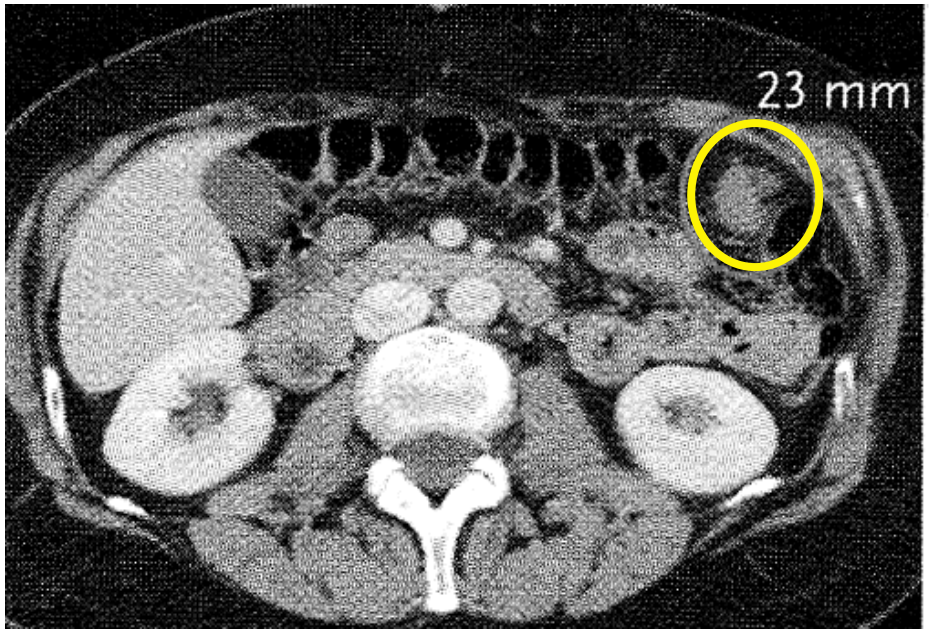
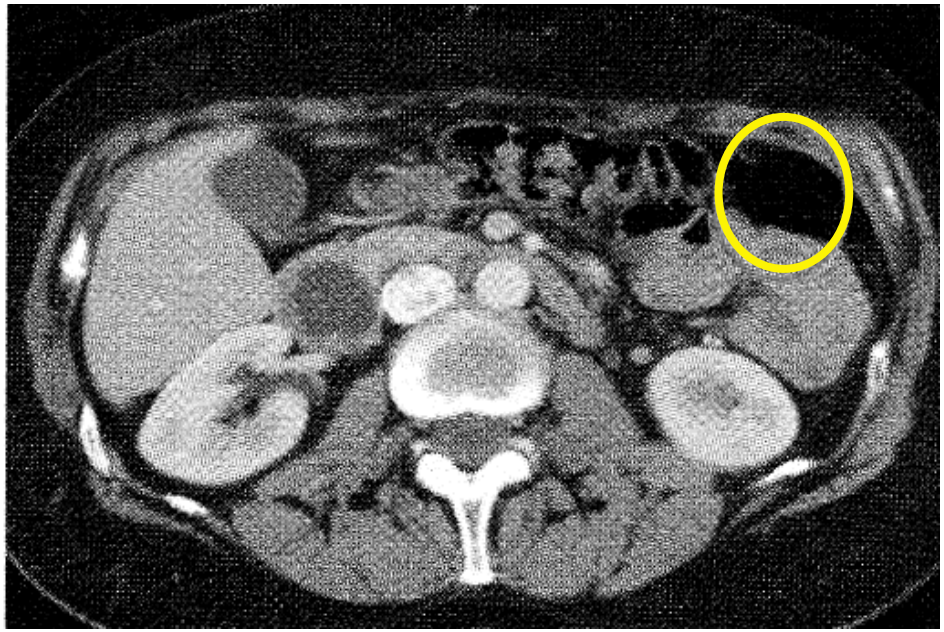
NATIONAL HUMAN GENOME RESEARCH INSTITUTE Division of Intramural Research

An Introduction to Genomics:
Breast cancer genes, risk assessment and screening

Lawrence Brody, Ph.D.



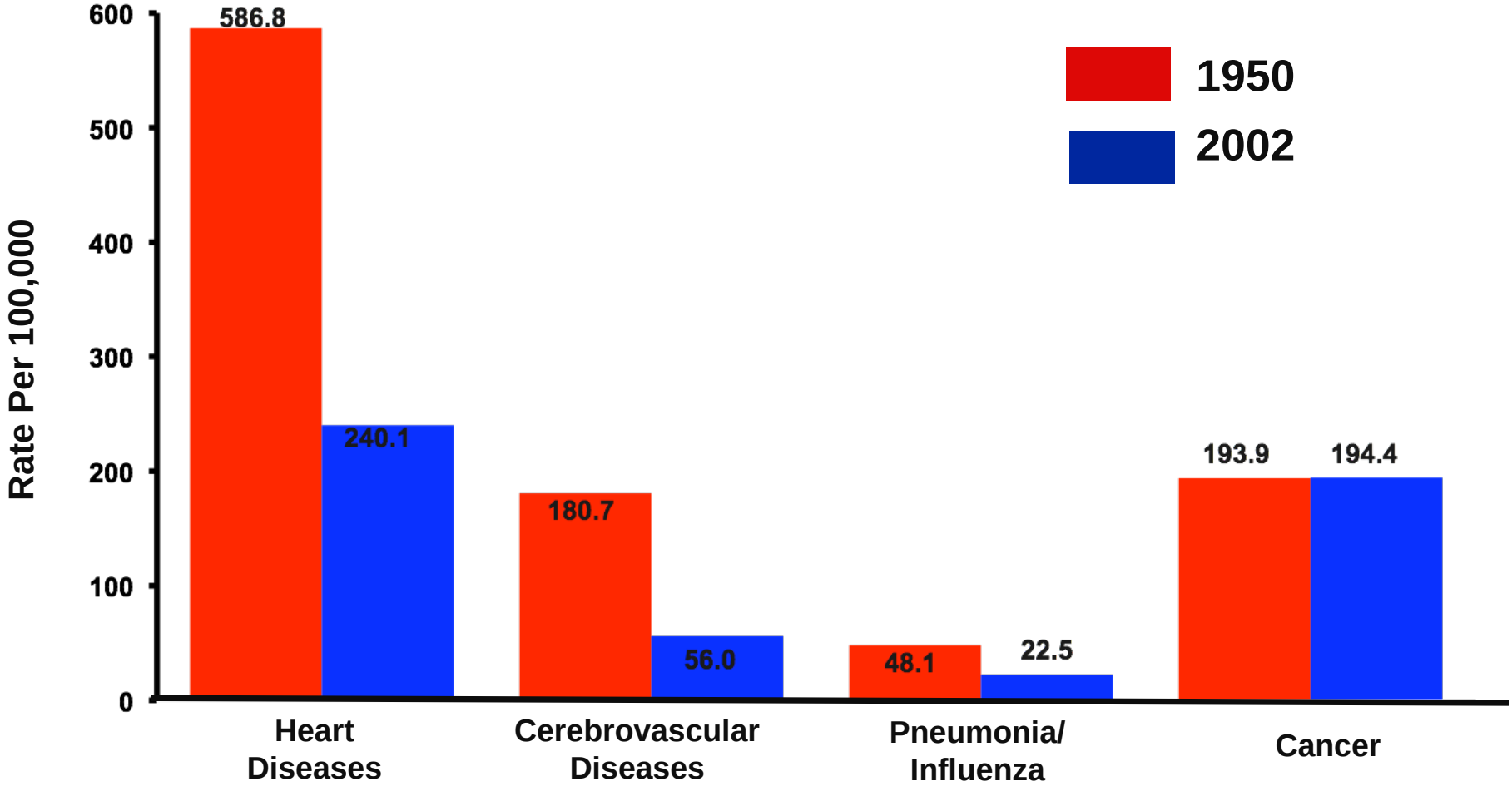


Fong et al., *NEJM*, 361:123-134, 2009

Breast Cancer Genes

- **What are they?**
- **How do we find them?**
- **What is their function?**
- **How can they be used to improve health?**

Change in the US Death Rates by Cause, 1950 & 2002



*** Age-adjusted to 2000 US standard population.**

Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2002 Mortality Data–NVSR-Death Final Data 2001–Volume 52, No. 3.

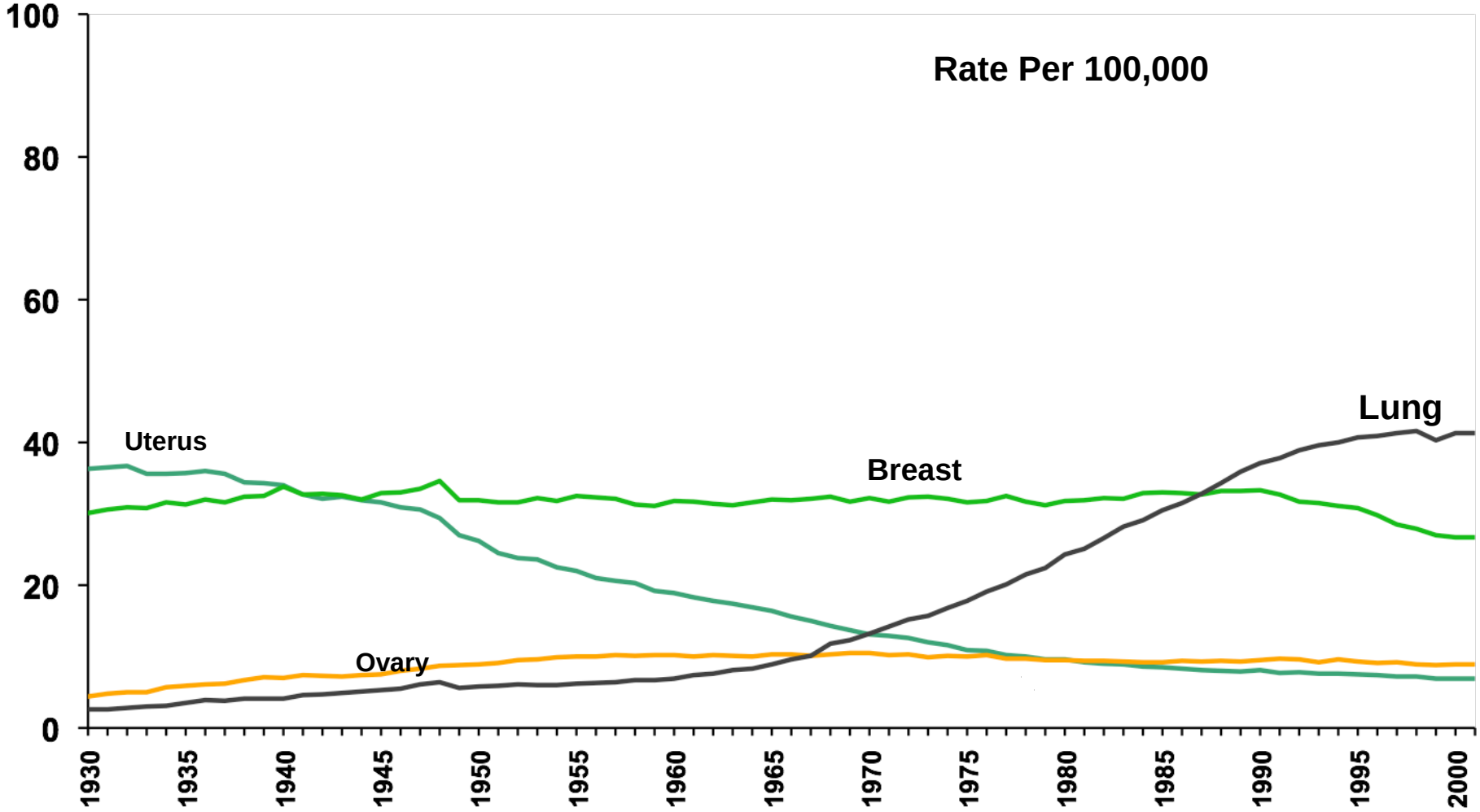
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf

Breast Cancer - USA

- **207,090 new cases**
- **39,840 deaths per year**
  - **lifetime risk of diagnosis ~ 12% (1/8)**
  - **risk of death from breast cancer - 3.4% (1/35)**

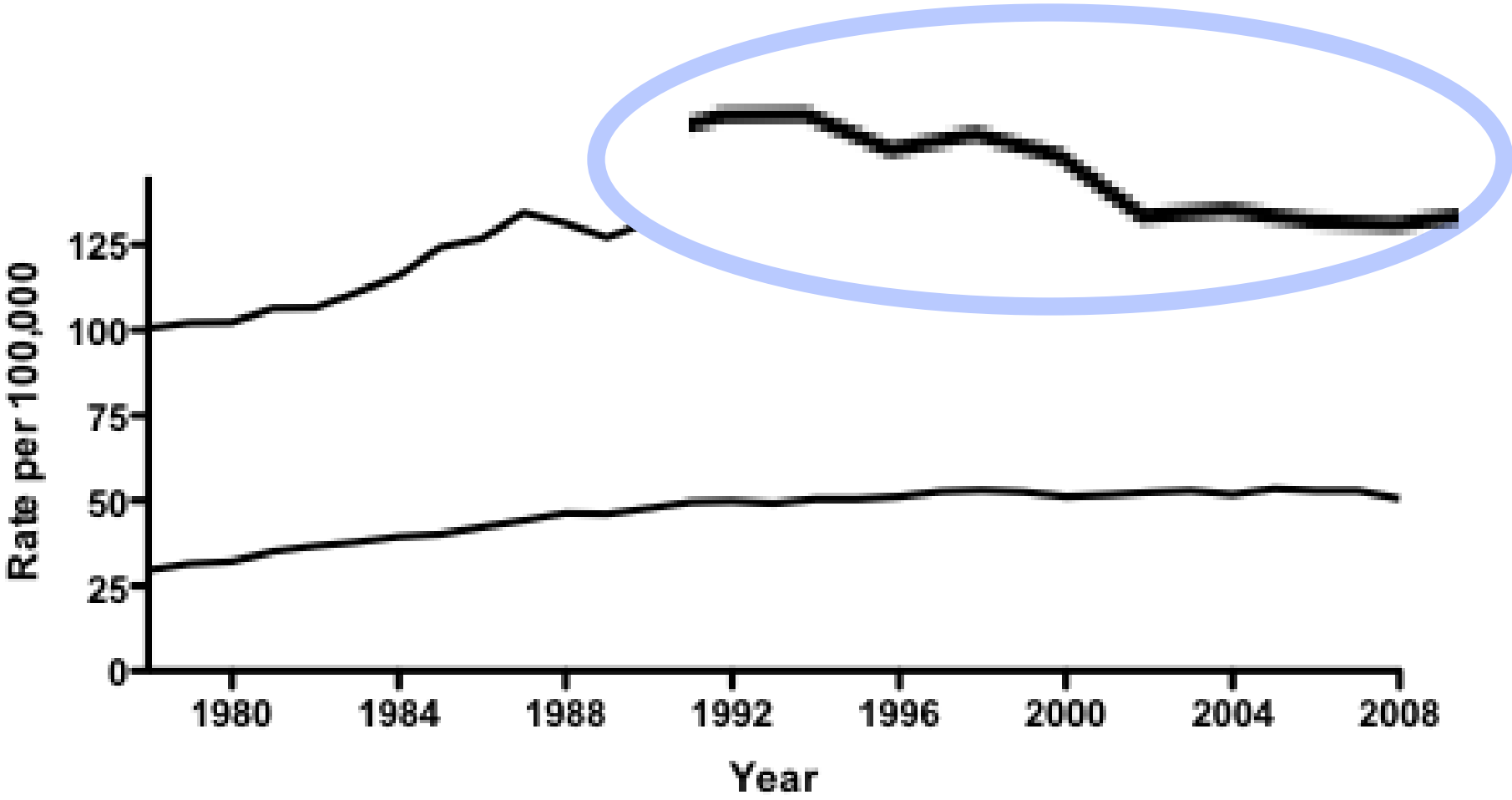
ACS estimates for 2010

Cancer Death Rates: US Women, 1930-2001



Age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes 1960-2000, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2003.

Cancer Incidence: US Women, 1978-2008



SEER Data

Why Genetics?

- Prevention
- Early Detection ←
- Prognosis
- Tailored Therapy ←

"cancer is a genetic disease"

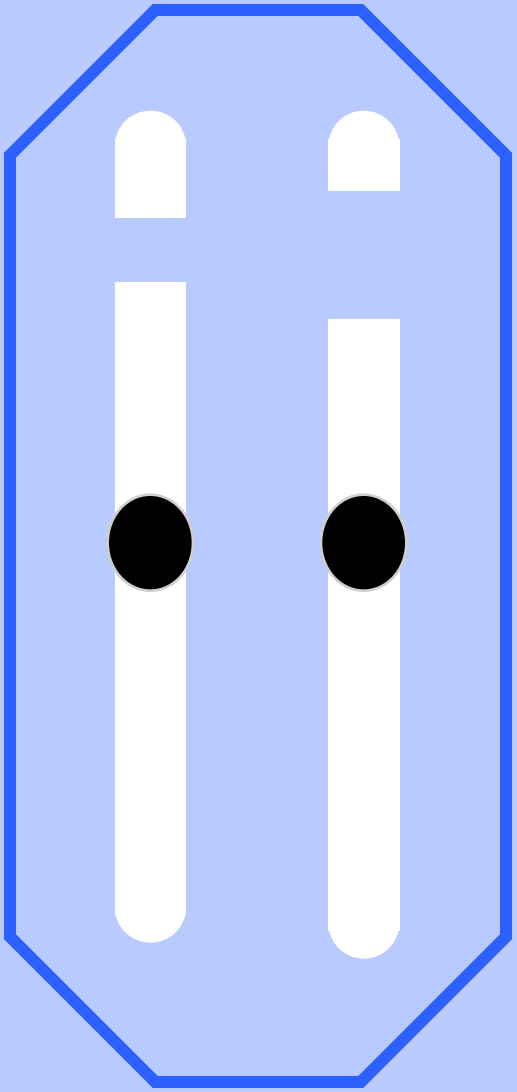
Cells: acquire mutations associated with growth advantage and/or escape from normal controls.

Somatic mutations

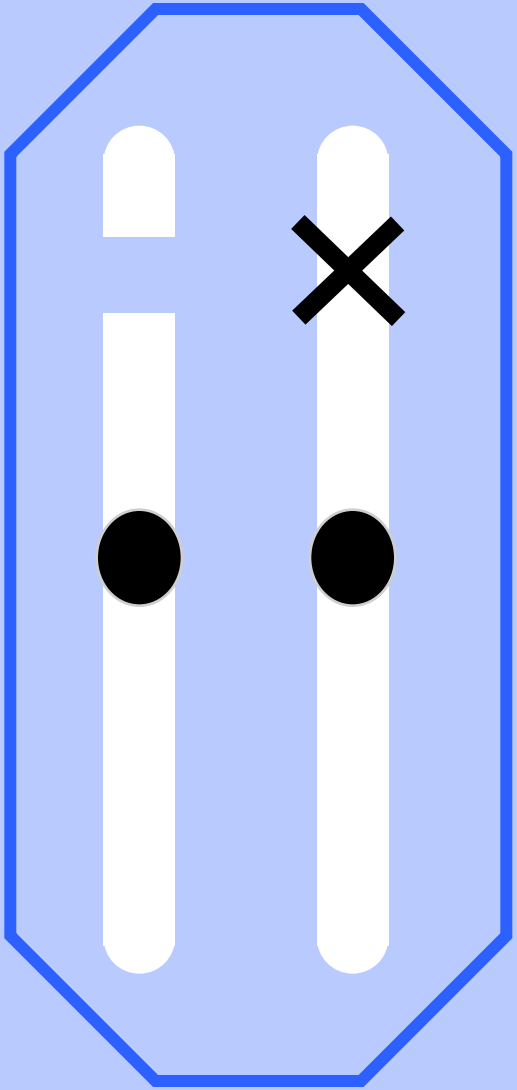
Individuals: may inherit genetic variants that lead to an increase in cancer risk.

Inherited variation

TUMOR SUPRESSOR GENES



Tumor Cell



Mutation Carriers

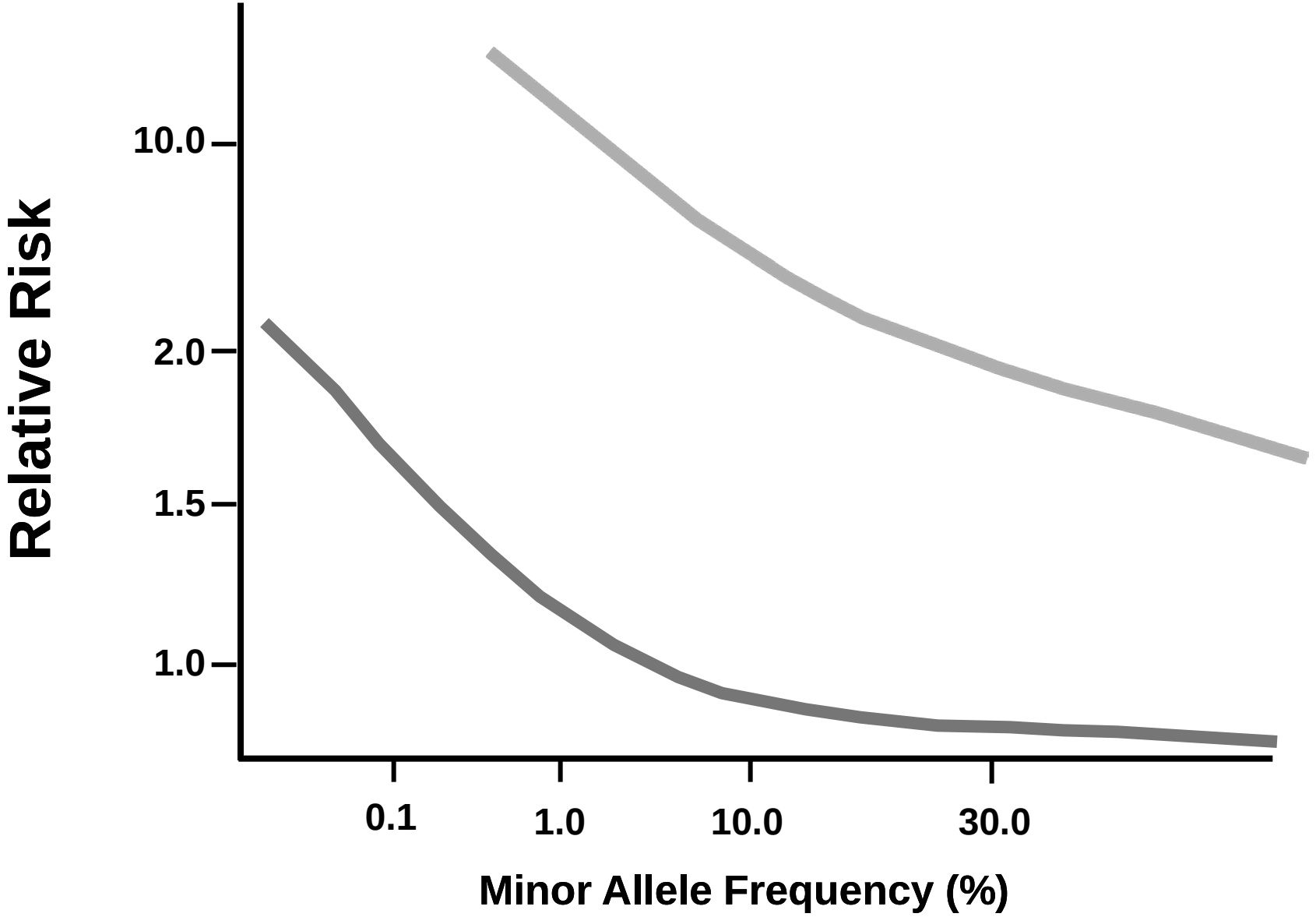
Family History and Cancer Risk

In small percentage of families cancer appears to be inherited as a mendelian trait.

3-8% of breast cancer

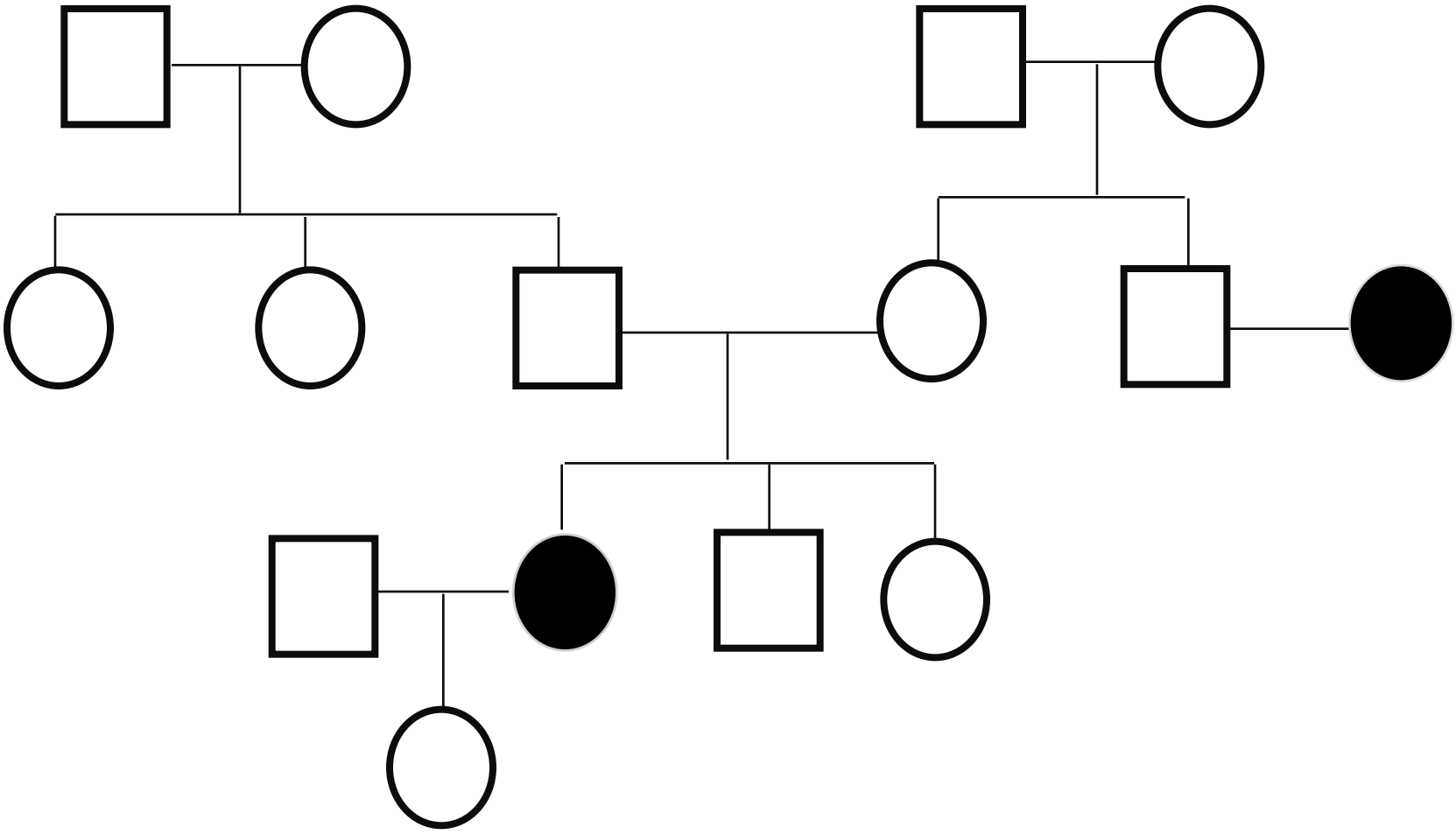
Topography of Cancer Risk

Topography of Cancer Risk

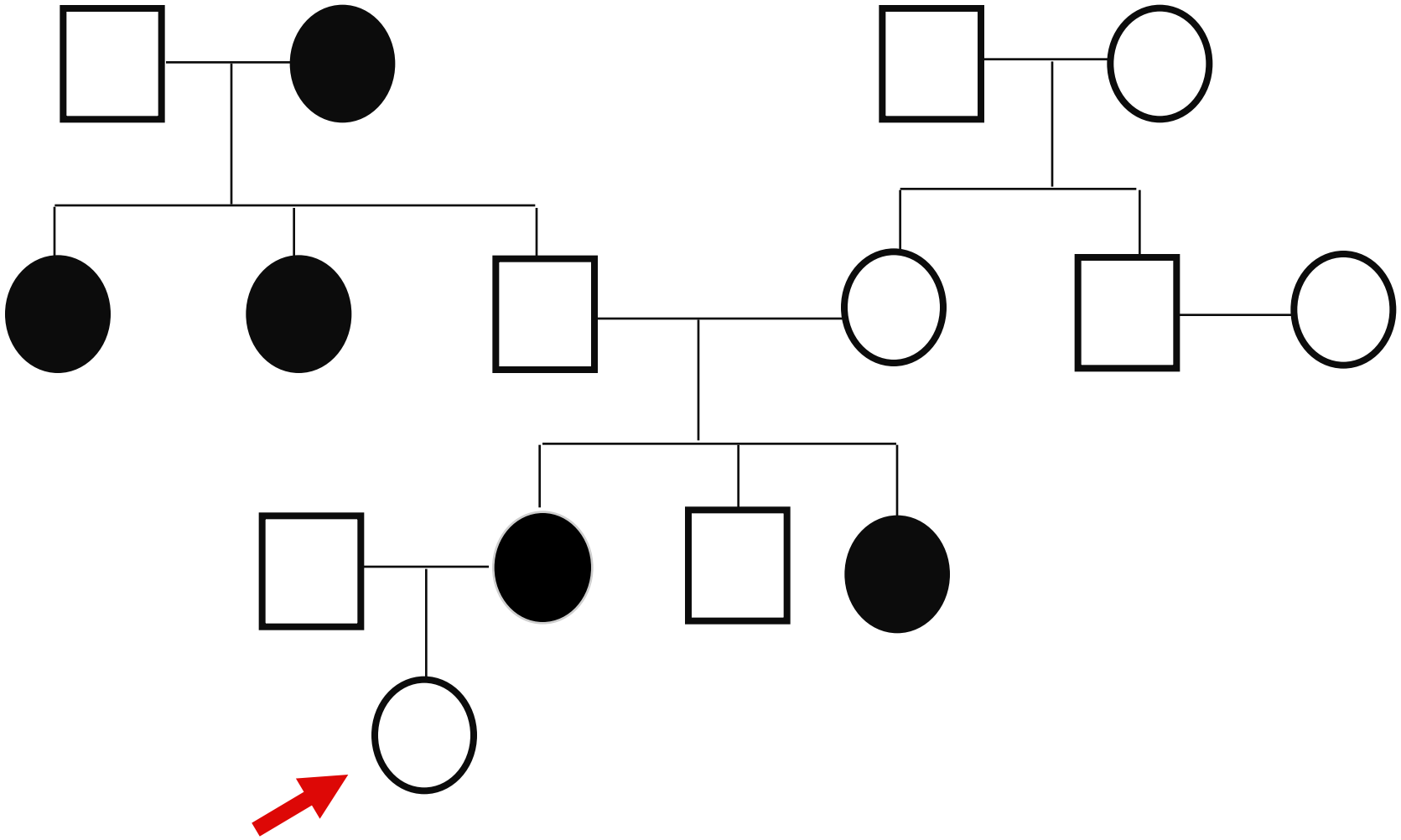


Adapted from Foulkes WD *NEJM*, 359:2143, 2008

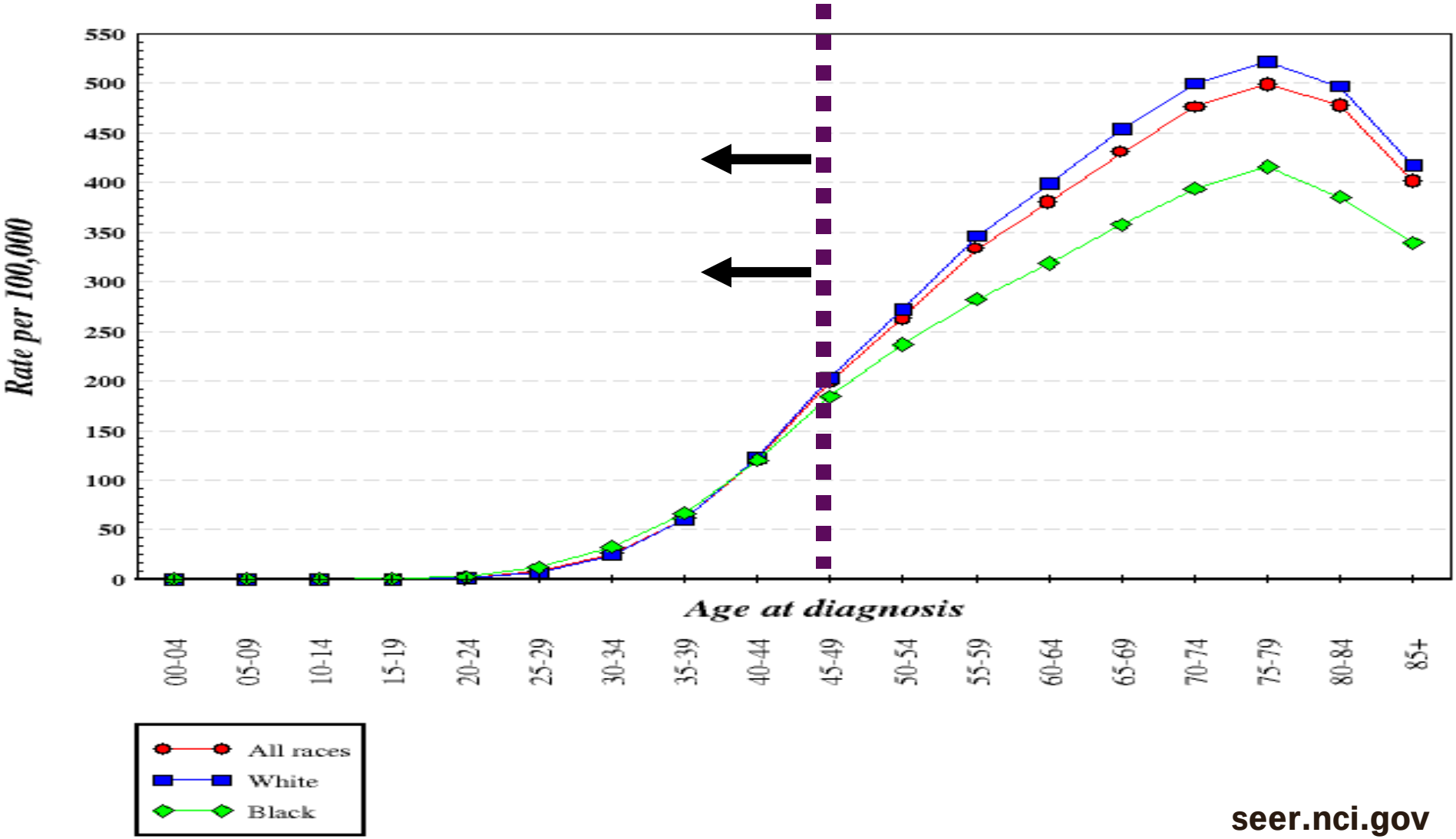
Sporadic Cancer



Inherited Cancer



Breast Cancer - Age at Dx



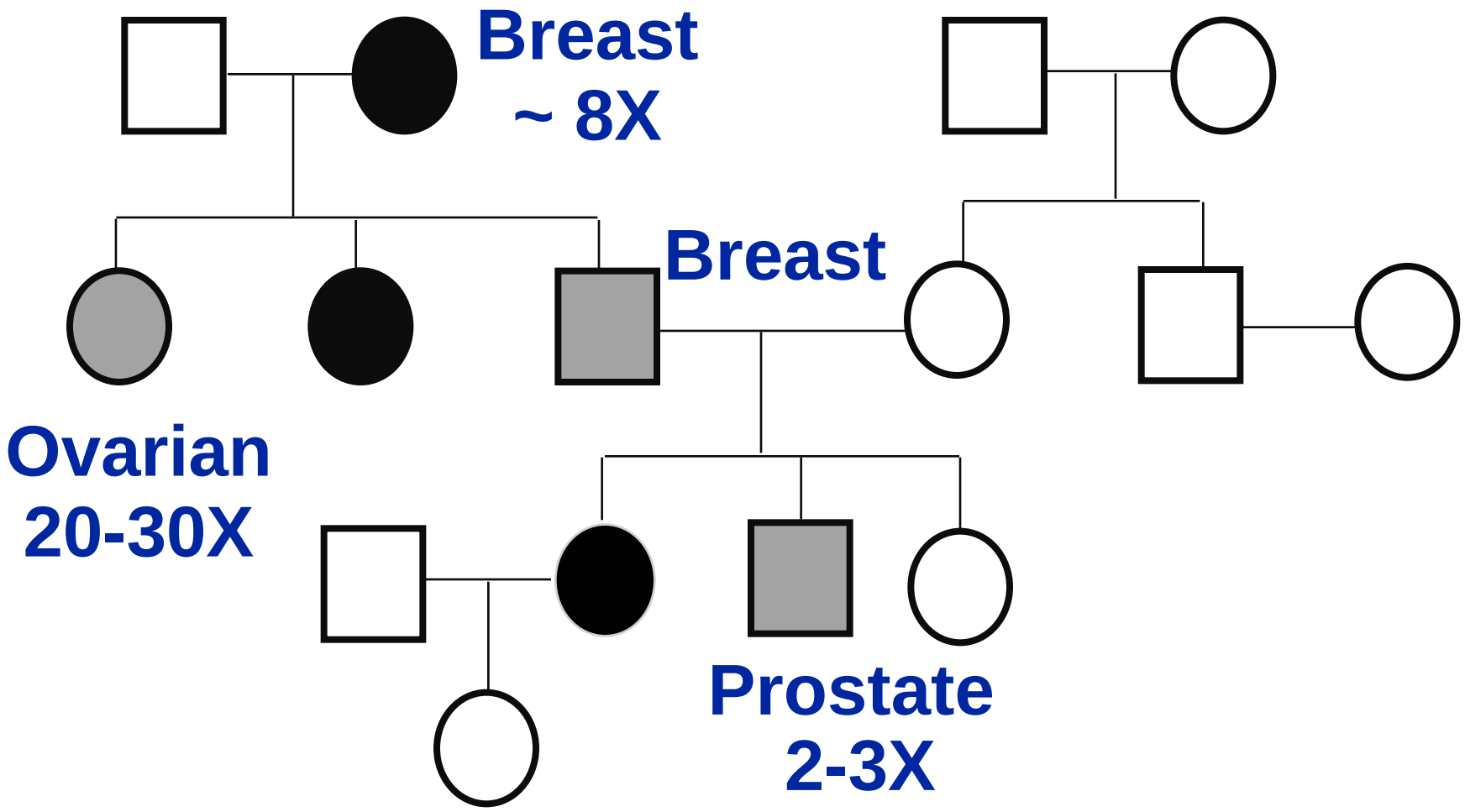
seer.nci.gov

BRCA1

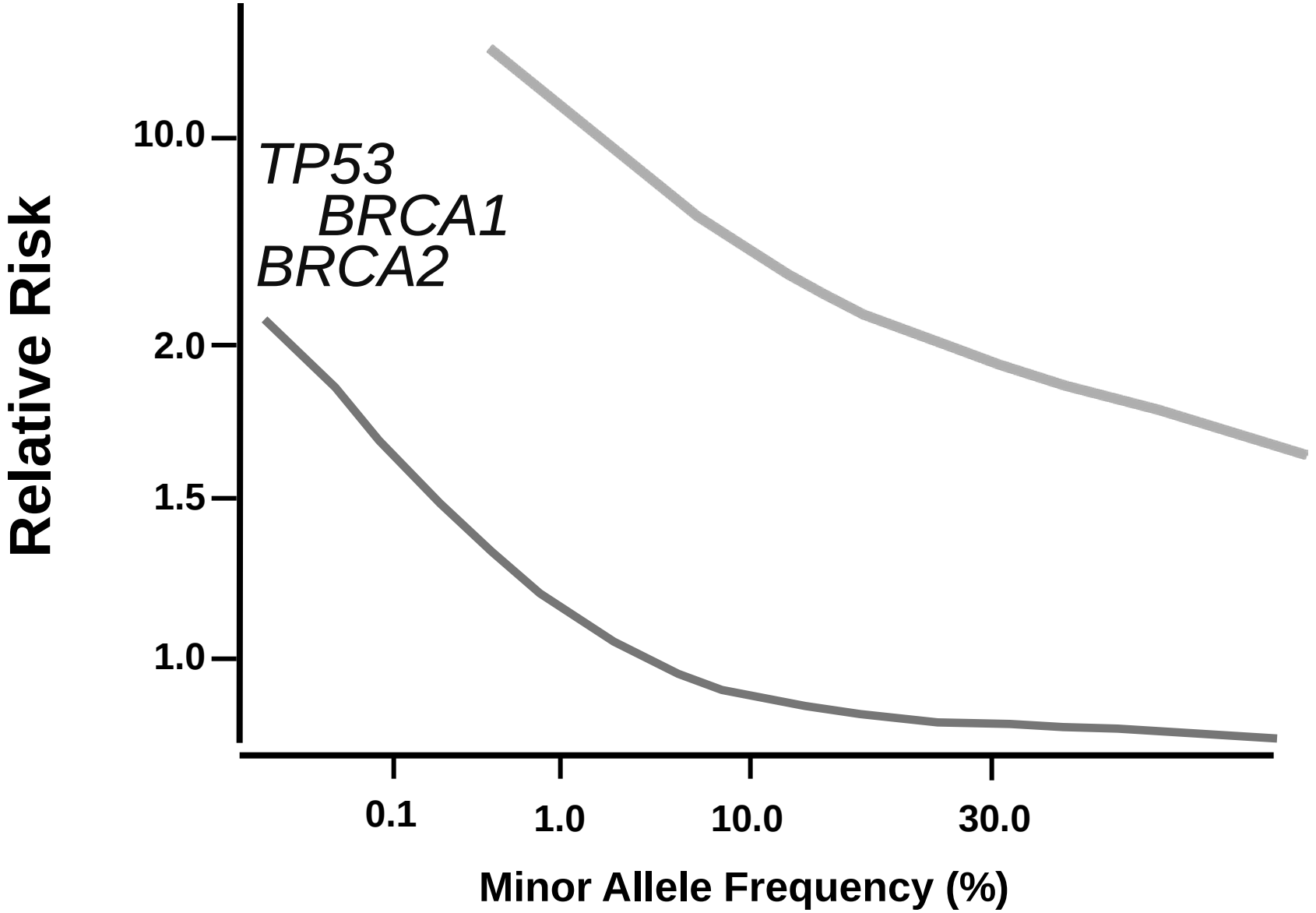
Breast Cancer Gene One

BRCA2

BRCA1 and BRCA2 Families

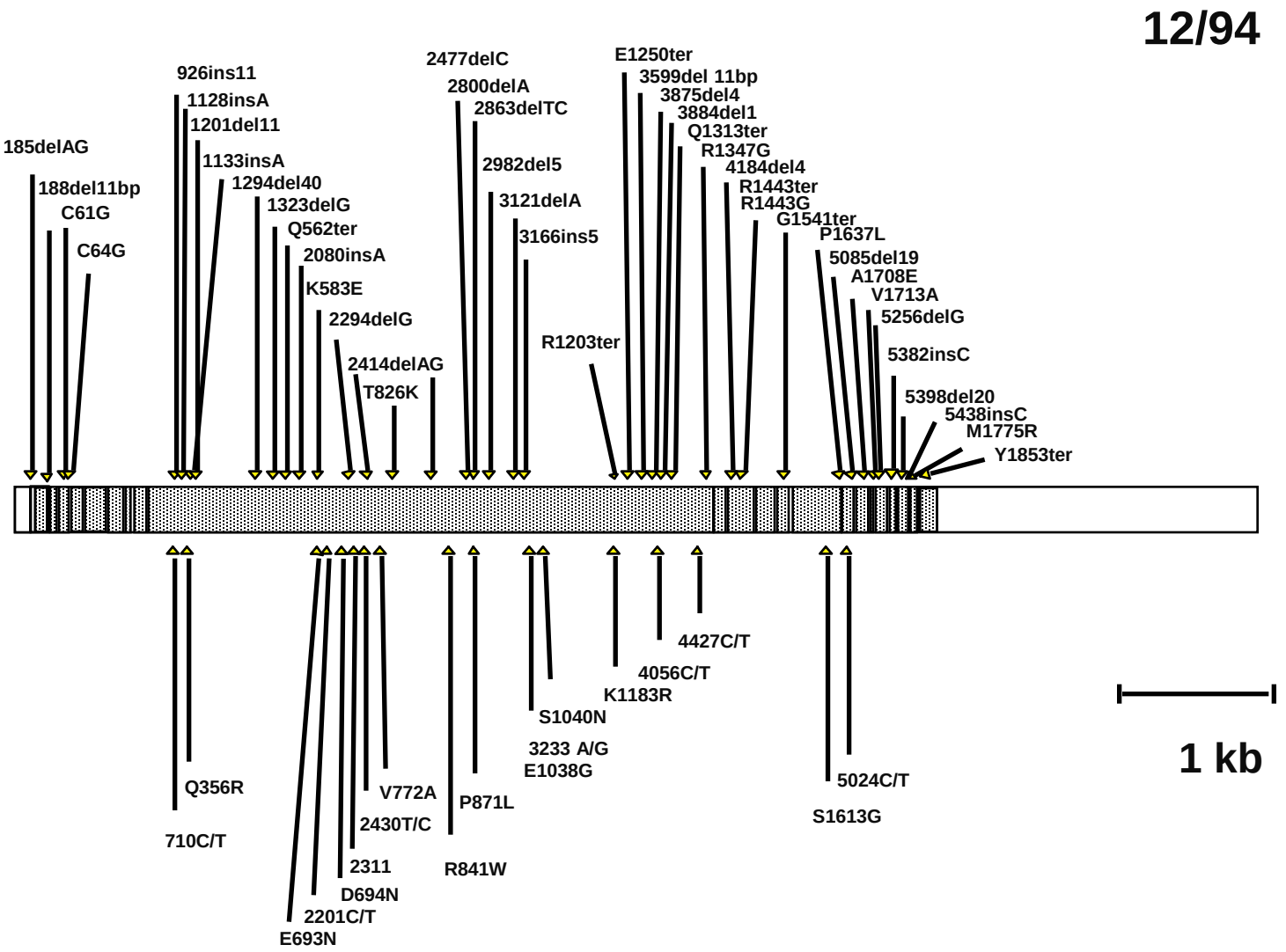


Breast Cancer Genes



Adapted from Foulkes WD *NEJM*, 359:2143, 2008

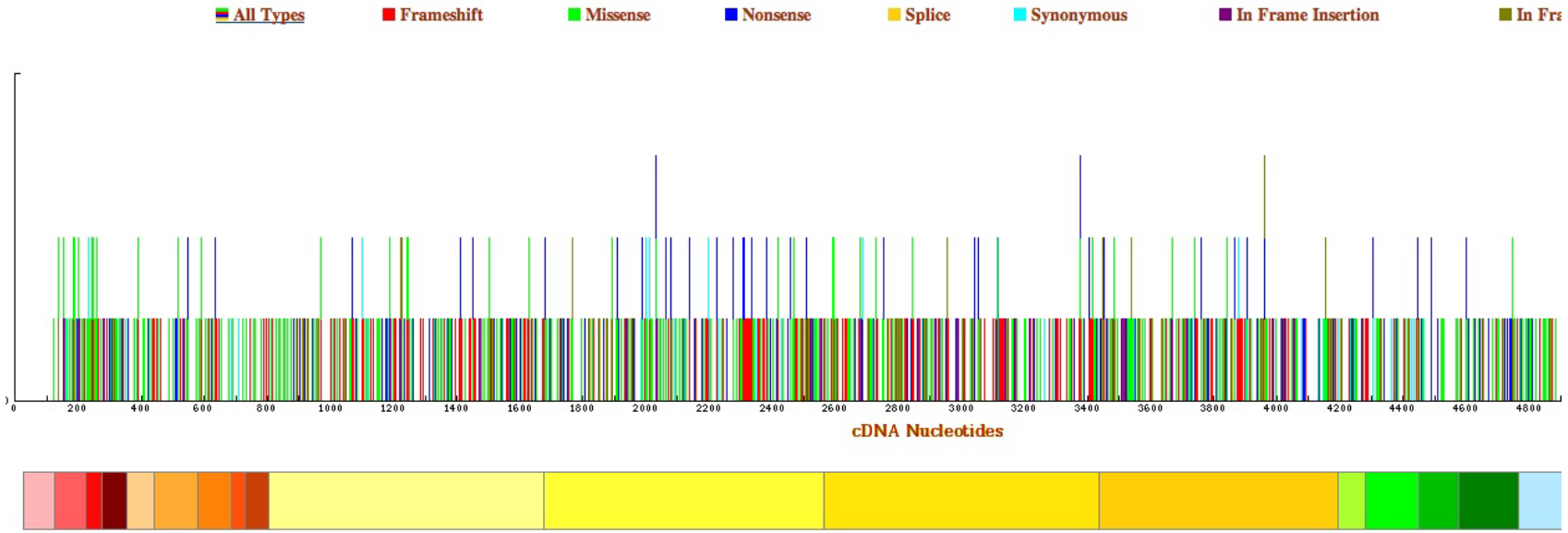
BRCA1 Mutations and Polymorphisms



BRCA1 & BRCA2

The World's most sequenced genes.

BRCA1 – BIC Database



BRCA1 and BRCA2 Founder Mutations

Ashkenazi Jews	1/40
Icelanders	1/170
Dutch	1/333

German, Swedish, Polish, Spanish, Cypriot, Afrikaner, Malaysian

BRCA1 Mutation Data

	Total Entries	Distinct Alterations	One Family Only
Nonsense	1046	176	84
Frameshift	4780	513	303
Splicing	598	175	100
Missense	2734	489	259

BRCA1 Mutation Data

The Unclassified Variant Problem

Missense	2734	489	259

Breast Cancer Genes

- high penetrance / low frequency

BRCA1, BRCA2

- low penetrance / high prevalence

low relative risk, high attributable risk

Association Studies!

CHEK2 - 1100delC

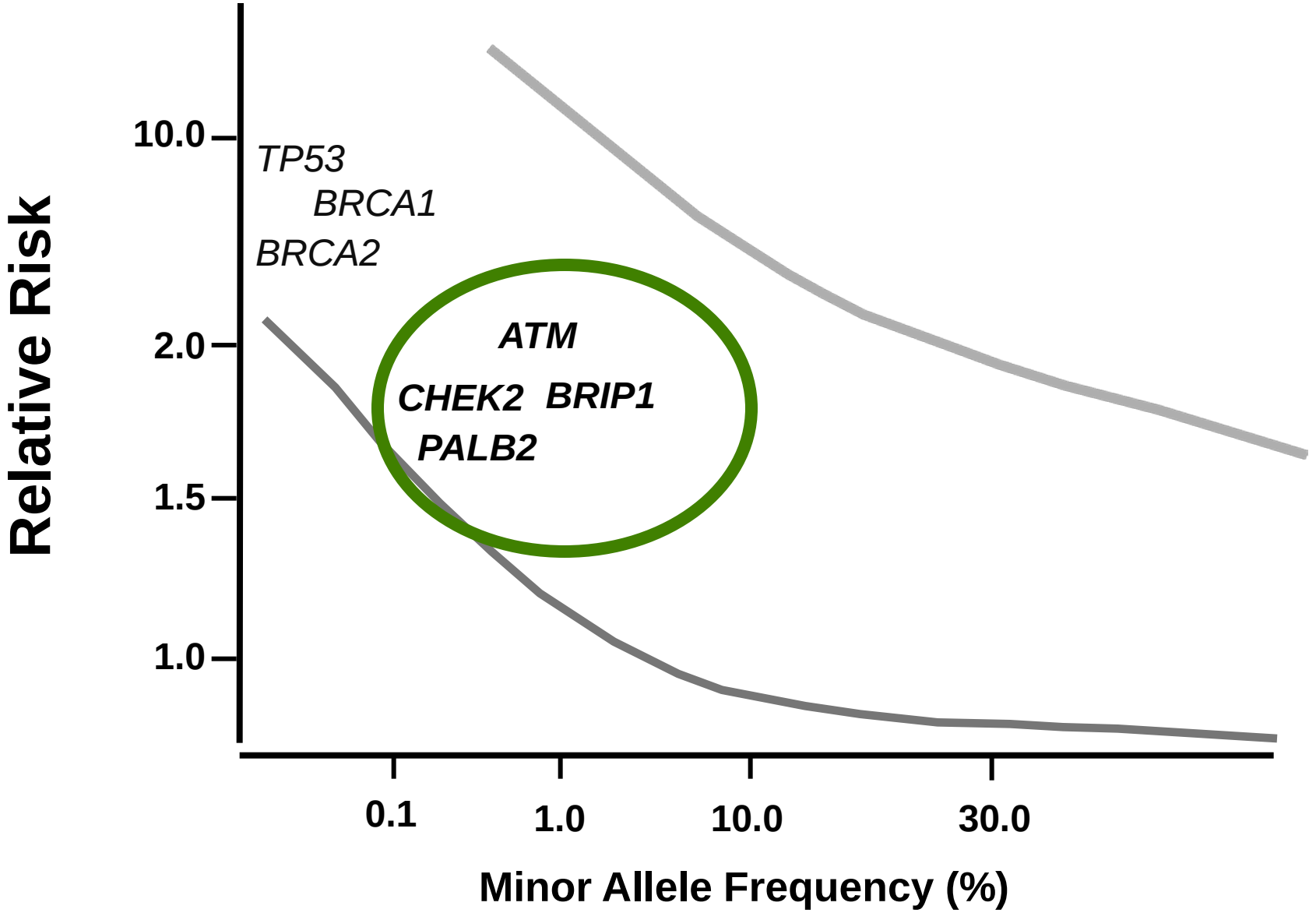
	n	Carriers
Controls	**10,860**	**0.7%**
Breast cancer	**9,065**	**1.9%**

OR= 2.34 CI 1.72-3.20

p= 0.0000001

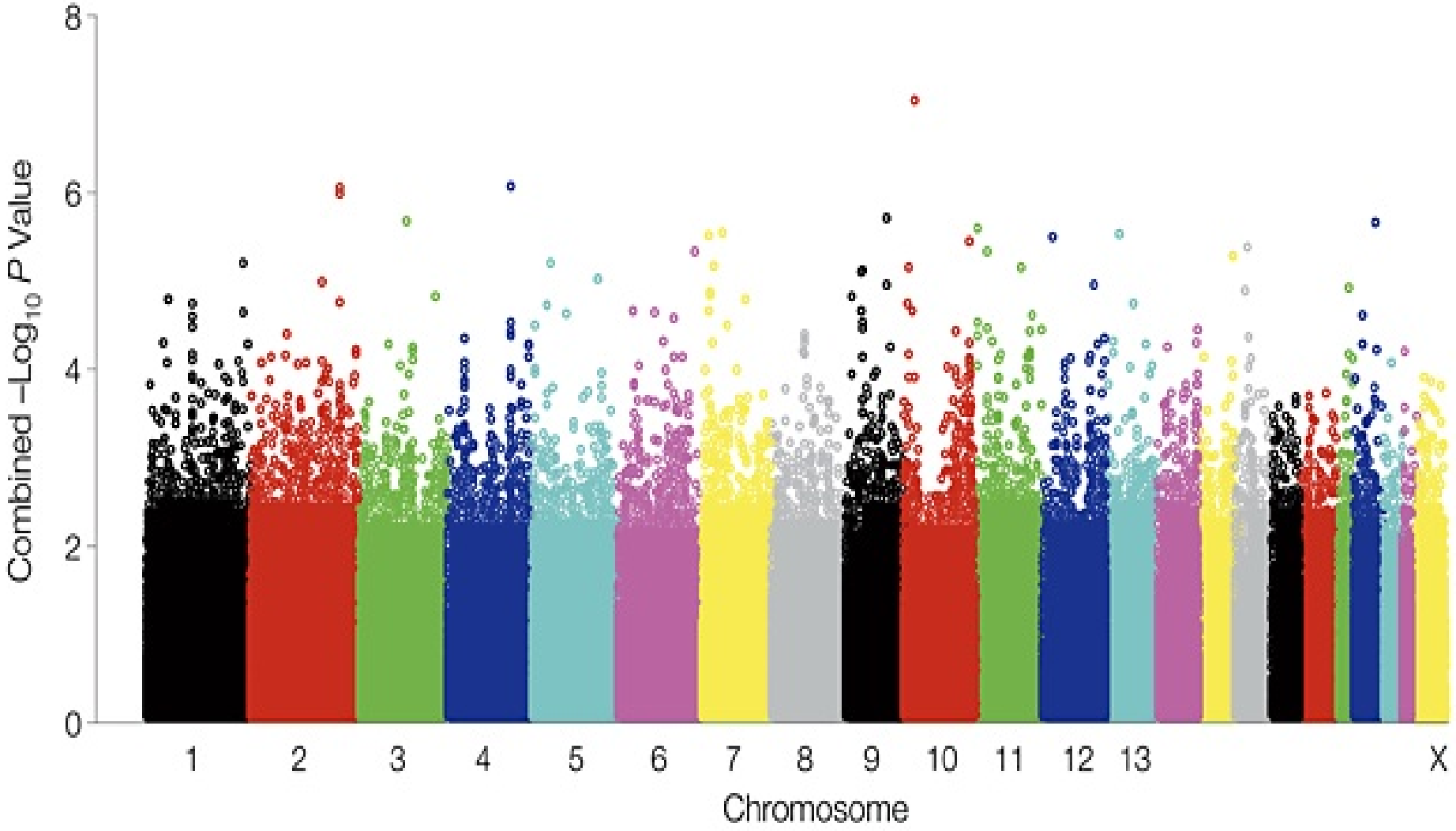
***AJHG* 74, 2004**

Breast Cancer Genes



Adapted from Foulkes WD *NEJM*, 359:2143, 2008

Genome Wide Association Study



Vol 447|28 June 2007|doi:10.1038/nature05887 nature

ARTICLES

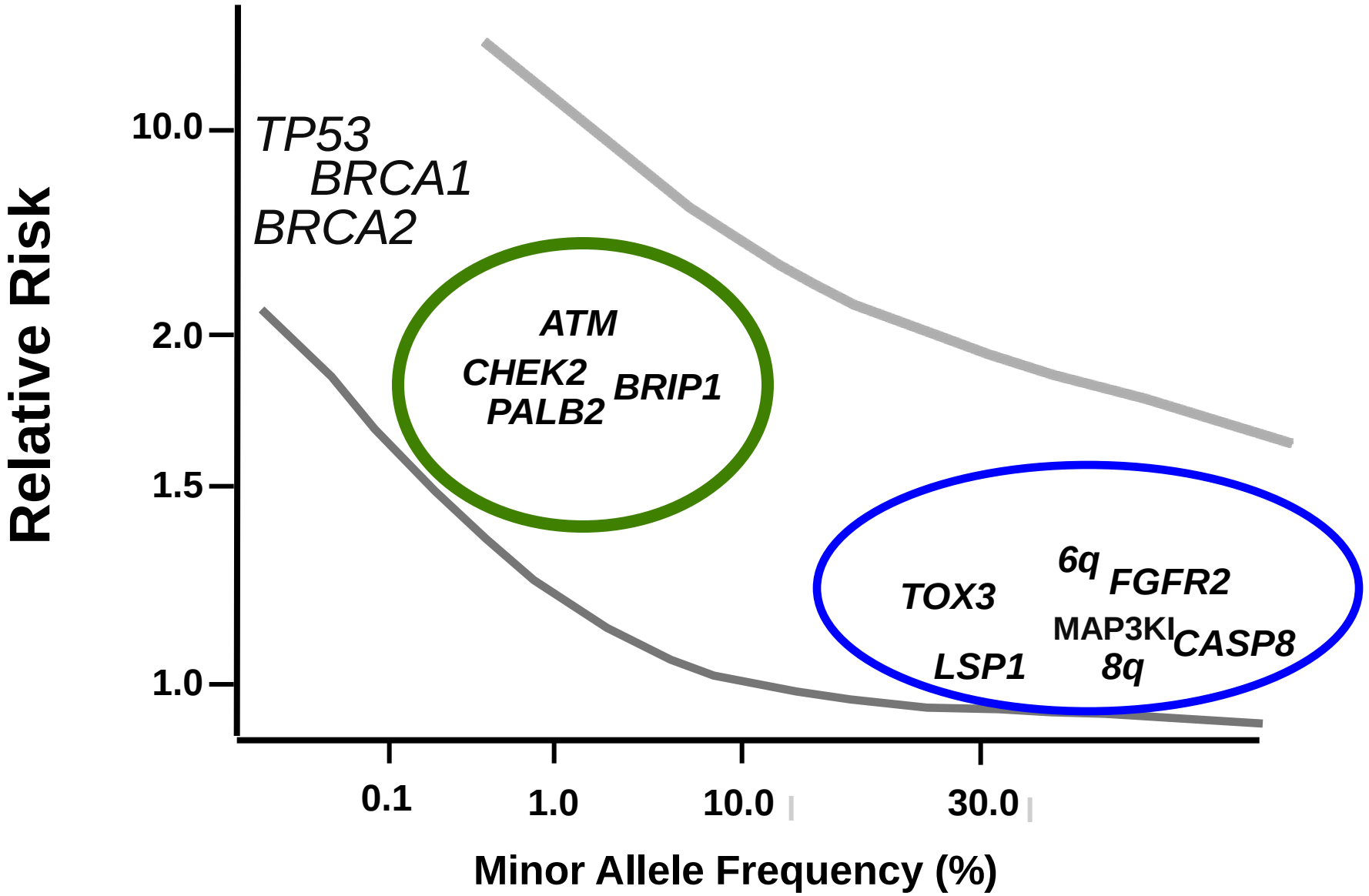
Genome-wide association study identifies novel breast cancer susceptibility loci

Douglas F. Easton[1], Karen A. Pooley[2], Alison M. Dunning[2], Paul D. P. Pharoah[2], Deborah Thompson[1], Dennis G. Ballinger[3], Jeffery P. Struewing[4], Jonathan Morrison[2], Helen Field[2], Robert Luben[5], Nicholas Wareham[5], Shahana Ahmed[2], Catherine S. Healey[2], Richard Bowman[6], the SEARCH collaborators[2]*, Kerstin B. Meyer[7], Christopher A. Haiman[8], Laurence K. Kolonel[9], Brian E. Henderson[8], Loic Le Marchand[9], Paul Brennan[10], Suleeporn Sangrajrang[11], Valerie Gaborieau[10], Fabrice Odefrey[10], Chen-Yang Shen[12], Pei-Ei Wu[12],

147 Institutional Affiliations

Nature 447:1087-109, 28 June 2007

Breast Cancer Genes



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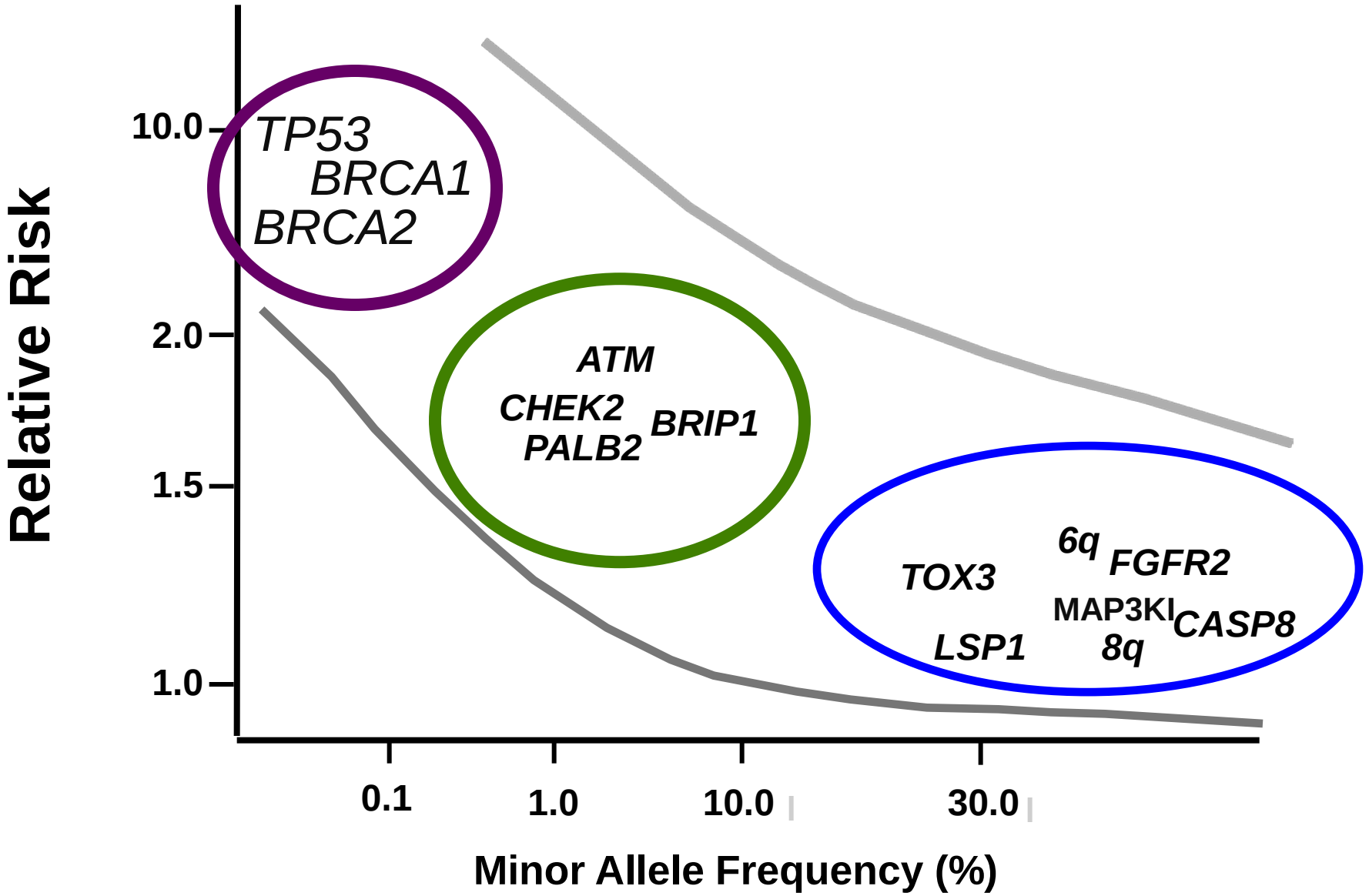
Topography of Cancer Risk

Why Genetics?

- Prevention
- Early Detection
- Prognosis
- Tailored Therapy

Breast Cancer Genes



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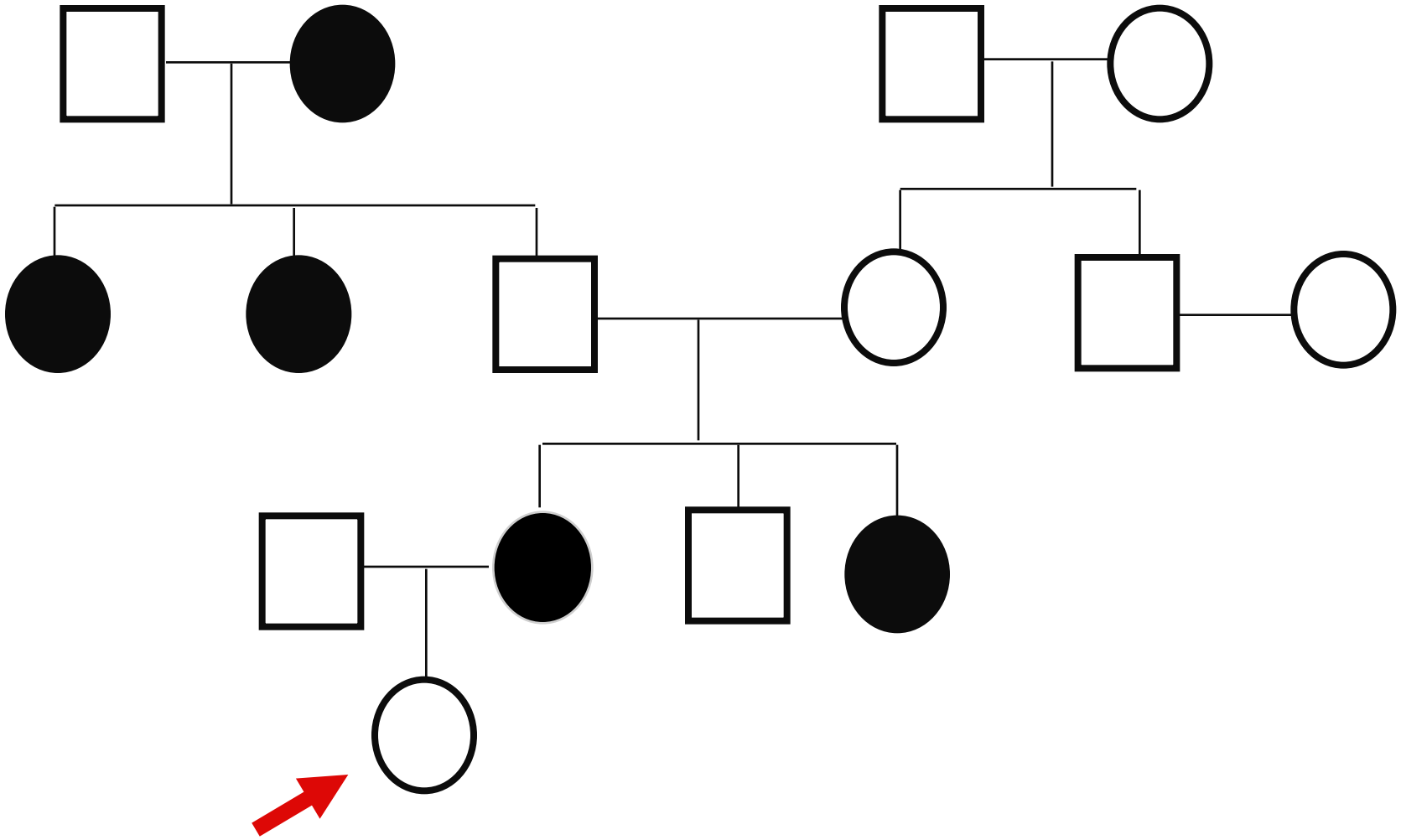
Inherited Cancer



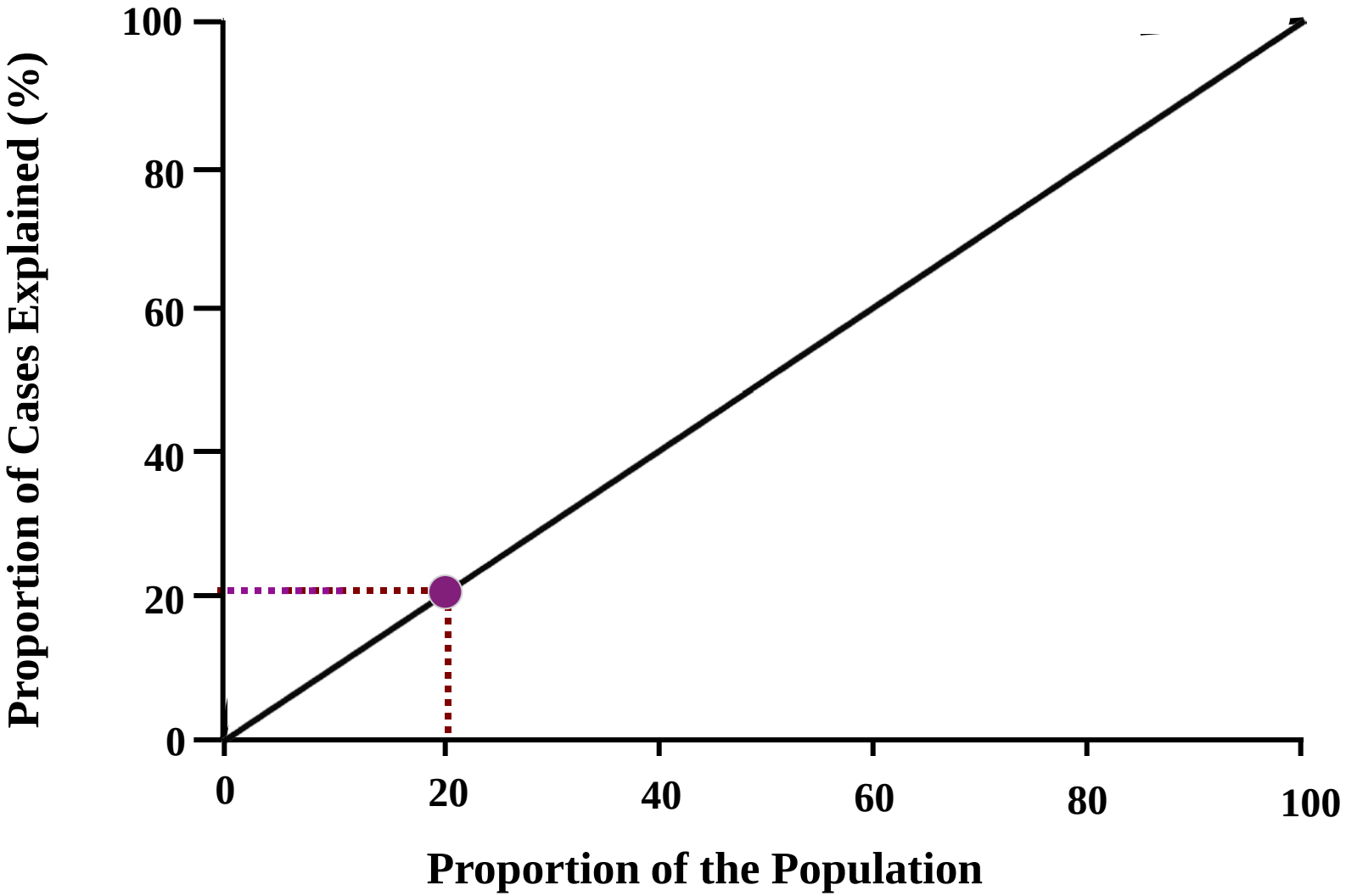
BRCA1/ BRCA2 Mutation Associated Risk

Study Type	Cancer by Age 70
Family-based	80-90%
Proband-based	75-85%
Community-based	50-70%
Population-based	30-50%

Low penetrance / High prevalence

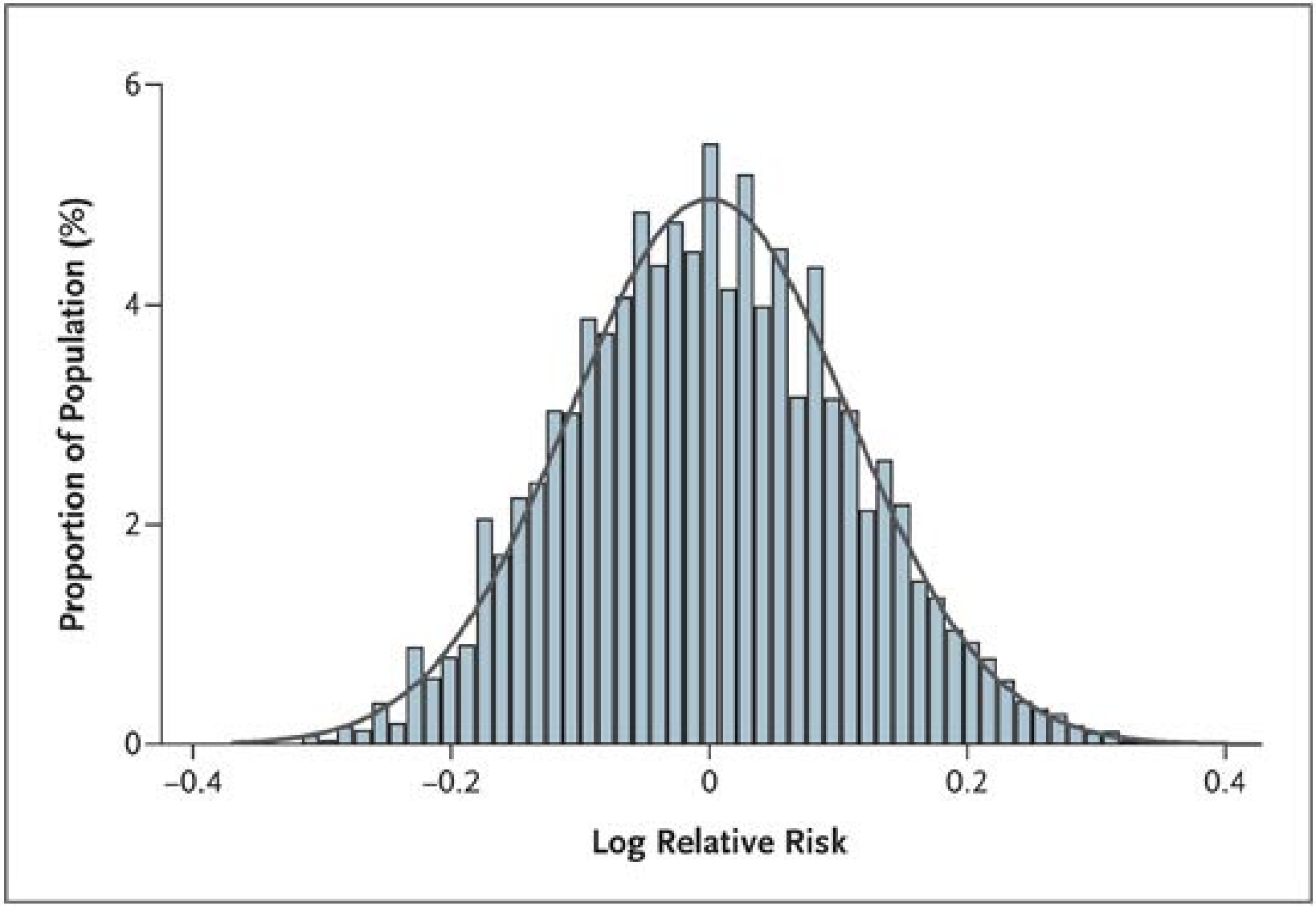
- Clinical Significance?
  - Individual health
  - Public health

Genotype Driven Screening



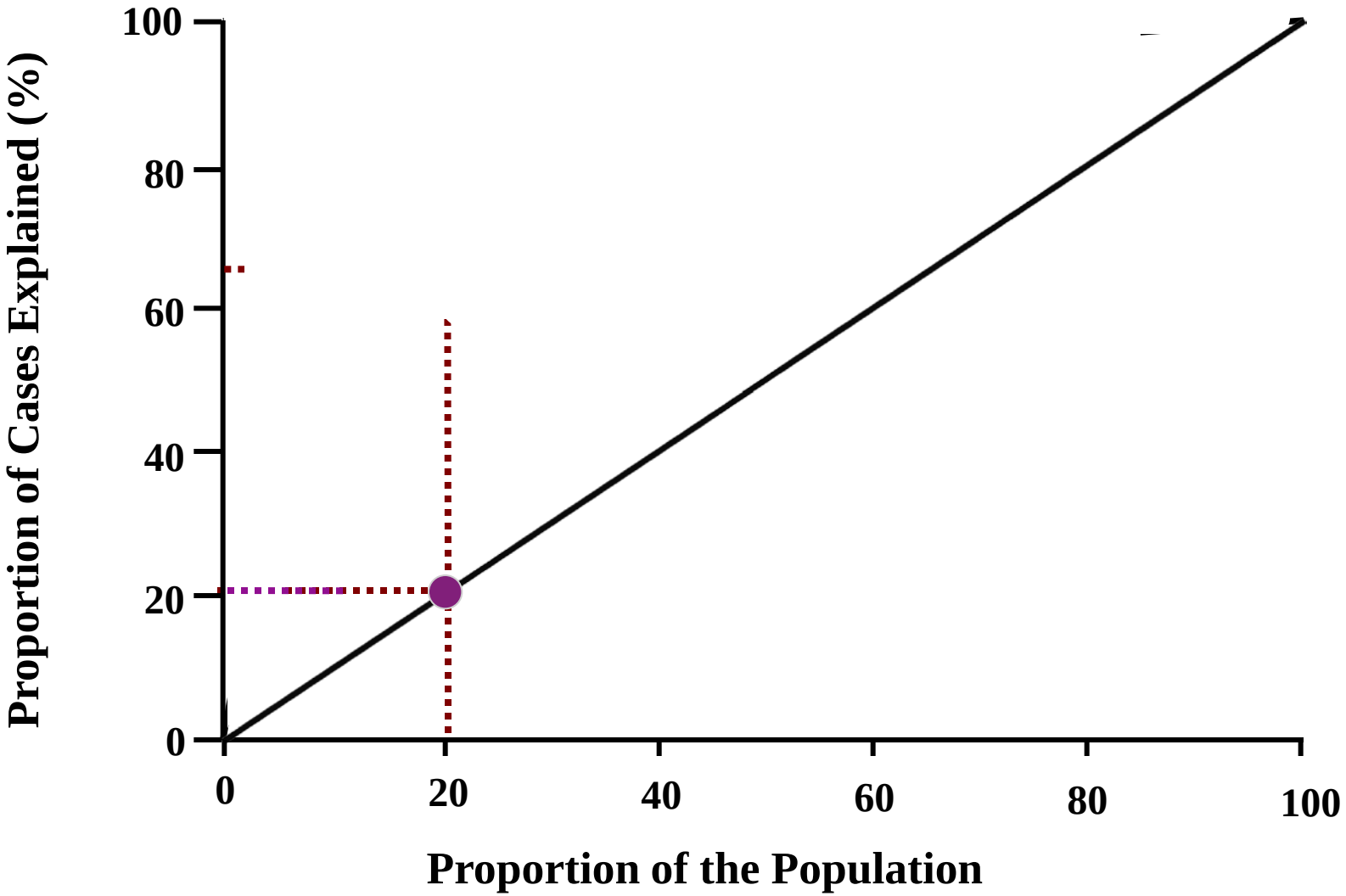
Adapted from Pharoah PD *NEJM* 358, 2008

Distribution of Genetic Risk in the Population



Pharoah PD *NEJM* 358, 2008

Genotype Driven Screening



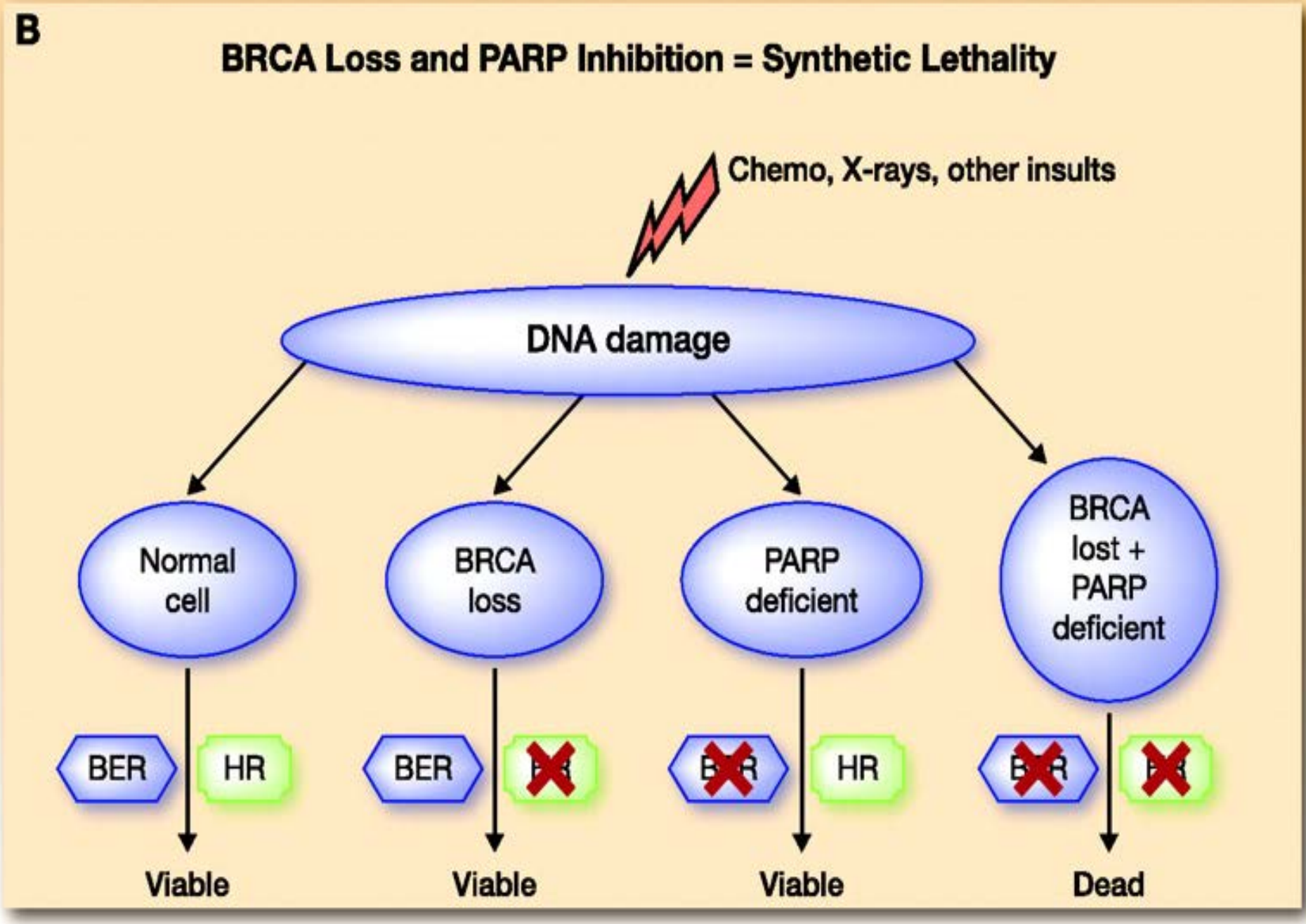
Adapted from Pharoah PD *NEJM* 358, 2008

Why Genetics?

- Prevention
- Early Detection
- Prognosis
- Tailored Therapy

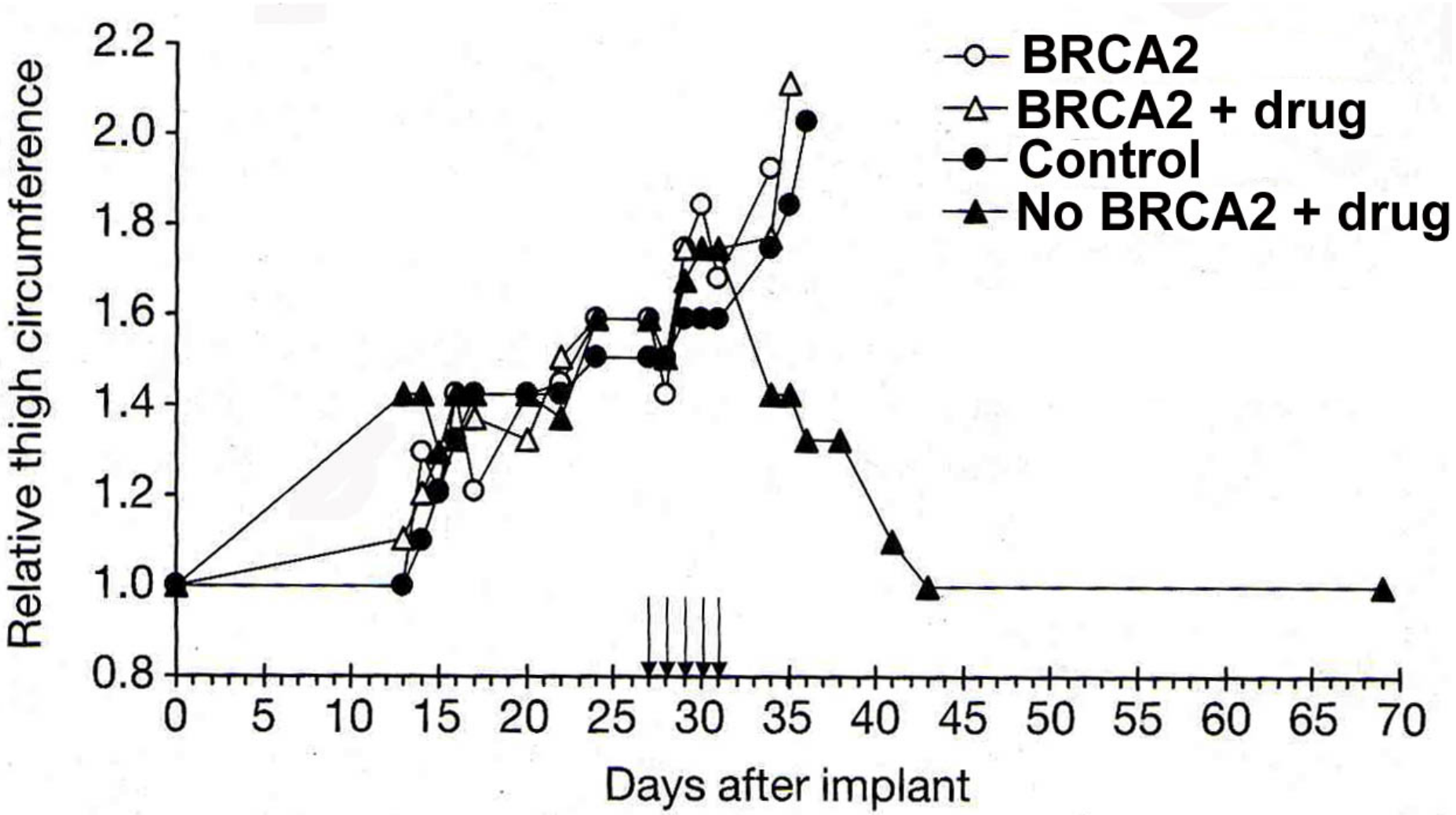
BRCA1 & BRCA2

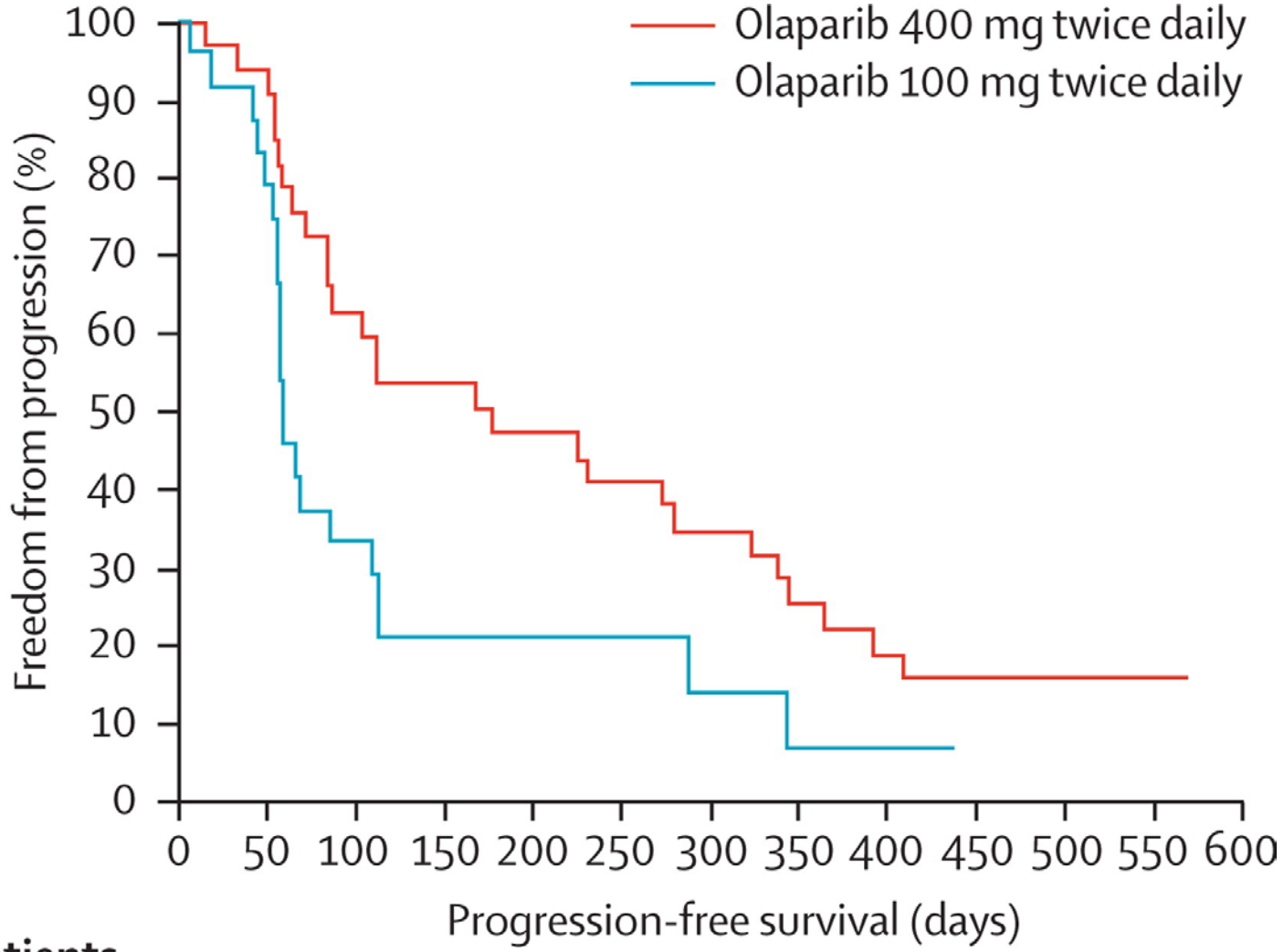
are DNA repair proteins



Anders C K et al. Clin Cancer Res 2010;16:4702-4710

PARP1 inhibitors kill established tumors





Number of patients

Olaparib 400 mg	33	31	20	17	15	13	11	8	6	4	4	3	0
Olaparib 100 mg	24	19	8	5	4	3	2	1	1	0	0	0	0

Audeh et al., *Lancet*, 6 July 2010

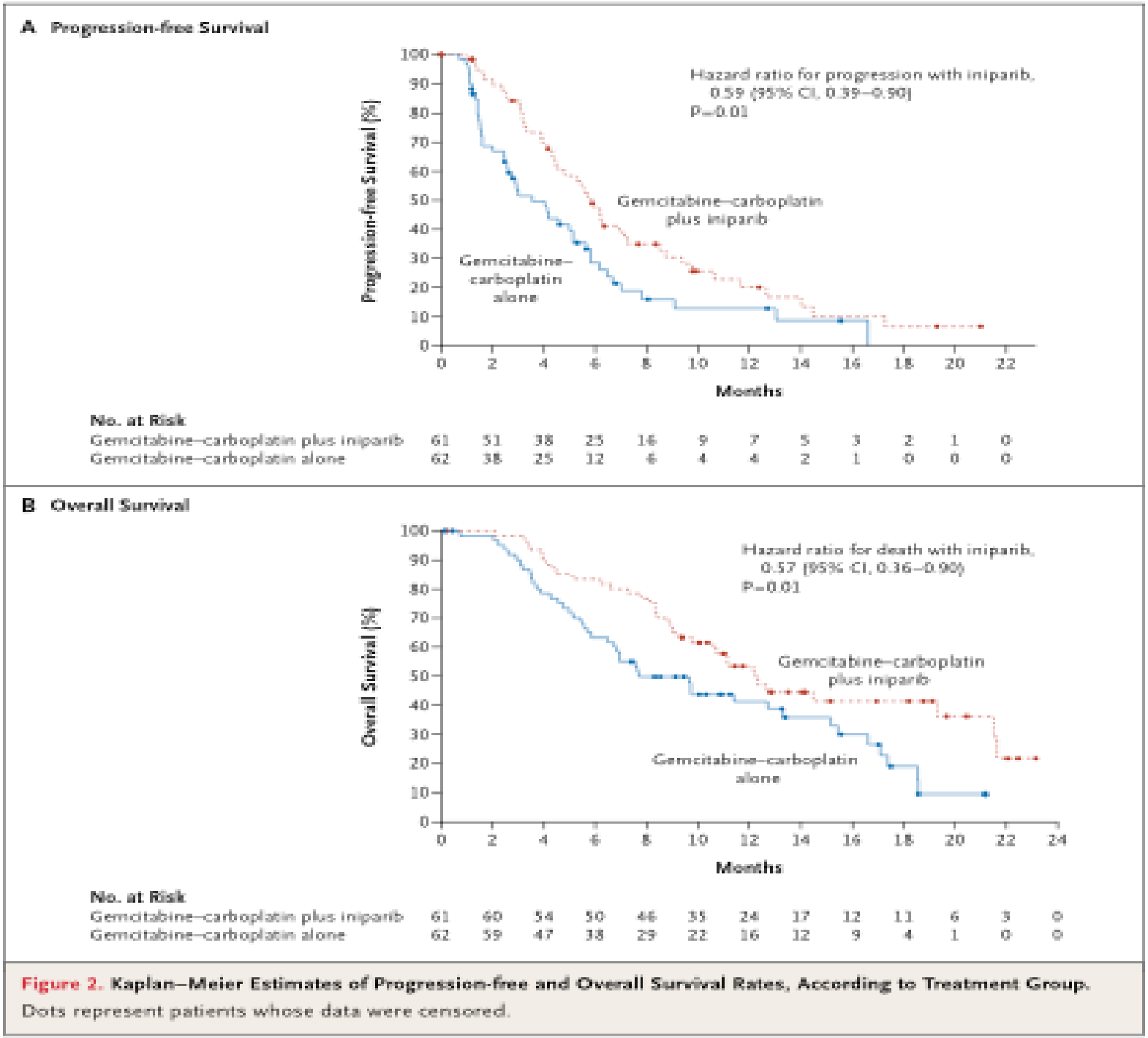
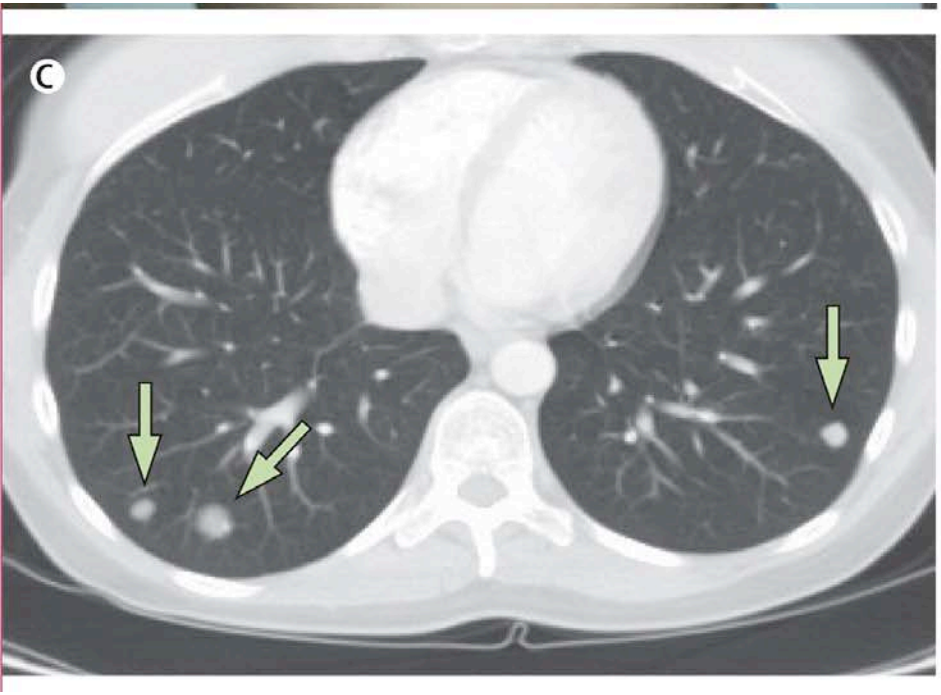


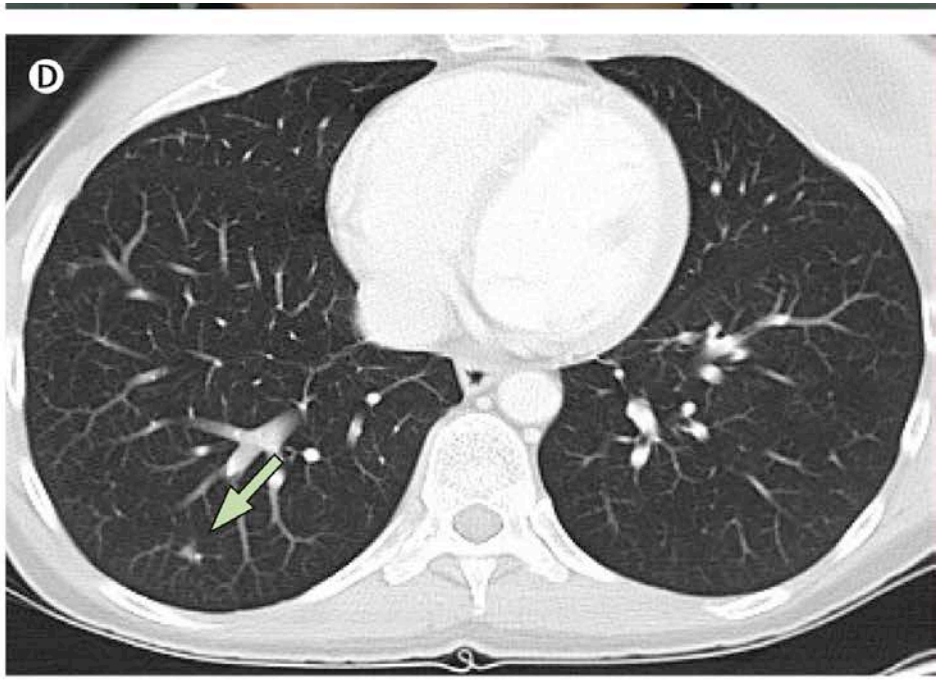
Figure 2. Kaplan–Meier Estimates of Progression-free and Overall Survival Rates, According to Treatment Group.
Dots represent patients whose data were censored.

O'Shaughnessy

NEJM

Jan 2011
vol. 364





Tutt et al., *Lancet*, 6 July 2010

Why Genetics?

- Understand Mechanism
- Refine Characterization

Why Genetics?

- Prevention
- Early Detection
- Prognosis
- Tailored Therapy

Last slide

Mutation Database (BIC)

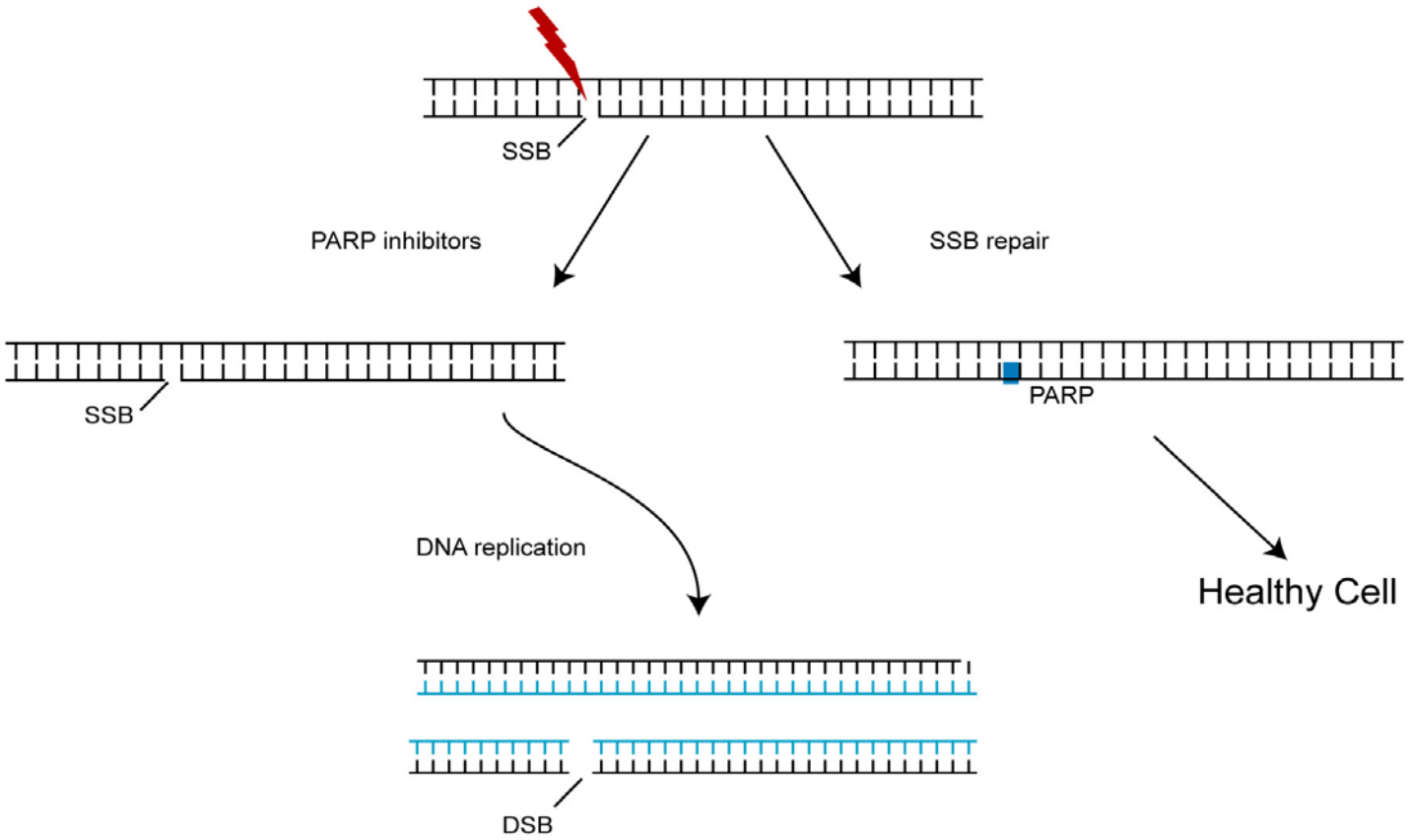
BRCA1	11,672
BRCA2	11,171

Breast Cancer Genes - GWAS Genes

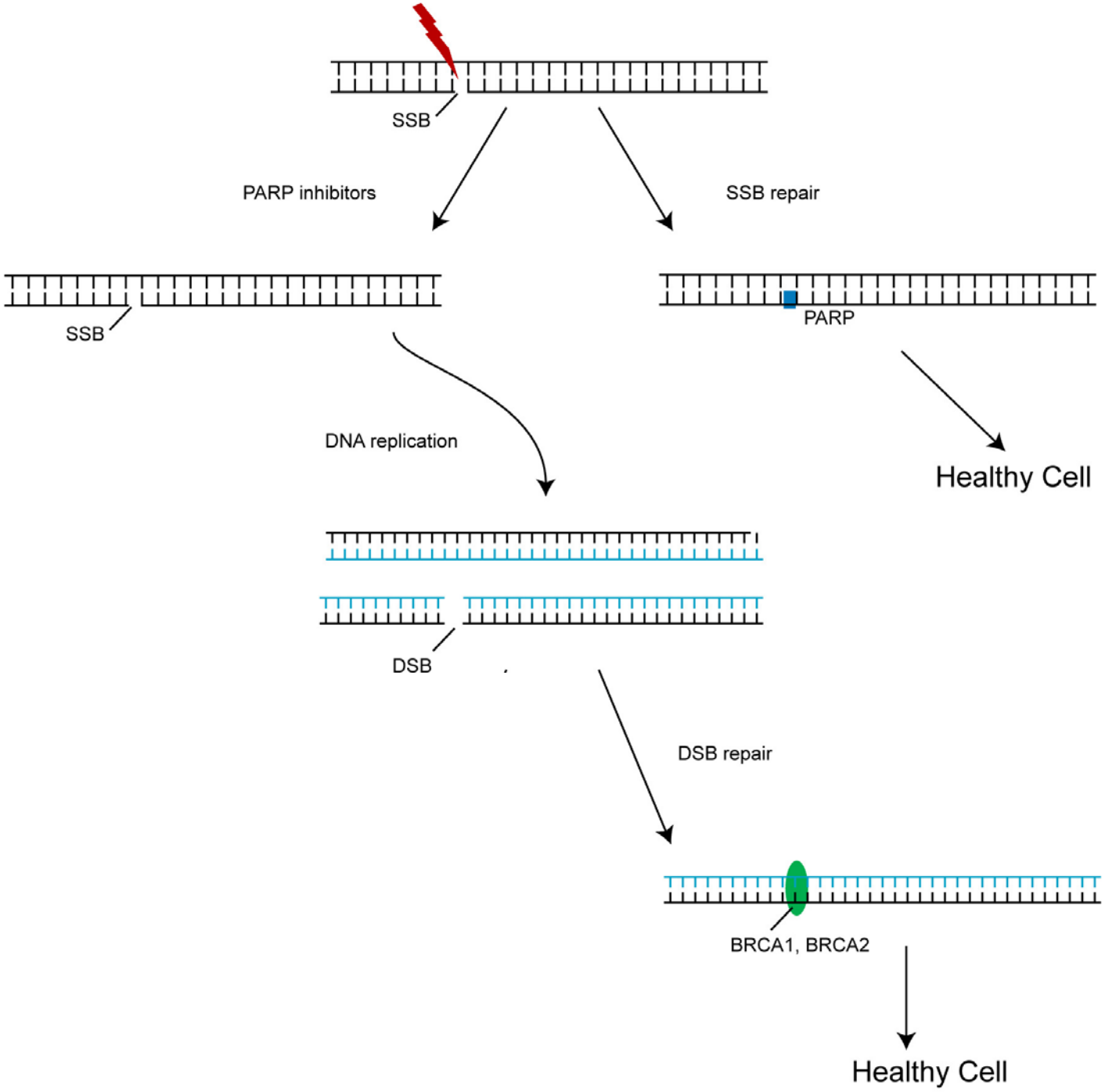
Gene	Risk Allele Freq	Relative Risk	Pop. Attributable Risk
TNRC9	0.25	1.20	10%
FGFR2	0.38	1.26	19%
“2q”	0.58	1.20	7%
CASP8	0.86	1.13	20%

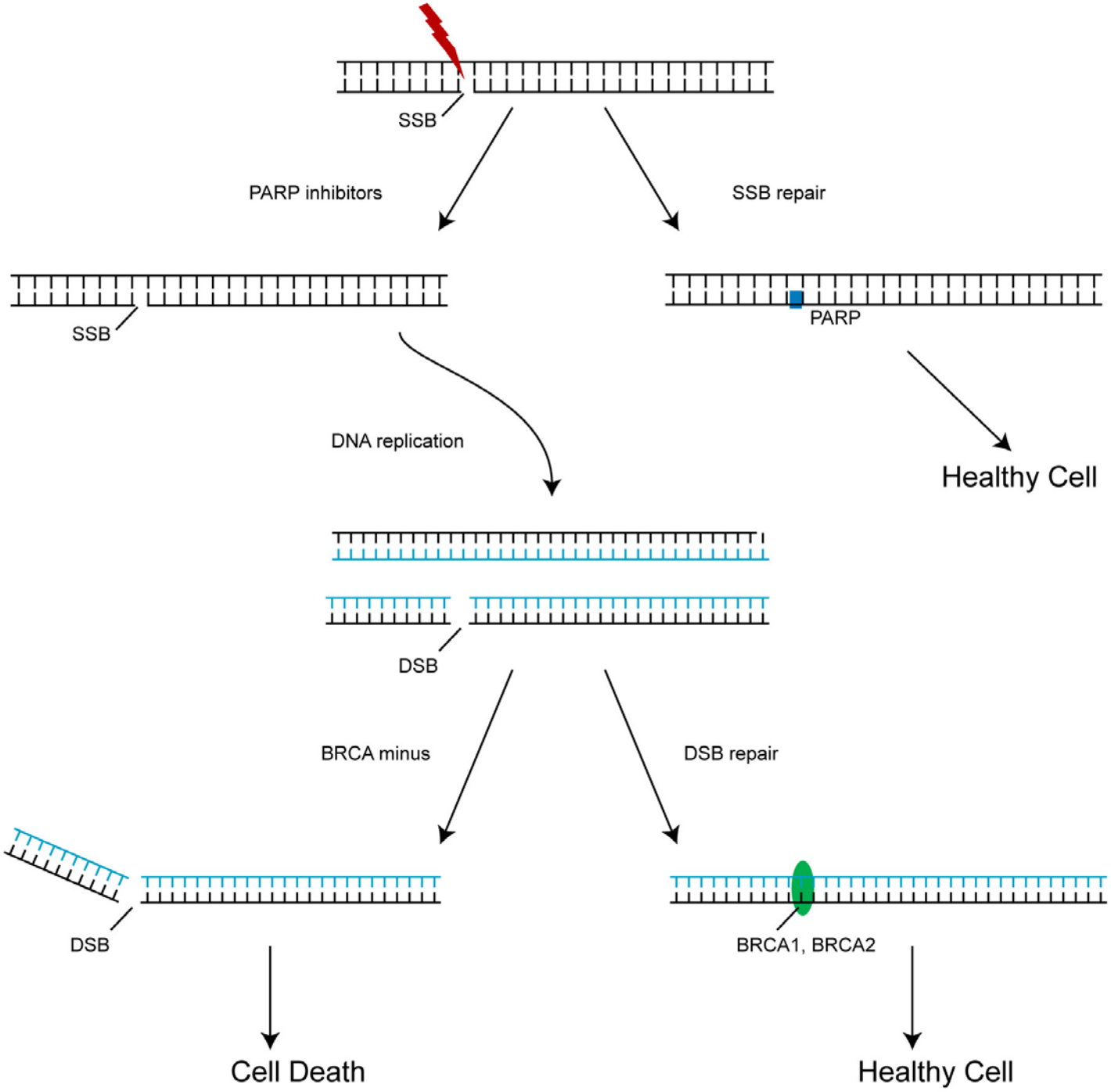
Adapted from Pharoah P et al. N Engl J Med 2008;358:2796-2803

Tailored therapy?



Bryant et al., *Nature,* 434: 913, 2005 Farmer et al., *Nature,* 434: 917, 2005


SSB
PARP inhibitors
SSB repair
SSB
PARP
DNA replication
Healthy Cell
DSB
DSB repair
BRCA1, BRCA2
Healthy Cell


SSB
PARP inhibitors
SSB repair
SSB
PARP
DNA replication
Healthy Cell
DSB
BRCA minus
DSB repair
DSB
BRCA1, BRCA2
Cell Death
Healthy Cell