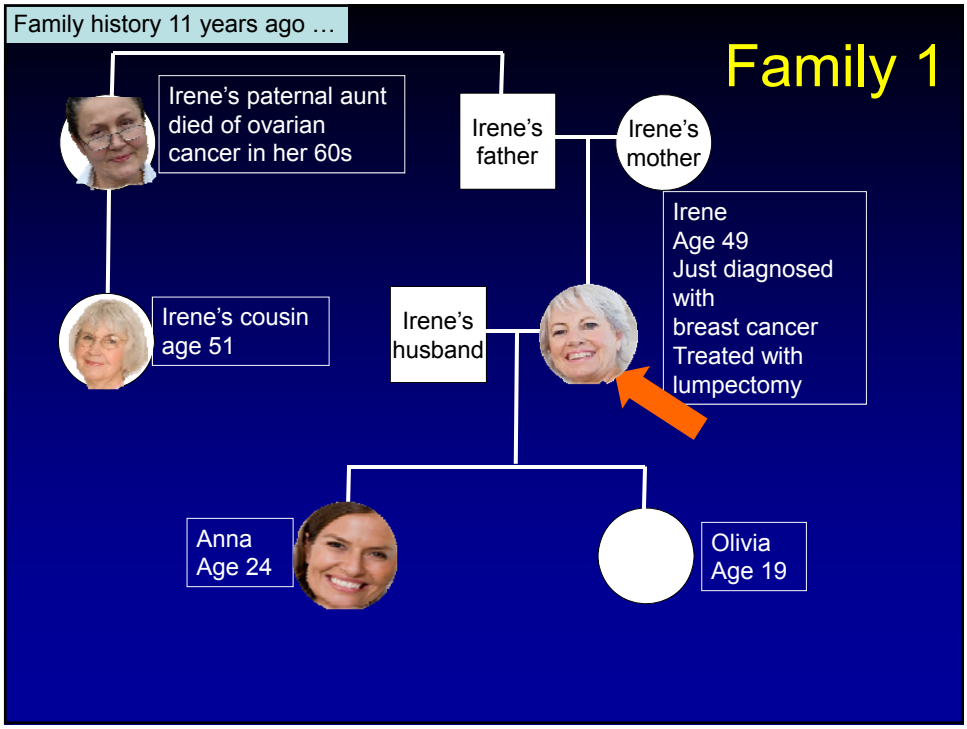

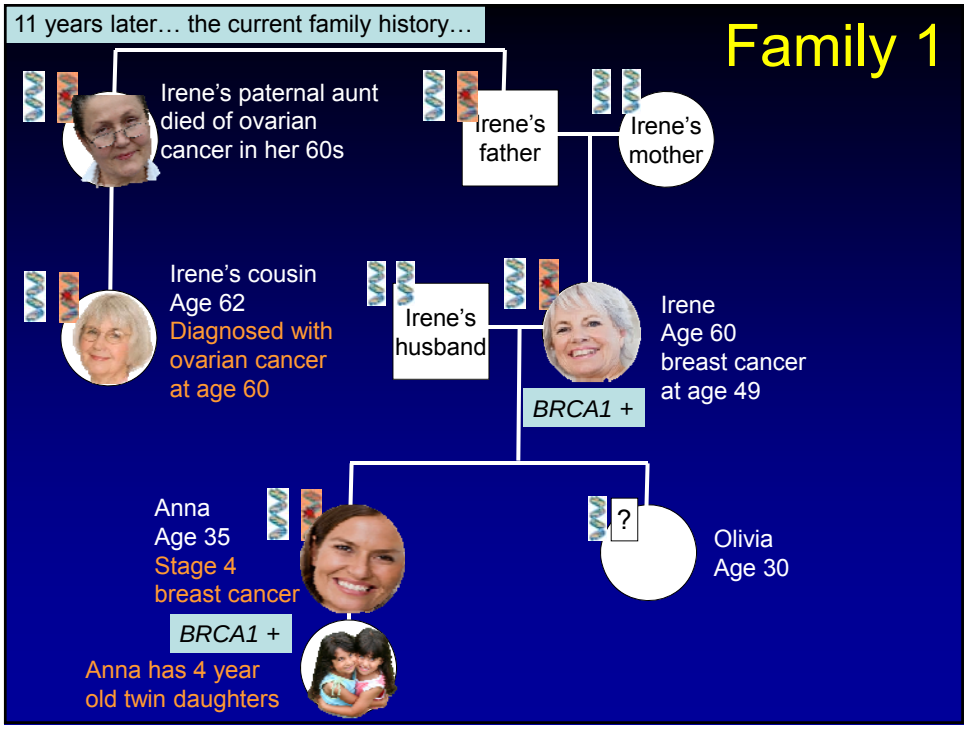

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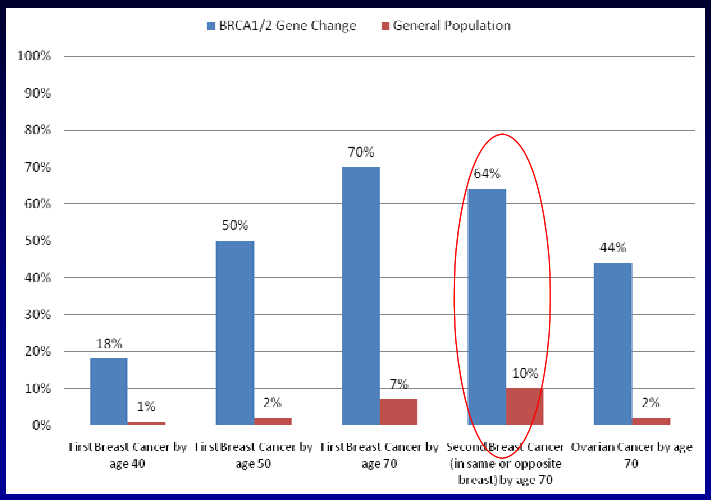
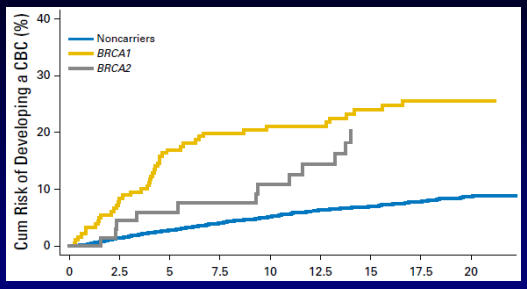
A *BRCA* Mutation Increases Breast and Ovarian Cancer Risks



Antoniou A, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003 May;72(5):1117-30. Epub 2003 Apr 3. Erratum in: Am J Hum Genet. 2003 Sep;73(3):709. PubMed PMID: 12677558

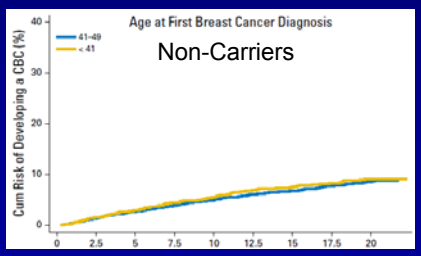
Chen S, et al. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007 Apr 10;25(11):1329-33. PubMed PMID: 17416853

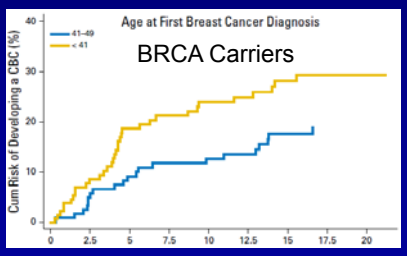
Contralateral Breast Cancer Risks



Dutch Study of 6294 women with invasive breast cancer <50 y, including 200 BRCA1+, 71 BRCA2+

10-year cumulative breast cancer risk:
BRCA1: 21.1%
BRCA2: 10.8%
Non-carriers: 5.1%





van den Broek AJ, et al. Impact of Age at Primary Breast Cancer on Contralateral Breast Cancer Risk in BRCA1/2 Mutation Carriers. J Clin Oncol. 2016 Feb 10;34(5):409-18. doi: 10.1200/JCO.2015.62.3942. Epub 2015 Dec 23. PubMed PMID: 26700119.

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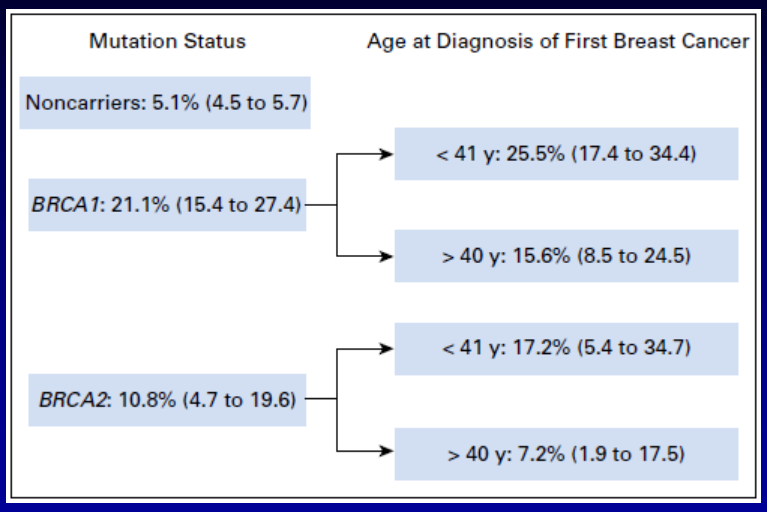
Contralateral Breast Cancer Risks



van den Broek AJ, et al. Impact of Age at Primary Breast Cancer on Contralateral Breast Cancer Risk in BRCA1/2 Mutation Carriers. J Clin Oncol. 2016 Feb 10;34(5):409-18. doi: 10.1200/JCO.2015.62.3942. Epub 2015 Dec 23. PubMed PMID: 26700119.

NCCN Guidelines Version 2.2016
BRCA-Related Breast and/or Ovarian Cancer Syndrome

BRCA MUTATION-POSITIVE MANAGEMENT

WOMEN

- Breast awareness starting at age 18 y.
- Clinical breast exam, every 6–12 mo, starting at age 25 y.
- Breast screening
  - Age 25–29 y, annual breast MRI screening (preferred) or mammogram if MRI is unavailable or individualized based on family history if a breast cancer diagnosis before age 30 is present.
  - Age 30–75 y, annual mammogram and breast MRI screening.
  - Age >75 y, management should be considered on an individual basis.
  - For women with a *BRCA* mutation who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.
- Discuss option of risk-reducing mastectomy
  - Counseling may include a discussion regarding degree of protection, reconstruction options, and risks.
- Recommend risk-reducing salpingo-oophorectomy (RRSO), typically between 35 and 40 y, and upon completion of child bearing. Because ovarian cancer onset in patients with *BRCA2* mutations is an average of 8–10 years later than in patients with *BRCA1* mutations, it is reasonable to delay RRSO until age 40–45 y in patients with *BRCA2* mutations who have already maximized their breast cancer prevention (ie, undergone bilateral mastectomy). See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer- Principles of Surgery.

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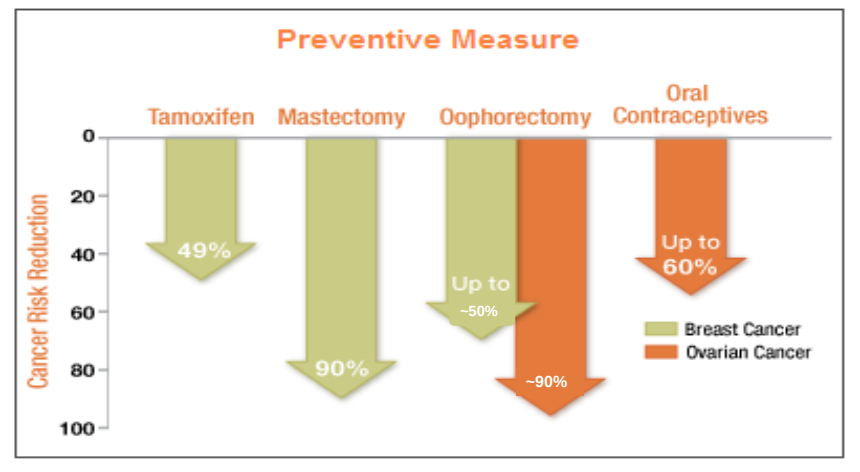
Cancer Prevention Options



http://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq
Garcia C, Powell CB. A comprehensive approach to the identification and management of the BRCA patient. Obstet Gynecol Surv. 2015 Feb;70(2):131-43. Review. PubMed PMID: 25671374.
Pruthi S, Gostout BS, Lindor NM. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. Mayo Clin Proc. 2010 Dec;85(12):1111-20. doi: 10.4065/mcp.2010.0414. Review. PubMed PMID: 21123638; PMC2996153.

What about salpingectomy?

Salpingectomy (removal of the fallopian tubes only) is proven to reduce the risk of ovarian cancer.

1. TRUE
2. FALSE

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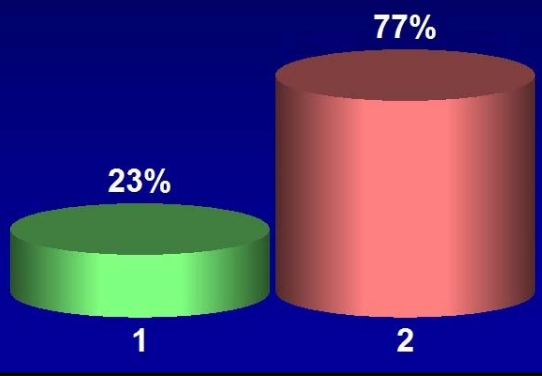
Audience Polling Results

What about salpingectomy?

Salpingectomy (removal of the fallopian tubes only) is proven to reduce the risk of ovarian cancer.

1. TRUE
2. **FALSE**



What about salpingectomy?


Published OnlineFirst January 13, 2015; DOI: 10.1158/1940-6207.CAPR-14-0293

Review

Cancer Prevention Research

Salpingectomy as a Means to Reduce Ovarian Cancer Risk

Mary B. Daly[1], Charles W. Dresher[2], Melinda S. Yates[3], Joanne M. Jeter[4], Beth Y. Karlan[5], David S. Alberts[6], and Karen H. Lu[3]

- Evidence to suggest that many ovarian cancers may begin in the fallopian tube epithelium
- Thus, bilateral salpingectomy (removal of the fallopian tubes) suggested as an interim procedure to reduce ovarian cancer risk
  - Preserves ovarian function which prevents premature menopause
- Currently: No data prove that salpingectomy reduce ovarian cancer risks
- Next steps: Gather evidence, preferably through an RCT:
  - Single-step (BSO) versus two-staged approach

Daly MB et al. Salpingectomy as a means to reduce ovarian cancer risk. Cancer Prev Res (Phila). 2015 May;8(5):342-8. doi: 10.1158/1940-6207.CAPR-14-0293. Epub 2015 Jan 13. Review. PubMed PMID: 25586903; PubMed Central PMCID: PMC4417454.

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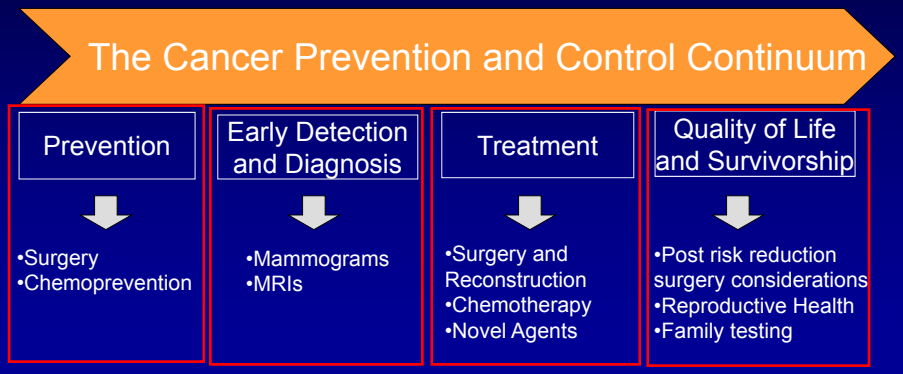
Why is inherited cancer important to identify?

- Using Inherited Breast Cancer as an example:



If this family had *BRCA* mutation identified 11 years ago, how could that have changed their lives?

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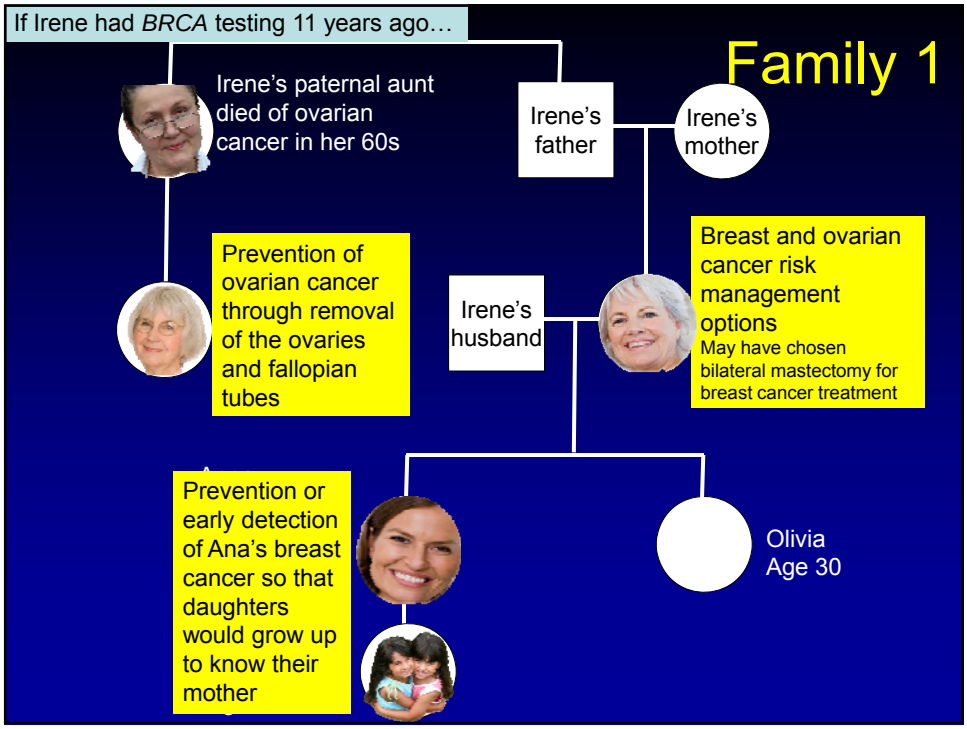

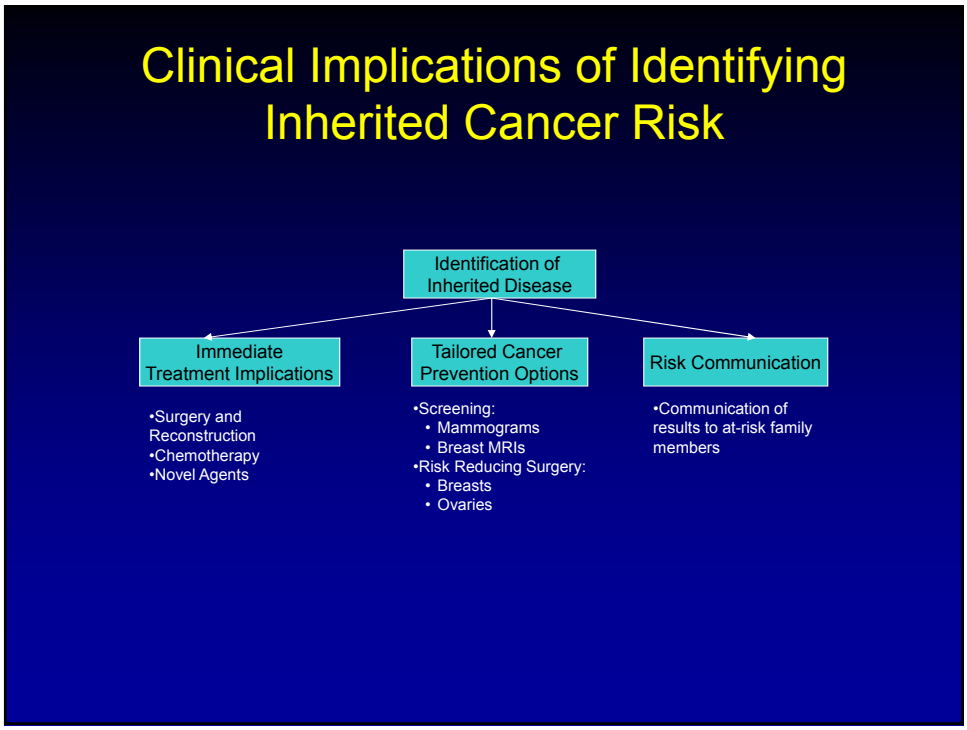

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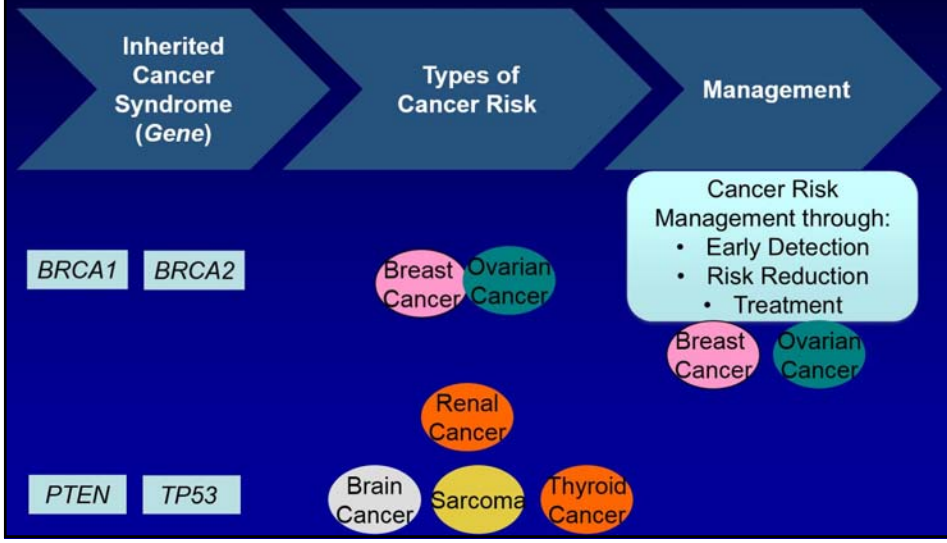
The "Ripple Effect" of Cancer Risk

- FAMILIES are the unit of care
- Prior data suggests a few family members are tested on average
- "Missed opportunity" for cancer prevention!!!

Inherited Cancers and Medical Care



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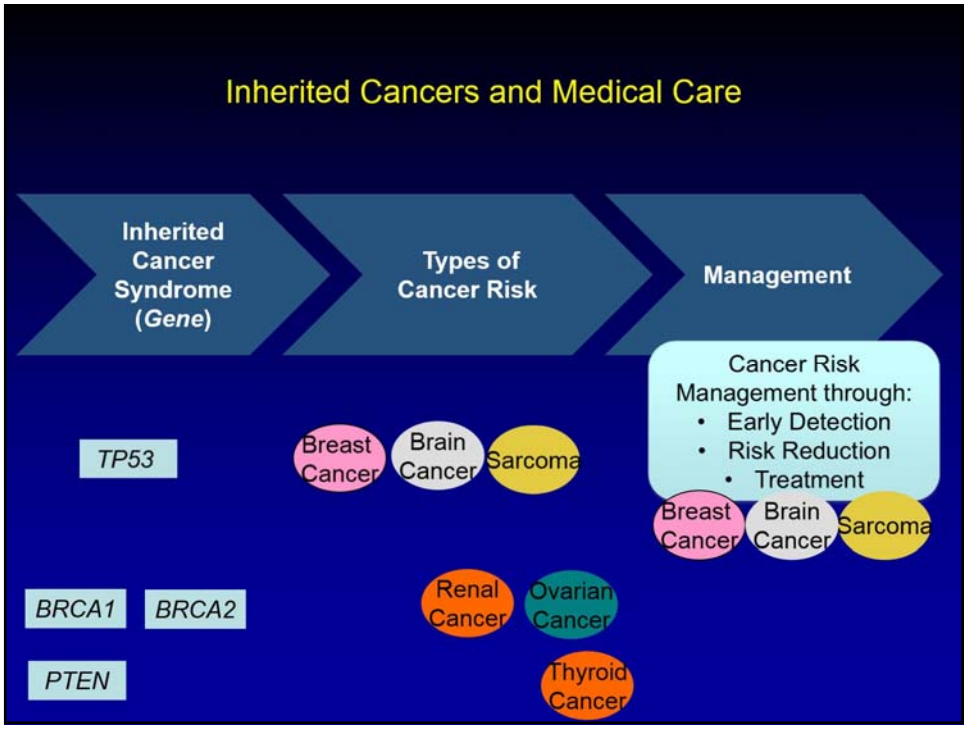

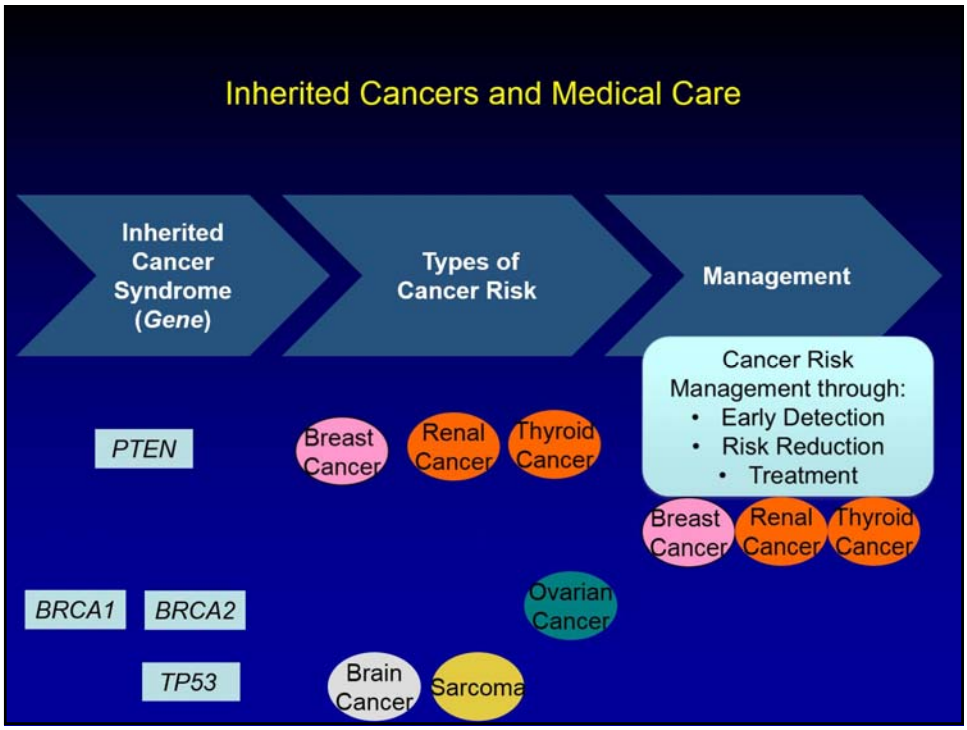

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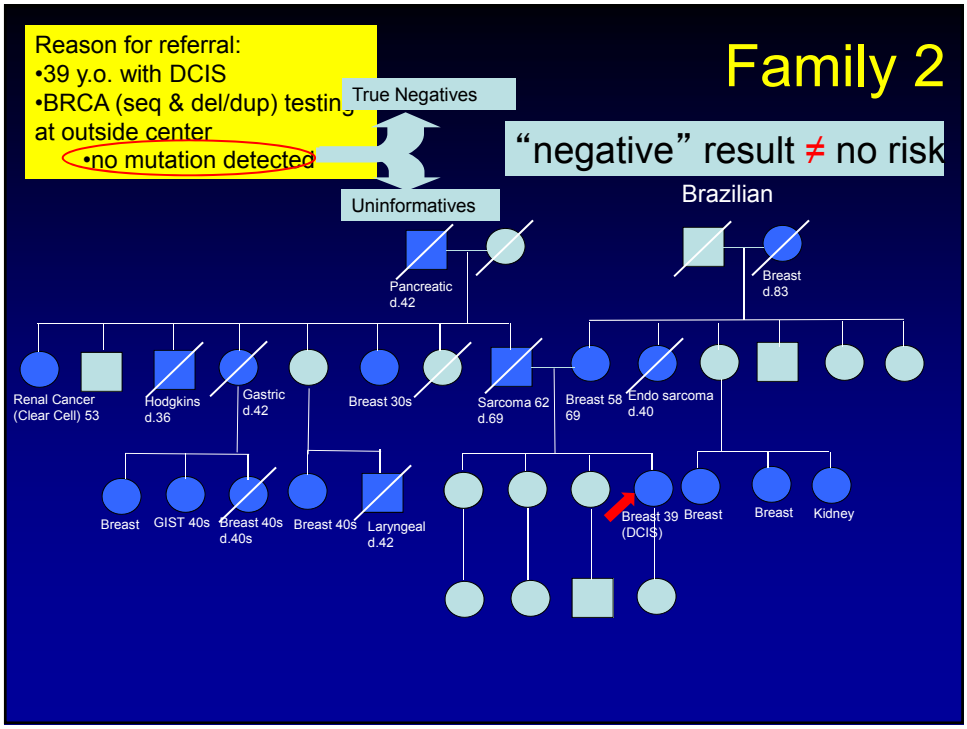

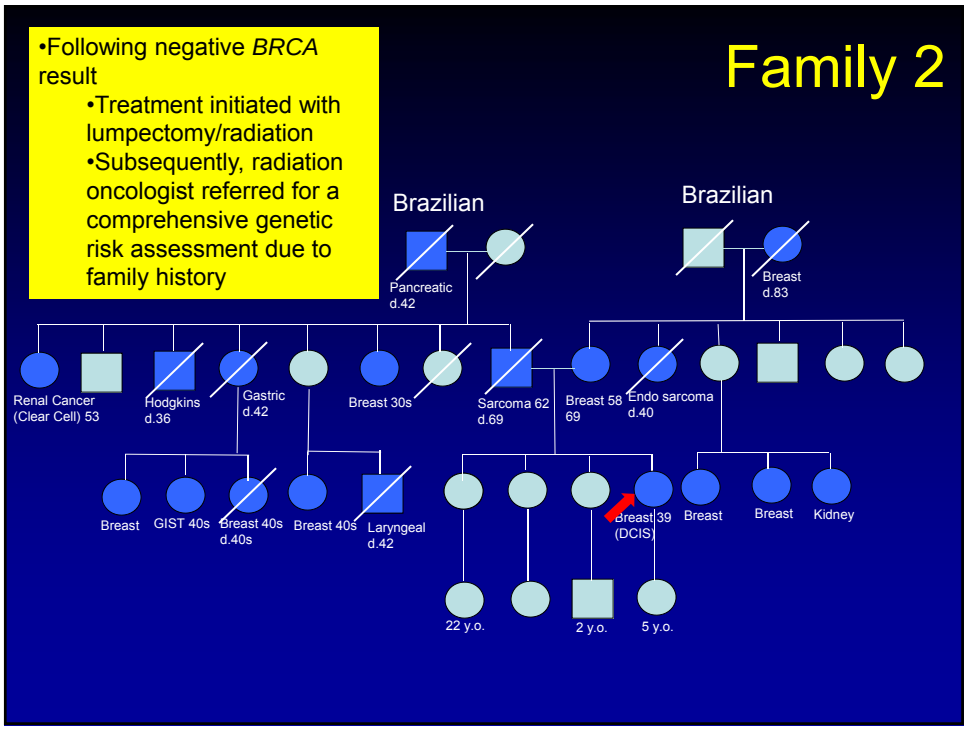

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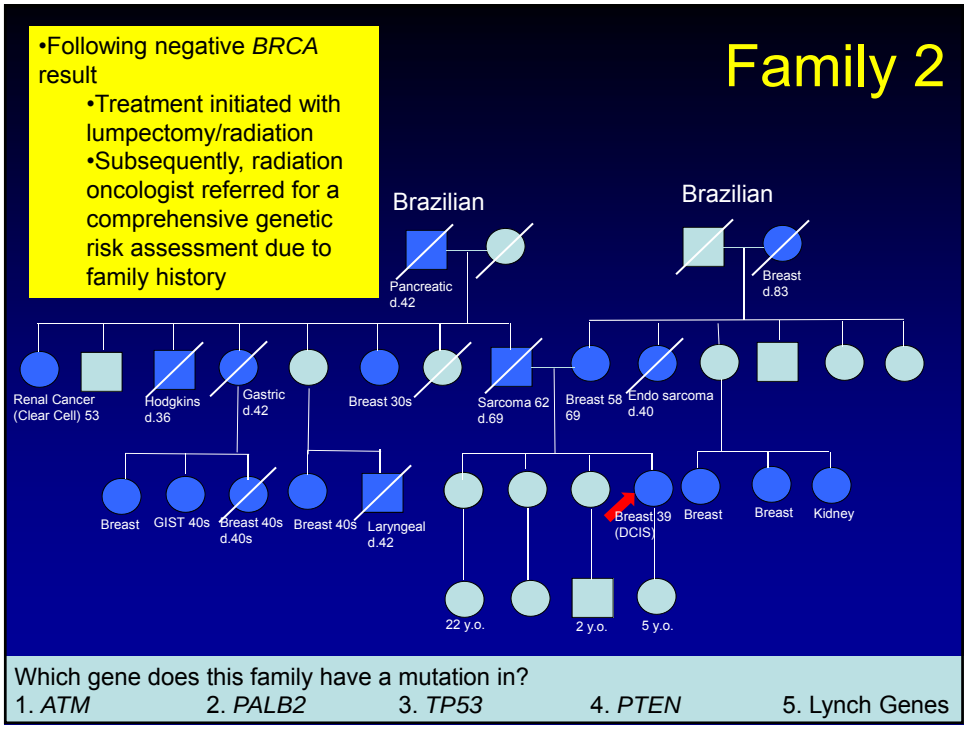

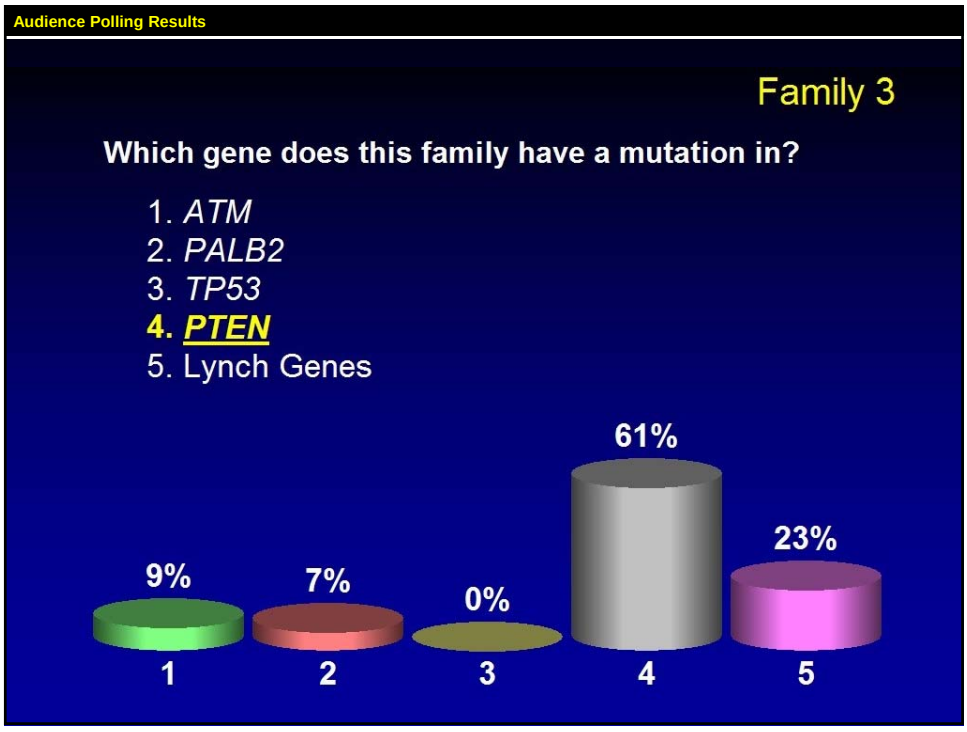

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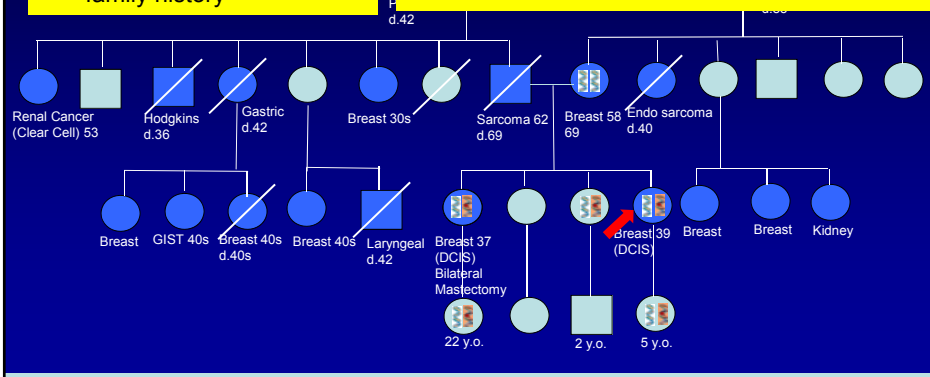
Family 2

- Following negative *BRCA* result
  - Treatment initiated with lumpectomy/radiation
  - Subsequently, radiation oncologist referred for a comprehensive genetic risk assessment due to family history

- Screening implemented for *TP53*+ family members:
  - Breast cancer risk management
  - Colonoscopy
  - Total body MRI +/- head MRI depending on resolution



Which gene does this family have a mutation in?

1. *ATM* 2. *PALB2* 3. *TP53* 4. *PTEN* 5. Lynch Genes

VOLUME 33 · NUMBER 21 · JULY 20 2015
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Revisiting Li-Fraumeni Syndrome From *TP53* Mutation Carriers

Gaëlle Bougeard, Marieve Renaux-Petel, Jean-Michel Flaman, Camille Charbonnier, Pierre Fermey,

Bougeard G, et al. Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. J Clin Oncol. 2015 Jul 20;33(21):2345-52. doi: 10.1200/JCO.2014.59.5728. Epub 2015 May 26. PubMed PMID: 26014290.

Table 3. 2015 Version of Chompret Criteria

Familial presentation	Proband with tumor belonging to LFS tumor spectrum (eg, premenopausal breast cancer, soft tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma) before age 46 yr, AND at least one first- or second-degree relative with LFS tumor (except breast cancer if proband has breast cancer) before age 56 yr or with multiple tumors
Multiple primitive tumors	Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before age 46 yr
Rare tumors	Patient with adrenocortical carcinoma, choroid plexus tumor, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history
Early-onset breast cancer	Breast cancer before age 31 yr

Abbreviation: LFS, Li-Fraumeni syndrome.

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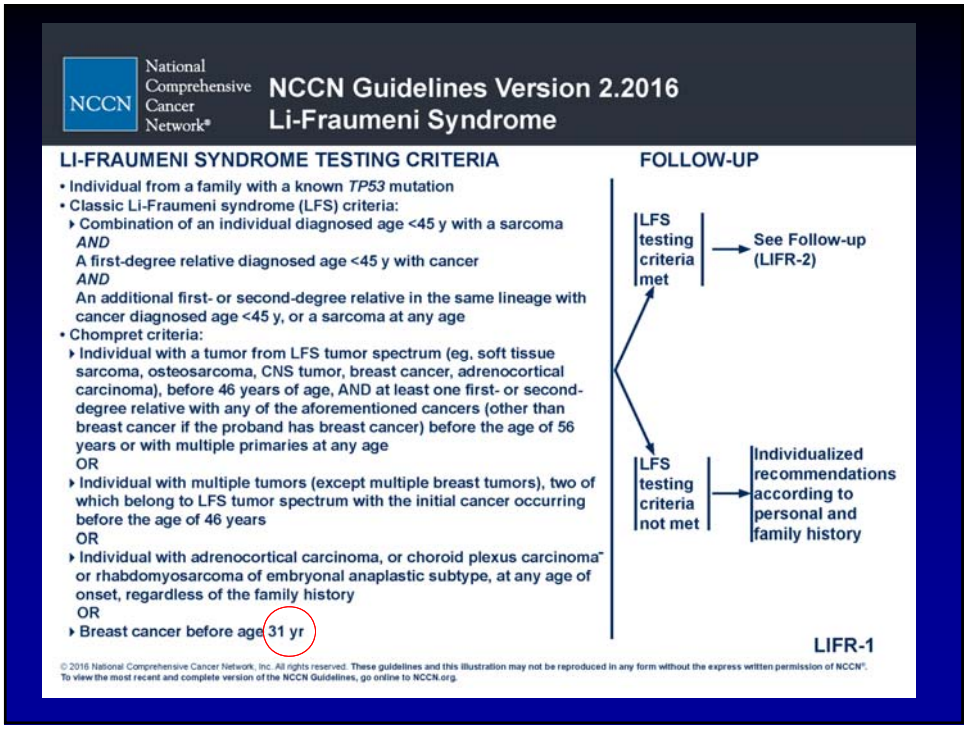

Considerations: Implications to treatment

- This scenario demonstrates implications to treatment:
  - Following initiation of radiation (Initial patient)
  - Prior to initiation of treatment (Second patient)
- Treatment implications of germline *TP53* mutations:
  - Suggestions of an increased frequency of radiation-induced secondary malignancies
  - Recent study of 400 patients with Li-Fraumeni Syndrome: Among subset with treatment records and who received radiation for their first malignancy, 30% developed secondary tumors in the radiation field (Mean latency: 10.7 years)
  - Li-Fraumeni syndrome patients cautioned to avoid radiation therapy when possible and may be advised to pursue mastectomy for treatment

Bougeard G, et al. Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. J Clin Oncol. 2015 Jul 20;33(21):2345-52. doi: 10.1200/JCO.2014.59.5728. Epub 2015 May 26. PubMed PMID: 26014290.

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Considerations: Implications to treatment

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NCCN Guidelines Version 2.2016
Li-Fraumeni Syndrome

LI-FRAUMENI SYNDROME MANAGEMENT

OTHER CANCER RISKS

- Address limitations of screening for many cancers associated with LFS. Because of the remarkable risk of additional primary neoplasms, screening may be considered for cancer survivors with LFS and a good prognosis from their prior tumor(s).
- Pediatricians should be apprised of the risk of childhood cancers in affected families.
- Annual comprehensive physical exam with high index of suspicion for rare cancers and second malignancies in cancer survivors: include neurologic examination.
- Therapeutic RT for cancer should be avoided when possible.
- Consider colonoscopy every 2–5 y starting at 25 y or 5 y before the earliest known colon cancer in the family (whichever comes first).
- Perform annual dermatologic examination.
- Perform annual whole body MRI (rapid non-contrast exams per ACRIN model).
- The brain may be examined as part of whole body MRI or as a separate exam.
- Provide additional surveillance based on family history of cancer.
- Provide education regarding signs and symptoms of cancer.

LIFR-A

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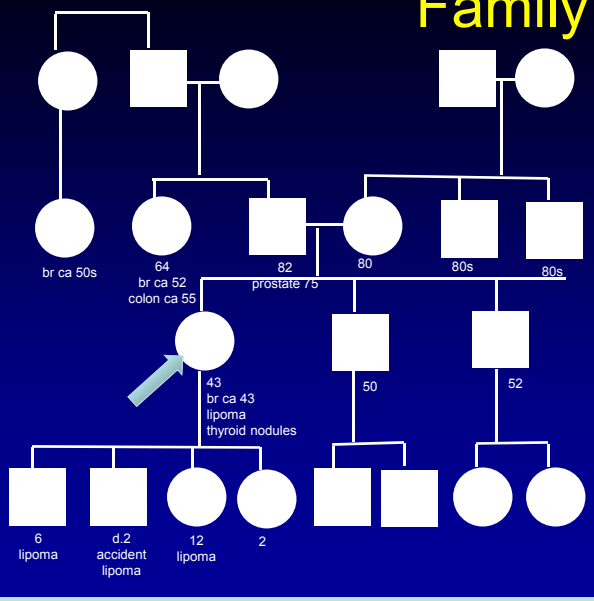
Family 3

- Patient referred based on personal and family history of breast cancer
- 43 year old female with recent diagnosis of DCIS
- History of thyroid nodules, lipomas, and fibrocystic breast disease

Motivation for testing:
- Surgical decision
- Risk for future cancers



Which gene does this family have a mutation in?

1. *ATM* 2. *PALB2* 3. *TP53* 4. *PTEN* 5. Lynch Genes

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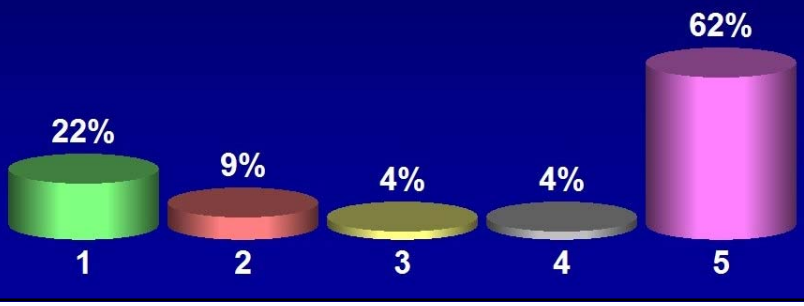
Audience Polling Results

Family 6

Which gene does this family have a mutation in?

1. ***ATM***
2. *PALB2*
3. *TP53*
4. *PTEN*
5. Lynch Genes



PTEN Revised Criteria

Main Changes:

- Insufficient evident to support inclusion of:
  - Benign breast disease
  - Uterine fibroids
  - Genitourinary malformations
- Evidence to include:
  - Autism spectrum disorders
  - Colon cancer
  - Esophageal gycogenic acanthosis
  - Penile macules
  - Renal cell carcinoma
  - Testicular lipomatosis
  - Vascular anomalies

Table 1. Revised *PTEN* hamartoma tumor syndrome clinical diagnostic criteria

Major criteria
- Breast cancer
- Endometrial cancer (epithelial)
- Thyroid cancer (follicular)
- Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)
- Lhermitte-Duclos disease (adult)
- Macrocephaly (≥97 percentile: 58 cm for females, 60 cm for males)
- Macular pigmentation of the glans penis
- Multiple mucocutaneous lesions (any of the following):
  - Multiple trichilemmomas (≥3, at least one biopsy proven)
  - Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
  - Mucocutaneous neuromas (≥3)
  - Oral papillomas (particularly on tongue and gingiva), multiple (≥3)
  - OR biopsy proven OR dermatologist diagnosed

Minor criteria
- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthosis (≥3)
- Lipomas (≥ 3)
- Mental retardation (ie, IQ ≤ 75)
- Renal cell carcinoma
- Testicular lipomatosis
- Thyroid cancer (papillary or follicular variant of papillary)
- Thyroid structural lesions (eg, adenoma, multinodular goiter)
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

Operational diagnosis in an individual (either of the following)
1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; or
2. Two major and three minor criteria.

Operational diagnosis in a family where one individual meets revised *PTEN* hamartoma tumor syndrome clinical diagnostic criteria or has a *PTEN* mutation:
1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria.

Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. J Natl Cancer Inst. 2013 Nov 6;105(21):1607-16. Epub 2013 Oct 17. Review. PubMed PMID: 24136893.

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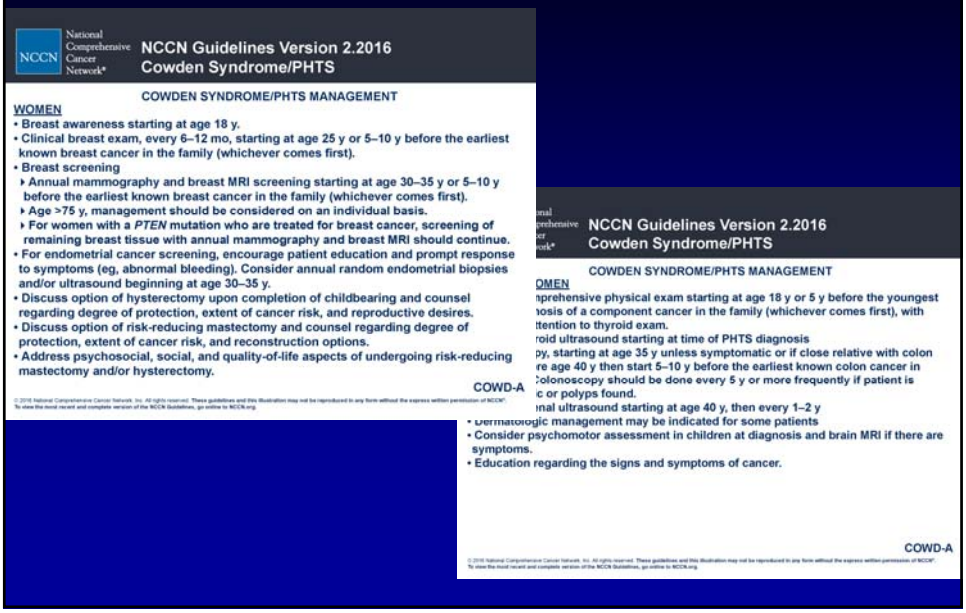
NCCN 2016 Guidelines

Genetic/Familial High-Risk Assessment: Breast and Ovarian



NCCN Guidelines Version 2.2016
Cowden Syndrome/PHTS

COWDEN SYNDROME/PHTS MANAGEMENT

WOMEN

- Breast awareness starting at age 18 y.
- Clinical breast exam, every 6–12 mo, starting at age 25 y or 5–10 y before the earliest known breast cancer in the family (whichever comes first).
- Breast screening
  - Annual mammography and breast MRI screening starting at age 30–35 y or 5–10 y before the earliest known breast cancer in the family (whichever comes first).
  - Age >75 y, management should be considered on an individual basis.
  - For women with a *PTEN* mutation who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.
- For endometrial cancer screening, encourage patient education and prompt response to symptoms (eg, abnormal bleeding). Consider annual random endometrial biopsies and/or ultrasound beginning at age 30–35 y.
- Discuss option of hysterectomy upon completion of childbearing and counsel regarding degree of protection, extent of cancer risk, and reproductive desires.
- Discuss option of risk-reducing mastectomy and counsel regarding degree of protection, extent of cancer risk, and reconstruction options.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy.

COWD-A

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NCCN Guidelines Version 2.2016
Cowden Syndrome/PHTS

COWDEN SYNDROME/PHTS MANAGEMENT

- Comprehensive physical exam starting at age 18 y or 5 y before the youngest ...osis of a component cancer in the family (whichever comes first), with ...ttention to thyroid exam.
- ...roid ultrasound starting at time of PHTS diagnosis
- ...py, starting at age 35 y unless symptomatic or if close relative with colon ...re age 40 y then start 5–10 y before the earliest known colon cancer in ...Colonoscopy should be done every 5 y or more frequently if patient is ...c or polyps found.
- ...nal ultrasound starting at age 40 y, then every 1–2 y
- ...Dermatologic management may be indicated for some patients
- Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms.
- Education regarding the signs and symptoms of cancer.

COWD-A

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NCCN 2016 Guidelines

Genetic/Familial High-Risk Assessment: Breast and Ovarian

Women

- Mammogram and breast MRI (~30-35 y.o)
- Consider endometrial cancer screening
- Discuss risk-reducing mastectomy and hysterectomy

High-risk breast screening/surgery

Men and Women

- Annual comprehensive physical exam
- Annual thyroid ultrasound (age 18 or 5 years prior to earliest dx)
- Colonoscopy (age 35, every 5 years or more)
- Consider renal ultrasound (age 40, every 1-2 years)
- Dermatologic management as indicated
- Psychomotor testing for children at dx, and MRI if symptoms

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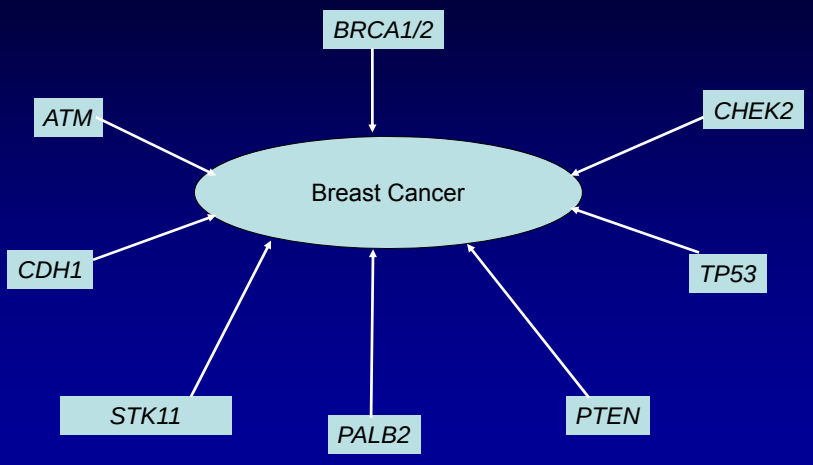
Patient Follow-Up

- Implementation of multidisciplinary care including:
  - Colonoscopy: identified multiple hyperplastic polyps
  - Renal Ultrasound: identified early stage kidney cancer

Genetic Heterogeneity



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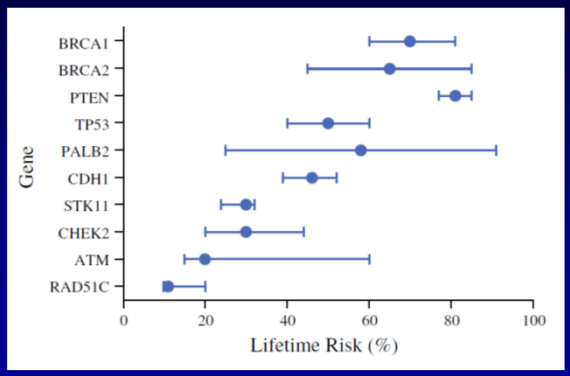
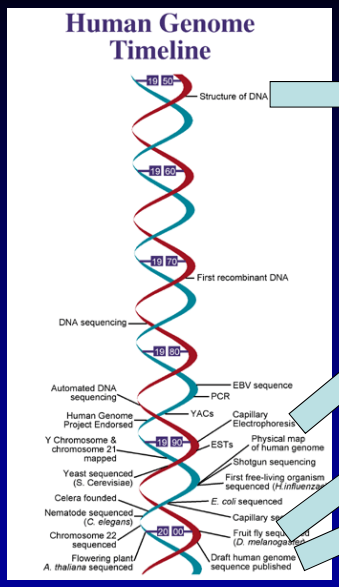
Breast Cancer Risks



Euhus D. Genetic testing today. Ann Surg Oncol. 2014 Oct;21(10):3209-15. doi: 10.1245/s10434-014-3906-0. Epub 2014 Jul 17. PubMed PMID: 25029991.

To put things into perspective…



1953 – Watson and Crick discover DNA's double helix structure

1990 – human genome project begins

2000 – completion of draft sequence announced

2001 – Initial working draft published

2003 – Human Genome Project declared complete

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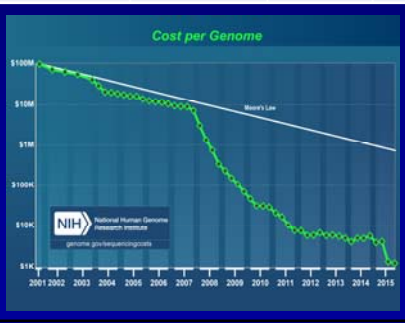
Driver of Medical Genomics: Next Generation Sequencing

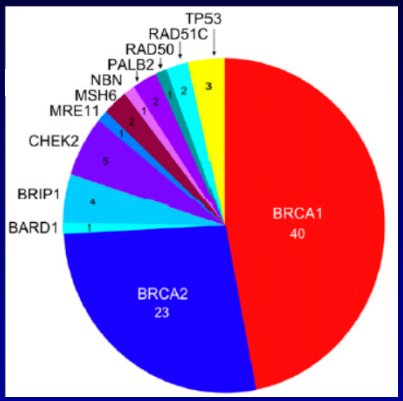
Time Period	Genomes	Turn-around time	FTEs	Cost per genome
1990-2003	1. NIH reference 2. Celera reference	~5 years	~2,000	~$2-3 billion
2003-2009	~10 additional	~6 months	Dozens	$300,000→38,000
2010-2014	10^3-10^5	4-6 weeks	3-4	$ 6,000 exome $ 9,500 genome
2015-2020	Millions	15 minutes	<<1	$100-250



Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP) Available at: www.genome.gov/sequencingcosts

Use of Next Gen Sequencing to Evaluate Inherited Predisposition to Ovarian Cancer

- 360 women with ovarian, peritoneal or fallopian tube cancer
- 24% with germline loss of function mutations:
  - 18% - *BRCA1/2*
  - 6% - *BARD1, BRIP1, CHEK2, MRE11A, MSH6, NBN, PALB2, RAD50, RAD51C, TP53*



Walsh T, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A. 2011 Nov 1;108(44):18032-7.

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With advances in sequencing technologies, how is the paradigm for genetic testing changing?

Testing for single conditions at a time (sequentially)
'genetic testing'

Test 1

Test 1 neg
Test 2

Test 2 neg
Test 3

Often cost prohibitive

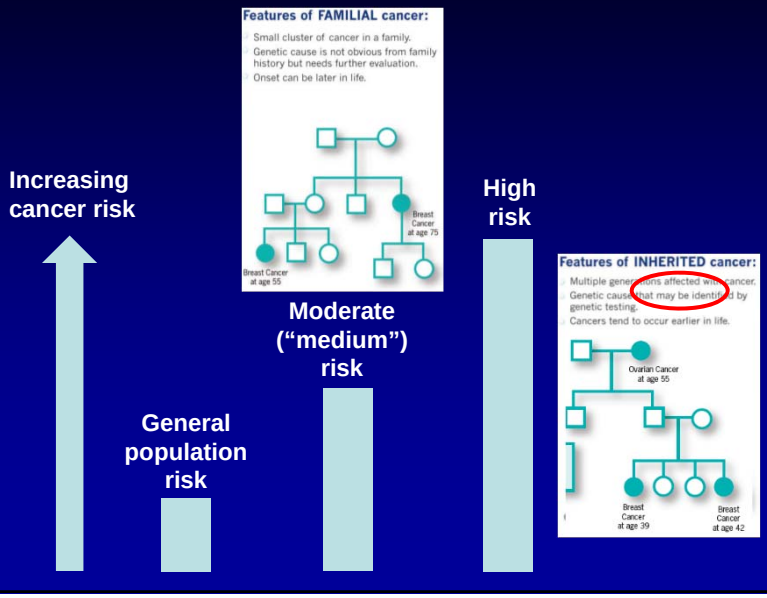
Testing over time

Test 1
Test 2 "Multi-gene testing"
Test 3

MUCH CHEAPER but…
•Interpretation of results complex

Testing for multiple conditions simultaneously (in parallel)
'genomic testing'

What are the cancer risks for gene changes detected through multi-gene tests?



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What are the cancer risks for gene changes detected through multi-gene tests?

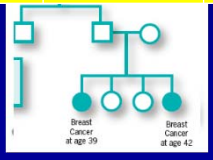
Important to discuss:
- Variations in cancer spectrum and level of risk
- More genes tested will lead to more variants detected

Increasing cancer risk

High risk

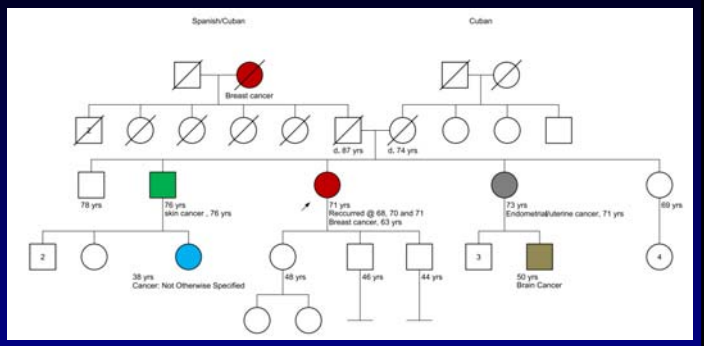
IMPACT ON MEDICAL MANAGEMENT:	Mutation	Variant
Genes associated with Cancer Risks which warrant intervention	YES	NO
Genes with uncertain or unknown penetrance	NO	NO

General population risk



Family 4

Reason for referral:
- "somatic" (tumor) genetic test results:
  *PALB2 K353fs*7*
  PALB2 loss exons 1-10



History: 71 y.o. female
- Age 63: left breast cancer treated with lumpectomy, radiation
- Age 70: chest wall recurrence treated with chemotx
- Age 71: another chest wall recurrence treated with chemotx; somatic tumor genetic test ordered

Results: *PALB2+*
Deletion of exons 1-10

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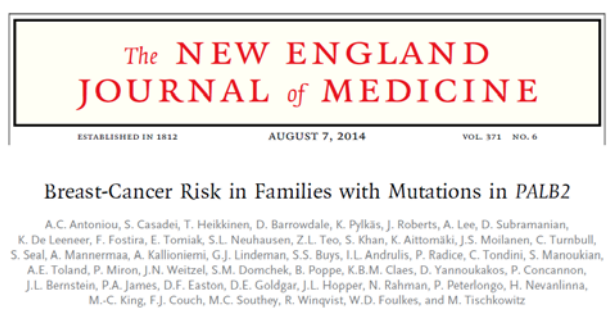
Implications of *PALB2*+ result

- Personal/family history fits with carrying *PALB2* mutation
- *PALB2*-associated cancer risks:
  - 33-58% (modified by family history)
  - Increased risk of pancreatic cancer
- Family implications



Cybulski C, et al. Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis. Lancet Oncol. 2015 Jun;16(6):638-44. PubMed PMID: 25959805.
Antoniou AC, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014 Aug 7;371(6):497-506. PMID: 25099575.
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Implications of *PALB2*+ result

- Personal/family history fits with carrying *PALB2* mutation
- *PALB2*-associated cancer risks:
  - 33-58% (modified by family history)
  - Increased risk of pancreatic cancer
- Family implications

Clinical outcomes in women with breast cancer and a *PALB2* mutation: a prospective cohort analysis

*Cezary Cybulski, *Wojciech Kluźniak, *Tomasz Huzarski, *Dominika Wokołorczyk, Aniruddh Kashyap, Anna Jakubowska, Marek Szwiec, Tomasz Byrski, Tadeusz Dębniak, Bohdan Górski, Victoria Sopik, Mohammad R Akbari, Ping Sun, Jacek Gronwald, Steven A Narod, Jan Lubiński, and the Polish Hereditary Breast Cancer Consortium†*

Lancet Oncology 2015;
16: 638–44

- Confirmed substantially elevated risk of breast cancer (24-40%)
- 5 yr cumulative contralateral br ca risk 10% (vs. 17% in *BRCA1* carriers and 3% in non-carriers)
- Survival at 10 yrs was 50% vs. 72% in *BRCA1* carriers and 74.7% in non-carriers

Cybulski C, et al. Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis. Lancet Oncol. 2015 Jun;16(6):638-44. PubMed PMID: 25959805.
Antoniou AC, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014 Aug 7;371(6):497-506. PMID: 25099575.
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Implications of *PALB2*+ result

- Personal/family history fits with carrying *PALB2* mutation
- *PALB2*-associated cancer risks:
  - 33-58% (modified by family history)
  - Increased risk of pancreatic cancer
- Family implications

	Recommend Breast MRI (>20% risk of breast cancer)	Discuss Option of RRM	Recommend/Consider RRSO
Intervention warranted based on gene and/or risk level	*ATM* *BRCA1* *BRCA2* *CDH1* *CHEK2* *PALB2* *PTEN* *STK11* *TP53*	*BRCA1* *BRCA2* *CDH1* *PTEN* *TP53* *PALB2*	*BRCA1* *BRCA2* Lynch syndrome *BRIP1* *RAD51C* *RAD51D*
Insufficient evidence for intervention	*BRIP1*	*ATM* *CHEK2* *STK11*	*PALB2*

Cybulski C, et al. Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis. Lancet Oncol. 2015 Jun;16(6):638-44. PubMed PMID: 25959805.
Antoniou AC, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014 Aug 7;371(6):497-506. PMID: 25099575.
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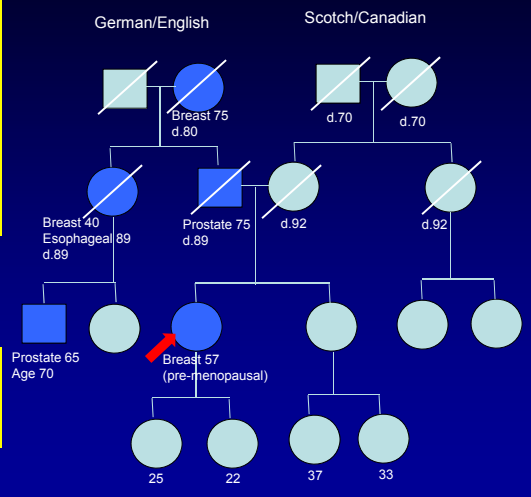
Family 5

- Reason for referral:
  - personal and family history of breast cancer
- Patient:
  - 57 y.o. woman diagnosed with premenopausal breast cancer
  - treated with bilateral mastectomy at outside hospital

Results:
CHEK2 1236delT
(truncating mutation)



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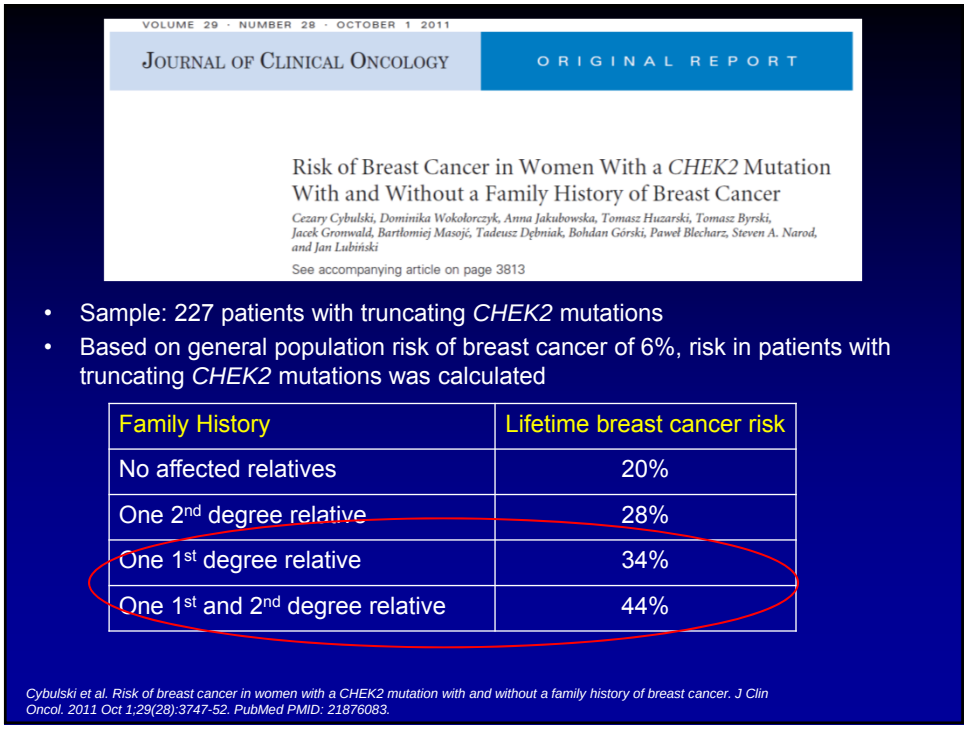
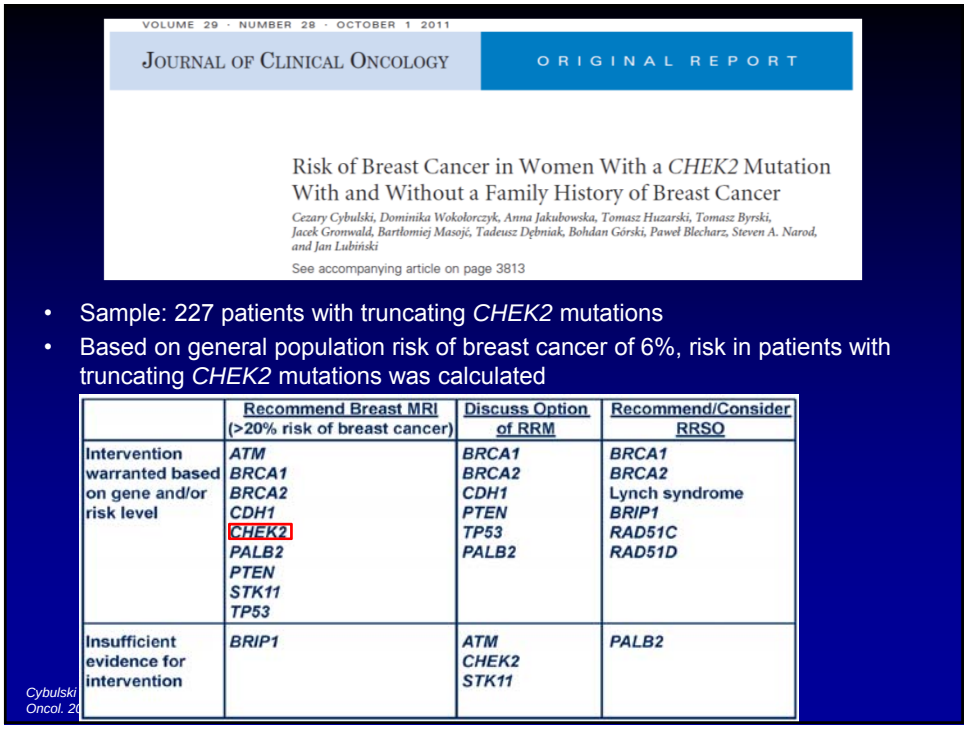


- Sample: 227 patients with truncating *CHEK2* mutations
- Based on general population risk of breast cancer of 6%, risk in patients with truncating *CHEK2* mutations was calculated

Family History	Lifetime breast cancer risk
No affected relatives	20%
One 2nd degree relative	28%
One 1st degree relative	34%
One 1st and 2nd degree relative	44%

Cybulski et al. Risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer. J Clin Oncol. 2011 Oct 1;29(28):3747-52. PubMed PMID: 21876083.



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- Based on general population risk of breast cancer of 6%, risk in patients with truncating *CHEK2* mutations was calculated

	Recommend Breast MRI (>20% risk of breast cancer)	Discuss Option of RRM	Recommend/Consider RRSO
Intervention warranted based on gene and/or risk level	*ATM* *BRCA1* *BRCA2* *CDH1* *CHEK2* *PALB2* *PTEN* *STK11* *TP53*	*BRCA1* *BRCA2* *CDH1* *PTEN* *TP53* *PALB2*	*BRCA1* *BRCA2* Lynch syndrome *BRIP1* *RAD51C* *RAD51D*
Insufficient evidence for intervention	*BRIP1*	*ATM* *CHEK2* *STK11*	*PALB2*

Cybulski
Oncol. 2

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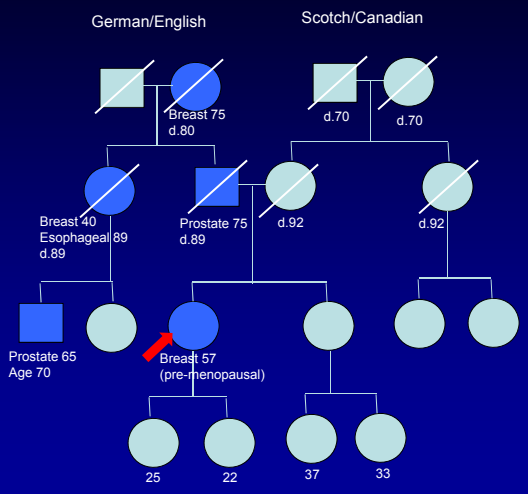
Family 5

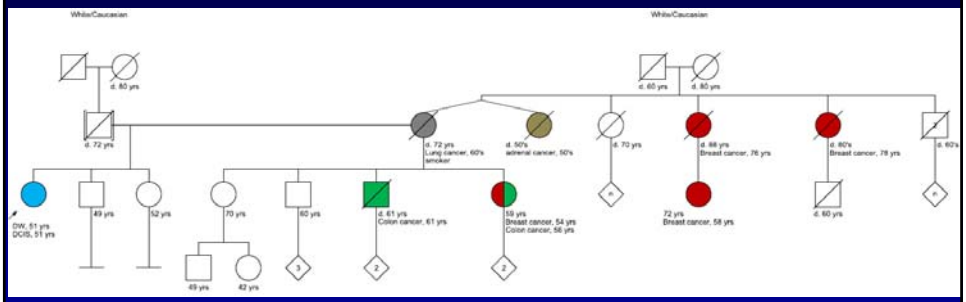
- Reason for referral:
  - personal and family history of breast cancer
- Patient:
  - 57 y.o. woman diagnosed with premenopausal breast cancer
  - treated with bilateral mastectomy at outside hospital

Results:
CHEK2 1236delT
(truncating mutation)



Family 6

Reason for referral:
•51 y/o female newly diagnosed with left DCIS with family history of cancer
•Referred for surgical decision making and evaluation of risk for family members
•*BRCA1/2* Risk Assessment: 0.4-2.2%



Which gene does this family have a mutation in?
1. *ATM* 2. *PALB2* 3. *TP53* 4. *PTEN* 5. Lynch Genes

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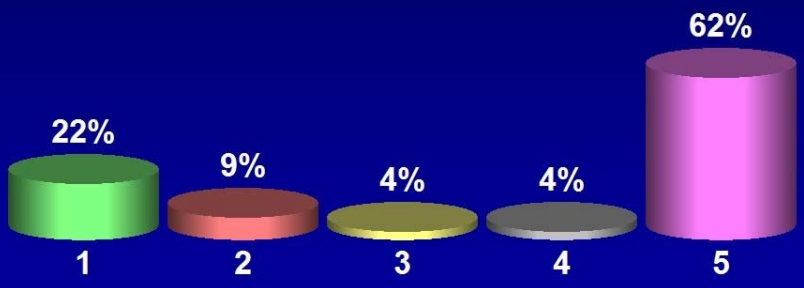
Audience Polling Results

Family 6

Which gene does this family have a mutation in?

1. ***ATM***
2. *PALB2*
3. *TP53*
4. *PTEN*
5. Lynch Genes



Cancer Risks

ATM-associated cancer risks

- Absolute female breast cancer risk: 27%
- Increased risk for pancreatic cancer
- Certain environmental risk factors (e.g., smoking) may increase *ATM*-associated cancer risks

High Risk Allele: c.7271T>G

- 60% risk of breast cancer to age 70 (15.7 fold relative risk)

van Os NJ, et al: A systematic review, Meta-analysis and evidence-based guideline. Clin Genet. 2015 Dec 10. doi: 10.1111/cge.12710. [Epub ahead of print] Review. PubMed PMID: 26662178.

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Management

- ***ATM*-associated cancer risk management**
  - Given high-risk breast cancer genes were negative, patient proceeded with lumpectomy + XRT
  - Recommended annual breast MRI per national practice guidelines

	Recommend Breast MRI (>20% risk of breast cancer)	Discuss Option of RRM	Recommend/Consider RRSO
Intervention warranted based on gene and/or risk level	*ATM* *BRCA1* *BRCA2* *CDH1* *CHEK2* *PALB2* *PTEN* *STK11* *TP53*	*BRCA1* *BRCA2* *CDH1* *PTEN* *TP53* *PALB2*	*BRCA1* *BRCA2* Lynch syndrome *BRIP1* *RAD51C* *RAD51D*
Insufficient evidence for intervention	*BRIP1*	*ATM* *CHEK2* *STK11*	*PALB2*

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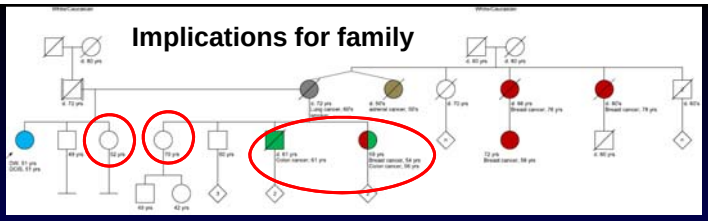

- **Implications for family planning**
  - Ataxia telangiectasia (AT) - progressive ataxia, immune deficiency, frequent infections, increased risk cancer risks (leukemia and lymphoma)
  - Carrier frequency: 1/100 (1%)
- **Testing in relatives?**
  - Full sister without breast cancer : Lifetime risk of breast cancer 29% (IBIS v7)
  - Maternal half sister without breast cancer: Lifetime risk of breast cancer 11.7% (IBIS v7)
  - Maternal half siblings with breast/colon and colon cancer: Makes more sense to consider multi-gene testing rather than single-site ATM

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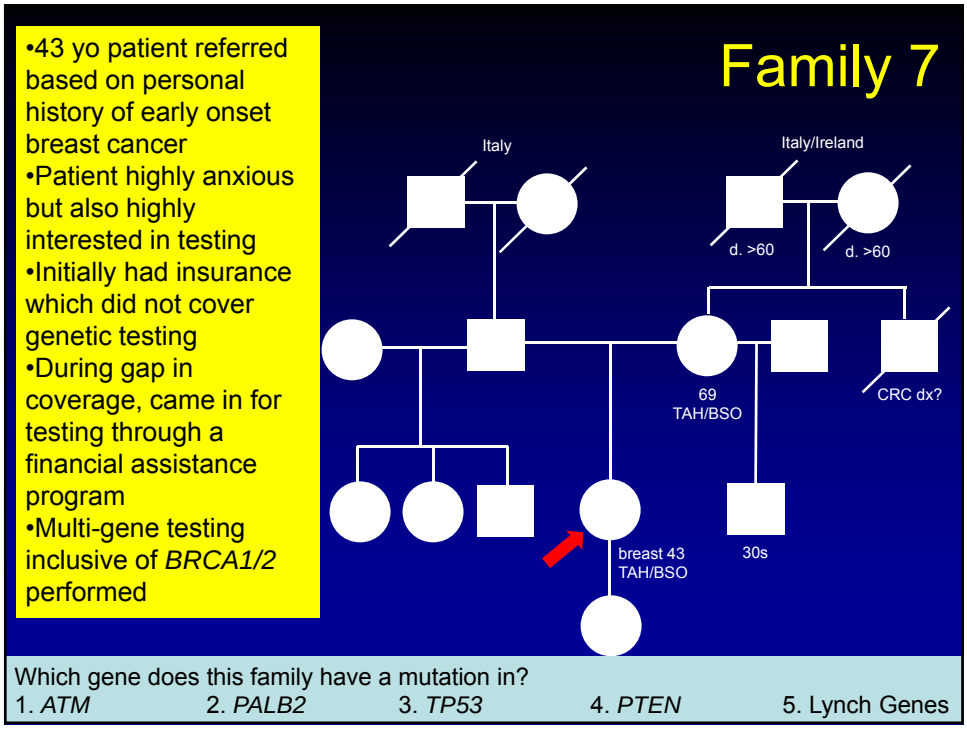

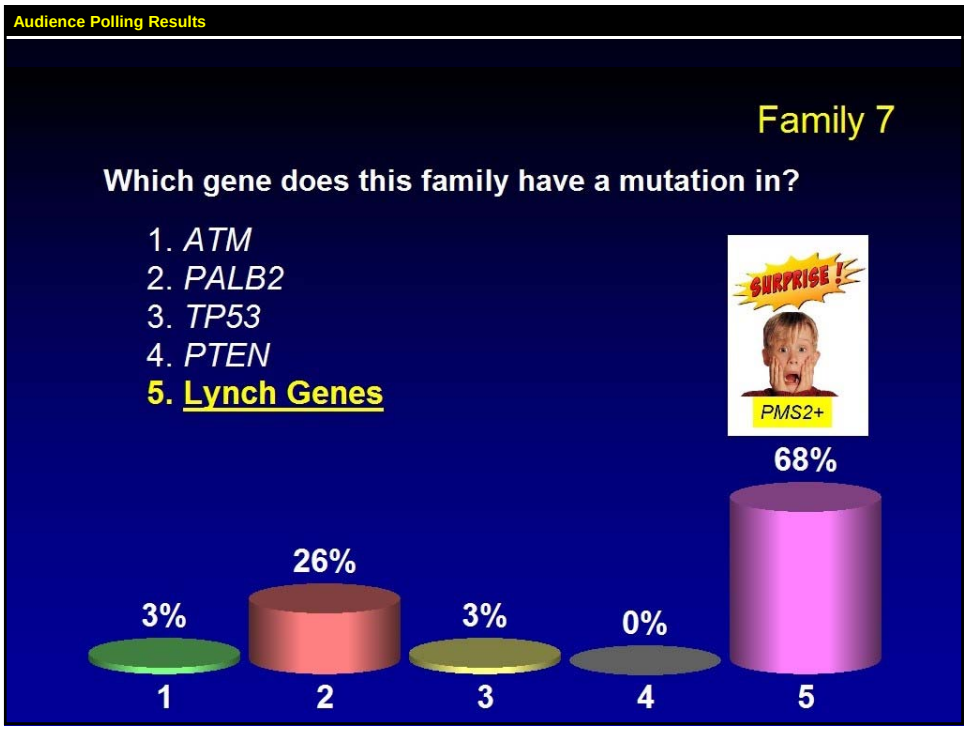

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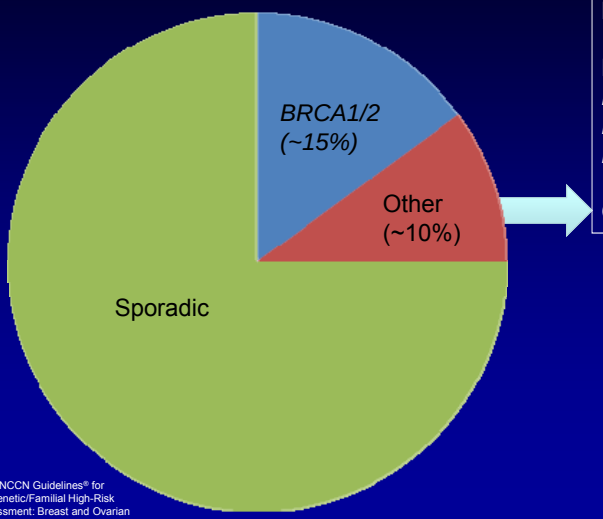
Inherited Ovarian Cancer



Lynch Genes

Newer genes:
RAD51C
RAD51D
BRIP1

Others…

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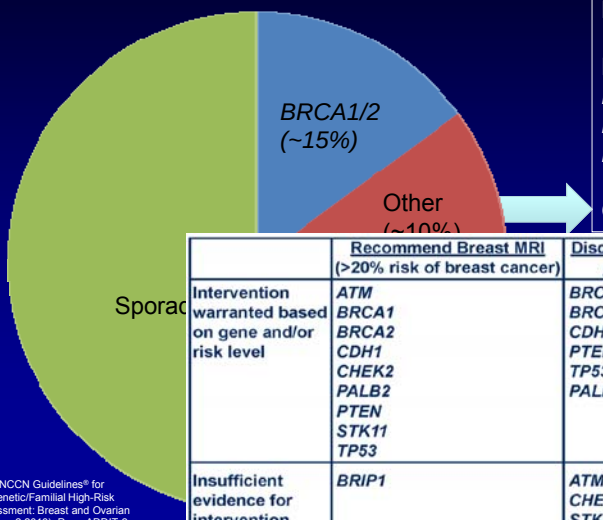
Inherited Ovarian Cancer



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Insufficient evidence for intervention	*BRIP1*	*ATM* *CHEK2* *STK11*	*PALB2*

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RAD51C

Study	OR/RR (95% CI)	Lifetime Risk
Loveday et al, 2012	5.88 (2.88-11.88)	>9% by age 80
Pelttari et al, 2011	6.3 (1.15-34.6)	~
Song et al, 2015	5.2 (1.1-24)	~
Norquist et al, 2015	15.8 (1.9-128)	~

- Ovarian cancer risks: 5-6 fold (although 16-fold in recent Norquist et al study)
- Lifetime risk: 9% to age 80

Pelttari LM et al.RAD51C is a susceptibility gene for ovarian cancer. Hum Mol Genet. 2011 Aug 15;20(16):3278-88. PMID: 21616938.
Loveday, C, et al. Germline RAD51C mutations confer susceptibility to ovarian Cancer. Nat Genet 44:475-476, 2012
Song H et al.Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. J Clin Oncol. 2015 Sep 10;33(26):2901-7. Epub 2015 Aug 10. PMID: 26261251.
Norquist BM et al. Inherited Mutations in Women With Ovarian Carcinoma. JAMA Oncol. 2015 Dec 30:1-9. PMID: 26720728.

RAD51D

Study	OR/RR (95% CI)	Lifetime Risk
Loveday et al, 2011	6.3 (2.86-13.85)	10% by age 80
Pelttari et al, 2012	7.17 (0.74-69.1)	~
Song et al, 2015	12 (1.5-90)	~
Norquist et al, 2015	9 (1.9-42.5)	~

- Ovarian cancer risks: 6-12 fold
- Lifetime risk: 10% to age 80

Loveday C, Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet. 2011 Aug 7;43(9):879-82. PMID: 21822267.
Song H et al.Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. J Clin Oncol. 2015 Sep 10;33(26):2901-7. Epub 2015 Aug 10. PMID: 26261251.
Pelttari LM et al. A Finnish founder mutation in RAD51D: analysis in breast, ovarian, prostate, and colorectal cancer. J Med Genet. 2012 Jul;49(7):429-32. PMID: 22652533.
Norquist BM et al. Inherited Mutations in Women With Ovarian Carcinoma. JAMA Oncol. 2015 Dec 30:1-9. PMID: 26720728.

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BRIP1

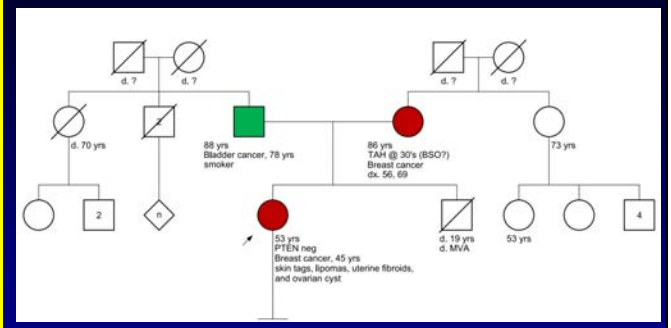
Study	OR/RR (95% CI)	Lifetime Risk
Rafnar et al, 2011	8.13 (4.74-13.95)	~
Ramus et al, 2015	3.14 (2.12-5.54)	5.8% by age 80
Norquist et al, 2015	9.1 (3.4-24.2)	~

- Ovarian cancer risks: 3-9 fold
- Lifetime risk: 5.8% to age 80

Norquist BM et al. Inherited Mutations in Women With Ovarian Carcinoma. JAMA Oncol. 2015 Dec 30:1-9. PMID: 26720728.
Ramus SJ et al. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. J Natl Cancer Inst. 2015 Aug 27;107(11). PMID: 26315354.
Rafnar T et al. Mutations in BRIP1 confer high risk of ovarian cancer. Nat Genet. 2011 Oct 2;43(11):1104-7. PMID: 21964575.

Family 8

- 53 year old female
- breast cancer age 45 treated with bilateral mastectomy, at which time:
- *PTEN: negative*
- *No BRCA testing*
- Follow-up: planned hysterectomy thus gyn/onc wanted *BRCA* results to determine need to remove ovaries



Which gene does this family have a mutation in?
1. *BRCA1/2* 2. *Lynch* 3. *RAD51C* 4. *RAD51D* 5. *BRIP1*

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Audience Polling Results

Family 8

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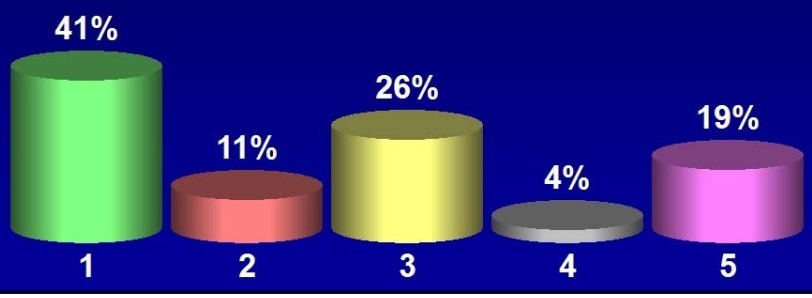
2. Lynch
3. ***RAD51C***
4. *RAD51D*
5. *BRIP1*



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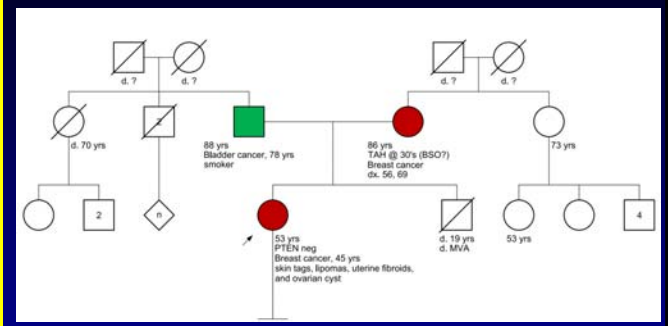

Implications to:

Medical management, Predictive testing, Family planning

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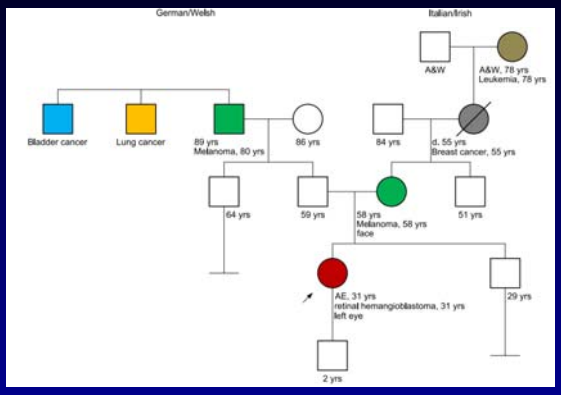
Family 9

- 31 y/o female referred with recent diagnosis of unilateral retinal hemangioblastoma
- researched VHL in depth
- Significant concern about impact of testing on 2 y/o son



Which gene does this family have a mutation in?
1. *BRCA1/2* 2. *Lynch* 3. *RAD51C* 4. *RAD51D* 5. *BRIP1*

Audience Polling Results

Family 9

Which gene does this family have a mutation in?

1. BRCA1/2
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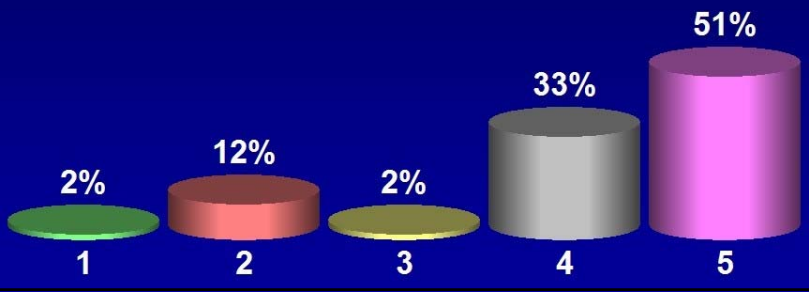
3. RAD51C
4. RAD51D
5. **BRIP1**



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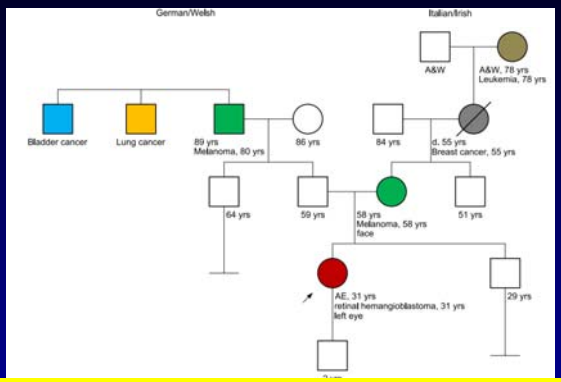


Implications to:

Medical management, Predictive testing, Family planning

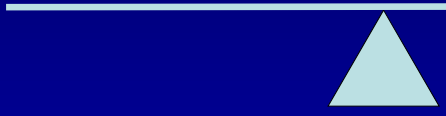
VUS: *EPCAM* and *MET*

Which gene does this family have a mutation in?

A. *BRCA1/2* B. *Lynch* C. *RAD51C* D. *RAD51D* E. *BRIP1*

Genetic Testing Practices

BRCA1/2, Reflex to other single genes if indicated	Smaller multi-gene tests: *BRCA1/2, TP53, PTEN, PALB2, CDH1, STK11*	PAN-cancer multi-gene tests (20+ genes)



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