Liverpool Women's
NHS Foundation Trust

Mainstream Genomic Testing for Inherited Breast Cancer (R208)

Introduction

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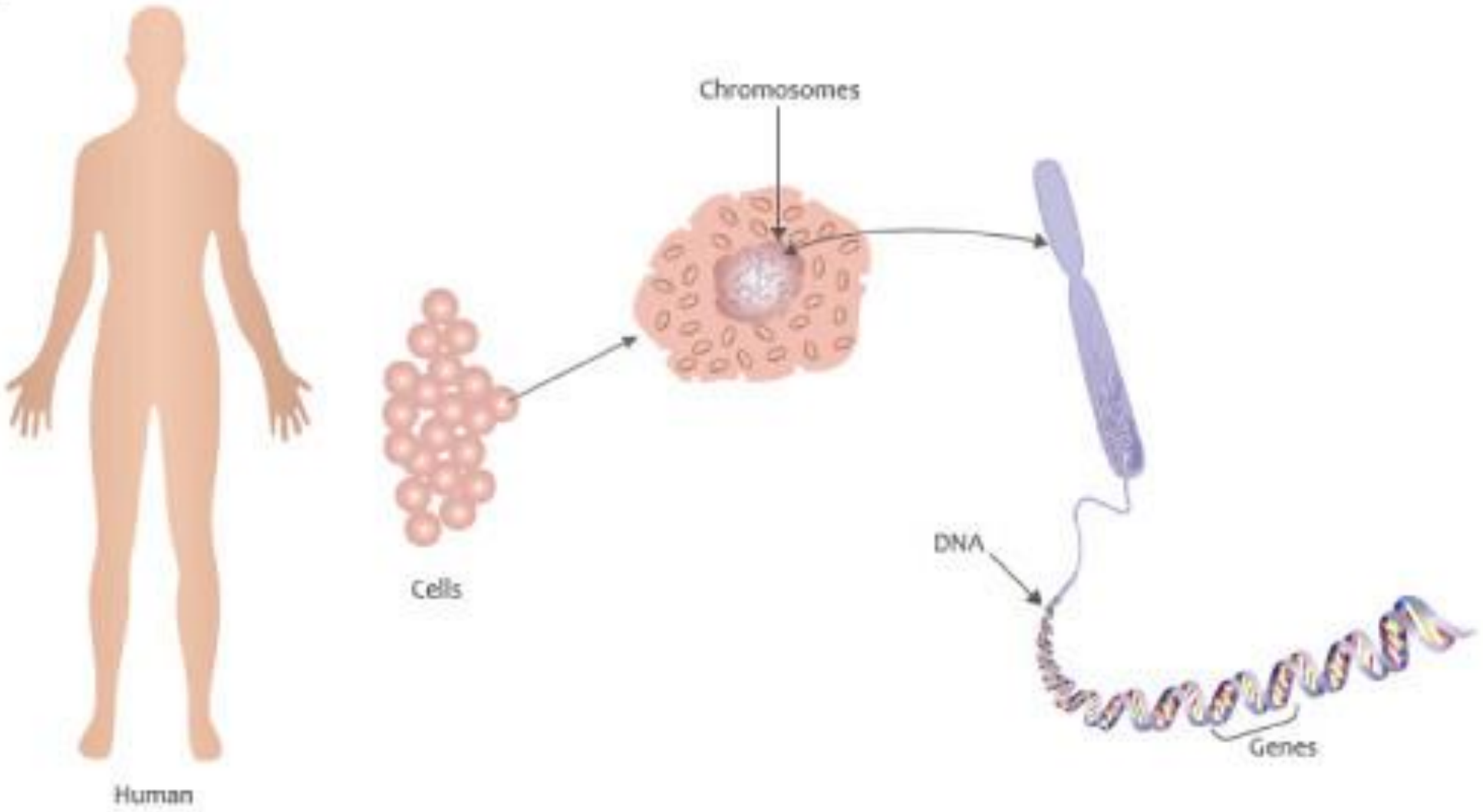
*The **best people**, giving the **safest care**, providing **outstanding experiences***

Overview

- Genes/Chromosomes and DNA
- Genetics vs genomics
- Cancer and genetics, pathogenic variants and penetrance
- Germline and sporadic variants
- What genes are relevant
- Management implications
- Evolving field



Genomics Health Facts

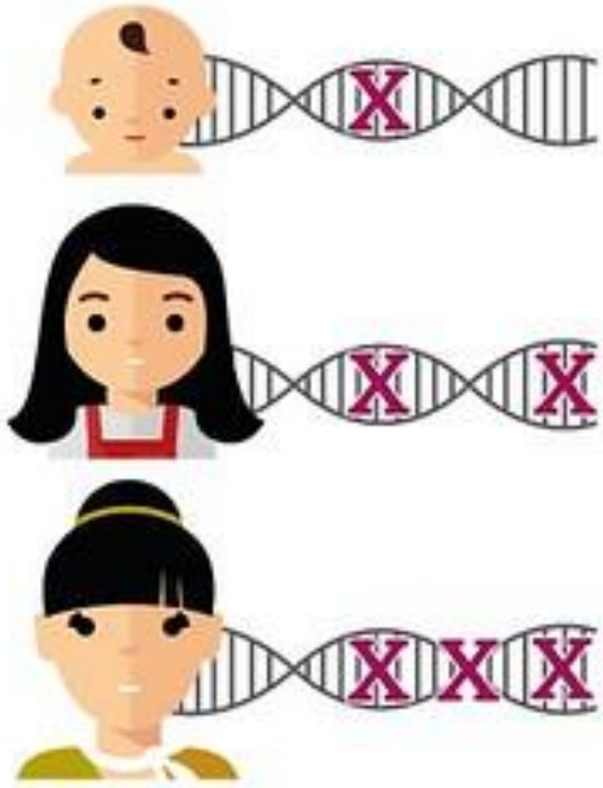
Cancer

Cancer is a disease of the genome.

It is caused by changes to DNA

that can occur over a person's lifetime, though around

5% of cancers also have an inherited component



Genomics

- The study of an organism's complete set of genetic information.
- The genome includes both genes (coding) and non-coding DNA.
- 'Genome': the complete genetic information of an organism.

vs

Genetics

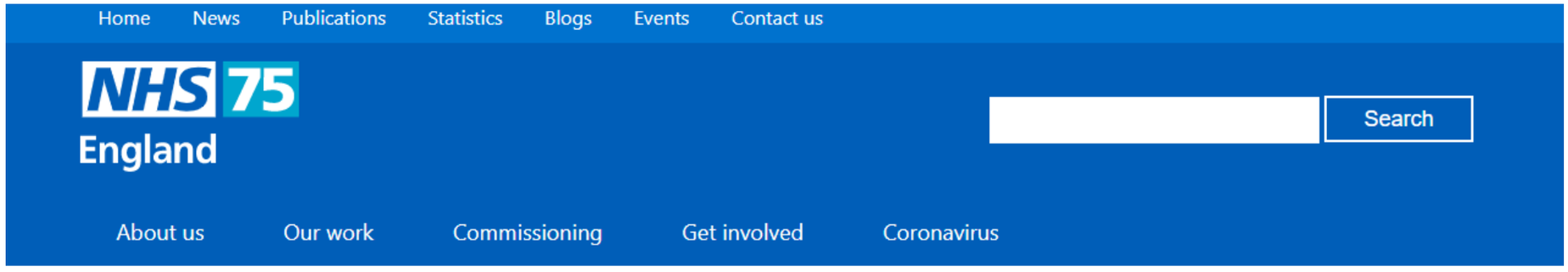
- The study of heredity
- The study of the function and composition of single genes.
- 'Gene': specific sequence of DNA that codes for a functional molecule.

MYTH "I have the breast cancer gene."

FACT We all have the same genes. For example, every person has the 'breast cancer gene' *BRCA1*. It doesn't cause breast cancer in itself; however, individuals with certain rare variants in the *BRCA1* gene have a much higher chance of developing breast cancer.

The Genomic Test Directory

https://www.england.nhs.uk/publication/national-genomic-test-directories/



National genomic test directory

Document first published: 3 August 2018
Page updated: 31 October 2022
Topic: Commissioning, Genomics, Specialised commissioning
Publication type: Guidance

The National genomic test directory specifies which genomic tests are commissioned by the NHS in England, the technology by which they are available, and the patients who will be eligible to access to a test. The National genomic test directory for rare and inherited disorders and cancer can be accessed below.

If you have any questions about the genomic testing available in your area, please contact your local genomic laboratory hub.

Document

.xls

National genomic test directory for rare and inherited disease

Microsoft Excel 179 KB

Summary

The National genomic test directory for rare and inherited diseases specifies the genomic tests commissioned by the NHS in England for rare and inherited disorders, the technology by which they are available, and the patients who will be eligible to access to a test.

Version 4. Updated 31 October 2022.

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Version 4. Updated 31 October 2022.

Document

Rare and inherited disease eligibility criteria

PDF 4 MB 405 pages

Summary

This eligibility criteria document supplements the National genomic test directory by setting out which patients should be considered for testing under that indication, and the requesting specialties is a list of the clinical specialties who would be expected to request the test.

Version 4. Updated 31 October 2022.

Document

Summary

The National genomic test directory for cancer specifies the

What genes are relevant?

R208 inherited breast cancer genomic testing currently reports pathogenic variants in

- BRCA1
- BRCA2
- PALB2
- CHEK2
- ATM
- RAD51C
- RAD51D

Expanding list

What genes are relevant?

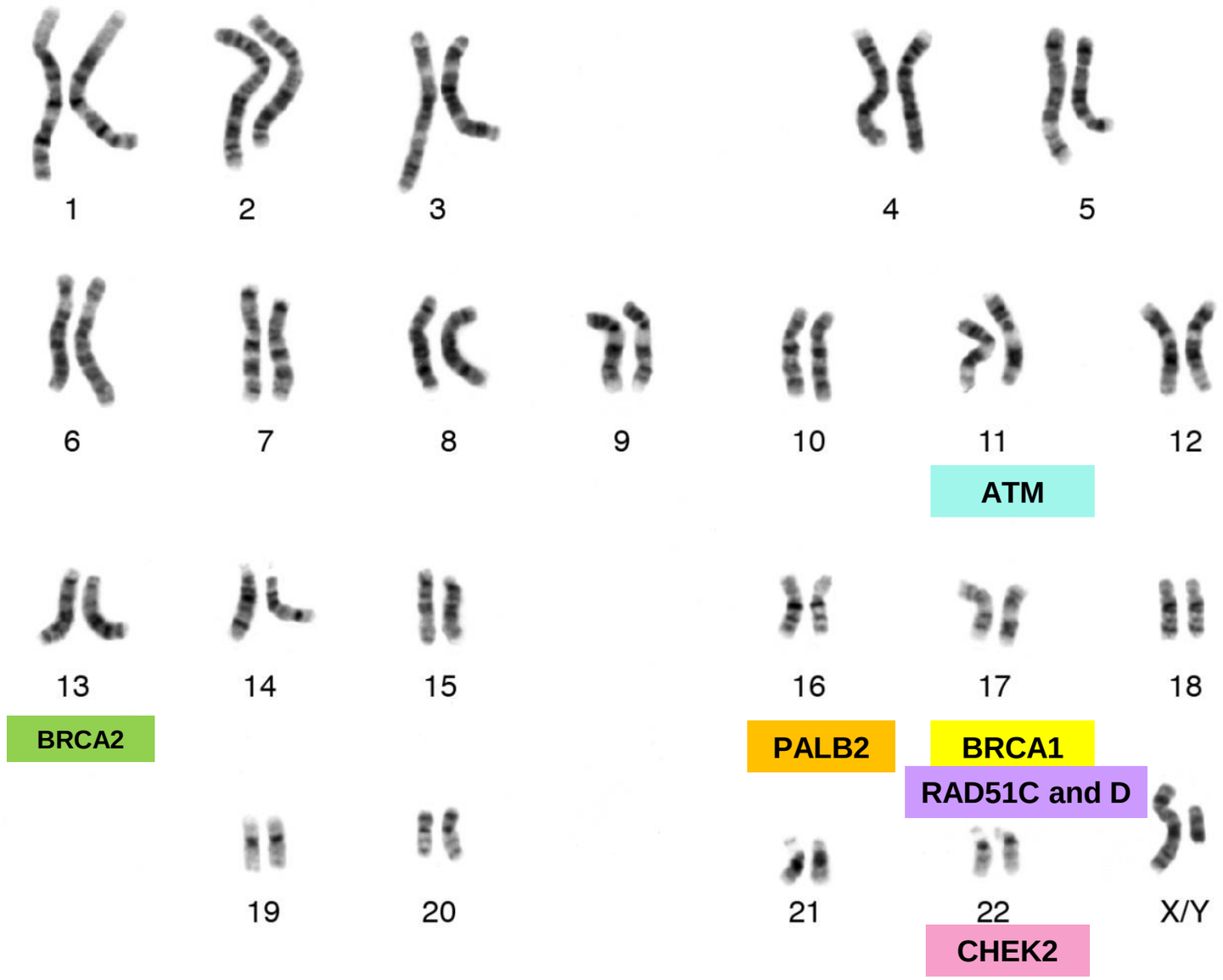
BRCA1 and BRCA2
- High risk of breast/ovarian cancer

PALB2
- High risk of breast cancer

CHEK2 or ATM
- Moderate risk of breast cancer
- *Is one very high risk ATM variant

RAD51C and RAD51D
- Moderate risk of ovarian cancer

Assess risk in context of family history of cancer
- CanRisk assessment to create individualised risk estimates


1
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ATM
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14
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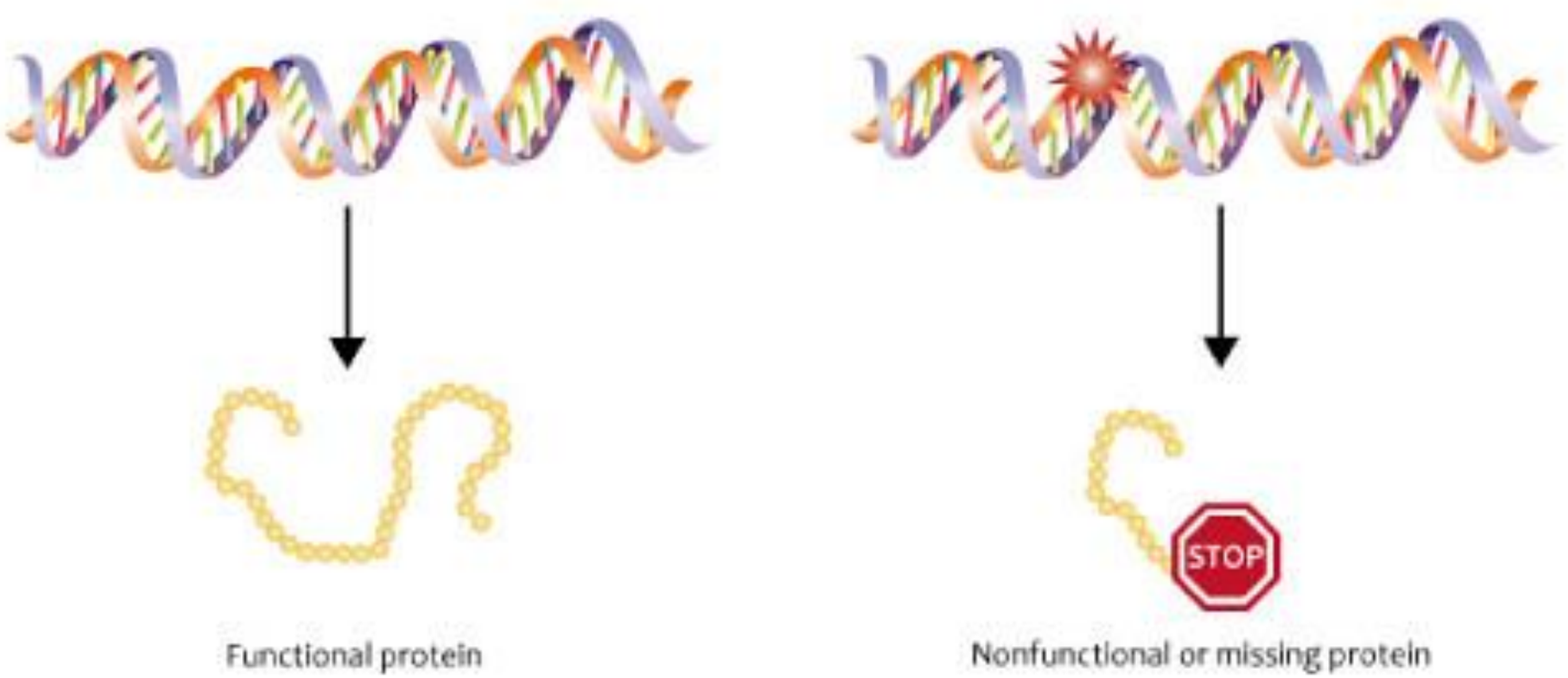
16
17
18
BRCA2
PALB2
BRCA1
RAD51C and D
19
20
21
22
X/Y
CHEK2

Genes and cancer risk

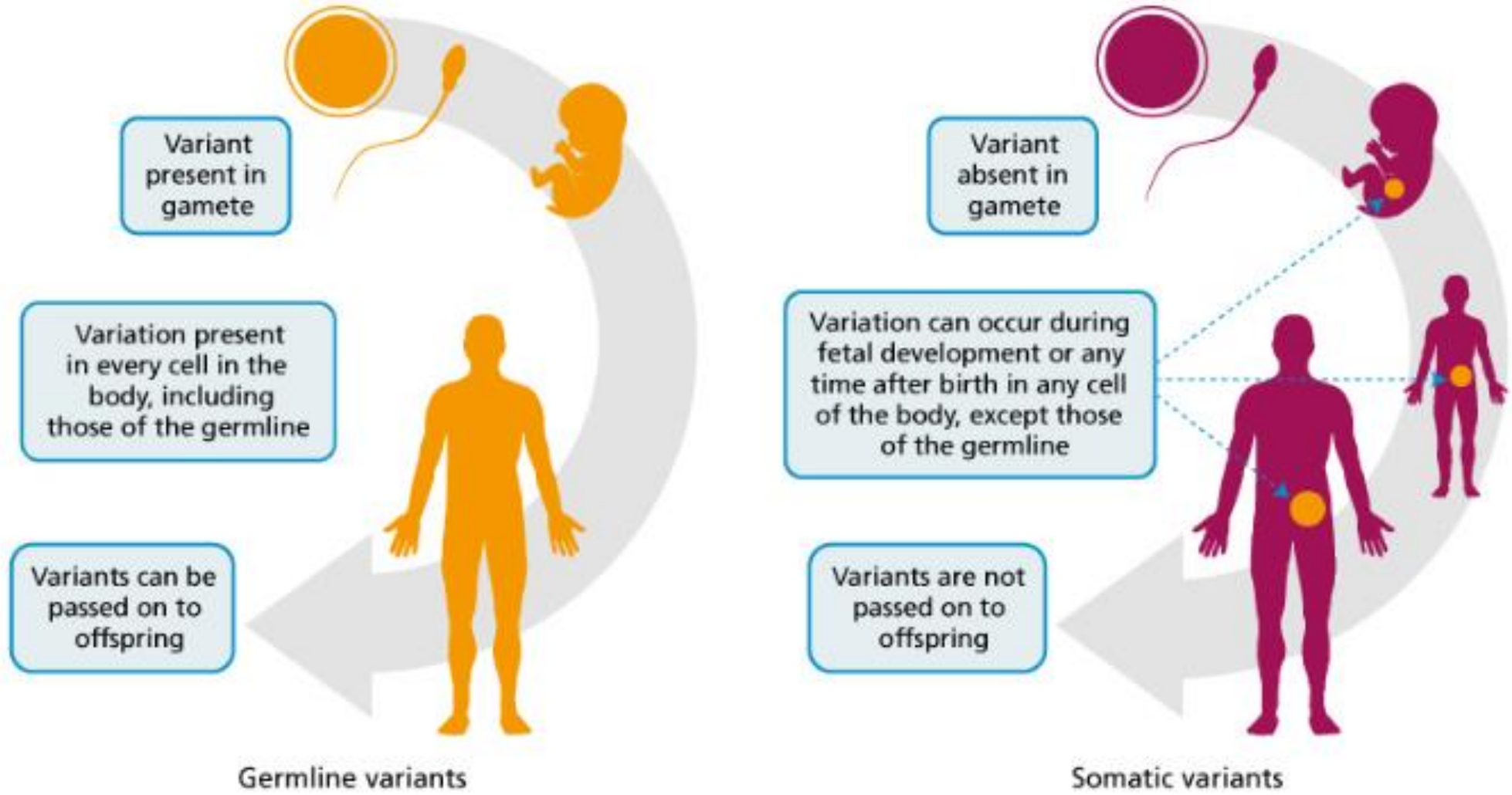
Normal function of cancer genes: tumour suppression
Role in regulating cell division and replication

Pathogenic variant alters cancer gene
Higher chance of cancer

Implications of a pathogenic variant

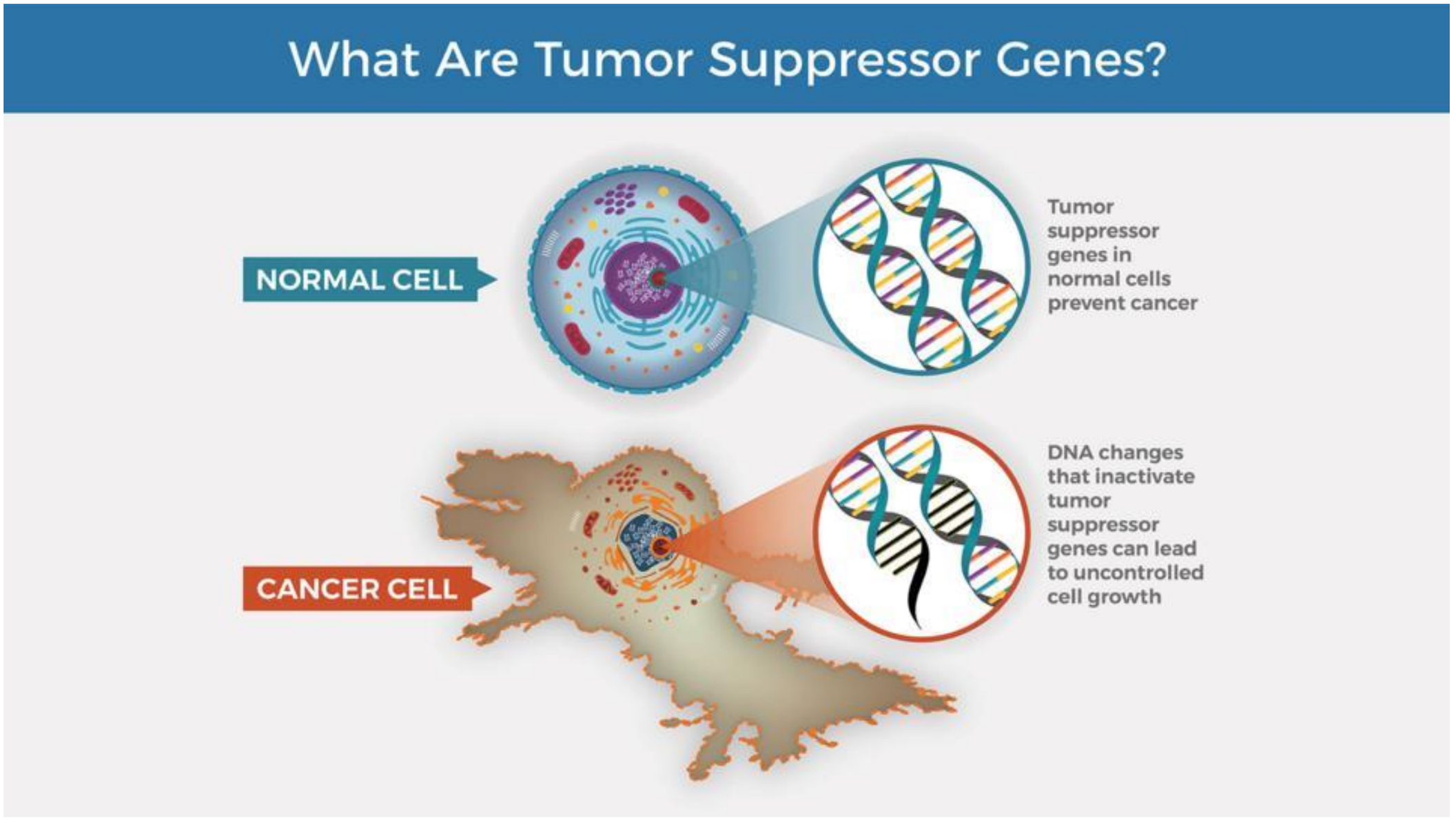


Inherited (germline) genomics variants vs acquired (somatic) variants



Germline variants – present in gametes and can be passed onto offspring (every cell in the entire organism will be affected)

Somatic variants – occur in a single body cell initially and cannot be inherited (only tissues derived from original altered cell are affected)



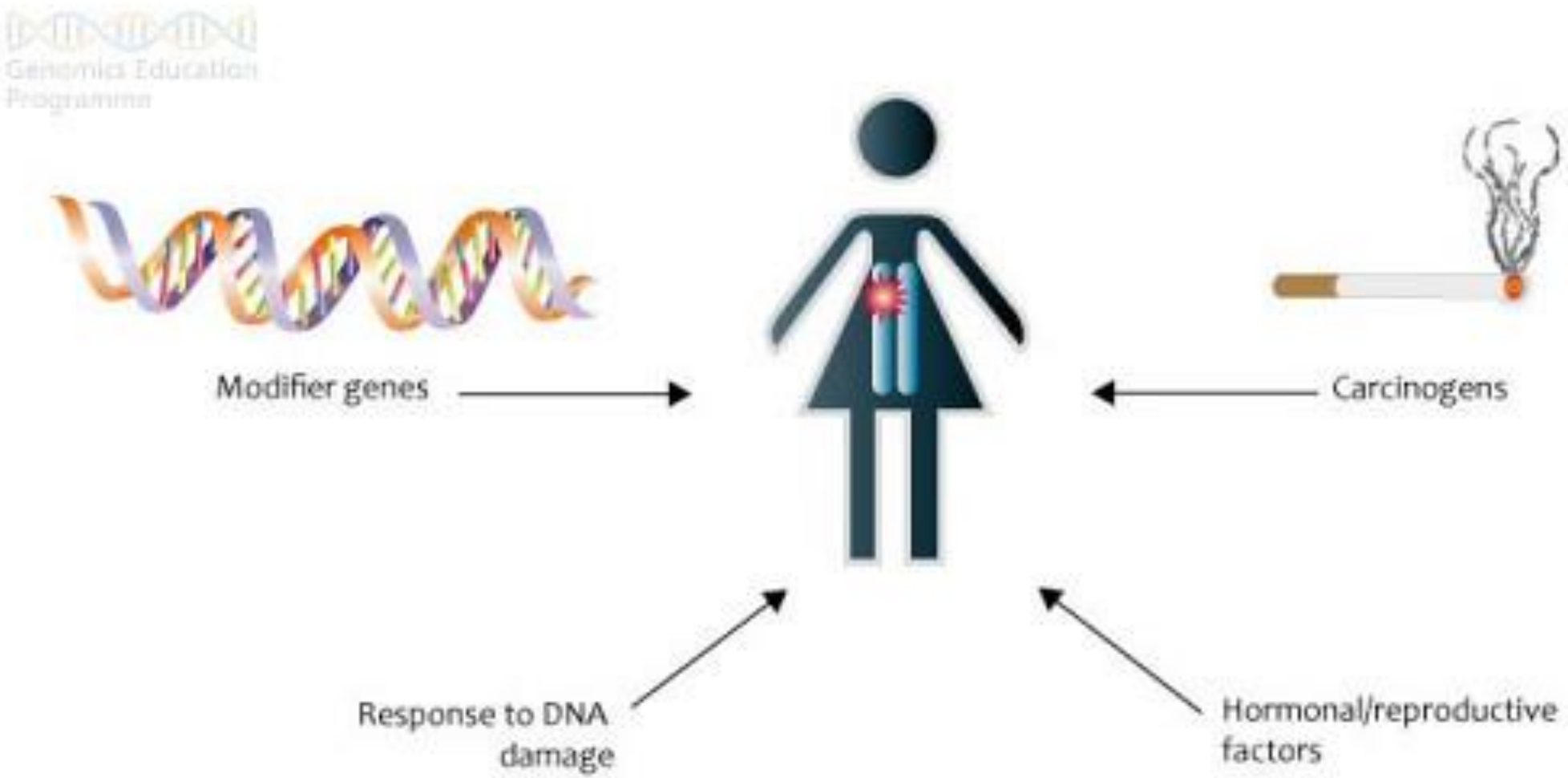
Which cancer depends on which gene is involved
Cancer risk is affected by sex and age of person
Penetrance affected by other genetic and lifestyle factors

Inheritance of risk is dominant

https://www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/autosomal-dominant-inheritance/ accessed 27.02.23

https://visualsonline.cancer.gov/details.cfm?imageid=12495 accessed 05.12.22

Risk and disease penetrance



Not everyone with an altered gene develops cancer

Genes and their role

BRCA1 and **BRCA2** (**BR**east **CA**ncer genes 1 and 2) provide instructions for making a protein involved in repairing damaged DNA, double stranded breaks, by homologous recombination

PALB2 works with the BRCA2 protein, '**P**artner **A**nd **L**ocaliser of **B**RCA**2**'

CHEK2 or checkpoint kinase 2, a protein kinase that is activated in response to DNA damage, is involved in cell cycle arrest.

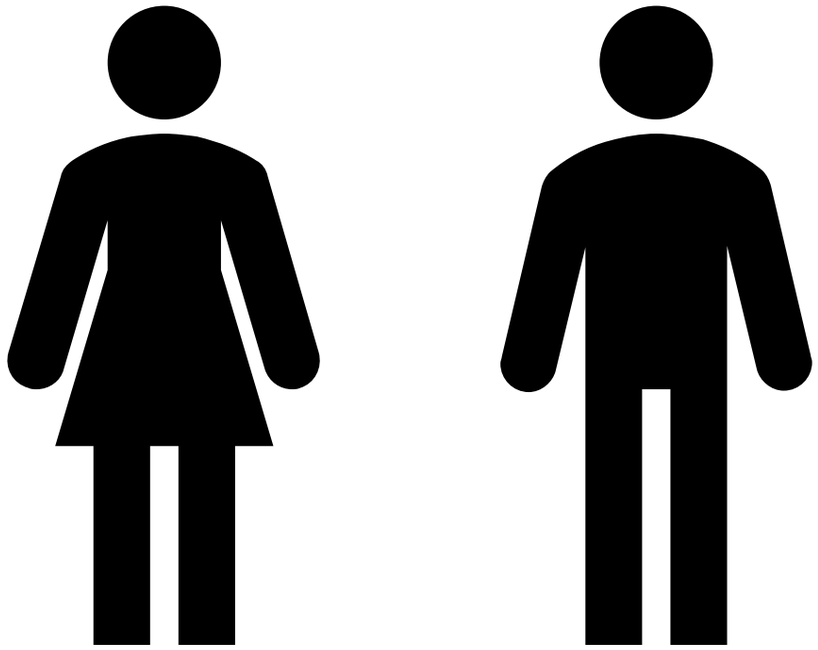
The ATM protein is a member of a family of proteins that respond to DNA damage by phosphorylating key substrates involved in DNA repair and/or cell cycle control.

People with **two** pathogenic variants (both copies of the ATM gene) have Ataxia-Telangiectasia. In the classic form this causes progressive cerebellar ataxia beginning between ages one and four year.

Management implications

What gene?

Age?
Sex?



Significant family history?

Life stage?
Family planning?

Current cancer histology? prognosis?

Patient's wishes?

Previous surgery?
Suitability for further surgery?

Living relatives in contact?

Interest in research?

Management implications

Patient with current breast cancer

Does a genetic result influence surgical management?

- consider contralateral risk (CanRisk can inform this calculation)
- is more extensive breast surgery suitable?

Does this affect treatment options?

PARP inhibitors?

Management implications

Genomic medicine service can discuss

- Family matters – testing other relatives
- Options for future cancer risk management

Research options

EMBRACE

https://ccge.medschl.cam.ac.uk/embrace/

PROTECTOR

http://protector.org.uk/information-for-participants/

BRCA1 Germline Pathogenic Variant Carriers Management Guidelines for Healthcare Professionals

Female *BRCA1* Germline Pathogenic Variant (GPV) carrier age-dependent cumulative cancer risks (95% confidence intervals)		
Age (years)	**Breast cancer**	**Ovarian cancer**
21-30	4% (2 to 7)	-
31-40	24% (21 to 29)	2% (1 to 3)
41-50	43% (39 to 48)	8% (6 to 12)
51-60	56% (51 to 61)	20% (16 to 26)
61-70	66% (61 to 72)	41% (33 to 50)
71-80	72% (65 to 79)	44% (36 to 53)

Cumulative risk for contralateral breast cancer by time since first breast cancer	
≤5 years	13% (10 to 16)
>5-10 years	23% (20 to 27)
>10-15 years	32% (28 to 36)
>15-20 years	40% (35 to 45)
>20-45 years	53% (44 to 62)

Patient resources

-A Beginner's Guide to *BRCA1* and *BRCA2* (patientinfolibrary.royalmarsden.nhs.uk)
-breastcancernow.org
-coppafeel.org
-https://www.macmillan.org.uk/cancer-information-and-support/worried-about-cancer/causes-and-risk-factors/brca-gene

Other cancers		*BRCA1* GPV carrier risk (95% confidence interval)	Population lifetime risk
Male breast cancer		0.4% (0.1 to 1.5) by age 80	Rare
Prostate cancer	Nyberg 2020	29% (17 to 45) by age 85	18%
	Li 2022	No significant association	
Nyberg PCa risk estimate likely incorporates effects of PSA screening*			
Pancreatic cancer	**Male**	3% (2 to 5) by age 80	2%
	Female	2% (2 to 4) by age 80	
No significant association consistently found for other cancers.			

Notes

It is important to manage patients in the context of their family history of cancer. Individualised risk estimates available from https://canrisk.org/ should be used instead of the general risk estimates wherever possible.
*See FAQ document for further information and references.

Management recommendations	
Screening	**Breast**: Annual MRI Breast from 30 years. Annual mammography from 40 years. Earlier commencement of annual MRI breast from age 25 may be considered for women with an individualised 10 year breast cancer risk of ≥ 8%*. For women with previous breast cancer, as above if residual breast tissue.
	Ovarian: Not currently recommended. No evidence based screening programme.
	Prostate: No national screening programme. Men can discuss pros and cons of PSA screening with their GP.
	Pancreatic: Not recommended.
Risk-reducing surgery	**Breast**: Discuss risk-reducing bilateral mastectomy. Individualised* risk assessment recommended
	Ovarian: Discuss risk-reducing bilateral salpingo-oophorectomy (RRBSO), offer when childbearing is complete and no earlier than age 35 – 40. Due to continued risk of ovarian cancer at older ages, RRBSO should be discussed with all women, with consideration of general fitness/co-morbidities.
Hormone replacement	Women undergoing RRBSO who have no previous history of breast cancer, should consider taking HRT until 50.
Chemoprevention	Not recommended because of high risk of triple negative breast cancer.
Cancer management	*BRCA1* GPV carrier status may influence management of current cancers – ensure oncologist aware of carrier status and manage as part of a multidisciplinary team. Consider long term prognosis / competing risks prior to considering risk-reducing surgery.
Lifestyle information	Provide information about regular self-breast examination and ovarian cancer symptom awareness. Provide information on the benefits of smoking cessation, minimising alcohol intake and maintaining a healthy weight to lower the chance of getting cancer.
Family matters	Refer to clinical genetics to facilitate genetic testing in at-risk family members. Refer to clinical genetics for discussions on reproductive options.
Psychological	Consider referral for clinical psychology support if appropriate.

*See FAQ document for further information and references.

BRCA2 Germline Pathogenic Variant Carriers Management Guidelines for Healthcare Professionals

Female *BRCA2* Pathogenic Variant (GPV) carrier age-dependent cumulative cancer risks (95% confidence intervals) *		
Age (years)	**Breast cancer**	**Ovarian cancer**
21-30	4% (2-9%)	-
31-40	13% (9-19%)	<0.5%
41-50	35% (29-41%)	1-2%
51-60	53% (46-59%)	7% (4-11%)
61-70	61% (55-68%)	15% (10-23%)
71-80	69% (61-77%)	17% (11-25%)‡

‡Risk of OC >70 is likely underestimated by referenced study, see management below and FAQ

Cumulative risk for contralateral breast cancer by time since first breast cancer *	
≤5 years	8% (6-12%)
>5-10 years	16% (12-21%)
>10-15 years	21% (17-26%)
>15-20 years	26% (20-33%)
>20-43 years	65% (25-98%)

Patient resources

- A Beginner's Guide to *BRCA1* and *BRCA2* (patientinfolibrary.royalmarsden.nhs.uk)
- breastcancernow.org "Someone like me" https://breastcancernow.org/information-support/support-you/someone-me-telephone-support
- coppafeel.org
- https://www.macmillan.org.uk/cancer-information-and-support/worried-about-cancer/causes-and-risk-factors/brca-gene

Other cancers *		*BRCA2* GPV carrier risk (95% confidence interval)	Population lifetime risk
Male breast cancer		4% (2-8%) by age 80	Rare
Prostate cancer	Nyberg 2020	41% (22-54%) by age 85¶	18%
	Li 2022	27% (21-35%) by age 80	
¶ Adjusted for screening effect, please see FAQ for unadjusted figures			
Pancreatic cancer	**Male**	3% (2-5%) by age 80	2%
	Female	2% (1-4%) by age 80	
No significant association consistently found for other cancers.			

Notes

It is important to manage patients in the context of their family history of cancer. Individualised risk estimates available from https://canrisk.org/ should be used instead of the general risk estimates wherever possible. *See FAQ document for further information and references.

Management recommendations	
Screening	**Breast**: Annual MRI Breast from 30 years. Annual mammography from 40 years. Earlier commencement of annual breast MRI from age 25 may be considered for women with an individualised 10 year breast cancer risk of ≥ 8%*. For women with previous breast cancer, as above if residual breast tissue.
	Ovarian: Not currently recommended. No evidence based screening programme.
	Prostate: Annual PSA from 40 with onward referral if PSA >3.0ng/ml.
	Pancreatic: Not currently recommended outside of research. Consider the EUROPAC study.
Risk-reducing surgery	**Breast**: Discuss bilateral mastectomy. Individualised* assessment recommended.
	Ovarian: Discuss risk-reducing bilateral salpingo-oophorectomy (RRBSO), offer when childbearing is complete and no earlier than age 40 – 45. Due to continued risk of ovarian cancer at older ages, RRBSO should be discussed with all women, with consideration of general fitness/co-morbidities.
Hormone replacement	Women undergoing RRBSO with no previous history of breast cancer, should consider taking HRT until 50. For women with previous breast cancer, individualised discussion with Oncologist is advised.
Chemoprevention	Discuss the pros and cons of chemoprevention. Can be offered if no contraindications. No studies have been conducted to date on efficacy of chemoprevention in *BRCA2* GPV carriers.
Cancer management	*BRCA2* GPV carrier status may influence management of current cancers – ensure oncologist aware of carrier status and manage as part of a multidisciplinary team. Consider long term prognosis / competing risks prior to considering risk-reducing surgery.
Lifestyle information	Provide information about regular self-breast examination and ovarian cancer symptom awareness. Provide information on the benefits of smoking cessation, minimising alcohol intake and maintaining a healthy weight to lower the chance of getting cancer. Contraception: use of oral contraceptive pill (OCP) is not contraindicated, but requires informed discussion and consideration of alternative forms of contraception*.
Family matters	Refer to clinical genetics to facilitate genetic testing in at-risk family members. Refer to clinical genetics for discussions on reproductive options.
Psychological	Consider referral to clinical psychology support services if appropriate.

* Please see FAQ for more information

Management implications

Position statement

OPEN ACCESS

UK consensus recommendations for clinical management of cancer risk for women with germline pathogenic variants in cancer predisposition genes: *RAD51C*, *RAD51D*, *BRIP1* and *PALB2*

Helen Hanson ,[1,2] Anjana Kulkarni,[3] Lucy Loong,[2] Grace Kavanaugh,[2] Bethany Torr ,[2] Sophie Allen,[2] Munaza Ahmed,[4] Antonis C Antoniou ,[5] Ruth Cleaver,[6] Tabib Dabir,[7] D Gareth Evans ,[8,9] Ellen Golightly,[10] Rosalyn Jewell,[11] Kelly Kohut,[1] Ranjit Manchanda ,[12,13,14] Alex Murray,[15] Jennie Murray,[16] Kai-Ren Ong,[17] Adam N Rosenthal,[18] Emma Roisin Woodward ,[9,19] Diana M Eccles ,[20] Clare Turnbull ,[2] Marc Tischkowitz,[21] On behalf of Consensus meeting attendees, Fiona Lalloo[19]

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ABSTRACT
Germline pathogenic variants (GPVs) in the cancer predisposition genes *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, *BRIP1*, *PALB2*, *RAD51D* and *RAD51C* are identified in approximately 15% of patients with ovarian cancer (OC). While there are clear guidelines around clinical management of cancer risk in patients with GPV in *BRCA1*, *BRCA2*, *MLH1*, *MSH2* and *MSH6*, there are few guidelines on how to manage the more moderate OC risk in patients with GPV in *BRIP1*, *PALB2*, *RAD51D* and *RAD51C*, with clinical questions

PALB2, *RAD51D* and *RAD51C* as well as common, low-risk OC genetic susceptibility variants identified through genome-wide association studies.[3 4]

While guidelines around clinical management of cancer risk in patients with GPV in *BRCA1* and *BRCA2*[5 6] and the mismatch repair genes; *MLH1*, *MSH2*, *MSH6*[7] have been published, there are few guidelines on how to manage patients with GPV in genes associated with more moderate risks of OC: *BRIP1*, *PALB2*, *RAD51D* and *RAD51C*.

Population-based studies of genetic testing

Hanson H, Kulkarni A, Loong L*, et al*
UK consensus recommendations for clinical management of cancer risk for women with germline pathogenic variants in cancer predisposition genes: *RAD51C*, *RAD51D*, *BRIP1* and *PALB2*
Journal of Medical Genetics Published Online First: 21 November 2022. doi: 10.1136/jmg-2022-108898

Evolving field

Guidance changes over time
Cancer risk and management options will be influenced by genetic results and family history

National guidance including:

- NICE
- Cancer Genetics Group (CGG)
- Genomic Test Directory