Hereditary Breast and Ovarian Cancer

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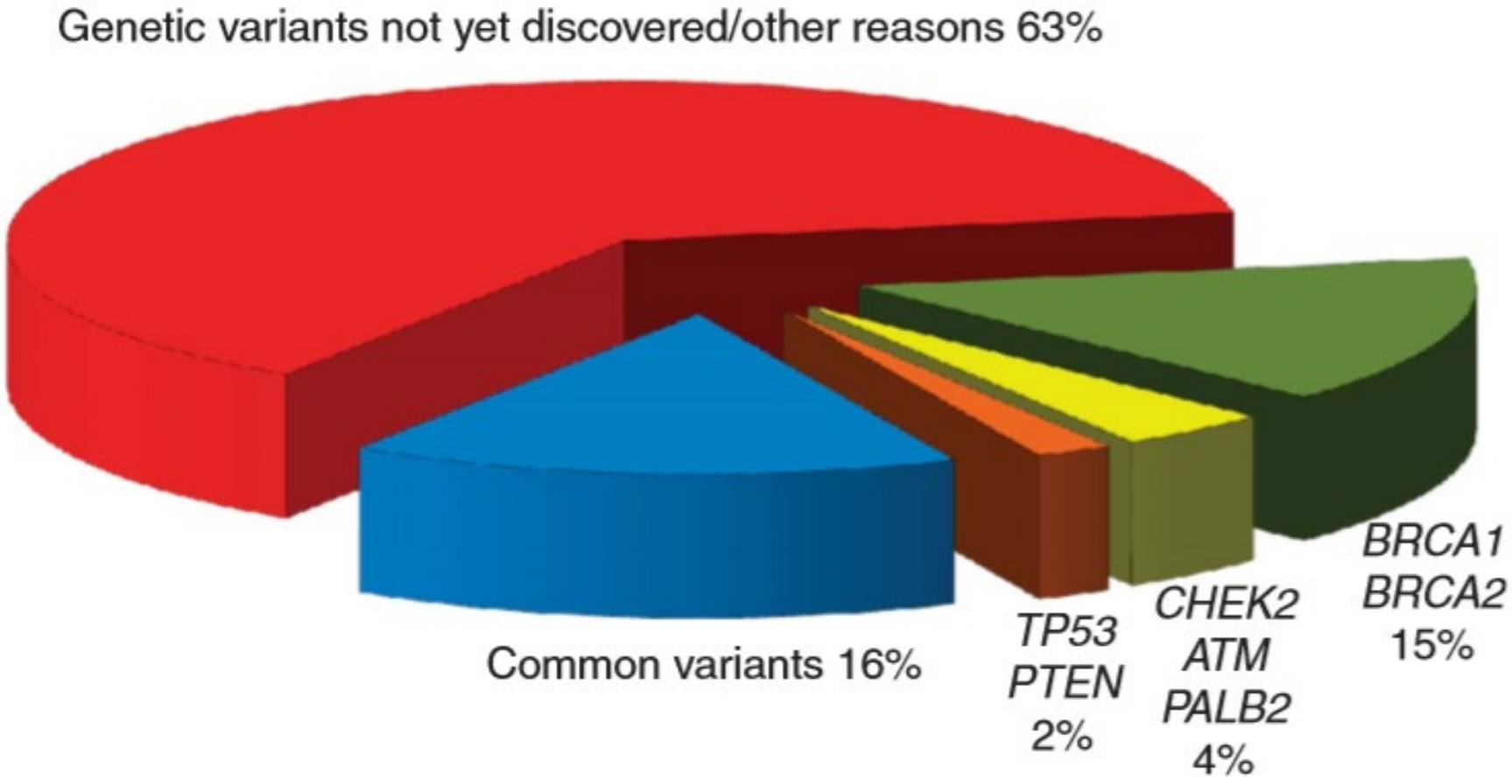
We will discuss

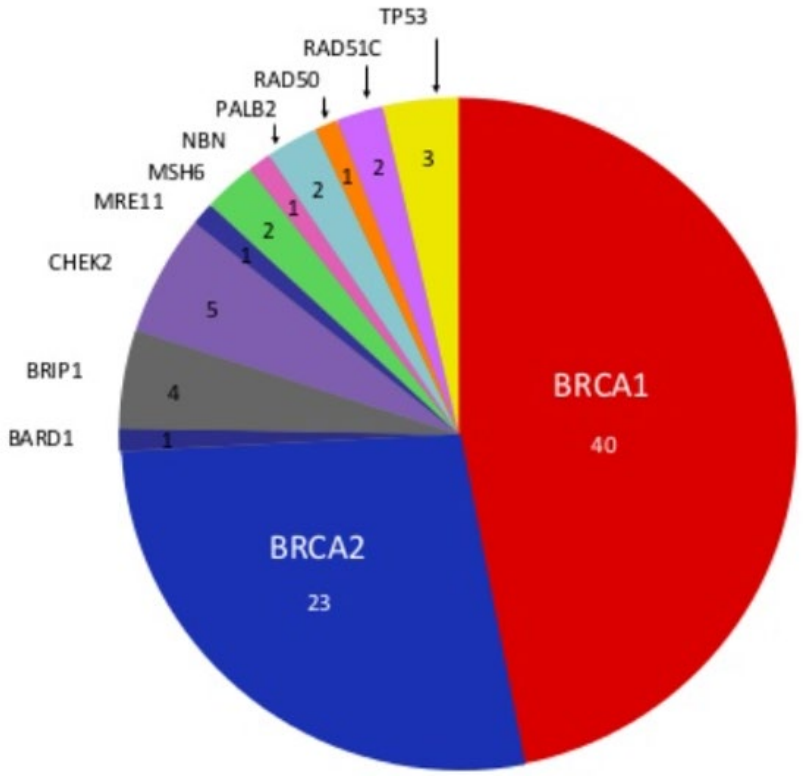
- Percentage of breast and ovarian cancer that is hereditary
- Genes involved in hereditary breast and hereditary ovarian cancer
- Management of Hereditary Breast and Ovarian Cancer
  - Affected
  - Unaffected
- Importance of Cascade Testing
- Indications for Genetic Testing in 2019

5-10% of all Breast Cancer is Hereditary



Rudolph BJC 2016

15-20% of all Ovarian Cancer is Hereditary



Histology	% Mutations
High Grade Serous	30.3
Low Grade Serous	16.7
High Grade Endometrioid	21.7
Low Grade Endometroid	14.3
Mucinous	11.1

Walsh PNAS 2011
Harper PLoS1 2017

Case 1

- 35 year old with 2 cm triple negative Breast Cancer
  - Starting neoadjuvant chemotherapy
  - Family history negative for cancer
- Should she have genetic testing?
- If yes, what genes?

Case 2

- 65 year old with Stage IV high-grade serous ovarian cancer
  - Family history negative
- Should she have genetic testing?
- If yes, what genes?

Societies with guidelines regarding genetic testing for hereditary breast and/or ovarian cancer

- National Comprehensive Cancer Center Network (NCCN)
- US Preventative Services Task Force (USPSTF)
- American Society of Clinical Oncology (ASCO)
- American Congress of Obstetrics and Gynecology (ACOG)
- National Society of Genetic Counselors (NSGC)
- Society of Gynecologic Oncology (SGO)

Indications for Genetic Testing

- Affected with cancer
  - Cancer type and pathology
  - Family History
  - Ethnicity
- Unaffected
  - Family history
  - Ethnicity

Indications for Genetic Testing based on Personal History

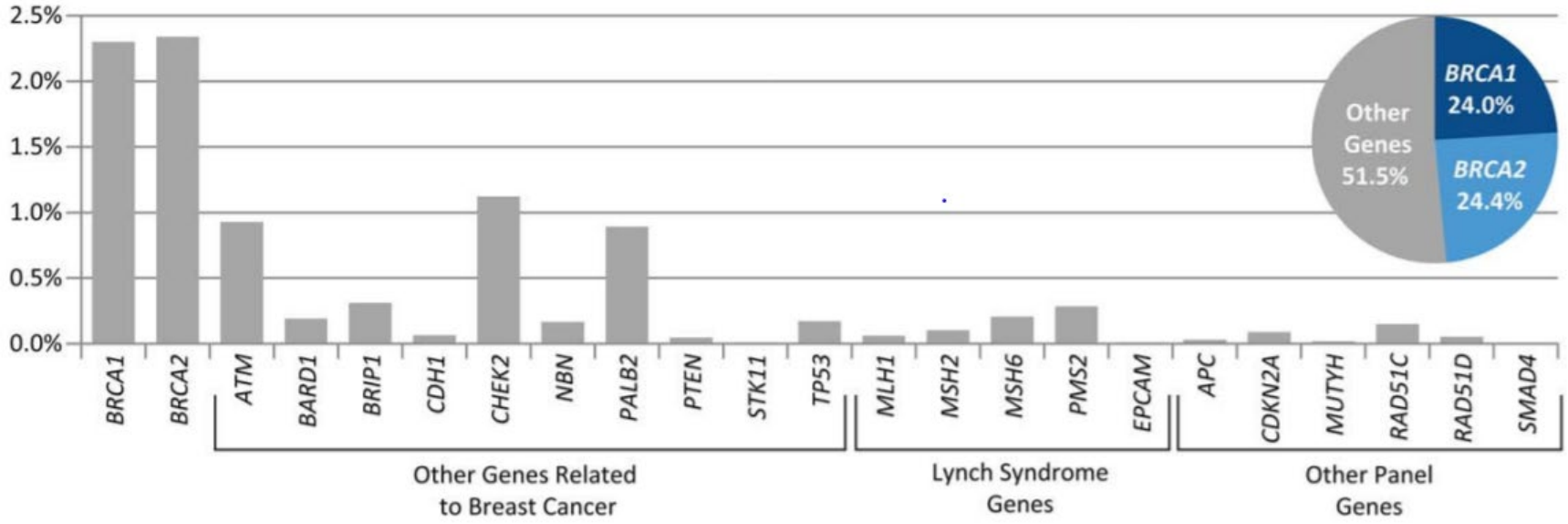
- Breast Cancer
  - Diagnosed under 45
    - 45-50 if +FHx
  - Triple negative diagnosed under 60
  - Bilateral breast cancer
- Ovarian Cancer
  - Epithelial or serous type (any high grade histology)
  - Ovarian, Fallopian Tube or primary peritoneal origin
- Male Breast Cancer
- Metastatic Prostate Cancer
  - High Grade Disease (Gleason >7) if +FHx
- Pancreatic Cancer
- More than 3 primary cancers
- Ashkenazi Jewish and breast or ovarian or pancreatic or HG prostate cancer

NCCN Guidelines v3.2019
Lu, Wood JCO 2014

Case 1

- 35 year old with 2 cm triple negative Breast Cancer
  - Starting neoadjuvant chemotherapy
  - Family history negative for cancer
- Should she have genetic testing?
  - Yes, she meets criteria for testing
- If yes, what genes?

Panel Testing for breast cancer



- Retrospective analysis of 35,409 women with breast cancer undergoing panel testing through Myriad genetics between 9/13-8/15
  - women with multiple primaries and men were excluded
  - 9.3% tested positive for a mutation
  - 51.5% were non-BRCA genes
  - 10.7% were in genes not associated with hereditary breast cancer

Buys Cancer 2017

Case 1

- 35 year old with 2 cm triple negative Breast Cancer
  - Starting neoadjuvant chemotherapy
  - Family history negative for cancer
- Multigene panel reveals
  - Pathogenic mutation in CHEK2

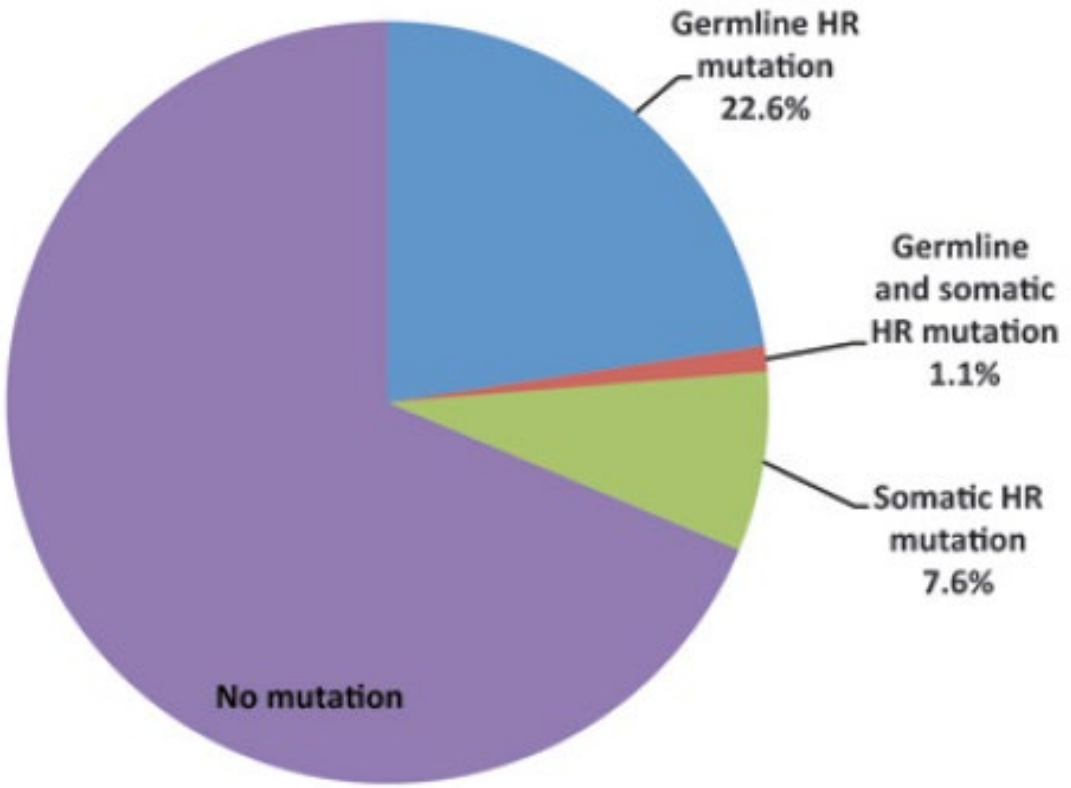
Breast Cancer Risk associated with Genes

Myriad Genetics

Case 2

- 65 year old with Stage IV high-grade serous ovarian cancer
  - Family history negative
- Should she have genetic testing?
  - Yes, she meets criteria for testing
- If yes, what genes?

Testing for Ovarian Cancer



- Patients with ovarian cancer can have either germline or somatic mutations in homologous repair genes
- Homologous repair deficiency predicts response to platinum agents or PARP inhibitors.
- Thus testing for patients with ovarian cancer must incorporate tumor testing

Pennington CCR 2014

Case 2

- 65 year old with Stage IV high-grade serous ovarian cancer
  - Family history negative
- Multigene panel reveals
  - Pathogenic mutation in BRCA2

Ovarian Cancer Risk associated with Genes

Myriad Genetics

Genes associated with HBOC with management guidelines

Breast	Ovarian
BRCA1/2	BRCA1/2
PALB2	BRIP1
CHEK2	RAD51C
ATM	RAD51D
TP53	MMR genes
PTEN	
STK11	
CDH1	
NF1	
NBN	

Breast and Ovarian Risk Management by Gene

	Screening breast MRI (>20% lifetime risk)	Discuss risk reducing mastectomy	Discuss risk-reducing BSO
Intervention warranted based on risk – Highly Penetrant Genes	BRCA1 BRCA2 CDH1 PALB2 PTEN STK11 TP53	BRCA1 BRCA2 PALB2 PTEN TP53	BRCA1 BRCA2 Lynch Genes BRIP1 RAD51C RAD51D
Intervention warranted based on risk – Moderately Penetrant Genes	ATM CHEK2 NBN NF1		
Insufficient evidence	BRIP1 BARD1	STK11, CDH1 ATM, CHEK2,NBN, NF1	PALB2

NCCN HBOC Guidelines v3.2019

Case 1

- 35 year old with 2 cm triple negative Breast Cancer
  - Starting neoadjuvant chemotherapy
  - Family history negative for cancer
- Multigene panel reveals
  - Pathogenic mutation in CHEK2
- Implications of Testing
- For the patient
  - Add annual screening breast MRI
  - No indication for prophylactic mastectomy
  - Colonoscopy at age 40

Case 2

- 65 year old with Stage IV high-grade serous ovarian cancer
  - Family history negative
- Tumor Based Testing + Multigene panel reveals
  - Pathogenic germline mutation in BRCA2

- Implications of Testing
- For Patient
  - PARP inhibitor therapy
    - Several PARP inhibitors are now approved for both maintenance and recurrence
  - Consider addition of annual screening breast MRI
  - Screening for melanoma and pancreatic cancer

Cascade testing

- Definition: Genetic testing in blood relative who have known pathogenic variants.
  - 1st degree relatives: 50% risk
  - 2nd degree relatives: 25% risk
- Impact of testing
  - Positive
    - Have cancer risk associated with mutation
    - Cancer screening and prevention can improve survival
  - Negative
    - Population cancer risk
    - Need to evaluate non-mutation side of the family

Case 1

- 35 year old with 2 cm triple negative Breast Cancer
  - Starting neoadjuvant chemotherapy
  - Family history negative for cancer
- Multigene panel reveals
  - Pathogenic mutation in CHEK2

- Implications of Testing
- For Family
  - Cascade testing of family members (men and women)
    - Positive: Screening for breast/colon
    - Negative: ACS screening

Case 2

- 65 year old with Stage IV high-grade serous ovarian cancer
  - Family history negative
- Tumor Based Testing + Multigene panel reveals
  - Pathogenic germline mutation in BRCA2

- Implications of Testing
- For Family
  - Cascade testing of family members (men and women)
    - Positive: Screening for breast/ovarian/prostate/pancreatic cancer and melanoma
    - Negative: ACS screening

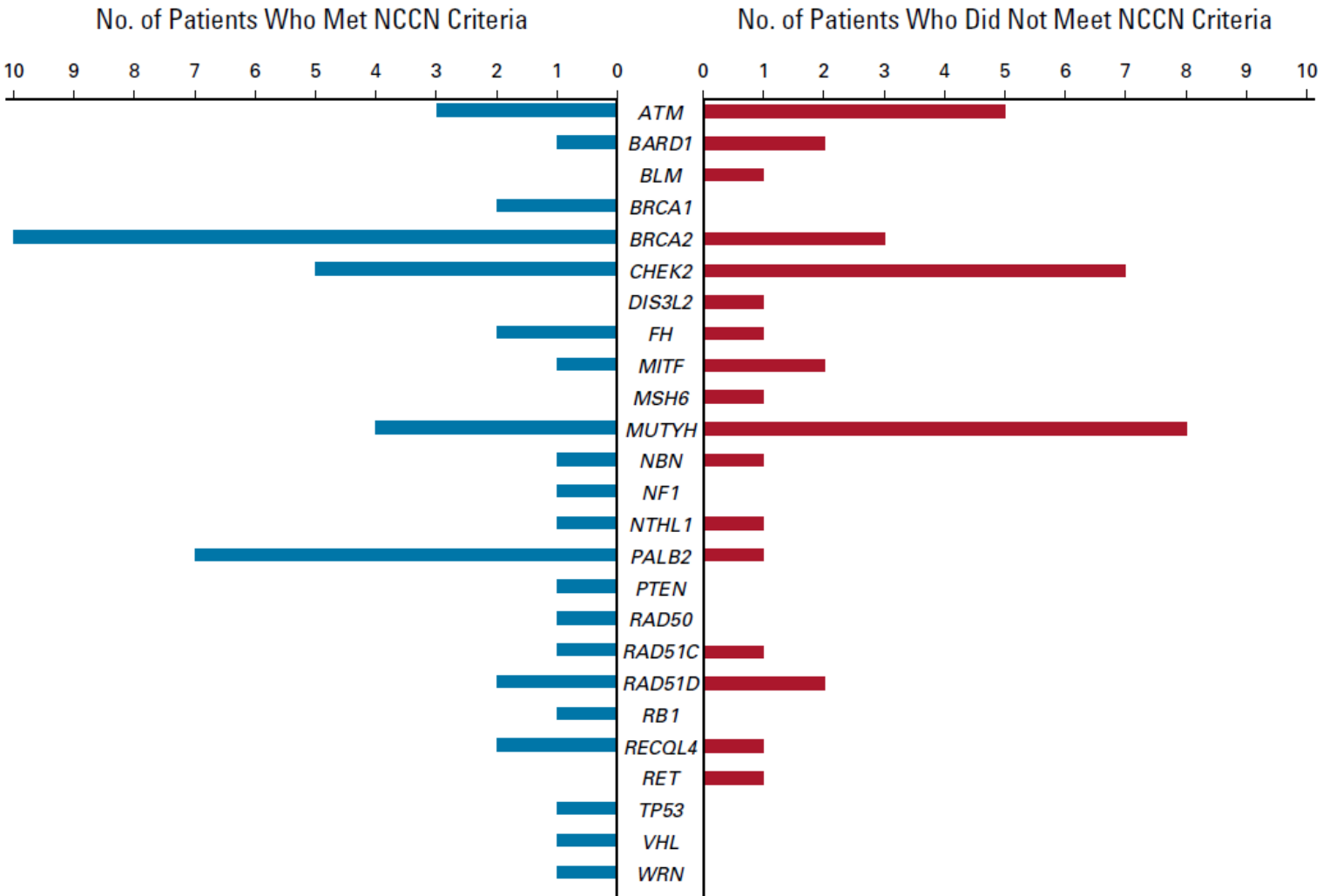
Are Guidelines Necessary?

- Methods
  - 20 sites across the US
  - Selected patient who did and did not meet guidelines
    - NCCN v 2.2017
  - Patients underwent 80 gene panel testing

	Positive Result (%)		
Group	*BRCA1/* Alone	HBOC Guidelines Panel (11 genes)	Large Cancer Panel (80 genes)
In guideline	2.51	6.26	9.39
Out of guideline	0.63	3.54	7.92

Beitsch JCO 2018

Pathogenic Mutations in patient who did and did not meet NCCN Criteria



Beitsch JCO 2018

Are Guidelines Necessary?

- Rational perspective is necessary
  - Testing for patients with cancer
    - Breast Cancer: Young, bilateral, multiple primaries or triple negative
    - Ovarian Cancer: All ovarian cancers regardless of histology
  - Testing for patients with breast and/or ovarian cancer with positive family history
  - Testing for patients with breast and/or ovarian cancer when it will change management

- Thank you!

The heart and science of medicine.

UVMHealth.org/CancerCenter

Inherited Prostate and Pancreatic Cancer

Wendy C. McKinnon, MS, CGC
Certified Genetic Counselor
University of Vermont Cancer Center
AACI Webinar, October 2, 1019

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What's in a name?

- Individuals and families with *BRCA1* or *BRCA2* mutations are referred to as having Hereditary Breast / Ovarian Cancer syndrome (HBOC)
- *BRCA* mutations are associated with other cancers, including prostate and pancreatic cancers that impact men
- 1 in 40 to 1 in 400 people carry a *BRCA* mutation
- 10 times more women then men have been tested for *BRCA* in the US
- Re-name to remove the sex and cancer specificity to aid in prevention and treatment

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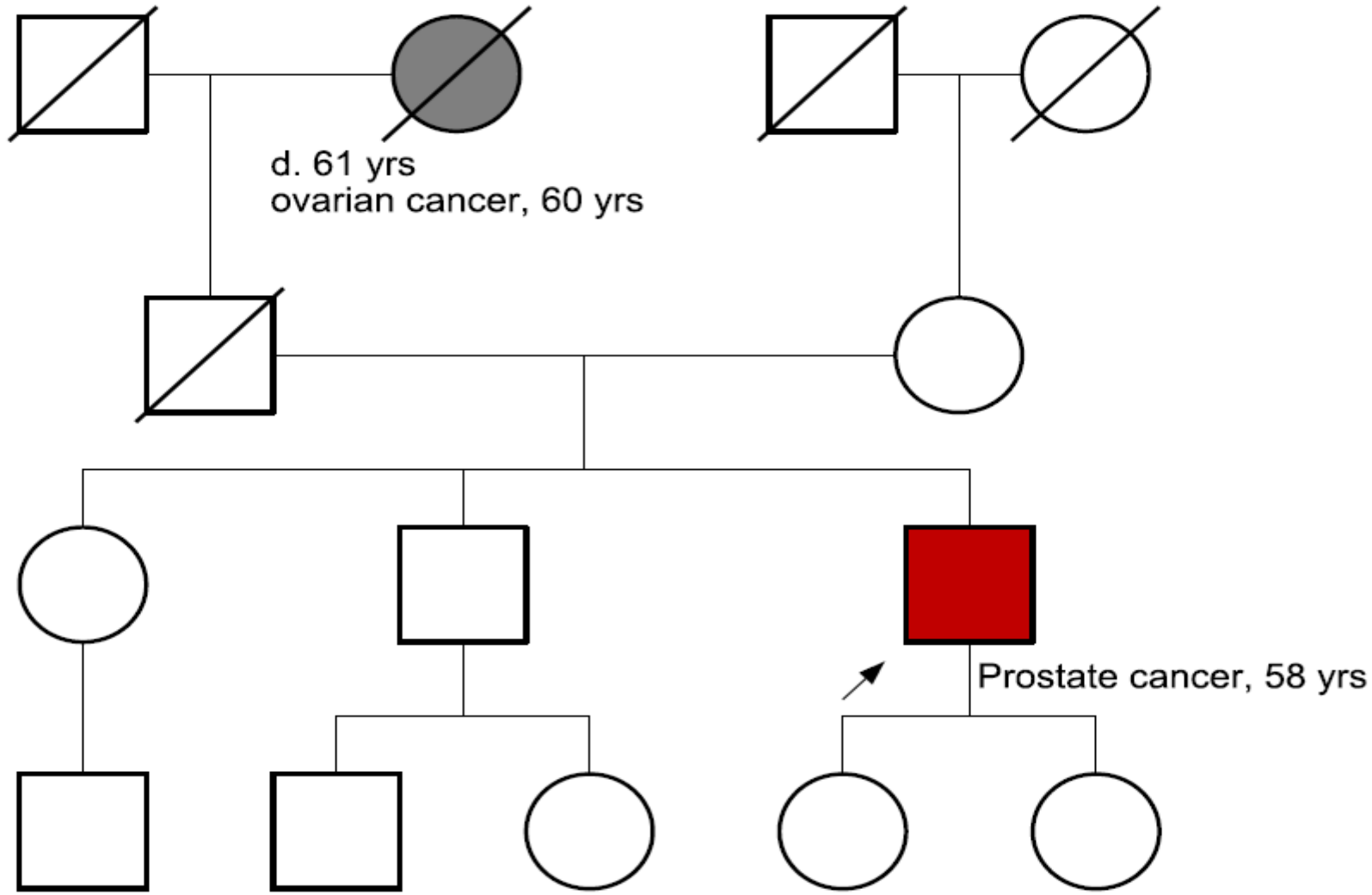
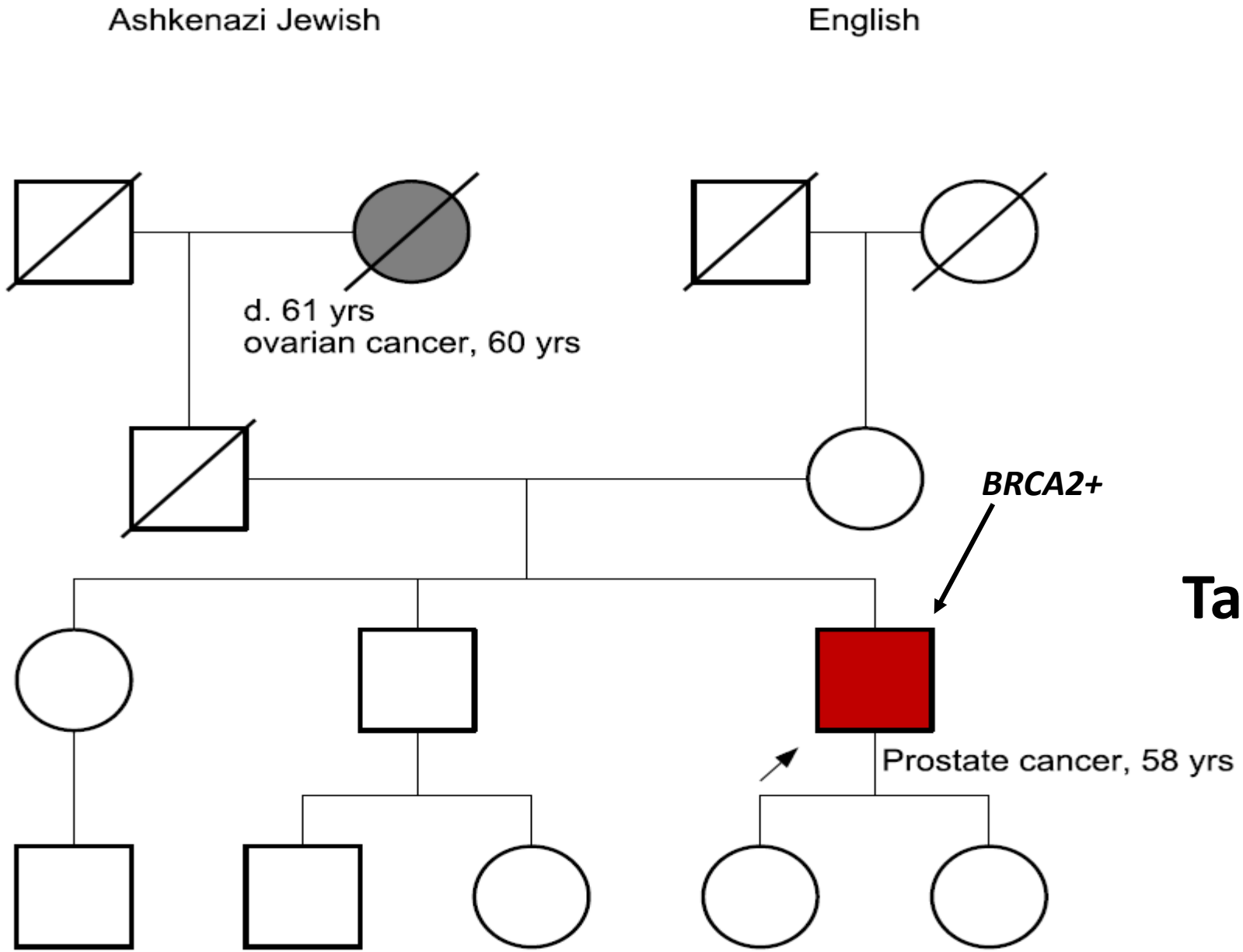
Pritchard, CC, July 2019, *Nature*

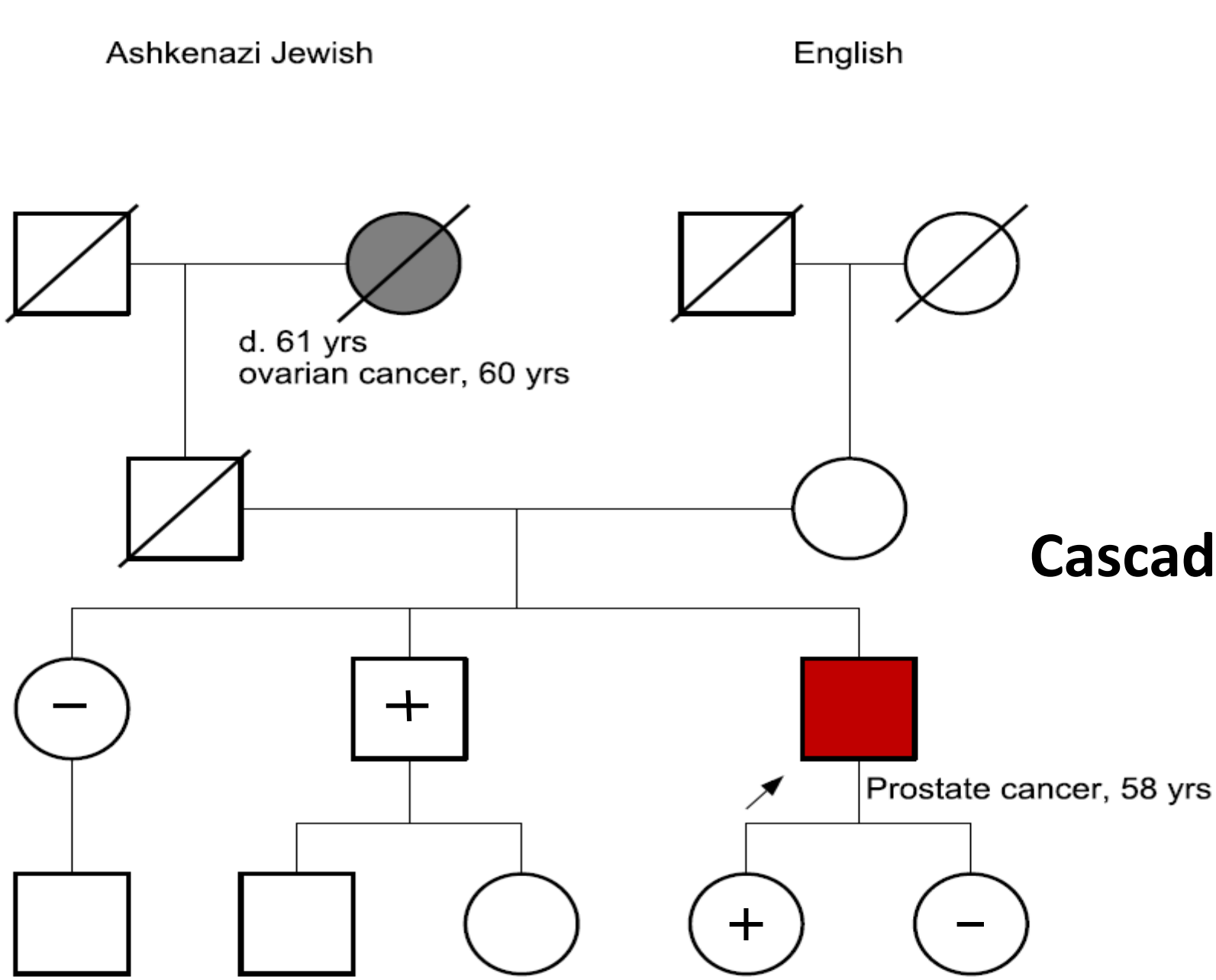
Ashkenazi Jewish

English





Targeted Therapy



Cascade Testing

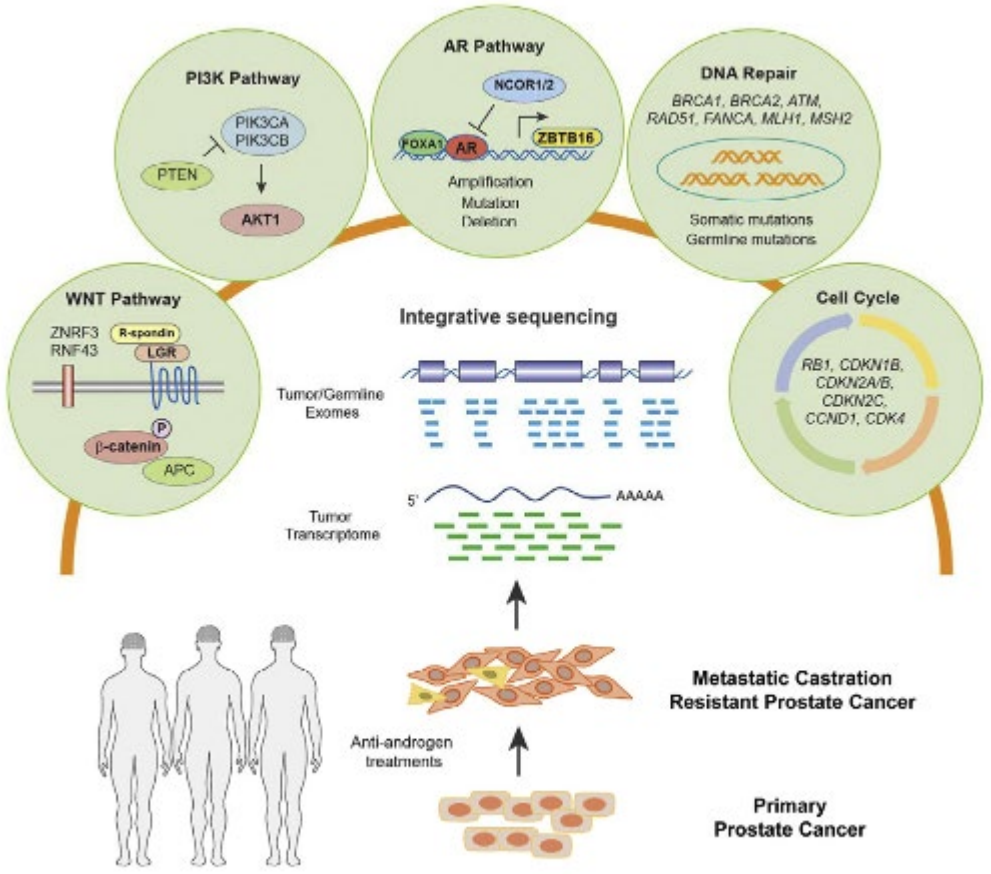
Prostate Cancer (PC)

- 220,000 men in US diagnosed and 30,000 deaths annually
- PC is 2nd leading cancer related death in men in US
- Inherited PC is associated with more aggressive disease and poorer outcomes
- Genes associated with inherited PC are targets for therapy in men with metastatic disease
- Identification of at-risk men may be lifesaving

How much prostate cancer is linked to germline variants in cancer susceptibility genes ?

Integrative Clinical Genomics of Advanced Prostate Cancer

- Multi-institutional prospective study sequencing tumors from men with metastatic, castration-resistant prostate cancer (mCRPC) to determine the landscape of somatic genomic alterations
  - 89% harbored a potentially clinically actionable aberration (somatic)
  - 8% harbored actionable pathogenic **GERMLINE** alterations



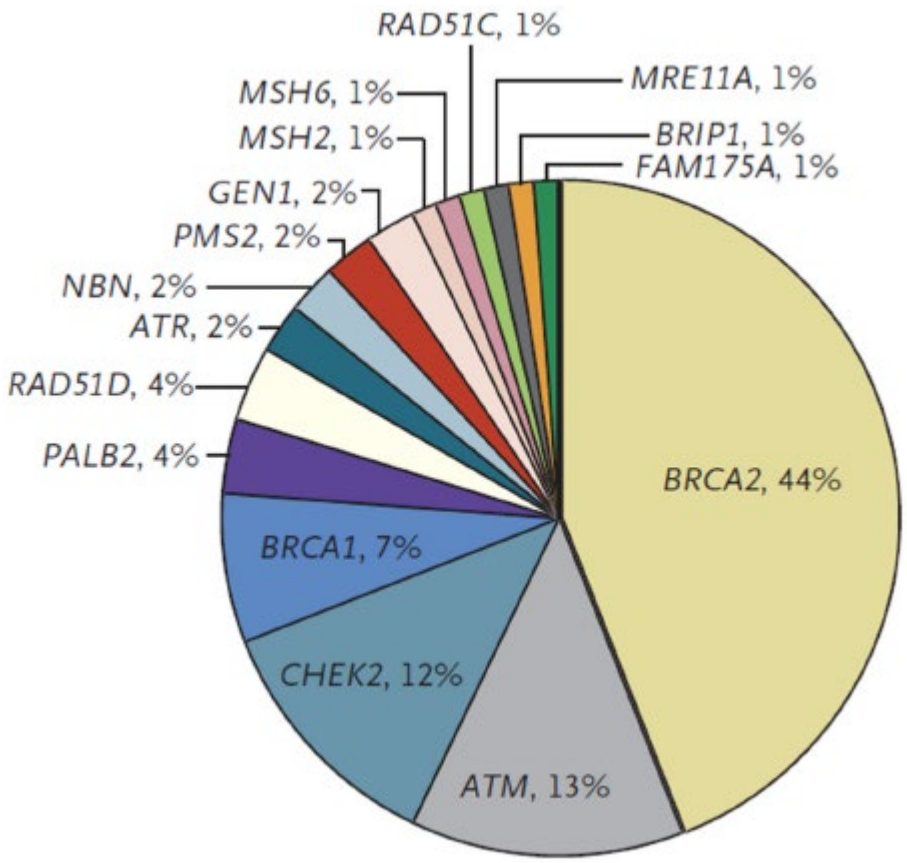
Robinson D, et al, 2015, *Cell*

Further evidence …….

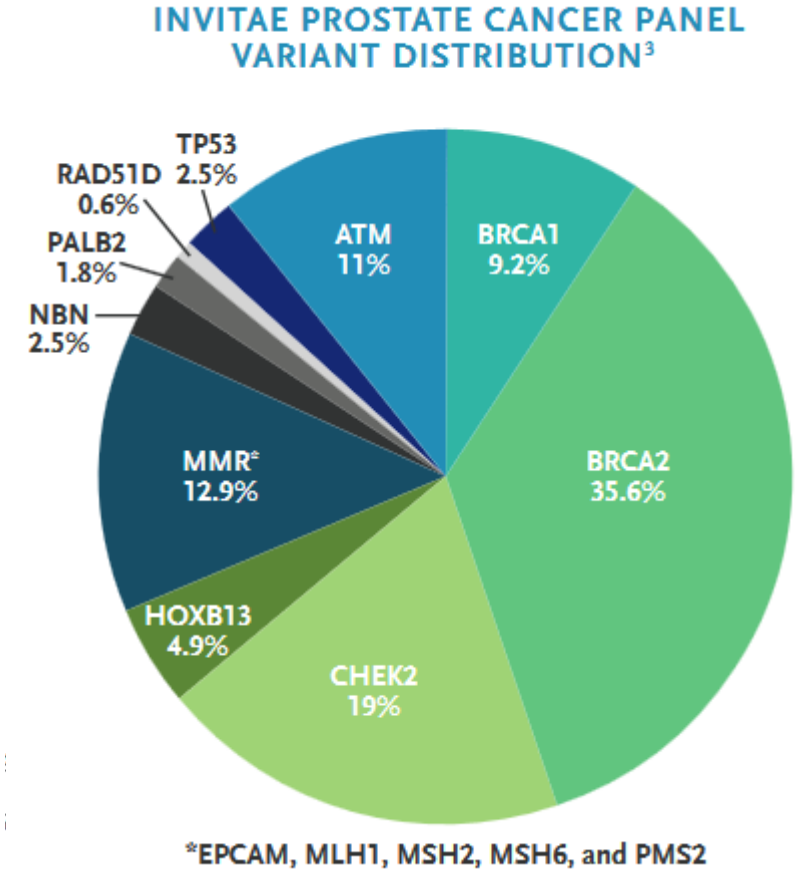
- 2016
  - *NEJM* study found that **11.8%** of men with metastatic prostate cancer had germline mutations in DNA-Repair genes (Pritchard C, et al)

- 2019
  - *JAMA Oncology* study found that **17.2%** of men with prostate cancer have germline mutations (Nicolosi P, et al)

Genes Associated with Prostate Cancer Risk



Pritchard C, et al, 2016, *NEJM*



Nicolosi P, et al, 2019, *JAMA*

Validated Genes That Increase Prostate Cancer Risk When Altered

Gene	Risk	Associated Cancer(s)
BRCA1	RR, 1.8-3.75	Breast, ovarian
BRCA2	RR, 4.5-8.6	Breast, ovarian, pancreatic, male breast, melanoma
MMR (Lynch syndrome)	RR, 2.11-3.67	Colon, endometrial, ovarian, urinary tract, upper GI, sebaceous skin, glioblastoma
HOXB13 (G84E)	OR, 4.51	
CHEK2	OR, 1.8-3.2	Breast, colon, male breast, ?thyroid
NBN	OR, 2.5-4.3	Breast
BRIP1	OR, 2.4	Ovarian, ?breast
ATM	OR, 2.1	Breast, pancreatic

Zhen JT, et al, 2018, *Cancer;* Sanjay D, et al, 2019*, JUrology*

Prostate cancer screening

Prostate Cancer Early Detection: NCCN Guidelines V2.2019

[c] If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional is recommended. *BRCA1/2* pathogenic mutation carriers have an increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline *BRCA2* mutations occurs earlier and is more likely to be associated with prostate cancer mortality. Consequently, it is reasonable for men with germline *BRCA1/2* mutations to consider beginning shared decision-making about PSA screening at age 40 and to consider screening at annual intervals rather than every other year.

Prostate Cancer Screening Trials

- IMPACT (**I**dentification of **M**en with a genetic predisposition to **P**rost**A**te **C**ancer: Targeted screening in men at higher genetic risk and controls; www.impact-study.co.uk); (NCT00261456)
  - Preliminary results support yearly PSA screening in men with BRCA2 mutations aged 40-69
  - Bancroft EK,et al, 2014, *Eur Urol*

- NCI Trial = Men at High Genetic Risk for Prostate Cancer (NCT03805919)
  - Incorporates annual PSA, DRE, and prostate MRI

Recommendations for prostate cancer early detection in carriers of high-risk mutations

For men with personal history of *BRCA1/2* mutation, Lynch syndrome, or mutations (ie, pathogenic variants) in prostate cancer-associated risk genes:

- Begin screening at age 40 y.
- Annual PSA and DRE.
- Men with a PSA level above the median for their age group are at higher risk for prostate cancer and aggressive prostate cancer. The higher above the median, the greater the risk.
- If PSA level is below age-adjusted median and no other indication for biopsy, repeat screening in 12 months.
- If PSA level is above age-adjusted median, recheck PSA in 6–12 months; if increased, consider extended pattern biopsy with mpMRI or TRUS-guidance.
- Upper limit age-adjusted median range PSA[38,39]:
    - Aged ≤49 y, PSA >1.5 ng/mL
    - Aged 50–59 y, PSA >2.0 ng/mL
    - Aged 60–69 y, PSA >2.5 ng/mL

Cheng HH, et al, 2019, *JNCCN*

Pancreatic cancer

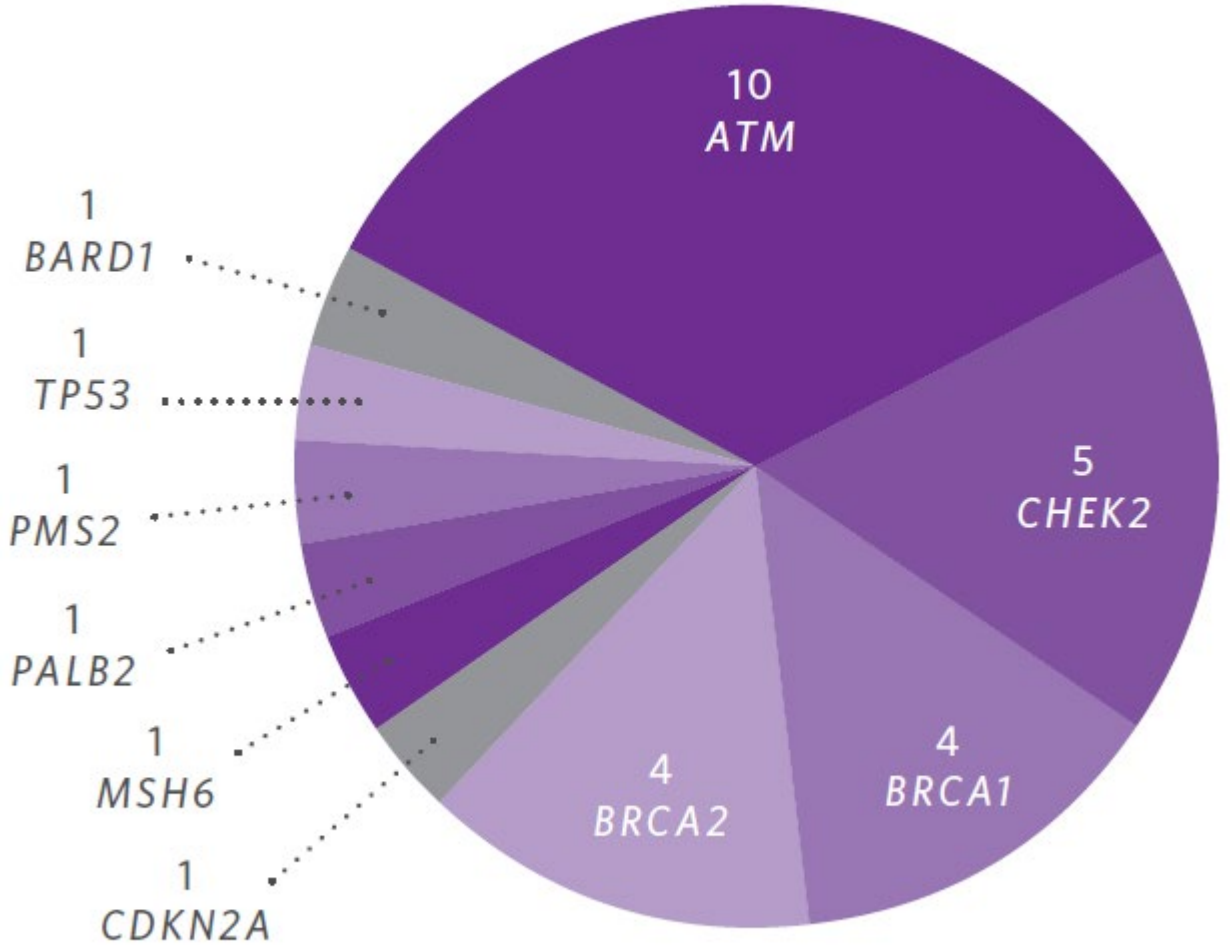
- 56,770 new cases in 2019
- Average lifetime risk is 1 in 65 (1.5%)
- 3rd leading cause of cancer death in US
- 90% diagnosed at late stage
  - 5 year survival = 8-10%
- Early diagnosis and detection of precursor lesions may decrease burden

SEER, 2018

How much pancreatic cancer is linked to germline variants in cancer susceptibility genes?

Prospective study of germline genetic testing in incident cases of pancreatic adenocarcinoma

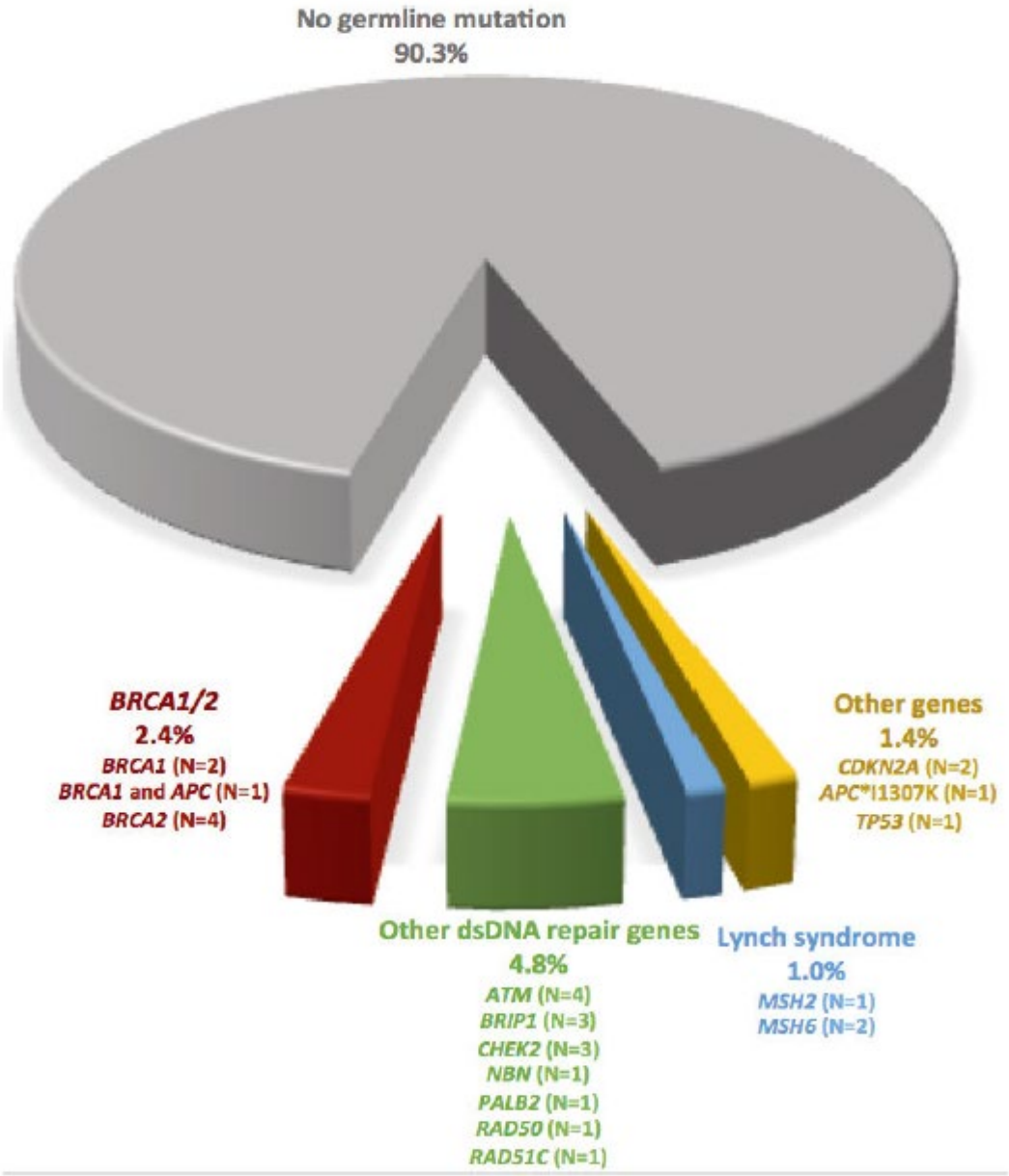
- Multi-center, prospective study of 298 unselected patients with PC
- 41/298 (14%) found to have a mutation in a cancer susceptibility gene
- 29/41 (71%) clinically actionable



Brand R, et al, 2018, *Cancer*

Germline cancer susceptibility variants in patients with resected pancreatic cancer

- 289 patients with PC, unselected
- 24 cancer susceptibility genes analyzed
- 10% found to have mutations

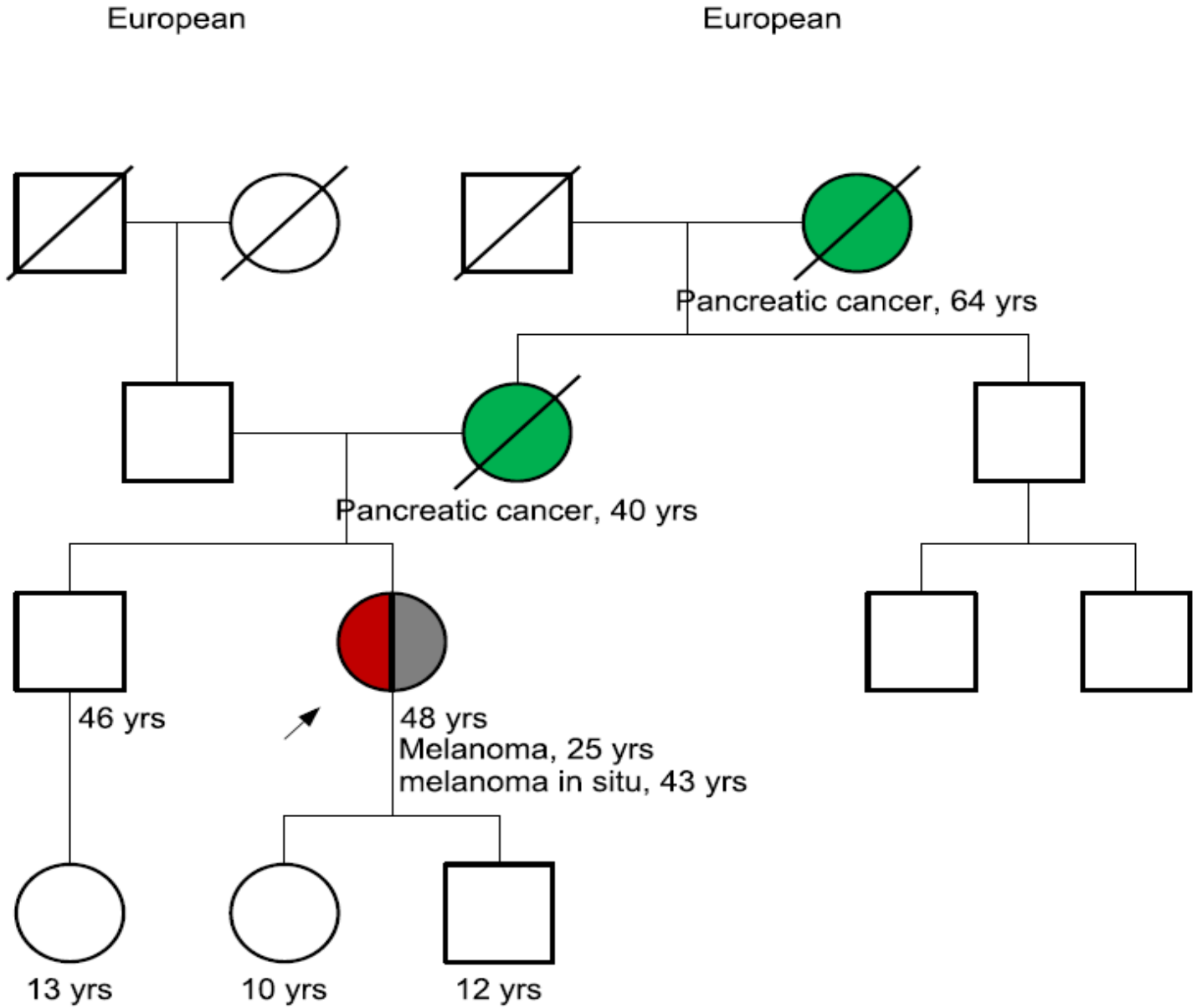


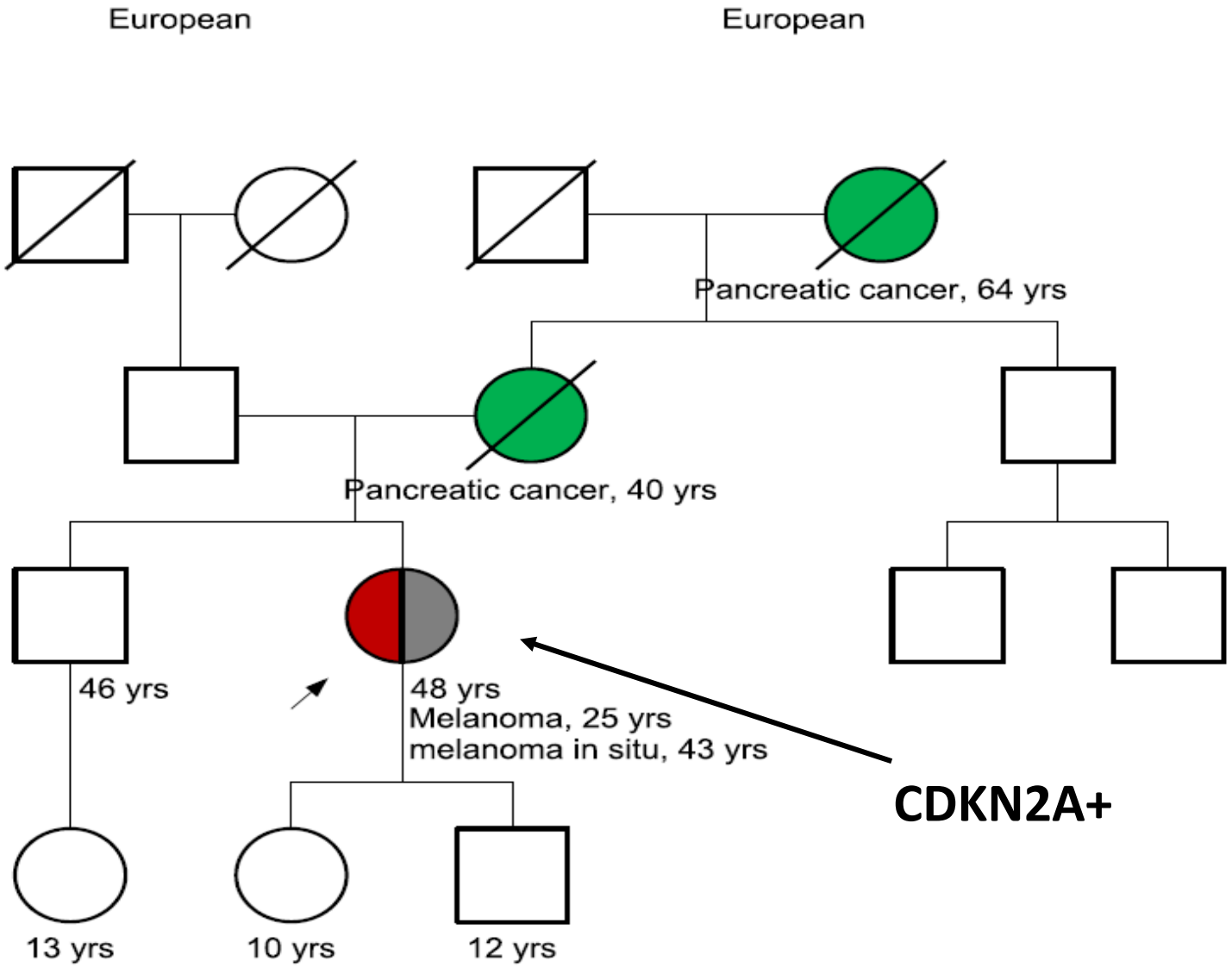
Yurgelun MB, et al, 2019, *Genet Med*

Risks for developing pancreatic cancer

Gene	Risk	Associated cancer(s)
ATM	Unclear	Breast, prostate
BRCA1	~2-5%	Breast, ovarian
BRCA2	~5-10%	Breast, ovarian, prostate, melanoma
CDKN2A	~15-20%	Melanoma, brain
MMR (Lynch syndrome)	~5%	Colon, endometrial, ovarian, gastric, small bowel, urinary tract, sebaceous skin tumors, CNS
PALB2	unclear	Breast
STK11	~11-36%	Breast, gynecologic, gastrointestinal

Pilarski R, 2019 ASCO Educational Book


European
European
Pancreatic cancer, 64 yrs
Pancreatic cancer, 40 yrs
46 yrs
48 yrs
Melanoma, 25 yrs
melanoma in situ, 43 yrs
13 yrs
10 yrs
12 yrs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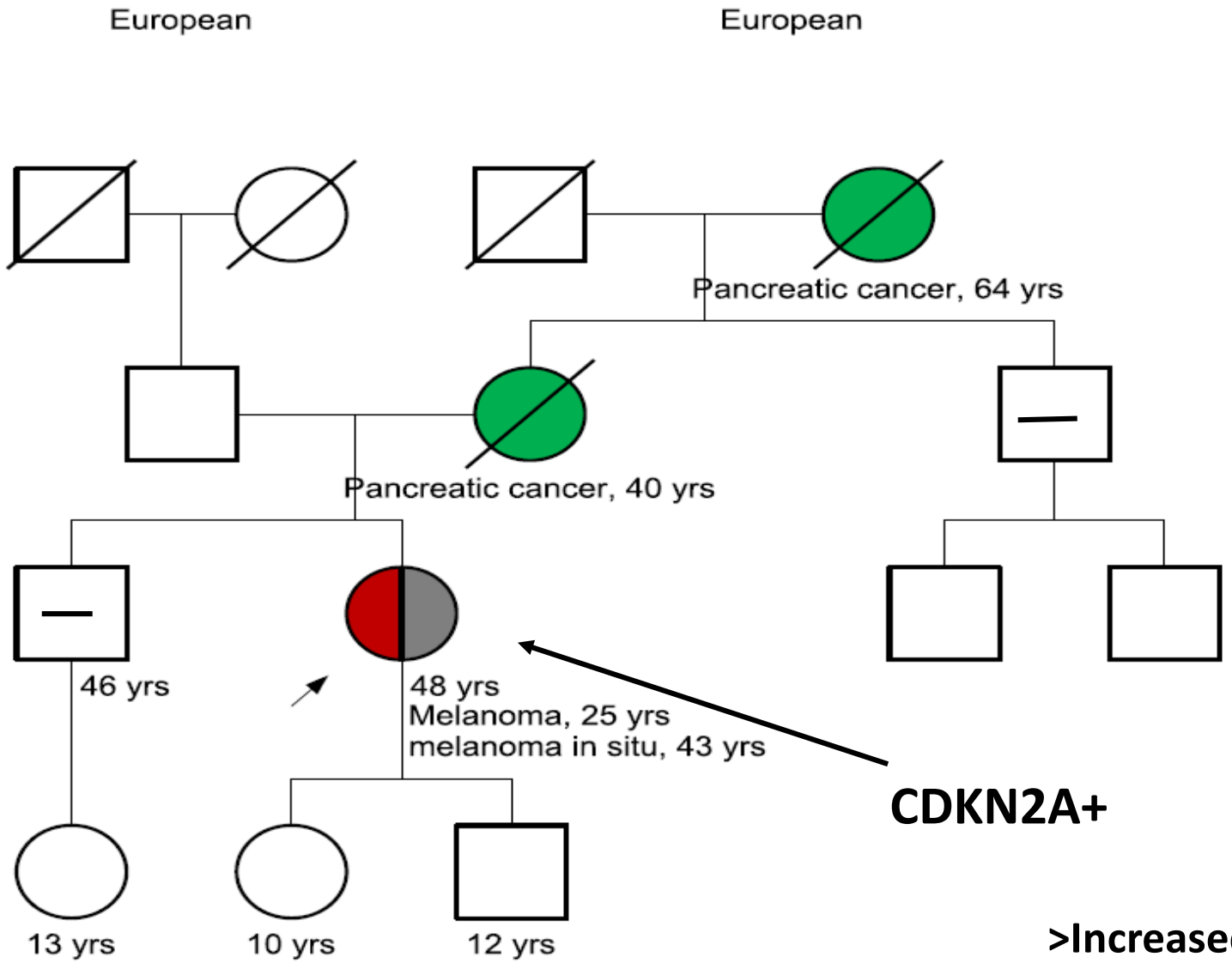
melanoma in situ, 43 yrs
CDKN2A+
13 yrs
10 yrs
12 yrs

CDKN2A

- Gene codes for two proteins, p16INKa and p14ARF
  - Mutations that affect the p16INKa protein are associated with melanoma and pancreatic cancer syndrome
    - Also referred to as Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome
    - Lifetime risk for developing melanoma is 28-67%
    - Lifetime risk for developing pancreatic cancer is approximately 17%
  - Mutations that affect p14ARF protein are associated with melanoma and neural tumors including astrocytoma, nerve sheath tumors
  - Medical management
    - Skin
      - Whole body skin exams with photography starting at age 10, every 6-12 months
    - Pancreas
      - Consider EUS/MRCP annually at age 50 or 10 years earlier than earliest age in family



CDKN2A+

>Increased risk for subsequent cancer

>Cascade testing

Pancreatic cancer screening in high risk individuals

- American College of Gastroenterology recommends screening for individuals with:
  - *STK11, CDKN2A* or pancreatitis gene mutations
  - *BRCA1/2, ATM, PALB2*, or MMR mutations with a 1st or 2nd degree relative with PC
  - Family history of two affected relatives with at least one being 1st degree
  - Methods:
    - Annual endoscopic ultrasound and/or MRI starting at age 50 or 10 years earlier than youngest case in the family (STK11 carriers begin @ 35)

- International Cancer of the Pancreas Screening Consortium (CAPS) recommends screening for individuals with:
  - *STK11* Mutation
  - *CDKN2A, BRCA1/2*, MMR mutations and 1st degree relative with PC
  - Anyone with two first degree relatives with PC, regardless of GT results
  - Methods:
    - EUS and MRCP; no consensus on optimal age to start screening or interval

Syngal S, et al, 2015, *Am J Gastro*; Canto MI, et al, 2014, *Gut*

Evidence for screening in high risk individuals

- CAPS Results
  - Preliminary data suggests survival benefit from surveillance
- Italian Association for the Study of the Pancreas (AISP) registry
  - Showed high rate of identification of early disease in high risk individuals with MRCP
- CAPS-5 study (NCT02000089)
  - Evaluate pancreatic juice for early cancer markers
  - Compare pancreas juice with pancreas cyst fluid
  - Time disease progression and prevalence

Canto MI et al, 2018, *Gastroenterology;* Paiella S et al, 2019, *AJGastroenterol*;

Implications of inherited Prostate and Pancreatic Cancer

- Targeted therapy
  - DNA Repair mutations
    - Platinum
    - PARP Inhibitors (i.e., olaparib, rucaparib)
  - MMR deficiency
    - Immunotherapy (i.e., pembrolizumab)
  - STK11
    - mTOR Inhibitors
- Risk for additional malignancies
  - Increase screening/prevention strategies
- Risk to relatives (cascade testing)
  - Personalize screening/prevention

Guidelines for Referral for Genetic Testing

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
***BRCA*-Related Breast and/or Ovarian Cancer Syndrome**

NCCN Guidelines Index
Table of Contents
Discussion

- **Personal history of pancreatic cancer[i]**
- **Personal history of metastatic prostate cancer[g]**
- **Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with**
  - **≥1 close blood relatives[e] with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer[g] at any age or breast cancer <50 y; or**
  - **≥2 close blood relatives[e] with breast, or prostate cancer (any grade) at any age; or**
  - **Ashkenazi Jewish ancestry[h]**

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www.NCCN.org (Genetic/Familial High Risk Assessment: Breast and Ovarian)

Genetic Counseling/Testing- Points to Consider

- GC / GT with a genetics provider (www.nsgc.org/findageneticcounselor)
  - Face to face
  - Telehealth
  - Telephone (Informed DNA, Genome Medical)
  - Through testing companies
- Direct to consumer
- Point of care testing with follow up GC for those testing + for a mutation
- Coordinated somatic/germline testing
- What genes/which panel to order?
- Informed consent?

Thank you!!

We will now take questions for our presenters. Please use the question box on the lower right to submit a question. Questions will be answered as time permits.

Thank you for joining this Association of American Cancer Institutes Physician Clinical Leadership Webinar. Information about this and other webinars can be found on our website at www.aaci-cancer.org.