Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Hereditary Cancer Syndromes

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Better together.

Objectives

- Review indications for genetic testing and genetic counseling in the oncology setting
- Review of specific hereditary cancer syndromes
- Discuss details of genetic testing and the possible implications for patient care

Genetic Counseling in Hereditary Cancer

- Genetic counselors can help determine which patients would benefit from genetic testing, as well as how genetic testing may help their oncology team when determining treatment recommendations
- Determine appropriate genetic testing based on personal and family history
- Discuss implications for family members based on testing results
- Referrals/recommendations for screening and prevention of future cancers based on most recent guidelines
- Address any insurance concerns regarding genetic testing
- Work with oncology with tumor/germline genetic testing for treatment recommendations
- Referrals for research studies or support groups

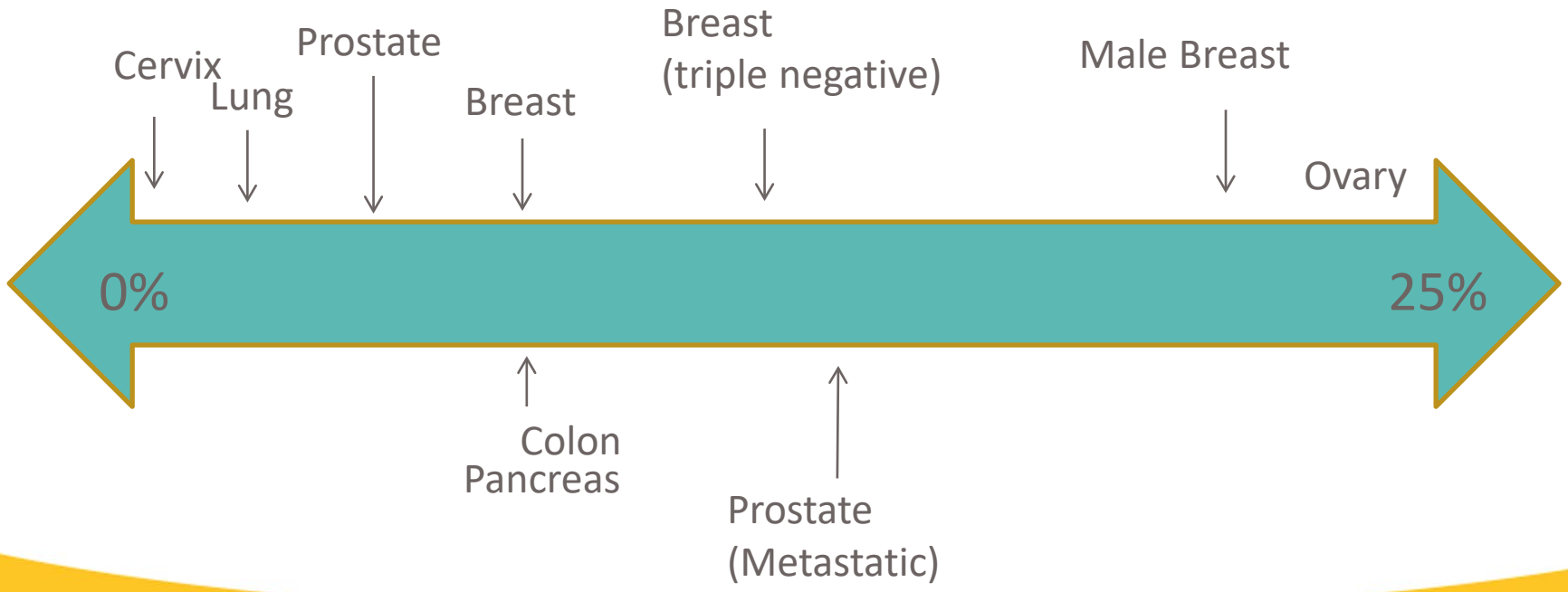
Which patients need genetics?

Approximately 5-10% of cancers are due to a pathogenic mutation in a known hereditary cancer gene.

Criteria for genetic testing:

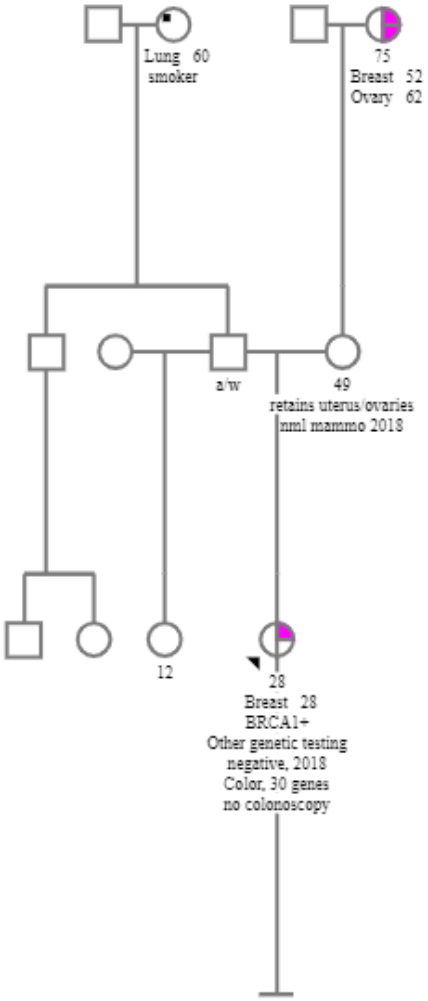
- Unusually early age of cancer onset (e.g., premenopausal breast cancer).
- Multiple primary cancers in a single individual (e.g., colorectal and endometrial cancer).
- Bilateral cancer in paired organs or multifocal disease (e.g., bilateral breast cancer or multifocal renal cancer).
- Clustering of the same type of cancer in close relatives.
- Cancers occurring in multiple generations of a family.
- Occurrence of rare tumors (e.g., male breast cancer, adrenocortical carcinoma, granulosa cell tumor of the ovary, ocular melanoma, or duodenal cancer).
- Occurrence of epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- Concern for germline mutations following tumor testing results (e.g. BRCA mutation in breast tumor tissue)
- Occurrence of metastatic prostate cancer, regardless of age
- Occurrence of pancreatic cancer, regardless of age
- All breast cancers??

Which cancers are more likely to be hereditary?



Hereditary breast and ovarian cancer syndrome (HBOC)

- Mutations in BRCA1 or BRCA2
- Autosomal dominant inheritance
- Associated with increased risk of breast, ovarian, prostate, and pancreatic cancer
- Approximately 1/500 individuals carry mutations in BRCA1 or BRCA2
  - 1/40-1/50 frequency in Ashkenazi Jewish individuals



Risk of malignancy in HBOC

Cancer Type	General Population Risk	Risk for Malignancy [1]	
		BRCA1	BRCA2
Breast	12%	46%-87%	38%-84%
Second primary breast	~10-15%	40% within 20 years	26% within 20 years
Ovarian	1%-2%	39%-55%	16.5%-27%
Male breast	0.1%	1.2%	Up to 8.9%
Prostate	10-15%	Slightly elevated	Elevated (high grade, metastatic)
Pancreatic	0.50%	1%-3%	2%-7%
Melanoma (cutaneous & ocular)	1.6%		Elevated Risk

Source: Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. 1998 Sep 4 [Updated 2016 Dec 15]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1247/

Management for HBOC

Surveillance

- Clinical breast exam every 6-12 months, starting at age 25
- Annual breast MRI starting at age 25
- Annual mammogram starting at age 30
- Pancreatic cancer screening considered if Fhx

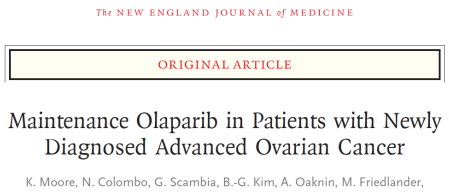
Surgical

- Discuss option of bilateral mastectomy
- Risk reducing salpingo-oophorectomy (RRSO)
    - Age 35-40 for BRCA1
    - Age 40-45 for BRCA2

Management for HBOC

- Men:
  - Breast self-exam training and education starting at age 35y
  - Clinical breast exam every year, starting at age 35y
  - Recommend prostate cancer screening at age 40-45

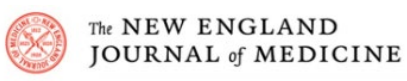
- Treatment implications of HBOC
  - Surgical planning
  - Radiation treatment
  - Possible use of PARP inhibitors


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

K. Moore, N. Colombo, G. Scambia, B.-G. Kim, A. Oaknin, M. Friedlander,


The NEW ENGLAND JOURNAL of MEDICINE

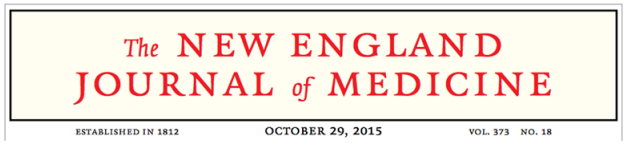

Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation

Jennifer K. Litton, M.D., Hope S. Rugo, M.D., Johannes Ettl, M.D., Sara A. Hurvitz, M.D., Anthony Gonçalves, M.D., Ph.D., Kyung-Hun Lee, M.D., Ph.D., Louis Fehrenbacher, M.D., Rinat Yerushalmi, M.D., Lida A. Mina, M.D., Miguel Martin, M.D., Ph.D., Henri Roché, M.D., Ph.D., Young-Hyuck Im, M.D., Ph.D., et al.


ORIGINAL ARTICLE

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D.,


The NEW ENGLAND JOURNAL of MEDICINE

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DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono

Cowden Syndrome

- Mutations in PTEN gene
- Autosomal dominant inheritance
- Increased risk of:
  - Breast
  - Uterine
  - Thyroid
  - Colon (polyps and/or cancer)
- Other Findings:
  - Macrocephaly
  - Intellectual disability
  - Hamartomas
  - Lipomas

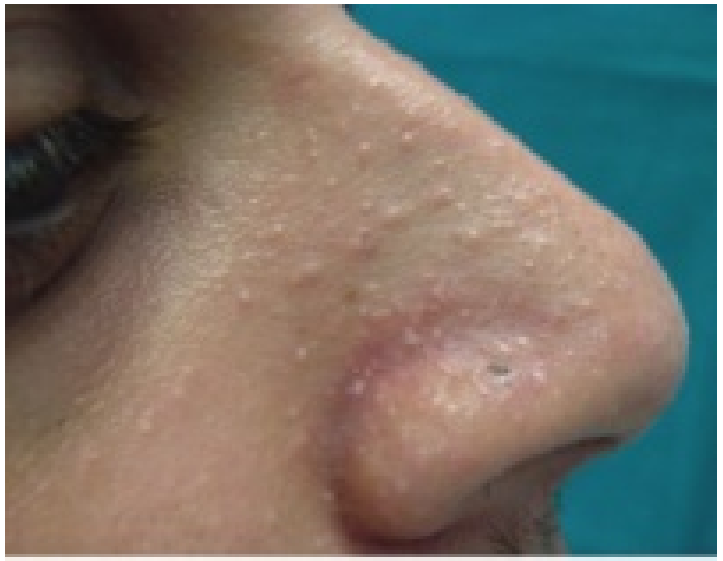


Figure. Hamartomas characteristic of Cowden syndrome.

Source: Marcio A Oliveira et al.

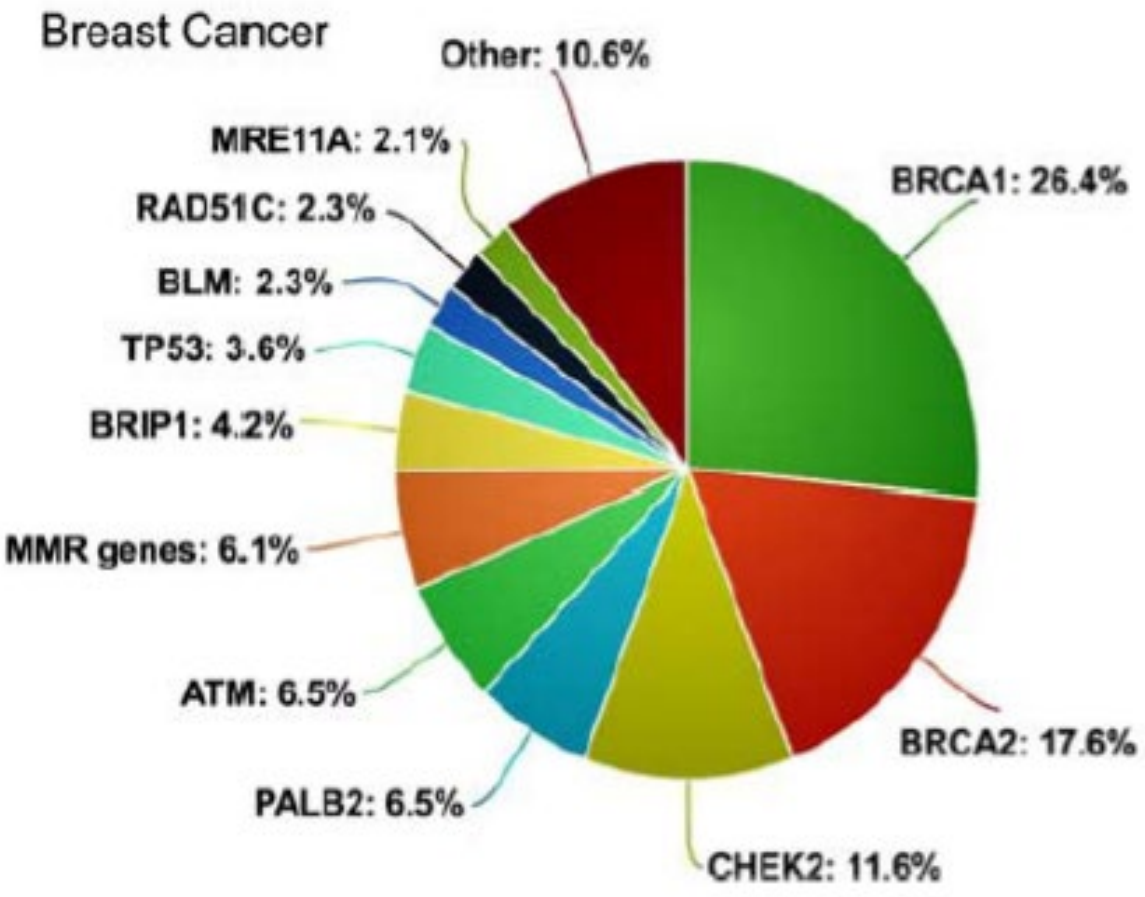
Li Fraumeni Syndrome (LFS)

- Mutations in TP53 gene
- Autosomal dominant inheritance
- Increased risk of:
  - Breast
  - Brain
  - Sarcoma
  - Adrenocortical Carcinoma
- Childhood cancers can be seen in LFS
- Highly penetrant cancer syndrome
  - 50% risk of cancer by age 40
  - 90% risk of cancer by age 60

Other hereditary breast cancer genes

- PALB2
  - Breast, ovary, pancreas, prostate
- ATM
  - Breast, pancreas
- CHEK2
  - Breast, colon
- CDH1
  - Diffuse gastric cancer and lobular breast cancer
- BARD1, BRIP1, RAD51C, RAD51D
  - Breast and/or ovary

Hereditary breast cancer



Hereditary Breast and Ovarian Cancer Syndrome: Moving Beyond BRCA1 and BRCA2 Lien N. Hoang, MD and Blake C. Gilks, MD, FRCPC

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[8-17] and Other Cancer Risks
ATM	• **Evidence for increased risk:** Strong • **Absolute risk:** 15-40%[3,4] • **Management:**[b] ▸ Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[c,d] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history	• **Evidence for increased risk:** Strong • **Absolute risk:** <3%[5-7] • **Management:**[e] ▸ Risk reduction: Evidence insufficient for RRSO; manage based on family history	**Pancreatic cancer** • **Evidence for increased risk:** Strong • **Absolute risk:** ~5-10% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A. **Prostate cancer** • Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring. Heterozygous ATM mutation should not lead to a recommendation to avoid radiation therapy at this time. See Discussion for information regarding the c.7271T>G variant.		
BARD1	• **Evidence for increased risk:** Limited, but stronger for triple-negative disease[18-19] • **Absolute risk:** Insufficient data to define • **Management:** ▸ Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40y[c,d] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history.	**Evidence for increased risk:** None	**Other cancers** • **Unknown or insufficient evidence**
BRCA1	• **Evidence for increased risk:** Very strong (with predisposition to triple negative disease) • **Absolute risk:** >60%[20-24] • **Management:** See *BRCA* Pathogenic Variant-Positive Management	• **Evidence for increased risk:** Very strong • **Absolute risk:** 39%-58%[25] • **Management:** See *BRCA* Pathogenic Variant-Positive Management	**Pancreatic cancer** • **Evidence for increased risk:** Strong • **Absolute risk:** ≤5% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A. **Prostate cancer** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: There have been a few case reports of Fanconi-like conditions in individuals with two *BRCA1* pathogenic variants.[27,28]		
BRCA2	• **Evidence for increased risk:** Very strong (with predisposition to ER+ disease) • **Absolute risk:** >60% [20-24] • **Management:** See *BRCA* Pathogenic Variant-Positive Management	• **Evidence for increased risk:** Very strong • **Absolute risk:** 13%-29%[25] • **Management:** See *BRCA* Pathogenic Variant-Positive Management	**Pancreatic cancer** • **Evidence for increased risk:** Very strong • **Absolute risk:** 5-10% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A. **Prostate cancer and Melanoma** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: Counsel for risk of autosomal recessive condition in offspring.		
BRIP1	• **Evidence for increased risk:** Limited; potential increase in female breast cancer (including triple negative)[19] • **Absolute risk:** Insufficient data to define • **Management:** Insufficient data; managed based on family history	• **Evidence for increased risk:** Strong • **Absolute risk:** >10%[5-7] • **Management:** ▸ Risk reduction: Consider RRSO at 45–50 y	**Other cancers** • Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *BRIP1* appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset of ovarian cancer.		

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[8-17] and Other Cancer Risks
MSH2, MLH1, MSH6, PMS2, EPCAM[f]	**MLH1, MSH2, MH6, PMS2 and EPCAM** • **Evidence for increased risk:** Limited • **Absolute risk:** <15%[34-35] • **Management:** Insufficient data; managed based on family history	**MLH1, MSH2, MH6** • **Evidence for increased risk:** Strong • **Absolute risk:** >10%[36-37] **PMS2** • **Evidence for increased risk:** Limited • **Absolute risk:** <3%[38-40] **EPCAM** • **Evidence for increased risk:** Limited • **Absolute risk:** <10% • **Management for all genes:** See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	**Pancreatic cancer** • **Evidence for increased risk:** Strong • **Absolute risk:** <5-10% (excluding PMS2) • **Management:** Screening mutation carriers with a family history of pancreatic cancer (insufficient evidence for *PMS2*), see PANC-A. **Colon, Uterine, Others** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
	Comment: Counsel for risk of autosomal recessive condition in offspring.		
NBN	• **Evidence for increased risk:** Current data suggest that breast cancer risks are not increased for pathogenic/ likely pathogenic variants other than 657del5, for which there is mixed evidence for increased risk.[b,41] • **Absolute risk:** Insufficient data to define • **Management:** Insufficient data; managed based on family history	• **Evidence for increased risk:** Limited[5-7] • **Absolute risk:** Insufficient data to define • **Management:** Manage based on family history	**Other cancers** • Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in children.		
NF1	• **Evidence for increased risk:** Strong • **Absolute risk:** 15-40%[42,43] • **Management:**[b] ▸ Screening: Annual mammogram with consideration of tomosynthesis starting at age 30 y and consider breast MRI with contrast from ages 30–50 y[c,d] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history	**Evidence for increased risk:** None	**Malignant peripheral nerve sheath tumors, GIST, others** • Recommend referral to *NF1* specialist for evaluation and management
	Comments: Screening recommendations only apply to individuals with a clinical diagnosis of NF. At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.		

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
NBN	**Increased risk of female breast cancer for individuals with 657del5 variant[f]** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[g,h] • RRM: Evidence insufficient, manage based on family history	**Potential increase in ovarian cancer risk,** • RRSO: Evidence insufficient; manage based on family history	**Unknown or insufficient evidence for other cancers**
	Comments: Current data suggest that breast cancer risks are not increased for pathogenic/likely pathogenic variants other than 657del5. Counsel for risk of autosomal recessive condition in children.		
NF1	**Increased risk of female breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis starting at age 30 y and consider breast MRI with contrast from ages 30–50 y[g,h] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	• **Malignant peripheral nerve sheath tumors, GIST, others** • Recommend referral to *NF1* specialist for evaluation and management
	Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Screening recommendations only apply to individuals with a clinical diagnosis of NF. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.		
PALB2	**Increased risk of female breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y[g,h] • RRM: Discuss option of risk-reducing mastectomy	**Potential increase in ovarian cancer risk** • RRSO: Evidence insufficient; manage based on family history	• **Pancreatic** ▸ See PANC-A • **Unknown or insufficient evidence for other cancers**
	Comments: Counsel for risk of autosomal recessive condition in offspring.		
PTEN	**Increased risk of female breast cancer** • See Cowden Syndrome Management	**No increased risk of ovarian cancer**	See Cowden Syndrome Management

RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Continued
Footnotes on GENE-A 5 of 5

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[8-17] and Other Cancer Risks
PALB2	• **Evidence for increased risk:** Strong • **Absolute risk:** 41-60%[17,18,44] • **Management:**[b] ▸ Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y[c,d] ▸ Risk reduction: Discuss option of RRM	• **Evidence for increased risk:** Strong • **Absolute risk:** 3-5%[5-7,17] • **Management:**[e] ▸ Risk reduction: Evidence insufficient; manage based on family history	**Pancreatic cancer** • **Evidence for increased risk:** Limited • **Absolute risk:** 5-10% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A **Other cancers** • Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring.		
PTEN	• **Evidence for increased risk:** Strong • **Absolute risk:** 40-60% (historical cohort data), >60% (projected estimates)[45-48] • **Management:**[b] See Cowden Syndrome Management	**Evidence for increased risk:** None	**Thyroid, colon, endometrial cancers** • See Cowden Syndrome Management
RAD51C	• **Evidence for increased risk:** Limited; potential increase in female breast cancer (including triple negative • **Absolute risk:** 15-40%[18,19,49,50] • **Management:** Insufficient data; managed based on family history	• **Evidence for increased risk:** Strong • **Absolute risk:** >10%[5-7,51] • **Management:** ▸ Risk reduction: Consider RRSO at 45–50 y	**Other cancers** • Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51C* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
RAD51D	• **Evidence for increased risk:** Limited; potential increase in female breast cancer (including triple negative • **Absolute risk:** 15-40%[18,19,49,50] • **Management:** Insufficient data; managed based on family history	• **Evidence for increased risk:** Strong • **Absolute risk:** >10% [5-7,51] • **Management:** ▸ Risk reduction: Consider RRSO at 45–50 y	**Other cancers** • Unknown or insufficient evidence
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51D* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[8-17] and Other Cancer Risks
STK11	• **Evidence for increased risk:** Strong • **Absolute risk:** 40-60%[52,53] • **Management:** ▸ Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome ▸ Risk reduction: Evidence insufficient RRM, manage based on family history	• **Evidence for increased risk:** Strong (non-epithelial ovarian tumors) • **Absolute risk:** >10[52] • **Management:** See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome	**Pancreatic cancer** • **Evidence for increased risk:** Very strong • **Absolute risk:** >15% • **Management:** Screening, see PANC-A **Other cancers** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome
	Comment: The precise risk estimates for pancreatic cancer for STK11 should be interpreted with caution given the relative paucity of data.		
TP53	• **Evidence for increased risk:** Strong • **Absolute risk:** >60%[54] • **Management:** See Li-Fraumeni Syndrome Management	**Evidence for increased risk:** None	**Pancreatic cancer** • **Evidence for increased risk:** Limited • **Absolute risk:** 5-10% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A **Other cancers** • See Li-Fraumeni Syndrome Management

Lynch Syndrome (formerly known as HNPCC)

- Mutations in mismatch repair genes (MLH1, MSH2, MSH6, and PMS2, EPCAM)
- Associated with an increased risk of colon, uterine, stomach, ovarian, and other cancers.
- Autosomal dominant inheritance
- Many patients have MSI or IHC testing to screen for Lynch Syndrome
  - Validated for colon and endometrial cancers, can be used on other tissue types
  - Based on results, further somatic testing may be indicated
    - MLH1 hypermethylation, BRAF testing
  - Germline testing may be indicated with or without MSI or IHC
  - Abnormal MSI/IHC is NOT diagnostic of Lynch Syndrome

Cancer Risks in Lynch Syndrome by Gene Compared to the General Population

	General Population Risk[1]	*MLH1*		*MSH2* (For EPCAM, see footnote 10)		*MSH6*		*PMS2*	
		Risk	Average age of diagnosis	Risk	Average age of diagnosis	Risk	Average age of diagnosis	Risk	Average age of diagnosis
Colorectal[1-6]	4.5%	46%–49%	43–45 years	43%–52%	44 years	15%–44%	51–63 years	12%–20%	47–66 years
Endometrial[1-6]	2.7%	43%–57%	49 years	21%–57%	47–48 years	17%–46%	53–55 years	0%–15%	49–56 years
Breast[2,3,7]	13%	12%–17%	53 years	12%	52 years	0%–13%	52 years	NE	
Ovarian[1,2,7]	1.3%	5%–20%	44–47 years	10%–38%	43–44 years	1%–11%	44–48 years	NE	
Gastric[1,2,7,8]	<1%	5%–7%	49–52 years	0.2%–16%	49–52 years	0%–5%	49–63 years	NE	
Pancreas[2]	1.5%	6%	52–57 years	NE		NE		NE	
Bladder[2,7,9]	2.5%	2%–4%	53–59 years	4%–17%	53–59 years	2%	53–71 years	NE	
Biliary tract[1,2]	<1%	2%–4%	50 years	0.02%	57 years	NE		NE	
Urothelial[1,2,7,9]	<1%	0.2%–5%	52-60 years	2%–18%	52–61 years	0.7%–7%	52–69 years	NE	
Small bowel[1,7]	<1%	0.4%–11%	46-47 years	1%–10%	46–48 years	0%–3%	46–54 years	NE	
Prostate[2,3,7,11]	11.6%	0%–17%	59 years	30%–32%	59 years	0%–5%	59 years	NE	
Brain/CNS[2]	<1%	NE		NE		Not reported	Not reported	NE	

Management for Lynch Syndrome

Surveillance

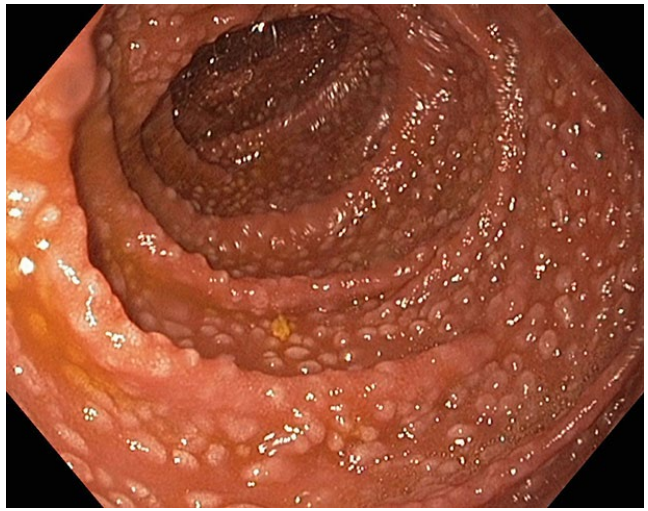
- Colonoscopy every 1-2 years, starting at age
  - 20-25 or 2-5 years prior to earliest colon ca (MLH1, MSH2)
  - 30-35 or 2-5 years prior to earliest colon cancer in the family (MSH6, PMS2)
- Consider upper endoscopy at age 40 and repeat every 3-5 years
- Consider annual urinalysis starting at age 30-35
- Consider endometrial biopsy starting at age 30-35
- Consider annual physical/neurologic exam starting at age 25-30
- Pancreatic cancer screening considered if Fhx

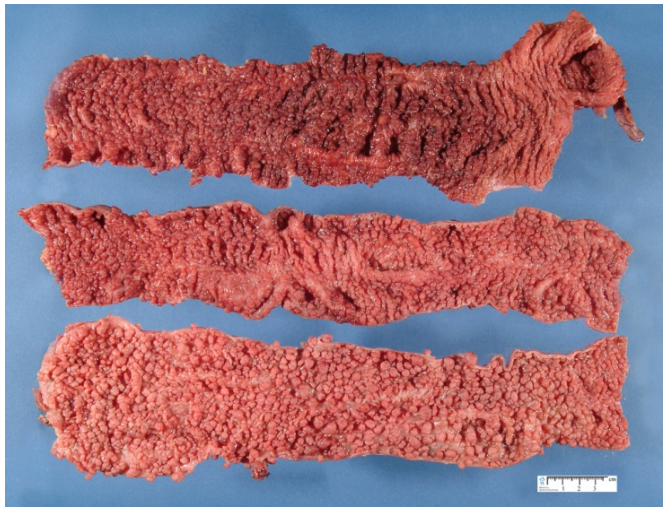
Surgical

- Discuss option of TAH+/-BSO (depending on gene) after family is complete
- Discuss surgical options with physician regarding future colon cancer risk

Familial Adenomatous Polyposis

- Caused by mutations in the APC gene
- Autosomal dominant
- Classic form:
  - 100-1000's of colon/rectal/gastric polyps
  - Risk of extracolonic findings
    - Desmoids
    - Osteomas
    - Supernumerary teeth
    - CHRPE
    - Thyroid cancer
  - Recommend colonoscopy annually starting at age 10-15y
    - Colectomy common in 20's
  - Attenuated form:
    - 10-100 polyps over a lifetime





Other polyposis conditions

- MYH-associated Polyposis (MUTYH)
  - Adenomas, can be throughout GI tract
  - Autosomal recessive
- Peutz-Jeghers Syndrome (STK11)
  - Hamartomatous polyps, increased cancer risk (breast colon cancer, pancreas), oral freckling (childhood)
- Juvenile Polyposis (BMPR1A and SMAD4)
  - Juvenile type polyps, colon & stomach cancer
  - SMAD4 also causes hereditary hemorrhagic telangiectasia (HHT)
- Serrated Polyposis Syndrome

Table 4: Recommended Management for Patients with Pathogenic Variants in Genes That May Confer a Risk for Colorectal Cancer

GENE	RECOMMENDATION
APC	See NCCN Guidelines for Familial Adenomatous Polyposis (FAP-1)
BMPR1A	See NCCN Guidelines for Juvenile Polyposis Syndrome (JPS-1)
LS genes *(MLH1, MSH2, MSH6, PMS2, EPCAM)*	See NCCN Guidelines for Lynch Syndrome (LS-1)
MUTYH biallelic pathogenic variants	See NCCN Guidelines for *MUTYH*-Associated Polyposis (MAP-1)
PTEN	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
STK11	See NCCN Guidelines for Peutz-Jeghers Syndrome (PJS-1)
SMAD4	See NCCN Guidelines for Juvenile Polyposis Syndrome (JPS-1)
TP53	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
GREM1[g]	• Begin high-quality colonoscopy at age 25–30 y and every 2–3 y if negative. If polyps are found, high-quality colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable by colonoscopy. • Surgical evaluation if appropriate.
POLD1[g]	
POLE[g]	
AXIN2[g]	
NTHL1 biallelic pathogenic variants[g]	
MSH3 biallelic pathogenic variants[g]	
APC I1307K pathogenic variant[g,i] *CHEK2*[g,h,i]	• For probands with CRC and one of these pathogenic variants: ‣ See surveillance recommendations for post-CRC resection: ◊ NCCN Guidelines for Colon Cancer and NCCN Guidelines for Rectal Cancer • For probands unaffected by CRC with a first-degree relative with CRC: ‣ High-quality colonoscopy screening every 5 y, beginning at age 40 or 10 y prior to age of first-degree relative's age at CRC diagnosis. • For probands unaffected by CRC and no first-degree relative with CRC: ‣ High-quality colonoscopy screening every 5 y, beginning at age 40. • For CHEK2, also see See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
MUTYH heterozygotes[g]	• For probands unaffected by CRC with a first-degree relative with CRC: ‣ High-quality colonoscopy screening every 5 y, beginning at age 40 y or 10 y prior to age of first-degree relative's age at CRC diagnosis. See screening recommendations in NCCN Guidelines for Colorectal Cancer Screening. • There are no specific data available to determine screening recommendations for a patient with an *MUTYH* heterozygous pathogenic variant and a second-degree relative affected with CRC. See NCCN Guidelines for Colorectal Cancer Screening. • For probands unaffected by CRC with NO family history of CRC: ‣ Data are unclear as to whether specialized screening is warranted for *MUTYH* heterozygous carriers unaffected by CRC with no family history of CRC.[i]
ATM, BLM, GALNT12, RNF43, RPS20	• Available data are insufficient to provide specialized colorectal cancer screening recommendations at this time. See NCCN Guidelines for Colorectal Cancer Screening.

Other hereditary cancer genes

- GREM1, POLD1, POLE, MSH3
  - Colon
- SDHA, SDHB, SDHC, SDHD
  - Pheochromocytoma, paraganglioma
- MEN1, RET
  - Endocrine neoplasias
- BAP1
  - Mesothelioma, ocular melanoma, cutaneous melanoma
- CDKN2A
  - Pancreatic cancer, melanoma
- Familial MDS/AML
  - Eg GATA2, DDX41, CEBPA, RUNX1

Genetic testing for hereditary cancers

- Past testing was targeted to specific genes
  - BRCA1, BRCA2, TP53
- Now NextGen panels are most widely used
  - Breast cancer panels (8-25 genes)
  - Breast and GYN panels (15-40 genes)
  - Colon panels (10-25 genes)
  - Comprehensive cancer panels (50-100+ genes)
- Allows for higher detection rate in shorter turn around time for patients
- Increased possibility of incidental findings and uncertain information

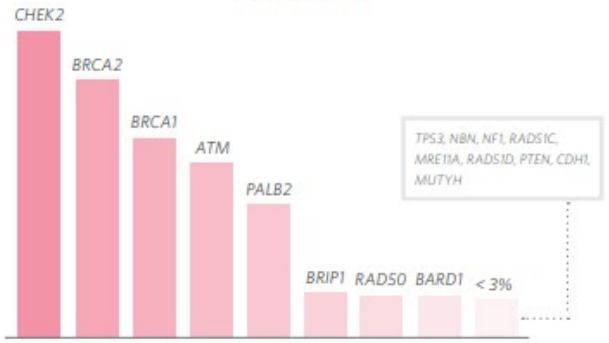
Genetic testing for hereditary cancers

- Possible results from genetic testing
  - Positive
    - Confirmed diagnosis of hereditary cancer syndrome
    - Discuss gene specific screening/surveillance recommendations
    - Discuss familial implications
  - Negative
    - May need further testing in the future
    - Make recommendations based on personal and family history
  - Variant of uncertain significance
    - Clinically treated like a negative test result
    - Can be very confusing for the patient
    - Recommendations should be made based on family history, not the specific variant
    - Reclassification is the goal
      - Family/segregation studies
      - RNA studies

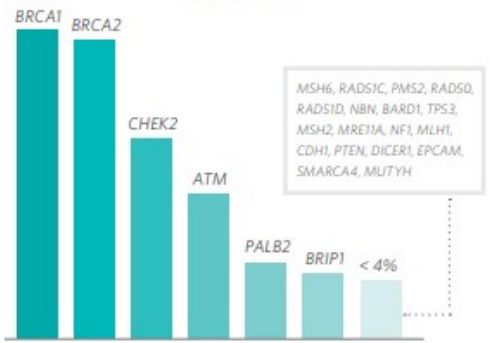
Mutation Distributions

ORDERING THE RIGHT TEST CAN PROVIDE THE MOST ACCURATE AND COMPREHENSIVE ANSWERS

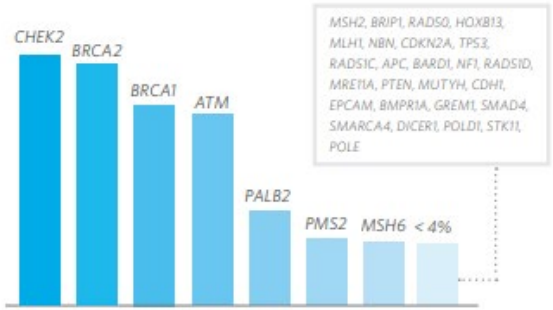
BreastNext*



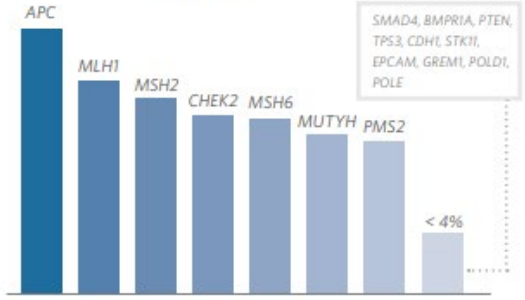
OvaNext*



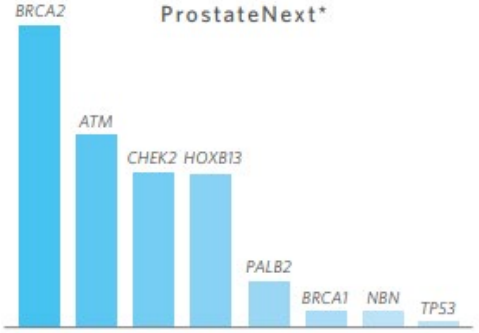
CancerNext*



ColoNext*

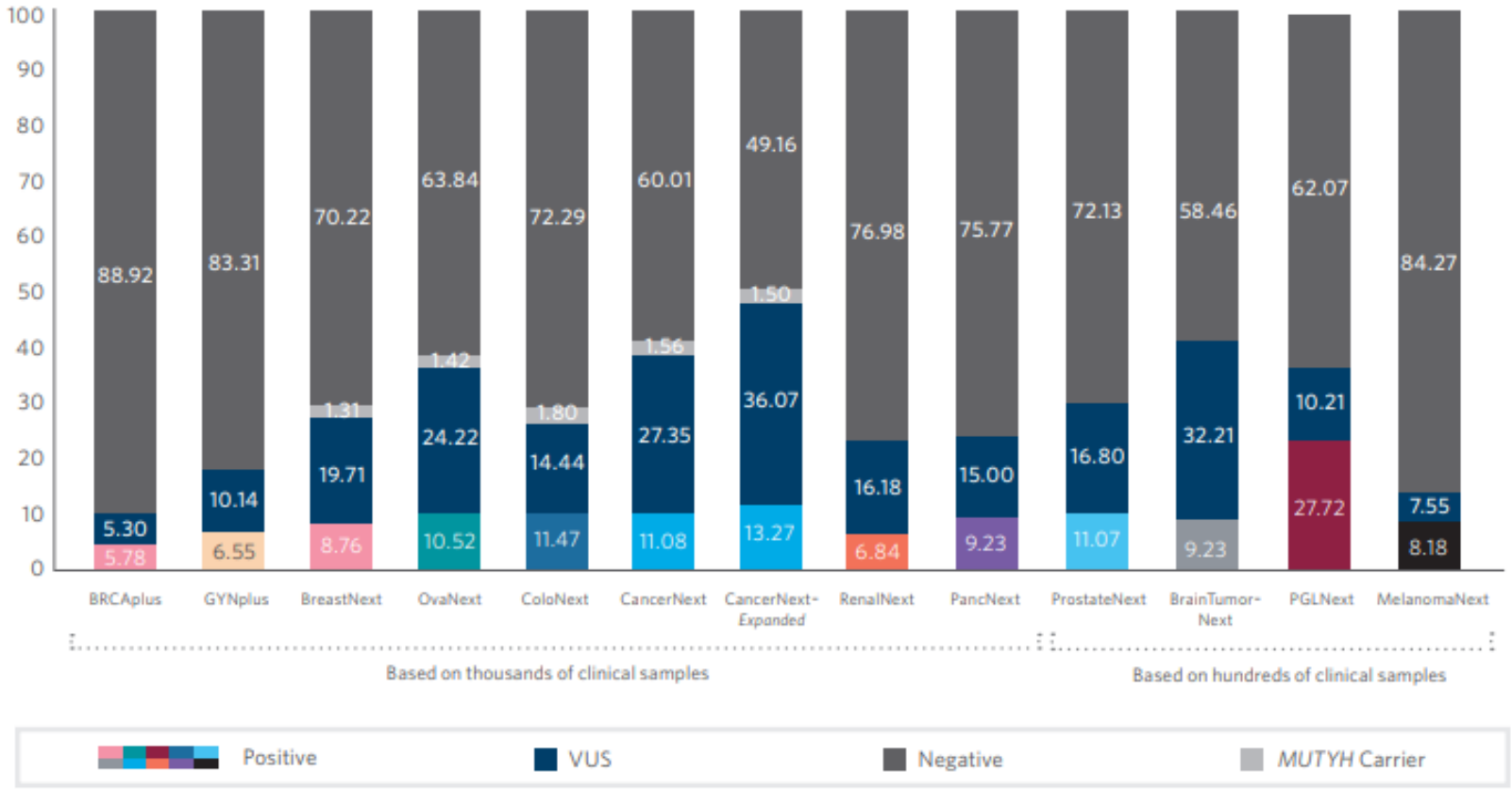


ProstateNext*



Hereditary Cancer Panel Experience

UNDERSTANDING DISEASE BETTER THROUGH DATA SHARING AND TRANSPARENCY

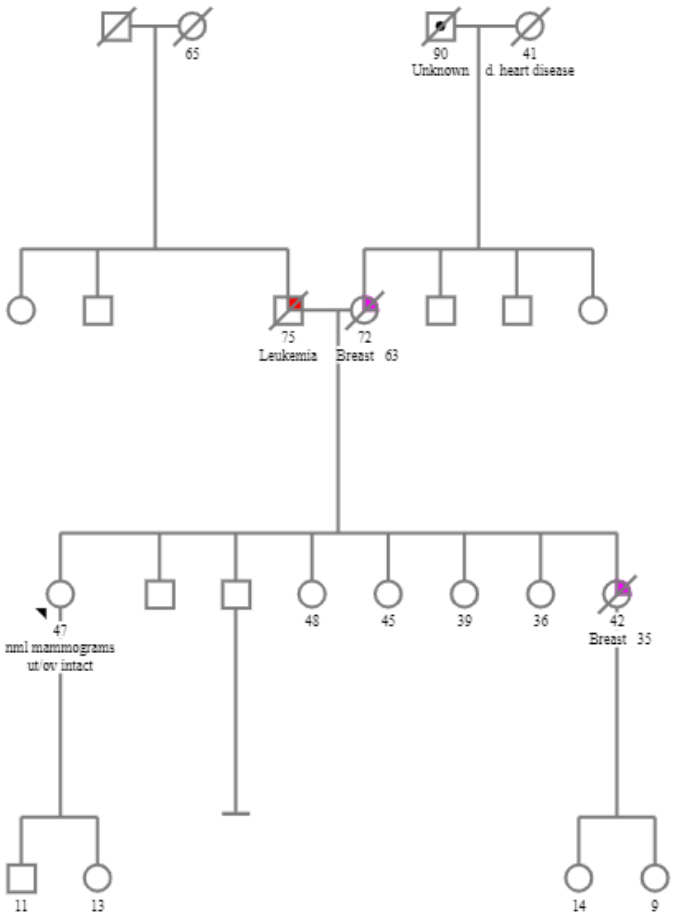


BRCA1 and *BRCA2* VUS Rate: 3.33%

Case Examples

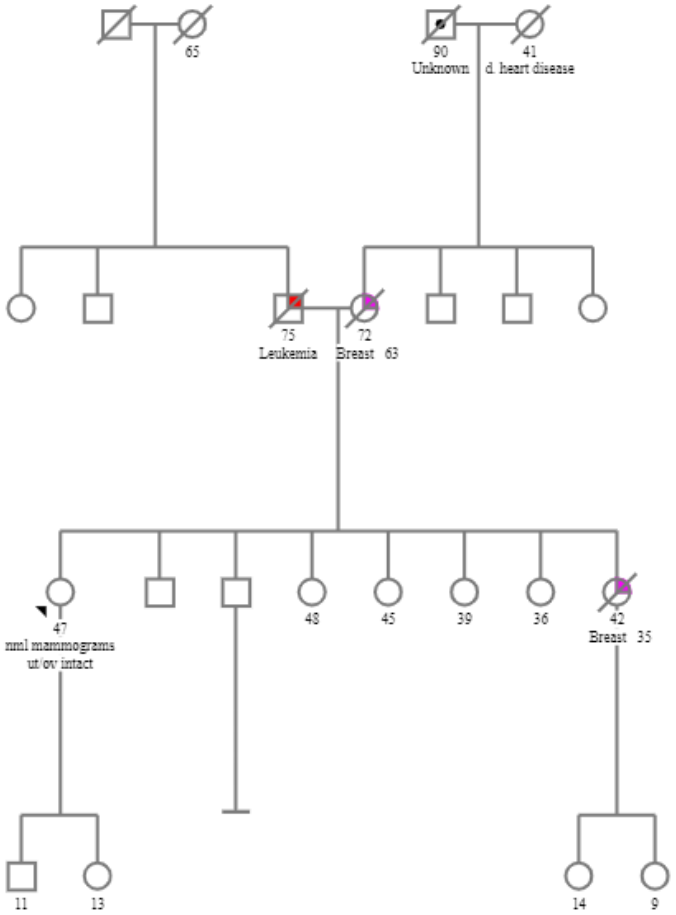
Case #1

- 47 year old woman presents to genetic counseling regarding family history of breast cancer and leukemia



Case #1

- 47 year old woman presents to genetic counseling regarding family history of breast cancer and leukemia
- Decides to proceed with genetic testing
  - BRCA1 and BRCA2 sequencing and rearrangement analysis



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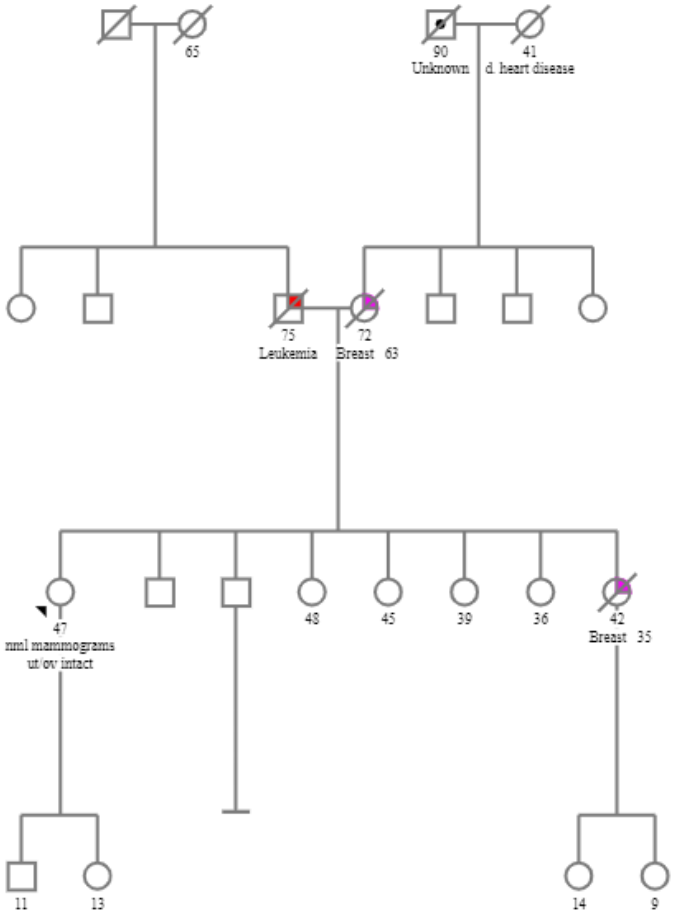
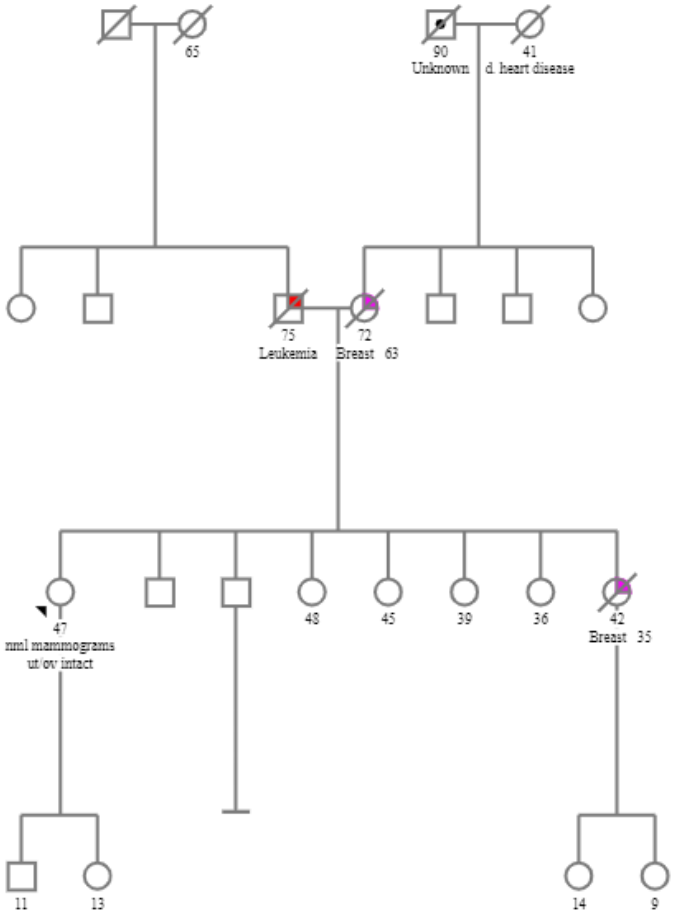


Case #1

- 47 year old woman presents to genetic counseling regarding family history of breast cancer and leukemia
- Decides to proceed with genetic testing
  - BRCA1 and BRCA2 sequencing and rearrangement analysis
    - Testing was done in 2011, prior to NextGen panels, and prior to Supreme Court ruling regarding gene patenting
  - Tests positive for a BRCA2 pathogenic mutation
  - Passes along information to family members
  - Sisters all pursue genetic testing
    - Individuals with positive testing proceed with increased breast cancer screening and surgical removal of ovaries and fallopian tubes



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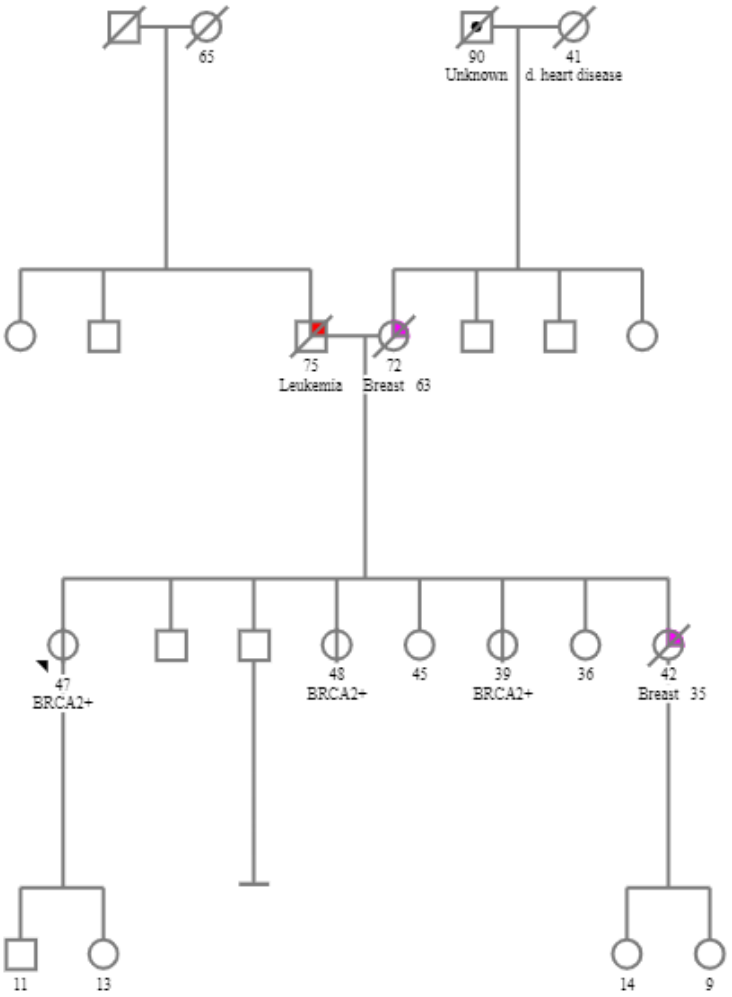
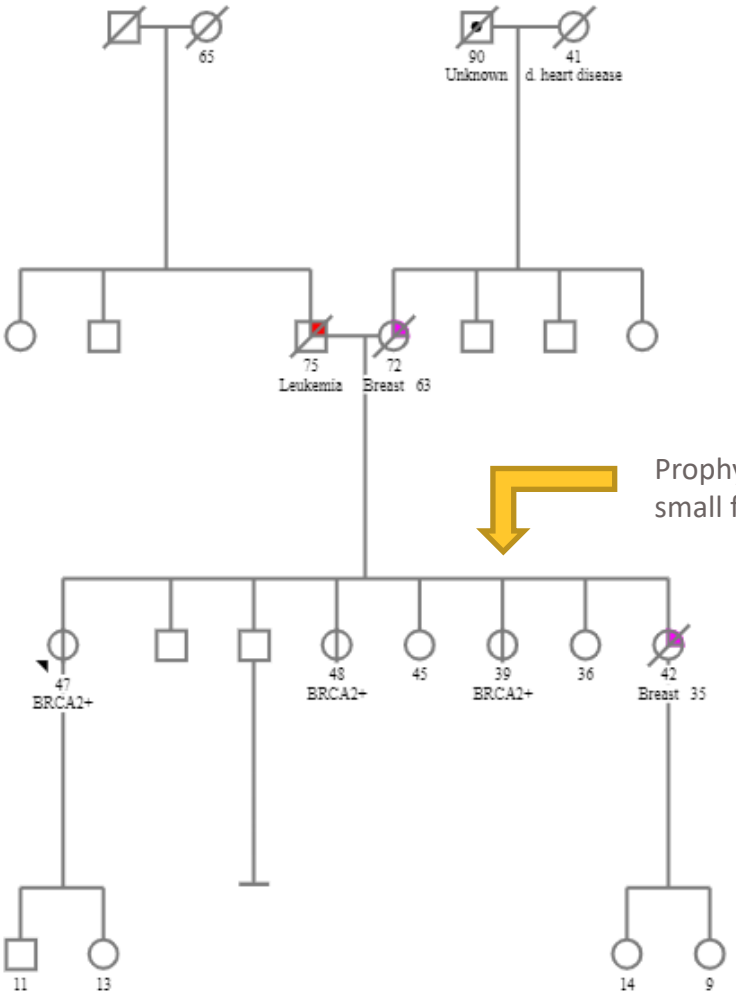

65
90
Unknown
41
d. heart disease
75
Leukemia
72
Breast 63
47
BRCA2+
48
BRCA2+
45
39
BRCA2+
36
42
Breast 35
11
13
14
9

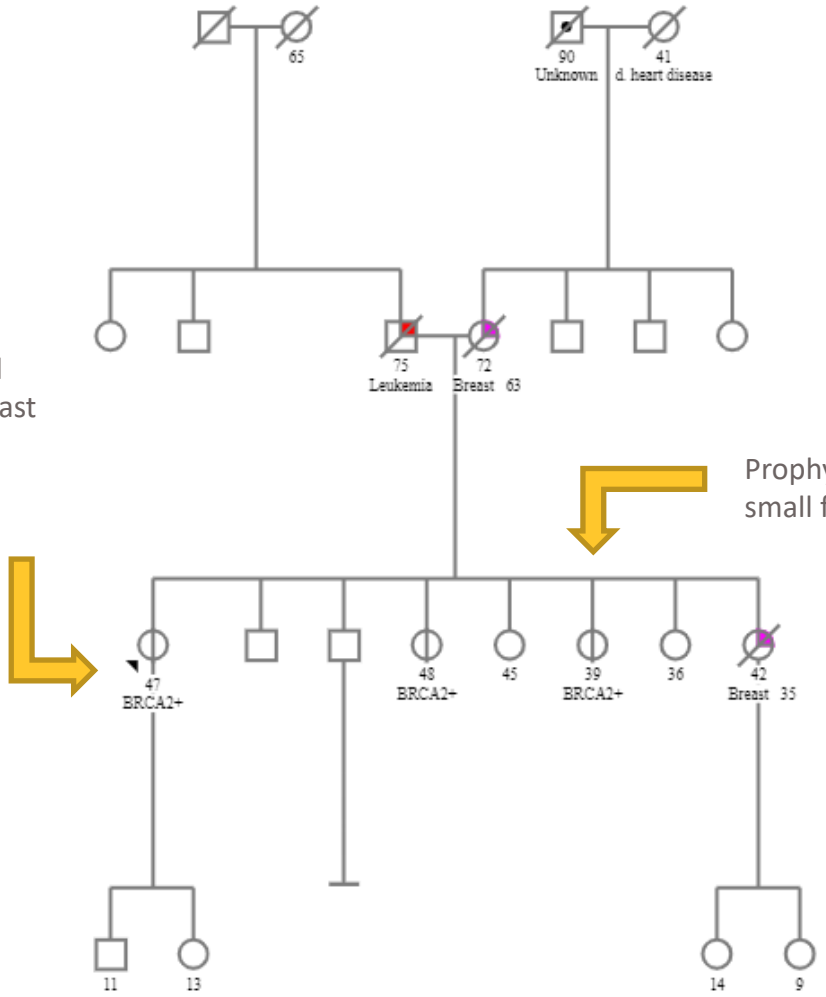
Case #1



Prophylactic mastectomy: pathology showed small focus of invasive breast cancer

Case #1

Follow up from proband:
GC received email 2 years after testing, stating that patient's employer bought her 23andMe for Christmas. Her results showed a "lower than average risk for breast cancer". Patient was confused as to why results were discordant.



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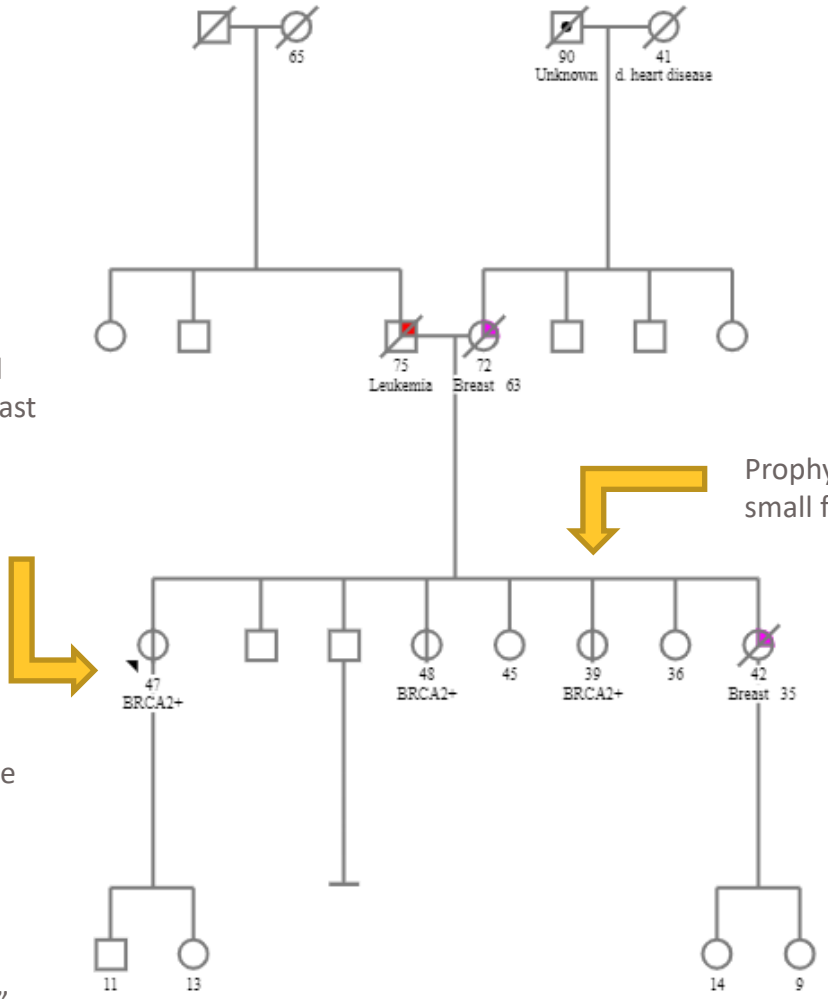


Prophylactic mastectomy: pathology showed small focus of invasive breast cancer

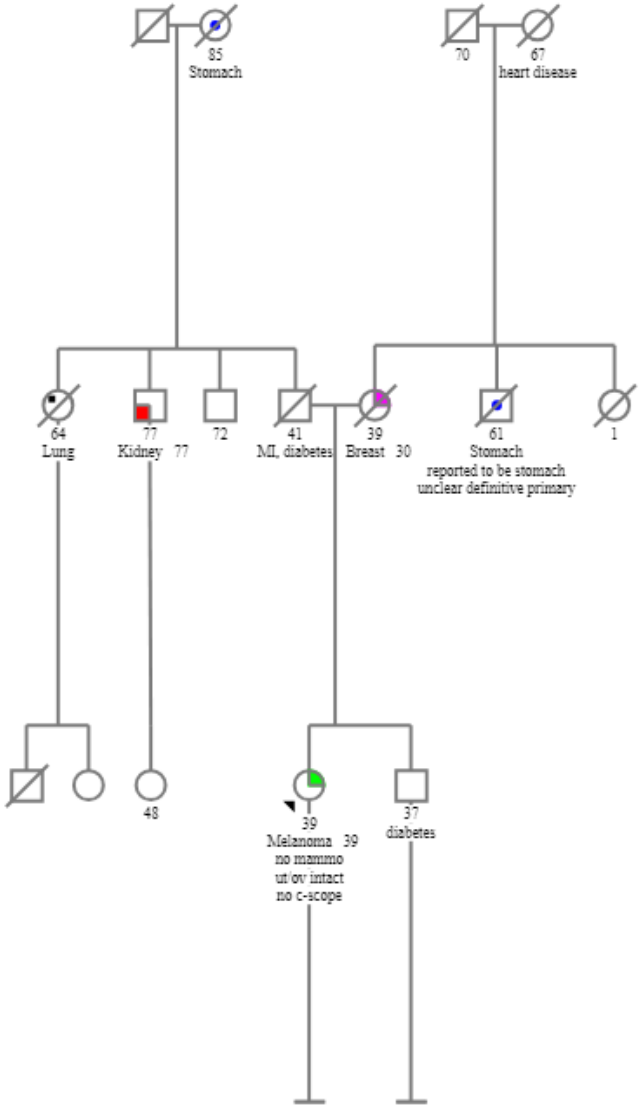
She stated "If I had done 23andMe before I had genetic testing with you, I never would have made that appointment. I would have assumed I was clear, and didn't need to worry about an increased risk of cancer."

Moral of the story…

- All genetic testing is not created equally!
- Choice of laboratory and specific test matters
  - Make sure appropriate genes are analyzed
  - Confirm appropriate gene coverage (PMS2 pseudogene region)
  - Insurance coverage/cost
  - Some labs contribute to research/databases, some do not
- Ideal to do it right the first time
  - Delay of treatment
  - Lack of insurance coverage for multiple genetic tests

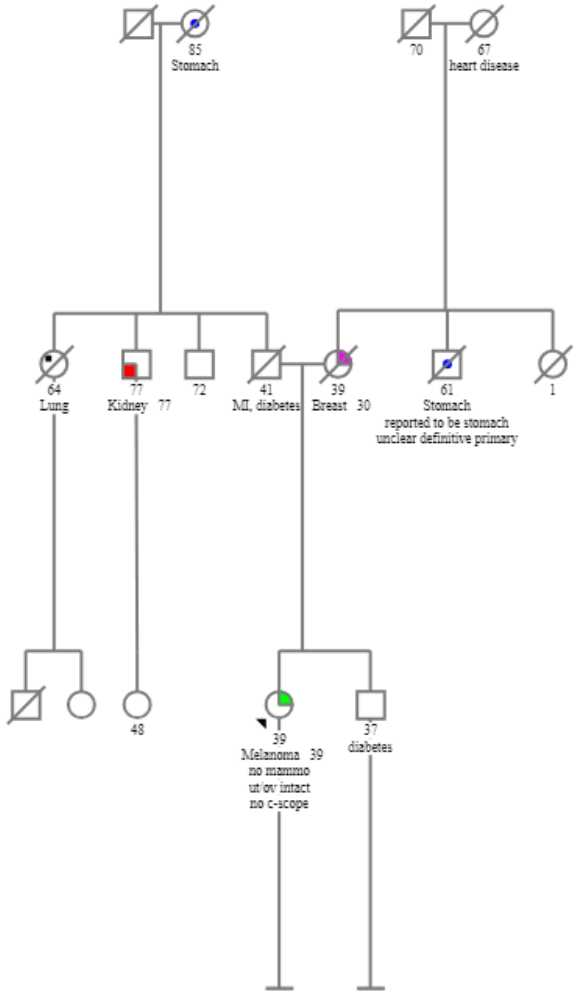
Case #2

- 39 year old woman recently diagnosed with melanoma presents for genetic counseling
- Family history includes breast, kidney, and gastric cancer



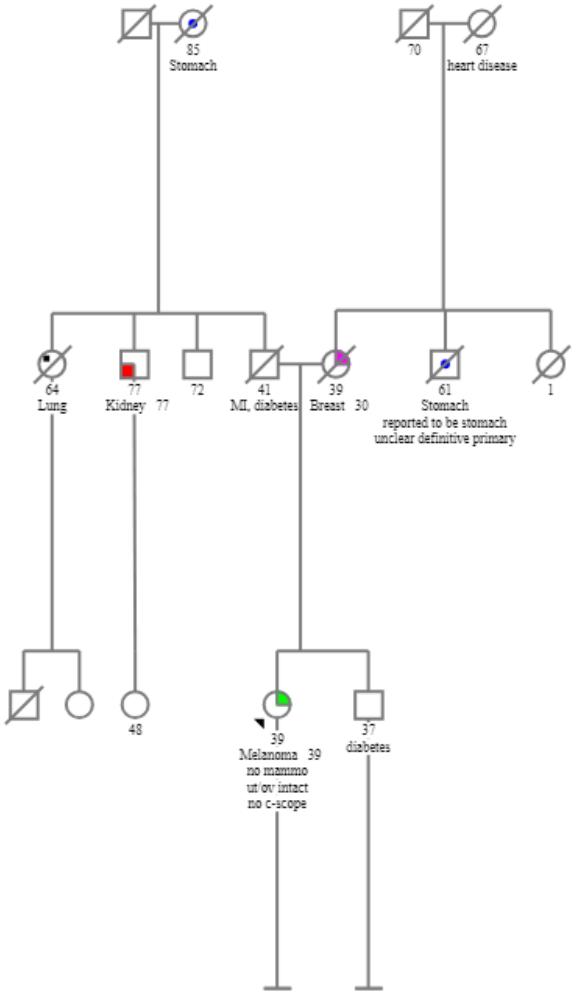
Case #2

- 39 year old woman recently diagnosed with melanoma presents for genetic counseling
- Family history includes breast, kidney, and gastric cancer
- Patient decides to proceed with comprehensive genetic testing
  - 46 genes



Case #2

- 39 year old woman recently diagnosed with melanoma presents for genetic counseling
- Family history includes breast, kidney, and gastric cancer
- Patient decides to proceed with comprehensive genetic testing
  - 46 genes
- Results show:
  - Pathogenic variant in ATM
  - 2 variants of uncertain significance
    - BRCA2
    - SMARCA4



Case #2

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Potential increase in ovarian cancer risk, with insufficient evidence for recommendation of RRSO**	Unknown or insufficient evidence for pancreas or prostate cancer
	Comments: Insufficient evidence to recommend against radiation therapy. Counsel for risk of autosomal recessive condition in offspring.		

- Patient referred to breast and ovarian cancer prevention clinic to discuss breast cancer screening
- Also referred to GI cancer prevention clinic to review data associated with ATM mutations and pancreatic cancer risk
- Considering enrollment in research study, with goal of reclassifying her BRCA2 and SMARCA4 variants

Responses to genetic testing

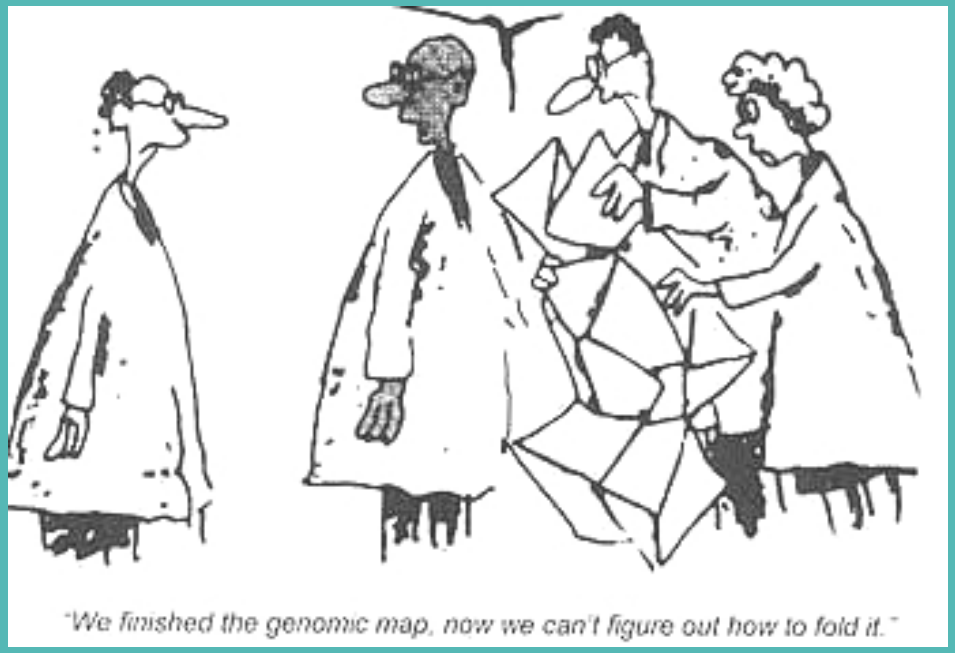
- Deciding to proceed with genetic testing can be a difficult decision
  - Many more patients pursue genetic testing than in the past
- Concern about privacy and genetic discrimination
  - Genetic Information Non-Discrimination Act of 2008 (GINA)
- Concern about family members
  - Parental guilt, survivor guilt, family dynamics
- Emotional responses vary
  - Range from devastation to complete relief
  - Most patients need time to cope with positive results
  - Support groups (FORCE, Lynch Syndrome international, etc.)
  - Anxiety, uncertainty, concern about future cancer risk

Conclusions

- Many patients may benefit from genetic counseling/testing at the time of diagnosis, in order to help determine best treatment plan
- The scope of hereditary cancer syndromes is complex and constantly changing
- Single gene testing is usually not the most appropriate for patients
  - Way more than just BRCA1, BRCA2 and/or Lynch Syndrome
  - Panel testing leads to higher VUS rate as well as incidental findings

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine



Thank you!

Questions | elally@seattlecca.org
Phone | 206-606-7211

Better together.