- Genetics vs genomics

- Somatic vs Germline

- Hereditary male-female cancers

- When earlier controls

- Benefit for patients already diagnosed

- An idea of what may happen in family tree men/ women

- Spectrum of tests

- When insisting to get a test, pay, or social

- Relation to Active Surveillance

29 March 2023

Gianluca Ingrosso

University of Perugia - Italy
Radiation Oncology Dept. - Perugia General Hospital

Biomarker:

A defined characteristic that is measured as an indicator of biological processes…..molecular, histologic, imaging or physiologic characteristics are examples of biomarkers

FDA & National Institutes of Health. BEST (Biomarkers, Endpoints, and other tools) resource. *NCBI* http://www.ncbi.nlm.nih.gov/books/ NBK326791


Biomarker uses:

screening for disease, diagnosis, and staging, targeting treatments, guiding patients stratification, predicting and monitoring therapeutic efficacy and/or toxicity

The genome is the entire genetic information of an organism

Analyzing the whole genome using next-generation sequencing (NGS) technology provides the analysis of the whole genome, which is the most comprehensive collection of an individual's genetic information.

Genomics refers to the whole genome

Genetics refers to a specific gene

Patient Sample   Nucleic Acid Extraction*   Library Preparation, Sequencing, & Analysis   Report
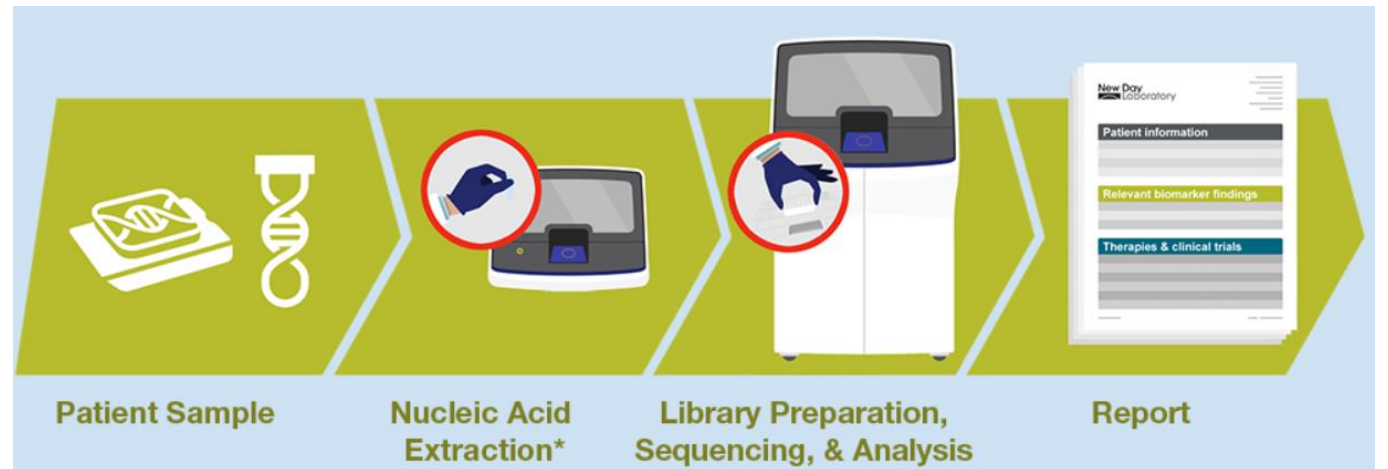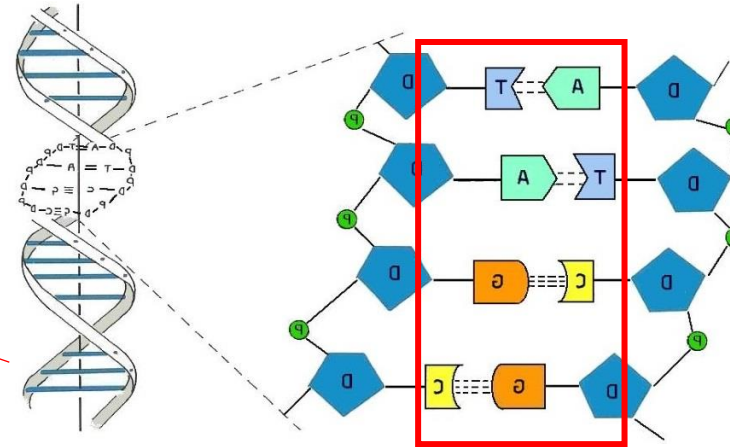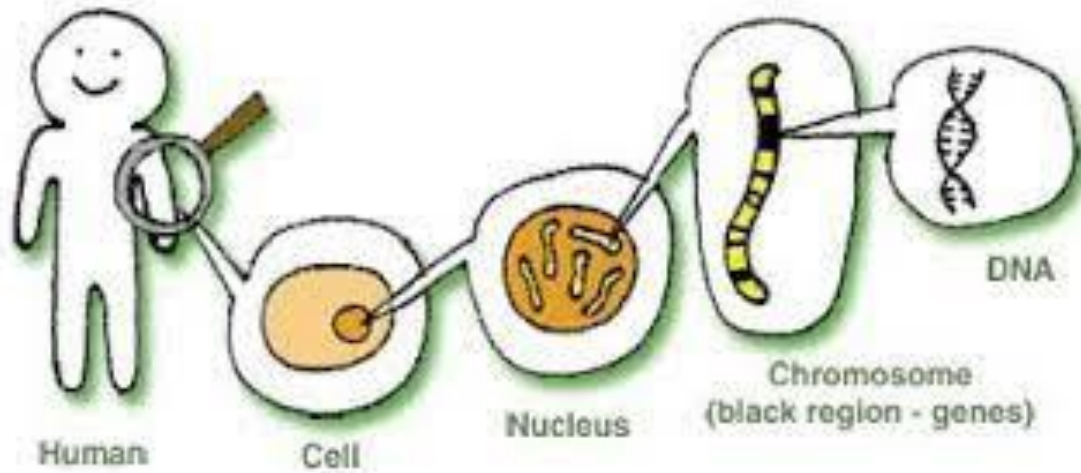
TCGA

The combination of words is a gene that encodes for a protein

Genes are like instructions for ingredients (proteins) of a recipe

Our genome is composed of about 20.000 genes

A mutation is a typo in the DNA

Mutations occur during our life and they are affected by environment, diet, lifestyle

Cancer is an uncontrolled cell growth caused by key DNA mutations that occur during a lifetime. Hence, cancer risk increases with age

DNA variations can include:
- single-nucleotide variants (SNVs)
- small insertions and deletions (indels)
- copy-number variations (CNVs)
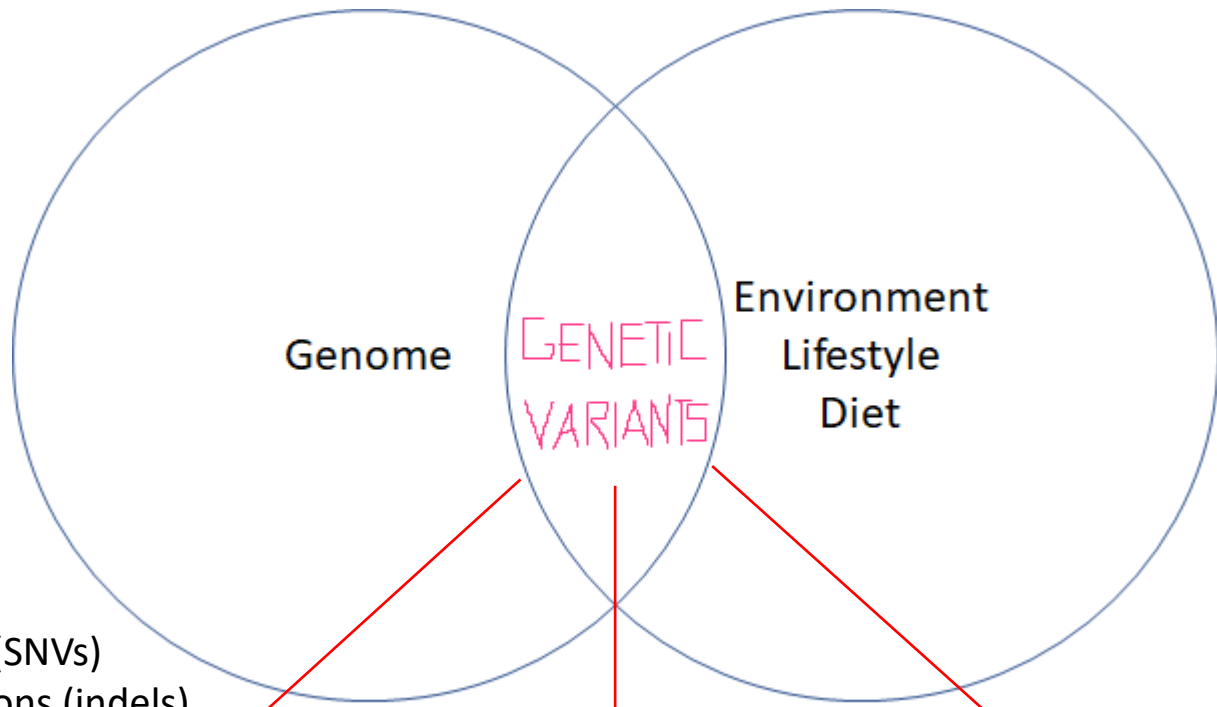- structural variants (SVs)

Genes are like instructions for ingredients of a recipe

benign variant
(Percorino)

benign variant
(Parmigiano)

pathogenic variant
(no pasta)

Genome

GENETIC VARIANTS

Environment
Lifestyle
Diet

DNA variations:
- single-nucleotide variants (SNVs)
- small insertions and deletions (indels)
- copy-number variations (CNVs)
- structural variants (SVs)

benign variant
(Percorino)

benign variant
(Parmigiano)

pathogenic variant
(no pasta)

Germ line (germ cells)
Haploid
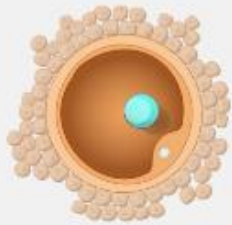23 chromosomes (n) in human
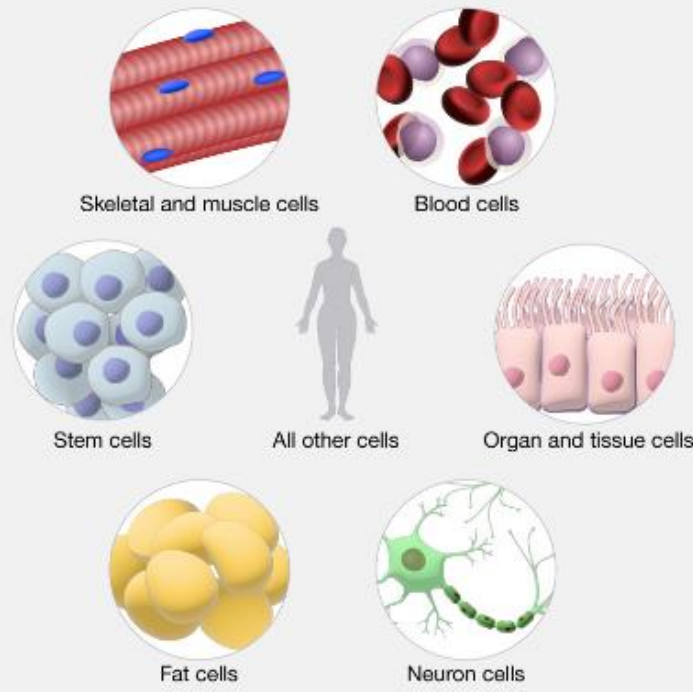
Somatic cells
Diploid
46 chromosomes (2n) in human

Sperm

Ovum (egg)

Fertilized egg

Skeletal and muscle cells

Blood cells

Stem cells

All other cells

Organ and tissue cells

Fat cells

Neuron cells

Prostate

Germ line

Tumour focus 1

Tumour focus 2

7

[Haffner MC et al, Nat Rev Urol 2020]

Germline: genomes inherited by the parents
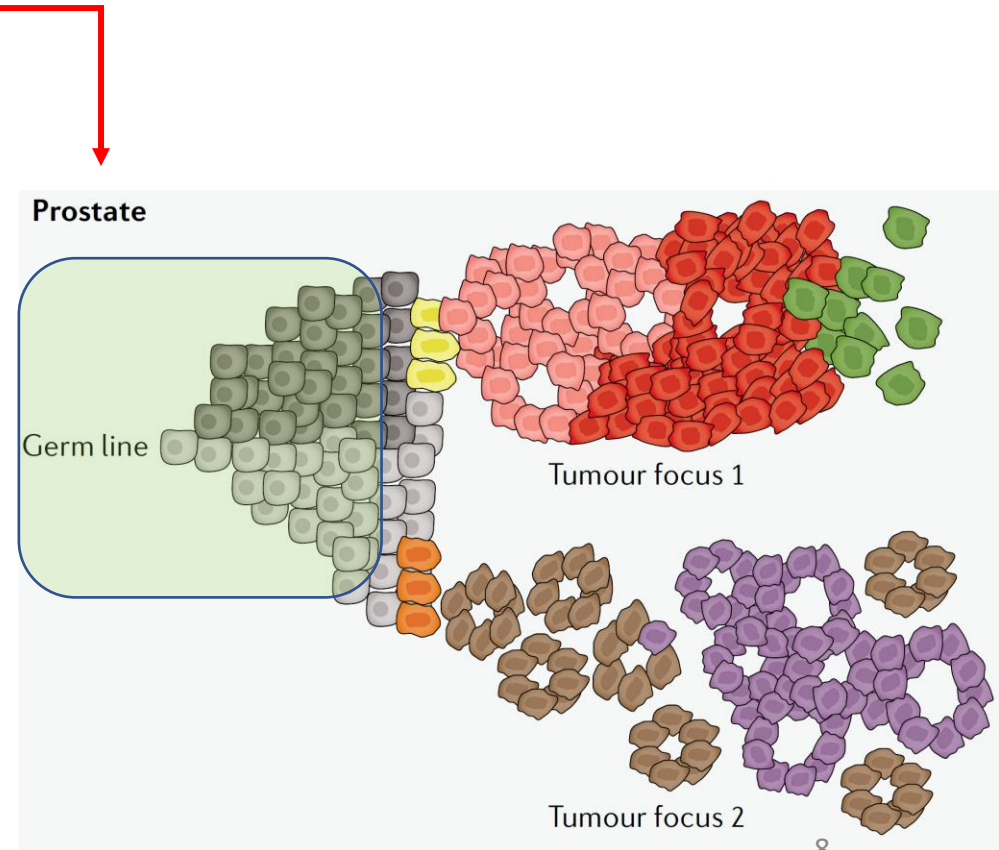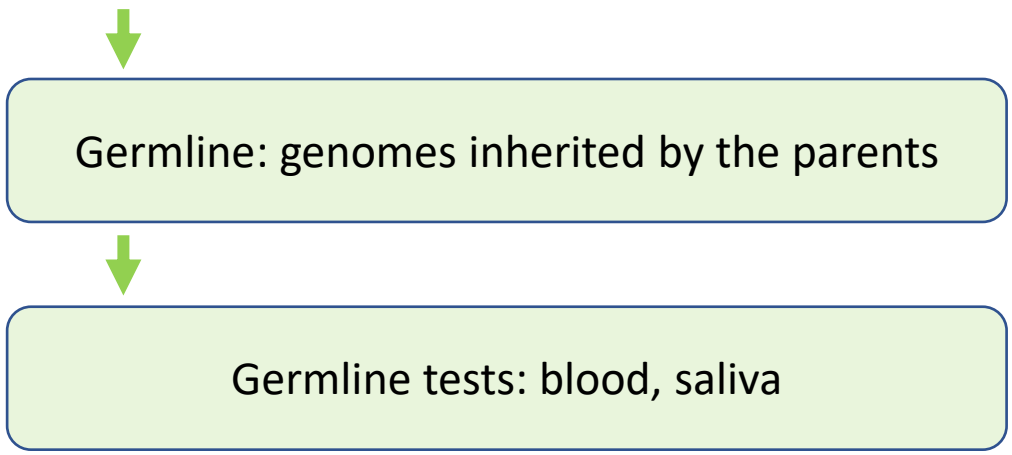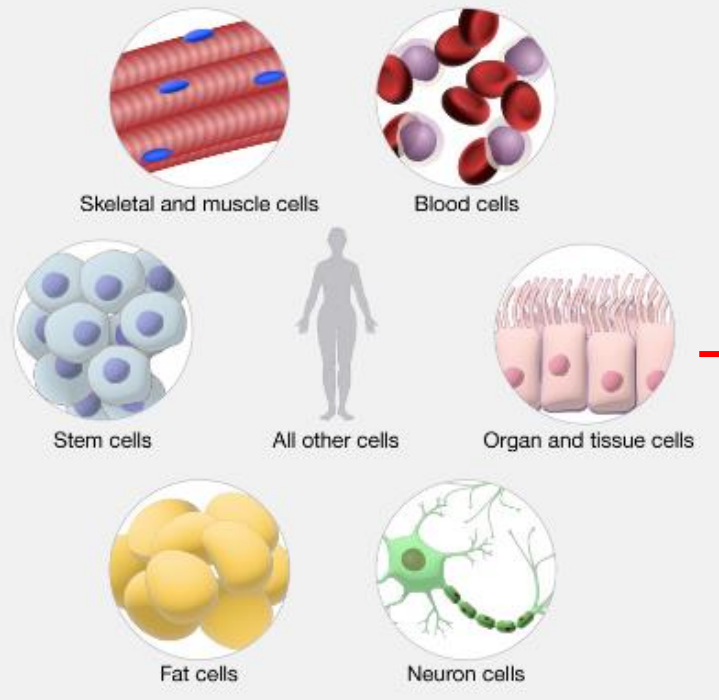
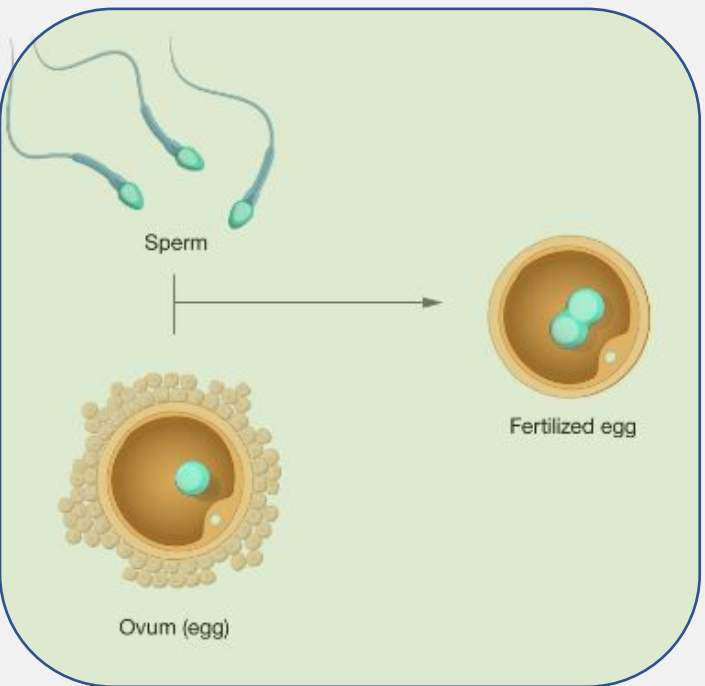Germline tests: blood, saliva

Prostate

Germ line

Tumour focus 1

Tumour focus 2

[Haffner MC et al, Nat Rev Urol 2020]

Germ line (germ cells)
Haploid
23 chromosomes (n) in human

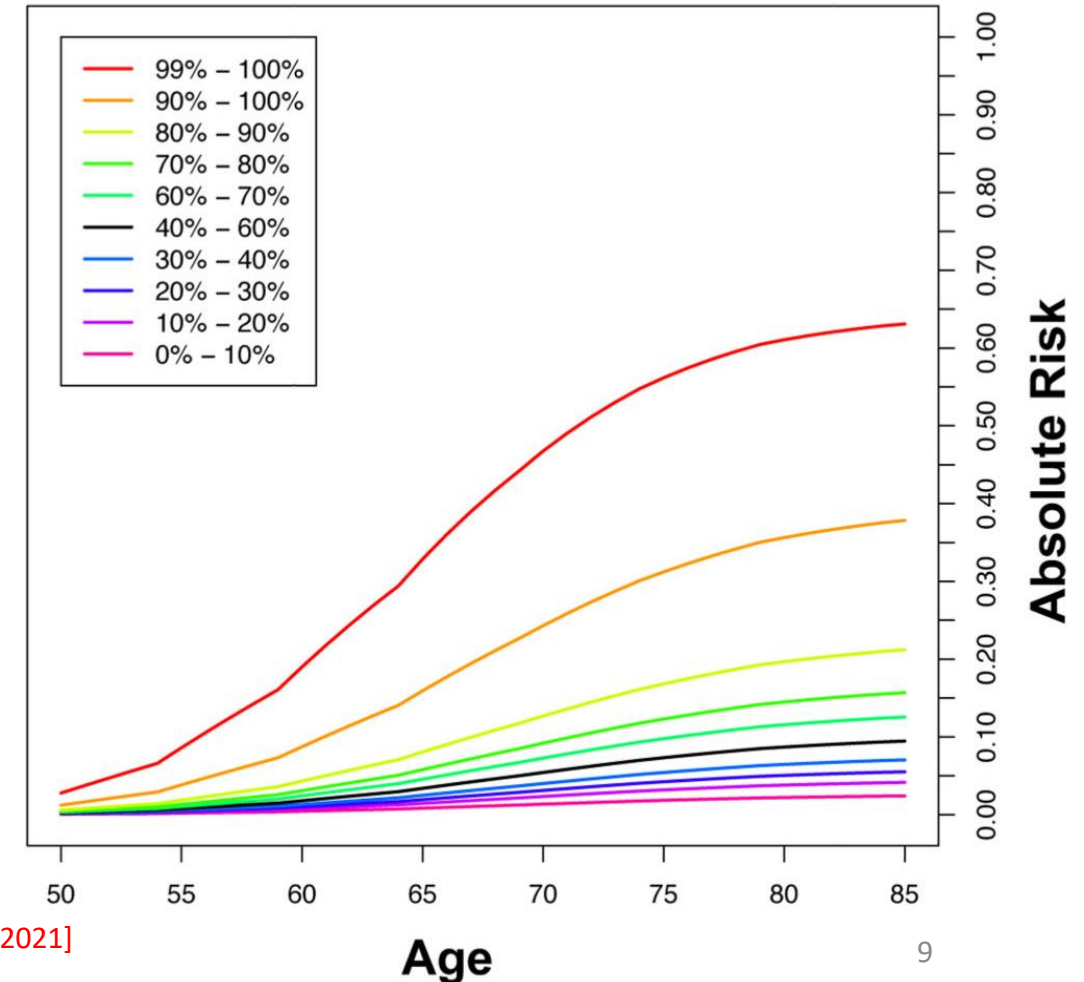**Somatic cells**
Diploid
46 chromosomes (2n) in human

Sperm

Ovum (egg)

Fertilized egg

Skeletal and muscle cells

Blood cells

Stem cells

All other cells

Organ and tissue cells

Fat cells

Neuron cells

8
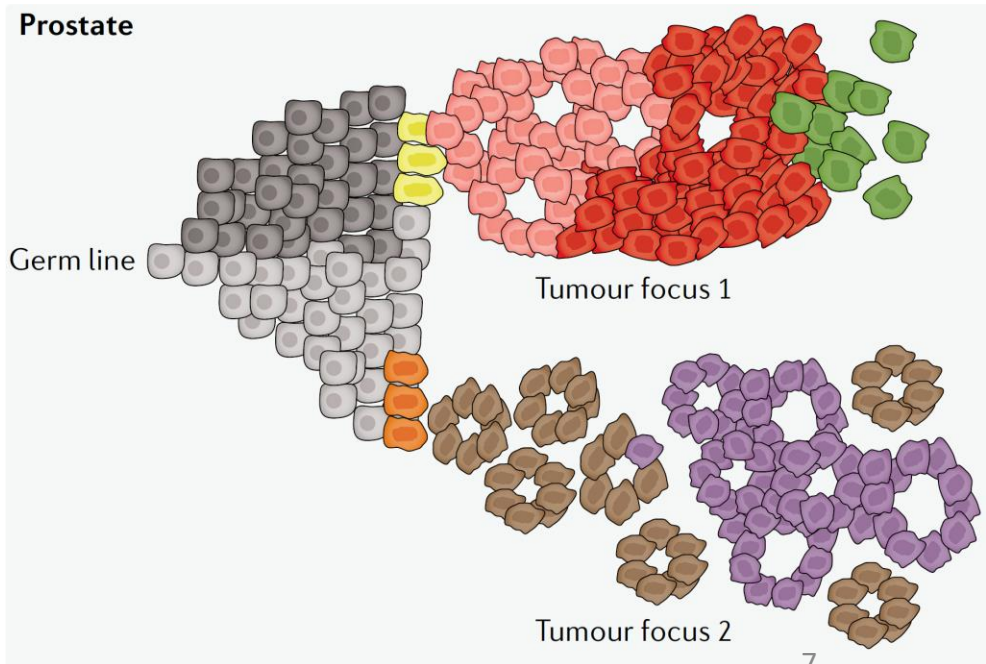
Genomic germline

Genome-wide association studies (GWAS)

Multiancestry Genetic Risk Score (GRS):
269 common germline genetic variants

Germline: genomes inherited by the parents
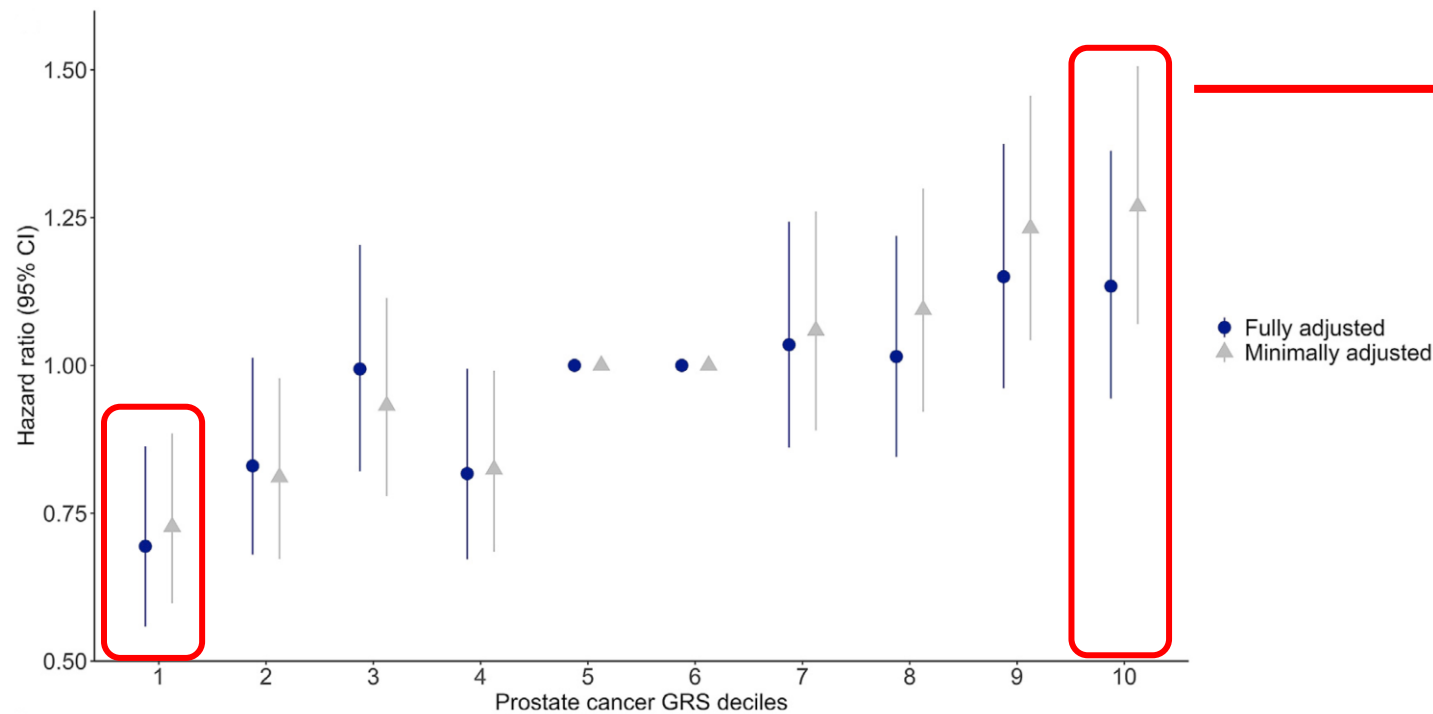
Germline tests: blood, saliva

Legend:
- 99% – 100%
- 90% – 100%
- 80% – 90%
- 70% – 80%
- 60% – 70%
- 40% – 60%
- 30% – 40%
- 20% – 30%
- 10% – 20%
- 0% – 10%

Absolute Risk vs Age

[Conti DV et al, Nat Genet 2021]

Genomic germline
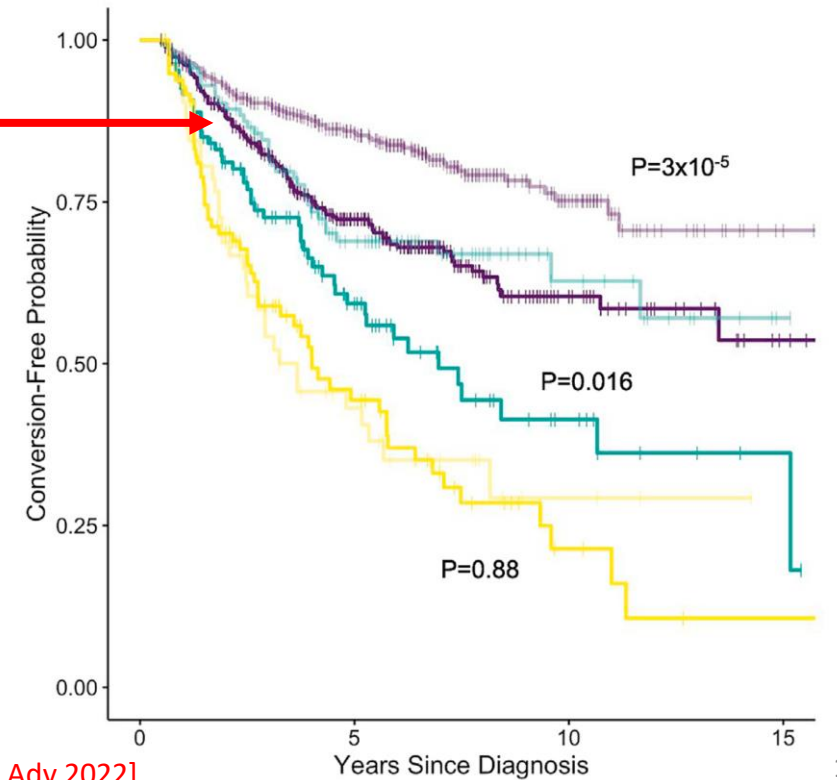
Genetic Risk Score (GRS) based on genomic analysis
- 5222 AS pts (70% low-risk)
- Median FU 6.7 y
- 1609 (30.8%) pts reclassified

Germline: genomes inherited by the parents

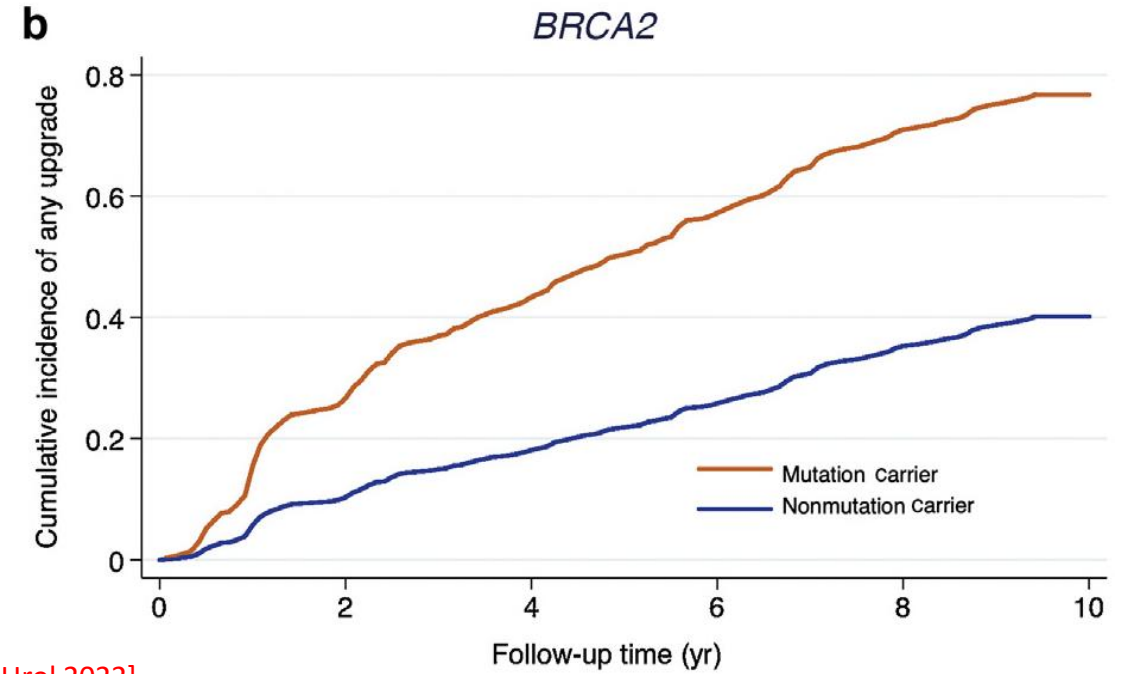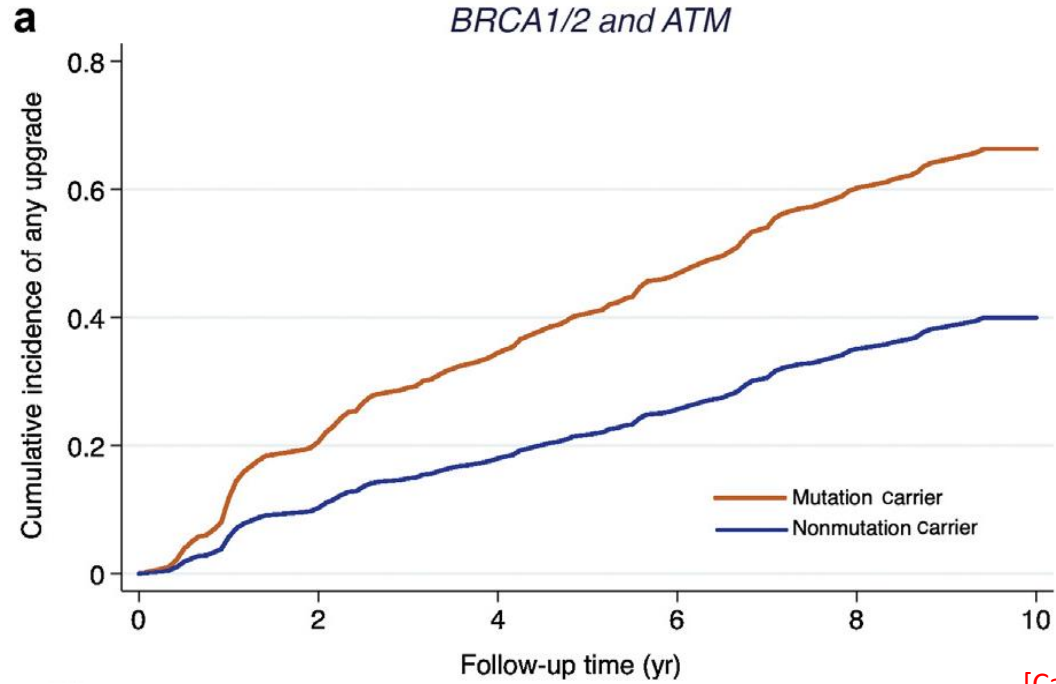Germline tests: blood, saliva

[Jiang Y et al, Human Genet Genom Adv 2022]

Genetic germline

Germline: genomes inherited by the parents

Germline tests: blood, saliva

[Carter HB et al, Eur Urol 2022]

Germ line (germ cells)
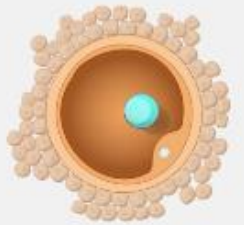Haploid
23 chromosomes (n) in human
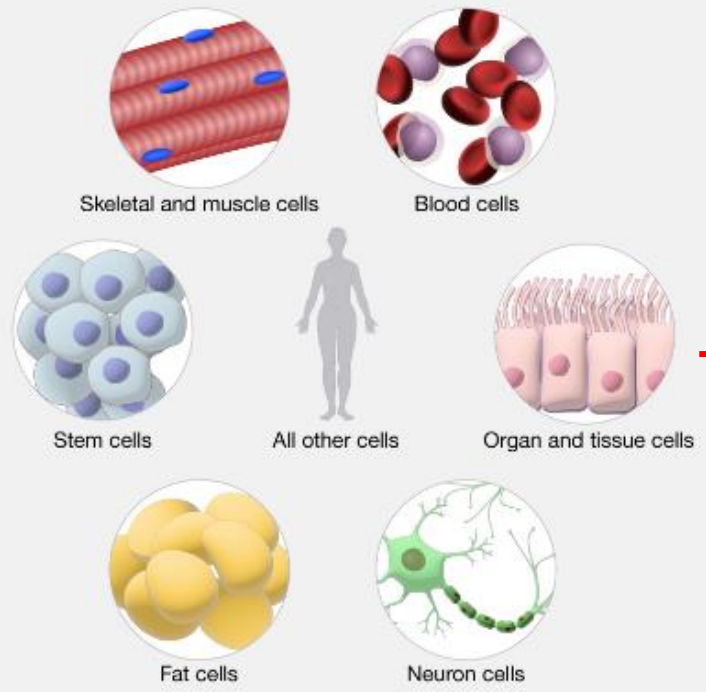
Somatic cells
Diploid
46 chromosomes (2n) in human

Sperm

Ovum (egg)

Fertilized egg

Skeletal and muscle cells
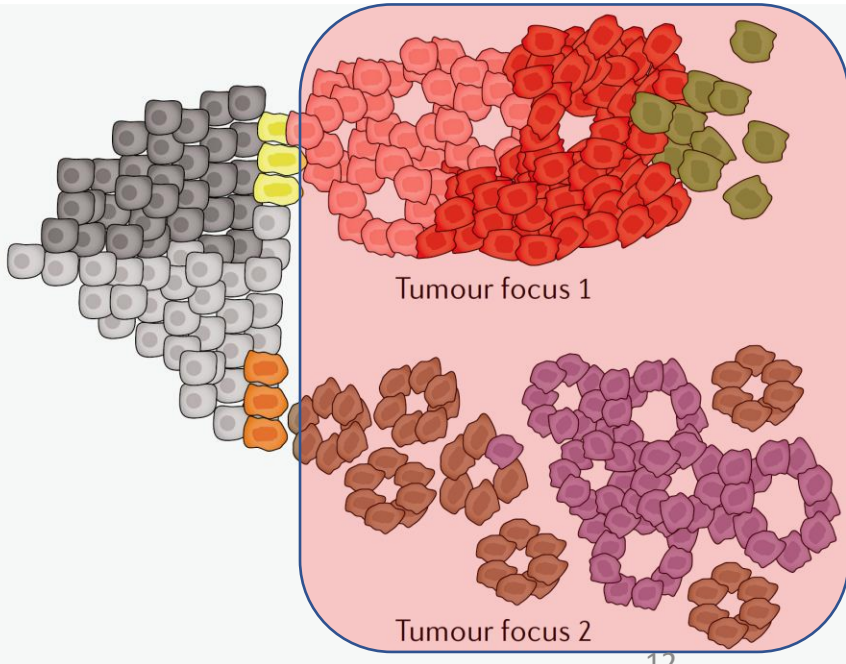
Blood cells

Stem cells

All other cells

Organ and tissue cells

Fat cells

Neuron cells

Somatic tests: tumor tissue, cancer cells in the blood

Somatic: tumor specific

Prostate

Germ line

Tumour focus 1

Tumour focus 2

[Haffner MC et al, Nat Rev Urol 2020]

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PCa genome

The
Cancer
Genome
Atlas

Somatic: tumor specific

Somatic tests: tumor tissue, cancer cells in the blood

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Genomic tissue-based biomarkers

Test(s)	Company	List Price,* USD	Sample Requirement	Clinical Utility/Intended Use	Comments
Decipher Biopsy and Decipher Postoperative	Decipher Biosciences (formally Genome Dx)	$5,150	FFPE tissue from prostate biopsy, or	Categorize patients into low/high risk to stratify patients to surveillance v treatment (and intensity of treatment)	Evaluates mRNA expression levels of 22 genes from FFPE tissue; generates score from 0 to 1.0
			Prostate tissue after RP	Postprostatectomy for patients with adverse pathologic features to guide whether surveillance, adjuvant, or salvage therapy may be warranted	
Oncotype Dx GPS	Genomic Health	$4,520	Tumor tissue from original biopsy in neutral buffered formalin; prostatectomy specimens not accepted	Biopsy-based likelihood of adverse pathologic features (Grade Group ≥ 3 or extracapsular extension); identify those who may benefit from surveillance v treatment	GPS ranges from 0 to 100 based on mRNA expression of 17 genes across four pathways
Prolaris Biopsy and Prolaris Postprostatectomy	Myriad Genetic Laboratories	$3,900	FFPE tissue from: prostate tumor biopsy, or prostatectomy specimens	Aggressiveness of cancer; provides a 10-year risk of metastasis after definitive therapy, and disease-specific mortality under conservative management	mRNA expression of cell-cycle progression genes are used to calculate the score; clinical factors are subsequently added for risk assessment
ProMark, Proteomic Prognostic test for prostate cancer	MetaMark	$3,900	Requires tissue collected with patented biopsy kit available from MetaMark	Uses automated image recognition technology to determine the likelihood of Grade Group ≥ 2 or stage ≥ T3b	Expression of 8 proteins; uses automated image recognition technology to generate a score from 1 to 100 indicating the aggressiveness of prostate cancer

Somatic: tumor specific

Somatic tests: tumor tissue, cancer cells in the blood

[Eggener SE et al, J Clin Oncol 2019]

Genomic tissue-based biomarkers

EAU – EANM – ESTRO – ESUR – ISUP – SIOG Guidelines on Prostate Cancer

© European Association of Urology 2022

Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline

Journal of Clinical Oncology®

ASCO
1474 Volume 38, Issue 13

Men who are considering active surveillance…with higher-risk…may benefit from a biomarker, although…test results are often equivocal in this scenario

eau European Association of Urology

Platinum Opinion

The State of the Science on Prostate Cancer Biomarkers: The San Francisco Consensus Statement

EUROPEAN UROLOGY 76 (2019) 268–272

- Several of the biomarkers are pre-diagnostic

- No validated risk thresholds

- No consensus on incremental improvement in accuracy compared with clinical models

- Literature on the "clinical utility" lacks meaningful clinical outcomes

- Studies among Caucasian men

- No prospective studies have validated the use of biomarkers in the decision-making process

Somatic: tumor specific

Somatic tests: tumor tissue, cancer cells in the blood

Germline: genomes inherited by the parents

Germline tests: blood, saliva

16

DNA variations:
- single-nucleotide variants (SNVs)
- small insertions and deletions (indels)
- copy-number variations (CNVs)
- structural variants (SVs)

benign variant
(Percorino)

benign variant
(Parmigiano)

pathogenic variant
(no pasta)

17

Family History and Probability of Prostate Cancer, Differentiated by Risk Category: A Nationwide Population-Based Study

Ola Bratt, Linda Drevin, Olof Akre, Hans Garmo, Pär Stattin

Table 1. Probabilities (95% confidence intervals) of prostate cancer at age 65 and 75 years in Swedish men according to their family history of prostate cancer*

| Family history	No.	Any PCa, %		Non-low-risk PCa, %		High-risk PCa, %	
		By age 65 y	By age 75 y	By age 65 y	By age 75 y	By age 65 y	By age 75 y
Population risk[†]	NA	4.8 (4.8 to 4.9)	12.9 (12.8 to 12.9)	2.8 (2.7 to 2.8)	8.9 (8.8 to 8.9)	1.4 (1.3 to 1.4)	5.2 (5.1 to 5.2)
1 brother, any PCa	38 921	14.9 (14.1 to 15.8)	30.3 (29.3 to 31.3)	7.3 (6.7 to 7.9)	18.8 (17.9 to 19.6)	3.0 (2.6 to 3.4)	8.9 (8.2 to 9.5)
1 brother low-risk PCa	13 660	13.8 (12.5 to 15.1)	28.8 (27.1 to 30.4)	6.3 (5.4 to 7.1)	16.9 (15.5 to 18.2)	2.4 (1.8 to 3.0)	8.0 (7.0 to 9.1)
1 brother non-low-risk PCa	24 404	15.7 (14.5 to 16.9)	31.4 (30.0 to 32.7)	7.9 (7.1 to 8.7)	19.9 (18.8 to 21.0)	3.4 (2.8 to 3.9)	9.4 (8.5 to 10.2)
1 brother high-risk PCa	12 769	16.1 (14.5 to 17.6)	31.7 (29.9 to 33.3)	8.0 (6.9 to 9.0)	19.7 (18.3 to 21.1)	3.4 (2.6 to 4.1)	9.3 (8.2 to 10.4)
Father (any age) + brother PCa	7757	29.8 (27.0 to 32.5)	47.8 (45.1 to 50.3)	13.7 (11.8 to 15.5)	28.2 (25.8 to 30.5)	5.6 (4.4 to 6.7)	13.8 (11.9 to 15.6)
Father (≥75 y) + brother PCa	3894	26.5 (22.1 to 30.6)	45.2 (41.2 to 48.9)	11.1 (8.4 to 13.6)	26.2 (22.9 to 29.4)	4.5 (2.9 to 6.1)	12.7 (10.1 to 15.2)
Father (<75 y) + brother PCa	3863	33.0 (29.3 to 36.5)	50.1 (46.5 to 53.6)	16.3 (13.6 to 18.9)	30.0 (26.5 to 33.2)	6.9 (5.1 to 8.6)	15.0 (12.2 to 17.8)
Father low-risk PCa + brother PCa	3007	28.9 (19.3 to 37.4)	47.3 (39.7 to 54.0)	11.0 (7.2 to 14.7)	26.2 (22.0 to 30.1)	3.9 (2.5 to 5.3)	12.2 (9.7 to 14.7)

Family History and Probability of Prostate Cancer, Differentiated by Risk Category: A Nationwide Population-Based Study

Ola Bratt, Linda Drevin, Olof Akre, Hans Garmo, Pär Stattin

Clinical Cancer Research
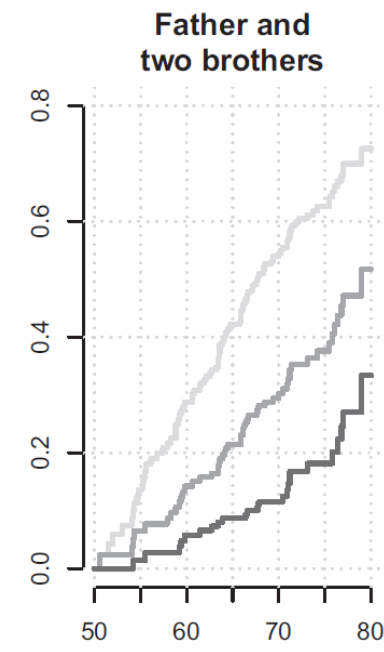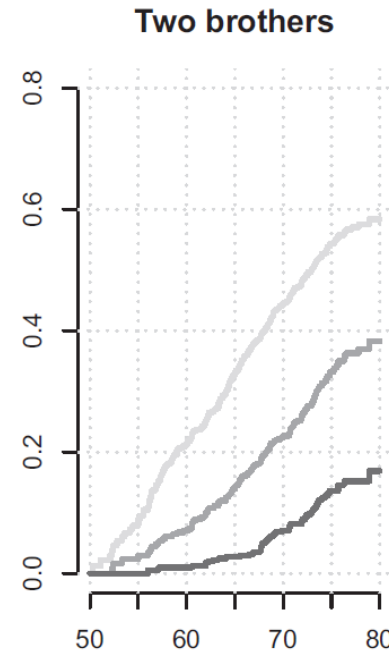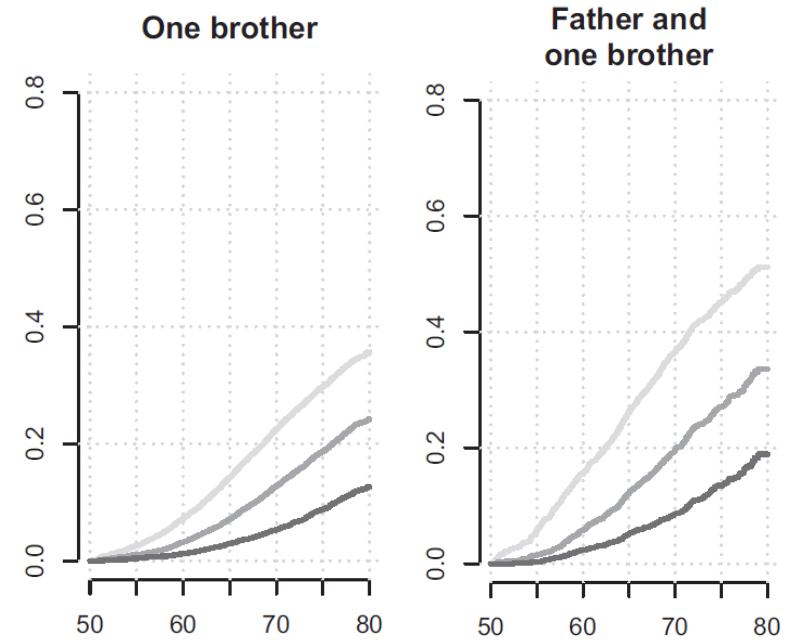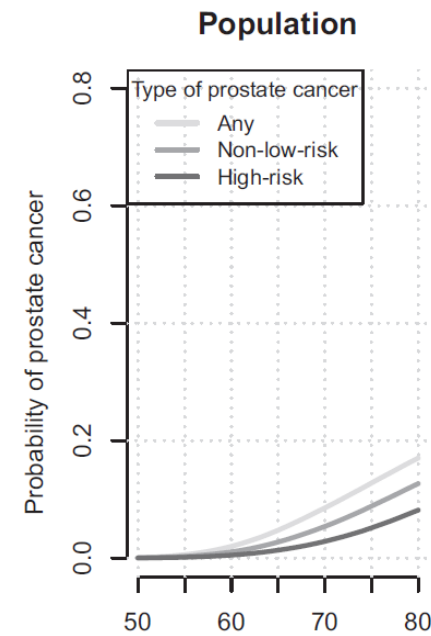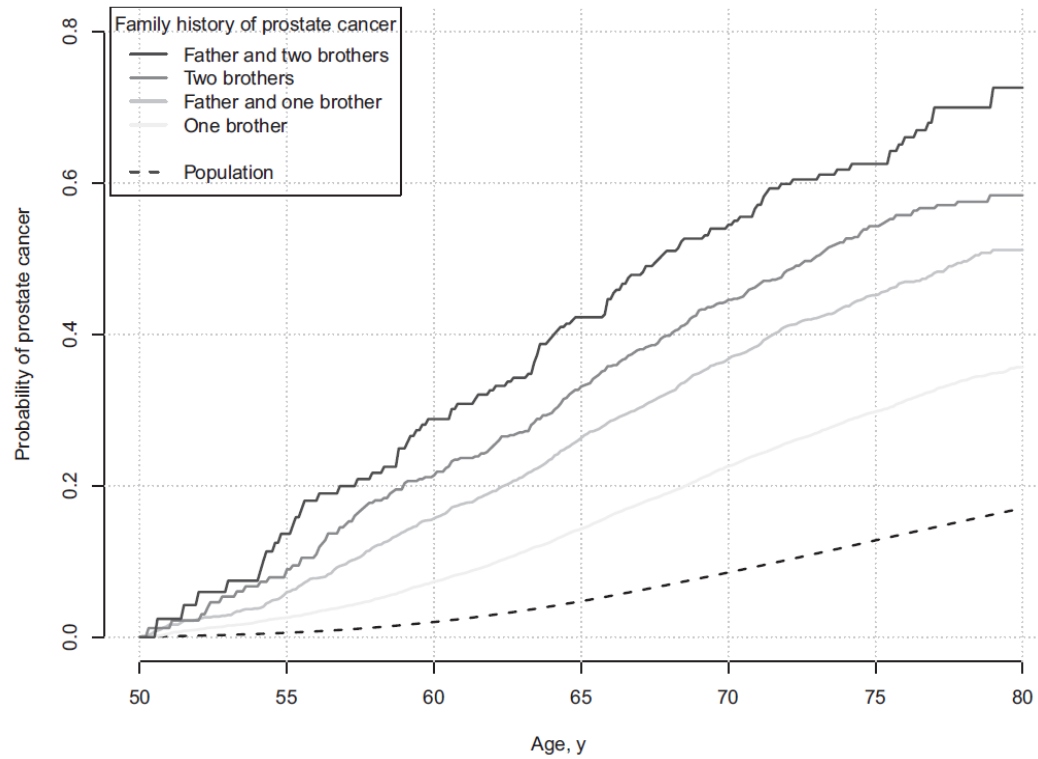
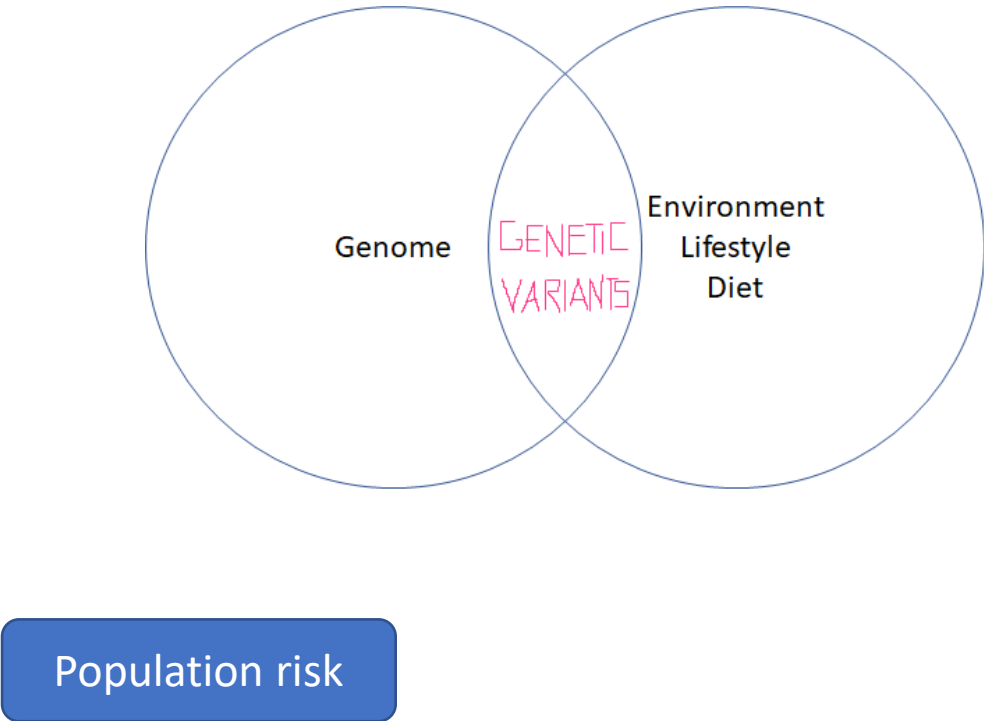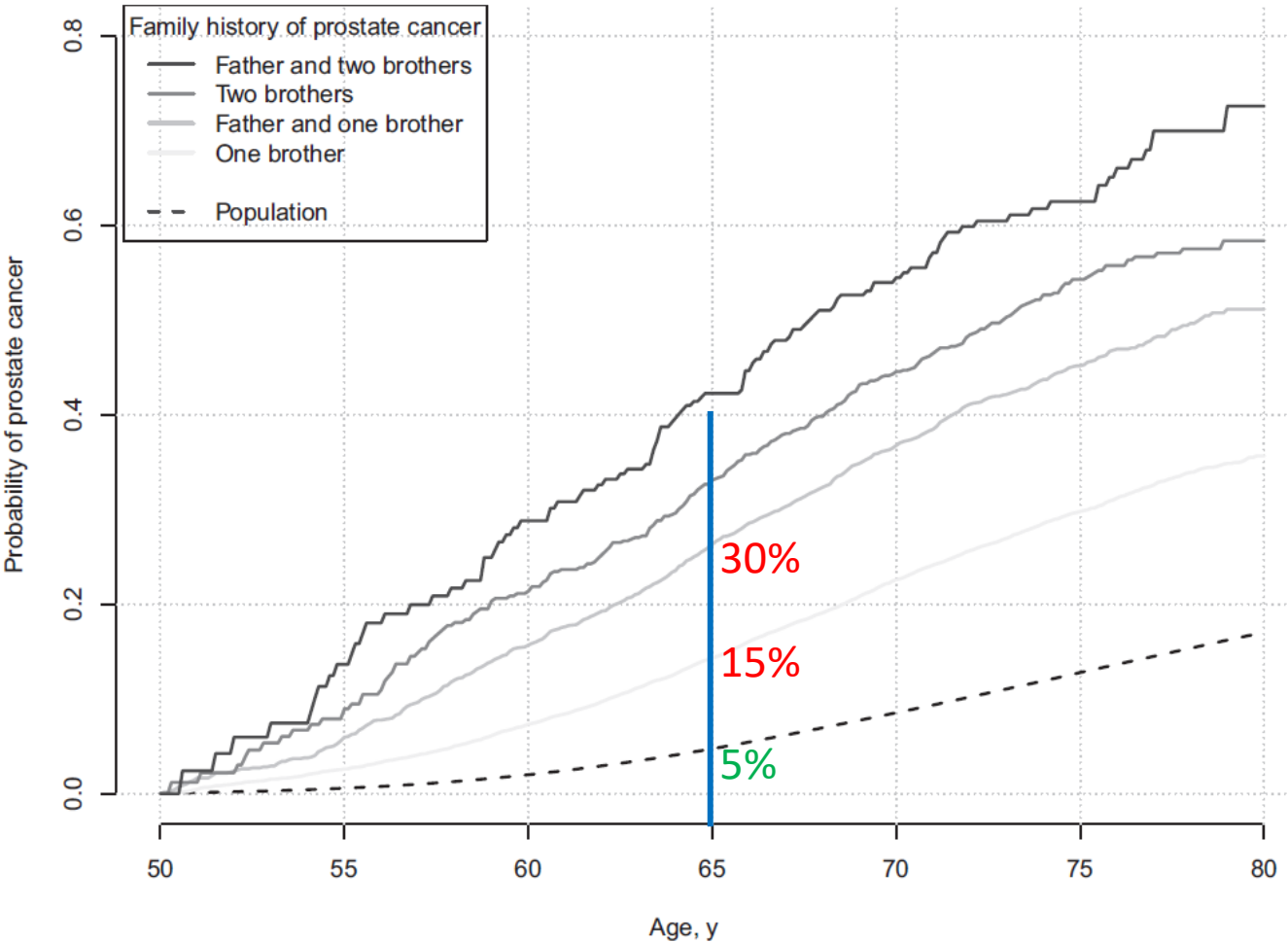# Family History of Breast or Prostate Cancer and Prostate Cancer Risk

Lauren Barber[1,2], Travis Gerke[1,3], Sarah C. Markt[1], Samuel F. Peisch[1], Kathryn M. Wilson[1,4], Thomas Ahearn[1,5], Edward Giovannucci[1,4,6], Giovanni Parmigiani[1,7,8], and Lorelei A. Mucci[1,4]

Table 2. Family history and risk of total prostate cancer among 37,002 male health professionals, 1996–2012

Variable	Prostate cancer cases Total (N = 4,208)	Age-adjusted HR[a] (95% CI)	Multivariable HR[b] (95% CI)	Multivariable P
Overall family history				
None	3,071 (73%)			
Breast cancer only	460 (10.9%)	1.26 (1.14–1.39)	1.21 (1.10–1.34)	<0.001
Prostate cancer only	582 (13.8%)	1.76 (1.60–1.92)	1.68 (1.53–1.83)	<0.001
Breast and prostate cancer	95 (2.3%)	1.68 (1.37–2.07)	1.61 (1.30–1.98)	<0.001
Age of mother or sister at breast cancer diagnosis				
No breast cancer family history	3,653 (86.8%)			
<60 years	282 (6.7%)	1.32 (1.17–1.49)	1.25 (1.11–1.42)	<0.001
≥60 years	215 (5.1%)	1.09 (0.95–1.26)	1.03 (0.89–1.18)	0.70
Age unknown	58 (1.4%)	1.39 (1.07–1.81)	1.32 (1.02–1.72)	0.04
Age of father or brother at prostate cancer diagnosis				
No prostate cancer family history	3,531 (83.9%)			
<60 years	73 (1.7%)	1.89 (1.49–2.39)	1.78 (1.40–2.25)	<0.001
≥60 years	513 (12.2%)	1.66 (1.51–1.82)	1.58 (1.44–1.74)	<0.001
Age unknown	91 (2.2%)	1.79 (1.45–2.21)	1.72 (1.39–2.12)	<0.001

Family History and Probability of Prostate Cancer, Differentiated by Risk Category: A Nationwide Population-Based Study
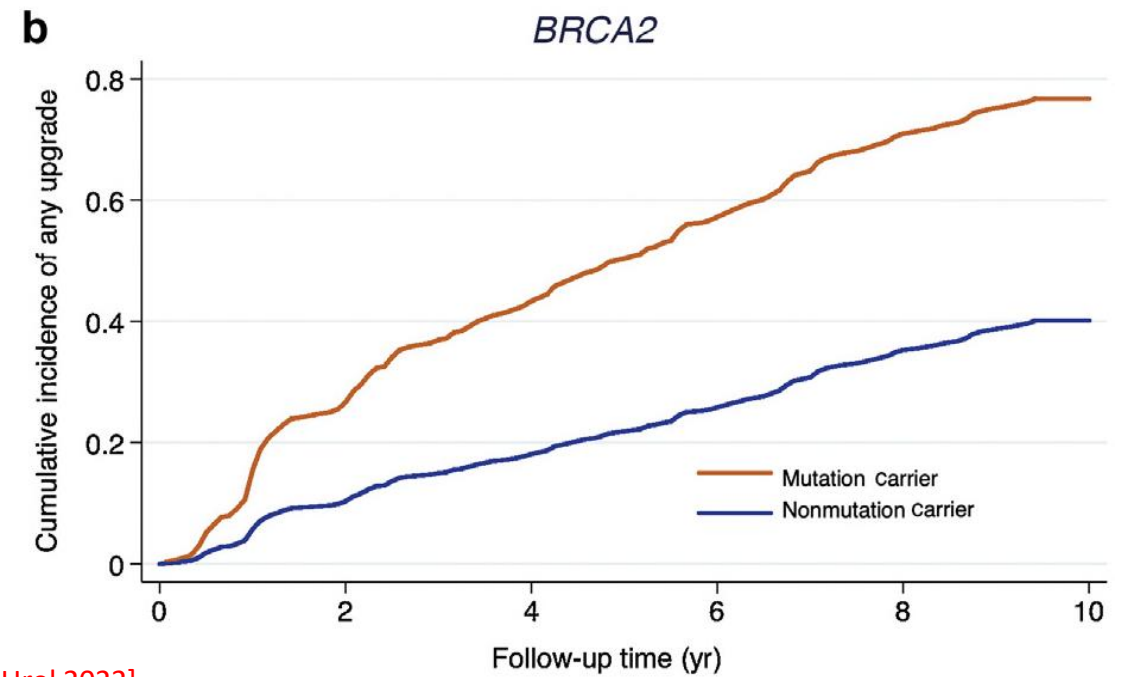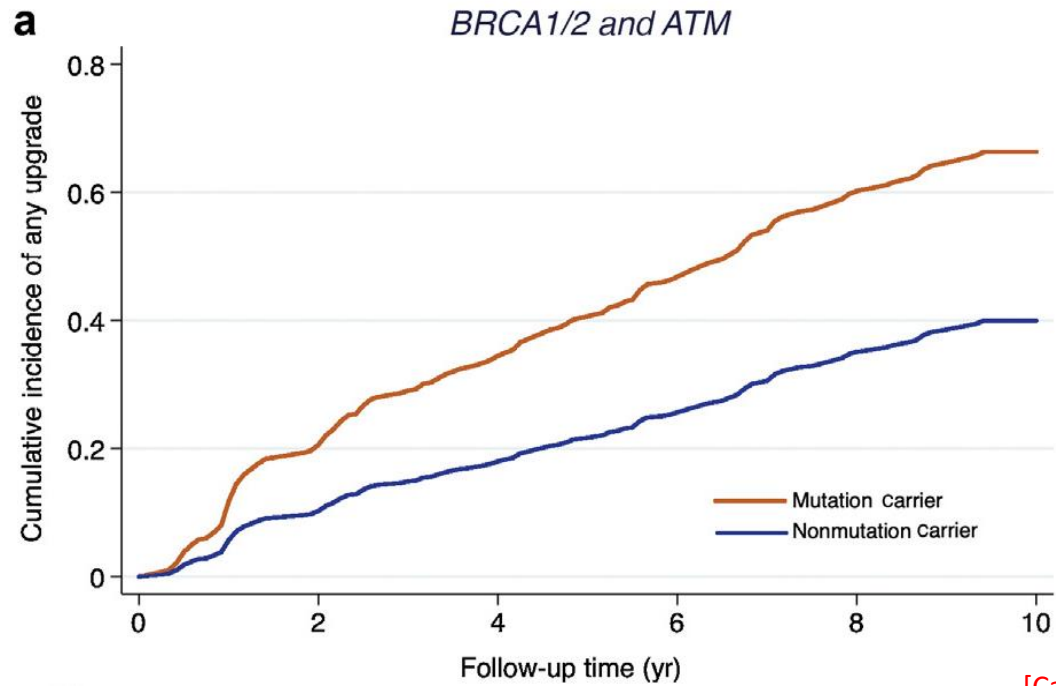
Ola Bratt, Linda Drevin, Olof Akre, Hans Garmo, Pär Stattin

Family history of prostate/breast/ovary/pancreas cancer

BRCA2 mutated-patients

- 1211 AS pts (96% GG1, 4% GG2)
- Median FU 3 y
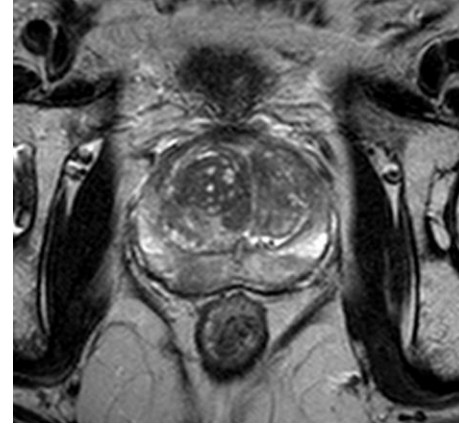- 289 (23.8%) pts reclassified

[Carter HB et al, Eur Urol 2022]

Tumor-based

Serum biomarkers

PHI=([-2]proPSA/fPSA) x √tPSA

4K (tPSA, fPSA, iPSA, hK2)
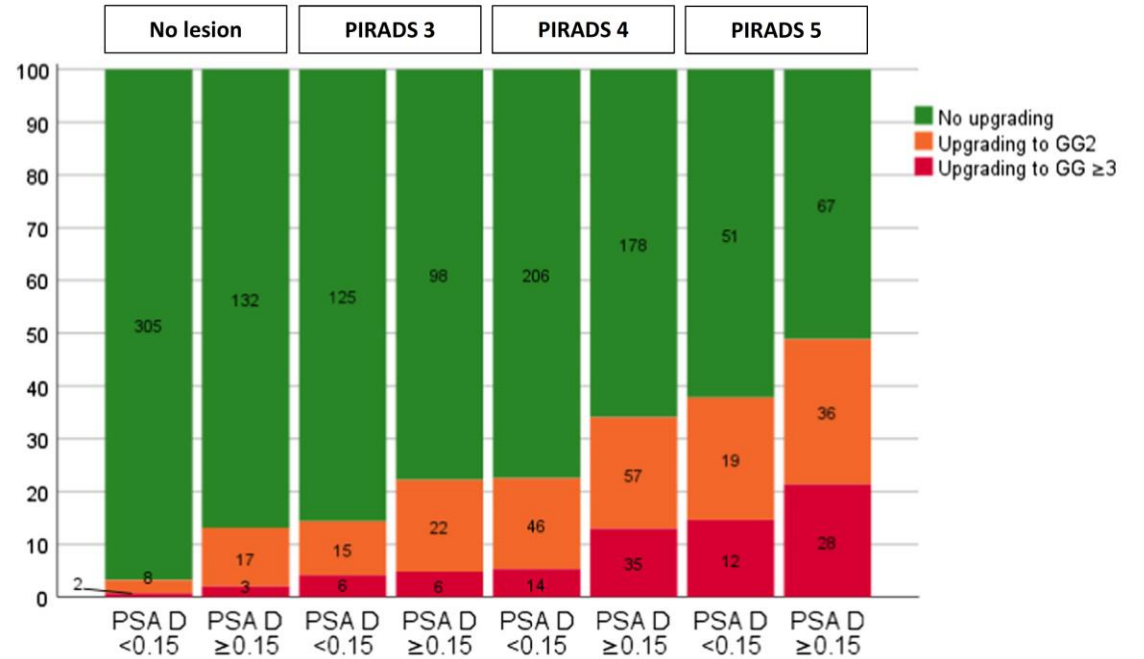

Urine biomarkers

PCA3

SelectMDx

ExoDx

Tissue biomarkers

Decipher

Oncotype

Prolaris

Promark

[Luiting HB et al, Eur Urol 2022]

- Genetics vs genomics

Genomics refers to the whole genome, genetics to some specific gene. We have BRCA genetic (germline and somatic) test which is available in clinical practice. Tumor tissue-based (Decipher, Prolaris, Oncotype, etc.) need further investigation

- Somatic vs Germline

Somatic refers to genomic or genetic mutations of tumor cells/Germline refers to genomic or genetic mutations of host cells

- Hereditary male-female cancers/an idea of what may happen in family/tree

There are epidemiologic data on familial and genetic predisposition, which means that a family history increases 3 to 8 fold the risk of PCa compared with the general population

- When earlier controls

Family history, BRCA2 mutated

- Benefit for patients already diagnosed

BRCA2 mutated – use of PARP inhibitors. Genomic tissue-based test (Decipher, Prolaris, Oncotype, etc.)?

- Spectrum of tests

PSA derivatives, genomic tissue-based biomarkers

- When insisting to get a test, pay, or social

No answer at the moment

- Relation to Active Surveillance

BRCA2 mutated more intensive AS protocol, PSA derivatives may be used to intensify or de-intensify AS protocols