

Cancer Genetic Susceptibility Testing: Disease prediction for Public Health Benefit



ICR The Institute of
Cancer Research

The Royal Marsden **NHS**
NHS Foundation Trust

NDRS
NATIONAL DISEASE REGISTRATION SERVICE

Funded by

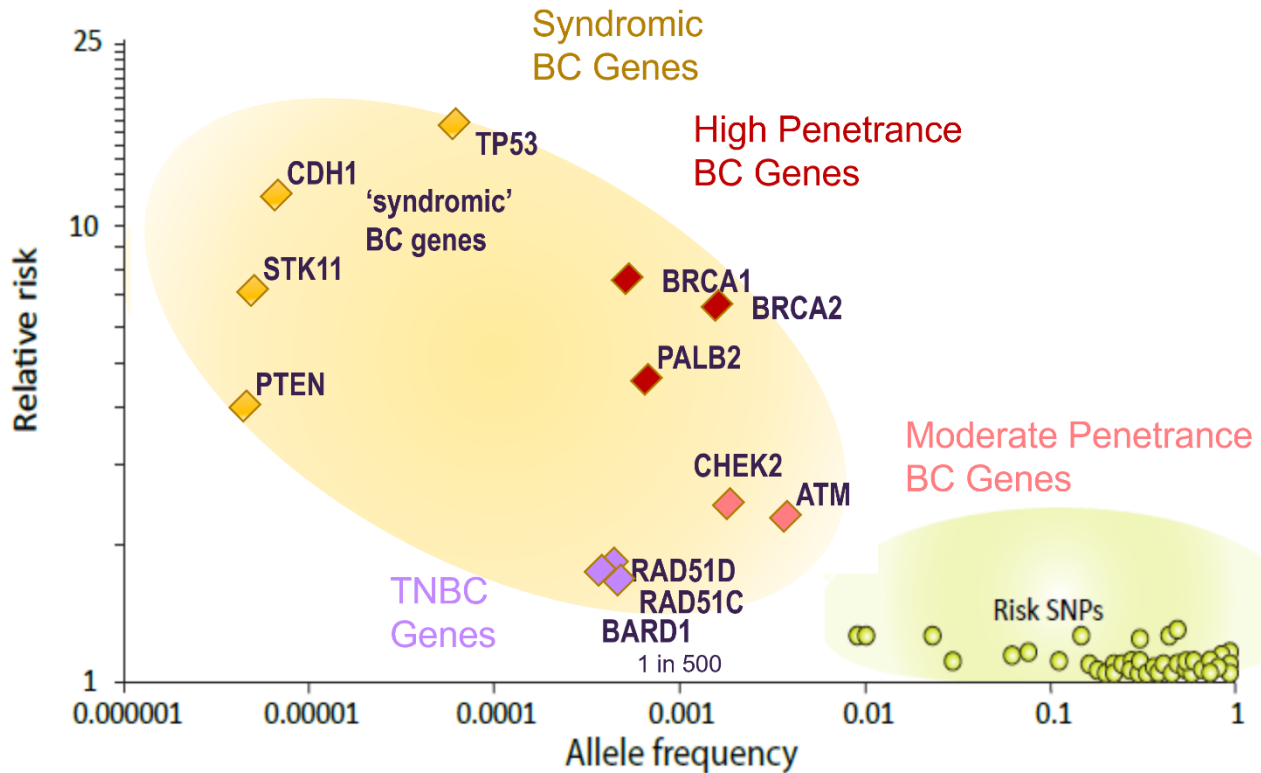
**CANCER
RESEARCH
UK**

**NICE
Manchester
March 2025**

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- **NHS Consultant in Clinical Cancer Genetics** (Honorary), Royal Marsden NHS Foundation Trust
- **Consultant in Public Health Medicine** (Honorary), National Diseases Registration Service, NHSE

Genomic architecture of breast cancer susceptibility and SPED (screening/prevention/early detection)



Turnbull C, Sud A, and Houlston, R.S
Nat Genet. 2018;50(9):1212–1218.

Screening



National screening programmes:
Breast, Colorectal, Cervix

Enhanced screening programmes:
 Modality **MRI**
 Age of starting **30**
 Frequency **annually**

Primary surgical prevention



Mastectomy
Oophorectomy
Colectomy
Gastrectomy

Primary chemoprevention



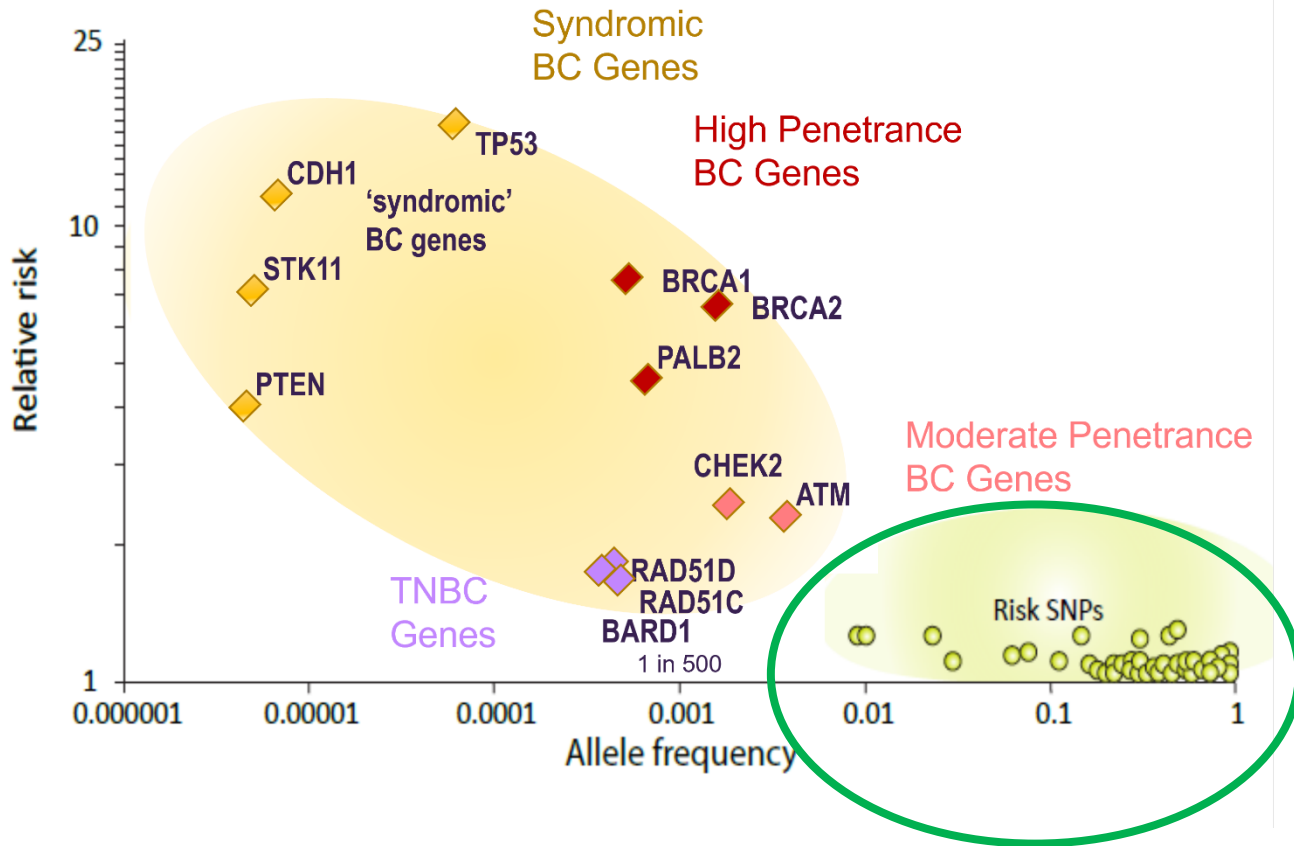
RE-PURPOSED: aspirin, metformin,
RE-POSITIONED: **Taxoxifen,**
Anastrozole
TARGETED: **denosumab, ?? PARPi**

Behavioural



Smoking
Sun exposure
Hormonal factors (? BF, age CB)

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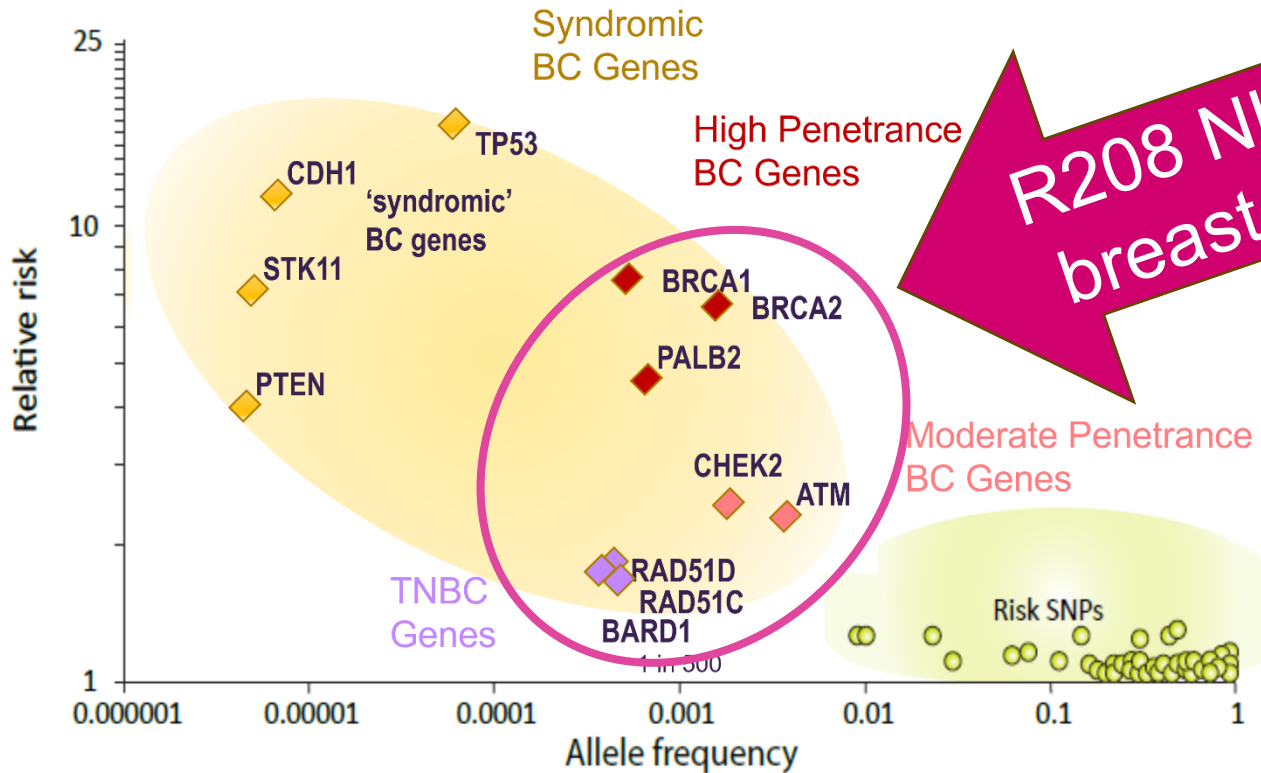
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Prevention

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Behavioural

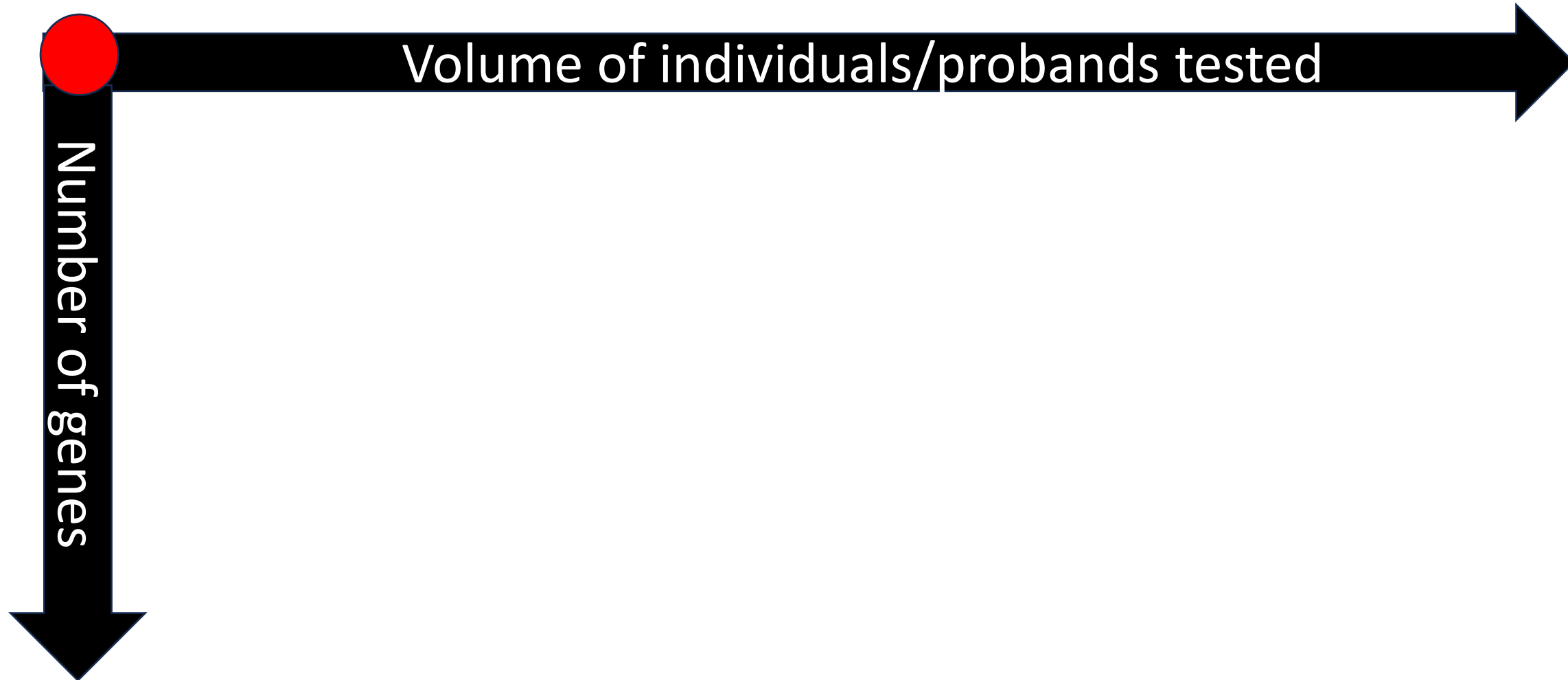
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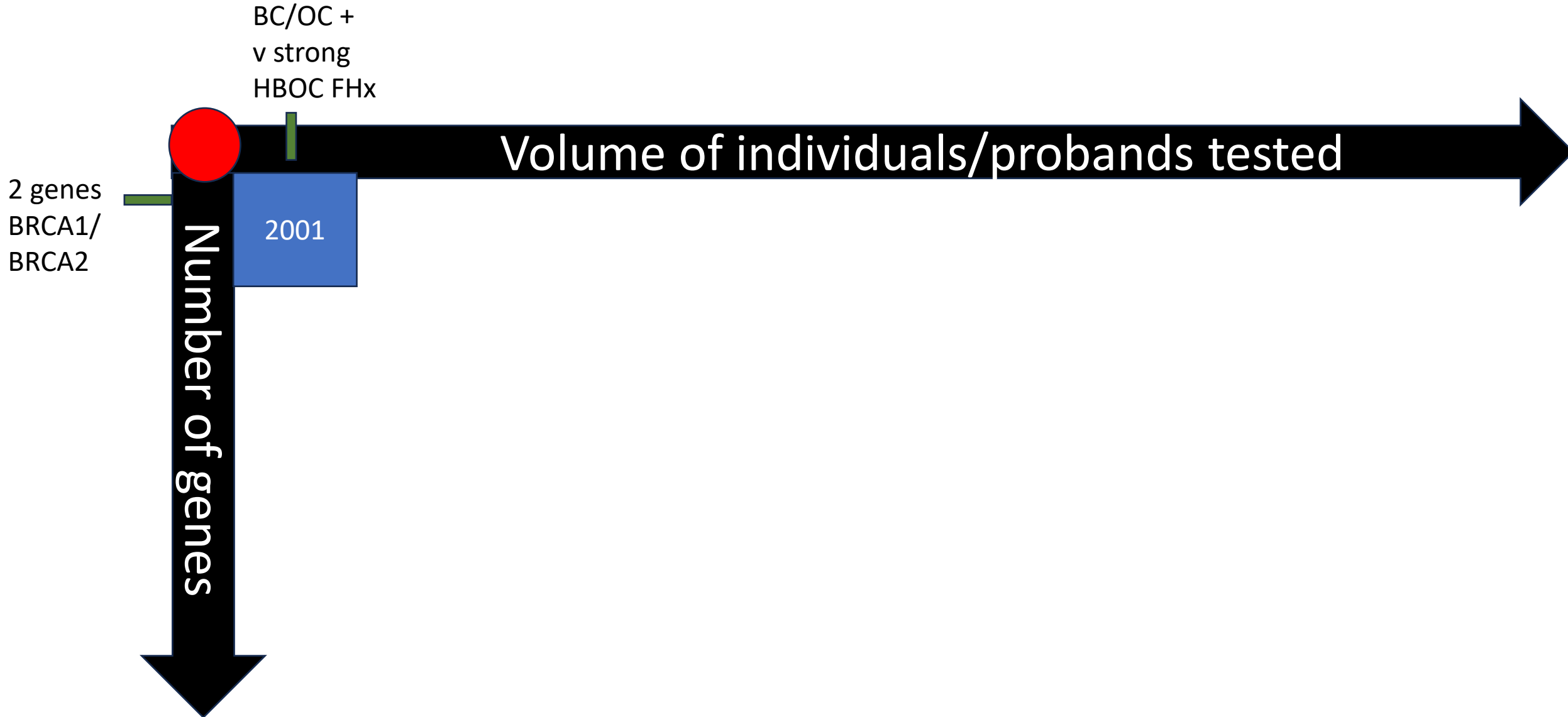
BRCA gene testing programmes: Novel, high throughput, ‘clinician-light’ pathways implemented in NHS

   	<p>BRCA-testing in breast cancer patients: peri-diagnostic (mainstream)</p> <ul style="list-style-type: none"> • CRUK-funded randomised research study (2010-2022) <ul style="list-style-type: none"> • 1000 unselected BC patients (3 gene panel) • NHSE SBRI-funded realworld transformation implementation programme (2023-2025) <ul style="list-style-type: none"> • 3500 unselected BC patients (7 gene panel)
<p>THE NHS JEWISH BRCA TESTING PROGRAMME</p> 	<p>BRCA-testing in (unaffected) Jewish population</p> <ul style="list-style-type: none"> • NHSE-funded realworld transformation implementation programme (2023-2026) <ul style="list-style-type: none"> • 30,000 people (>27,000 registered) so far (2 genes: BRCA1, BRCA2)
 	<p>BRCA-testing in breast cancer patients: historic diagnosis</p> <ul style="list-style-type: none"> • NHSE-funded realworld transformation implementation programme (2025-2028) <ul style="list-style-type: none"> • 12,000 patients with high-risk BC (<40 years, triple-negative, bilateral) or OC (7 gene panel) • historic diagnosis (2000-2020)

Expansion of genetic/genomic testing: Breast-Ovarian Cancer as exemplar



Expansion of genetic/genomic testing: Breast-Ovarian Cancer as exemplar

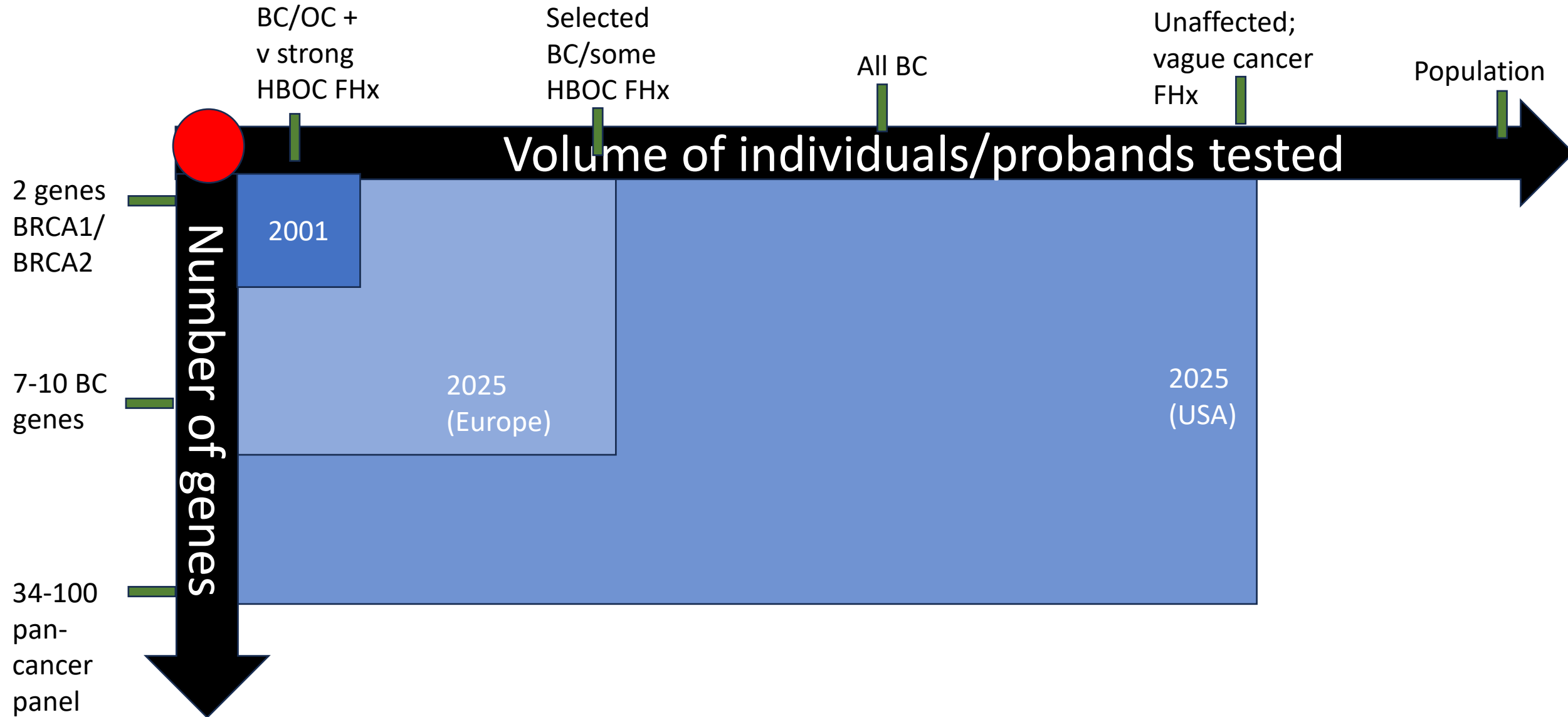


Expansion of genetic/genomic testing: Breast-Ovarian Cancer as exemplar



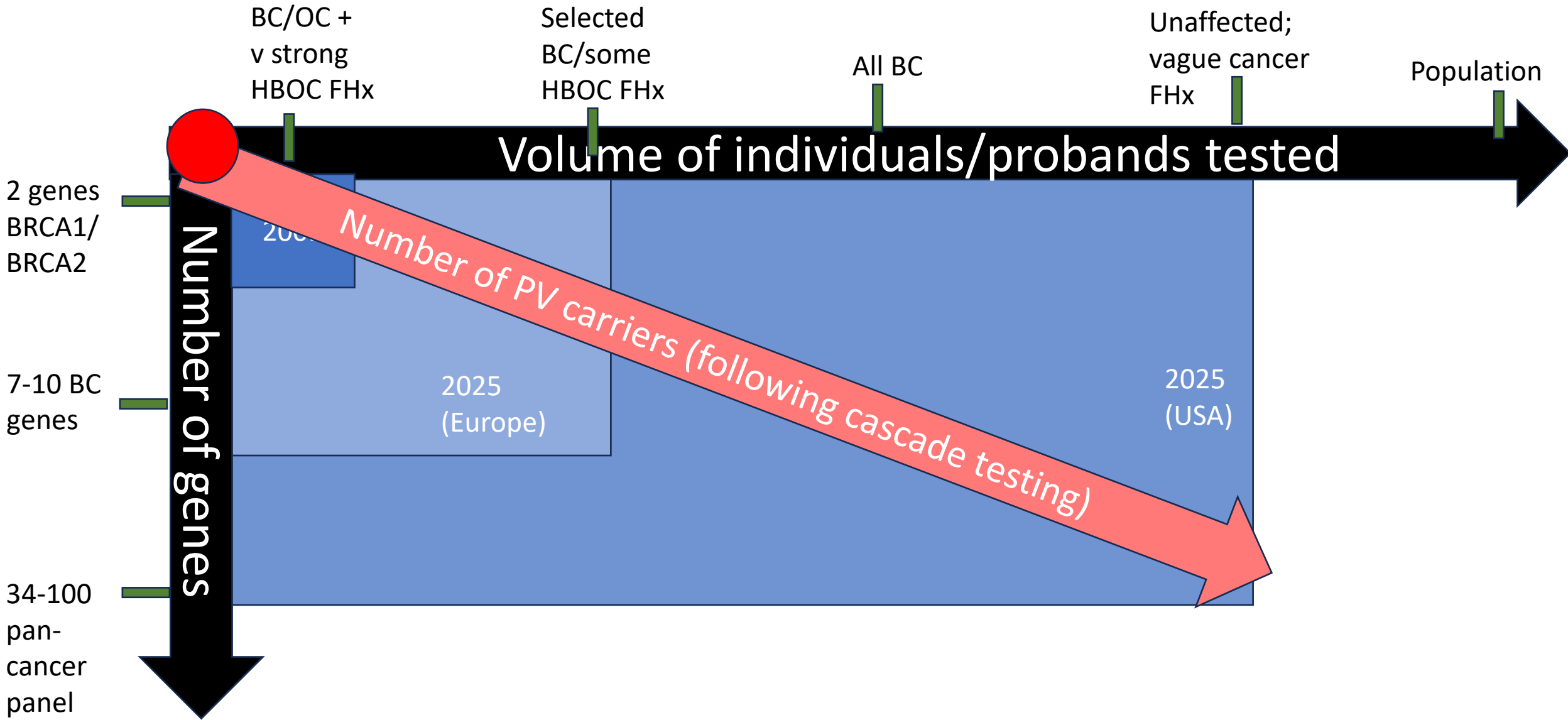
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NCCN guidance



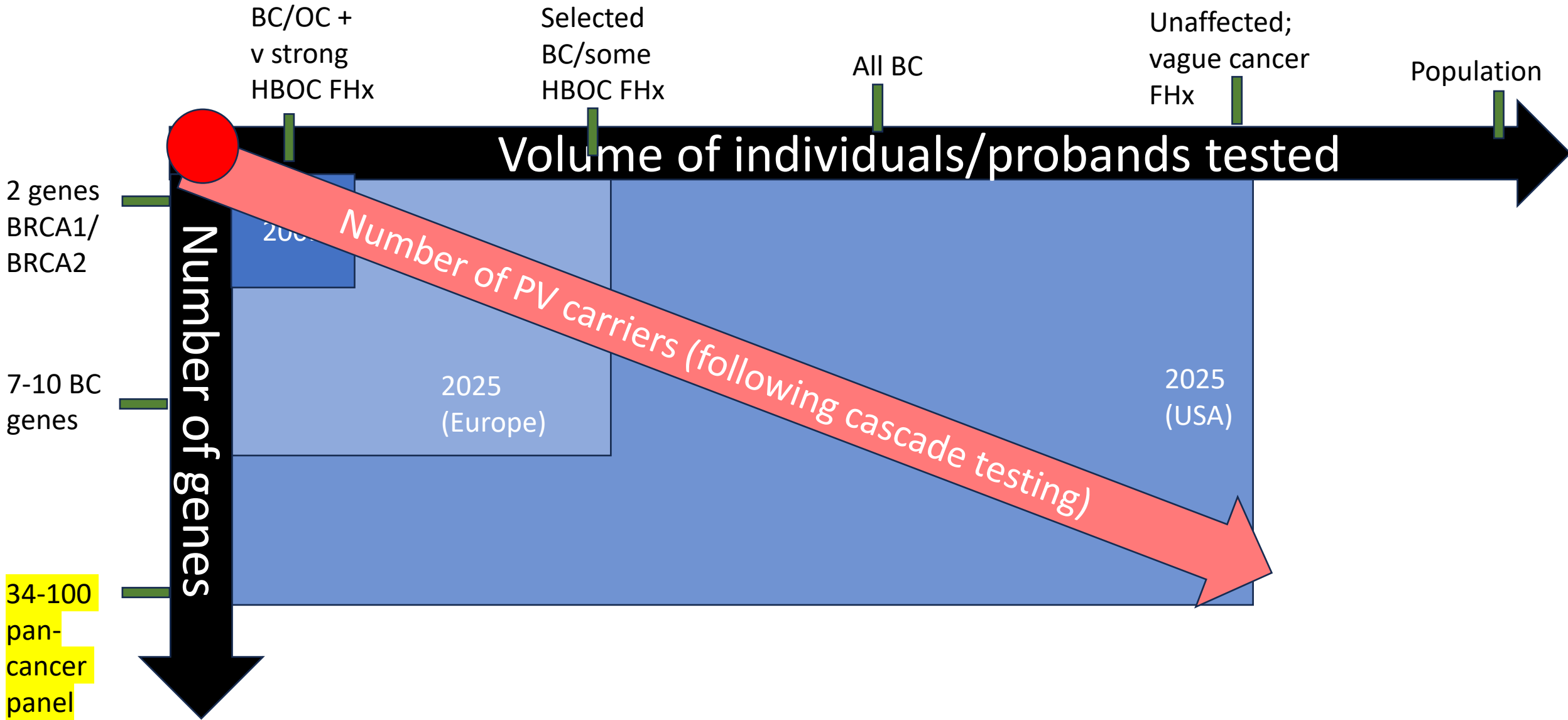
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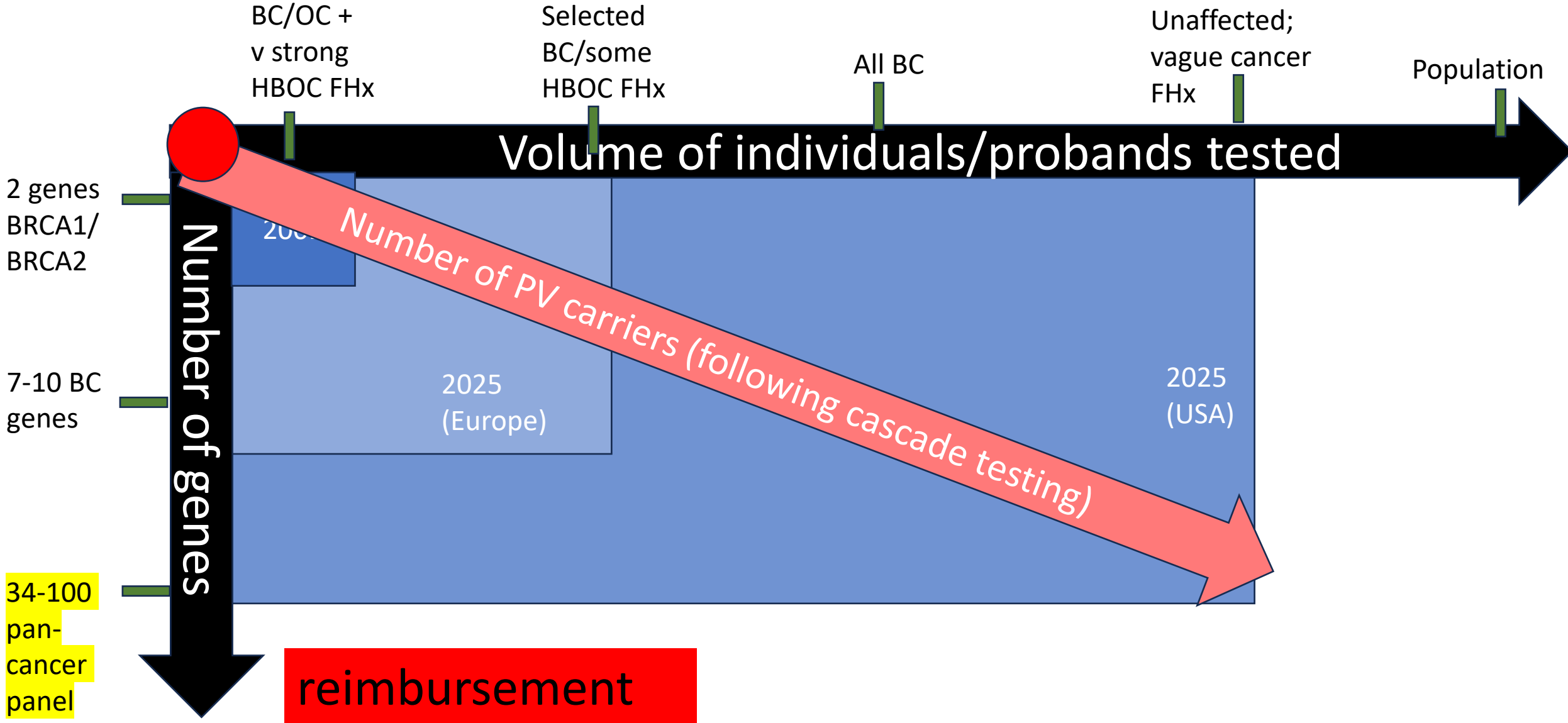
Expansion of genetic/genomic testing: Breast-Ovarian Cancer as exemplar

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Expansion of genetic/genomic testing: Breast-Ovarian Cancer as exemplar

NCCN guidance



For which CSGs is of clinical benefit to test?

What is the relevant outcome metric? CSGs: cancer susceptibility genes

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What is the relevant outcome metric?

PV=pathogenic variant
(gene mutation, gene fault)

GENE PV

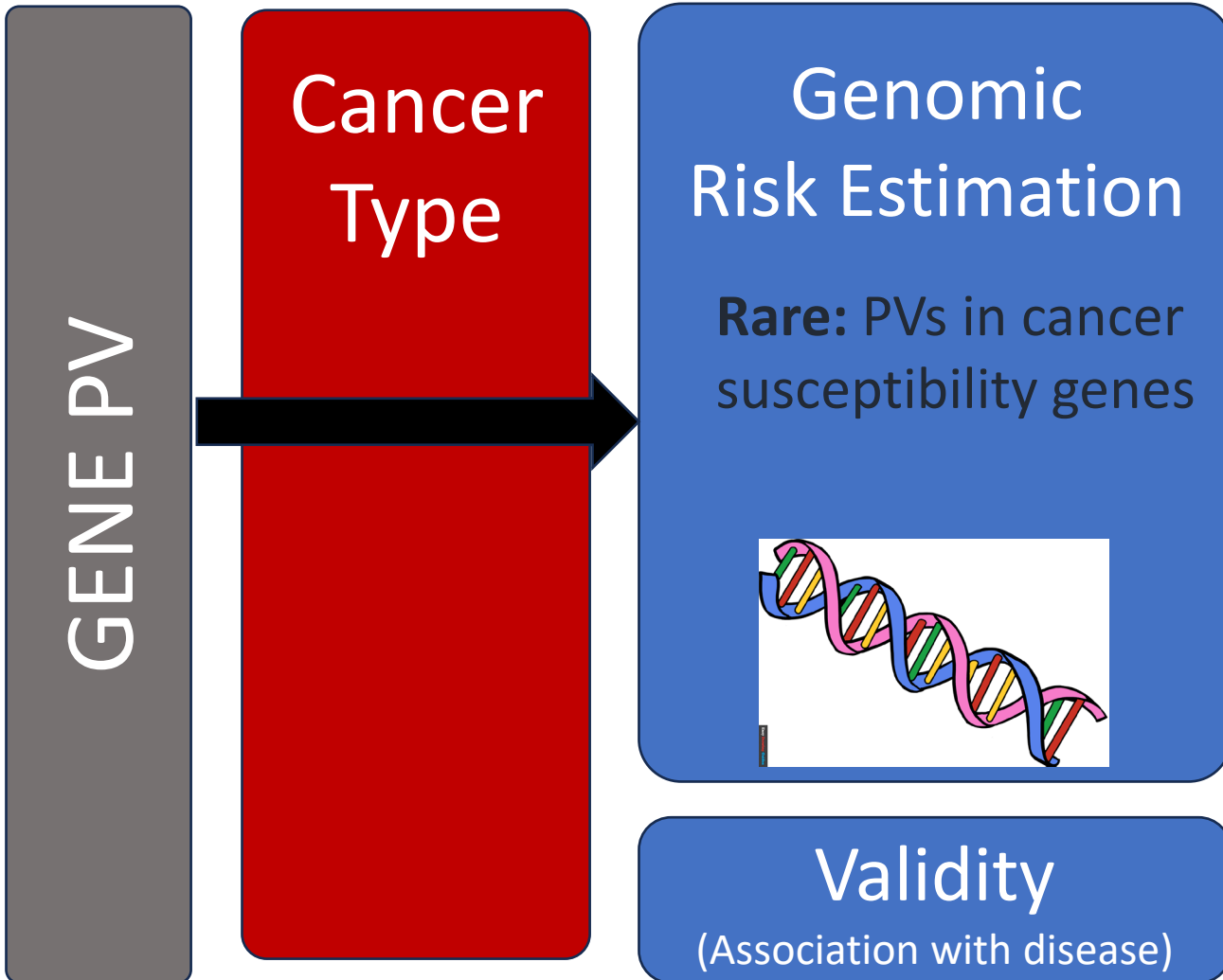


?Improves
Mortality
and/or
Morbidity/
Treatments Costs

Clinical/Public
-Health Utility

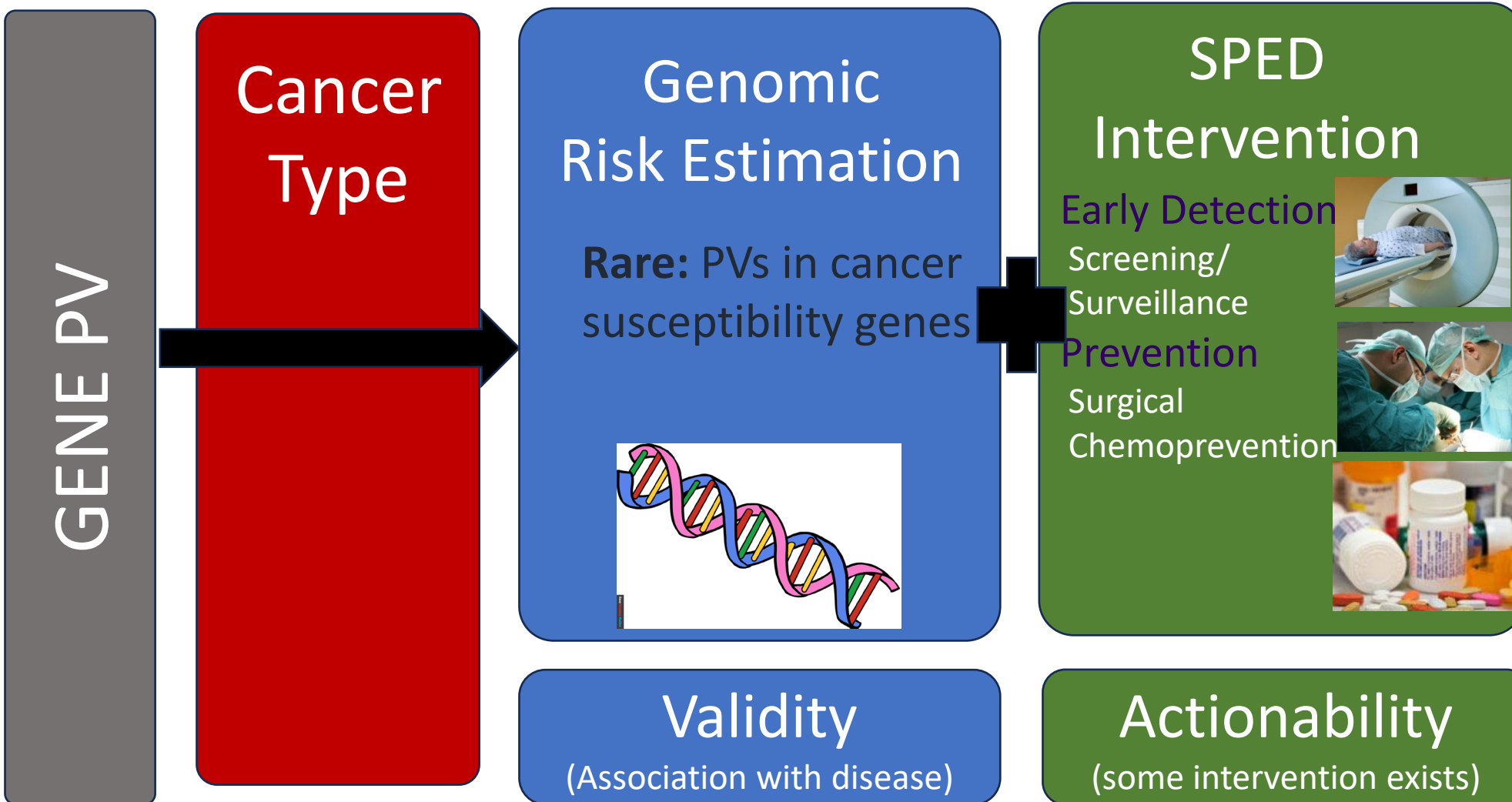
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Rationale for a gene being on a panel



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Rationale for a gene being on a panel



For which CSGs is of clinical benefit to test?

Often a presumptive leap...

GENE PV

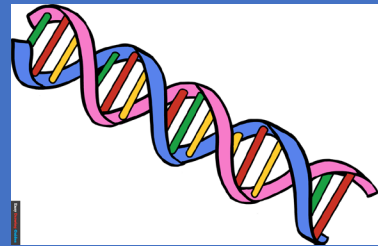
Cancer Type

Epidemiology

Natural History
Age profile
Treatment response
Mortality by stage

Genomic Risk Estimation

Rare: PVs in cancer susceptibility genes



Validity

(Association with disease)

SPED

Intervention

Early Detection
Screening/
Surveillance
Prevention
Surgical
Chemoprevention



Actionability

(some intervention exists)

?Improves
Mortality

and/or

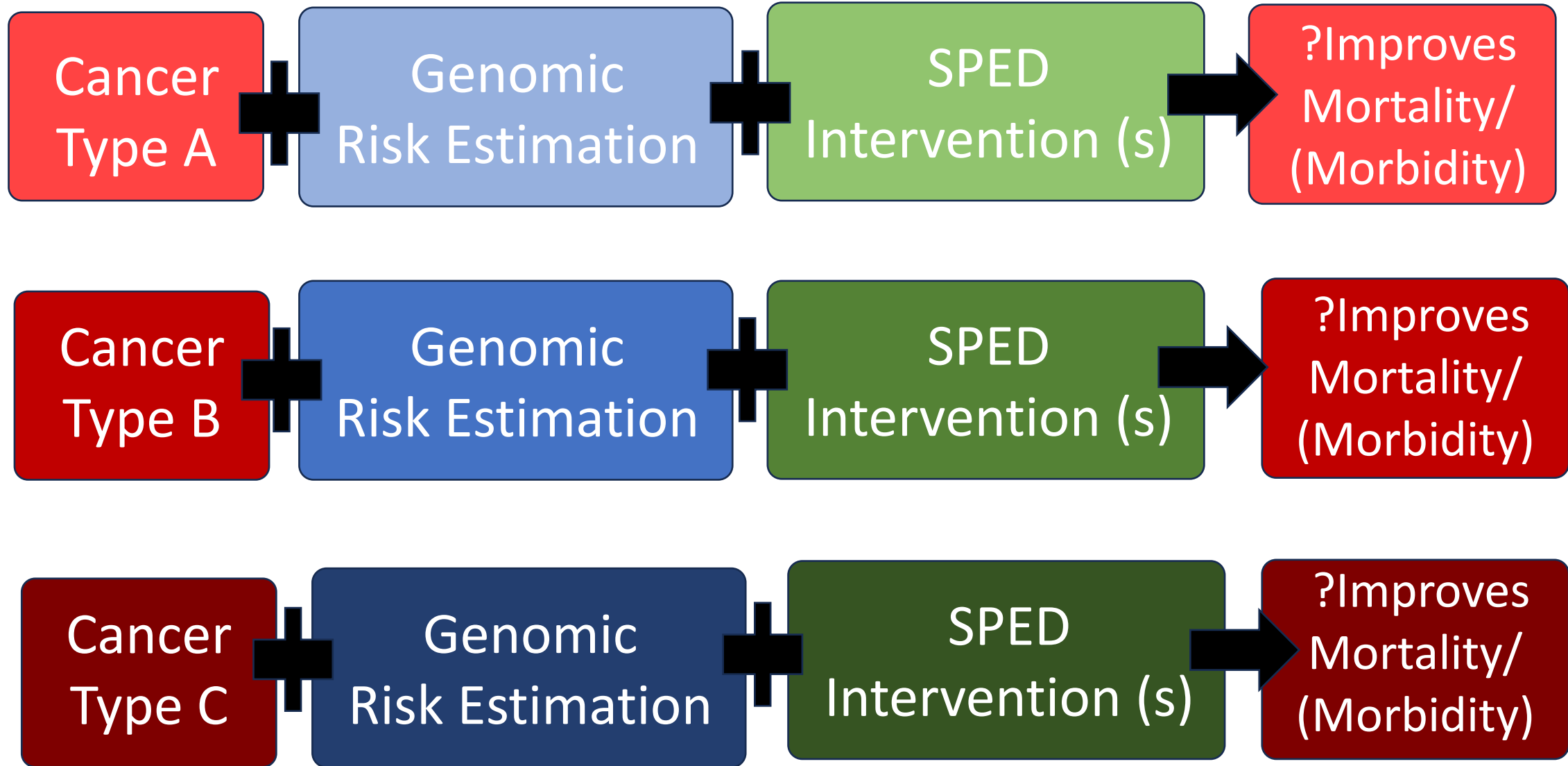
Morbidity/
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Clinical/Public
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For which CSGs is of clinical benefit to test?

Pleiomorphy...makes it more complicated

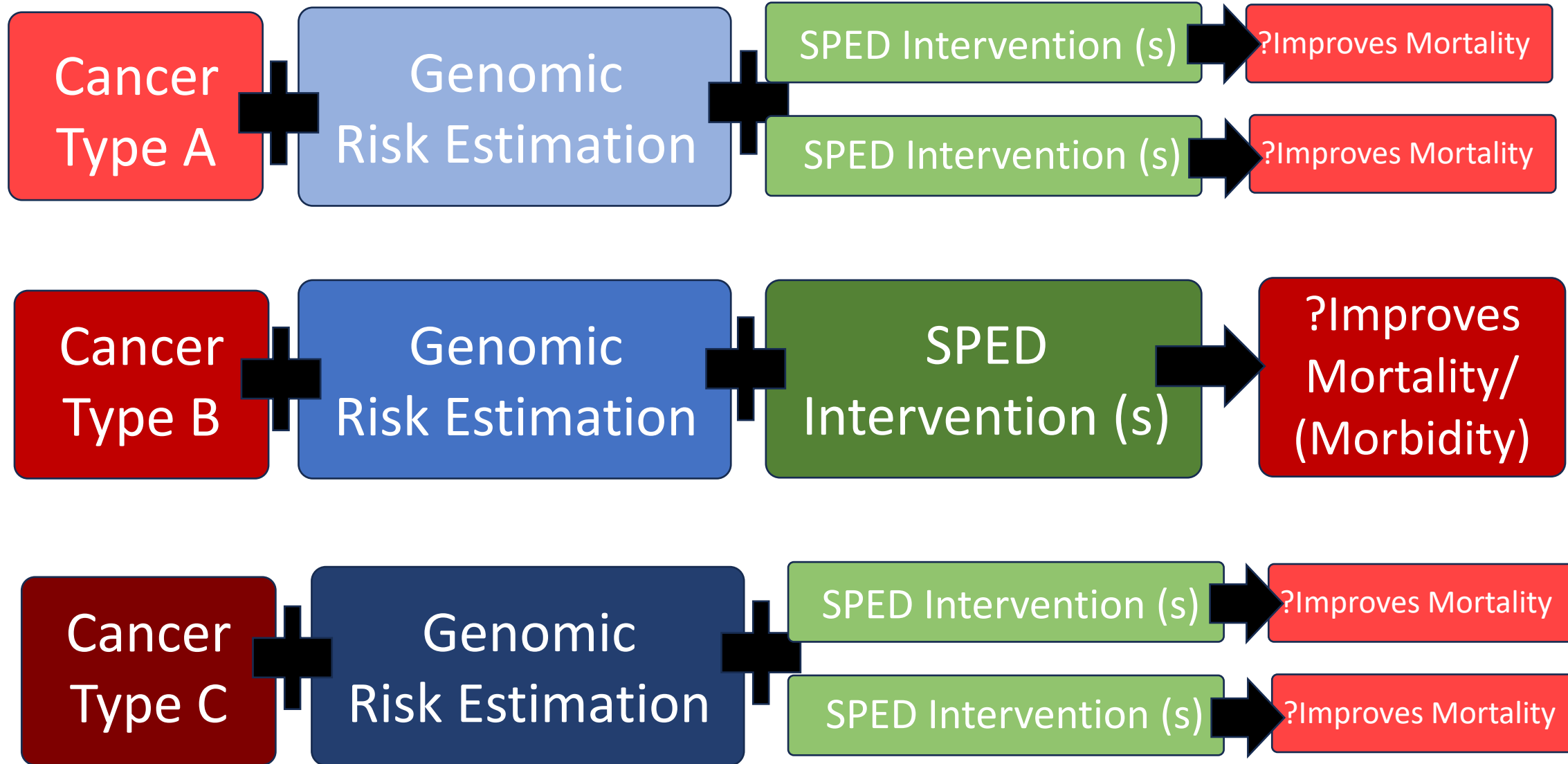
GENE PV



For which CSGs is of clinical benefit to test?

Multiple interventions for each cancer

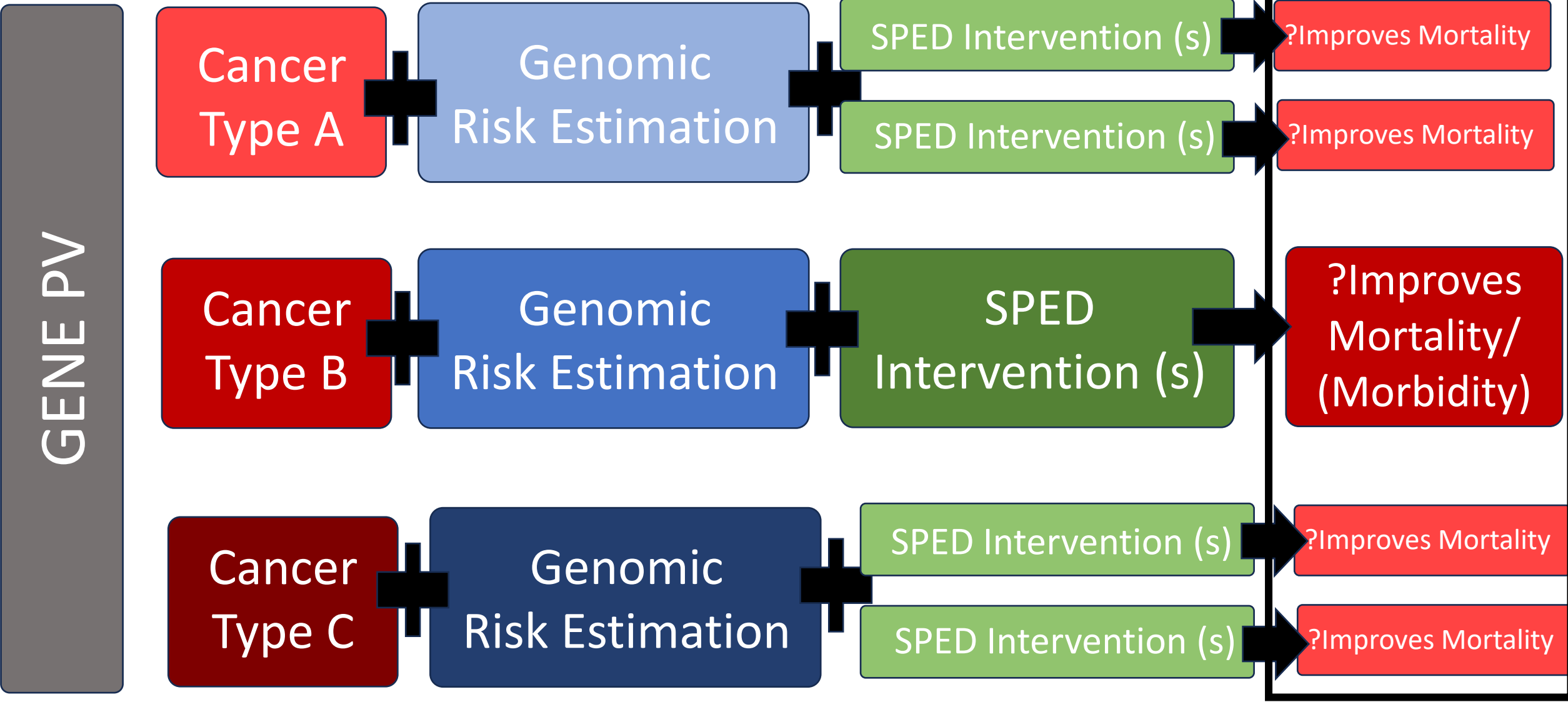
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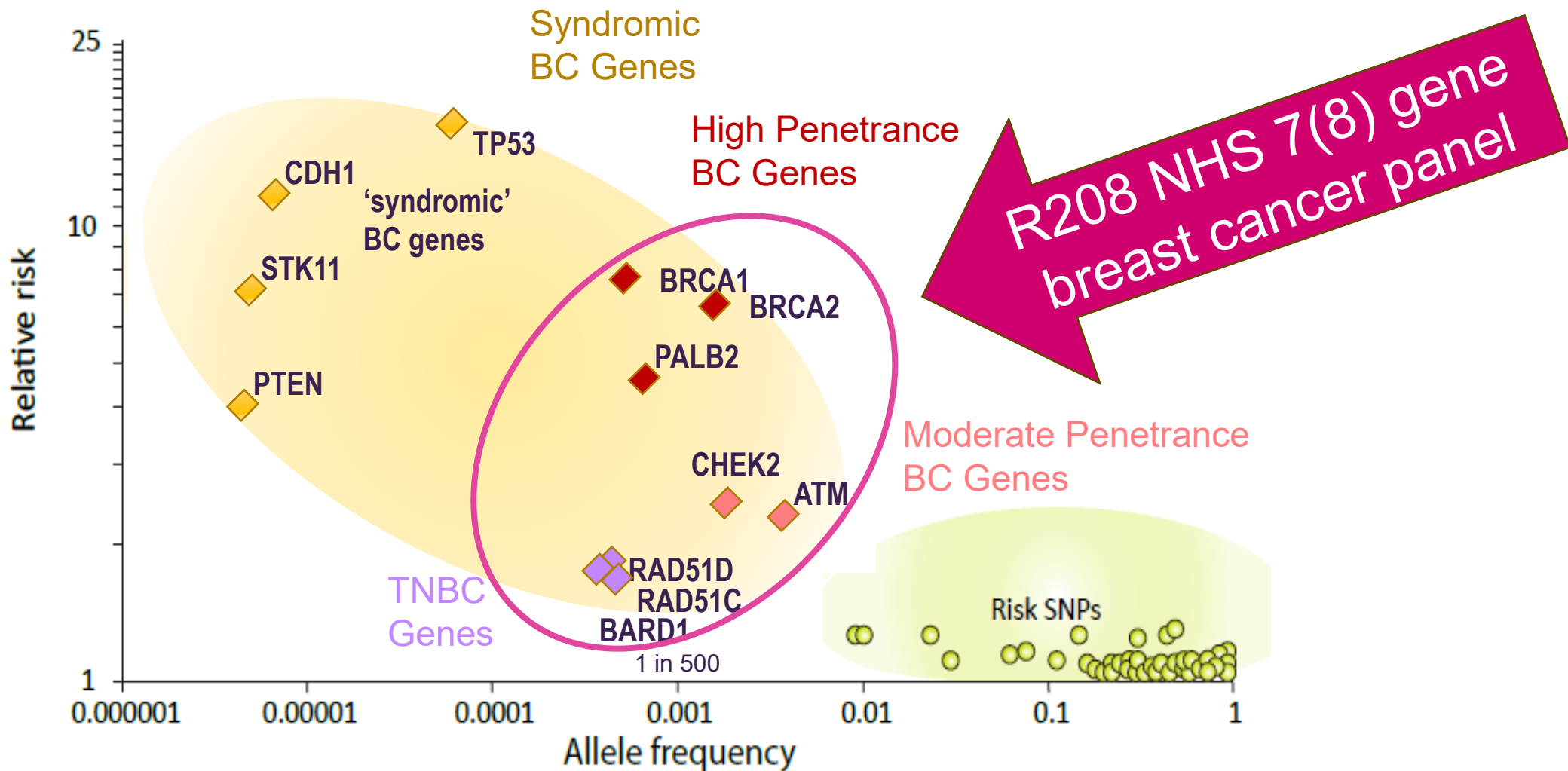
For which CSGs is of clinical benefit to test?

Total net summed impact

Summed impact



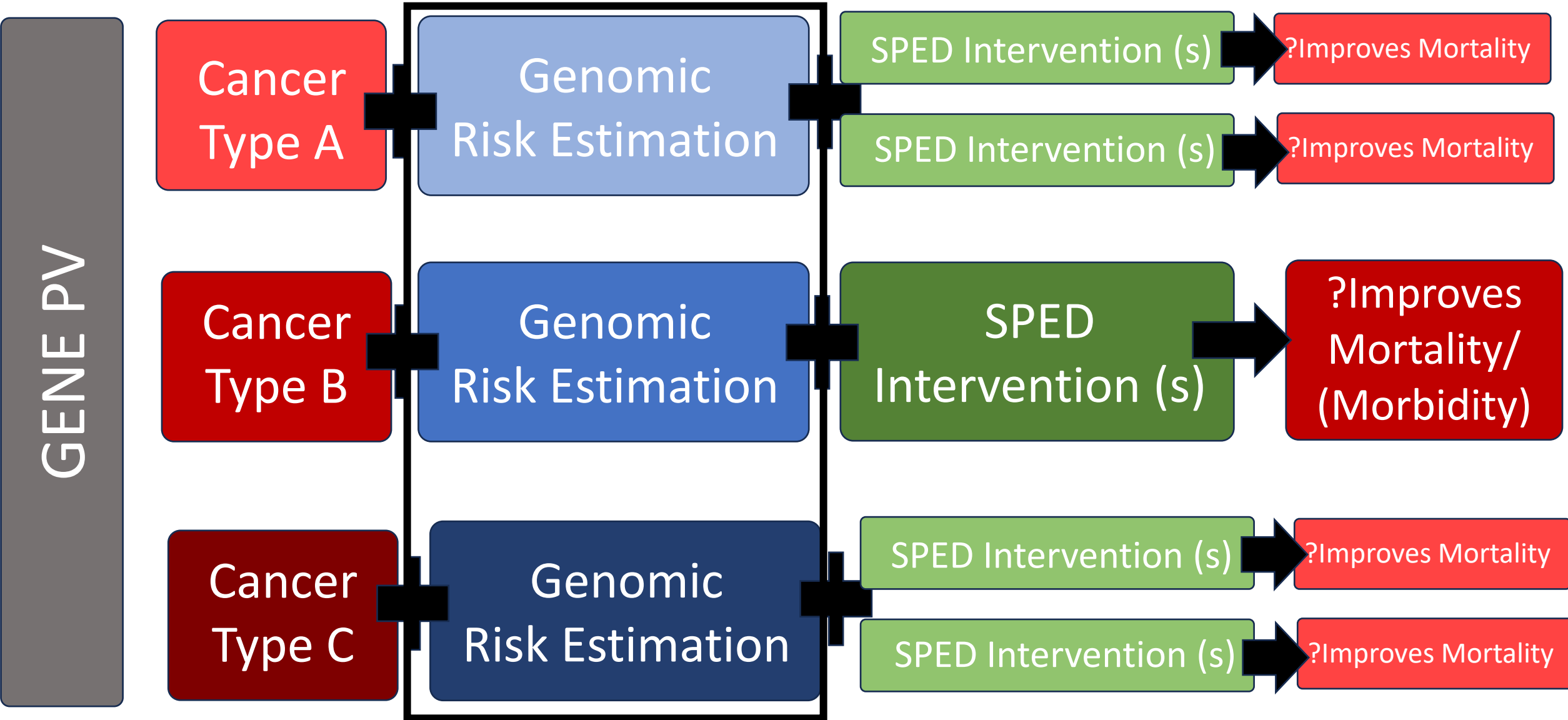
Breast Cancer Susceptibility Genetics



Turnbull, Sud, Houlston **Nat Genet** 2018 (50) 1212-1218
(adapted from Devilee and Easton)

For which CSGs is of clinical benefit to test?

Often a presumptive leap...



Pleiomorphism: Breast cancer susceptibility genes [NHS National Test Directory 7 (8) gene panel R208]

stable risk estimates
 *unstable risk estimates
 OR: odds ratio

	Population lifetime risk	BRCA1	BRCA2	PALB2	CHEK2	ATM	BARD1	RAD51C	RAD51D
Breast (Subtype)	14%	✓ OR=8.5 (Triple Neg)	✓ OR=5.5	✓ OR=4.5	✓ OR=2.5 (ER-positive)	✓ OR=2.0 (ER-positive)	✓ OR=2.5 (Triple Neg)	✓ OR=1.5 (Triple Neg)	✓ OR=2.0 (Triple Neg)

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Ovarian	<2%	✓ OR=25	✓ OR=10	✓ OR~2	? ?	? OR~2		✓ OR=6	✓ OR=7

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Prostate	15%		✓ OR~2		✓ OR~2	✓ OR=2.5			

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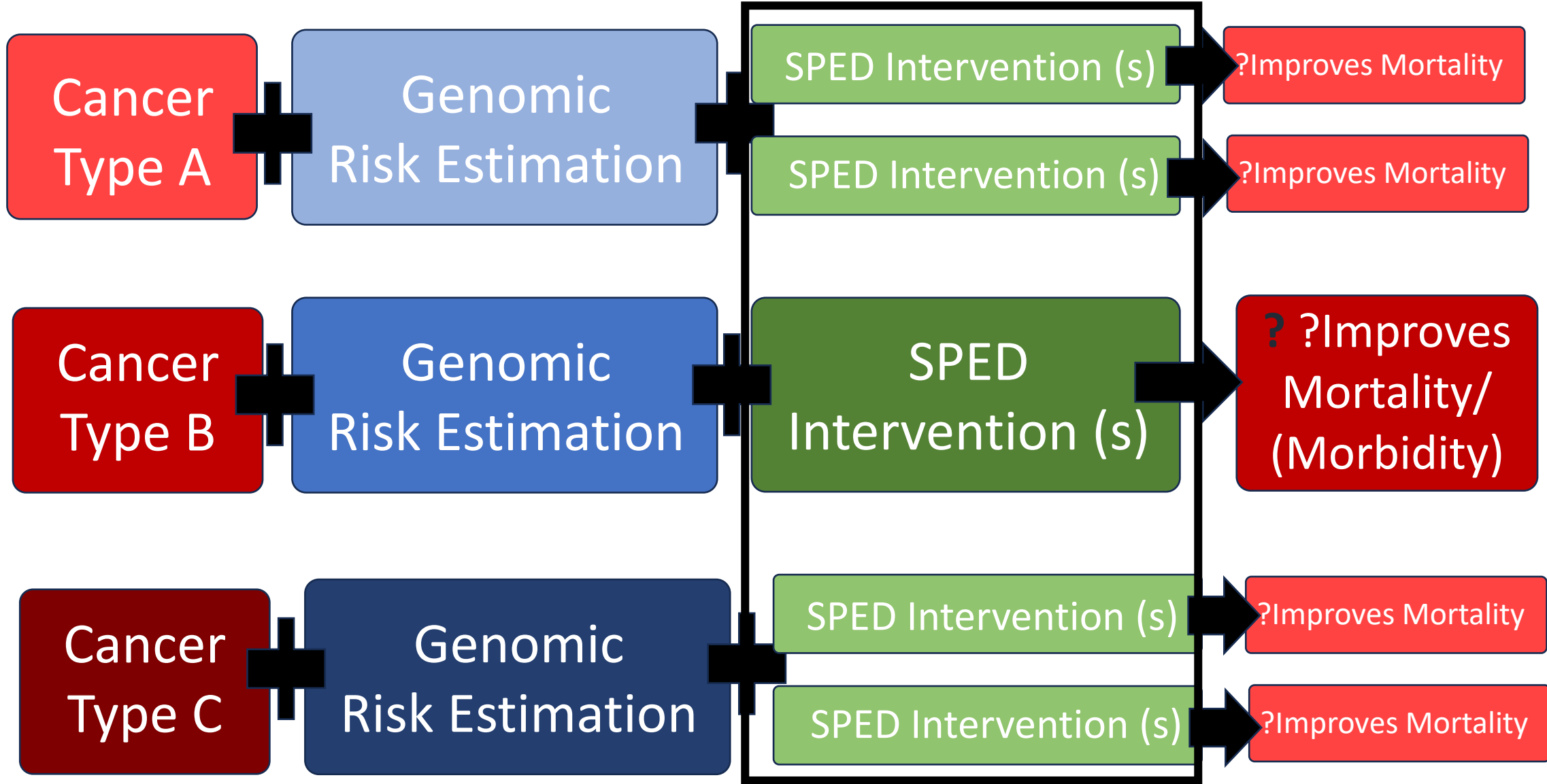
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Prostate	15%		✓ OR~2		✓ OR~2	✓ OR=2.5			
Pancreatic	1.5%		✓ OR~3.5	✓ OR~2		✓ OR~5-9			

For which CSGs is of clinical benefit to test?

Often a presumptive leap...

GENE PV



Review of SPED interventions

-used for gene PV-carriers

Risk-Reducing surgery

	Group	Cancer-specific mortality	Morbidity (negative QoL impact)
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	Mod-risk (ATM, CHEK2)	????	
Ovarian	High risk (BRCA1, BRCA2)	✓✓✓✓✓	+
	Mod-risk (RAD51C, RAD51D)	✓?✓?✓	

Chemoprevention (Taxoxifen, Anastrozole, SERMS)

Breast	High/mod-risk (BRCA2, ATM, CHEK2)	x?	+++
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Finch, A.P., et al., J Clin Oncol, 2014. 32

Domchek, S.M., et al., Jama, 2010. 304(9)





Manchanda, R., et al., J Med Genet, 2016

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Review of SPED interventions

-used for gene PV-carriers

	Group	Tool	Starting Age	Cancer-specific mortality (?or just lead-time)	Over-diagnosis
Breast	Population	mammo	50	✓ for >50 (old data; treatment improved)	++
	Mod- risk	MRI/ mammo	40	???? Age Trial, CNBSS-1	++
	High-risk	MRI/ mammo	25-30	✓ (BRCA1)	+
Ovarian	High-risk/ population	CA-125/ USS		xxxxx	
Prostate	population	PSA	~60	✓	+++++
	Elevated risk	PSA/MRI	~40	? ✓	+?+?+
Pancreatic	Elevated risk	CT/MRI	~50	????	+?

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Buys, S.S., et al.. Jama, 2011. **305**(22)


Jacobs, I.J., et al., Lancet, 2016. **387**

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UK-NSC AND USPSTF advise against


Draisma G, et al. *J Natl Cancer Inst* 2009; **101**
 Bancroft EK et al *Lancet Oncol.* 2021
 Li S, et al. *J Clin Onc* 2022

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Ovarian	High- risk/ Population	CA-125/ USS		xxxxxx	
Prostate	Population	PSA	~60	✓	+++++
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Pancreatic	Elevated Risk	CT/MRI	~50	???? <div style="border: 1px solid gray; padding: 2px; display: inline-block;">UK-NSC AND USPSTF advise against</div>	++

Dbouk, M., et al., J Clin Oncol, 2022. **40**.

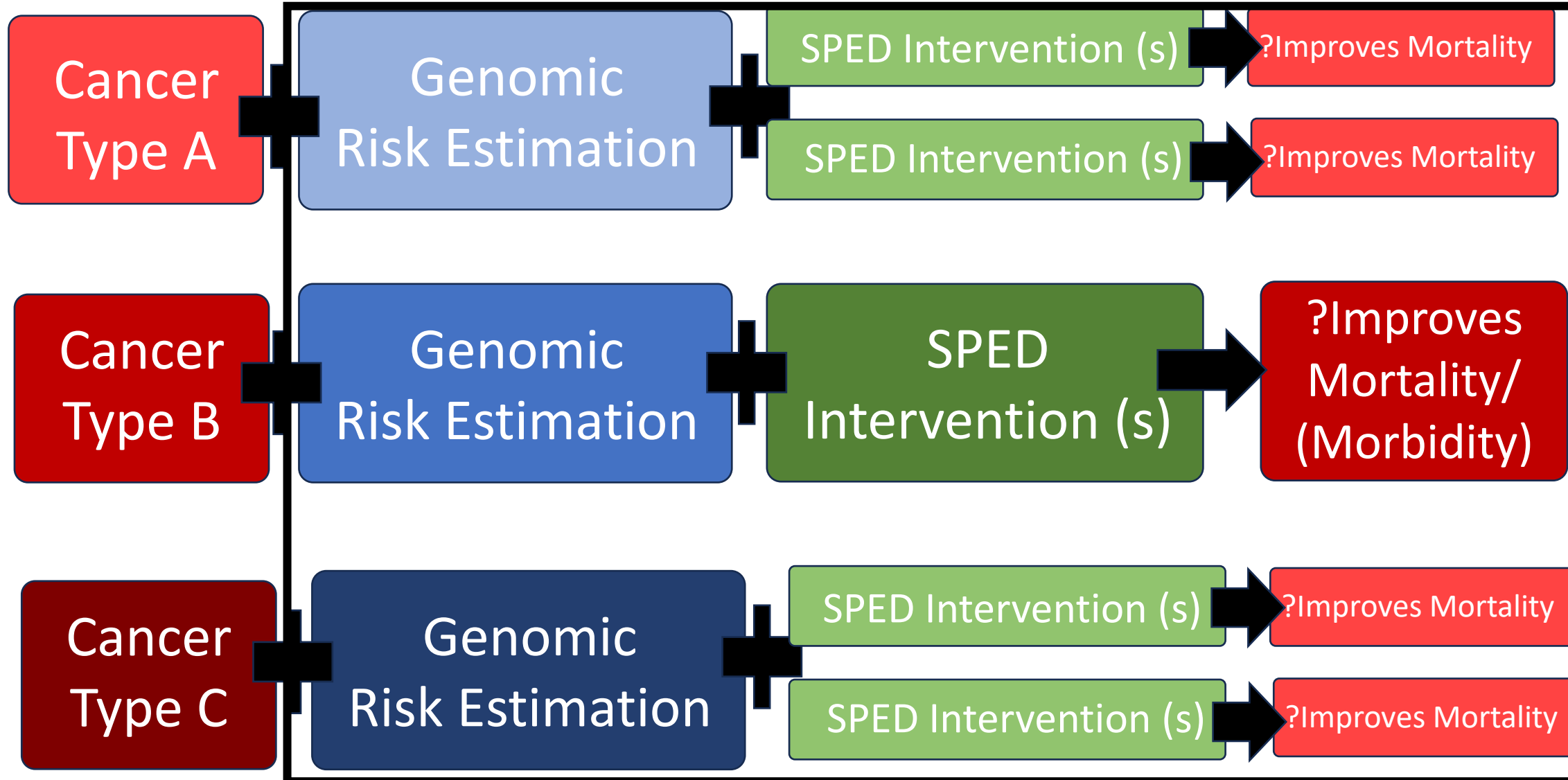
Sheel, A.R.G., et al., Am J Gastroenterol, 2019 **114**(1)

Blackford, A.L., et al., JAMA Oncol, 2025. **10**.

Are we net improving cancer-specific mortality (reducing cancer deaths) with testing our 7/8 breast gene panel?

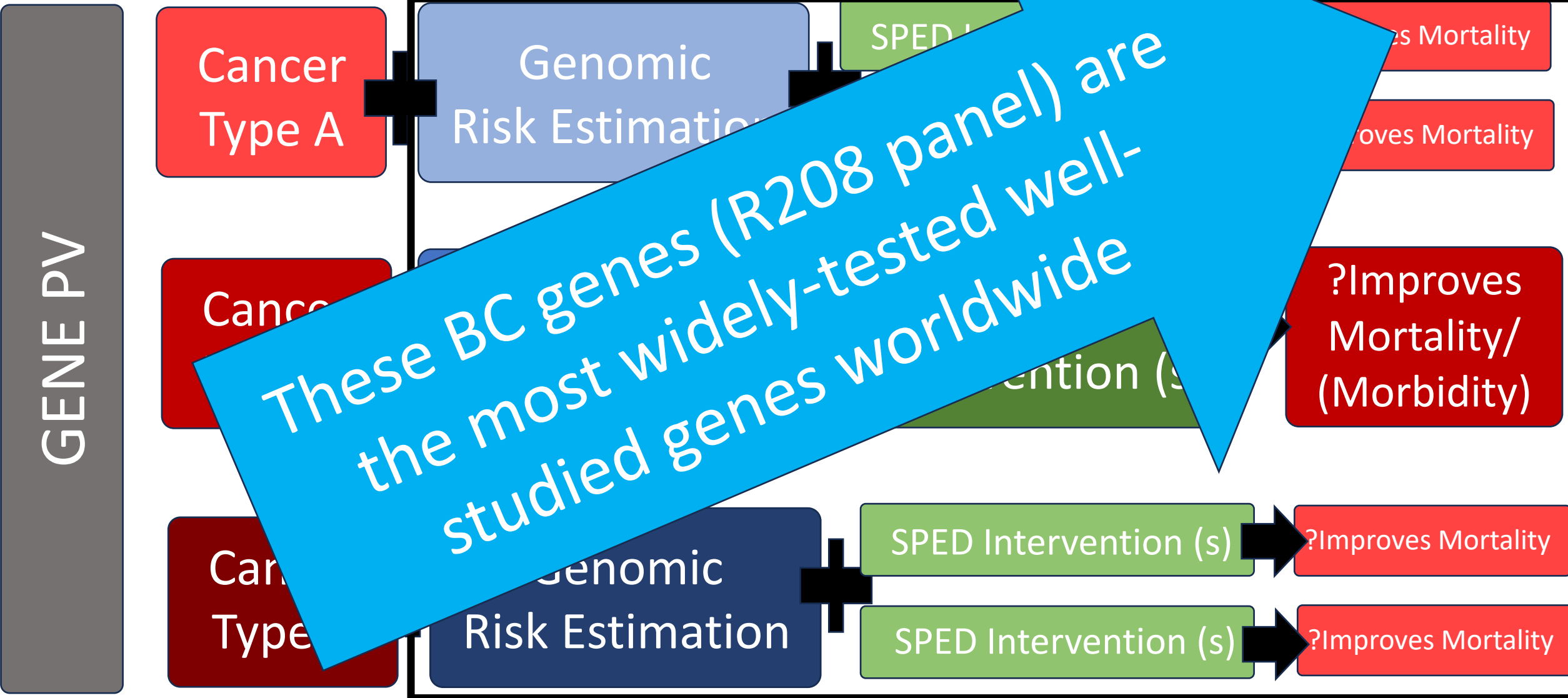
With acceptable harms? At reasonable cost?

GENE PV



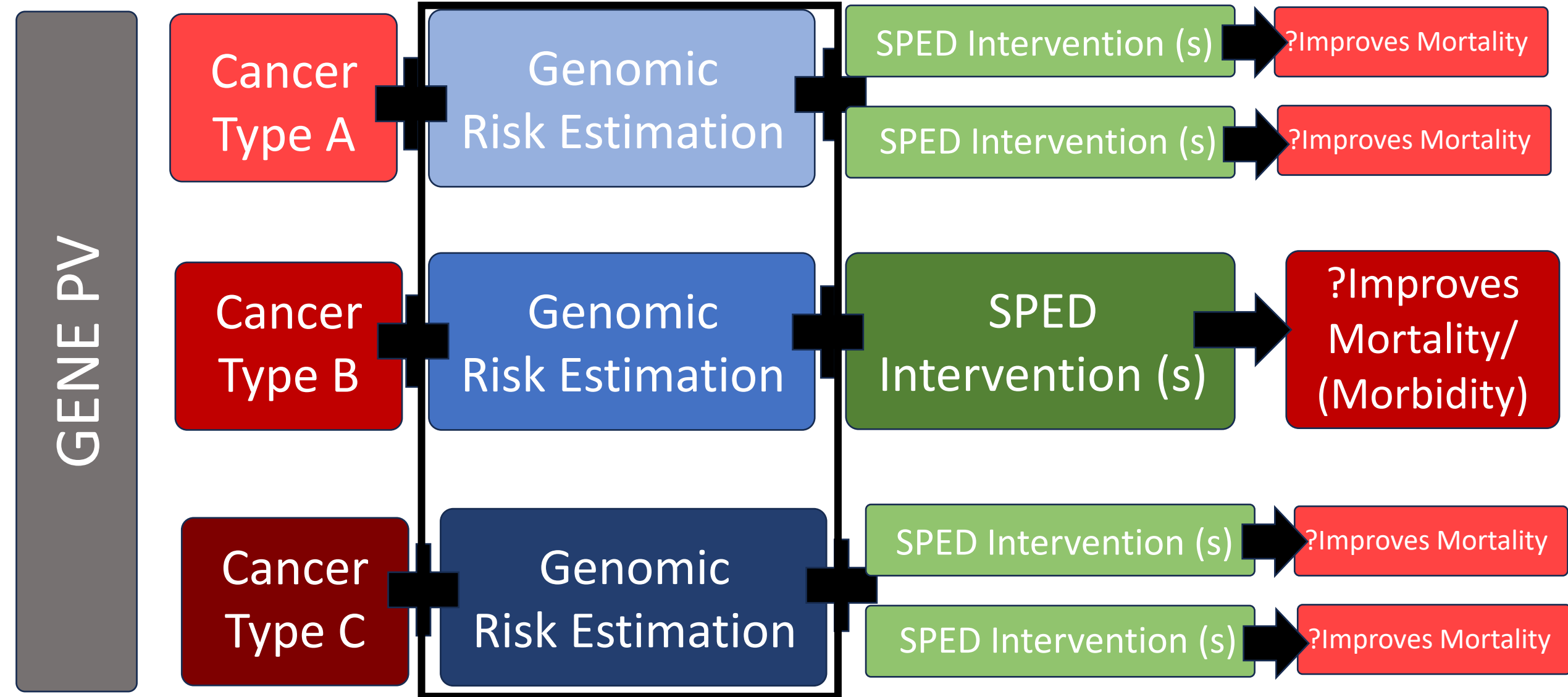
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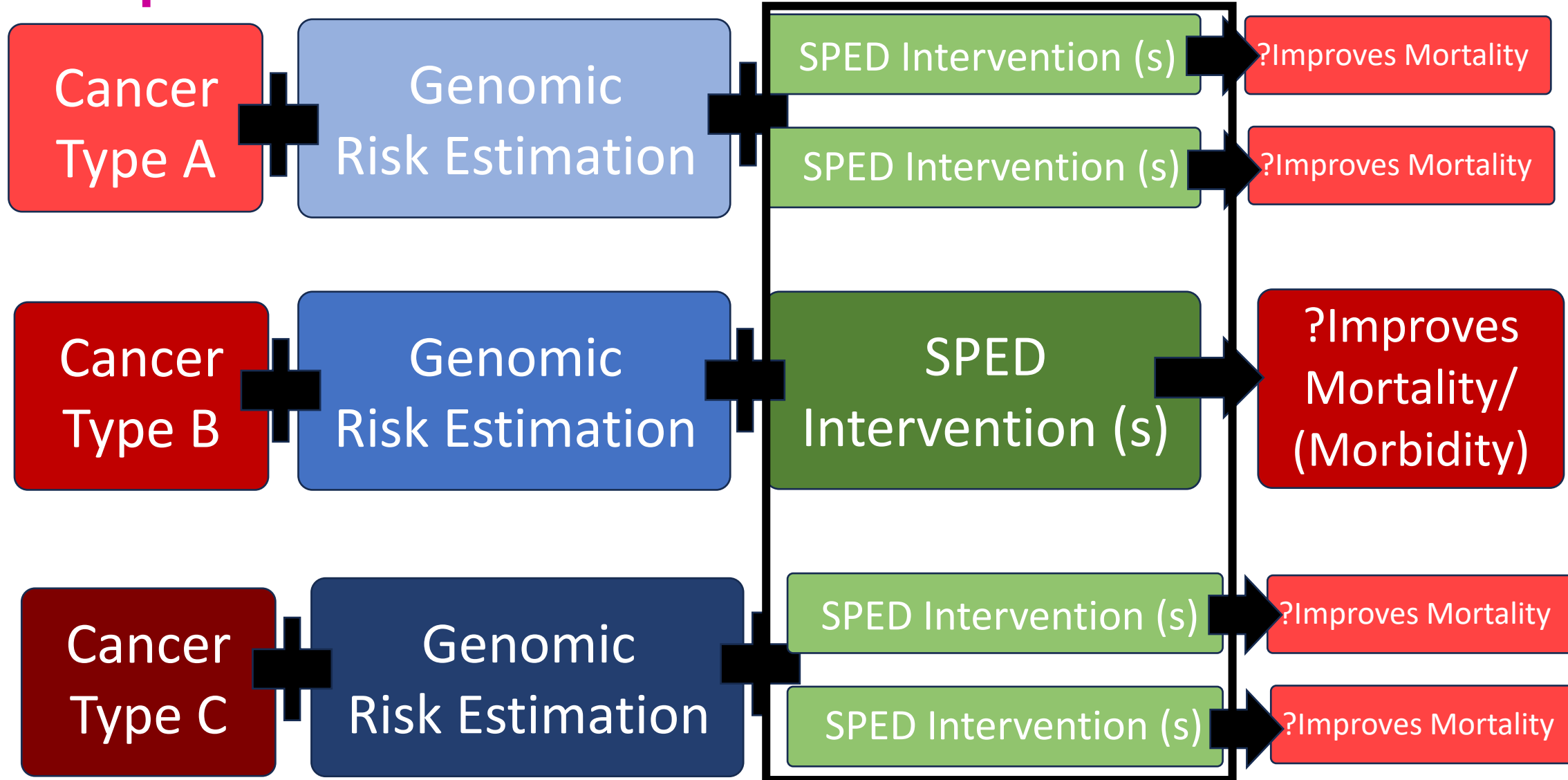
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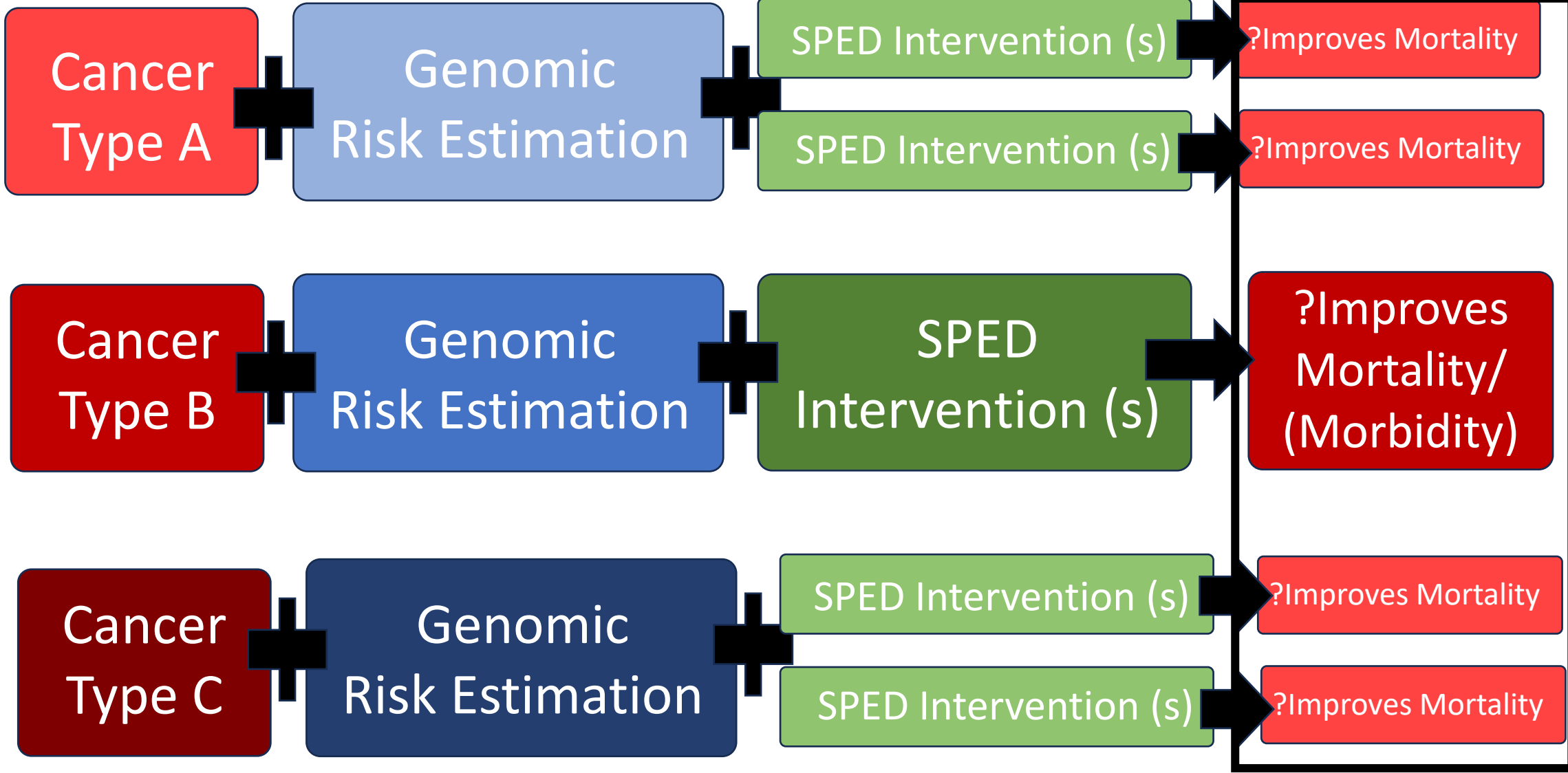


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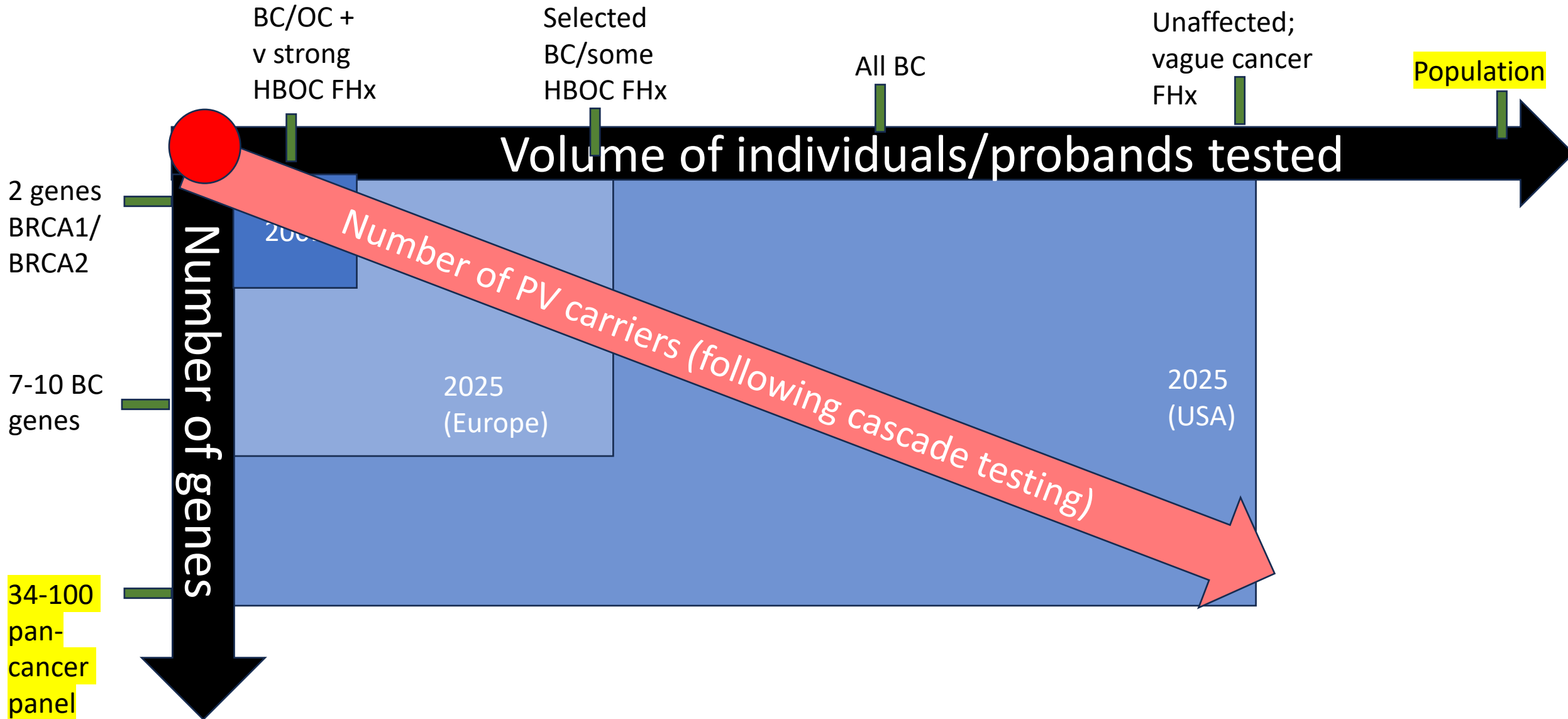
With acceptable harms? At reasonable cost?

Summed impact

GENE PV



Expansion of genetic/genomic testing: Breast-Ovarian Cancer as exemplar



The Four horsemen of Genomic Prediction

Less well characterised risks/interventions for:

- other cancer susceptibility gene
- cardiac genes
- newborn/paed disease genes



- 1. Penetrance** (gene-level risks biased by ascertainment)
- 2. Pathogenicity** (variant-level variability in risks; hypomorphism)
- 3. Pleiomorphism** (breadth of disease associations)
- 4. Performance** (of SPED (screening/prevention) interventions or drugs)

The Five ages of Genomics

- 1. The dark ages:** empirical observation; early technologies (linkage)
- 2. The age genomic enlightenment:** human genome project, Sanger sequencing
- 3. The age of genomic diagnosis** for rare diseases
- 4. The age of genomic technology:** next generation genomic sequencing and bioinformatics pipelines, gene editing
- 5. The age of genomic prediction:** can we use genomic prediction to significantly alter health outcomes?

