

From DNA to Diagnosis

Advancing Early Detection Strategies

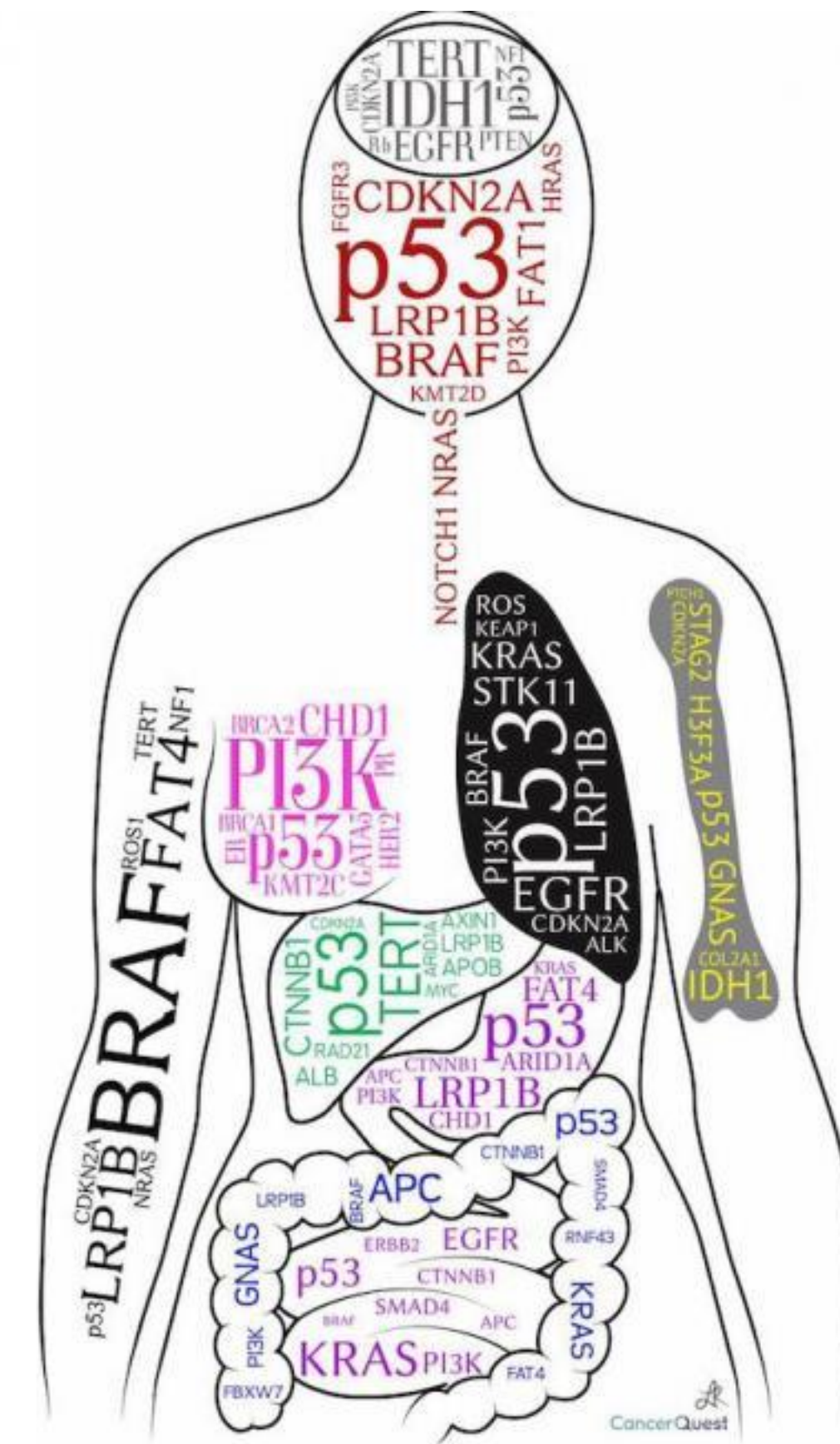
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Comprehensive Cancer Centers of
Nevada

Disclosures

- I have no financial relationships/conflicts of interest to disclose in relation to this presentation

Objectives

- Genetic Counseling
- Foundation of Cancer Genetics
- “Red Flags” & Integration into Clinical Practice
- Case Example
- Challenges

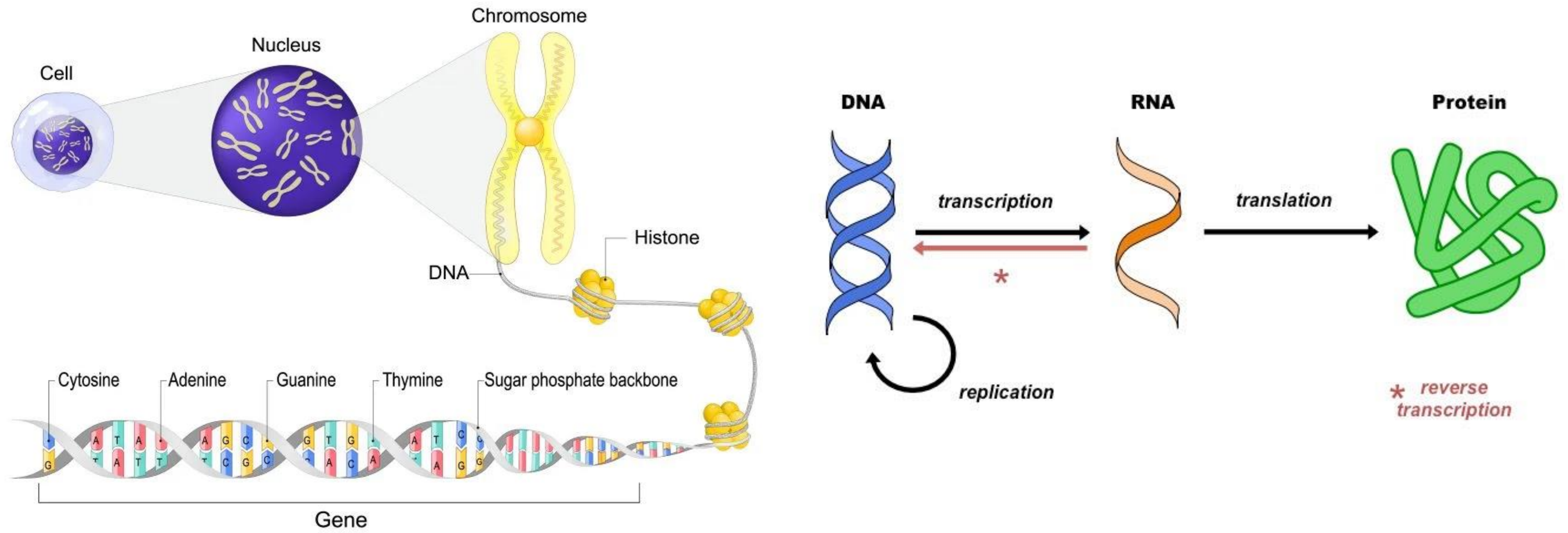


Genetic Counselors

- Healthcare professionals extensively trained in medical genetics and psychosocial counseling
- We work in multiple specialties, but in oncology, GC's perform risk assessment, educate and order appropriate genetic testing, interpret and integrate results into patient's clinical care and facilitate cascade testing
- SB189 passed and was implemented in 2026 providing licensure & regulation for genetic counselors in Nevada

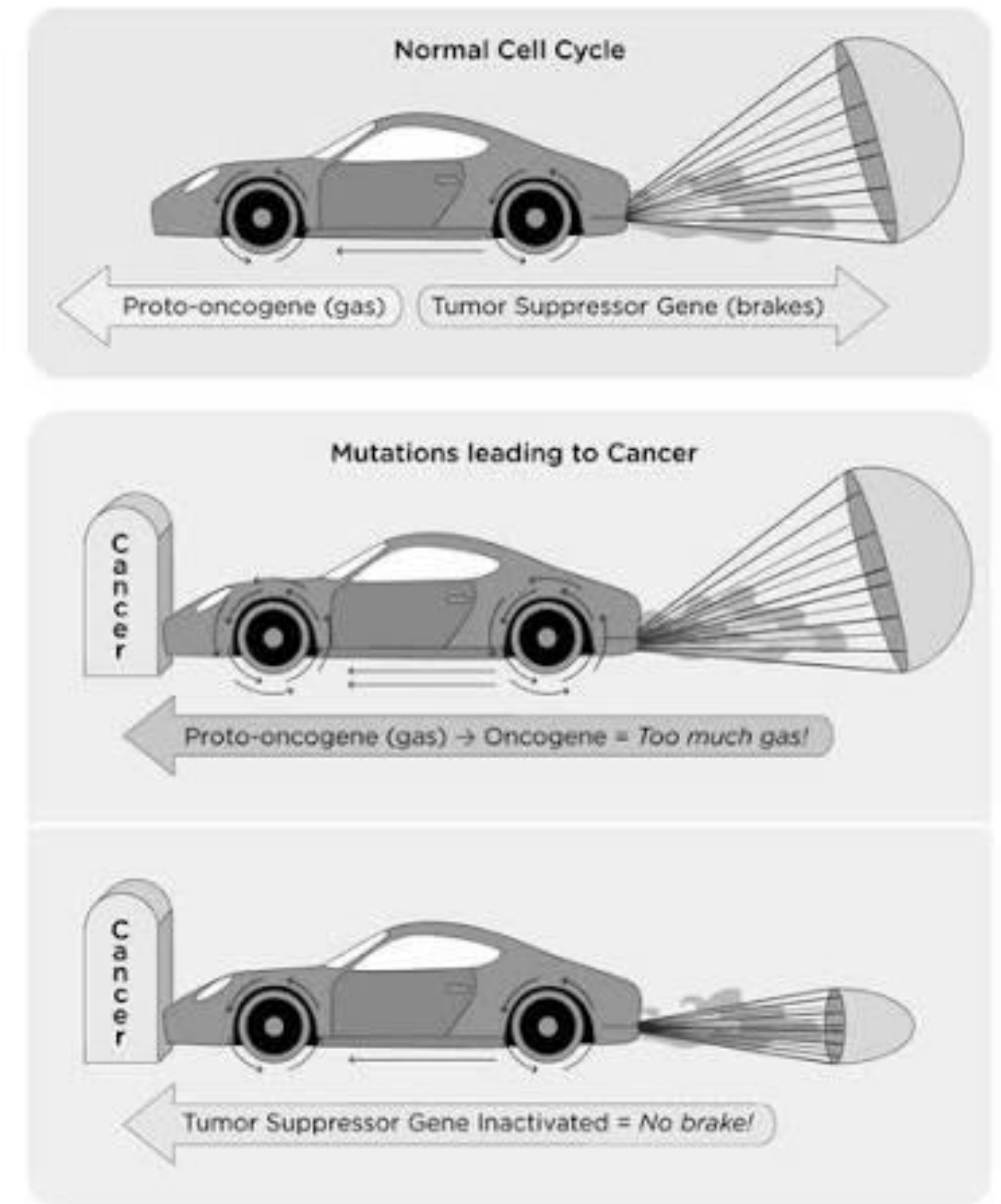


The Human Genome



Genes and Cancer

- Tumor Suppressor Genes: Protective genes. Normally, they limit cell growth
 - Monitor how quickly cells divide, repair damaged DNA, control when a cell dies
 - Ex. BRCA1/2, Can be inherited or acquired
- Oncogenes: Mutated form of proto-oncogenes
 - Normally help control how cells grow and divide
 - Abnormal activation pushes cells to divide, grow, and multiply uncontrollably
 - Ex. HER2, Generally not inherited
- DNA Repair Genes: Fix mistakes made when DNA is copied
 - Ex. BRCA1/2, TP53



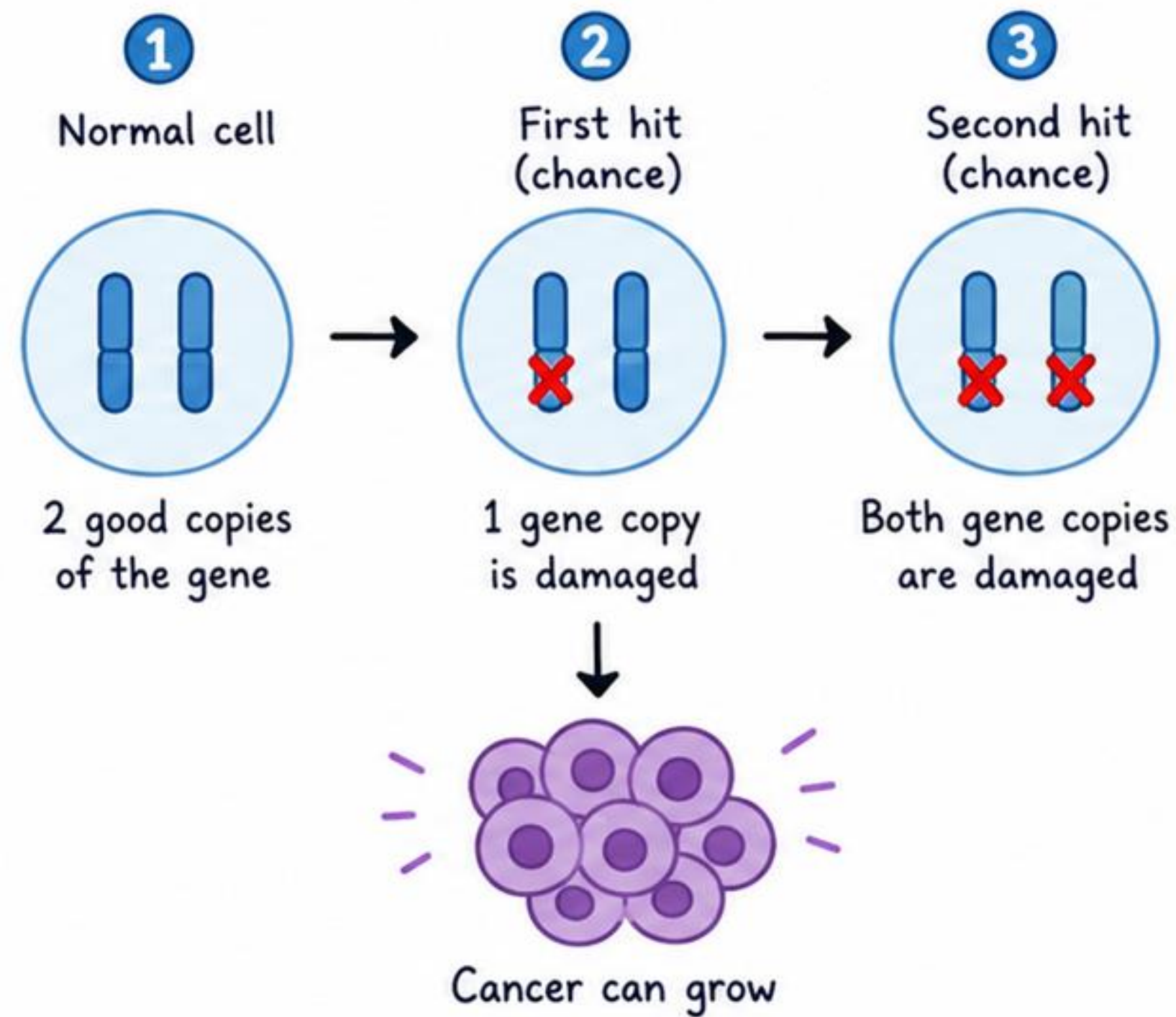
Is Cancer a Genetic Disease?

Sporadic vs. Inherited Cancer

(Knudson's Two-Hit Hypothesis)

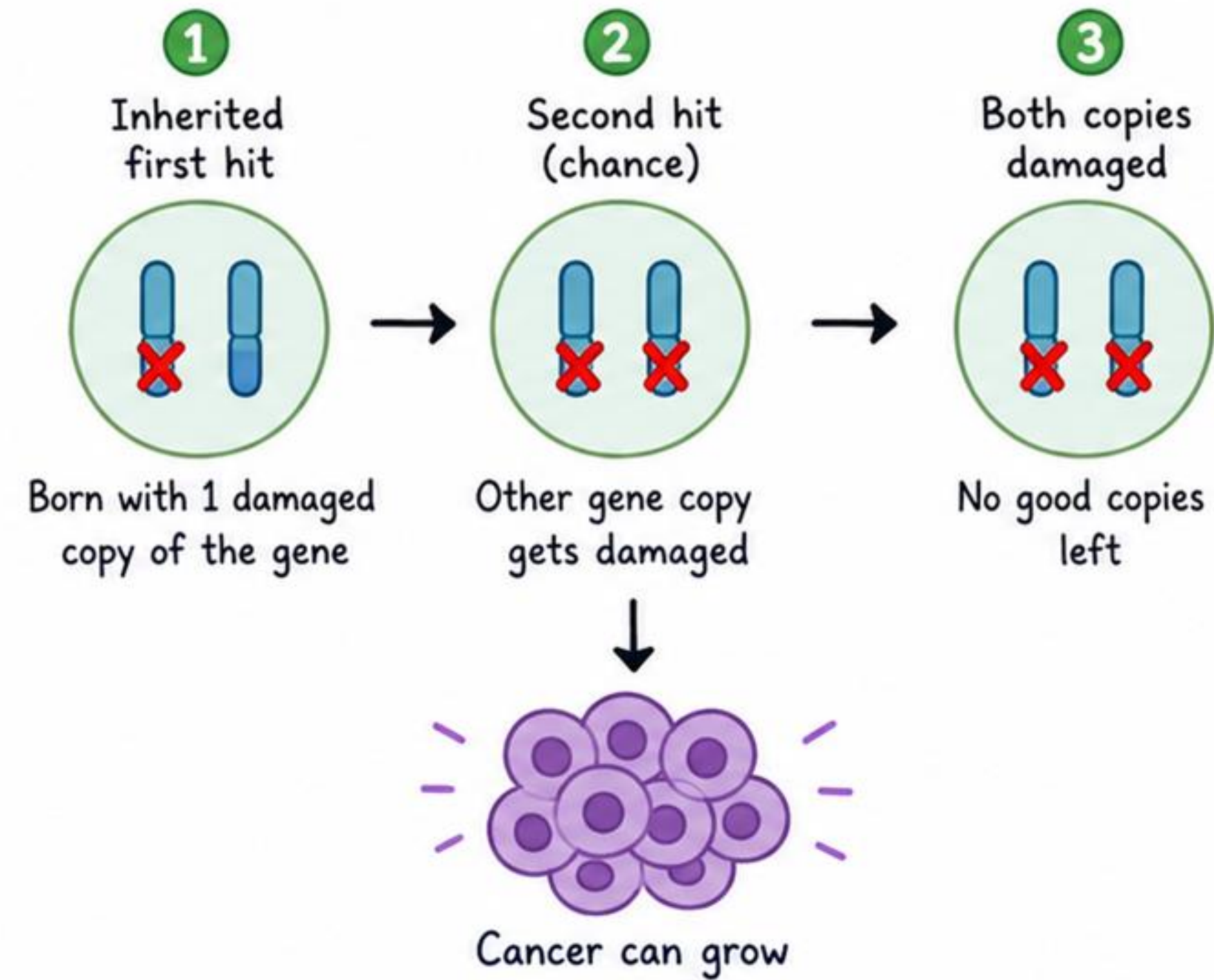
SPORADIC CANCER

Both "hits" happen by chance.



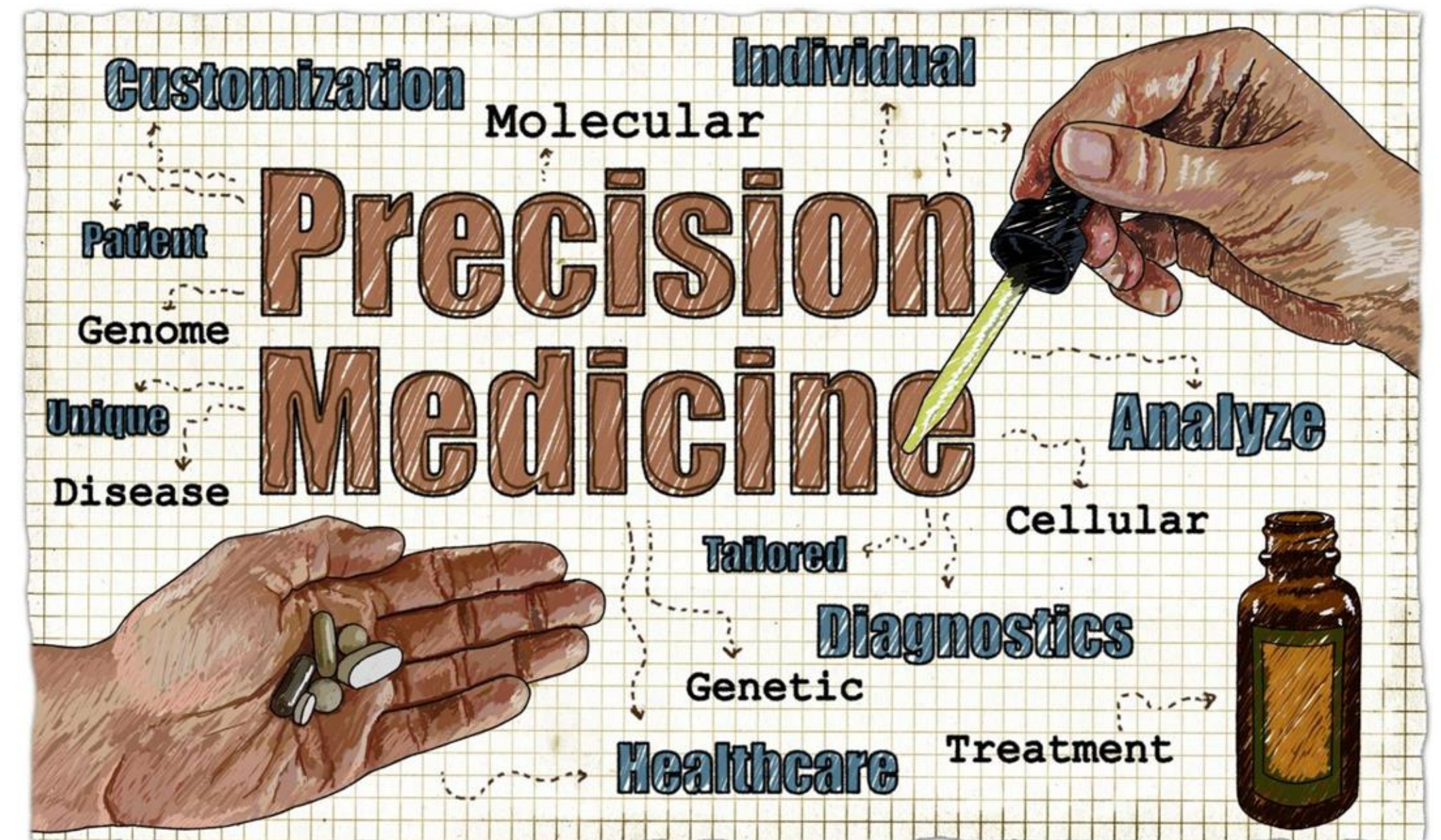
INHERITED CANCER

One "hit" is inherited, one happens by chance.



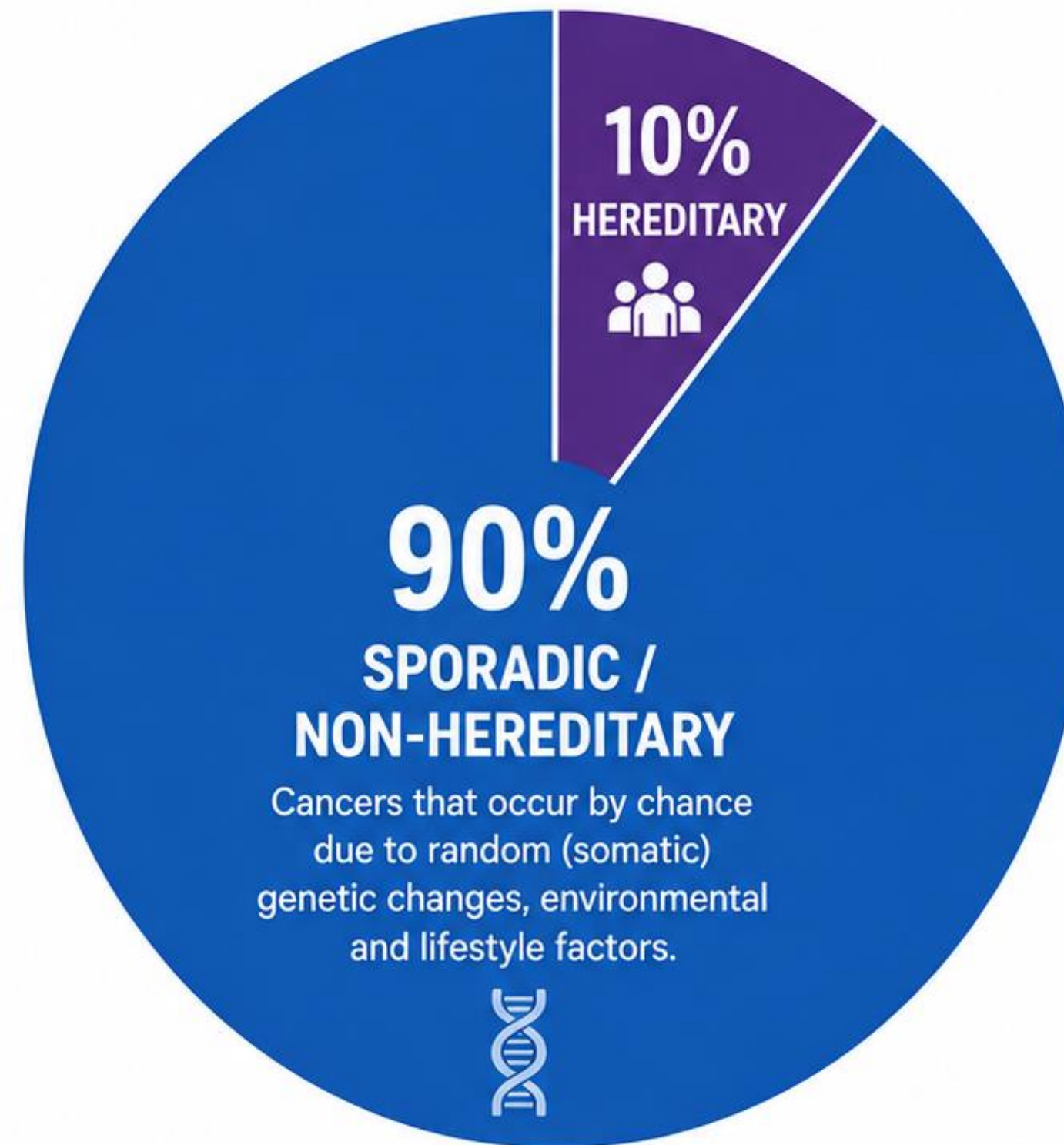
Germline vs Somatic

- Germline testing looks for DNA changes an individual is born with and is present in every cell of their body
 - Germline testing = Assessing Hereditary Disease
- Somatic testing looks for acquired DNA changes in a tumor or tissue cells, not inherited
 - Somatic testing = Assessing for Targeted Therapies
 - Ex. PARP Inhibitors
- Pharmacogenomics (PgX)
 - DYPD testing



ORIGIN OF ALL CANCERS

Sporadic vs. Hereditary



Most cancers are **sporadic** (~90%).
~10% are **hereditary** due to an inherited cancer predisposition gene.



Understanding the origin of cancer helps guide risk assessment, screening, prevention, and treatment for individuals and their families.

HEREDITARY CANCERS (~10% OF ALL CANCERS)

Caused by inherited pathogenic variants in cancer predisposition genes.



HIGH-PENETRANCE SYNDROMES (~3–5%)

Strongly increased cancer risk.
Examples: BRCA1/2, PALB2, Lynch syndrome (MMR genes), TP53 (Li-Fraumeni), PTEN (Cowden), CDH1 (Hereditary Diffuse Gastric Cancer), STK11 (Peutz-Jeghers), etc.



MODERATE-PENETRANCE GENES (~3–4%)

Moderate increase in cancer risk.
Examples: CHEK2, ATM, BARD1, RAD51C/D, BRIP1



RARE SYNDROMES (~1–2%)

Rare inherited syndromes with increased cancer risk.
Examples: Familial Adenomatous Polyposis (FAP), Peutz-Jeghers syndrome, Birt-Hogg-Dubé syndrome, etc.

Note: Percentages are approximate and based on current estimates from the literature.

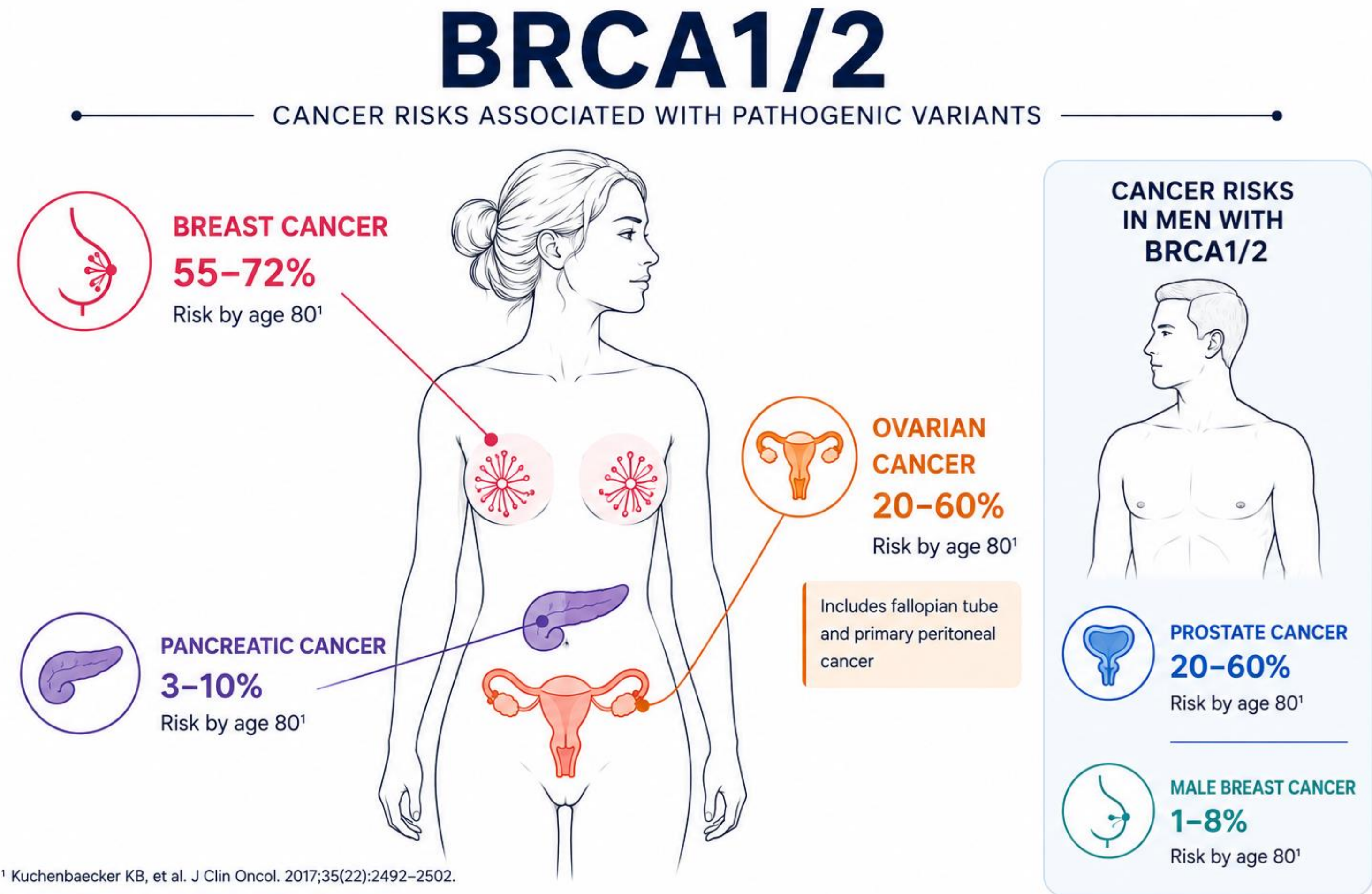
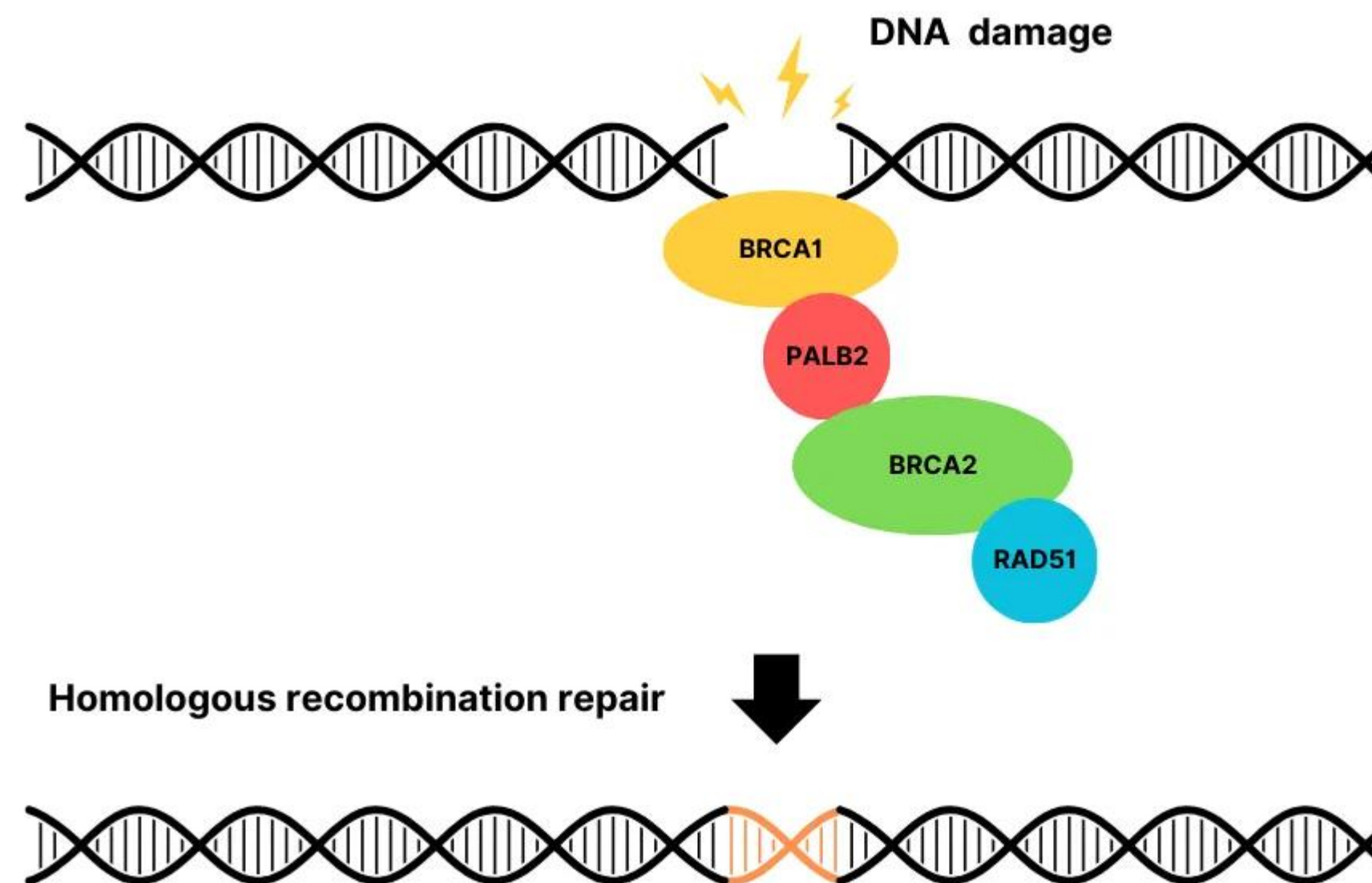
*Sources: National Cancer Institute (NCI) – Genetics of Cancer (PDQ®);
American Society of Clinical Oncology (ASCO)*

Hereditary Cancer syndromes

- Over 50 syndromes catalogued
- **Highly under-recognized and under-diagnosed**
- Asymptomatic identification allows us to implement tailored high-risk/preventative protocols for individuals and families
 - High-risk screening
 - Candidates for prophylactic procedures
 - Chemoprevention

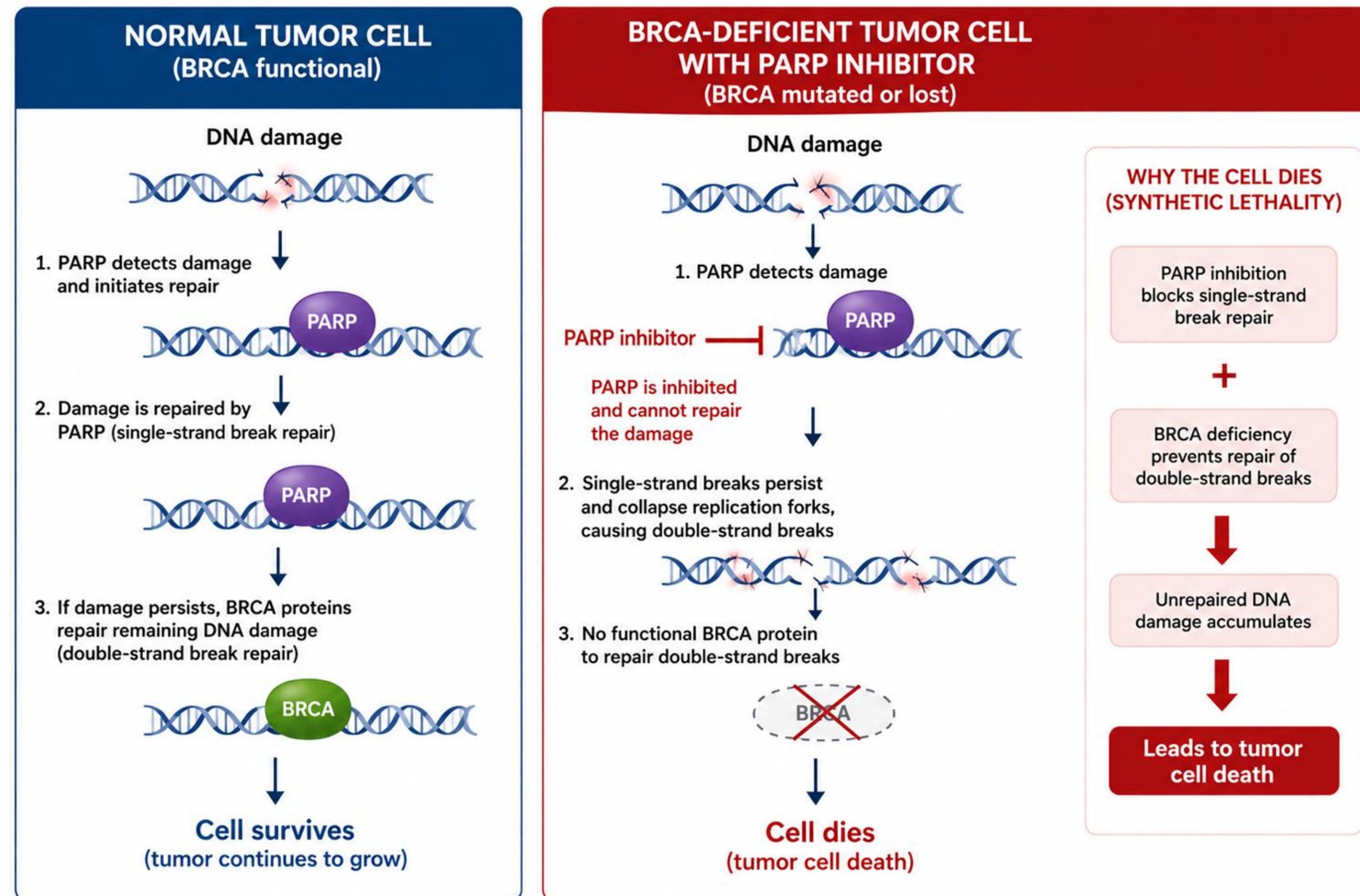
Hereditary Breast and Ovarian Cancer Syndrome

- *BRCA1/2*
 - Tumor suppressor genes involved in Homologous-Recombination Repair
- Prevalence: ~1 in 400



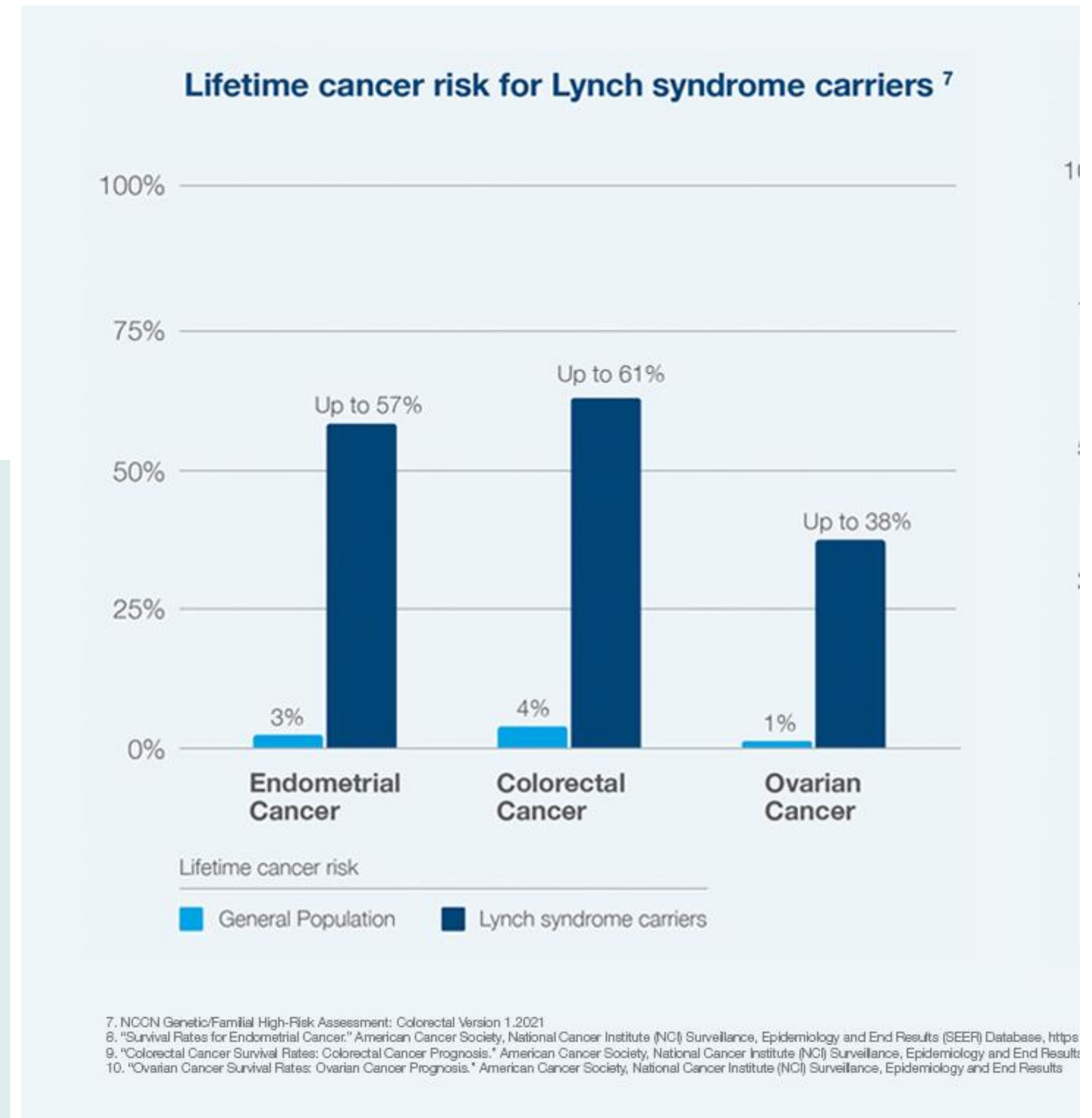
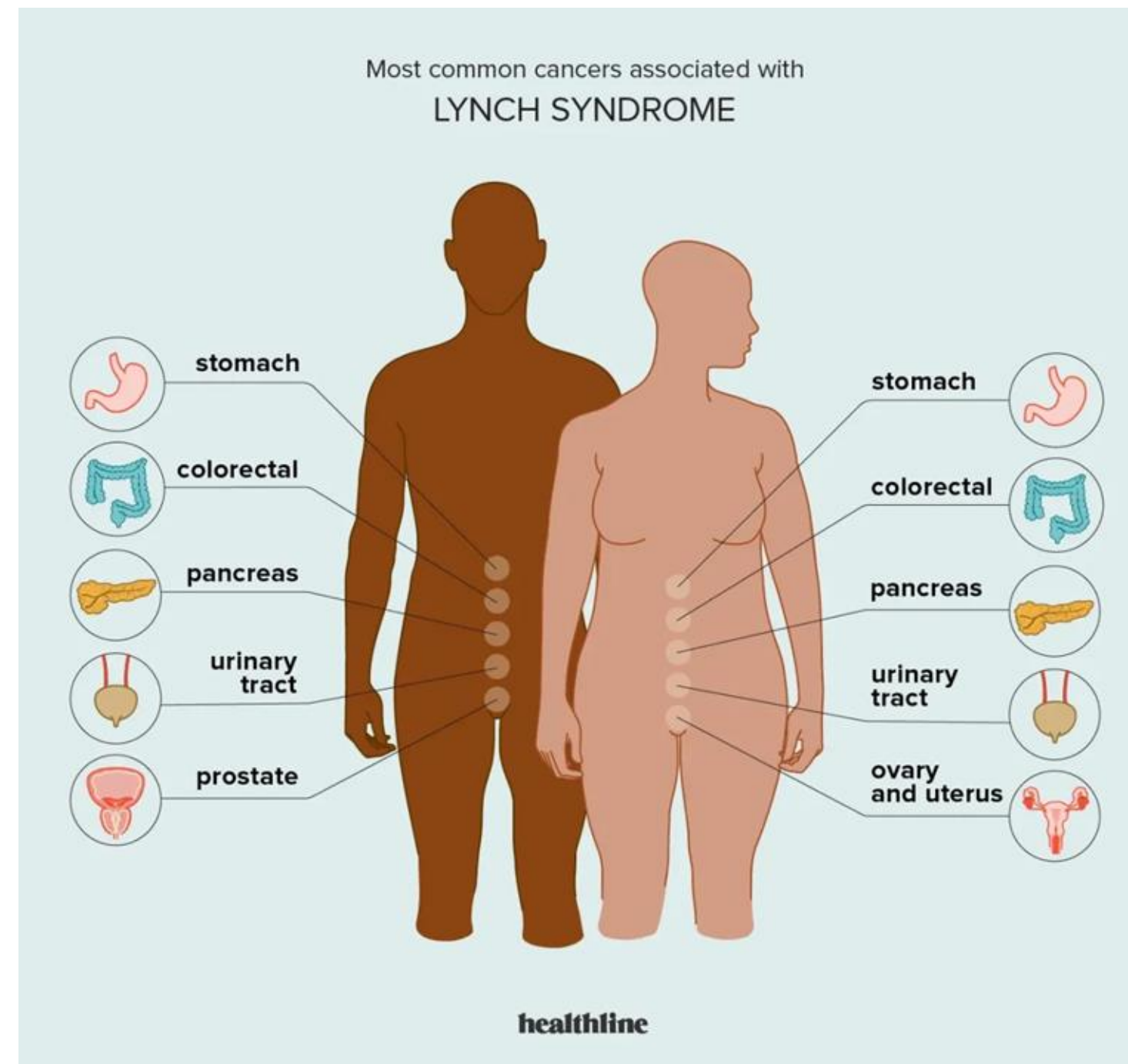
PARP Inhibition

- PARP inhibitors are a class of targeted cancer drugs that kill cells with BRCA mutations via a process called synthetic lethality



Lynch Syndrome

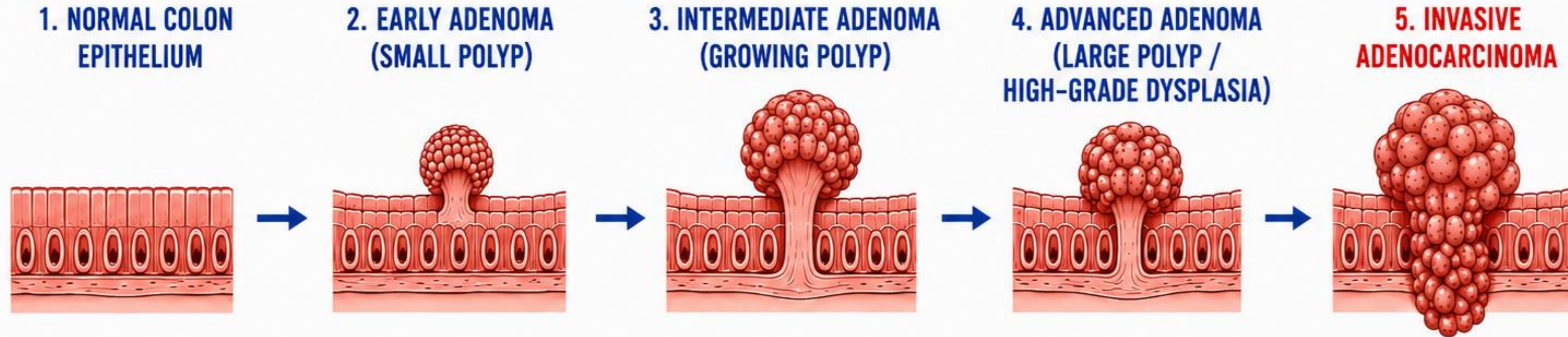
- Hereditary Non-Polyposis Colorectal Cancer Syndrome
- *MLH1, MSH2, MSH6, PMS2, EPCAM*
 - DNA Mismatch Repair Genes (MMR)
- Prevalence: ~1 in 300



COLORECTAL CANCER: POLYP-TO-CANCER PROGRESSION

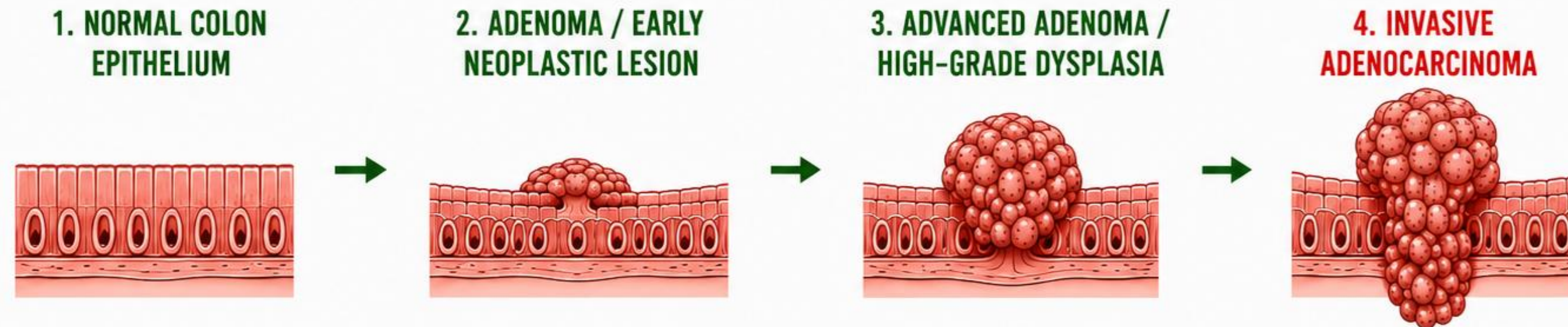
SPORADIC (CONVENTIONAL) ADENOMA-CARCINOMA PATHWAY

Typical timeline: ~10–15 years*



LYNCH SYNDROME (HNPCC) PATHWAY

Typical timeline: ~1–3 years*



Aspirin for cancer prevention in individuals with Lynch syndrome: first results from the CaPP3 multicentre, randomised, double-blind, non-inferiority trial

John Burn, Gillian M Borthwick, Faye Elliott, Finlay Macrae, Kai Ren Ong, Alison C Kraus, Nadir Arber, Jukka-Pekka Mecklin, Jeffrey S Alan, Robyn A Ward, Ignazio Castagliuolo, Orla G Sheils, Kathryn A Williams, Emma L Woodward, Anna L Price, Simon F Cotterill, Maria Teresa Rodriguez-Gironde, Louise L Allen, Susan M Farrington, Sze Hang Cheung, Zoe Mesteri, Noura Ahmadi, Sofia D Valeri, Ingela Tuupanen, Judith Church, David Thomas, Sian C Thomas, Clare Turnbull, Rachel Butler, Christopher P Young, on behalf of the CaPP3 (Cancer Prevention in Lynch Syndrome 3) investigators

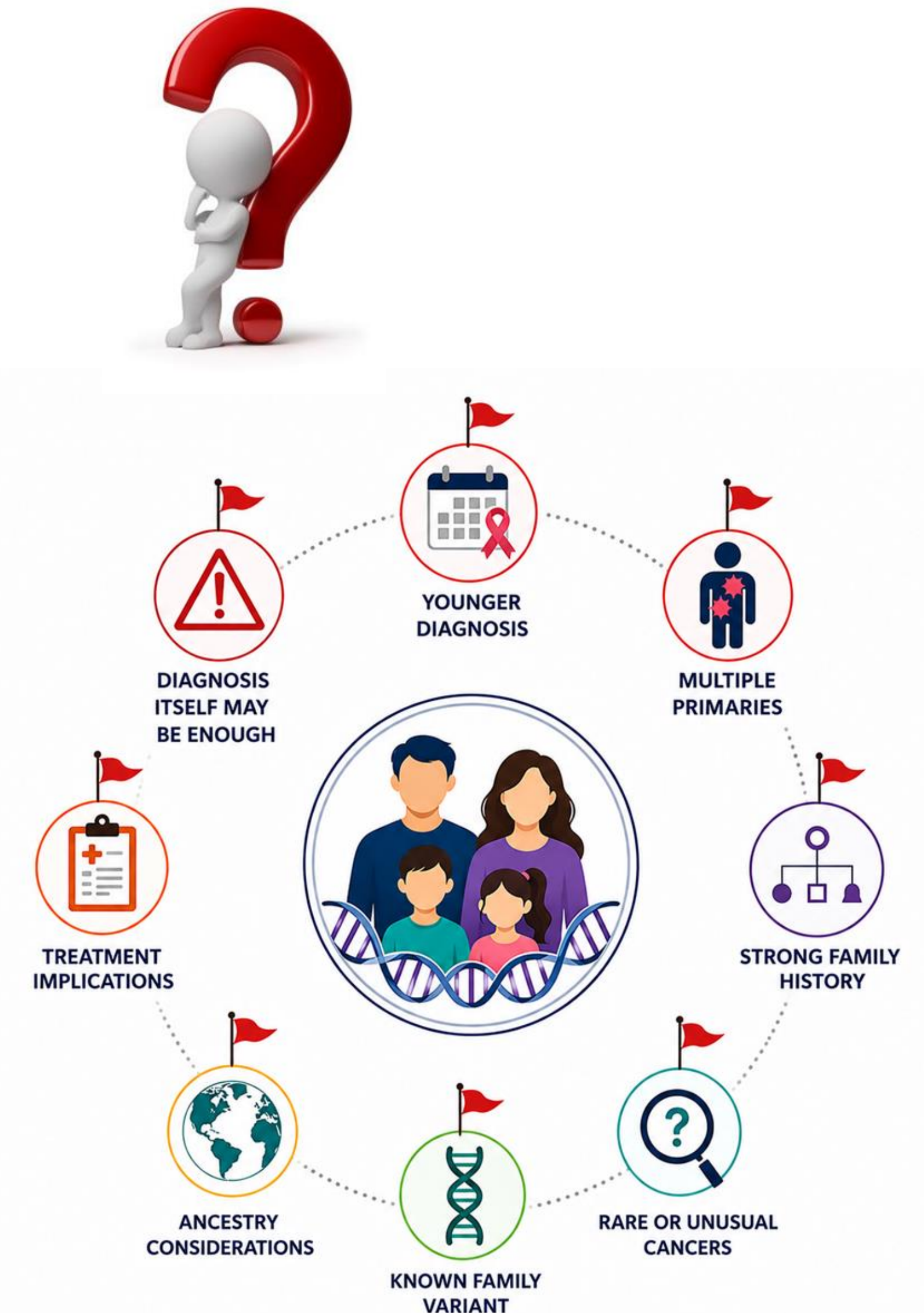
- Daily low-dose aspirin appears effective in reducing bowel cancers in people with Lynch syndrome
 - CaPP3 results demonstrated similar chemoprevention efficacy with 100mg daily use vs 300 and 600 mg group with lower risk of adverse effects
- Protection accrues with several years use, even if discontinued. Duration of protection unknown but possibly a decade

NCCN:

- The Panel recommends that all individuals with LS who have a risk for future CRC (ie, excluding those with prior total proctocolectomy [TPC]) consider using daily aspirin to reduce their future risk of CRC.^f The decision to use aspirin for reduction of CRC risk in LS and the dose chosen should be made on an individual basis, including discussion of individual risks, benefits, adverse effects, and childbearing plans.^g In determining whether an individual with LS should take aspirin and in deciding on the appropriate dosing, the Panel recommends that providers carefully review patient-specific factors that may increase the risk of aspirin therapy—including but not limited to increased age, prior allergy, concurrent use of antiplatelets/anticoagulants, untreated *Helicobacter pylori* or unconfirmed *H. pylori* eradication—as well as patient-specific factors that indicate a comparably low future cumulative risk of CRC (ie, increased age, PMS2-associated LS, history of prior colectomy) and who may thus be less likely to experience significant benefit.

Genetic Cancer Risk Assessment (GCRA)

- Interdisciplinary practice that uses genetic and genomic information to:
 - Identify individuals with inherited cancer risk
 - Enroll such individuals in high-risk surveillance programs
- Increasing demands for GCRA in community settings
 - Clinical integration of hereditary cancer genomics remains low which results in delays in diagnosis, fragmented treatment pathways and ultimately missed opportunities for proactive and preventative interventions
 - Let's circle back to this in a bit
- So how do we identify these individuals? Who should get tested?



Who should raise your Genetics Radar?

- NCCN (National Comprehensive Cancer Network) and U.S. Preventative Task Force have established criteria regarding clinical recommendations/considerations for hereditary cancer testing
- 2019 study conducted by Myriad Genetics demonstrated nearly 1 in 4 unaffected woman patients presenting for annual OB/GYN visits met NCCN genetic testing criteria for HCS.
 - Bucheit, L., Ready, K., Brown, J., & Goldberg, J. D. (2019). Opportunity for Cancer Prevention: 1 in 4 Unaffected Women Meet Hereditary Cancer Testing Criteria [26O]. Obstetrics & Gynecology, 133, 169.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment:

Breast, Ovarian, Pancreatic, and Prostate

Version 1.2027 — August 31, 2026

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment:

Colorectal, Endometrial, Esophageal, and Gastric

Version 1.2026 — June 16, 2026

Clinical Red Flags

- General testing criteria for HBOC
- Personal and/or family history of:
 - Breast cancer <50
 - Triple-negative B.C
 - 2 or more breast or similarly associated cancers on same side of family at any age
 - Uncommon cancers
 - Pancreatic, ovarian, metastatic prostate cancer
 - Multiple primaries
 - AJ Ancestry

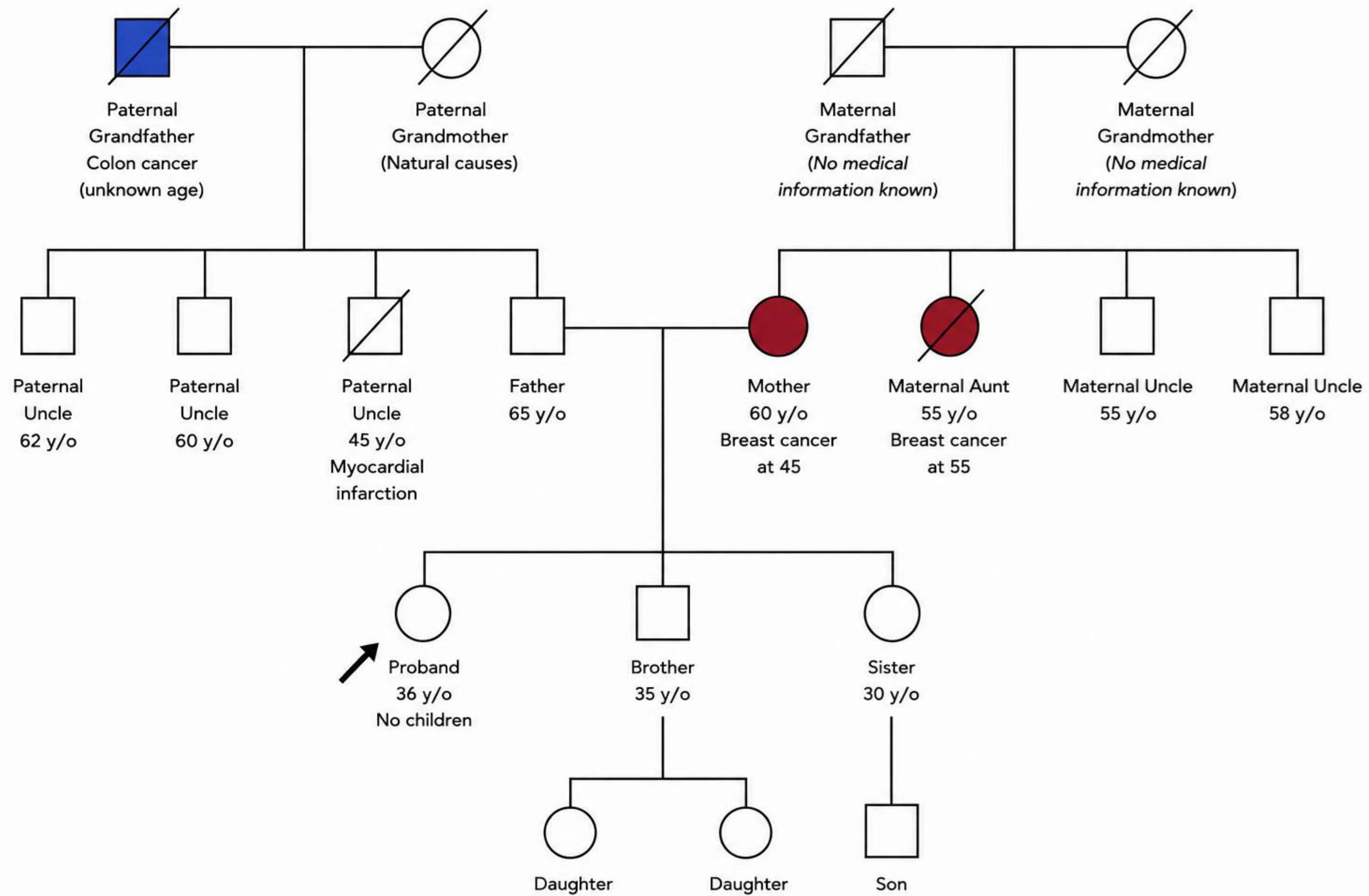
- General Testing criteria for Lynch
- Personal and/or family history of:
 - CRC, EC, GC <50
 - 2 or more similar cancers on same side regardless of age including those listed above
 - Uncommon cancers
 - Pancreatic, ovarian, metastatic prostate
 - Multiple Primaries

Germline Panel Testing

- In 2026, Comprehensive multi-gene panel testing (60-80 genes) is generally the standard clinical approach for hereditary cancer testing
- Testing is continually becoming more accessible due to:
 - Broader testing criteria
 - Telehealth Expansion
 - Mainstreaming/Point-of-Care Testing
 - Broader/Expanded insurance coverage
 - Lower Self-Pay Prices
 - Financial Assistance Programs

Case Example

- 36 y/o female, Maria, referred from gynecology to cancer genetic counseling during annual check up d/t maternal family hx of breast cancer
 - Patient states 10-year use of OCPs, patient is nulliparous
 - First MMG, done early d/t family history, showed heterogeneously dense breast tissue, unremarkable otherwise



Genetic Testing Considerations

- Informed Consent
- Autonomy
- Uncertainty
- Incidental Findings
- Family implications
- Privacy and Discrimination
- Legal/Liability Implications



PATIENT:	Jane Doe	ORDERING PROVIDER:	LABORATORY ID:
DATE OF BIRTH:	01/01/1985 (40 y/o)	Mary Smith, MD	GWG-24-123456
GENDER:	Female	CLINICAL INDICATION:	SPECIMEN TYPE:
MRN:	1234567	Personal and/or family history of breast cancer	Blood
		TEST REQUESTED:	DATE RECEIVED:
		Hereditary Cancer Panel	05/15/2024
			DATE REPORTED:
			05/22/2024

RESULT:

POSITIVE

Pathogenic variant identified in *BRCA1*.

RESULT DETAILS

GENE	VARIANT IDENTIFIED	ZYGOSITY	VARIANT CLASSIFICATION
<i>BRCA1</i>	c.5266dupC (p.Gln1756Profs*74)	Heterozygous	Pathogenic

INTERPRETATION

A pathogenic (disease-causing) variant was identified in the *BRCA1* gene.

This result is consistent with a diagnosis of Hereditary Breast and Ovarian Cancer syndrome (HBOC) and confers an increased risk for certain cancers, including breast and ovarian cancer.

Genetic counseling is recommended to discuss the implications of this result, including medical management options and cascade testing for at-risk relatives.

ABOUT *BRCA1* PATHOGENIC VARIANTS

Pathogenic variants in *BRCA1* are associated with increased lifetime risks for:

- Female breast cancer: 60–72%
- Ovarian cancer: 39–58%
- Additional risks: pancreatic cancer, prostate cancer, and others

Risks may vary based on family history and other factors.

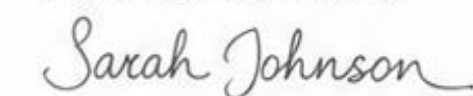
METHOD

Multi-gene panel analysis was performed using next-generation sequencing and deletion/duplication analysis.

Genes analyzed: A comprehensive panel of 70 genes associated with hereditary cancer predisposition.

This test was performed in a CLIA-certified and CAP-accredited laboratory.

Reviewed and Reported by:



Sarah Johnson, MS, CGC
Certified Genetic Counselor
05/22/2024

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www.genewise genetics.com



BRCA1 Management

- **Breast Cancer**

- 60-72% baseline risk vs 12% gen. population risk
- Non-Surgical Management
 - High-risk screening protocol involving biannual imaging alternating MMG w/ MRI
 - No degree of protection
- Surgical Management
 - Prophylactic bilateral mastectomy +/- reconstruction
 - Highly effective at reducing B.C incidence (~90-95% reduction)
- Chemoprevention

- **Ovarian Cancer**

- 39-58% baseline risk vs ~1% gen. population risk
- Recommendation for risk-reducing salpingo-oophorectomy b/w ages 35-40
- Many different possible personal considerations that need to be considered regarding joint-decision making
 - ex. Does patient still wish to conceive?
 - Previous 10-year use of OCPS-> Protective factor
 - Consider referral to fertility specialist for egg/embryo cryopreservation & possible PGT -> Proceed with RR-BSO leaving uterus in place allowing for pregnancy via IVF
 - Etc.

PATIENT:	Jane Doe	ORDERING PROVIDER:	LABORATORY ID:
		Mary Smith, MD	GWG-24-123456
DATE OF BIRTH:	01/01/1985 (40 y/o)	CLINICAL INDICATION:	SPECIMEN TYPE:
		Personal and/or family history of breast cancer	Blood
GENDER:	Female		DATE RECEIVED:
			05/15/2024
MRN:	1234567	TEST REQUESTED:	DATE REPORTED:
		Hereditary Cancer Panel	05/22/2024

RESULT:

VARIANT OF UNCERTAIN SIGNIFICANCE (VUS)

A variant of uncertain significance was identified in *BRCA1*.

RESULT DETAILS

GENE	VARIANT IDENTIFIED	ZYGOSITY	VARIANT CLASSIFICATION
BRCA1	c.4075G>A (p.Arg1359His)	Heterozygous	Variant of Uncertain Significance (VUS)

INTERPRETATION

A variant of uncertain significance (VUS) was identified in the *BRCA1* gene.

This means that a change was found in this gene, but there is not enough current evidence to determine whether it is associated with an increased risk for cancer or is a benign (normal) variation.

Genetic counseling is recommended to discuss the implications of this result, including the limitations of this finding and the potential for reclassification as more information becomes available.

Medical management decisions should not be based on this VUS result alone.

ABOUT BRCA1 VARIANTS

Variants of uncertain significance are common and do not confirm or rule out a diagnosis of hereditary cancer syndrome.

Classification of a variant may change over time as new information becomes available.

Management should be based on personal and family history.

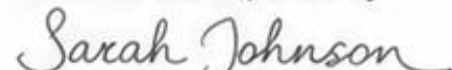
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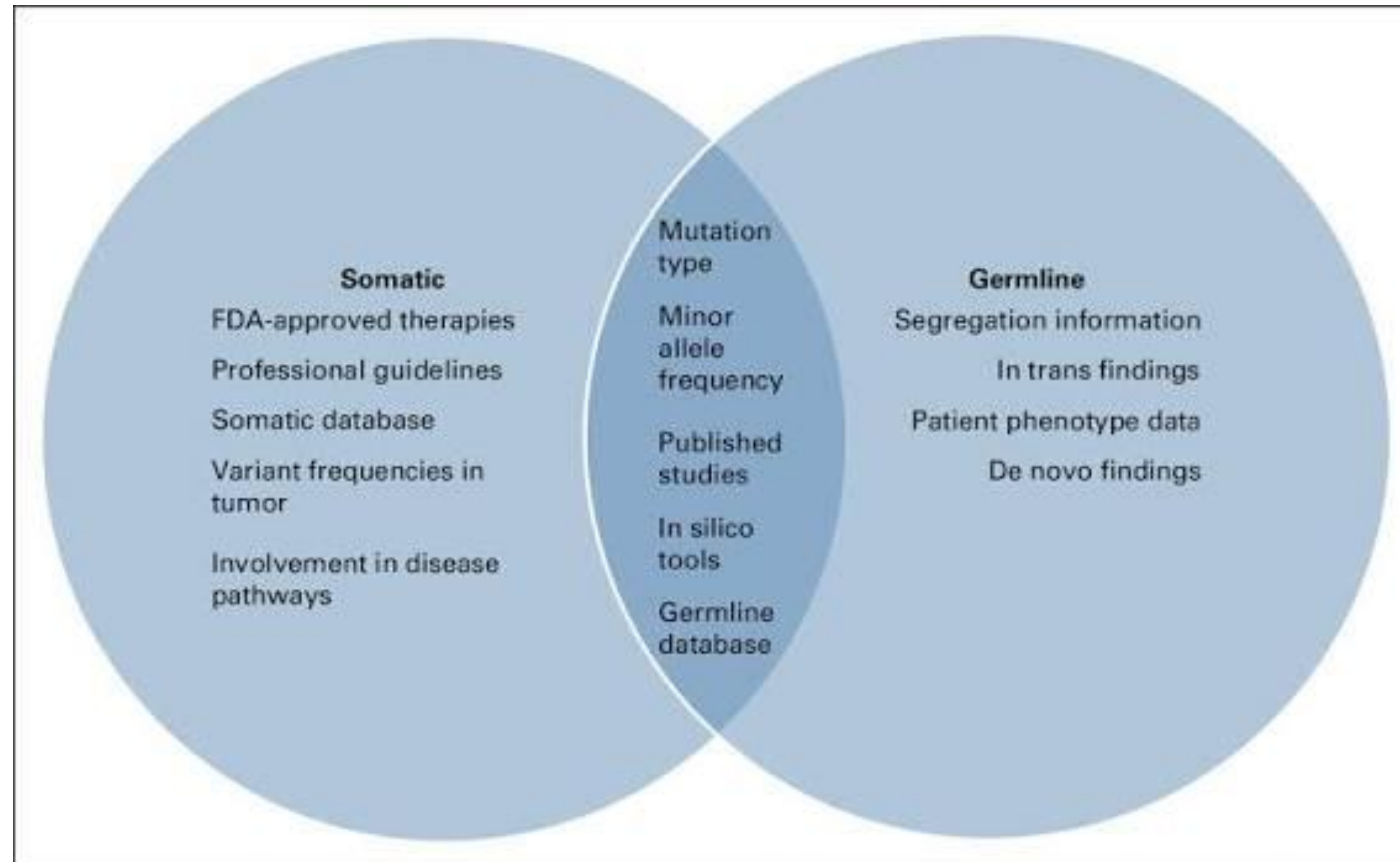
Genetic Testing Interpretation

- Positive (Pathogenic)
 - Harmful mutation found
 - “Have the gene”
 - Associated with disorder
 - Medical management changes
- Variant of Unknown Significance (Maybe)
 - Genetic change is found, but impact of change is unknown
 - Generally not seen in affected individuals
 - Can become reclassified
- Negative
 - No genetic change is identified
 - Possible limitation?
 - Possibly uninformative?



Variant Interpretation

- Process of analyzing an genetic change to determine if it causes or increases the risk of developing a specific disease
- Complex bioinformatic pipeline involving incorporation of multiple different lines of evidence



Variant classification	VUS temperature scale	Posterior probability
Pathogenic		99%
Likely pathogenic		90%
Uncertain significance	Hot	81.2%
	Warm	67.5%
	Tepid	50%
	Cool	32.5%
	Cold	18.8%
	Ice cold	10%
Likely benign		0.1%
Benign		

Conflicting Interpretations

- Certain genetic variants will have conflicting interpretations of impact between labs
- A lab could classify a variant as harmful, while another one classifies it as uncertain

NM_000059.3(BRCA2):c.67G>A (p.Asp23Asn) [Cite this record](#)

Interpretation: Conflicting interpretations of pathogenicity
Likely pathogenic(1);Uncertain significance(1)

Review status: ★☆☆☆ criteria provided, conflicting interpretations
Submissions: 2 (Most recent: Oct 5, 2017)
Last evaluated: Apr 28, 2017
Accession: VCV000225732.1
Variation ID: 225732
Description: single nucleotide variant

Variant details

Conditions

Gene(s)

Aggregate interpretations per condition

Interpreted condition	Interpretation	Number of submissions	Review status	Last evaluated	Variation/condition record
Breast-ovarian cancer, familial 2	Likely pathogenic	1	criteria provided, single submitter	Apr 21, 2016	RCV000211034.1
Hereditary breast and ovarian cancer syndrome	Uncertain significance	1	criteria provided, single submitter	Apr 28, 2017	RCV000548779.1

NM_00535.7(PMS2):c.142G>A (p.Asp48Asn) [Cite](#) [Follow](#)

Germline

Classification ★★☆☆ ?
Conflicting classifications of pathogenicity
Pathogenic (1); Likely pathogenic (1); Uncertain significance (7)
9 out of 9 submissions contributed to this classification ?

Somatic

No data submitted for somatic clinical impact

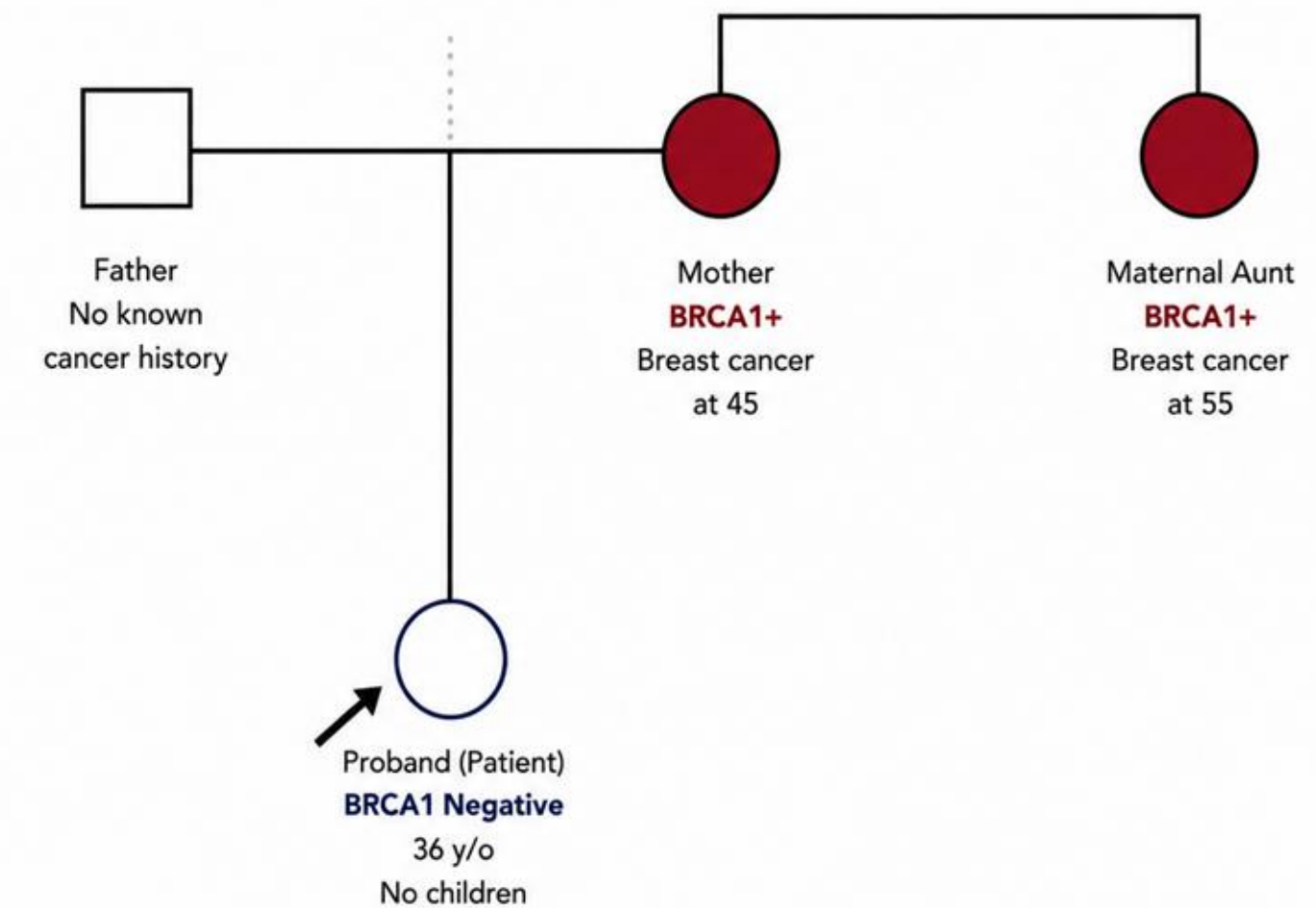
Somatic

No data submitted for oncogenicity

<https://www.ncbi.nlm.nih.gov/clinvar/>

What if patient results are negative?

- Would a negative result for this patient = no increased risk of breast cancer?
 - True negative: Patient negative for familial variant
 - Patient is at general population risk



- Slightly uninformative: Negative genetic testing results for affected family members or family genetics unknown
- Often, cancer risk isn't determined by a single test result
 - What's their risk now?

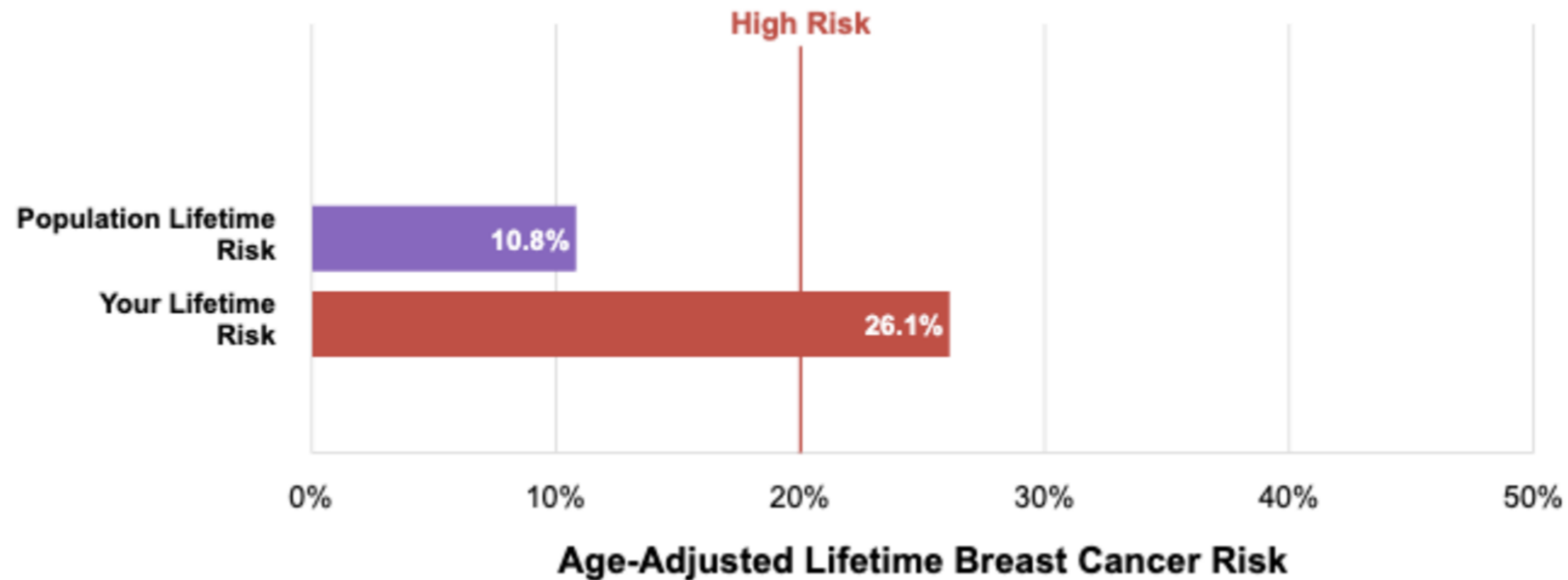
Breast Cancer Risk Models

Tyrer-Cuzick v8

- Risk model that incorporates comprehensive set of variables (Personal & family hx) to assess a woman's lifetime risk of breast cancer

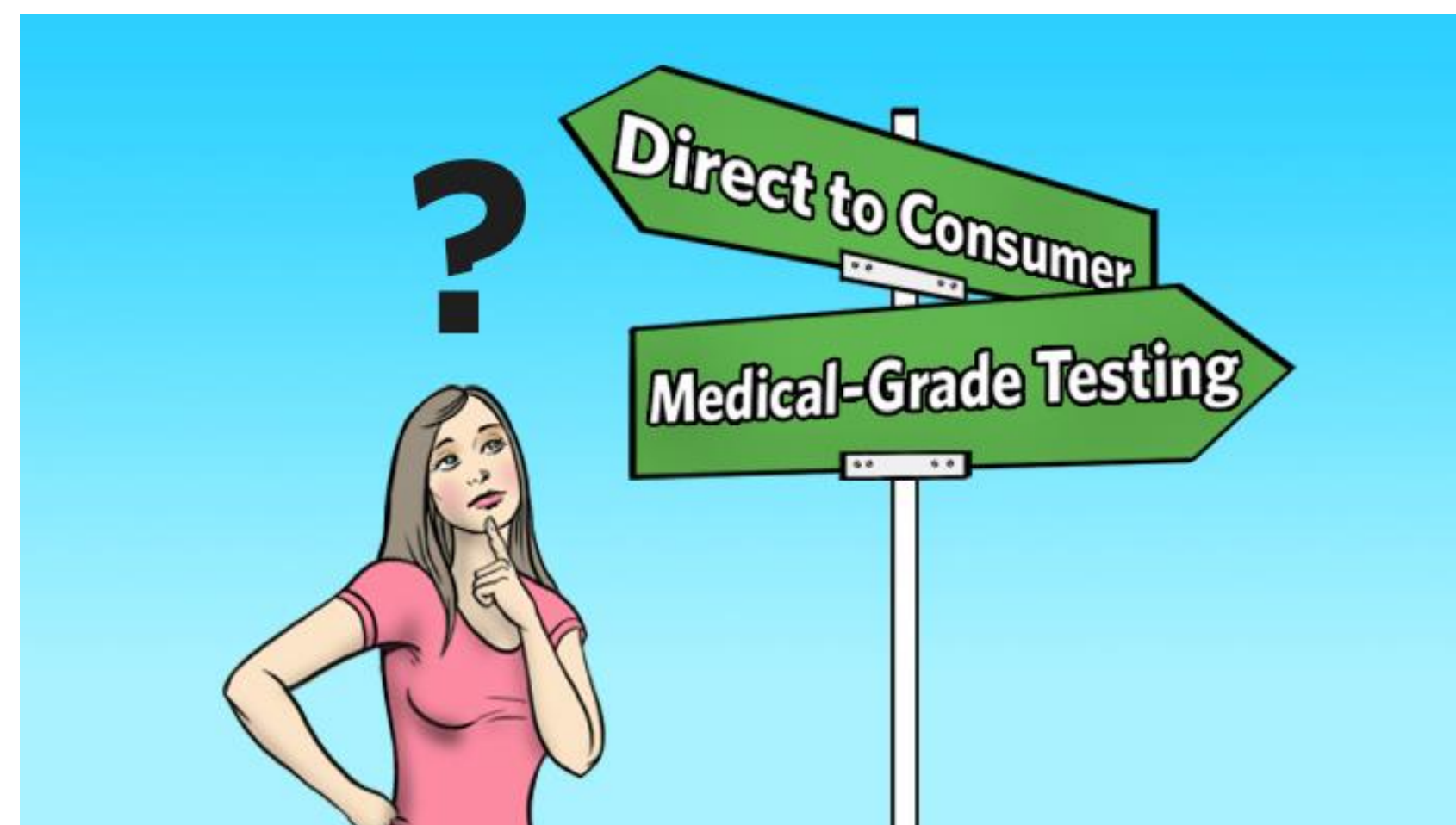
Your Breast Cancer Risk Assessment Score

The results below are based on the IBIS risk assessment model, also known as the Tyrer-Cuzick (v8) risk assessment model. These results show your lifetime risk for breast cancer compared to the U.S. population average.



Modern Challenges

- Genetic testing nowadays has been remarkably easy to access. Is this necessarily a good thing?
 - Rapid Rise in DTC Testing.
 - Some companies monetize off consumer fears, offer tests with little clinical validity, or not be properly certified
 - Greater access to testing does NOT automatically mean greater access to genetic expertise



So how do we actually advance early detection?

- If we dramatically expand GCRA, who is going to provide everything that comes after?
 - Mainstreaming testing requires additional access to genetics expertise.
- Genetic testing is more than ordering a test, it creates responsibilities beyond the patient
- Nevada has a significant genetics infrastructure gap
 - Genetic counselors, as well as additional genetic-trained healthcare professionals (Genetic-trained APPs), are key to bridge this gap, especially as testing continues to expand
 - When recruitment of a genetic counselor is not feasible, a motivated APP with additional training in hereditary cancer genetics can serve as an interim strategy to help establish and facilitate genetic longitudinal care
- Leveraging Hereditary Cancer labs high-risk identification platform in POC clinics for easier identification

“The names of the patients whose lives we save can never be known. Our contribution will be what did not happen to them.

And, though they are unknown, we will know that mothers and fathers are at graduations and weddings they would have missed, and that grandchildren will know grandparents they might never have known, and holidays will be taken, and work completed, and books read, and symphonies heard, and gardens tended that, without our work, would never have been.”

-Dr. Donald M. Berwick, Former Administrator for CMMS