Which genes increase breast cancer risks?

What are the cancer risks for each gene?

A/Prof Adrienne Sexton

Genetic counsellor, Epworth Freemasons

Acknowledgment of country

- I acknowledge the traditional custodians of the land on which we join this meeting today, the Wurundjeri people of the Kulin nation.
- I pay my respects to their Elders both past and present

Overview

- Breast cancer genes
  - Cancer risk assessment
  - What to look for in a family history
  - Guidelines
- Endometrial, ovarian and bowel cancer genes
- Adding polygenic risk into the picture
- Brief overview clinical genetics and genetic counselling
- When, where, how to refer

Current and future directions for genomic testing in breast cancer

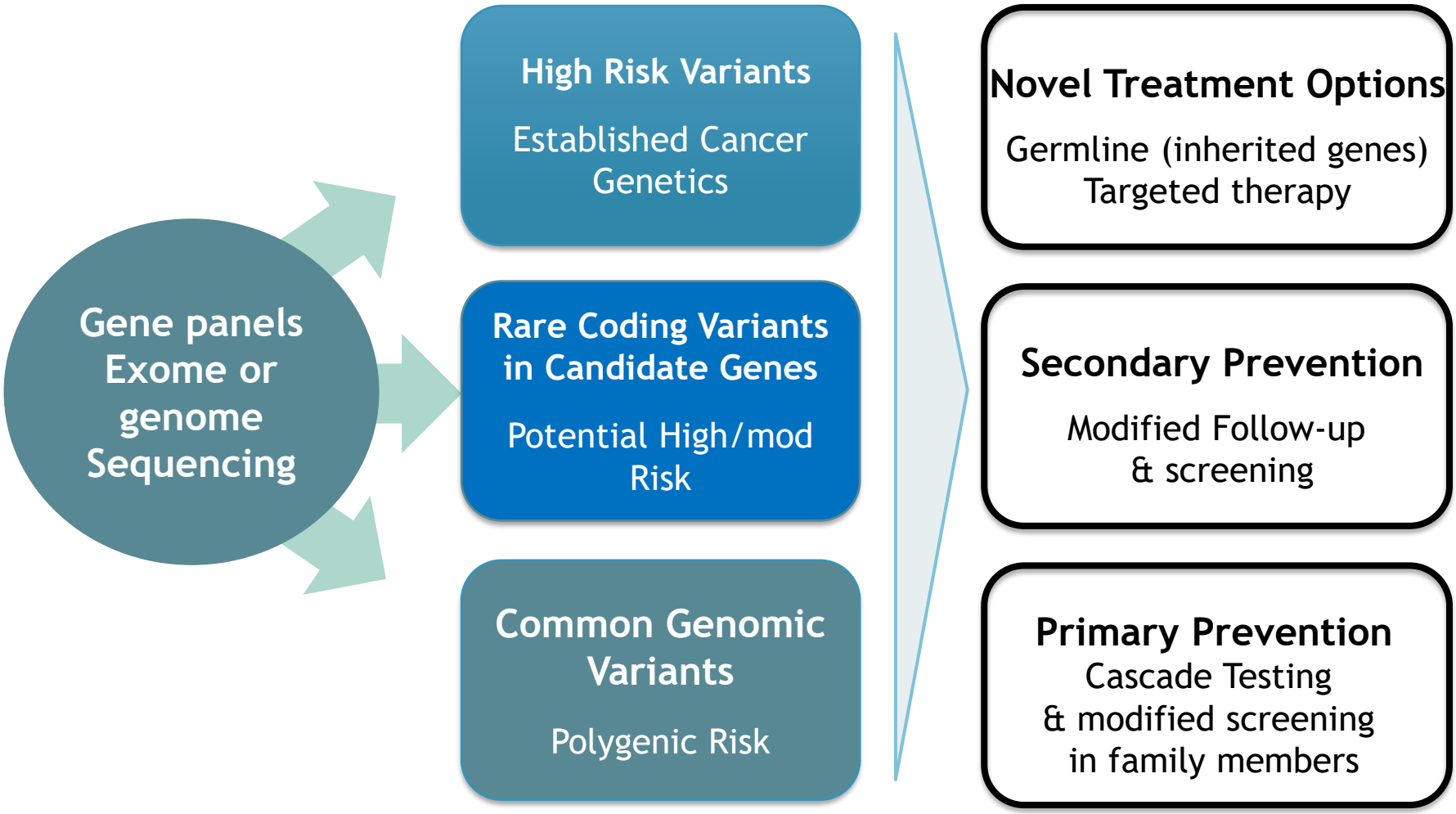
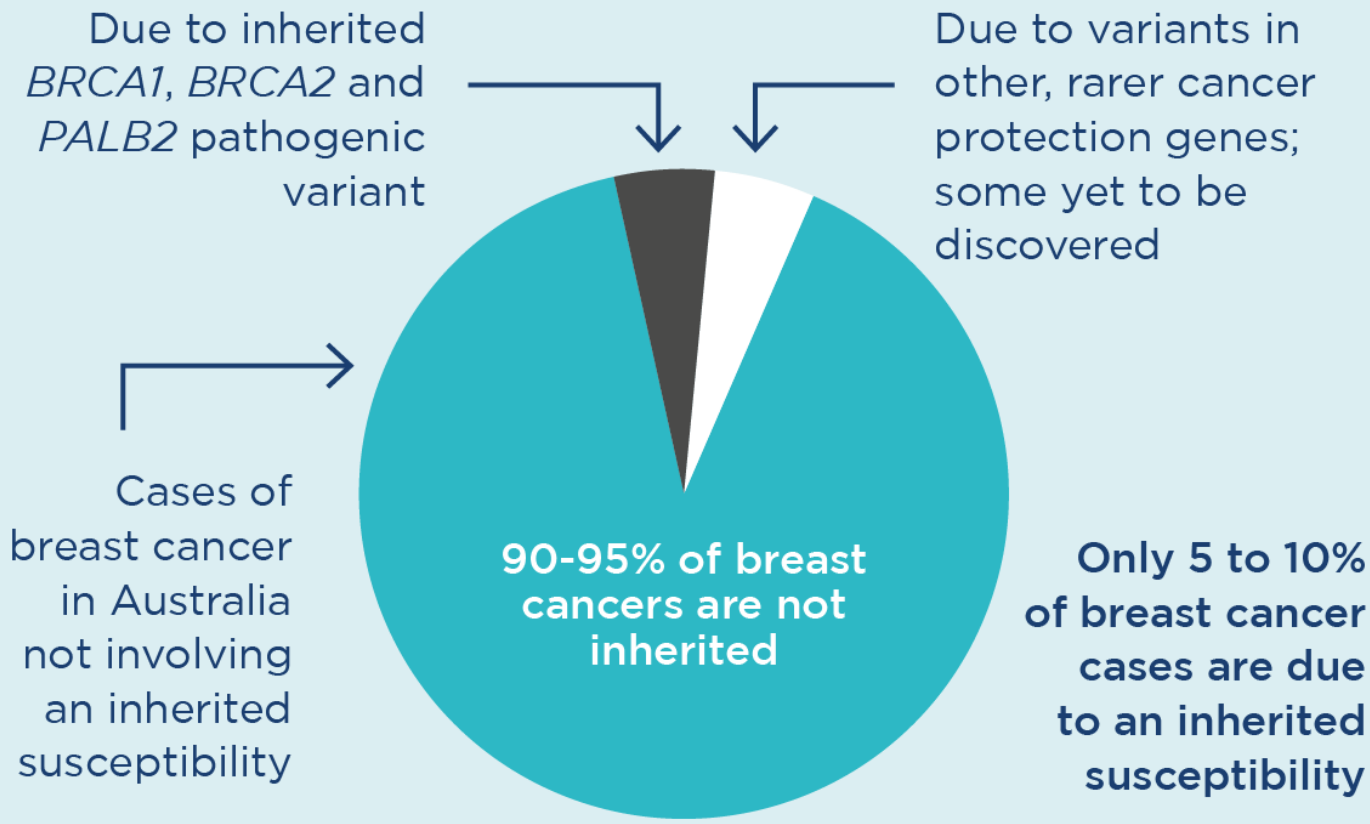
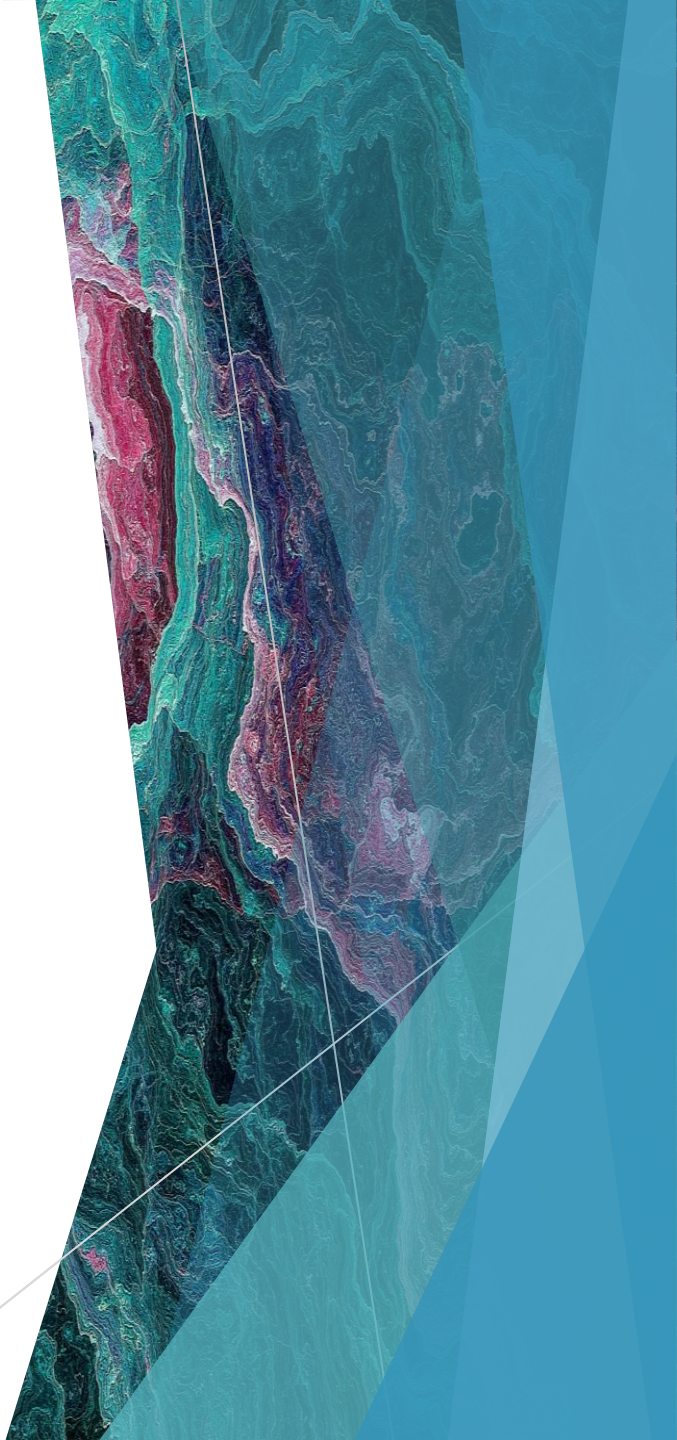


Figure 32.1:
Proportion of cases of breast cancers that involve an inherited susceptibility.



Inherited genetic predispositions for breast cancer

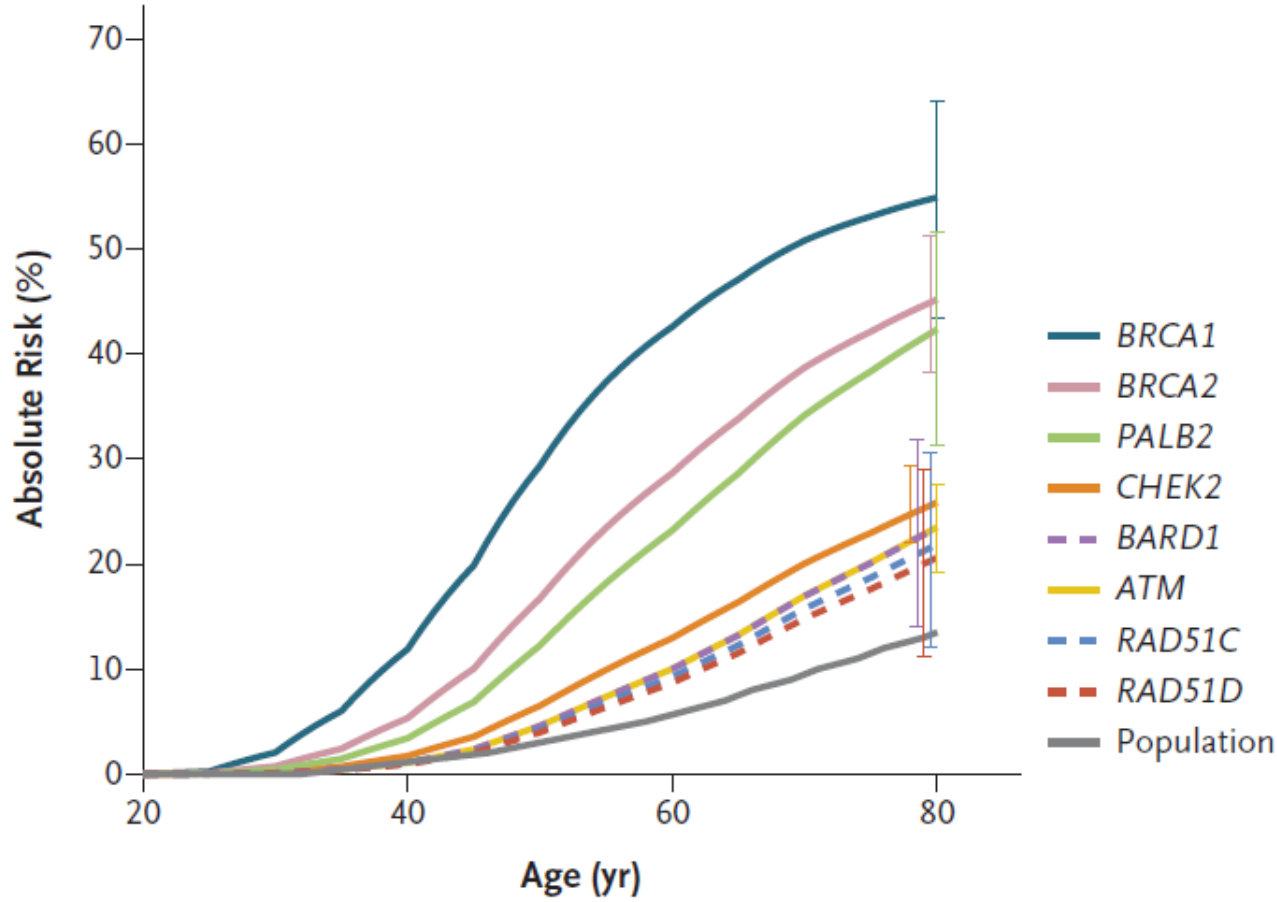
- >10 genes and growing…
- Mostly relevant for adults not children
- Syndromic or non-syndromic
- Dominantly inherited
- New technology allow testing of many genes simultaneously
  - Needs expert clinical lab scientists
  - MDT geneticists, genetic counsellors, bioinformatics scientists, colorectal specialists, etc
  - DNA variants of uncertain significance are often found



Inherited causes of breast cancer. Overview:

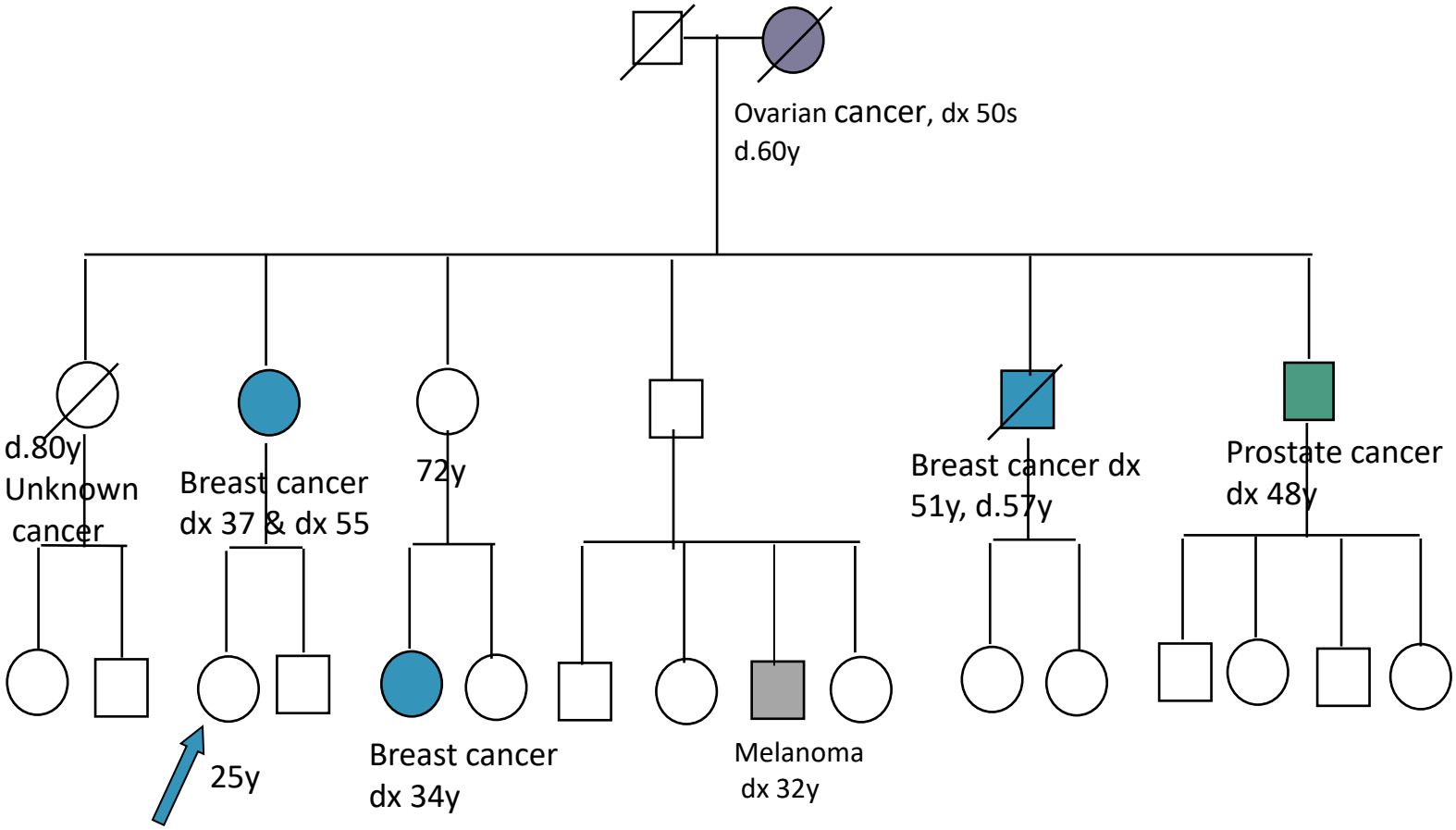
High risk	BRCA1 & BRCA2 – high risk breast and ovarian cancer
	PALB2 – high risk breast and moderate risk ovarian cancer
	CDH1 – high risk gastric and breast cancer
	Li Fraumeni syndrome (TP53) – high risk breast cancer, sarcoma, multiple cancers
	Peutz-Jegher Syndrome (STK11) – high risk breast cancer, bowel polyps, multiple cancer types
Moderate risk	ATM – moderate-high breast cancer
	CHEK2 – moderate risk breast cancer
	BARD1 - low-moderate risk breast cancer
	Familial breast cancer (polygenic/multifactorial)

Hu et al., A population-based study of genes previously implicated in breast cancer.
NEJM. 2021 384(5):440-51



Slide courtesy of Prof Paul James, Parkville FCC

3-generation family history



Family history, pathology, criteria, algorithms for risk assessment

From the breast cancer model, based on the woman's information, the mutation carrier probability for a pathogenic v

- BRCA1 is 10.41%
- BRCA2 is 31.95%
- BRCA1 or BRCA2 is 42.36%
- PALB2 is 0.55%
- CHEK2 is 1.17%
- ATM is 0.40%
- BARD1 is 0.10%

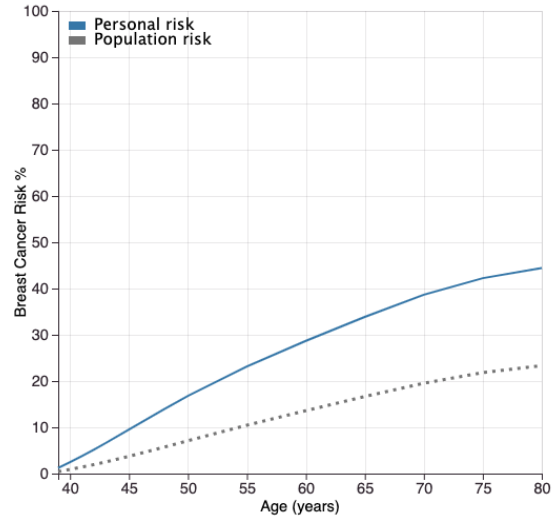
based on the woman's information, the mutation carrier probability for a pathogenic

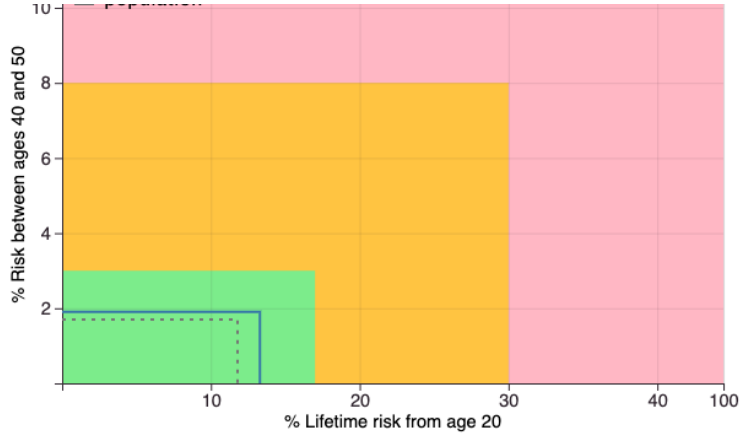
bility for a pathogenic variant in:
BRCA2, PALB2, CHEK2, ATM, BARD1, RAD51D, RAD51C or BRIP1 genes is 45.07%
BRCA2, PALB2, CHEK2, ATM, BARD1, RAD51D, RAD51C or BRIP1 genes is 54.93%

Personal Risk of Developing Breast Cancer Compared to the Population

The woman's risk of developing **breast cancer by the age of 80 is 44.4%**, compared to the **average population risk of 23.3%**.

In other words, about 444 out of 1000 women with these risk factors will develop breast cancer by the age of 80, compared to an average woman where 233 in 1000 will develop breast cancer.





The woman's risk between ages 40 and 50 of having breast cancer is 1.9%. According to the NICE guidelines† the woman would be in the **population** risk category.

	Near population risk	Moderate risk	High risk
Lifetime risk from age 20	**Less than 17%**	17% or greater but less than 30%	30% or greater
Risk between ages 40 and 50	**Less than 3%**	3% or greater to 8%	Greater than 8%

†NICE Guidelines

Probability of a heritable pathogenic variant

Factor	Gene	Probability of a heritable pathogenic variant
Unselected breast cancer	Combined probability 12 genes*	5% [2]
Distant metastatic breast cancer	Combined probability 12 genes*	14.7% (age <50 years)[3] 8.4% (age 51-60 years)[3] 6.9% (age 61-70 years)[3]
Invasive breast cancer ≤40 years	BRCA1 + BRCA2	12.3%[4]
Triple negative breast cancer (TNBC)	Combined probability 17 genes** BRCA1 + BRCA2	11.2% (any age)[5] 11.4-16.8% (age ≤ 60 years)[6, 7]
Male breast cancer	BRCA1 or BRCA2	11%[8]
Isolated breast cancer <30 years	TP53	2-8%[9]
Female breast cancer >46 years with no Chompret criteria (see TP53 genetic testing)	TP53	0.11%[9]
Unselected lobular breast cancer	CDH1	0.34%[10]
Bilateral invasive lobular carcinoma age <70 years	CDH1	7%[10]
Clinical diagnosis of NF1	NF1	>95%[11]
Meets revised PTEN hamartoma tumour syndrome clinical diagnosis criteria	PTEN	Up to 90%[12]
Clinical diagnosis Peutz-Jeghers syndrome	STK11	>90%[13]

BRCA1, BRCA2, PALB2 genes & associated risks

Gene variant	Breast & ovarian risk to age 80 (women)	Prostate or breast risk to age 70 (men)	Lifetime risk pancreatic
BRCA1	About 70% for breast cancer About 45% for ovarian or fallopian tube cancer	1% breast cancer 9% prostate cancer	Slightly increased risk
BRCA2	About 70% for breast cancer About 15% for ovarian or fallopian tube cancer	7% breast cancer 15% prostate cancer	Increased, but less than 5%
PALB2	About 55% for breast cancer About 5% for ovarian or fallopian tube cancer	1% breast cancer	2-3% risk pancreatic cancer
Population risk	12% for breast cancer 1% for ovarian or fallopian tube cancer	Much less than 1% breast cancer 5% for prostate cancer	Less than 1% for men

Information extracted from eviQ Risk Management Guidelines. Adapted from : Centre for Genetics Education

Cancer/tumour type	Recommendations	
Breast	**Surgical^**	• Consider bilateral risk-reducing mastectomy • The appropriateness and optimal timing should be individualised based on patient preference and risk trajectory (from CanRisk or iPrevent)
	Surveillance	• Begin screening from age 25-30 years[6] • Optimal timing should be individualised based on patient preference and risk trajectory (from CanRisk or iPrevent)
		Age / **Strategy and frequency**
		Under age 40 years / Annual MRI (US if MRI not possible)
		40-60 years / Annual MRI + MMG (MMG + US if MRI not possible)
		Over age 60 years / Annual MMG (consider MRI or US if over age 60 years with dense breast tissue)
		Pregnant / No MRI or MMG, consider US and CBE

	Risk-reducing medication	• Consider medication to reduce risk of developing breast cancer for women not planning bilateral mastectomy within 3 years:
		  ◦ Pre-menopausal women may consider tamoxifen
		  ◦ Post-menopausal women may consider raloxifene, aromatase inhibitors or tamoxifen
		• See COSA - Medications to lower the risk of breast cancer: clinician guide and offer COSA – Medications to lower the risk of breast cancer: patient guide

Ovarian/ fallopian tube	**Surgical (BRCA1)^^**	• Recommend RRSO between the age of 35-40 years[7] with peritoneal lavage and SEE-FIM histological examination.^^^ • Optimal timing should be individualised based on patient preference and risk trajectory (from CanRisk)
	Surgical (BRCA2)^^	• Recommend RRSO between the age of 40-45 years[7] with peritoneal lavage and SEE-FIM histological examination.^^^ • Optimal timing should be individualised based on patient preference and risk trajectory (from CanRisk)
	Surveillance	Do not offer serum CA125 and/or transvaginal ultrasound (TVU)

CHEK2 gene - 1 in every 75 people have a cancer risk variant in this gene

CHEK2 – risk management (female)

Lifetime risk of cancer/tumour

CHEK2 risk estimates cover a broad range due to the influence of modifying factors. Individualised risk requires formal assessment using a validated risk prediction tool (CanRisk).[4] See Risk assessment below.

Cancer/tumour type	Estimated average risk for CHEK2 pathogenic variant carrier	General female population risk by age 80 years
Breast (female)	Range 15-40%[2]	11%*

**Source: Australian Institute of Health and Welfare (AIHW) 2024 Cancer Data in Australia; Canberra: AIHW. <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-risk-data-visualisation>. (2020 data, unadjusted for competing mortality)*

Risk assessment

Most women with a CHEK2 pathogenic variant will be at moderately increased lifetime risk of breast cancer.[5, 6, 7, 2] For women with a CHEK2 pathogenic variant and family history of breast cancer, risk should be formally assessed using a validated risk prediction tool such as CanRisk.[4] Moderate-risk management applies when the lifetime risk from age 20 years is greater than 17% but less than 30%. High-risk management applies when the lifetime risk from age 20 years is 30% or greater.[8]

Risk management varies, depending on:

- Family history
- Age
- Specific DNA variant

CHEK2 – risk management (female)

Breast (female)		Strategy and frequency	
		Moderate lifetime^ risk individuals (see Risk assessment above)	**High lifetime risk^ individuals** (see Risk assessment above)
	Surgical	• Risk-reducing mastectomy is not recommended for CHEK2 pathogenic variant carriers assessed as having a **moderate lifetime risk** of breast cancer	• Discuss bilateral risk-reducing mastectomy for CHEK2 pathogenic variant carriers assessed as having a **high lifetime risk** of breast cancer
	Surveillance **All ages**	• Breast awareness with prompt reporting to GP of persistent or unusual changes	• Breast awareness with prompt reporting to GP of persistent or unusual changes
	Surveillance **Under age 40 years**	• No routine screening recommended	• Assess 10-year breast cancer risk using a validated risk model such as CanRisk • Annual breast MRI# if screening is advised
	Surveillance **Age 40-50 years**	• Recommend annual MMG • Assess 10-year breast cancer risk using a validated risk model such as CanRisk • Consider annual breast MRI# if 10-year risk is >5%	• Recommend annual breast MRI# + annual MMG (MMG + US if MRI not possible)
	Surveillance **Age 50-60 years**	• Recommend MMG every second year • Consider annual MMG or MRI# if concerning features e.g. dense breast tissue	• Recommend annual breast MRI# + annual MMG (MMG + US if MRI not possible)
	Surveillance **Over age 60 years**	• Recommend MMG every second year • Consider other imaging modalities depending on individual risk factors, such as breast density	• Recommend annual MMG • Consider annual breast MRI if over age 60 years with dense breast tissue (US if MRI not possible)
	Surveillance in pregnancy	• No MRI or MMG, consider US or CBE	
	Risk-reducing medication	• Consider use of medication to reduce risk of developing breast cancer for women not planning bilateral mastectomy within 3 years: ◦ Pre-menopausal women may consider tamoxifen ◦ Post-menopausal women may consider raloxifene, aromatase inhibitors or tamoxifen • See COSA – Medications to lower the risk of breast cancer: clinician guide and offer COSA – Medications to lower the risk of breast cancer: patient guide	

ATM gene - 1 in every 250 people have a cancer risk variant in this gene

ATM (monoallelic pathogenic variants) – risk management

Lifetime risk of cancer/tumour

Cancer/tumour type	Risk for ATM pathogenic variant carriers		General population risk*
Breast (female)	ATM c.7271T>G	Age specific cumulative risk: 52% (95% CI 28-80%) to age 70 years[2]	7.6% to age 70 years
	All other ATM pathogenic variants (excluding c.7271T>G)	May be increased**	
Pancreatic	All ATM pathogenic variants	9.5% to age 80 years[6]***	1.2% to age 80 years
Prostate	All ATM pathogenic variants	Increased but not well quantified****	8.6% to age 70 years 16.7% to age 80 years

* *Source: Australian Institute of Health and Welfare (AIHW) 2024 Cancer Data in Australia; Canberra: AIHW. <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-risk-data-visualisation>. (2020 data, unadjusted for competing mortality).*

** *Individualised risk requires formal assessment using a validated risk prediction tool (e.g. CanRisk).*

*** *Based on 130 families, however predominantly European ancestry and variant details not provided.*[6]

**** *OR 4.4 (95% CI 2.0 to 9.5)* [7] *(studies of Europeans only).*

Risk management varies, depending on:

- Family history risk assessment
- Age
- Specific DNA variant

ATM (monoallelic pathogenic variants) – risk management

Cancer/tumour type	Recommendations			
Breast (female)		**Strategy and frequency**		
		Moderate lifetime risk individuals^ **(Other ATM pathogenic variant carriers excluding c.7271T>G)**	**High lifetime risk individuals^** **(Other ATM pathogenic variant carriers excluding c.7271T>G)**	**High lifetime risk individuals^** **(ATM c.7271T>G pathogenic variant carriers)**
	Surgical	• Risk reducing mastectomy is not recommended for ATM pathogenic variant carriers assessed as having a **moderate lifetime risk** of breast cancer	• Consider bilateral risk-reducing mastectomy for ATM pathogenic variant carriers assessed as having a **high lifetime risk** of breast cancer • The appropriateness and optimal timing should be individualised based on patient preference and risk trajectory	• Consider bilateral risk-reducing mastectomy for ATM c.7271T>G pathogenic variant carriers • The appropriateness and optimal timing should be individualised based on patient preference and risk trajectory
	Surveillance **All ages**	• Breast awareness with prompt reporting to GP of persistent or unusual changes	• Breast awareness with prompt reporting to GP of persistent or unusual changes	• Breast awareness with prompt reporting to GP of persistent or unusual changes
	Surveillance **Age 30-40 years**	• No routine screening recommended	• Assess 10-year breast cancer risk using a validated risk model such as CanRisk^ • Annual breast MRI# if screening is advised	• Recommend annual breast MRI# (US if MRI not possible) • In families with breast cancer diagnosed under age 35 years individualised screening recommendations may apply. Otherwise screening should start at age 30 years
	Surveillance **Age 40-50 years**	• Recommend annual MMG • Assess 10-year breast cancer risk using a validated risk model such as CanRisk • Consider annual breast MRI# if 10-year risk is >5%	• Recommend annual breast MRI# + annual MMG (MMG + US if MRI not possible)	• Recommend annual breast MRI# + annual MMG (MMG + US if MRI not possible)
	Surveillance	• Recommend MMG every	• Recommend annual breast	• Recommend annual breast

Multifactorial and polygenic inheritance

- POLYGENIC RISK = Many genes, additive combinations of variations in our 20,000 genes

- More data needed on
  - Variants in different ancestries/populations
  - Variants per breast cancer sub-type

Risk depends on combination of :

- Major gene cause (rare)
- Polygenic profile (common variants)
- Environmental and biological factors
- Epigenetics

Non-genetic risk factors:

- Age
- Sex
- Breast density
- Smoking
- High alcohol intake
- Obesity
- HRT use

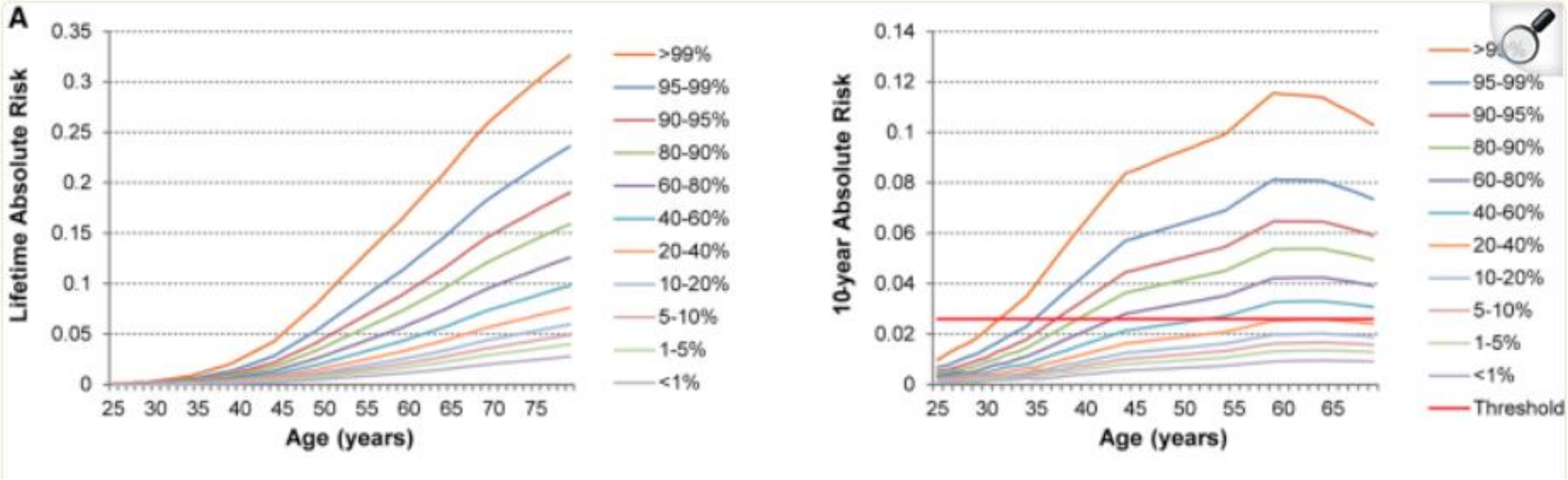
Clinical use of common variants for polygenic risk

1. High risk families (based on family history) where no major gene cause has been found

2. Population – risk stratification for screening advice

3. People with cancer – tumour profiling for personalised treatment

Polygenic risk stratification



Maddavat et al. Am J Hum Genet
. 2018 Dec 13;104(1):21–34. doi: 10.1016/j.ajhg.2018.11.002

JAMA Network Open

Original Investigation | Oncology

Association of a Polygenic Risk Score With Breast Cancer Among Women Carriers of High- and Moderate-Risk Breast Cancer Genes

Shannon Gallagher, MPH; Elisha Hughes, PhD; Susanne Wagner, PhD; Placede Tshiaba, MS; Eric Rosenthal, PhD, MSc; Benjamin B. Roa, PhD; Allison W. Kurian, MD; Susan M. Domchek, MD; Judy Garber, MD, MPH; Johnathan Lancaster, MD, PhD; Jeffrey N. Weitzel, MD; Alexander Gutin, PhD; Jerry S. Lanchbury, PhD; Mark Robson, MD

152,000 Clinical tests from Myriad
33,000 BC, 119,000 Unaffected
86 SNP PRS + 25 BC Gene panel
9802 carriers of a PV

Measured the average risk and modification from the PRS

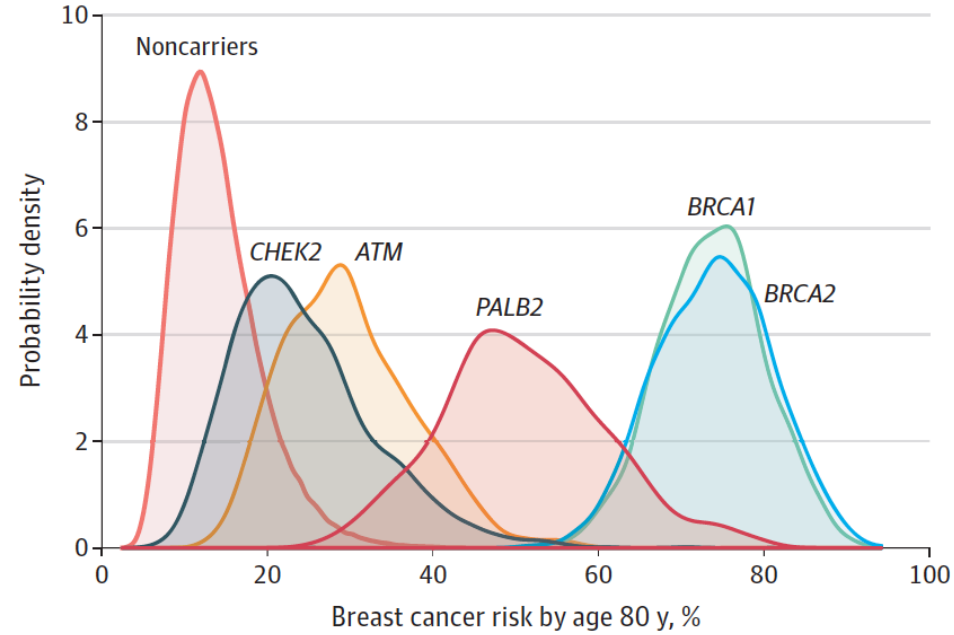


Table 4. Estimated Lifetime Breast Cancer Risk to Age 80 Years and Modification by an 86-SNV Score

Gene[a]	Gene-based risk, %	Adjusted lifetime risk, %				
		Minimum	Quintile 1	Median	Quintile 3	Maximum
ATM[31]	28.2	12.9	23.9	29.0	34.7	58.3
BRCA1[31]	73.5	53.1	69.4	73.8	77.9	91.5
BRCA2[31]	73.8	50.8	69.0	74.2	78.9	94.2
CHEK2[17]	22.1	6.6	18.1	23.0	29.1	70.6
PALB2[31]	50.1	26.2	44.4	50.3	57.3	79.2
Noncarriers[32,33]	12.7	2.5	10.4	13.2	16.9	62.4

Abbreviation: SNV, single-nucleotide variant.

[a] References denote sources of gene-based risk.

Slide courtesy of Prof Paul James, Parkville FCC

Genes for ovarian, bowel and endometrial cancer:

HIGH RISK GENES:

Lynch Syndrome (HNPCC) – bowel, endometrial, ovarian cancer

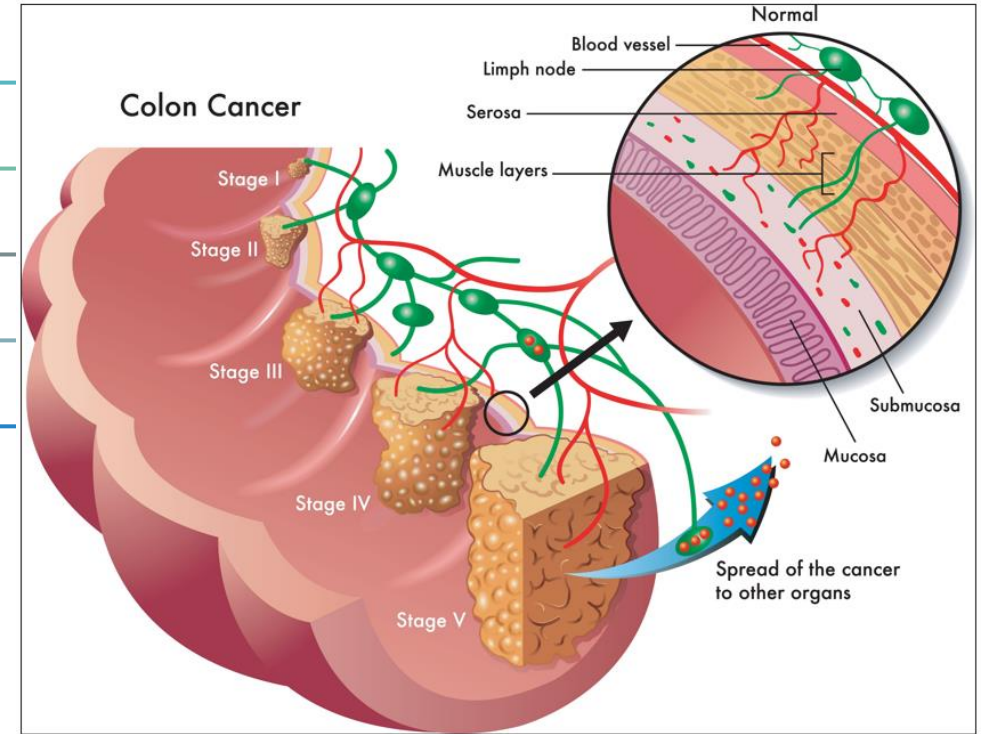
MYH-Associated Polyposis (MAP) – bowel cancer, bowel polyps

MODERATE RISK GENES:

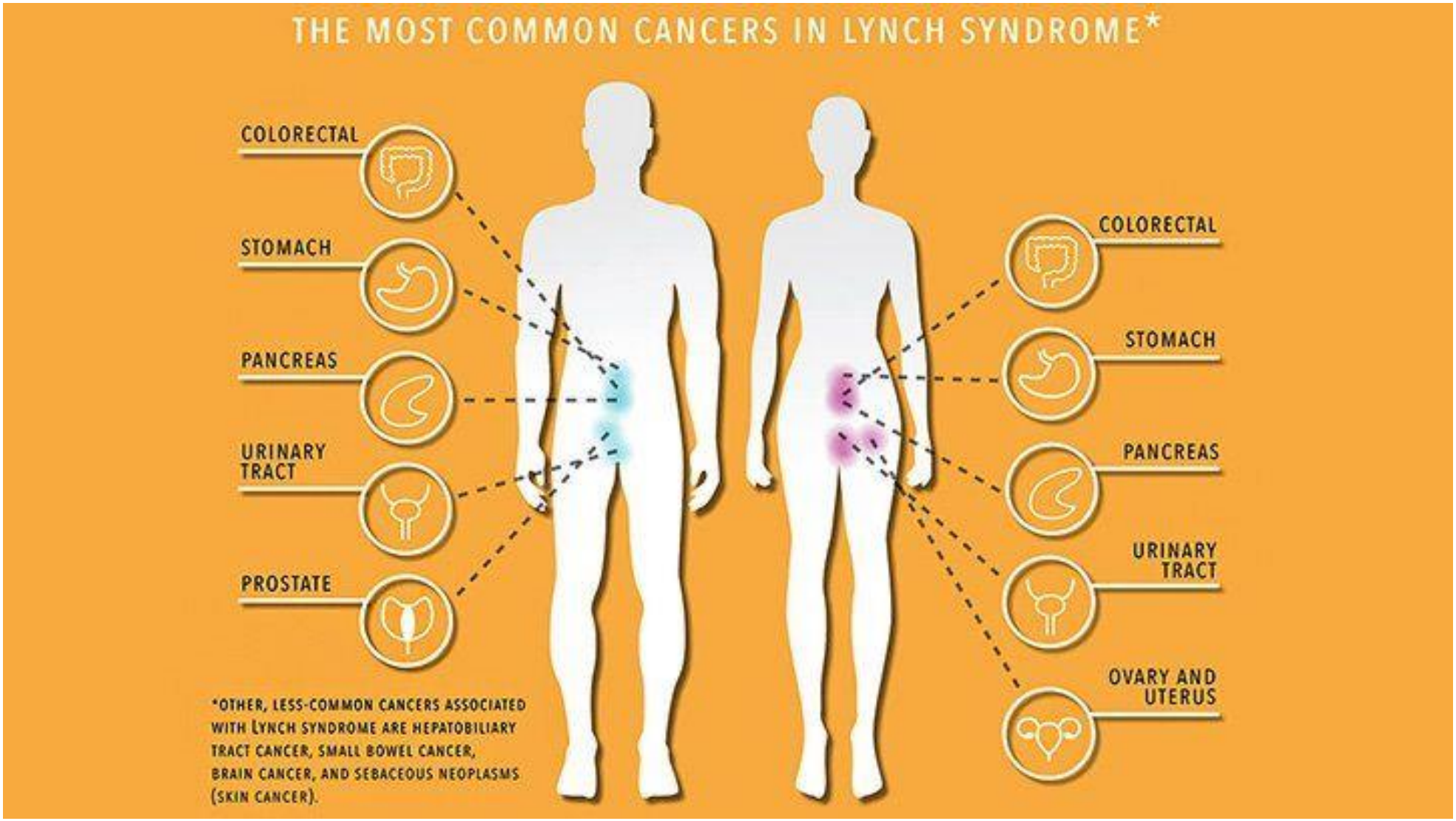
BRIP1 - ovarian cancer

RAD51C & RAD51D - ovarian cancer

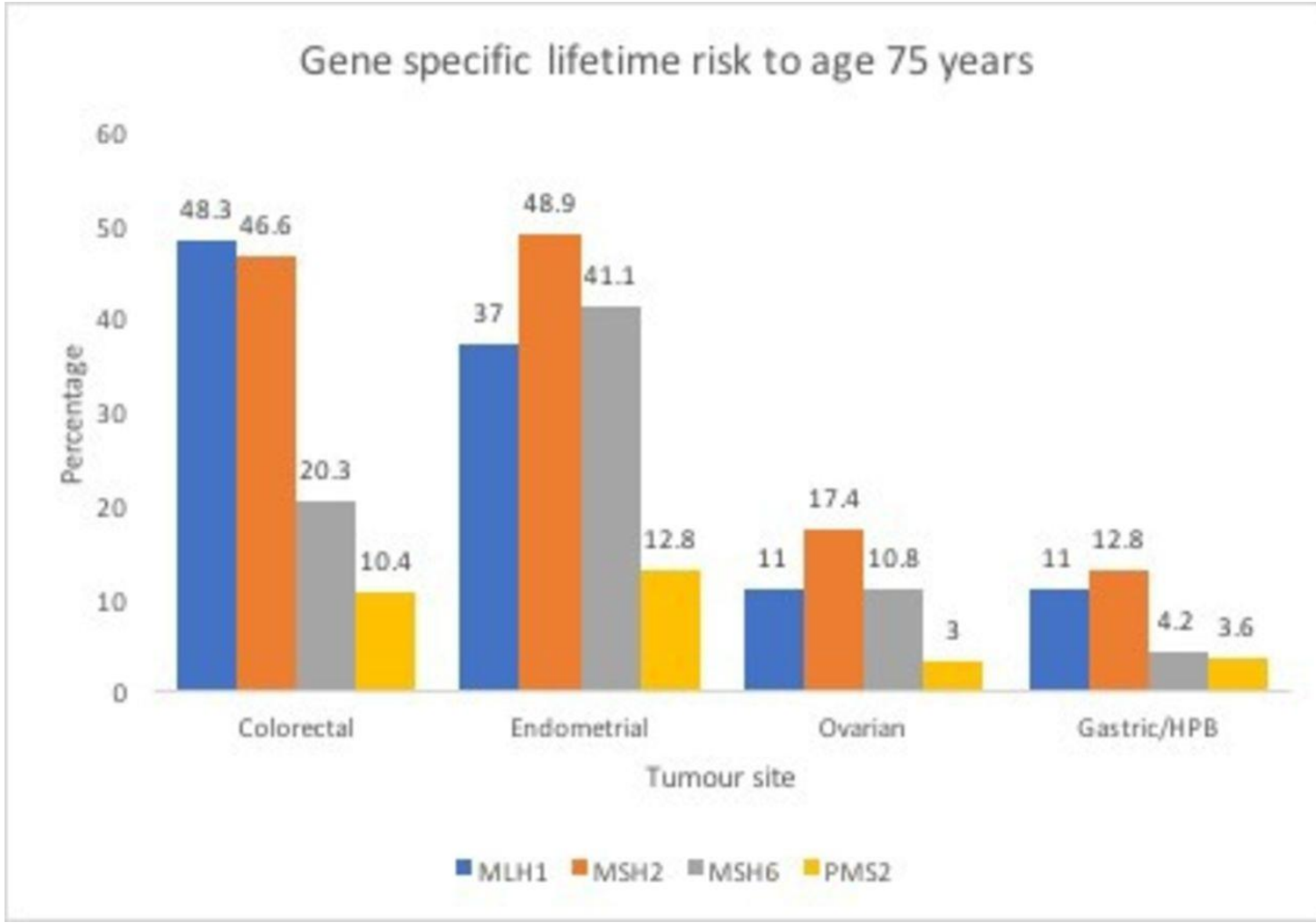
POLE & POLD1 - endometrial cancer , bowel polyps



Lynch syndrome 1 in 300 people



Lynch syndrome: Gene-specific lifetime risks



Penelope Edwards, and Kevin J Monahan Frontline Gastroenterol 2022;13:e80-e87

FG

If gene positive: Prevention & screening !

Cancer/ tumour type	Recommendations		www.eviq.org.au
Colorectal	**Surgical**	Consider subtotal colectomy in selected individuals	
		Age	**Strategy and frequency**
	Surveillance MLH1/MSH2	From age 25 years[5]	• Colonoscopy every 1 to 2 years
	Surveillance MSH6/PMS2	From age 35 years[5]	• Colonoscopy every 1 to 2 years • Review frequency of colonoscopy at age 60 years with a view to reducing frequency
	Risk-reducing medication	Unless contraindicated, aspirin should be actively considered to reduce the risk of colorectal cancer. A low dose (100–300 mg per day) is recommended from the commencement of colonoscopy screening	
Endometrial	**Surgical** MLH1/MSH2/MSH6	Recommend hysterectomy after childbearing complete or from age 40 years	
	Surgical PMS2	Recommend hysterectomy after childbearing complete or from age 50 years	
	Surveillance	There is no evidence for transvaginal ultrasound (TVU) and/or aspiration biopsy	
Ovarian	**Surgical**	• Consider risk-reducing salpingo-oophorectomy (RRSO) at time of risk-reducing hysterectomy • Recommend menopausal hormone therapy (MHT) at the time of RRSO and continue until the usual time of menopause	
	Surveillance	Do not offer serum CA125 and/or transvaginal ultrasound (TVU). See Cancer Australia for further information	
Gastric	**Surveillance**	• Consider 2nd yearly gastroscopy from age 30 years in families with gastric cancer or those at high ethnic risk e.g. Chinese, Korean, Chilean and Japanese • Screen for *Helicobacter pylori* and gastritis	

Referring to a Genetics/Familial Cancer Clinic

Consider:

- Personal history
- Family history
- Pathology indications
- Level of anxiety or interest

- Some tests are covered by medicare or clinic
- Patient can pay for gene test, eg. ~$450-$600 depending on how many genes

Indications for referral – breast cancer:

Epworth private genetic counselling service: All referrals welcome

Public hospital FCCs – high risk patients/families

Eg.:

- Breast cancer dx<40y or triple negative pathology <60y
- Breast cancer with family history of :
  - Multiple relatives with breast cancer
  - Relative with ovarian cancer
  - Male breast cancer
  - Ashkenazi Jewish ancestry and family history of breast cancer
  - Bilateral breast cancer (first dx <50)
  - Sarcoma, brain cancer, young age leukaemia
- Breast and ovarian cancer in the same person
- Lobular breast cancer and family history of diffuse gastric cancer
- Breast and thyroid cancer in the same person

Indications for referral – colorectal cancer:

Epworth private genetic counselling service: All referrals welcome

Public hospital FCCs – high risk patients/families

Eg.:

- Multiple bowel polyps (adenomas/hyperplastic) >10 polyps
- Colorectal or endometrial cancer with abnormal IHC results
- Colorectal cancer < 40 years of age
- More than one colorectal or endometrial primary tumour
- Colorectal cancer plus history of another cancer (*eg. gastric, endometrial, ovarian, hepatobiliary, ureter/renal angle, small intestine, sebaceous tumours*

Genetic counselling for panel tests

- Explore personal/family experience of cancer
- Beliefs, motivations, anxiety, grief
- Informed consent
  - Having gene problem does NOT mean cancer will develop, but risks are higher
  - Unexpected findings with known cancer risk (rare)
  - Possible uncertain findings (these are frequent!)
  - Implications for self
  - Implications for relatives
  - Insurance issues
- Coping and support
- Prenatal and IVF testing options
- Referrals for management of cancer risk
- Assistance with family communication about genetic risk

Summary

- BRCA1/2, PALB2, ATM, CHEK2 are the most common causes of inherited breast cancer risk (and ovarian risk for BRCA1/2, PALB2).
- Lynch syndrome is the most common cause of inherited bowel and endometrial cancer risk
- Screening and prevention for genetic cancer risk starts at young age
- A main goal of familial cancer clinics is risk assessment, provision of management advice, counselling, support resources, and informing relatives
- Family history is an important tool, plus pathology records
- Improved genetic test access and methods, and treatment-focussed testing

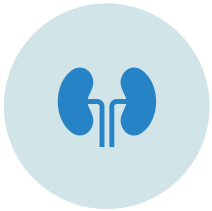
Thank you to:
- Jean Hailes for Women's Health
- Epworth Freemasons & Epworth Foundation
- Prof Ingrid Winship

Email: Adrienne.sexton@epworth.org.au

- **Other resources:**
- https://www.eviq.org.au/cancer-genetics
- Eviq cancer genetics criteria and guidelines www.eviq.org.au
- Centre for Genetics Education (NSW) www.genetics.edu.au
- Genetic Support Network of Victoria
- Cancer Council of Victoria (specific support for inherited cancer)

Extra slides

Clinical genetics & genetic counselling



Specialised clinics in breast, bowel, endocrine and rare cancers

Risk assessment:

likelihood of carrying a gene variant and/or developing specific cancers

Genetic counselling and testing options

Recommendations for risk management

Psychosocial support for patients and their families affected by familial cancer syndromes

Help informing relatives about a genetic condition

Which genes lack evidence for including on gene panels?

Consistent large-scale evidence indicates:

No Significant Risk:

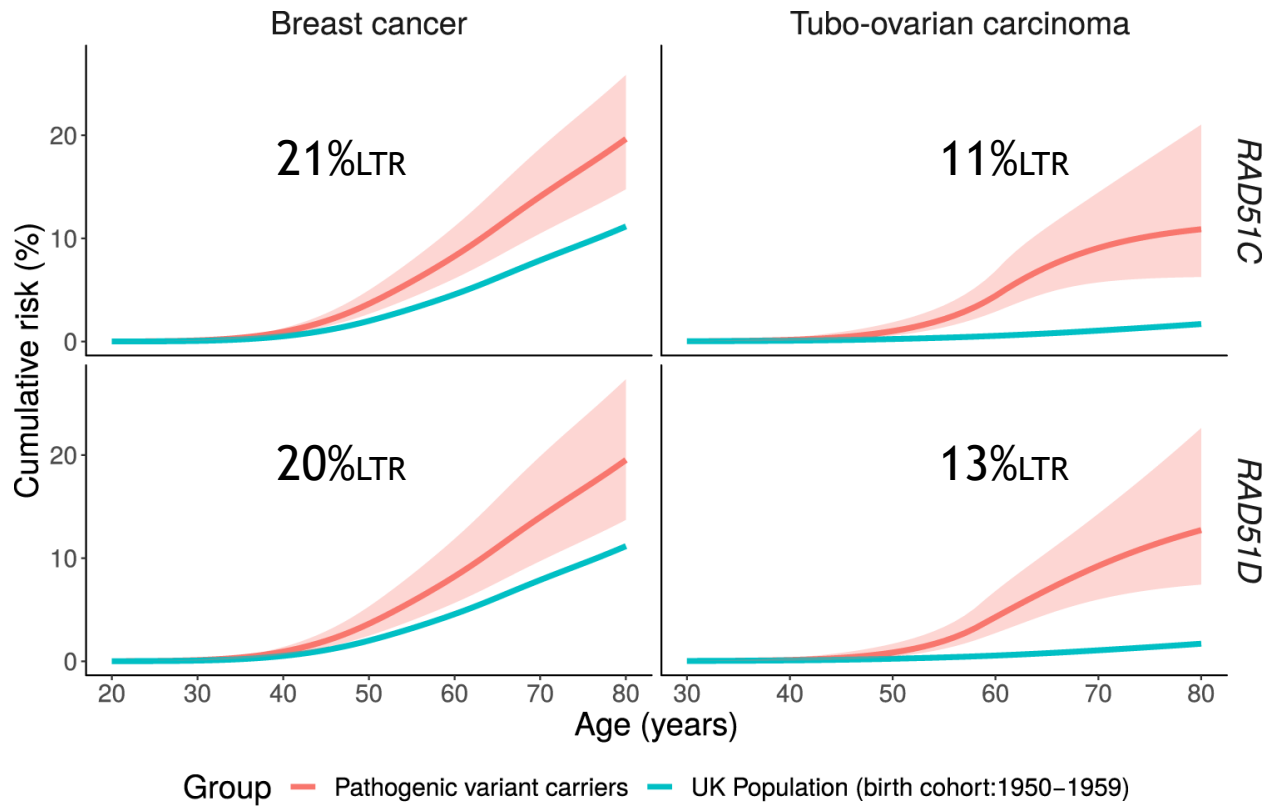
NBN
RAD50
MMR genes
RECQL
RINT1
XRCC2
MRE11A
GEN1
AKT1
MEN1
PIK3CA

No General Risk
But ? Specific variants

FANCC
FANCM
BRIP1

Slide courtesy of Prof Paul James, Parkville FCC

Figure 1. Estimated age-specific tubo-ovarian carcinoma and breast cancer cumulative risks in RAD51C and RAD51D ...



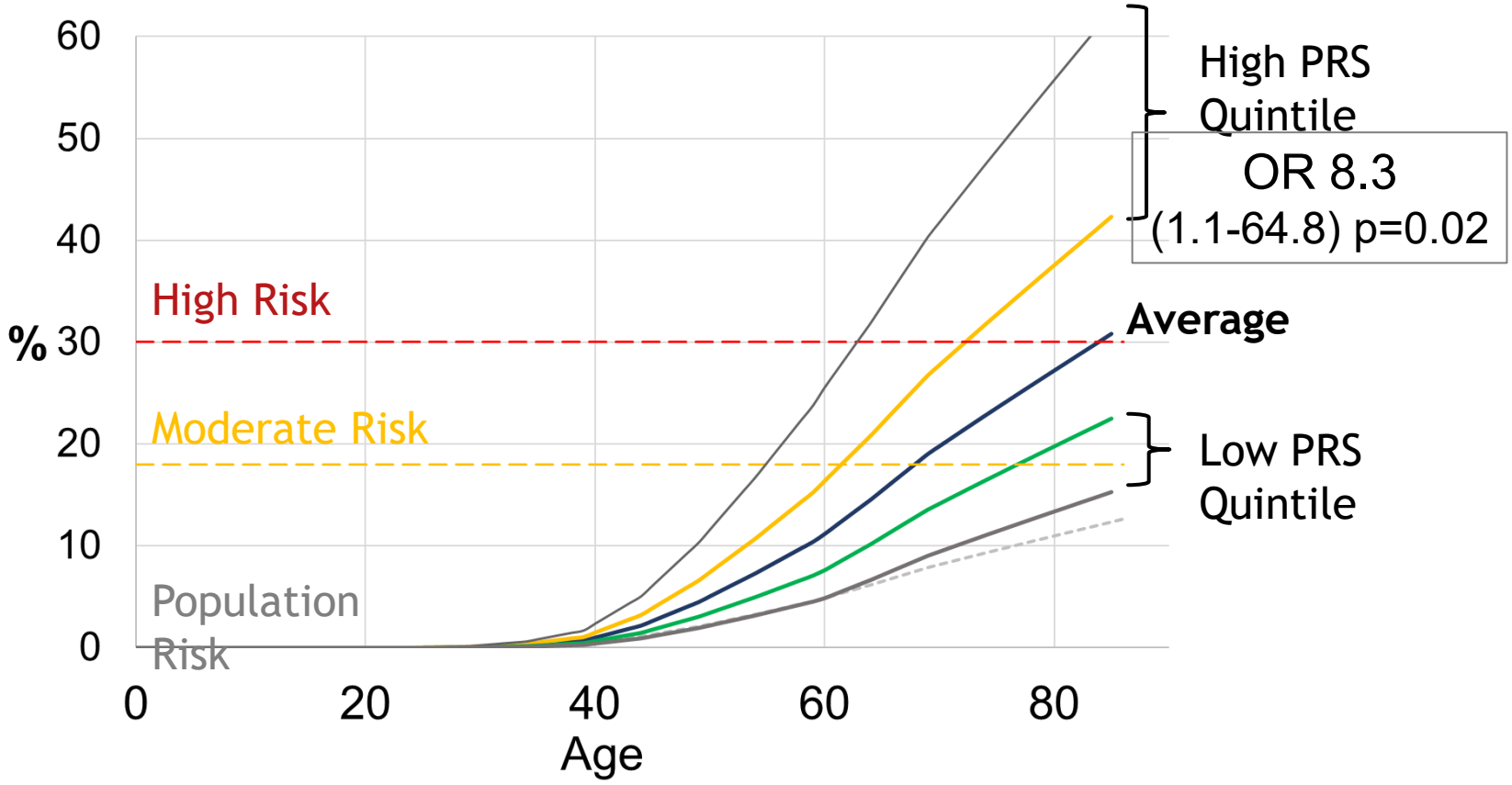
125 families (215 women)

60 families (92 women)

Yang et al., J Natl Cancer Inst, 28 Feb 2020

PALB2: PRS Modification

Logistic Regression: 53 LoF variants, 5524 non-carriers



Risk Group	Proportion of Individuals
~Population	5%
Moderate	41%
High	54%

Slide courtesy of Prof Paul James, Parkville FCC

ViP Study VARIANTS IN PRACTICE

lifepool