Fred Hutch
Cancer Center

Cancer Genetics for primary care
November 2nd, 2023

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Medical Director of the Cancer Genetics & high-risk service at FHCC / UW

Cancer Predispositions for primary care

Hereditary cancer syndromes to know

How to screen for hereditary cancer syndromes (HCS)

Tips to remember!

Cases

Hereditary Cancers in big numbers

It is a lot more people than we anticipated

- 5-10% of cancer diagnosis are explained by a genetic predisposition
  - **If you test everyone at a cancer center, positive rate is ~13% or 1 in 8**

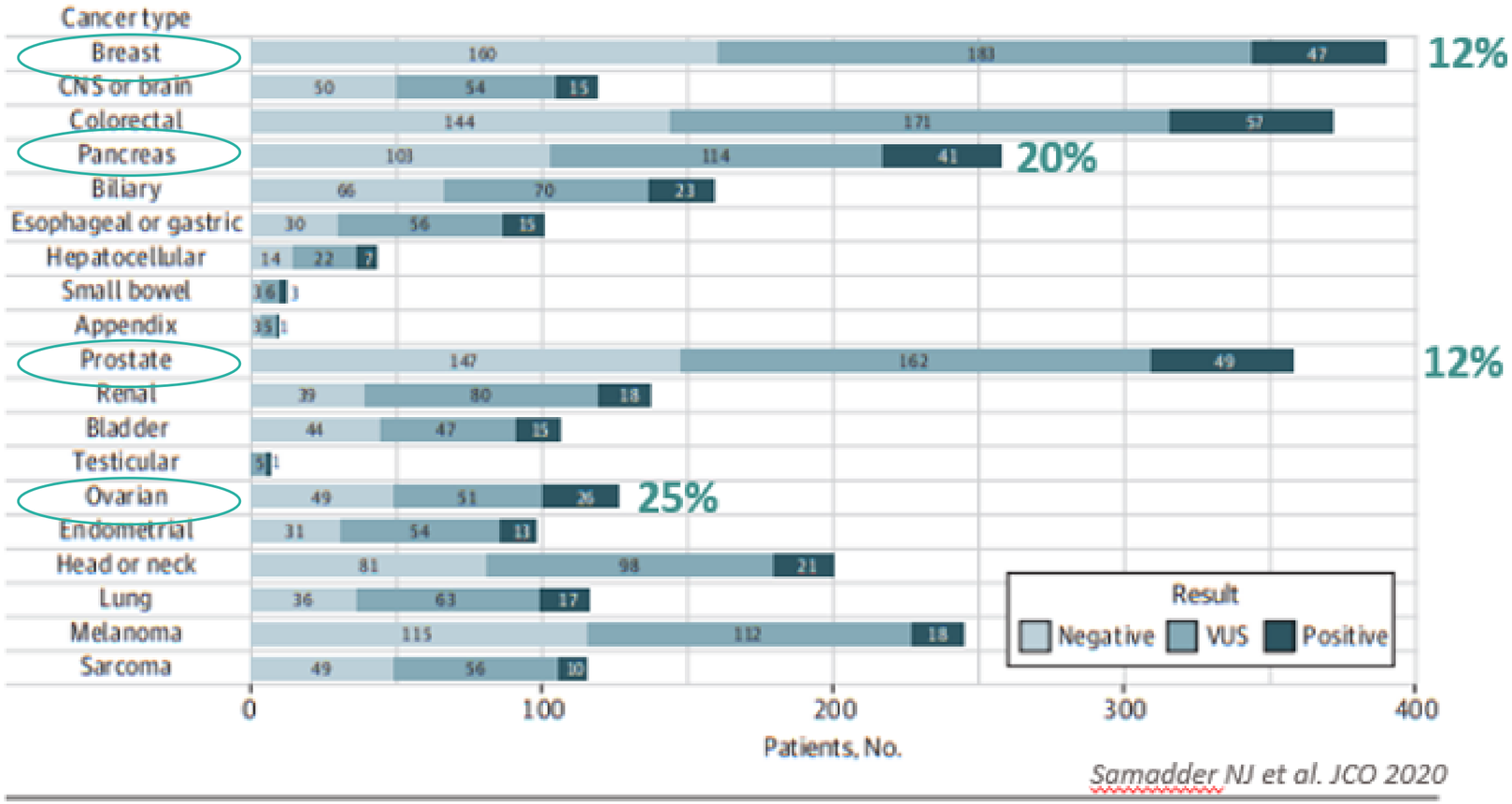
- ~ 2 million people in the US are at an increased risk of cancer because they have a pathogenic variant in a cancer gene
  - Most at-risk individuals don't know they are at risk

- ~40,000 Washington state residents are affected by either Hereditary Breast and Ovarian Cancer syndrome (King syndrome) or Lynch syndrome

[1] Tier 1 Genomics Applications and their Importance to Public Health https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm
[2] Yoshida, R., *Hereditary breast and ovarian cancer (HBOC): review of its molecular characteristics, screening, treatment, and prognosis*. Breast Cancer, 2021. 28(6): p. 1167-1180.
[3] Hampel, H. and A. de la Chapelle, *How do we approach the goal of identifying everybody with Lynch syndrome?* Familial cancer, 2013. 12(2): p. 313-317.

1 in 8 patients at a cancer center has a hereditary cancer syndrome

2984 patients with cancer	**Mean age 62**	84 gene panel
Mayo clinic 2018-2020	30% FHx	50% stage III/IV
397 positive (13%)	1415 VUSs (47%)	



Samadder NJ et al. JCO 2020

Universal genetic testing 1 in 8

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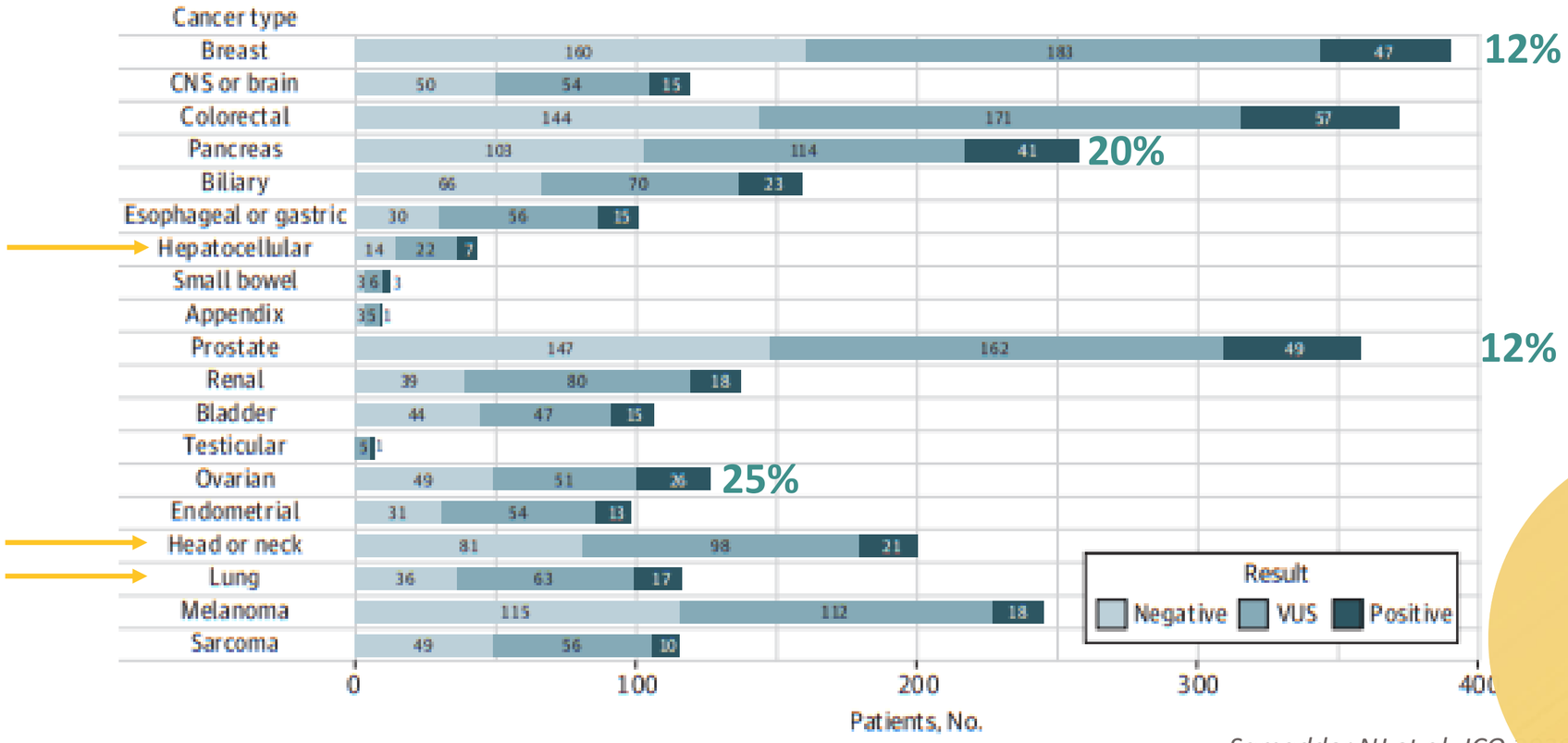
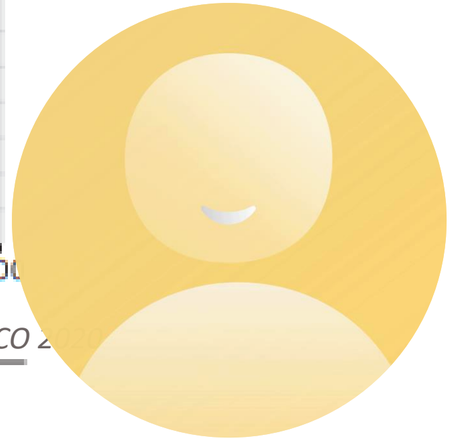


Samadder NJ et al. JCO 2

r of PGVs in the particular genes, with light to dark representing the fewest to the most.



Time Trends in Receipt of Germline Genetic Testing and Results for Women Diagnosed With Breast Cancer or Ovarian Cancer, 2012-2019

Allison W. Kurian, MD, MSc[1]; Kevin C. Ward, PhD, MPH[2]; Paul Abrahamse, MA[3]; Irina Bondarenko, MS[3]; Ann S. Hamilton, PhD[4]; Dennis Deapen, DrPH[4]; Monica Morrow, MD[5]; Jonathan S. Berek, MD, MMSc[6]; Timothy P. Hofer, MD, MSc[7]; and Steven J. Katz, MD, MPH[3]

PURPOSE Genetic testing is important for breast and ovarian cancer risk reduction and treatment, yet little is known about its evolving use.

METHODS SEER records of women of age ≥ 20 years diagnosed with breast or ovarian cancer from 2013 to 2017 in California or Georgia were linked to the results of clinical germline testing through 2019. We measured testing trends, rates of variants of uncertain significance (VUS), and pathogenic variants (PVs).

RESULTS One quarter (25.2%) of 187,535 patients with breast cancer and one third (34.3%) of 14,689 patients with ovarian cancer were tested; annually, testing increased by 2%, whereas the number of genes tested increased by 28%. The prevalence of test results by gene category for breast cancer cases in 2017 were *BRCA1/*

0.5%; and other genes, PVs 0.3%, and VUS 2.6%. For ovarian cancer cases in 2017, the prevalence of test results were *BRCA1/2*, PVs 11.0%, and VUS 0.9%; breast or ovarian genes, PVs 4.0%, and VUS 12.6%; other actionable genes, PVs 0.7%, and VUS 0.4%; and other genes, PVs 0.3%, and VUS 0.6%. VUS rates doubled over time (2013 diagnoses: 11.2%; 2017 diagnoses: 26.8%), particularly for racial or ethnic minorities (47.8% Asian and 46.0% Black, *v* 24.6% non-Hispanic White patients; $P < .001$).

CONCLUSION A testing gap persists for patients with ovarian cancer (34.3% tested *v* nearly all recommended), whereas adding more genes widened a racial or ethnic gap in VUS results. Most PVs were in 20 breast cancer–associated genes or ovarian cancer–associated genes; testing other genes yielded mostly VUS. Quality improvement should focus on testing indicated patients rather than adding more genes.

J Clin Oncol 00. © 2021 by American Society of Clinical Oncology

comments and controversies

Universal Germline and Tumor Genomic Testing Needed to Win the War Against Cancer: *Genomics Is the Diagnosis*

Vivek Subbiah, MD[1,2] and Razelle Kurzrock, MD[3,4]

Universal germline testing may not only transform the outlook for those with traditional hereditary cancer syndromes but also identify a wider range of associations and penetrance for germline variants. If we are serious about winning the war against cancer, we need to have every bit of intelligence about it, both to treat cancer and to detect it early. The potential impact of the host should be considered in every patient with cancer. Applying universal germline testing to patients with cancer routinely is one of the major opportunities that can revolutionize precision medicine practice and is needed to win the war against cancer (and possibly many other diseases).

whitehouse.gov/briefing-room/statements-releases/2022/02/02/fact-sheet-president-biden-reignites-cancer-moonshot-to-end-cancer-as-we-know-it/

THE WHITE HOUSE

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FEBRUARY 02, 2022

Fact Sheet: President Biden Reignites Cancer Moonshot to End Cancer as We Know It

Biden-Harris Administration Sets Goal of Reducing Cancer Death Rate by at least 50 Percent Over the Next 25 Years, and Improving the Experience of Living with and Surviving Cancer

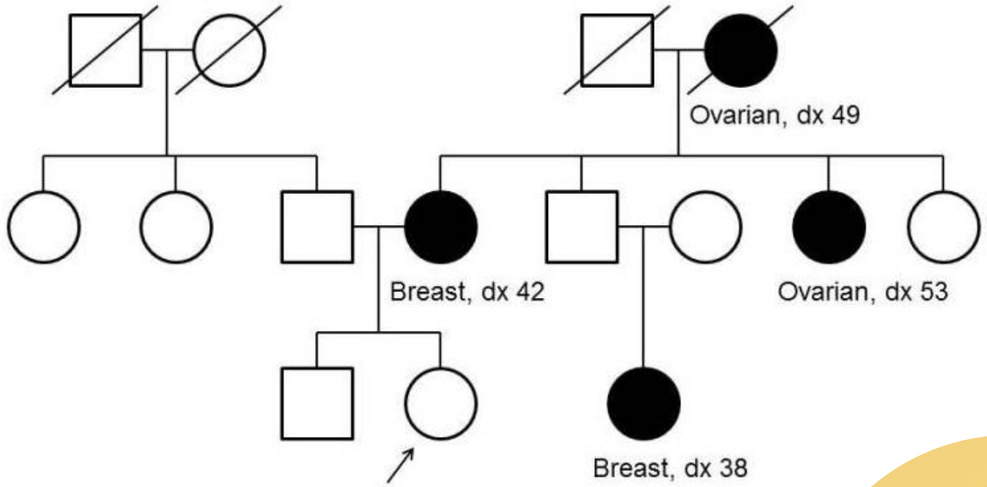
As Vice President, in 2016, Joe Biden launched the Cancer Moonshot with the mission to accelerate the rate of progress against cancer. The cancer and patient community and medical researchers responded with tremendous energy and ingenuity.

Today, President Biden is **reigniting the Cancer Moonshot with renewed White House leadership of this effort**. Because of recent progress in cancer therapeutics, diagnostics, and patient-driven care, as well as the scientific advances and public health lessons of the COVID-19 pandemic, it's now possible to set ambitious goals: to **reduce the death rate from cancer by at least 50 percent over the next 25 years,** and **improve the experience for people and their families living with and surviving cancer**— and, by doing this and more**, end cancer as we know it today.**

Breast and Ovarian (PP) cancer syndrome

- **Genetic predisposition to**
  - Breast
  - Ovarian
  - **Prostate**
  - **Pancreatic cancers**

- Abbreviated HBOC or King syndrome
- Genes
  - *BRCA1*
  - *BRCA2*
    - **Men**
      - **breast cancer**
      - **prostate cancer**



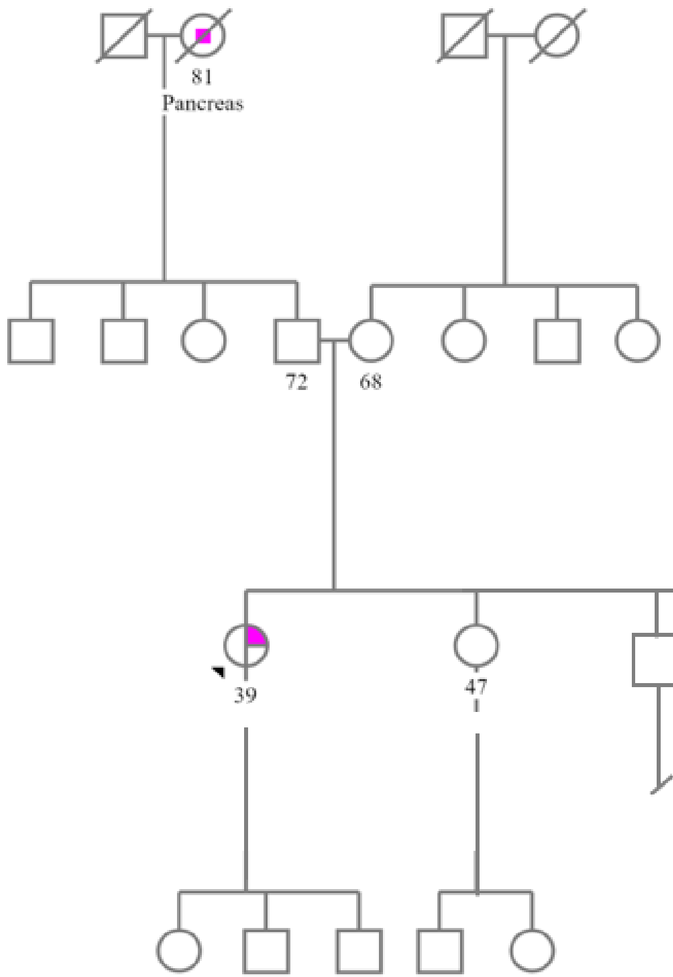
- Mutation in 1/500 and Founder mutation in up to 1/40 people

- High risk breast cancer screening with MRI
- Risk reducing surgeries
  - Double mastectomy
  - Risk Reducing **or Lifesaving** Salpingo-Oophorectomy

- Chemoprevention with Tamoxifen to ↓ ER+ breast cancers

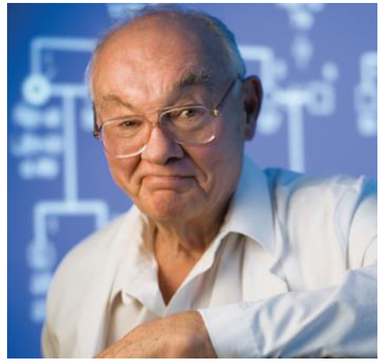
Breast and other cancers

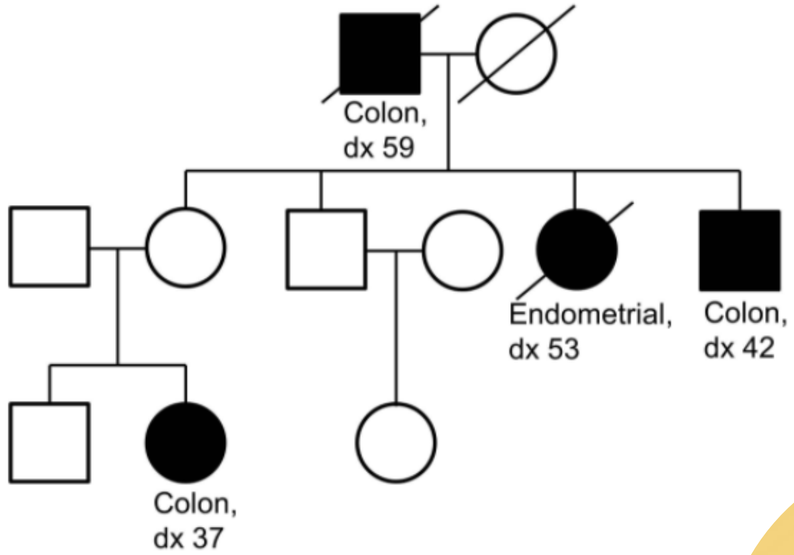
- More recently discovered genes
  - –*PALB2*
  - –*ATM* breast, pancreas and prostate
  - –*CHEK2* breast, colon, prostate,…
- More common than we think
- Panel test of genes > single gene



Colorectal and Endometrial cancer

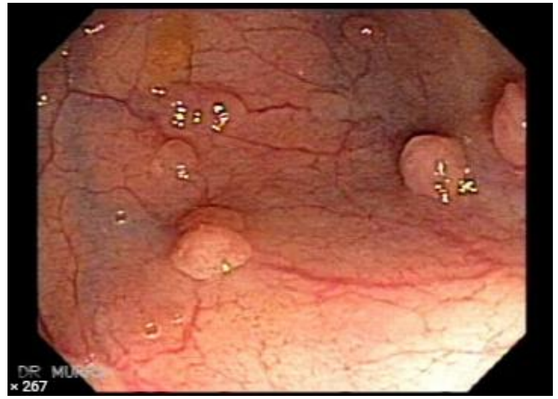
- Hereditary Non Polyposis Colorectal Cancer (HNPCC) or Lynch syndrome
- Genetic predisposition to
  - Colorectal
  - Uterus
  - **and many others**
- Present in ~1/280 people in the US
- Genes
  - *MLH1*
  - *MSH2* and *EPCAM*
  - *MSH6*
  - *PMS2*
- High risk screening
  - EGD and Colonoscopy
- AICR 10 recommendations for cancer prevention
- CAPP2 and CAPP3 studies



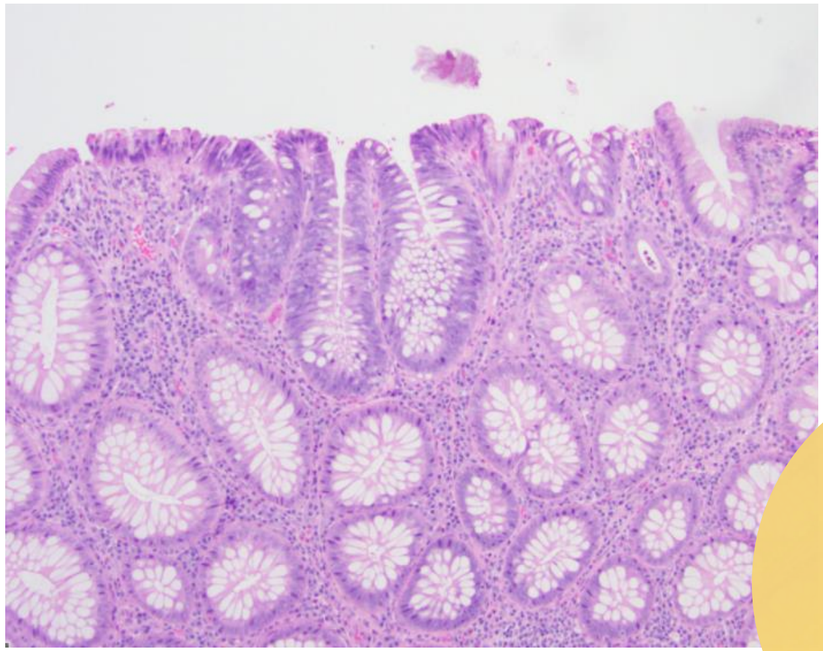


Colorectal Polyps or Polyposis

- Polyps all along the GI tract
  - –20 - 100 polyps
  - –50 - >1000 polyps
    - **Tubular adenomas or villous adenomas**
- *APC* gene



- Increased lifetime risk of CRC **up to 100%**
- Other manifestations
  - –Thyroid cancer
  - –Osteomas and skin lesions
  - –Retinal pigmentation
- Lifesaving colectomy
- Clinical trials for chemoprevention



Other polyposis conditions

- MYH-associated Polyposis (*MUTYH*)
  - Adenomas, can be throughout GI tract
  - Autosomal recessive

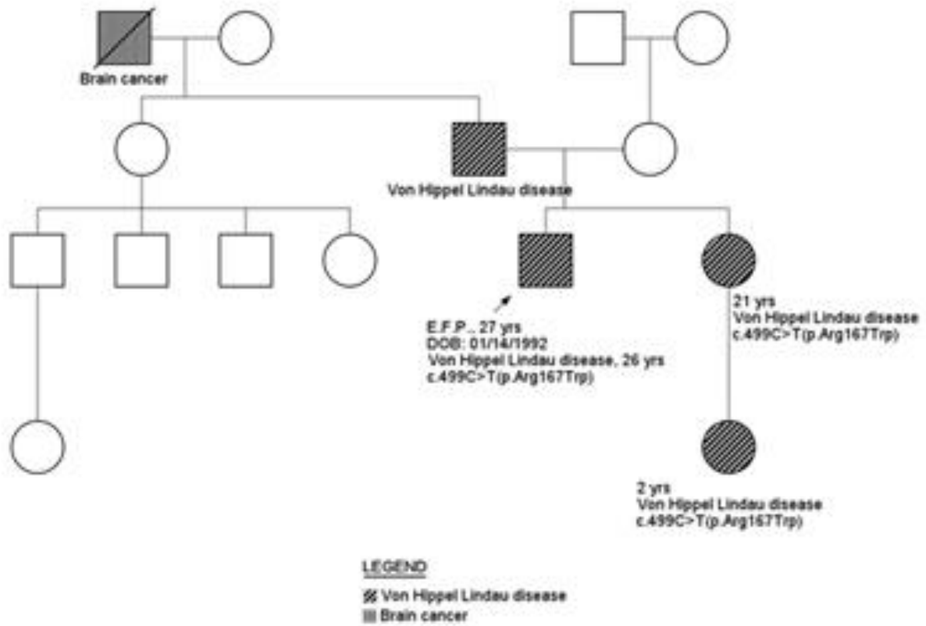
- Peutz-Jeghers syndrome (*STK11*)
  - oral freckling (childhood, fade with time)
  - hamartomatous polyps
  - increased cancer risk
    - breast cancer
    - GI cancers
    - pancreas x10 population risk

https://www.aocd.org/page/PeutzJeghersSyndro

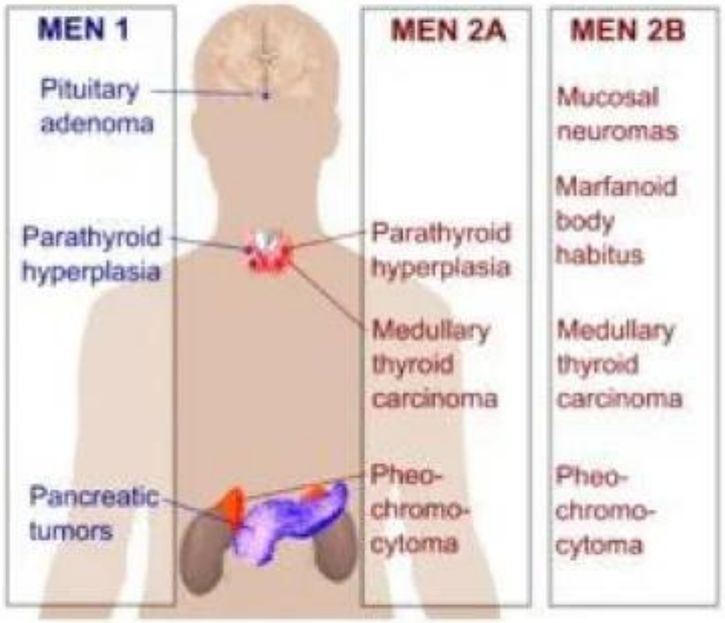
- Juvenile Polyposis (*BMPR1A* and *SMAD4*)
  - Juvenile type polyps, colon & stomach cancer
  - SMAD4 also causes hereditary hemorrhagic telangiectasia (HHT)
- Serrated Polyposis Syndrome (gene not yet found)
- Hereditary mixed polyposis (GREM1)

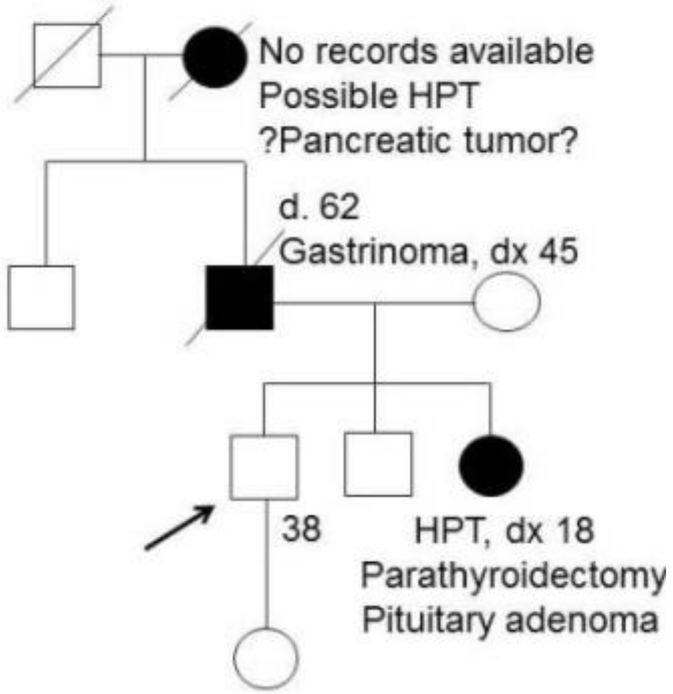
Renal cancer predispositions

- Increased risk for
  - Uni or bilateral kidney tumors
  - Benign cysts
    - Brain and along the spine
    - Lung cysts
  - Bleeding retina/brain
  - Other cancers
    - Thyroid, uterine, brain and skin
    - Neuroendocrine tumors
- Genes
  - *VHL, FLCN* for Birt Hogg Dube*, FH* for HLRCC
  - *TSC1* and *TSC2*
- Ongoing clinical trials for oral targeted therapies
  - **mTOR** example Everolimus
  - **HIF2a** inhibitors with Belzutifan



Multiple Neuroendocrine neoplasias





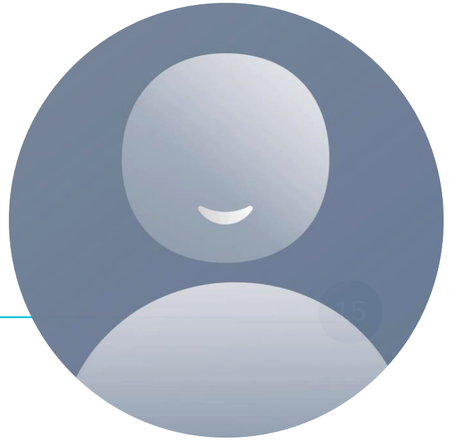
- Genes
  - –MEN1
  - –RET
- Screening and Risk reducing surgeries
- Clinical trials for RET inhibitors

Cancer Predispositions for primary care

How to screen for hereditary cancer syndromes (HCS)

Tips to offer testing or to refer to genetic counselors

Cases



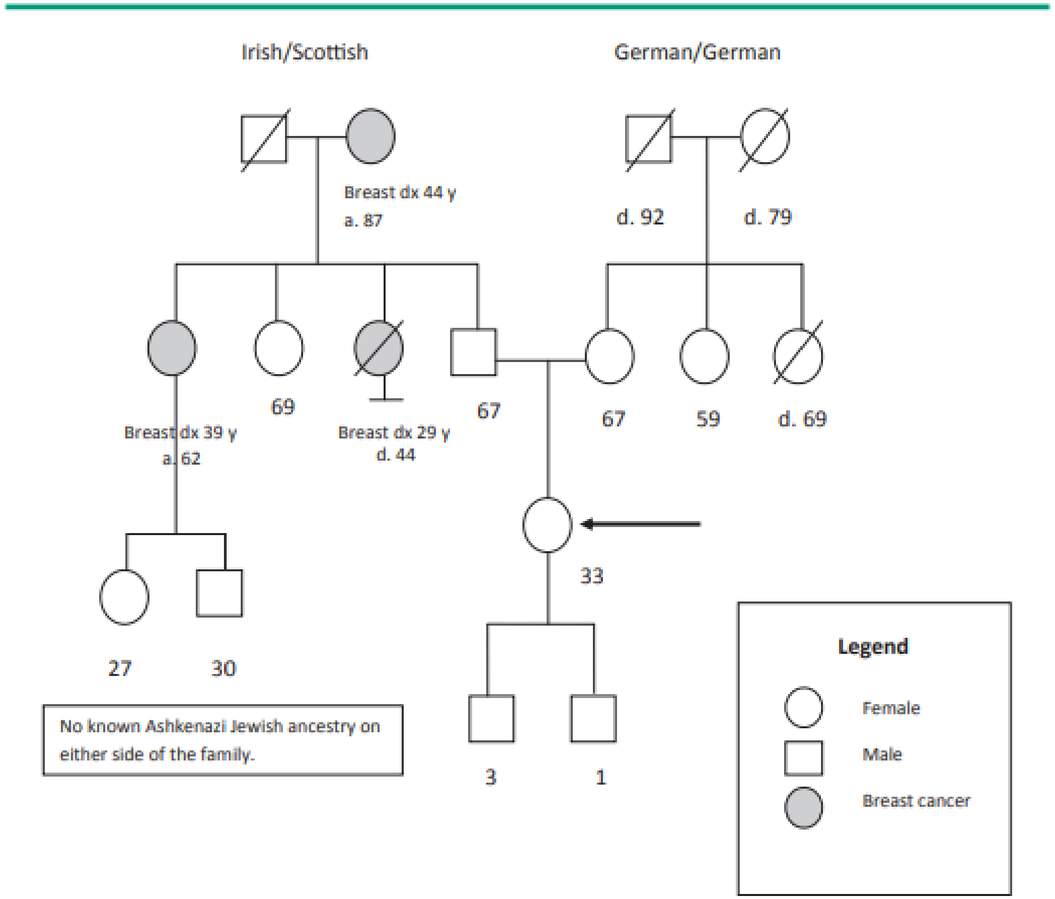
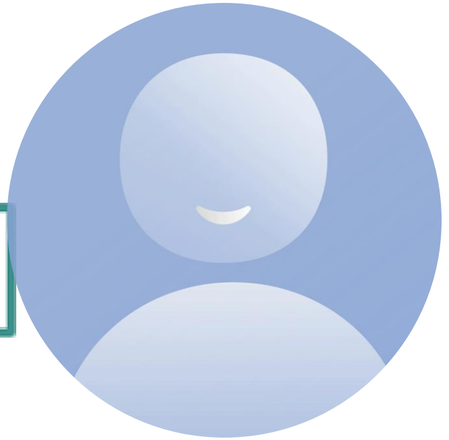


Figure 1. Example of a cancer history family tree. The arrow points to the patient seeking consultation or the proband. This family tree includes the proband's children (two sons), her parents (directly above her), aunts/uncle, grandparents, and children of those who have been diagnosed with breast cancer. It is also important to document ancestry for maternal and paternal sides of the family and whether there is known Ashkenazi Jewish ancestry. This allows the clinician to more easily visualize patterns and assists with the identification of familial risk.

PMID: 24689498

J Genet Couns. 2020;29:423–434



Questions we ask for every patient in the cancer genetic clinic 1

The reason for performing the test?
- Active cancer
- Personal history of cancer
- Family history of cancer

Any testing done in the past?
- Technology
- Team

The question to ask before sending the test?
- Who is the best person to test?
- What are you looking for?

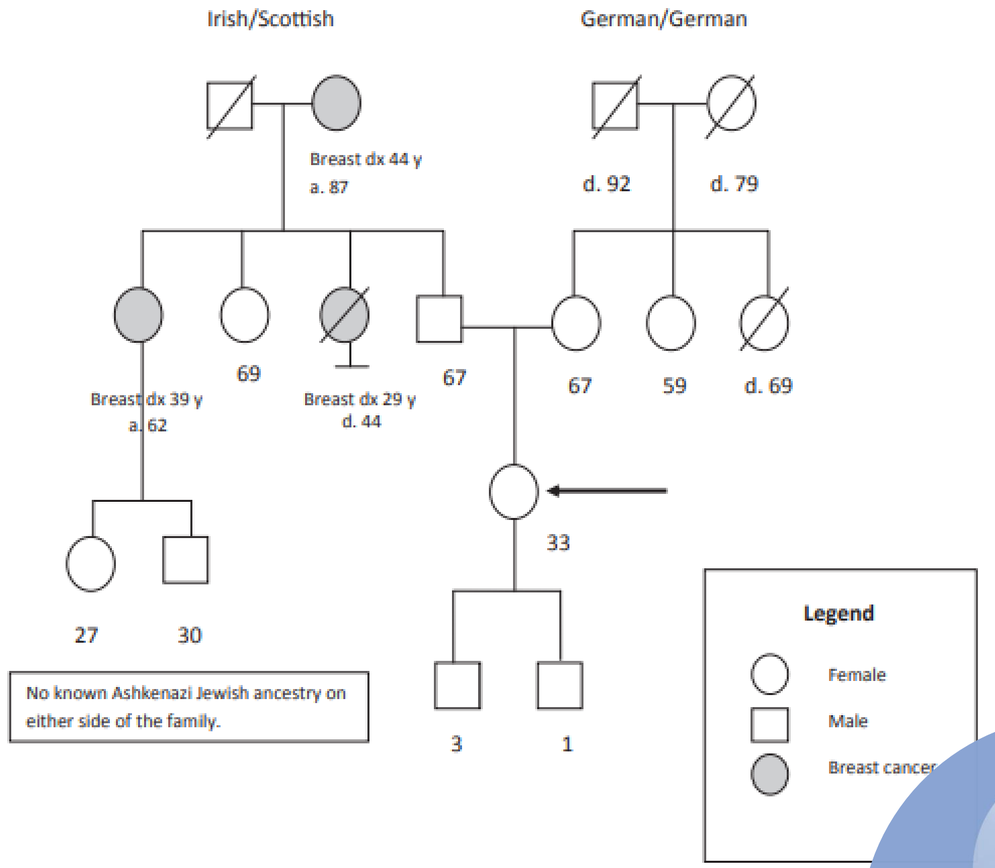
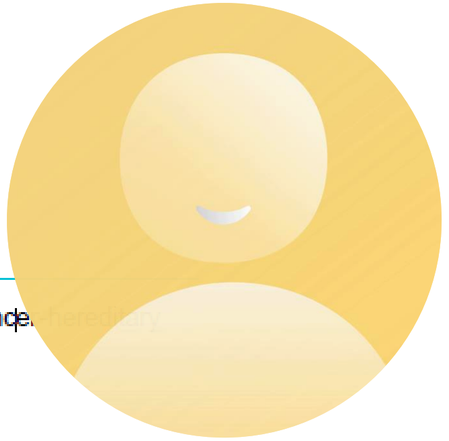


Figure 1. Example of a cancer history family tree. The arrow points to the patient seeking consultation or [illegible] family tree includes the proband's children (two sons), her parents (directly above her), aunts/uncle, grandpa[illegible] of those who have been diagnosed with breast cancer. It is also important to document ancestry for maternal [illegible] of the family and whether there is known Ashkenazi Jewish ancestry. This allows the clinician to more easily [illegible] and assists with the identification of familial risk.

PMID: 24689498

Features of Hereditary Cancer[4]

- Young age at diagnosis (< 50 years)
- Individuals with multiple cancer diagnoses
- Multiple family members with cancer
- Rare or related cancers
- Other clinical features suggestive of a particular hereditary cancer syndrome
- Suggestive tumor studies and/or known germline pathogenic variant in the family



[4] National Cancer Institute https://www.cancer.gov/about-cancer/causes-prevention/genetics#is-cancer-hereditary

Which patients need genetics?

- All patients with ovarian, fallopian & peritoneal cancers
- All patients with metastatic prostate
- All patients with pancreatic cancer

- Unusually early age of cancer onset
  - premenopausal breast cancer
- Clustering of the same type of cancer in close relatives.
- Cancers occurring in multiple generations of a family

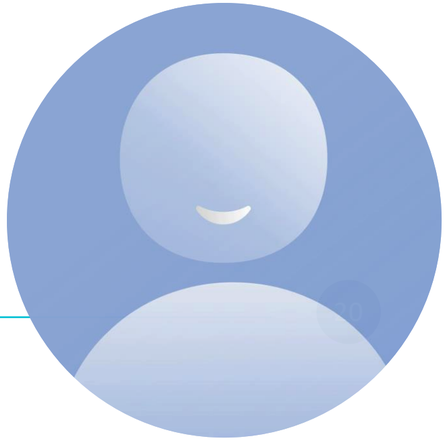
- Multiple primary cancers in a single individual
  - colorectal & endometrial cancer
- Bilateral cancer in paired organs or multifocal disease
  - bilateral breast cancer or multifocal renal cancer
- Occurrence of rare tumors
  - male breast cancer, adrenocortical carcinoma, Sertoli Leydig cell tumor of the ovary, ocular melanoma, or duodenal cancer

- **Concern for germline mutations following tumor testing results**
  - BRCA2 frameshift mutation in breast tumor

Cancer Predispositions for primary care

Tips to offer testing or to refer to genetic counselors

Cases



Clinical Genetics & Genetic Counseling Team

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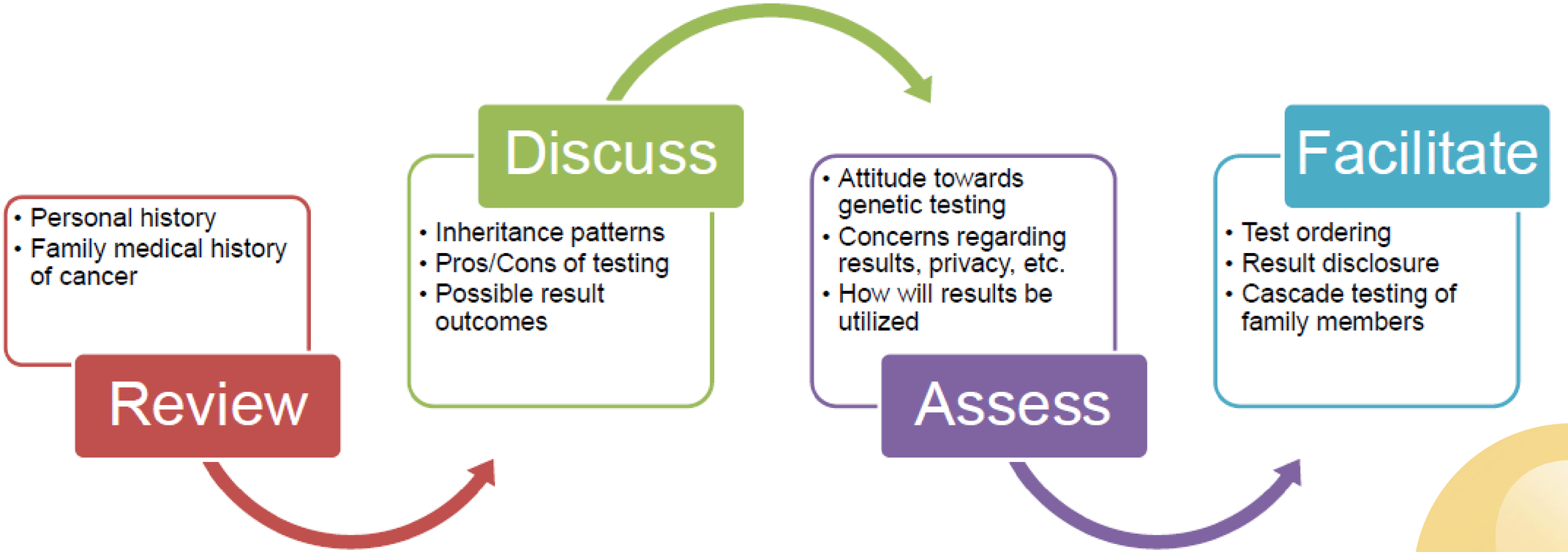
Genetic Counseling

"The process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease[8]"



[8] National Society of Genetic Counselors www.nsgc.org

Resources

Fred Hutch Clinical Genetics
Genetic Counseling Service

Phone: 206.606.6100
Fax: 206.606.6135

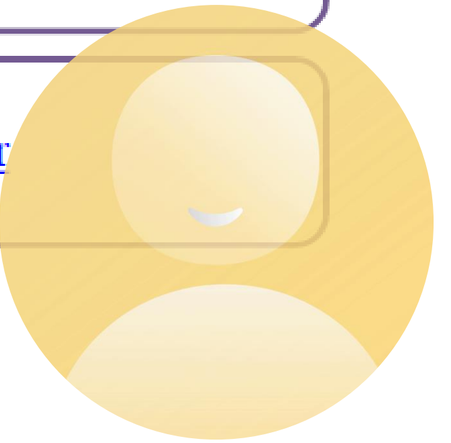
Gastrointestinal Cancer Prevention Program | Fred Hutchinson Cancer Center

Breast and Ovarian Cancer Prevention | Fred Hutchinson Cancer Center

Hematologic Malignancy Genetics | Fred Hutchinson Cancer Center

High Risk Cancer Surveillance | Fred Hutchinson Cancer Center

Prostate Cancer Genetics Clinic | Fred Hutchinson Cancer Center



If you decide to or feel comfortable ordering genetic testing

Feel free to reach out!

We can meet with you or answer questions

Tips to remember!

- **There are many options to choose from**

- **Certain laboratories are in-network, others are not**
- **Out-of-pocket costs vary widely**
  - Example of a pregnant patient in Bellevue in 2022 who was charged $30,000 for carrier screening

- **Certain insurances have a very strict policy for who meets criteria**
  - Certain groups require genetic counseling. If insurance group ends with an “A”, better to refer

- **Certain results are not consistent with a HCS – Variants of Uncertain Significance and CHIP**
- **Certain hereditary cancer syndromes (HCS) go beyond cancer**
  - Example of HHT (previously known at Osler Rendu disease) ENG versus SMAD4

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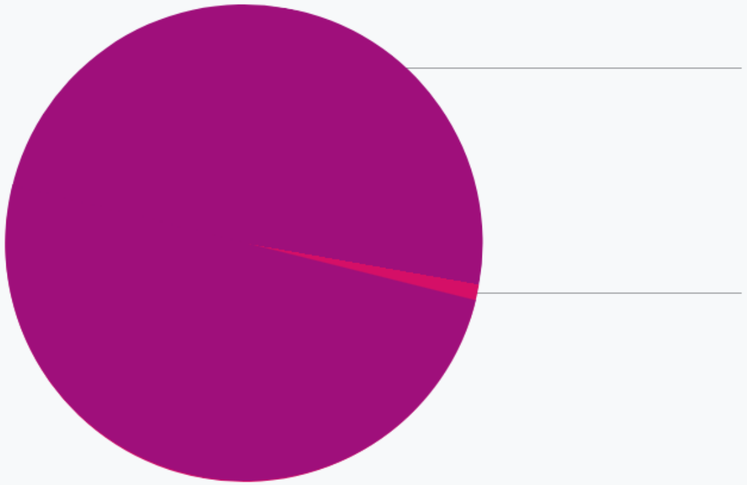
ABOUT THE REPORT

The BRCA1/BRCA2 (Selected Variants) Genetic Health Risk report is not a comprehensive cancer screening test.

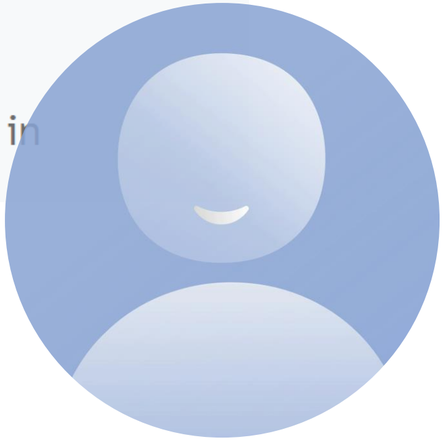


More than 1,000 variants in the BRCA1 and BRCA2 genes are known to increase cancer risk.

Our Genetic Health Risk report focuses on only three out of the more than 1,000 risk variants that are among the most studied and best understood. These three variants are most common in people of Ashkenazi Jewish descent and are much less common in people of other ethnicities.

ABOUT THE REPORT

It's a small percentage, but for some people it's a big deal. Specific BRCA genetic variants are more common in certain populations.



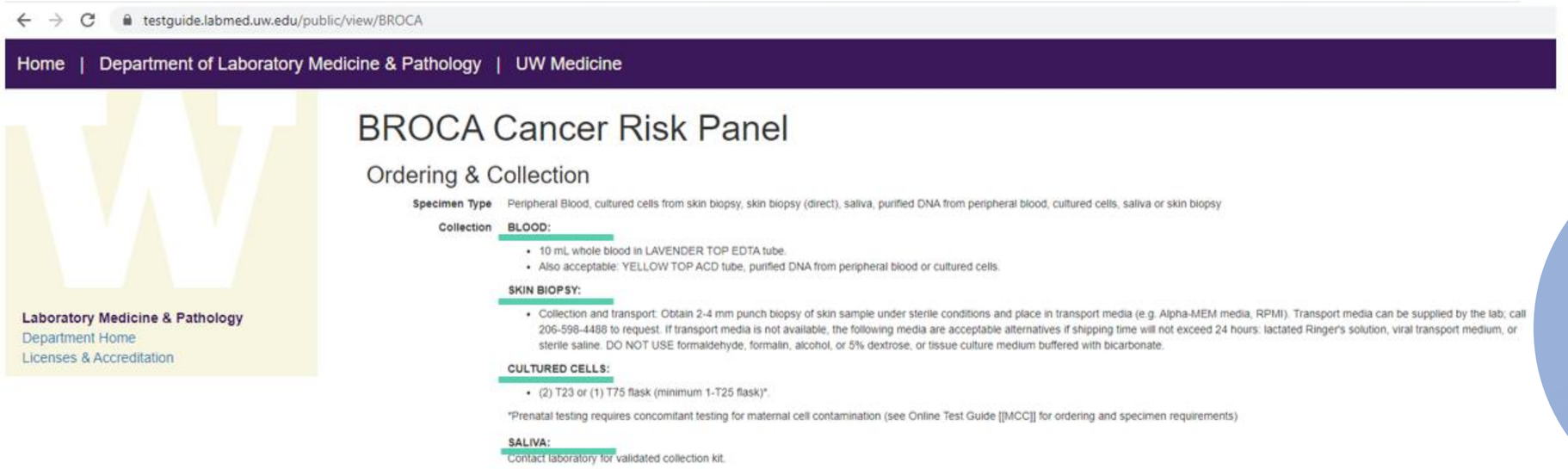
Questions we ask for every patient in the cancer genetic clinic 2

What is the best laboratory for the test?
- Academic
- Commercial
- Consumer

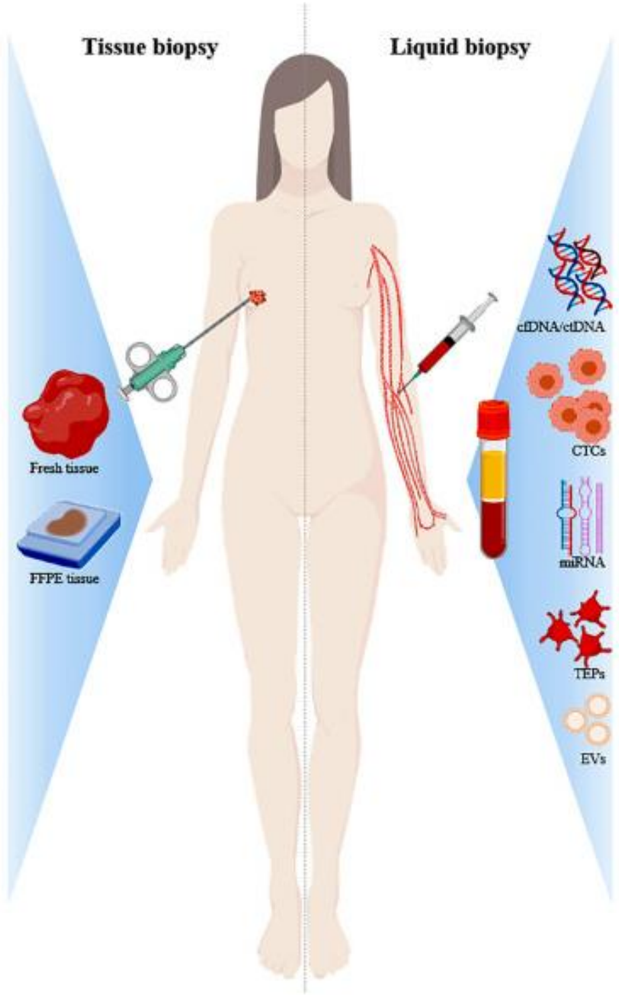
What platform was used?
- Somatic
- Germline

Which sample would provide the answers?
- Certain laboratories have vast array of validated assays

What are likely outcomes of the test?
- P/LP, VUS, LB/B



Different types of tumor profiling or somatic testing in cancer



Invasive •
Longer time procedure •
Higher cost for sample obtention •
Molecular information limited to constraint areas •
Not compatible with tumour monitoring during surveillance/treatment •

• Minimal Invasive
• Shorter time procedure
• Lower cost for sample obtention
• More complete tumour molecular information
• Compatible with tumour monitoring during surveillance/treatment

Fig. 1 Diagram summarizing the main components in blood liquid biopsies as well as the advantages over the conventional ones.

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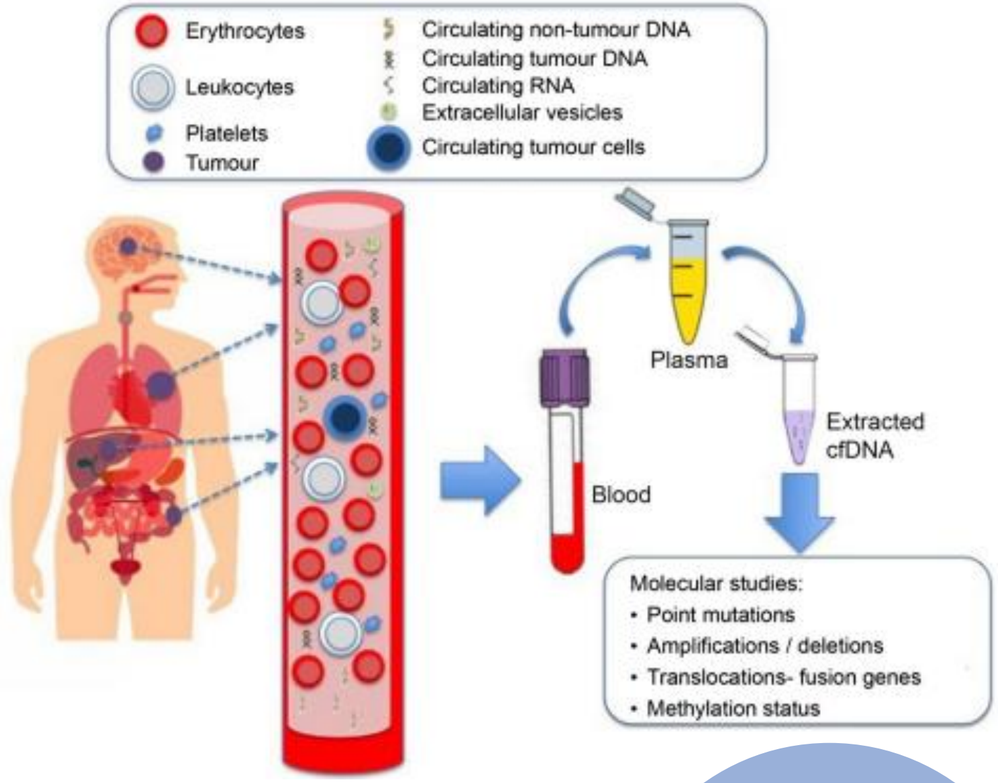

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Clonal Hematopoiesis of Indeterminate potential (CHIP) or Aberrant Clonal Evolution (ACE)

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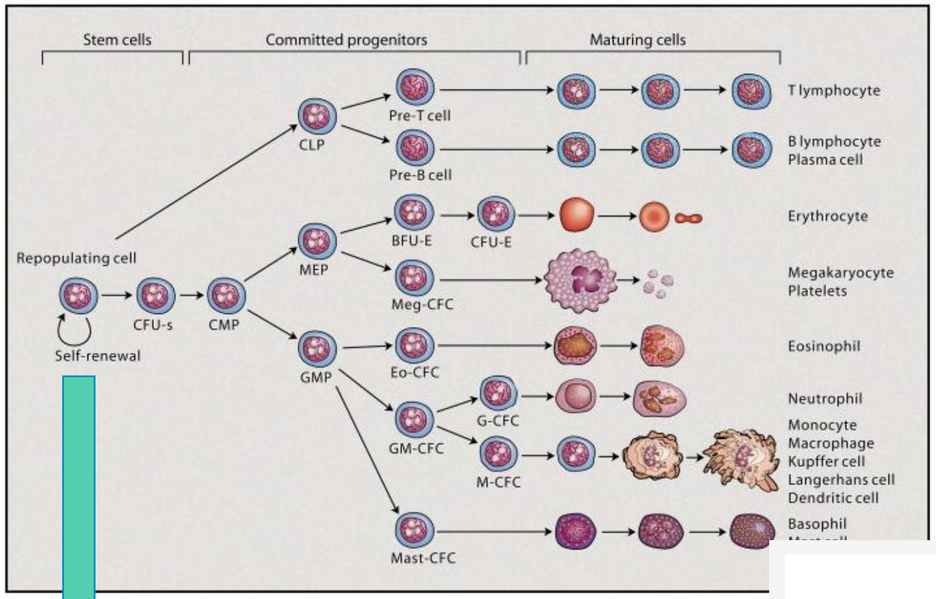
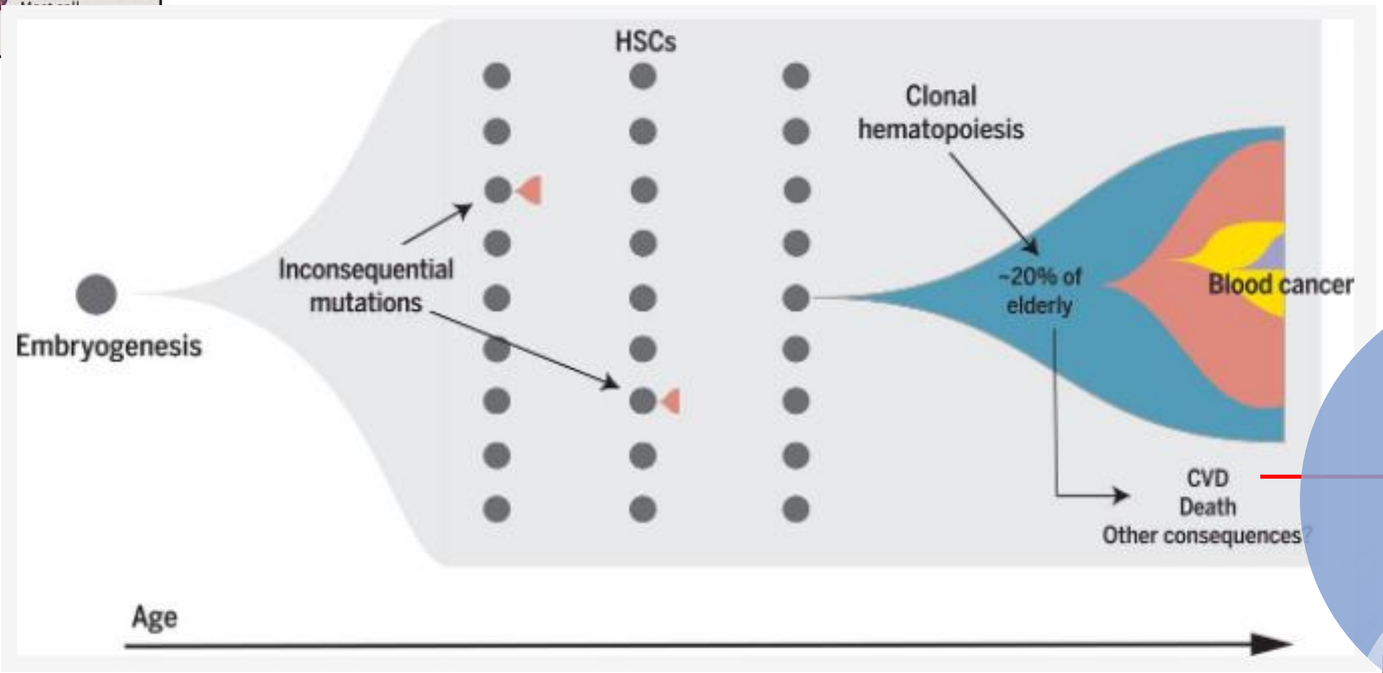


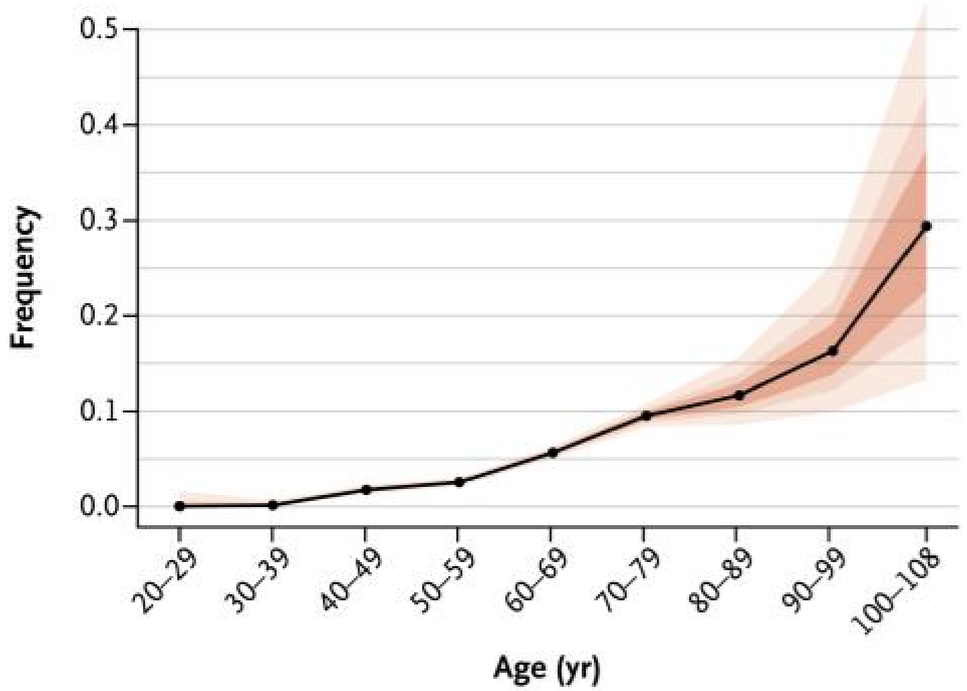
50,000 - 200,000 HSCs



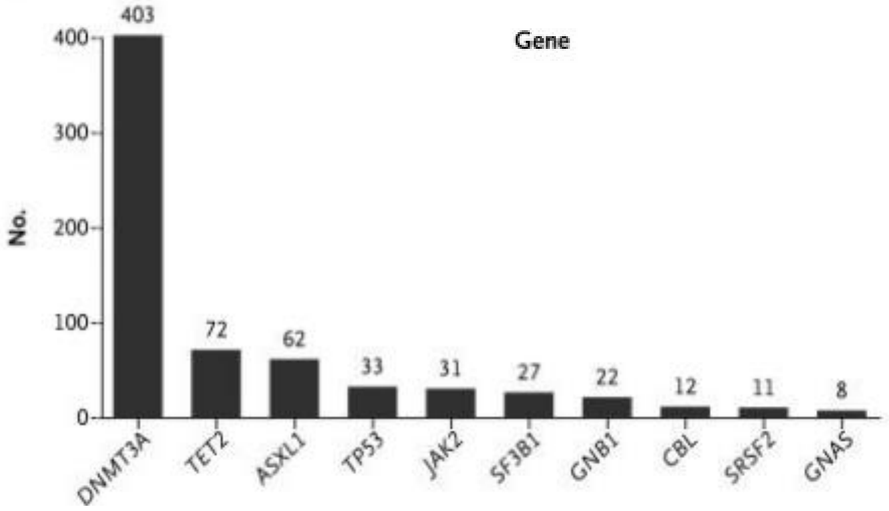
Risk is x2

PMID: 31672865

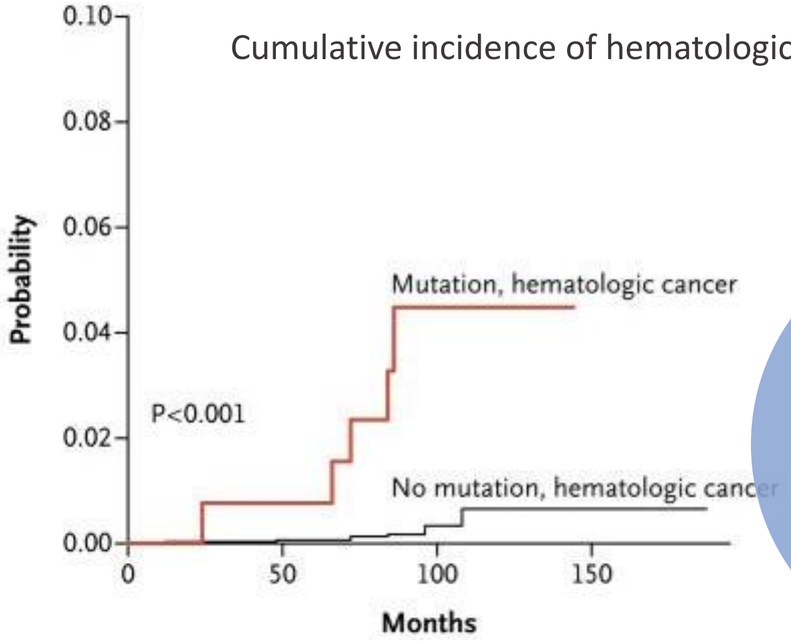
CHIP or ACE

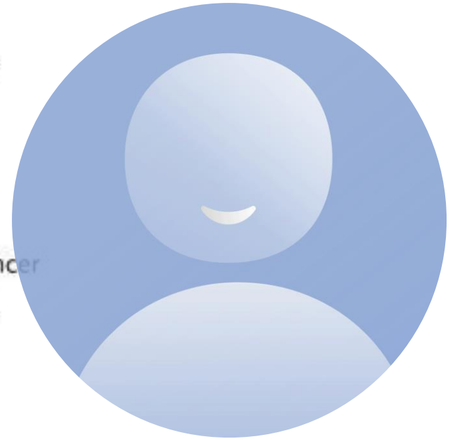


No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17



Cumulative incidence of hematologic cancer





PMID: 25426837

Estimating lifetime risk of breast cancer

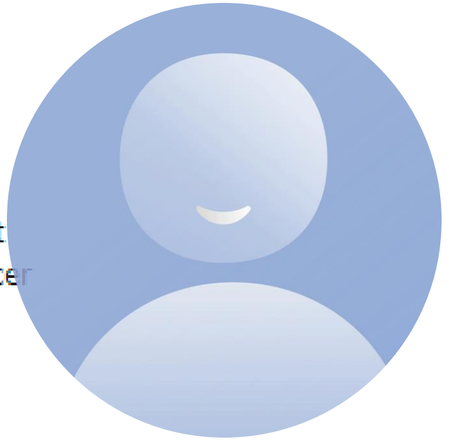
- Family History B&O cancers

- Personal risk factors
  - BMI, alcohol intake, ..
  - Fibro Glandular Density,
  - ObGyn history

- Risk calculators
  - Tyrer Cuzick 8.0
  - BRCAPro
  - BOADICEA V5 -> CanRisk tool

20%

BWA v4 *Beta* is not for commercial use. We are now licensing BOADICEA V5 for commercial use. BOADICEA V5 is the first comprehensive breast cancer risk prediction model using information on rare genetic variants in high- and moderate-risk cancer susceptibility genes, Polygenic Risk Scores, family history and other lifestyle or hormonal risk factors for breast cancer.



At a health maintenance appointment, it is easier to be confused

American Cancer Society and the US Preventative Services task force (USPSTF) agree that screening for breast cancer saves lives but don't agree on who, when and how to screen for breast cancer.

Frequently Asked Questions

What is the Task Force recommending? –

In this draft recommendat
women get screened for b
their risk of dying from thi

We are also urgently callin
existing recommendation
Specifically, we need to kn
screening and treatment e
Islander, Native American,

We also need studies shov
MRI might help women w
harms of screening in older women. These are **I statements**.

Why did your recommendation change for women in their 40s? –

New and more inclusive science about breast cancer in people younger than 50 has enabled us to expand our prior recommendation and encourage all women to get screened in their 40s. We have long known that screening for breast cancer saves lives, and the science now supports all women getting screened, every other year, starting at age 40.

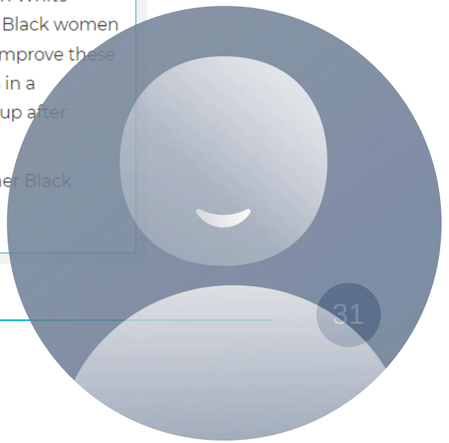
Is there specific guidance for women with dense breasts? –

Nearly half of all women have dense breasts, which increases their risk for breast cancer and means that mammograms do not work as well for them. Women are generally told by their clinician that they have dense breasts after they've had a mammogram. These women deserve to know whether and how additional screening might help them stay healthy. Unfortunately, there is not yet enough evidence for the Task Force to recommend for or against additional screening with breast ultrasound or MRI. We are urgently calling for more research on whether and how additional screening might help women with dense breasts find cancers earlier.

Is there specific guidance on breast cancer screening for Black women? –

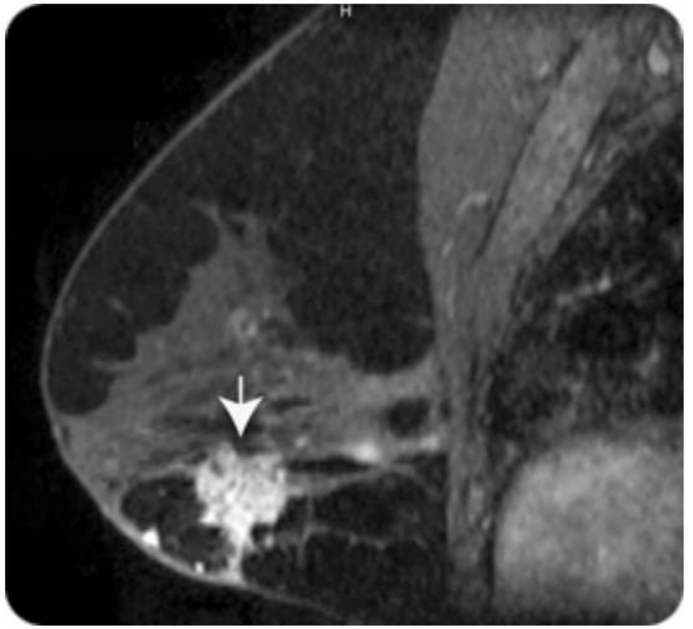
Black women are 40 percent more likely to die from breast cancer than White women and too often get aggressive cancers at young ages. Ensuring Black women start screening at 40 is an important first step, yet it is not enough to improve these inequities. It's important that healthcare professionals involve patients in a conversation on how best to support them to ensure equitable follow-up after screening and timely and effective treatment of breast cancer.

We are urgently calling for more evidence to better understand whether Black women could potentially be helped by different screening strategies.

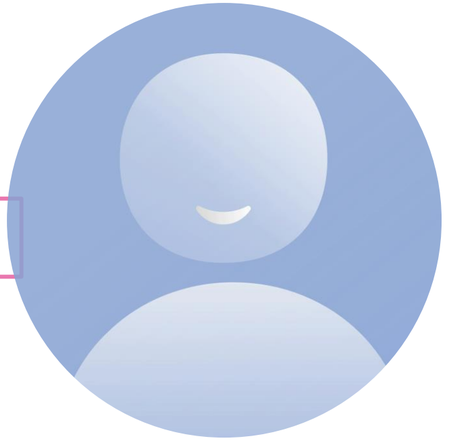


High risk breast cancer screening guidelines

- Starting at age 18: breast self awareness
- Ages 25-29:
  - Clinical Breast Exam Q6months
  - Annual Bilateral Breast MRI w/ contrast
- Age 30:
  - Clinical Breast Exam Q6months
  - Bilateral screening mammogram
  - Annual Bilateral Breast MRI w/ contrast (One test Q6 months)

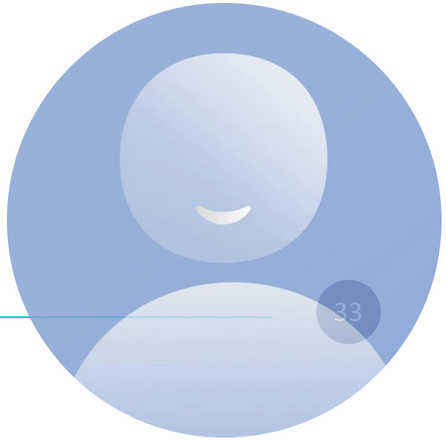


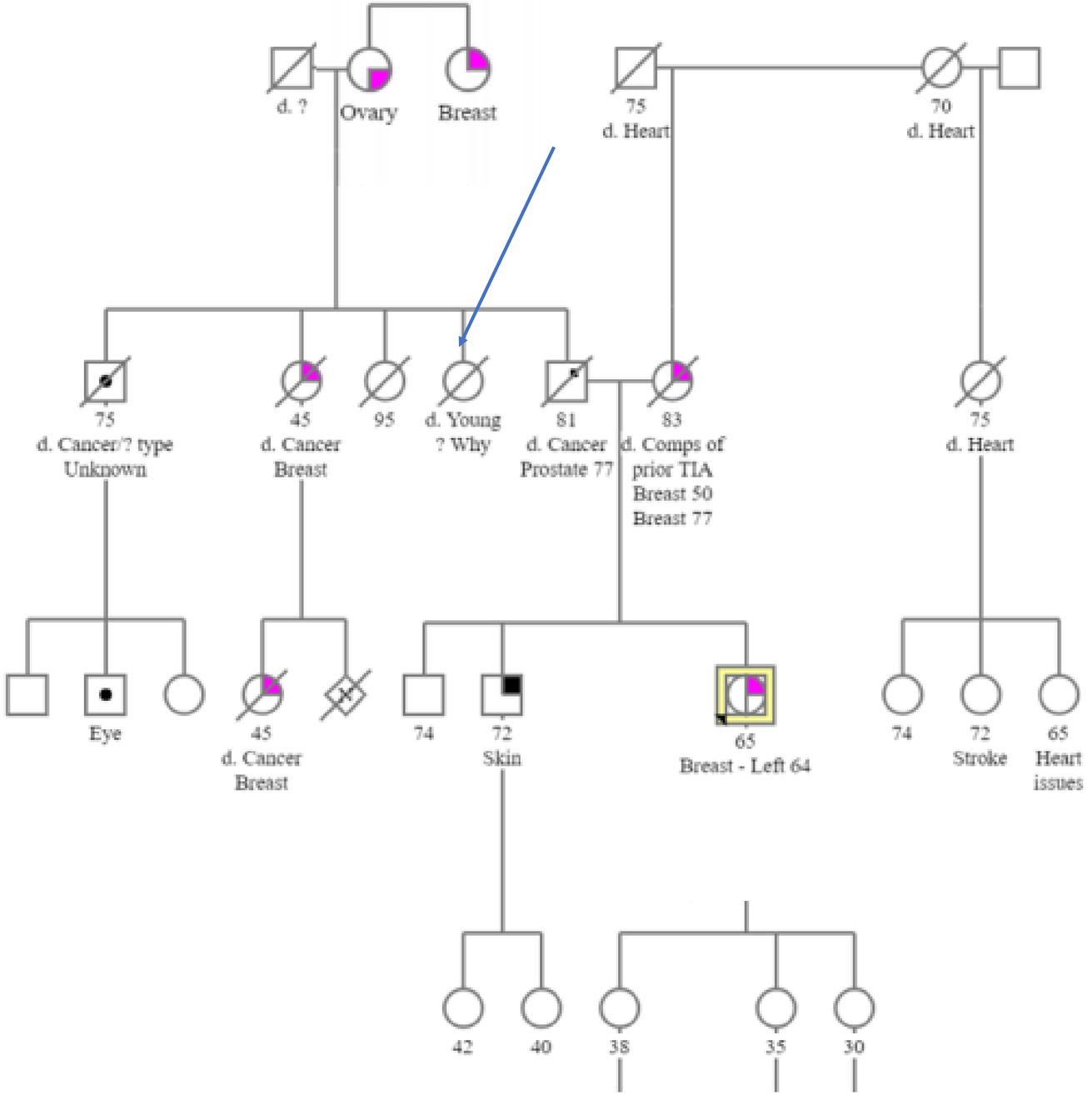
Discuss option of risk-reducing mastectomy (RRM) w/ or w/o reconstruction

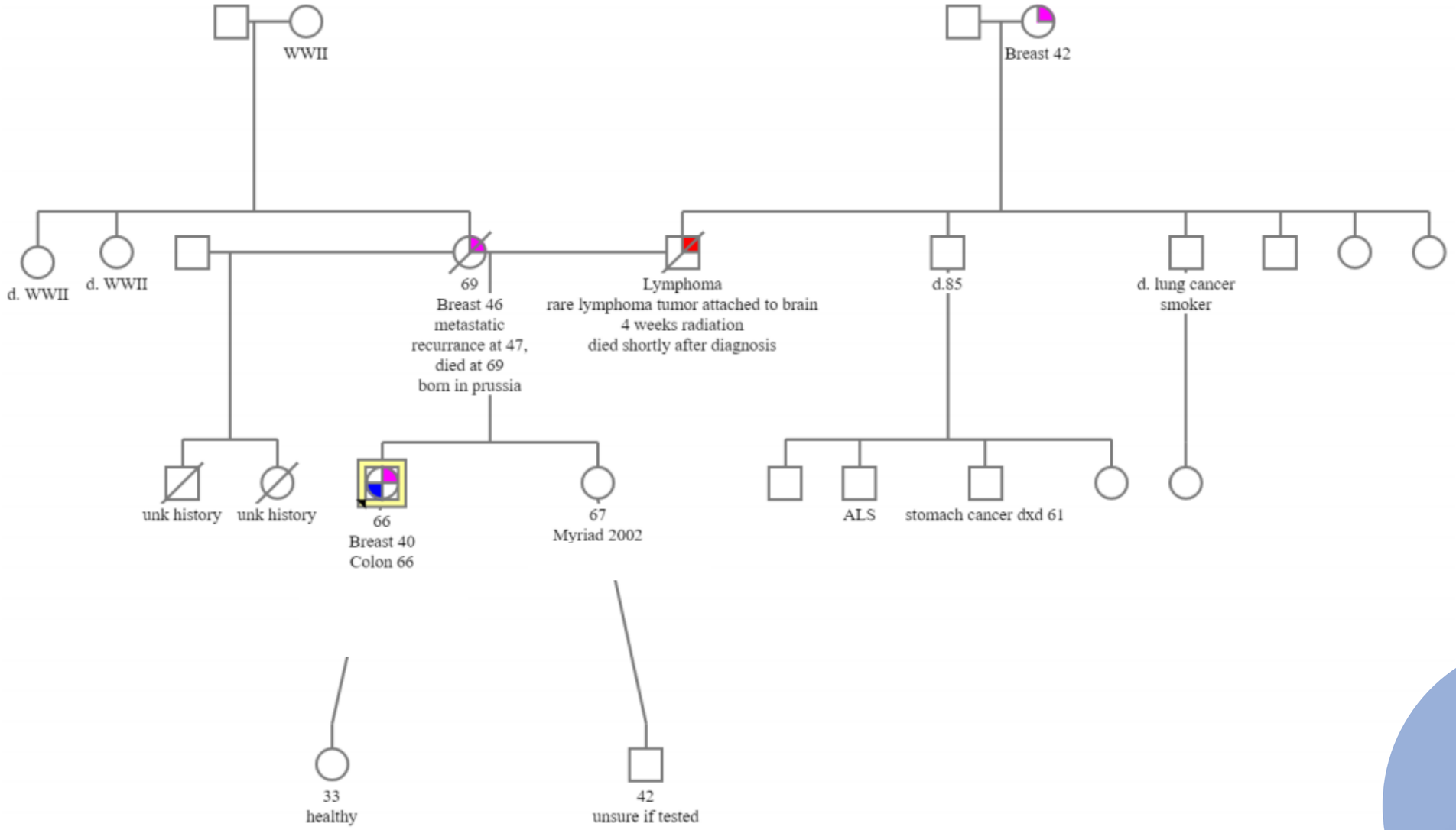


Cancer Predispositions for primary care

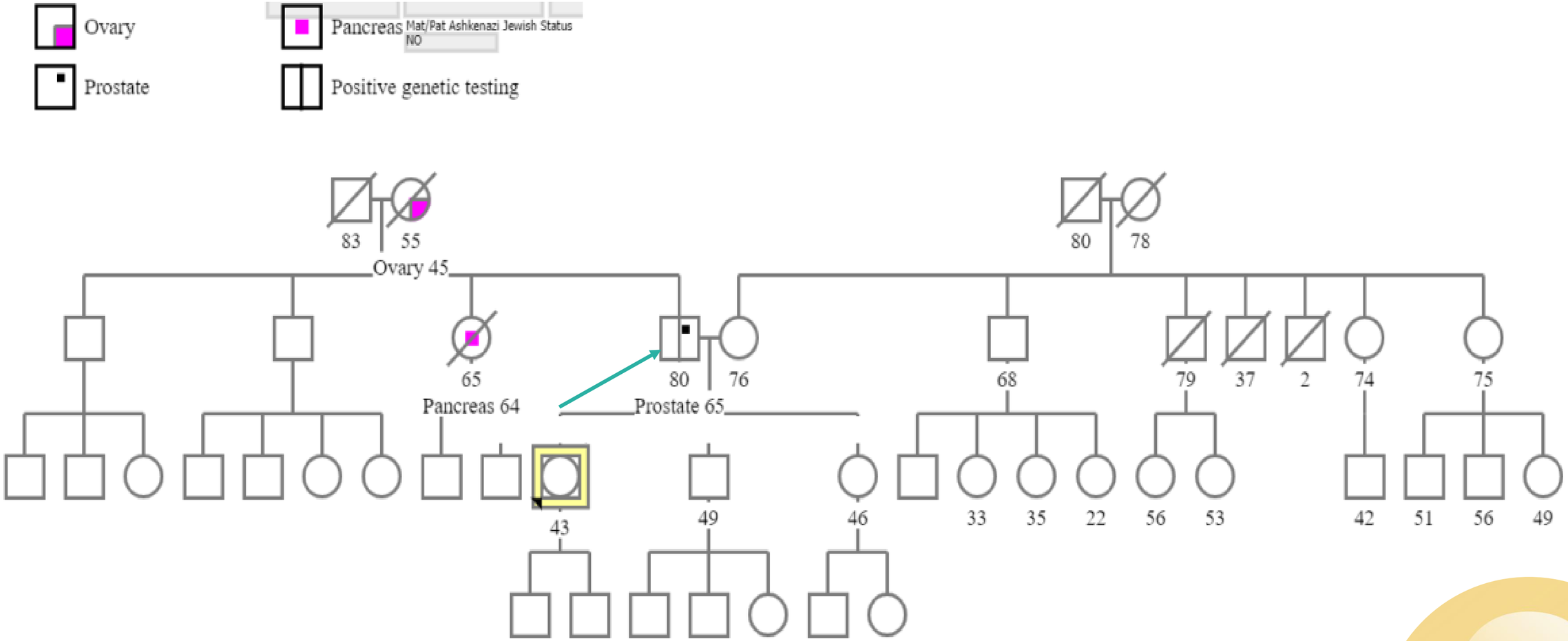
Cases




d. ?
Ovary
Breast
75
d. Heart
70
d. Heart
75
d. Cancer/? type
Unknown
45
d. Cancer
Breast
95
d. Young
? Why
81
d. Cancer
Prostate 77
83
d. Comps of
prior TIA
Breast 50
Breast 77
75
d. Heart
Eye
45
d. Cancer
Breast
74
72
Skin
65
Breast - Left 64
74
72
Stroke
65
Heart
issues
42
40
38
35
30

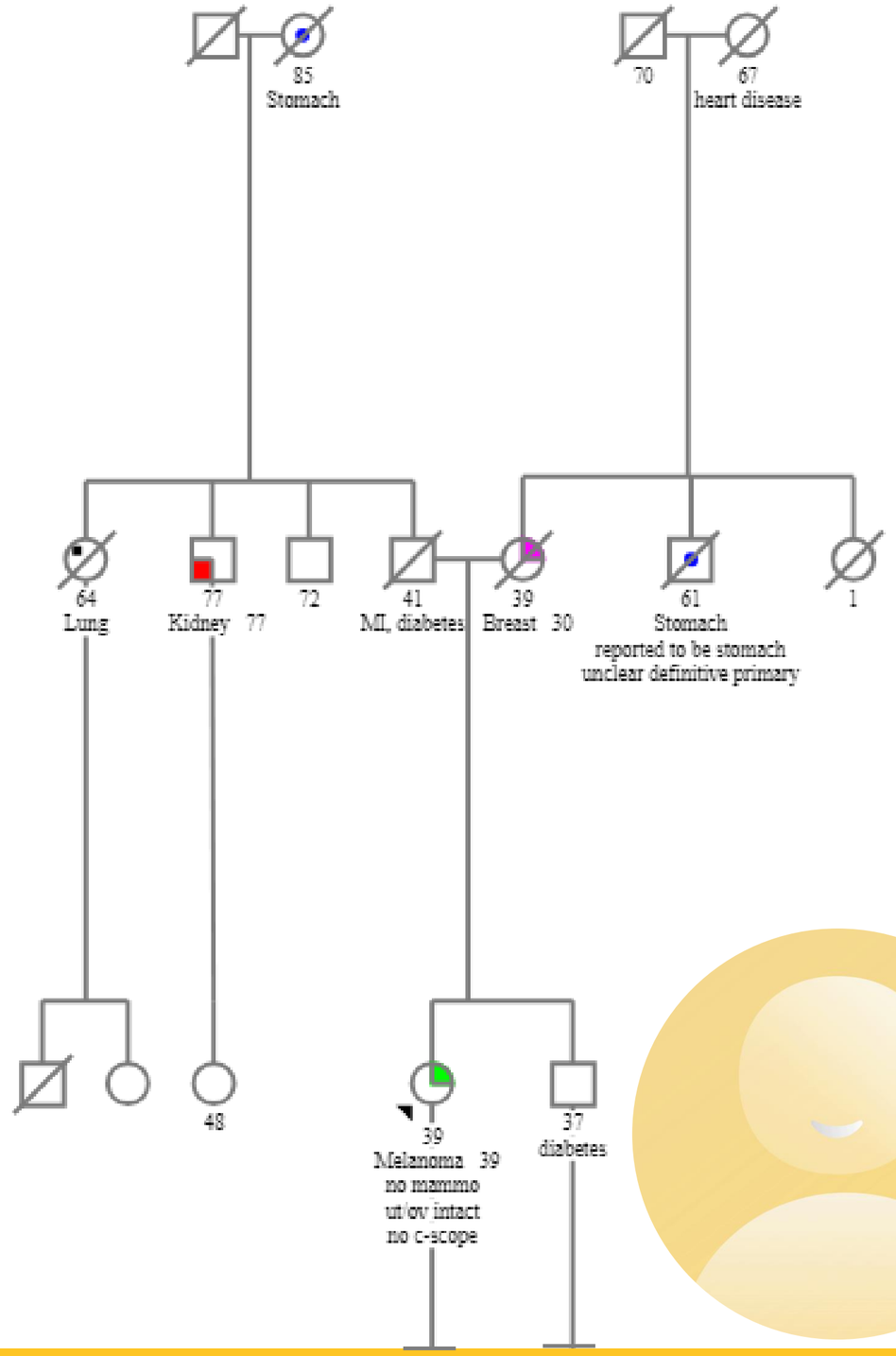

WWII
Breast 42
d. WWII
d. WWII
69
Breast 46
metastatic
recurrance at 47,
died at 69
born in prussia
Lymphoma
rare lymphoma tumor attached to brain
4 weeks radiation
died shortly after diagnosis
d.85
d. lung cancer
smoker
unk history
unk history
66
Breast 40
Colon 66
67
Myriad 2002
ALS
stomach cancer dxd 61
33
healthy
42
unsure if tested

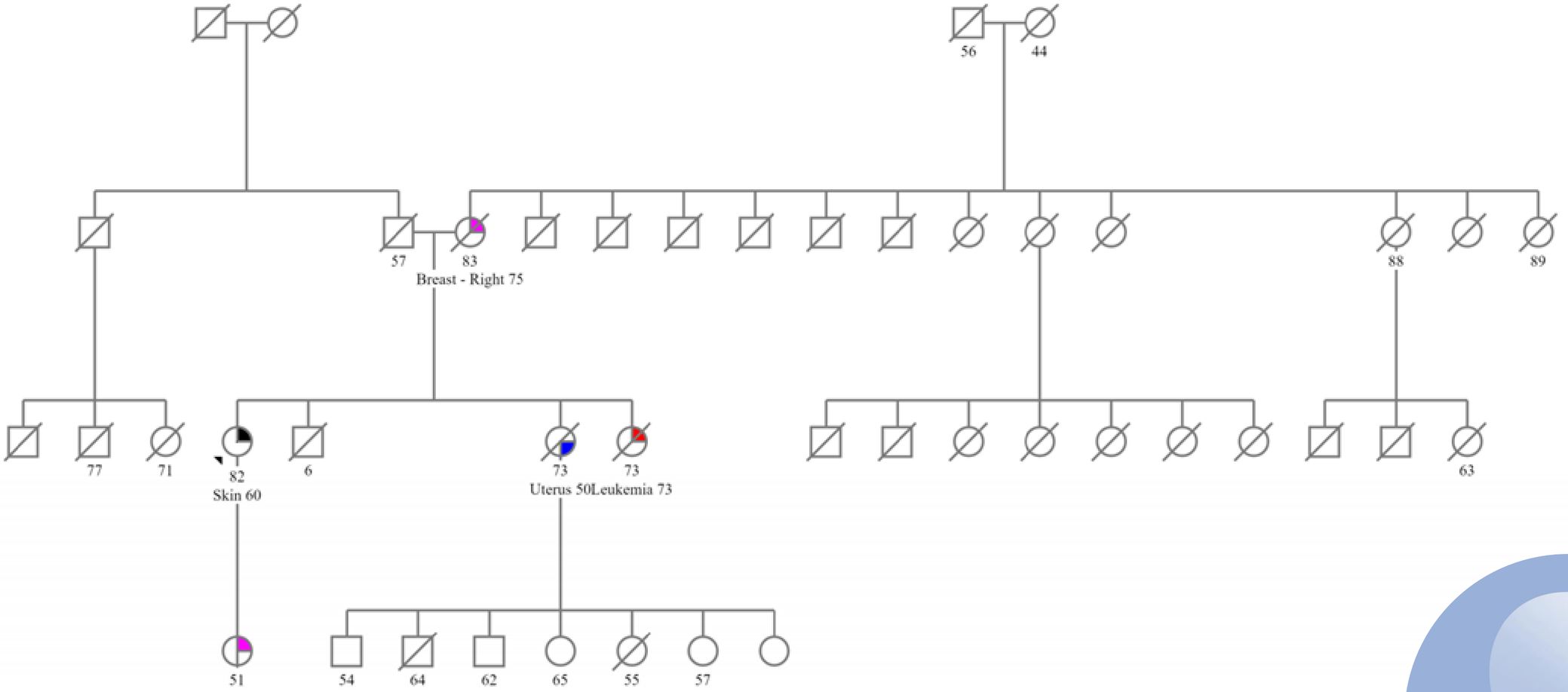
Importance of 3 generation family history

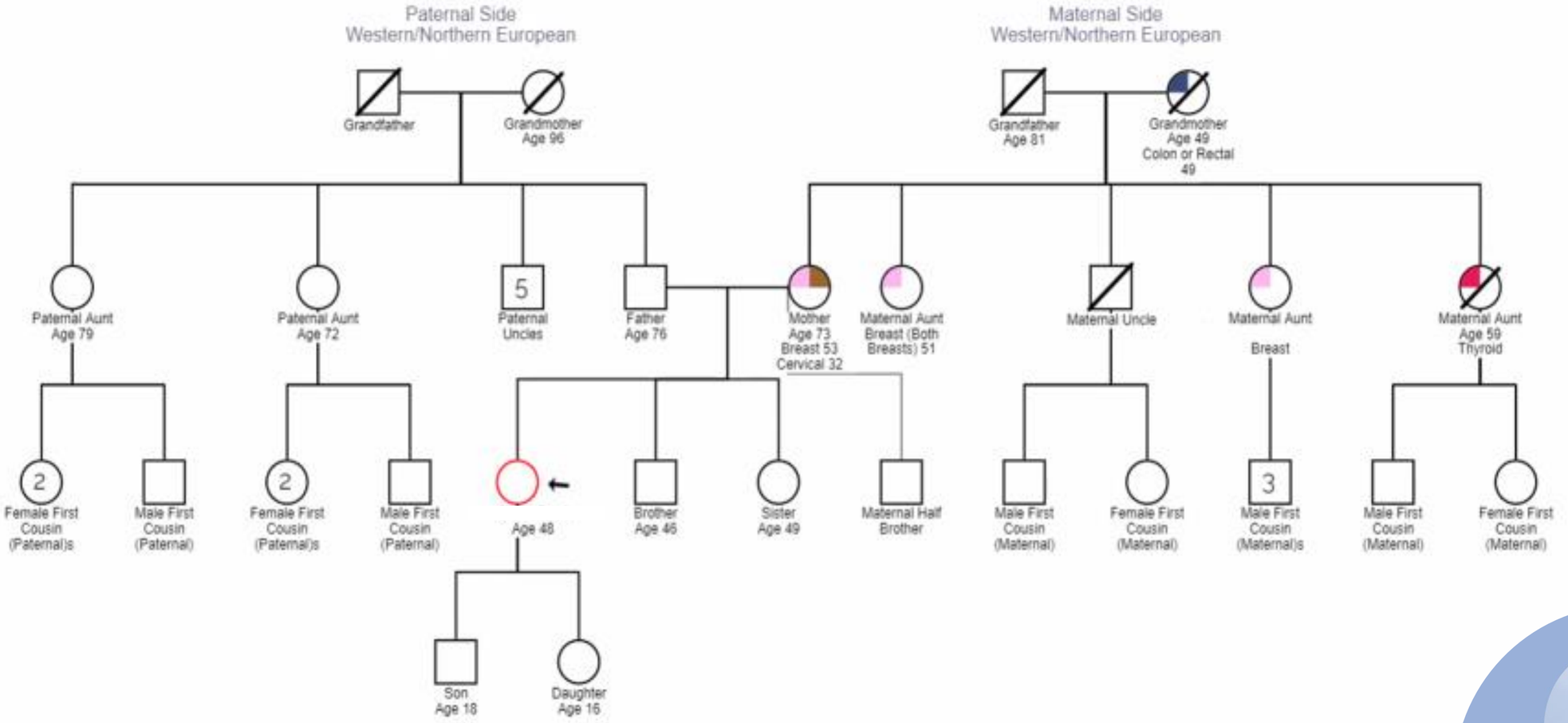


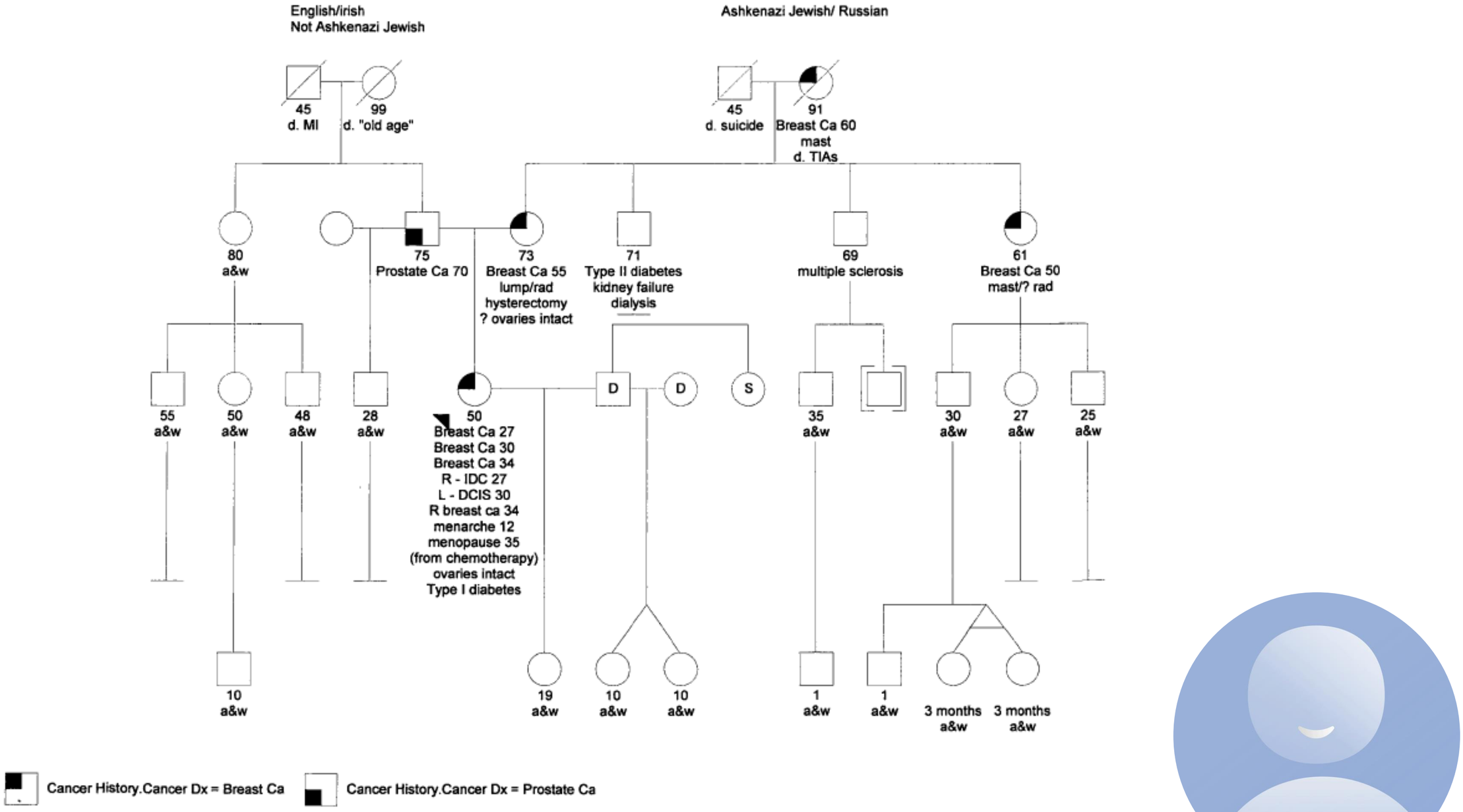
Case #2

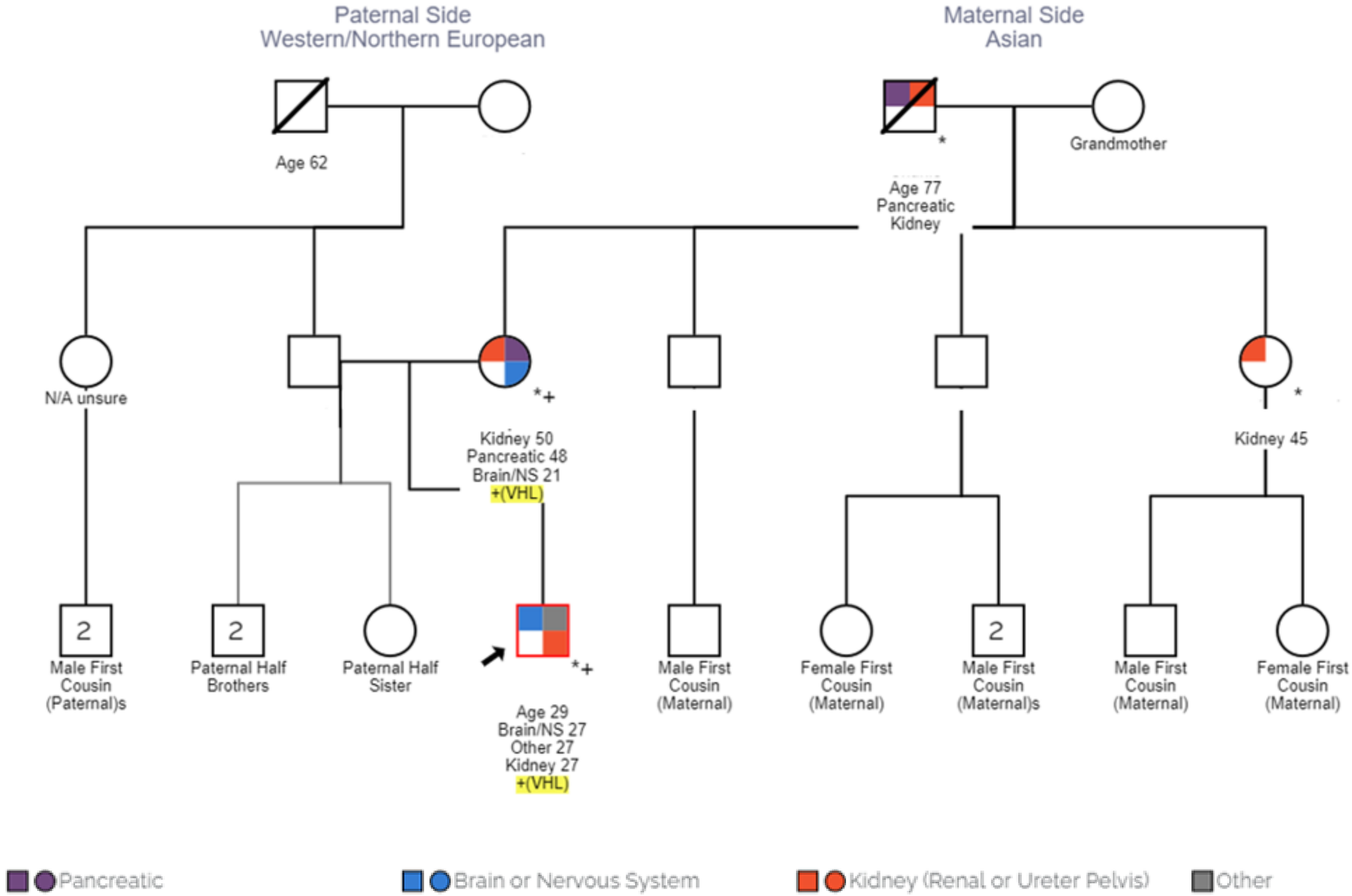
- 39 year old woman recently diagnosed with melanoma presents for genetic counseling
- Family history includes breast, kidney, and gastric cancer
- Patient decides to proceed with comprehensive genetic testing
  - 46 genes
- Results show:
  - Pathogenic variant in ATM
  - 2 variants of uncertain significance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

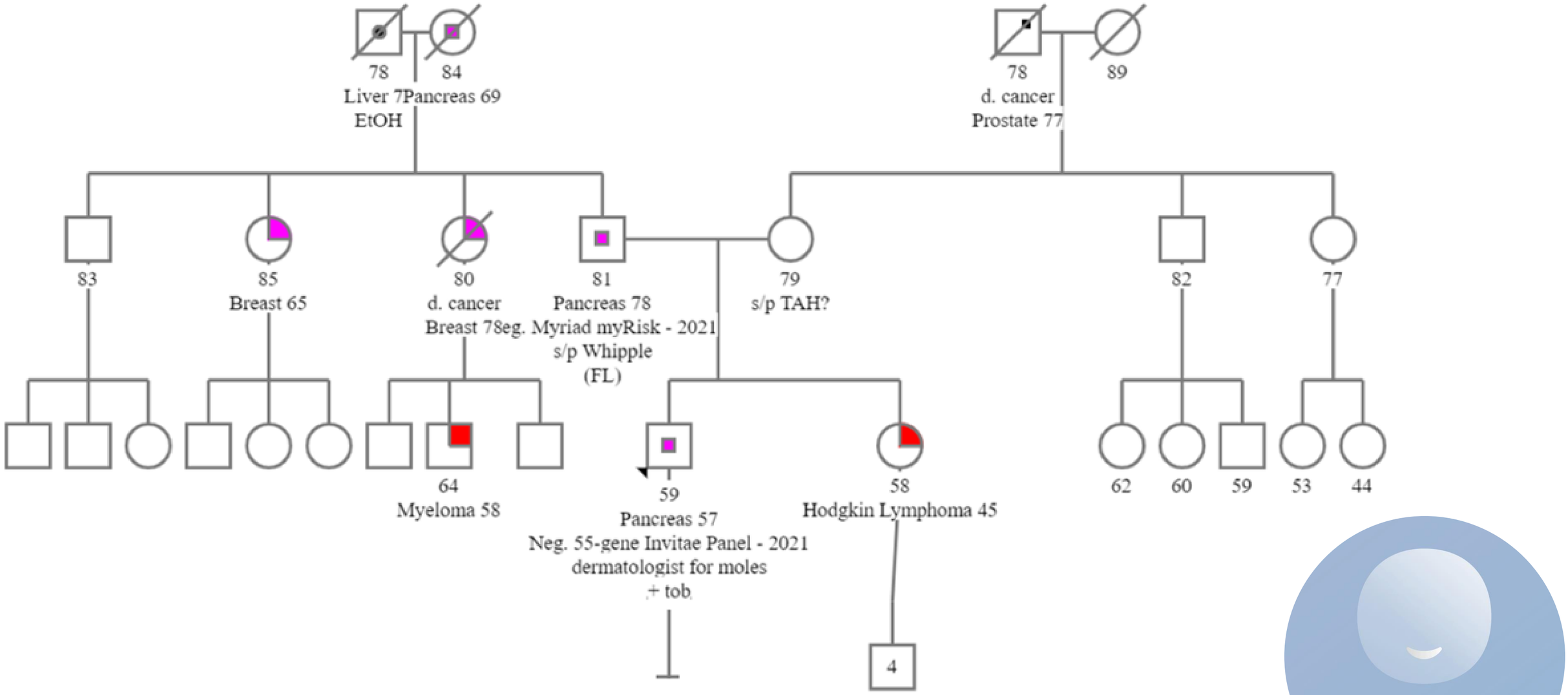


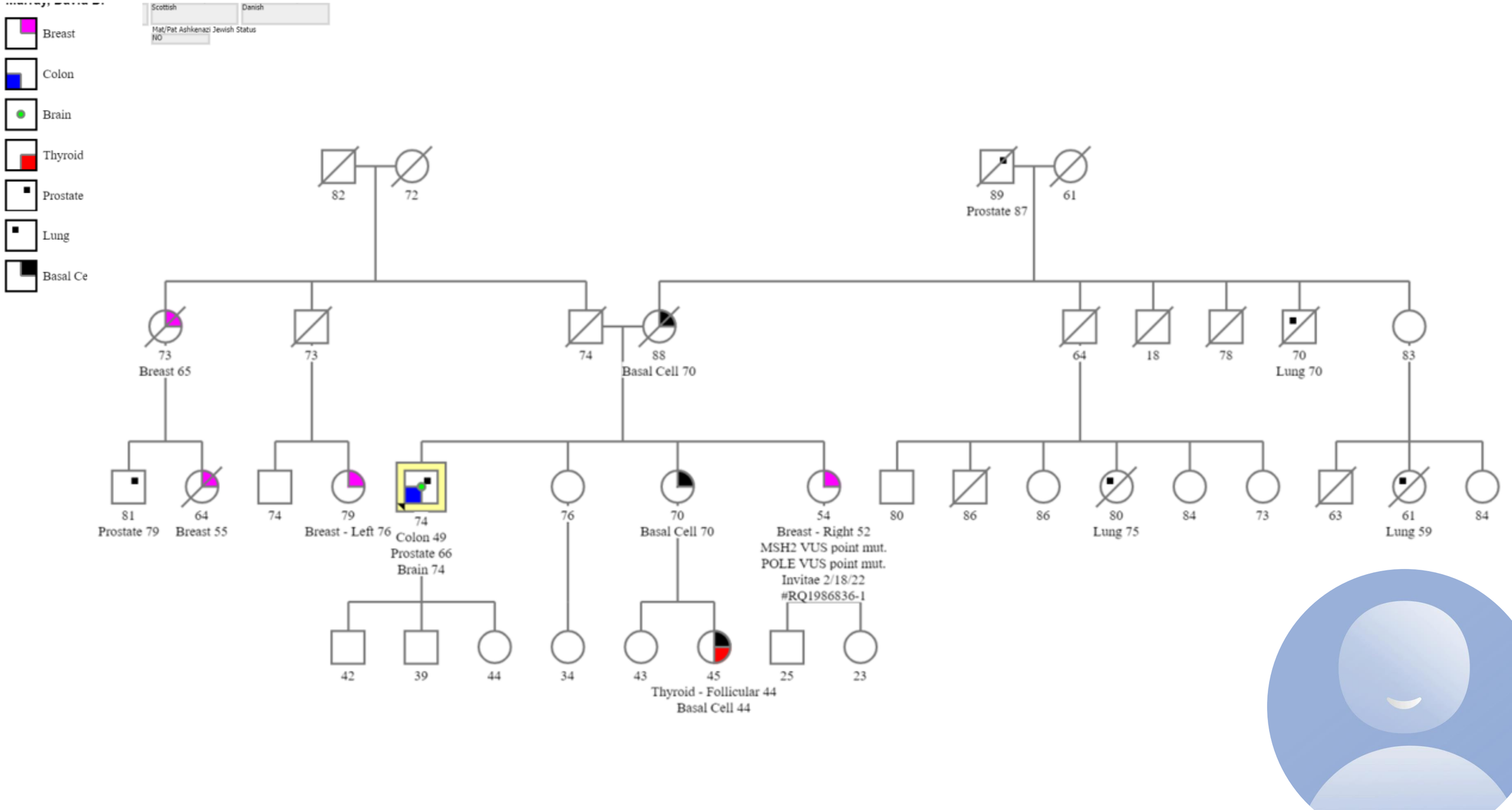

56
44
57
83
Breast - Right 75
88
89
77
71
82
Skin 60
6
73
73
Uterus 50Leukemia 73
63
51
54
64
62
65
55
57

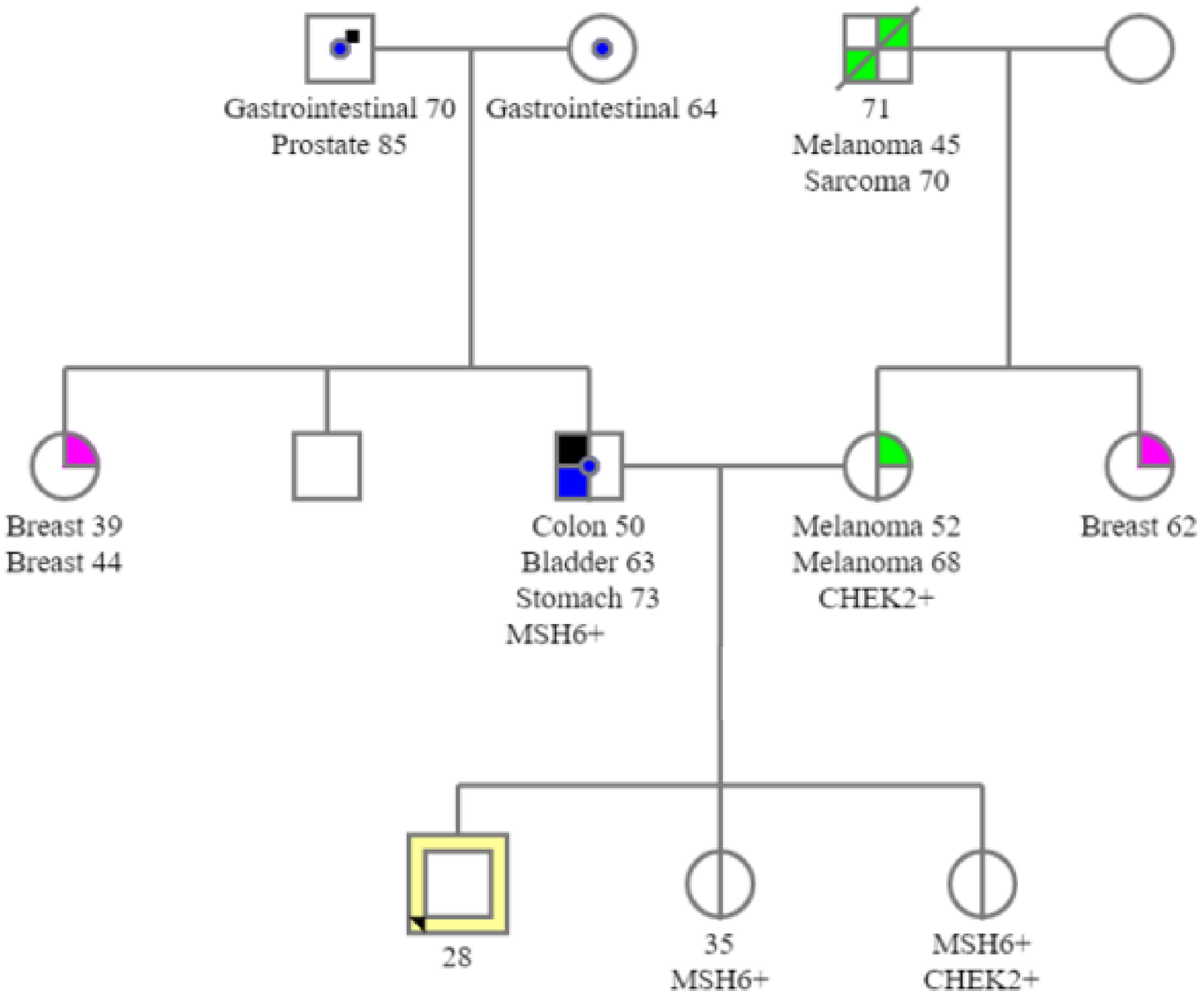

Paternal Side
Western/Northern European
Maternal Side
Western/Northern European
Grandfather
Grandmother
Age 96
Grandfather
Age 81
Grandmother
Age 49
Colon or Rectal
49
Paternal Aunt
Age 79
Paternal Aunt
Age 72
5
Paternal
Uncles
Father
Age 76
Mother
Age 73
Breast 53
Cervical 32
Maternal Aunt
Breast (Both
Breasts) 51
Maternal Uncle
Maternal Aunt
Breast
Maternal Aunt
Age 59
Thyroid
2
Female First
Cousin
(Paternal)s
Male First
Cousin
(Paternal)
2
Female First
Cousin
(Paternal)s
Male First
Cousin
(Paternal)
Age 48
Brother
Age 46
Sister
Age 49
Maternal Half
Brother
Male First
Cousin
(Maternal)
Female First
Cousin
(Maternal)
3
Male First
Cousin
(Maternal)s
Male First
Cousin
(Maternal)
Female First
Cousin
(Maternal)
Son
Age 18
Daughter
Age 16


English/irish
Not Ashkenazi Jewish
Ashkenazi Jewish/ Russian
45
d. MI
99
d. "old age"
45
d. suicide
91
Breast Ca 60
mast
d. TIAs
80
a&w
75
Prostate Ca 70
73
Breast Ca 55
lump/rad
hysterectomy
? ovaries intact
71
Type II diabetes
kidney failure
dialysis
69
multiple sclerosis
61
Breast Ca 50
mast/? rad
55
a&w
50
a&w
48
a&w
28
a&w
50
Breast Ca 27
Breast Ca 30
Breast Ca 34
R - IDC 27
L - DCIS 30
R breast ca 34
menarche 12
menopause 35
(from chemotherapy)
ovaries intact
Type I diabetes
D
D
S
35
a&w
30
a&w
27
a&w
25
a&w
10
a&w
19
a&w
10
a&w
10
a&w
1
a&w
1
a&w
3 months
a&w
3 months
a&w
Cancer History.Cancer Dx = Breast Ca
Cancer History.Cancer Dx = Prostate Ca


Paternal Side
Western/Northern European
Maternal Side
Asian
Age 62
Grandmother
Age 77
Pancreatic
Kidney
*
N/A unsure
*+
Kidney 50
Pancreatic 48
Brain/NS 21
+(VHL)
*
Kidney 45
2
Male First Cousin (Paternal)s
2
Paternal Half Brothers
Paternal Half Sister
*+
Age 29
Brain/NS 27
Other 27
Kidney 27
+(VHL)
Male First Cousin (Maternal)
Female First Cousin (Maternal)
2
Male First Cousin (Maternal)s
Male First Cousin (Maternal)
Female First Cousin (Maternal)
Pancreatic
Brain or Nervous System
Kidney (Renal or Ureter Pelvis)
Other


78
84
Liver 7Pancreas 69
EtOH
78
89
d. cancer
Prostate 77
83
85
Breast 65
80
d. cancer
Breast 78eg. Myriad myRisk - 2021
81
Pancreas 78
s/p Whipple
(FL)
79
s/p TAH?
82
77
64
Myeloma 58
59
Pancreas 57
Neg. 55-gene Invitae Panel - 2021
dermatologist for moles
+ tob
58
Hodgkin Lymphoma 45
62
60
59
53
44
4


Scottish
Danish
Mat/Pat Ashkenazi Jewish Status
NO
Breast
Colon
Brain
Thyroid
Prostate
Lung
Basal Ce
82
72
89
Prostate 87
61
73
Breast 65
73
74
88
Basal Cell 70
64
18
78
70
Lung 70
83
81
Prostate 79
64
Breast 55
74
79
Breast - Left 76
74
Colon 49
Prostate 66
Brain 74
76
70
Basal Cell 70
54
Breast - Right 52
MSH2 VUS point mut.
POLE VUS point mut.
Invitae 2/18/22
#RQ1986836-1
80
86
86
80
Lung 75
84
73
63
61
Lung 59
84
42
39
44
34
43
45
Thyroid - Follicular 44
Basal Cell 44
25
23


Gastrointestinal 70
Prostate 85
Gastrointestinal 64
71
Melanoma 45
Sarcoma 70
Breast 39
Breast 44
Colon 50
Bladder 63
Stomach 73
MSH6+
Melanoma 52
Melanoma 68
CHEK2+
Breast 62
28
35
MSH6+
MSH6+
CHEK2+

Example of a 73 year-old with metastatic breast cancer

Next Generation Sequencing Panel: Breast Cancer

Specimen Source:
Specimen Description: Left axillary lymph node, core biopsy
Diagnosis: Invasive Breast Carcinoma
Tumor Content: 90%
Genes in Panel:
AKT1, BRCA1, BRCA2, CDKN2A, ERBB2, ESR1, PIK3CA, PTEN

Actionable: Variants of Strong Clinical Significance

BRCA2
Mutation(s): BRCA2_Ile2588TyrfsTer60

Actionable Comments:
BRCA2_Ile2588TyrfsTer60 (NM_000059.3:c.7762delA) is likely an inactivating mutation. The PARP inhibitors olaparib and talazoparib are FDA-approved for the treatment of patients with HER2-negative, metastatic breast cancer with deleterious or suspected deleterious germline BRCA1 or 2 mutations. There is promising clinical activity with olaparib in breast cancer patients with somatic mutations in BRCA1/2.

Please note that this assay is designed for detection of somatic mutations in the tumor tissue, but may also detect germline mutations in this mixed cell population. If a germline mutation is suspected clinically, appropriate genetic counseling and testing of peripheral blood is recommended.

ncbi.nlm.nih.gov/clinvar/variation/52405/

NIH National Library of Medicine
National Center for Biotechnology Information

ClinVar Genomic variation as it relates to human health

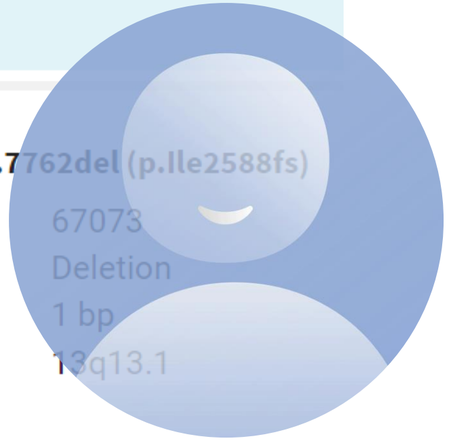
NM_000059.4(BRCA2):c.7762del (p.Ile2588fs)

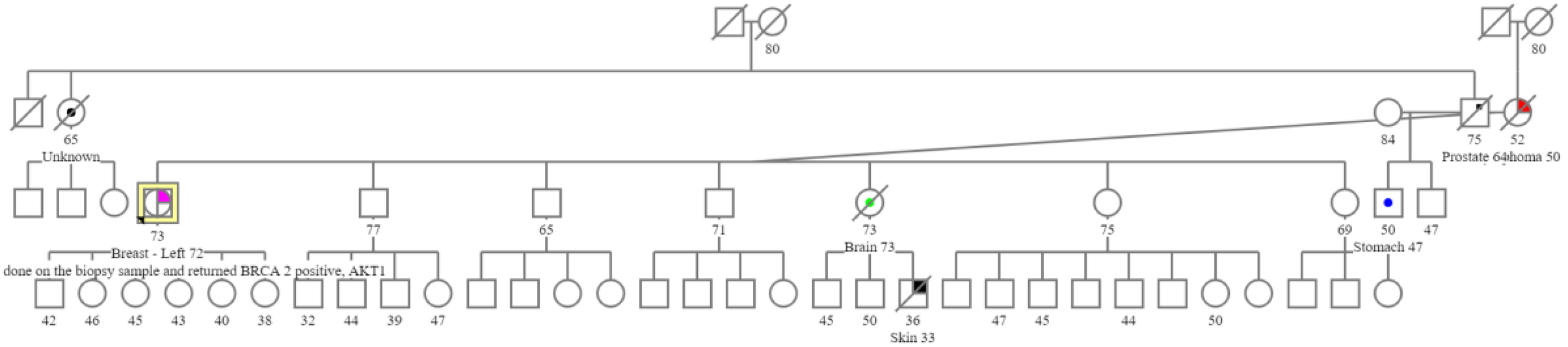
Interpretation:	**Pathogenic**
Review status:	★★★☆ reviewed by expert panel
Submissions:	6 (Most recent: Nov 30, 2020)
Last evaluated:	Sep 8, 2016
Accession:	VCV000052405.5
Variation ID:	52405
Description:	1bp deletion

Variant details
Conditions
Gene(s)

NM_000059.4(BRCA2):c.7762del (p.Ile2588fs)

Allele ID:	67073
Variant type:	Deletion
Variant length:	1 bp
Cytogenetic location:	13q13.1




80
80
65
Unknown
84
75
52
Prostate 64
homa 50
73
77
65
71
73
75
69
50
47
Breast - Left 72
done on the biopsy sample and returned BRCA 2 positive, AKT1
Brain 73
Stomach 47
42
46
45
43
40
38
32
44
39
47
45
50
36
Skin 33
47
45
44
50

Knowing before developing cancer

Table. Comparison of PreDx vs PostDX Awareness of *BRCA* Carrier Status in Women With Breast Cancer

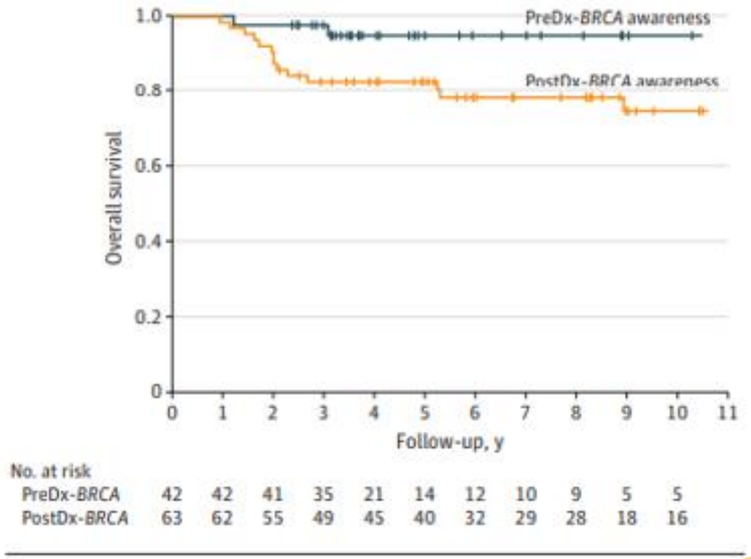
Characteristic	No. (%)	
	PreDx (n = 42)	PostDx (n = 63)
Age, mean (SD), y	50.4 (14.4)	50.4 (12.7)
Year of diagnosis, mean (SD)	2012.9 (3.1)	2010.4 (3.3)
Family history[b,c]		
None-low	3/42 (7.1)	22/63 (34.9)
Moderate-high	37/42 (88.1)	37/63 (58.7)
Gene		
BRCA1	27/42 (64.3)	40/63 (63.5)
BRCA2	15/42 (35.7)	23/63 (36.5)
SI, mean (SD)[d]	6.39 (2.45)	4.99 (2.59)
Detection modality		
Clinical/self-examination	4/42 (9.5)	40/63 (63.5)
Mammography	8/42 (19.0)	17/63 (27.0)
MRI	27/42 (64.3)	1/63 (1.6)
Tumor characteristics		
Pure DCIS	18/42 (42.9)	2/63 (3.2)
Invasive carcinoma[e]	24/42 (57.1)	61/63 (96.8)
ER		
Positive	16/24 (66.7)	29/61 (47.5)
Negative	8/24 (33.3)	28/61 (45.9)
PR		
Positive	11/24 (45.8)	17/61 (27.9)
Negative	11/24 (45.8)	38/61 (62.3)
ERBB2		
Positive	1/24 (4.2)	4/61 (6.6)
Negative	22/24 (91.7)	56/61 (91.8)
Clinical stage at diagnosis		
DCIS	16/42 (38.1)	2/63 (3.2)
T1N0	18/42 (42.9)	17/63 (27)
>T2 or N1	4/42 (9.5)	33/63 (52.4)

Hadar T et al. JAMA Oncology 2020

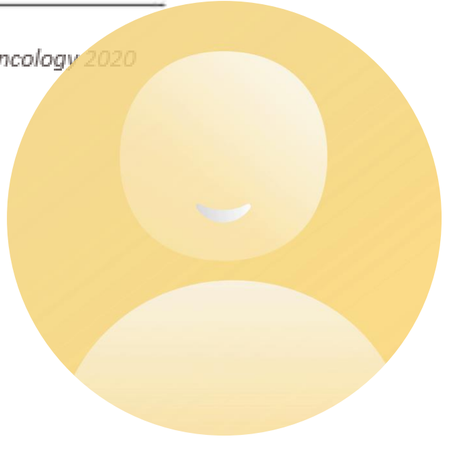
Table. Comparison of PreDx vs PostDX Awareness of *BRCA* Carrier Status in Women With Breast Cancer

Characteristic	No. (%) PreDx (n = 42)	PostDx (n = 63)
Clinical stage at diagnosis		
DCIS	16/42 (38.1)	2/63 (3.2)
T1N0	18/42 (42.9)	17/63 (27)
>T2 or N1	4/42 (9.5)	33/63 (52.4)
Pathologic stage at diagnosis (in non-NAC), No.[f]	42	49
pT[g]		
pDCIS	18/42 (42.9)	2/49(4.1)
pT1	19/42 (45.2)	23/49 (46.9)
pT2	5/42 (11.9)	19/49 (38.8)
pT3	0	2/49 (4.1)
pN		
pN0	34/42 (81.0)	28/49 (57.1)
pN1-3	6/42 (14.3)	19/49 (38.8)
pTNMc[h]		
0-I	36/42 (85.7)	19/49 (38.8)
II-IV	6/42 (14.3)	30/49 (61.2)
Treatment		
Breast surgery		
Unilateral	14/42 (33.3)	49/63 (77.8)
Bilateral	27/42 (64.3)	10/63 (15.9)
Axillary surgery		
None	1/42 (2.4)	2/63 (3.2)
SNLB	36/42 (85.7)	32/63 (50.8)
ALND	3/42 (7.2)[i]	22/63 (34.9)
Chemotherapy		
None	23/42 (54.8)	3/63 (4.8)
Any[j]	12/42 (28.6)	50/63 (79.4)
Neoadjuvant	0	14/63 (22.2)
Adjuvant	12/42 (28.6)	39/63 (61.9)

Figure. Overall Survival in Carriers of *BRCA* Pathogenic Variants Diagnosed With Breast Cancer Who Were Aware of Their *BRCA* Status Before vs After Cancer Diagnosis



Hadar T et al. JAMA Oncology 2020



Thank You!

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