4rd TETRIS EDUCATIONAL WEBINAR "INTRODUCTION TO GENOMIC BIOMARKERS IN RADIATION ONCOLOGY"

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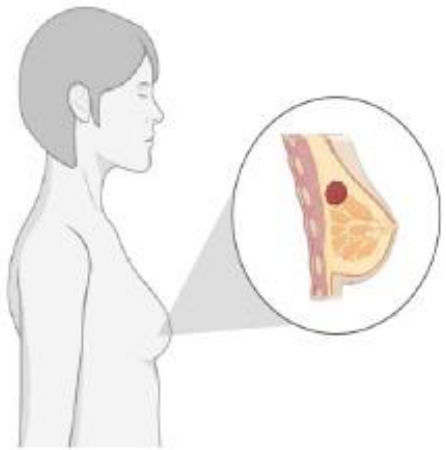
JUNE 10, 2026, TETRIS Young Researchers Week, Milano

CONTENT

- ✓Genetic susceptibility to side effects after radiotherapy
- ✓Genomic variants: single-nucleotide variants (SNVs) and single-nucleotide polymorphisms (SNPs)
- ✓Introduction to genome wide associations studies (GWAS)
- ✓Estimations of polygenic risk scores (PRS)
- ✓Objectives in TETRIS WP4

Radiotherapy (RT) plays a crucial role in breast cancer treatment

50%
of patients diagnosed with cancer will receive some form of radiation therapy.



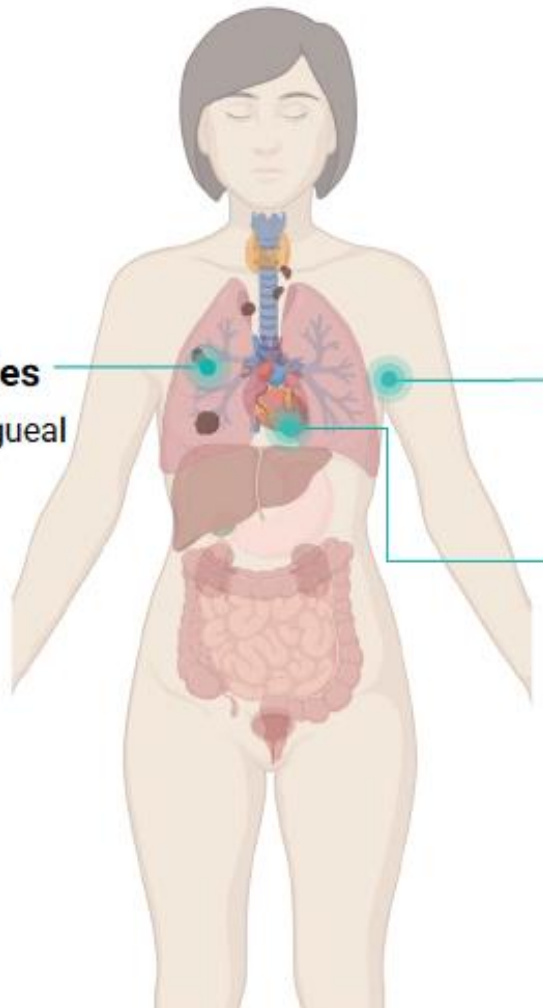
Radiotherapy has been shown to decrease local recurrence and to have a beneficial effect on survival.

Delaney G et al., Cancer (2005)
McGale et al., The Lancet (2014)

Adapted from a slide kindly shared by Ester Aguado.

Radiation-induced side effects

Breast Cancer



Secondary malignancies

Breast, lung and oesophageal cancers

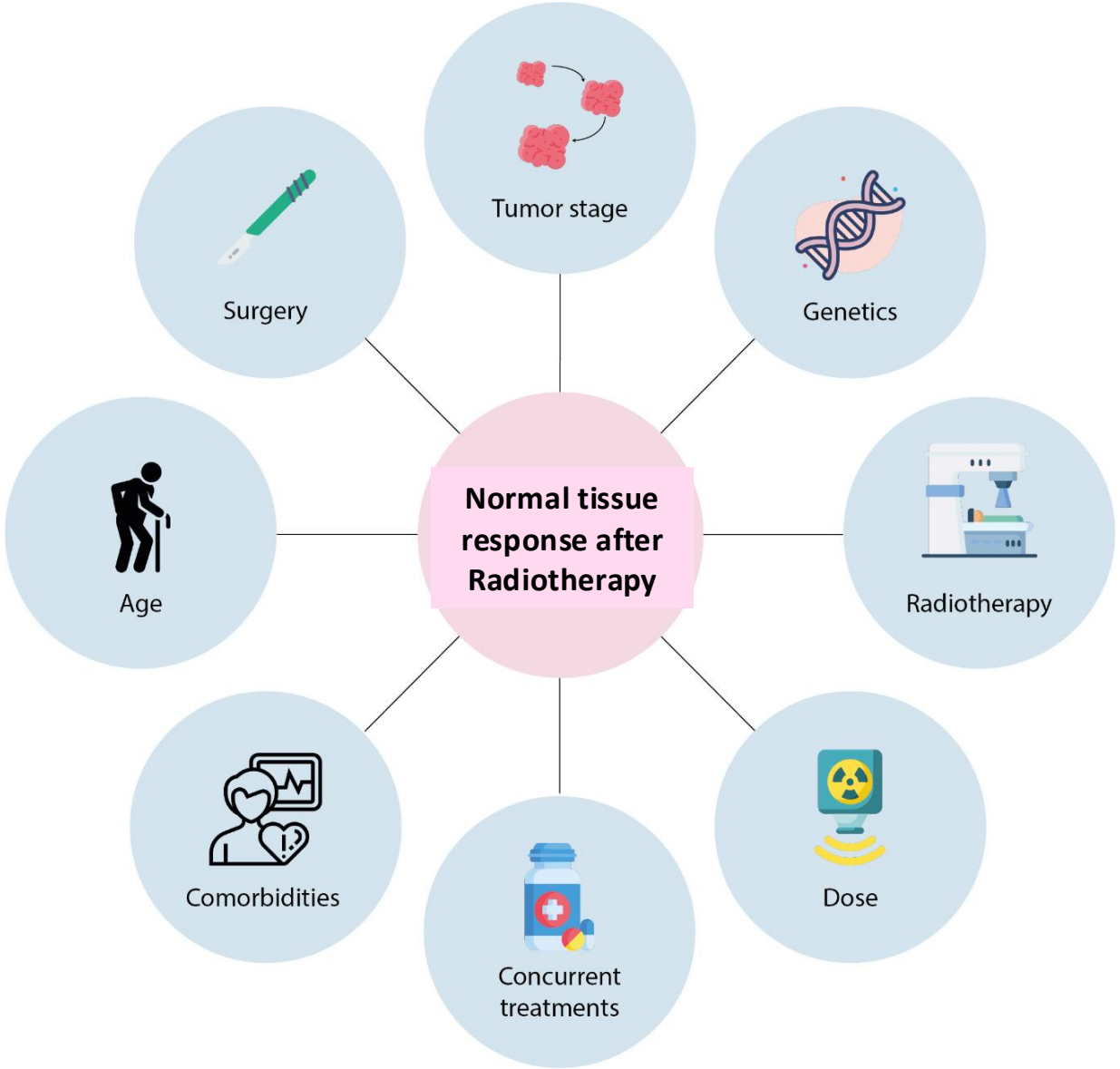
Skin side effects

Fibrosis, telangiectasia, skin atrophy and hyperpigmentation

Cardiac complications

Adapted from a slide kindly shared by Ester Aguado.

Germline genomic predictors of radiotherapy-induced side effects

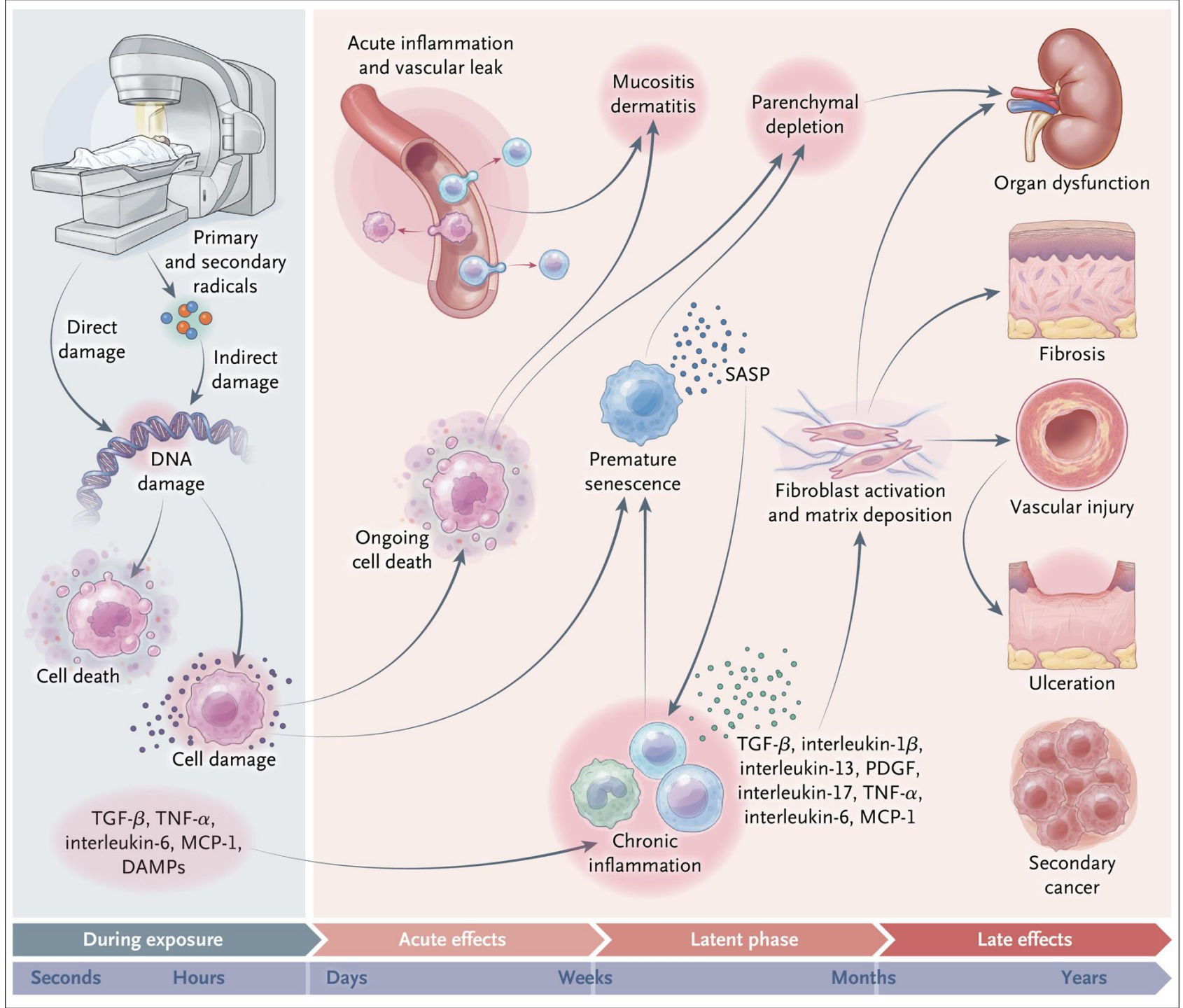


HYPOTHESIS

- Genetic variation modulates the appearance of complications in normal tissue after radiotherapy

Adapted from a slide kindly shared by Ester Aguado.

Radiobiologic Processes in Normal Tissue.



Citrin and Timmerman. Effects of Radiotherapy in Normal Tissue. N Engl J Med. 2026 Mar 5;394(10):996-1009. doi: 10.1056/NEJMra2506017. PMID: 41780002.

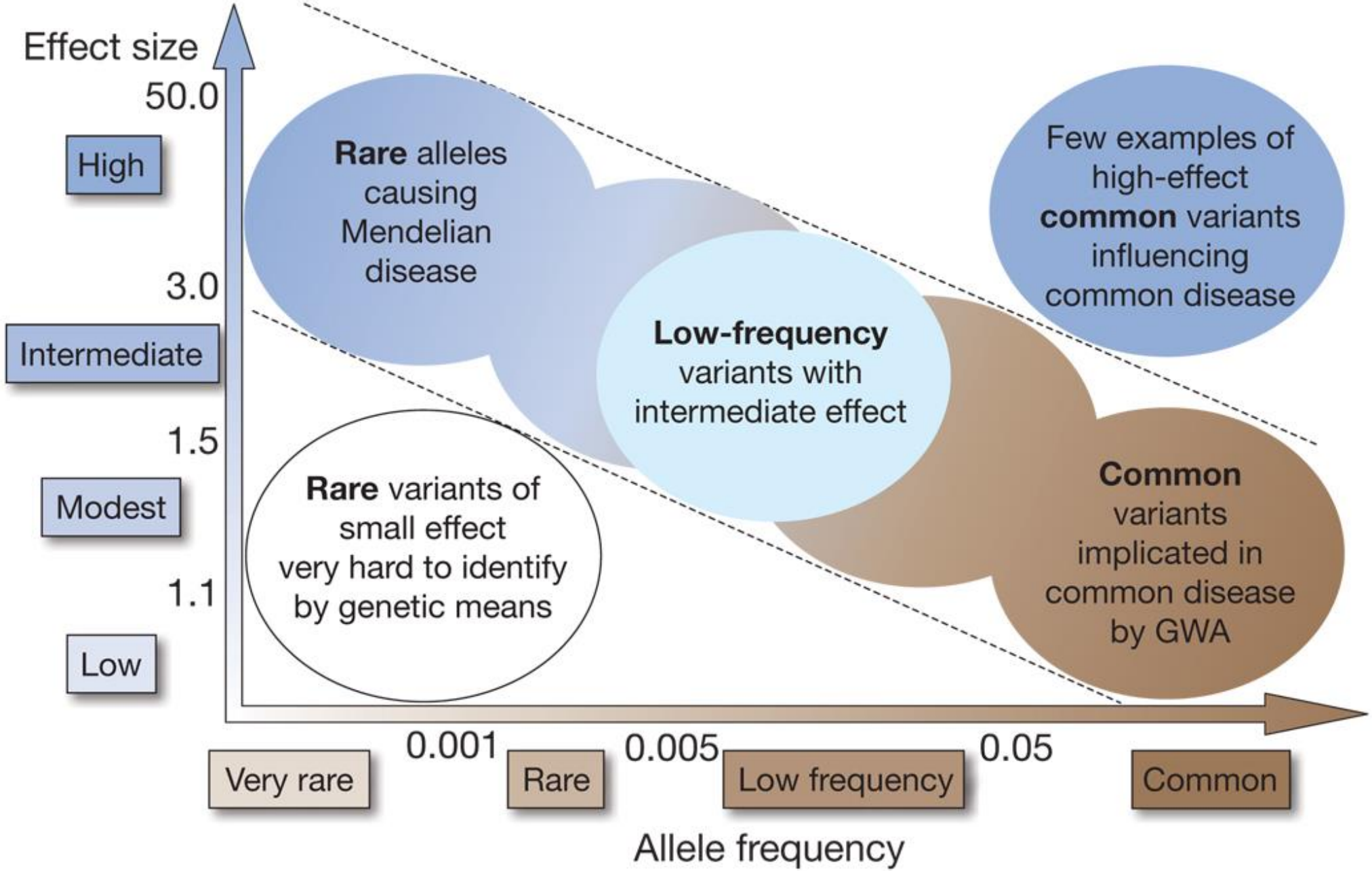
A few known rare radiation sensitivity-related clinical syndromes due to pathogenic variants in genes with essential roles in radiation response

Table 1 Known rare syndromes associated with sensitivity to radiation

Syndrome	Mutated gene(s)	Associated with
Ataxia telangiectasia	*ATM*	Clinical and cellular radiosensitivity, cancer predisposition[28]
Ataxia telangiectasia-like disorder	*MRE11*	Cellular radiosensitivity[30]
Cornelia de Lange syndrome	*SMCL1A*	Variable radiosensitivity, cellular radiosensitivity in G2, chromosome instability[31]
Cowden syndrome	*PTEN*	One report of severe toxicity in a patient with breast cancer with a heterozygous nonsense mutation at K322[39]
Fanconi anemia	Numerous genes	Cellular and clinical sensitivity in some[33,36]
Gorlin syndrome (nevoid basal cell carcinoma syndrome)	*PTCH1*	Cellular radiosensitivity in patients with severe PATCHED1 protein deficiency, cancer predisposition, risk of second malignancy[37,40]
Li-Fraumeni syndrome	*TP53*	Risk of second malignancy[37]
Ligase IV syndrome	*LIG4*	Clinical and cellular radiosensitivity[32,33]
Neurofibromatosis type 1	*NF1*	Risk of second malignancy[37]
Nijmegen breakage syndrome	*NBN*	Clinical and cellular radiosensitivity, cancer predisposition[33]
Nijmegen breakage syndrome–like syndrome	*RAD50*	Cellular radiosensitivity[34]
Radiosensitive SCID	*DCLRE1C (Artemis), PRKDC*	SCID associated with NHEJ defects, cellular radiosensitivity[35]
Retinoblastoma	*RB1*	Moderately radiosensitive with increased chromosomal G2 radiosensitivity, risk of second malignancy[37,38]
RIDDLE syndrome	*RNF168*	Cellular radiosensitivity[29]

Abbreviations: NHEJ = non-homologous end joining; SCID = severe combined immunodeficiency.

Bergom et al., 2019 Int J Radiation Oncol Biol Phys, https://doi.org/10.1016/j.ijrobp.2019.07.026

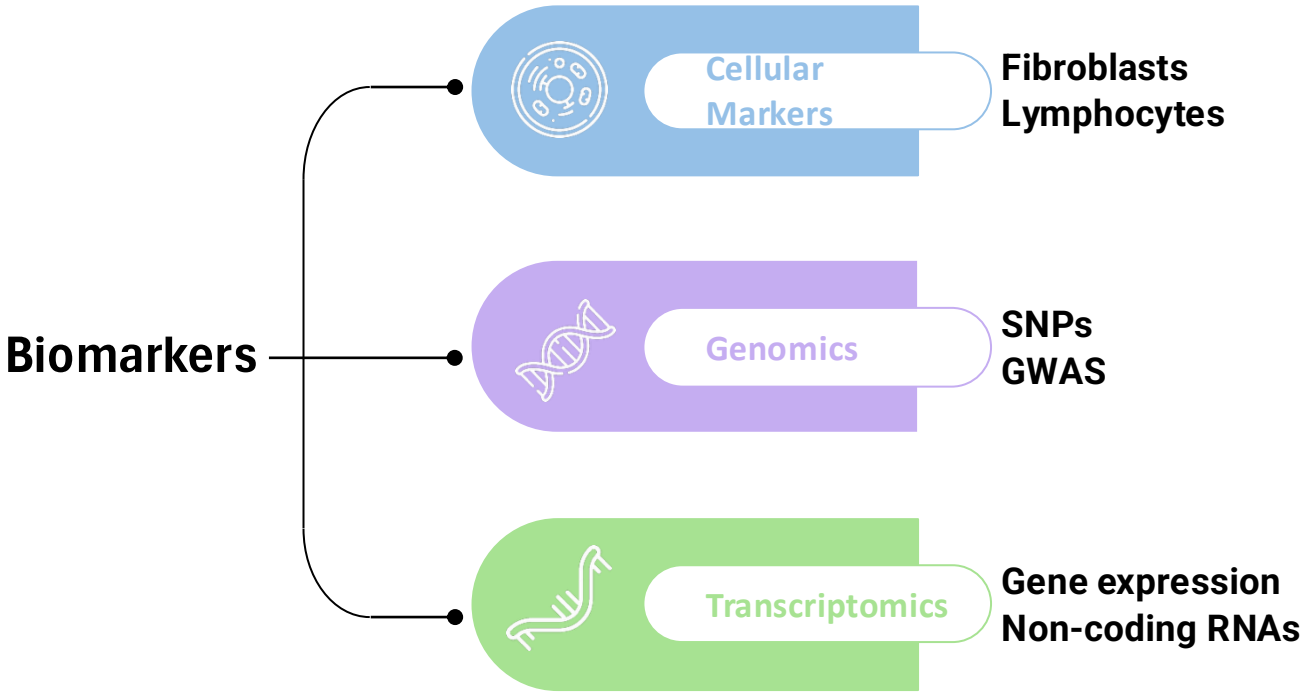


Manolio et al., Finding the missing heritability of complex diseases. Nature. 2009 Oct 8;461(7265):747-53. doi: 10.1038/nature08494. PMID: 19812666

Precision Radiotherapy Through Germline Genetic Predictors of Radiation Response

- **Identifying the genetic germline variants associated with response to radiation to personalize the use of radiotherapy would not only reduce side effects and improve quality of life in long-term cancer survivors but also enable individualized dose prescription**

The search for predictive biomarkers of radiotherapy side effects

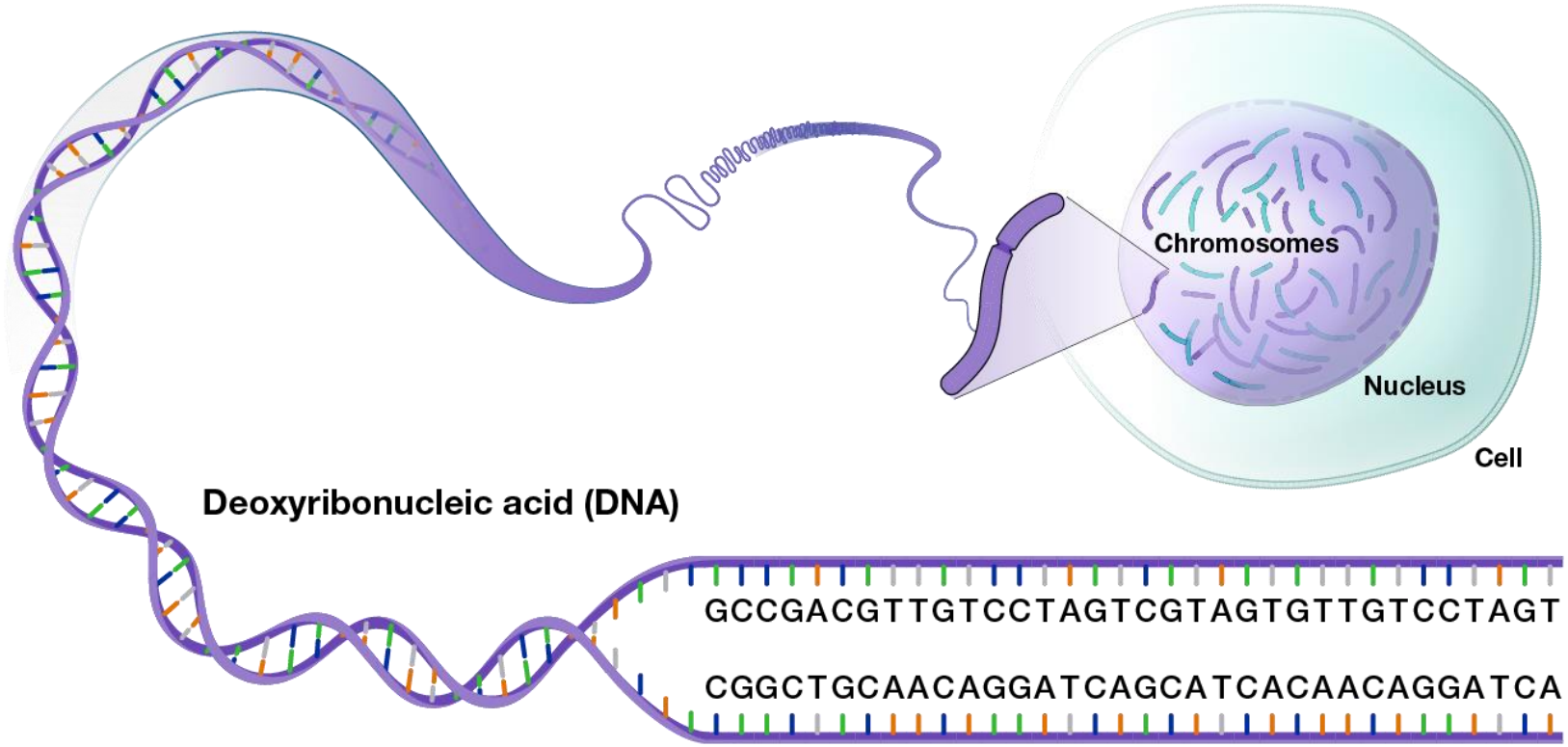


Still, there is not yet an optimisation of RT based on genomic, transcriptomic or cell markers in standard practice due to a lack of clinical validation of candidate biomarkers.

Adapted from a slide kindly shared by Ester Aguado.

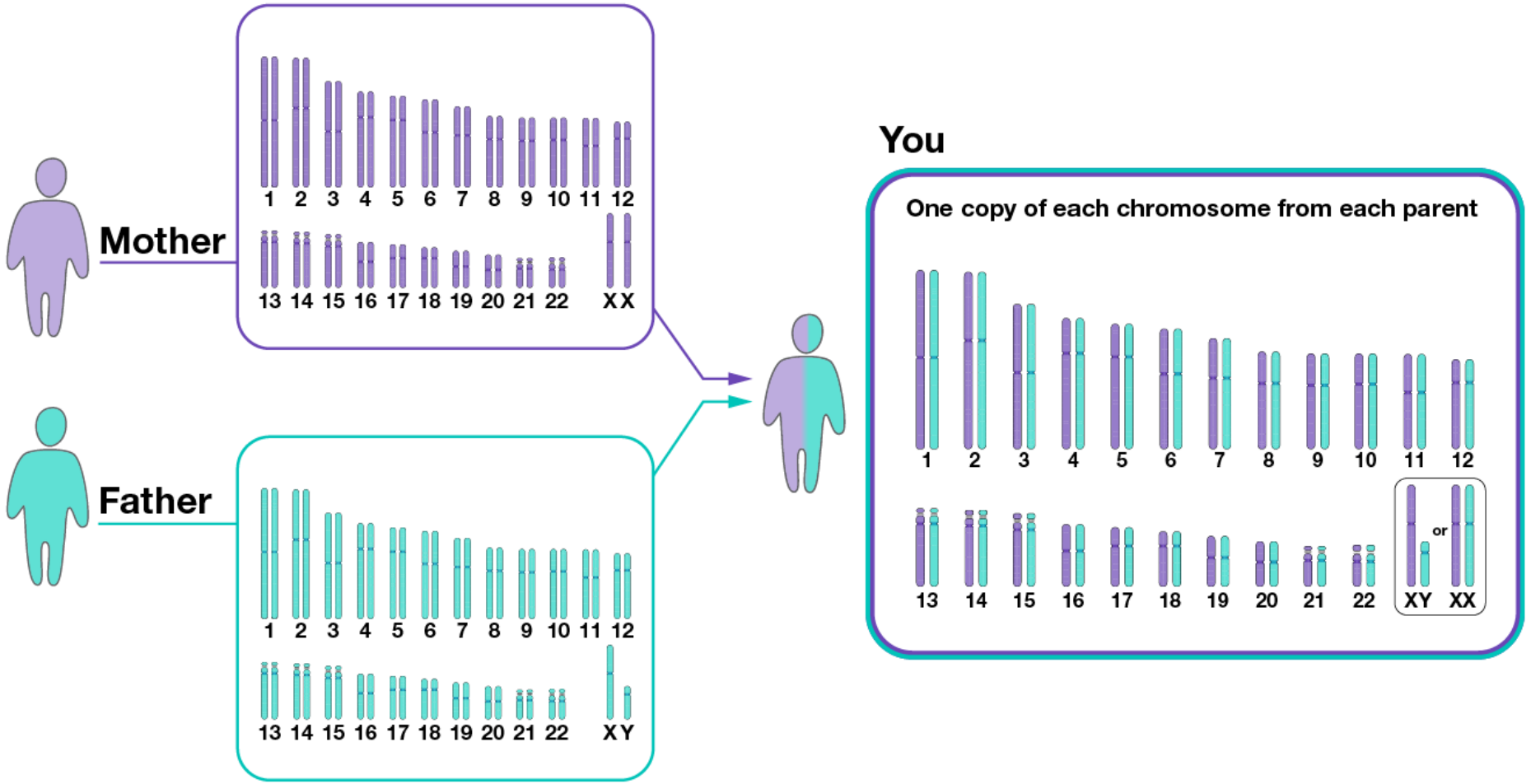
Genomic variants: single-nucleotide variants (SNVs) and single-nucleotide polymorphisms (SNPs)

A genome is the complete set of DNA instructions found in every cell needed for an individual to develop and function



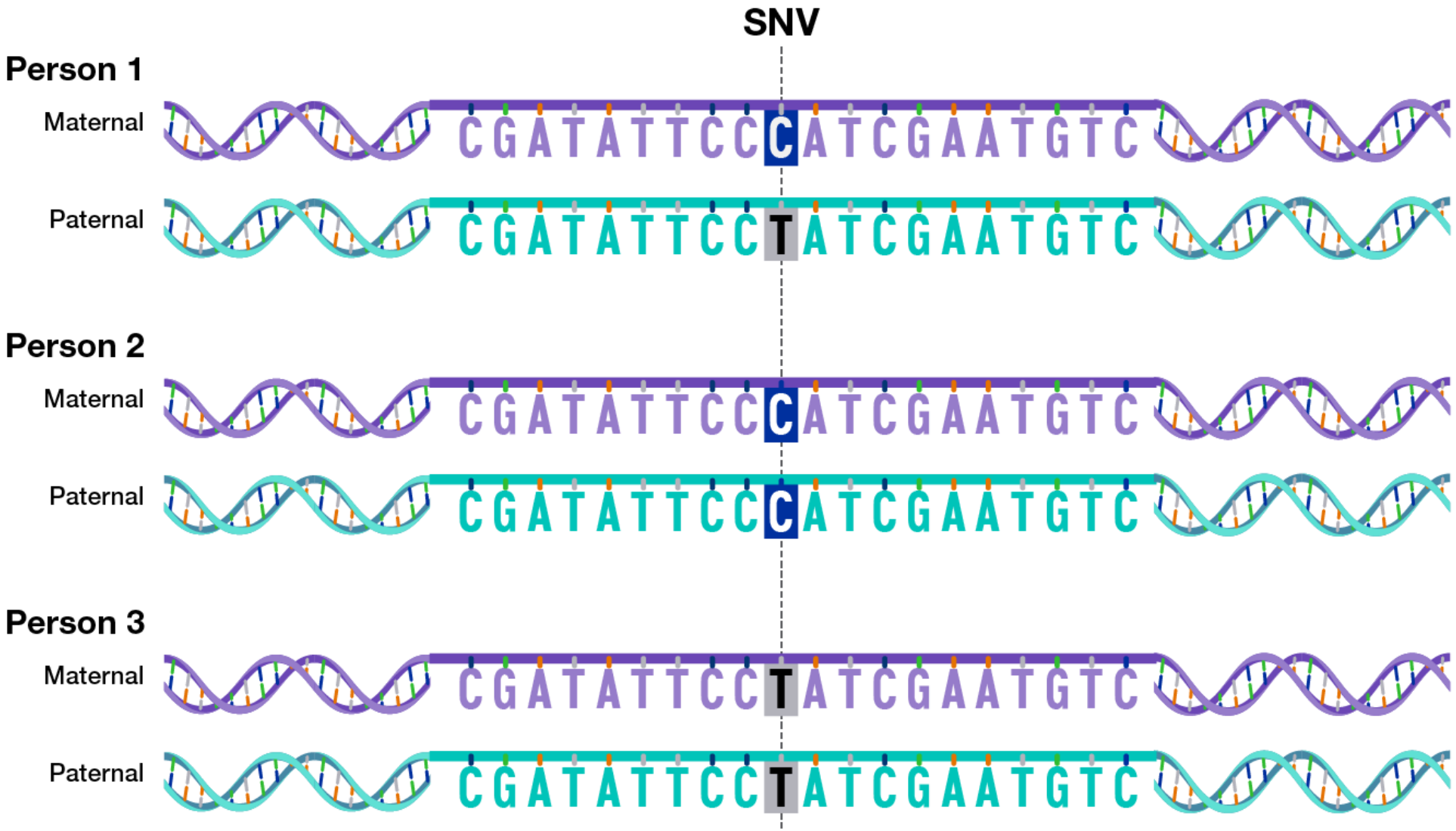
https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genomic-variation

A person's genome consists of 23 pairs of chromosomes. One copy of each chromosome is inherited from each parent.



https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genomic-variation

Single-nucleotide variants (SNVs) are differences of one nucleotide at a specific location in the genome



https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genomic-variation

To be considered a single-nucleotide polymorphism (SNP), a SNV must be present in at least 1% of the human population

Welcome to the Reference SNP (rs) Report
All alleles are reported in the Forward orientation. Click on the Variant Details tab for details on Genomic Placement, Gene, and Amino Acid changes. HGVS names are in the HGVS tab.

Reference SNP (rs) Report

The T variant of rs77311050 associated with Induration grade ≥ 2 in REQUITE breast cancer patients is present in about 5% of the population

Download

rs77311050

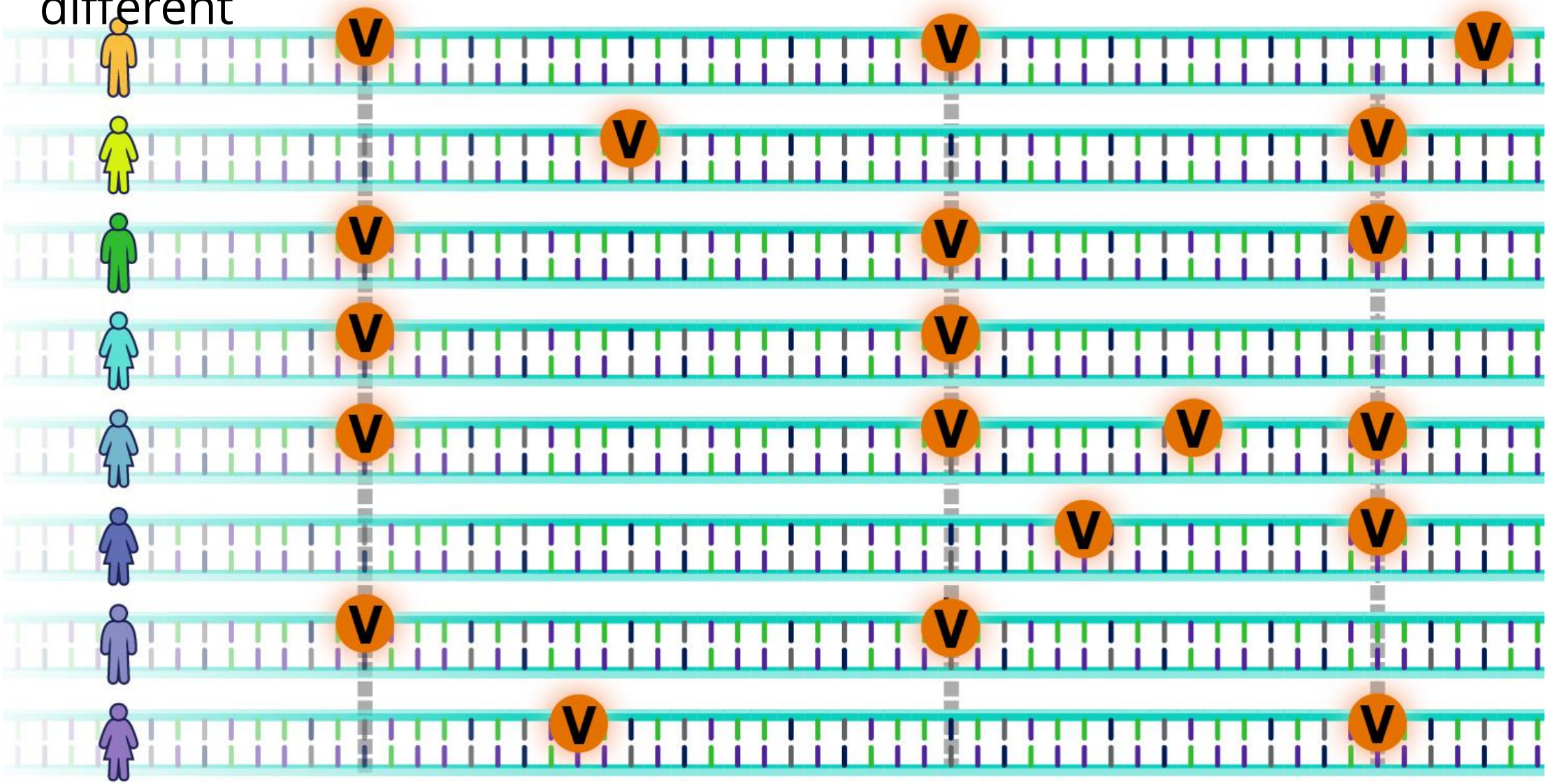
Current Build 157
Released September 3, 2024

Organism	*Homo sapiens*	**Clinical Significance**	Not Reported in ClinVar
Position	chr1:116203992 (GRCh38.p14)	**Gene : Consequence**	None
Alleles	C>A / C>T	**Publications**	0 citations
Variation Type	SNV Single Nucleotide Variation	**Genomic View**	See rs on genome
Frequency	T=0.048128 (12739/264690, TOPMED) T=0.048446 (7227/149176, GnomAD_genomes) T=0.02798 (2202/78702, PAGE_STUDY) (+ 14 more)		

https://www.ncbi.nlm.nih.gov/snp/rs77311050

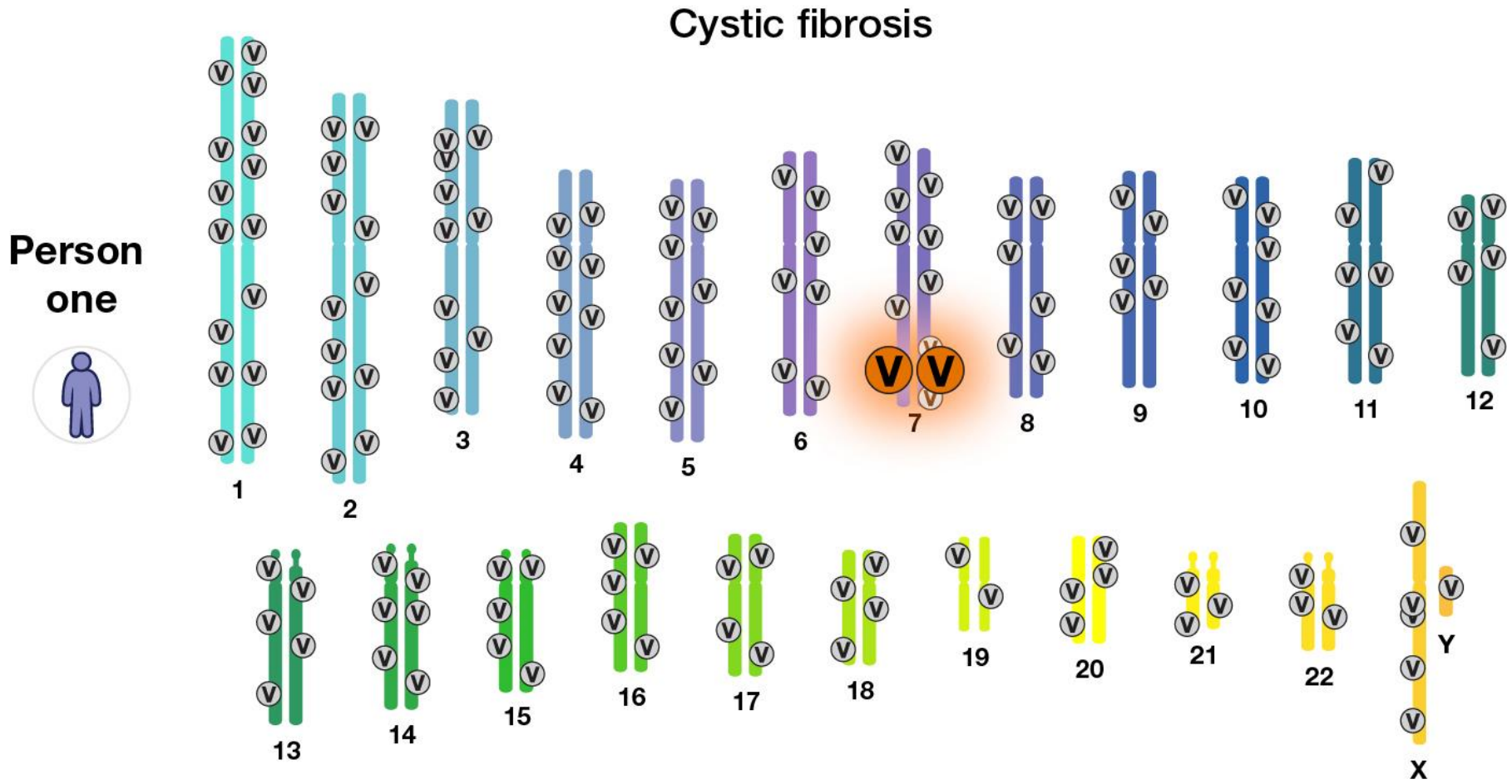
rs77311050 association in Jandu et al., Genome-wide association study of treatment-related toxicity two years following radiotherapy for breast cancer. Radiother Oncol. 2023. PMID: 37437607.

Any two peoples' genomes are, on average, ~99.6% identical and ~0.4% different



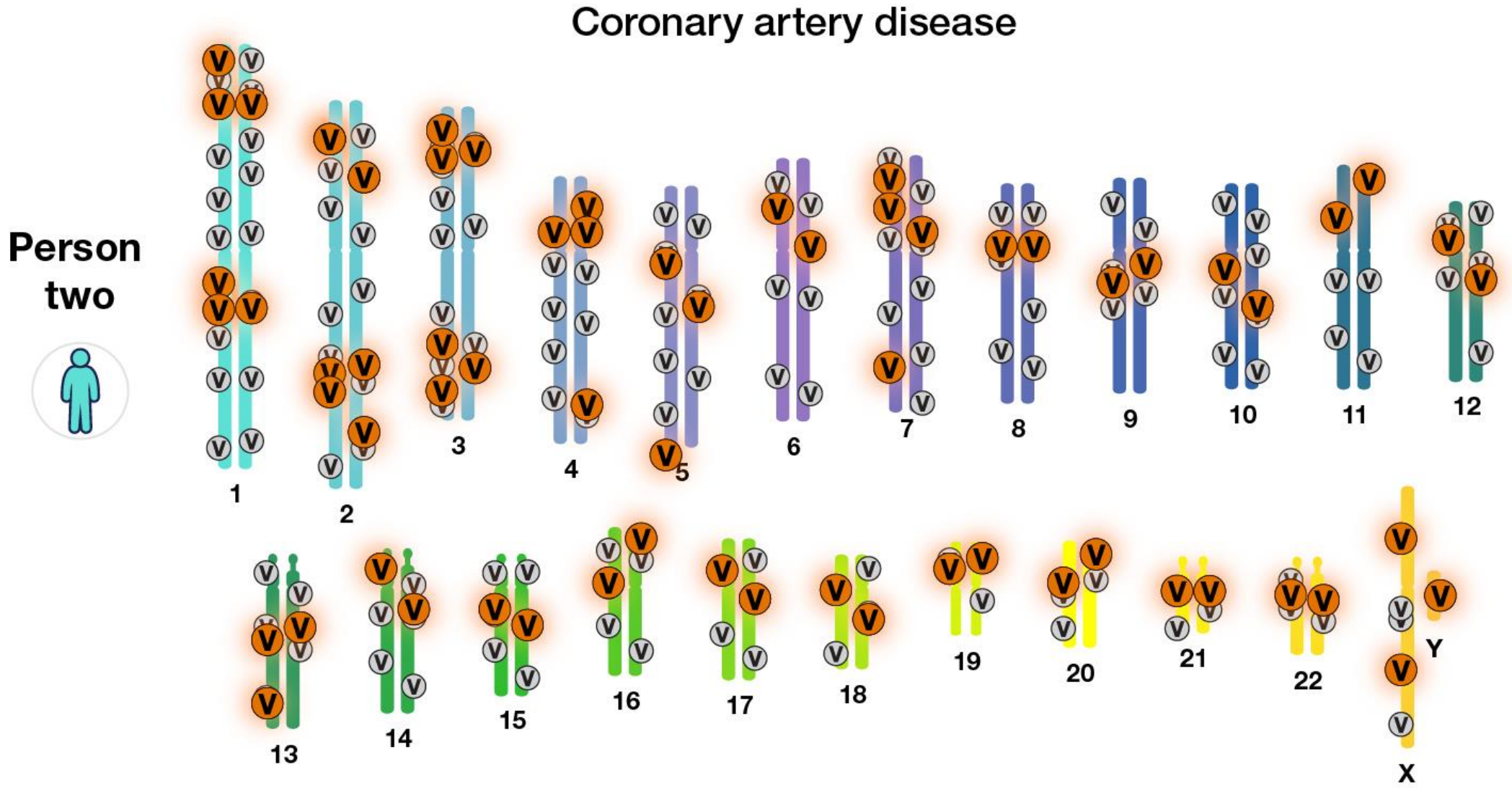
https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores

Single-gene diseases



https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores

Complex diseases

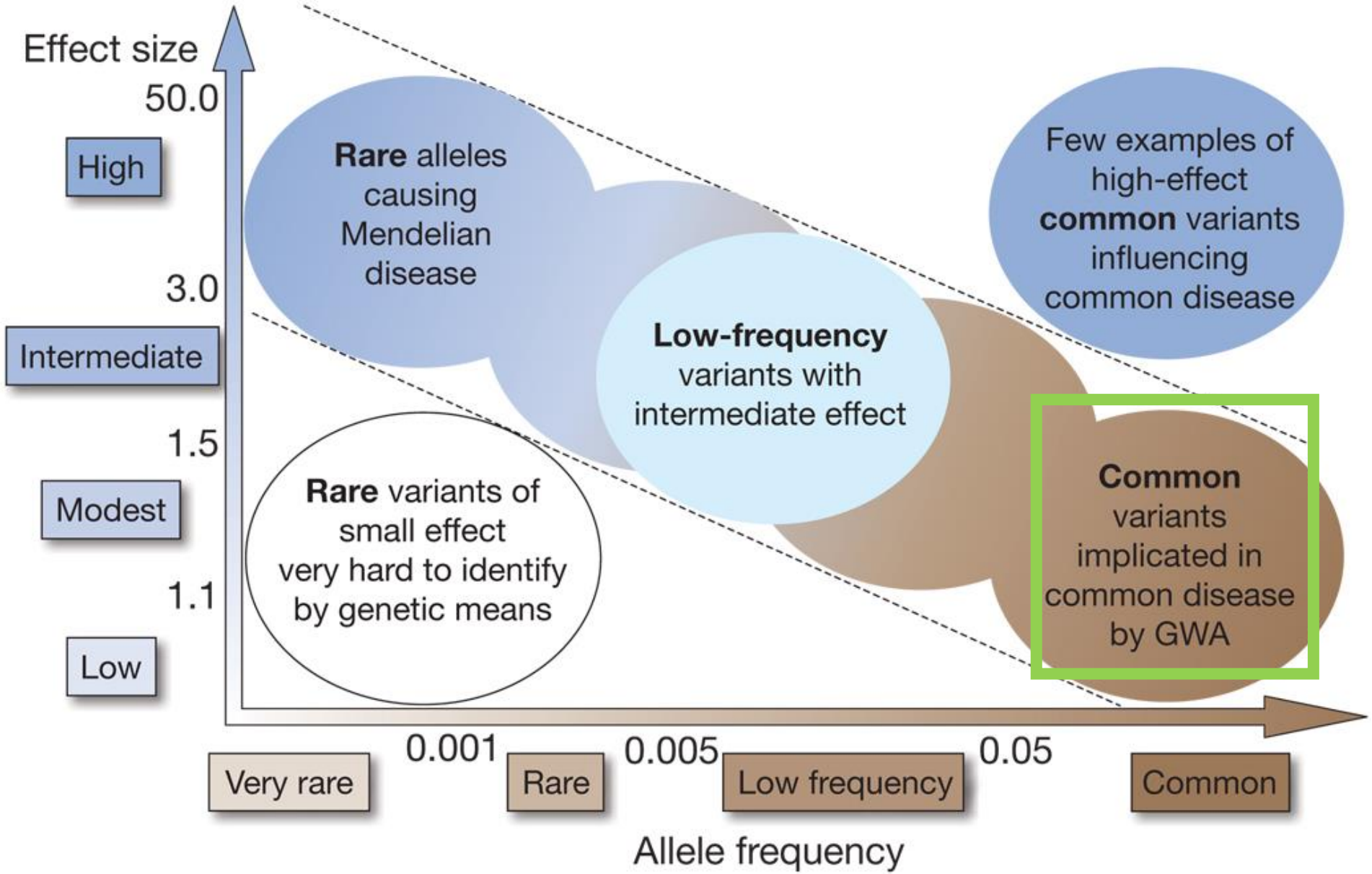


https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores

Genome wide association studies (GWAS)

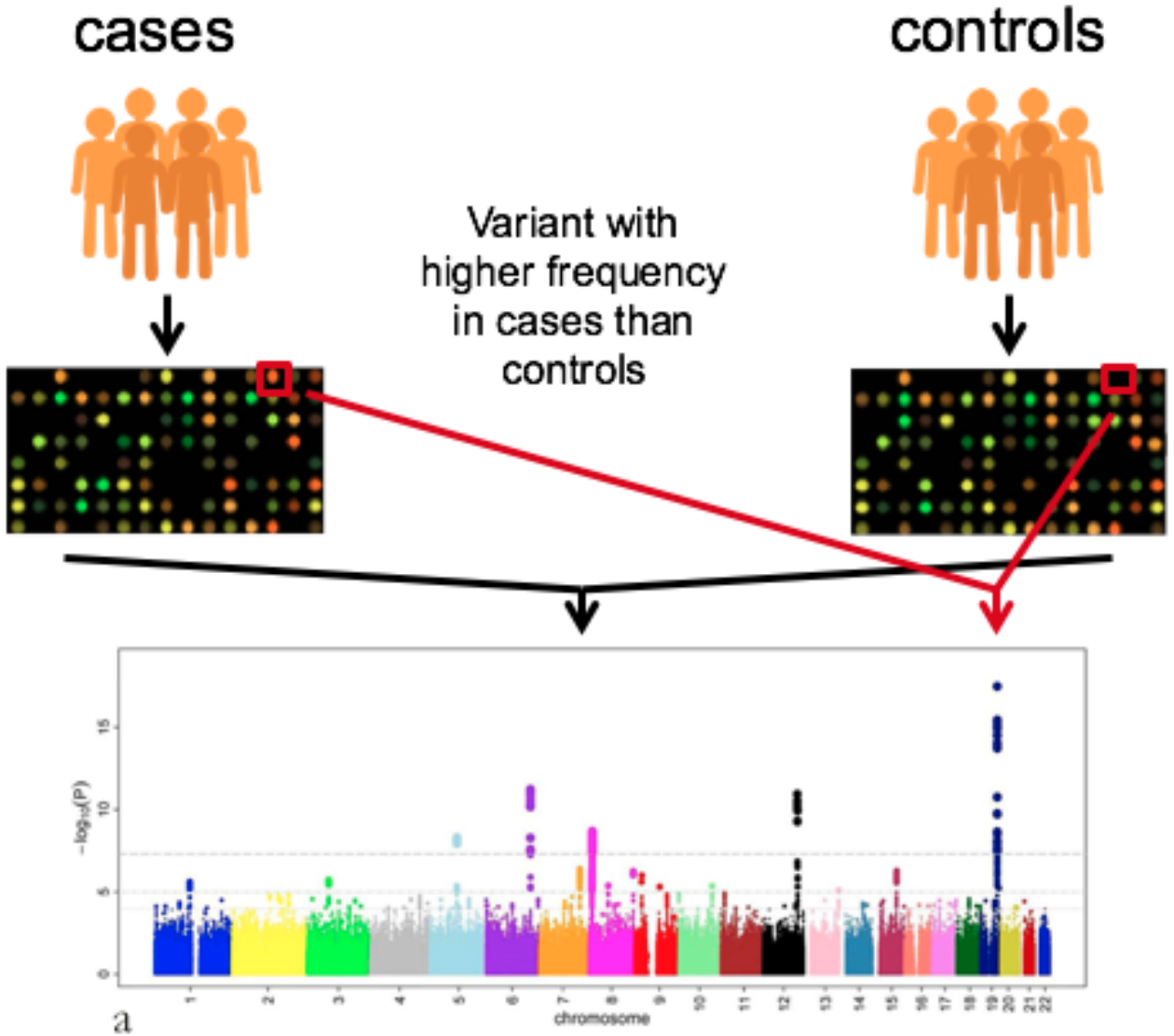
Do Common Genetic Variants (SNPs) Influence Radiotherapy side effects?

GWAS has become the standard approach for detecting SNP-radiotherapy side effects associations

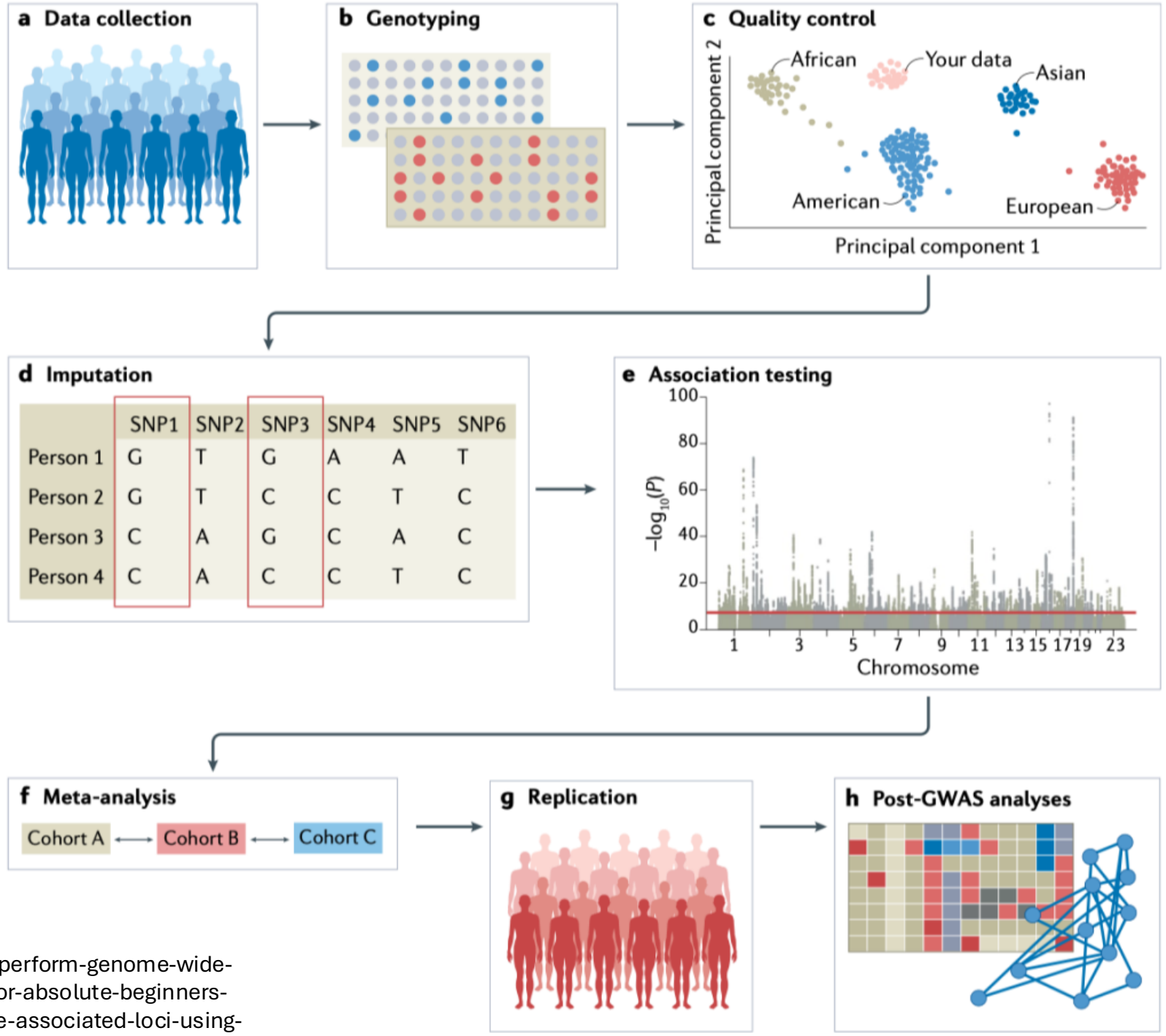


Manolio et al., Finding the missing heritability of complex diseases. Nature. 2009 Oct 8;461(7265):747-53. doi: 10.1038/nature08494. PMID: 19812666

GWAS



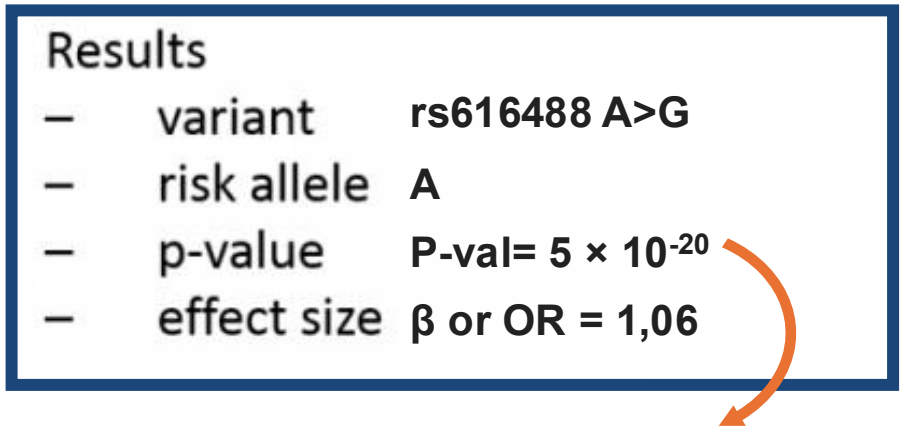
https://www.ebi.ac.uk/training/online/courses/human-genetic-variation-introduction/types-of-genetic-variation-studies/genome-wide-association-studies/



https://ngs101.com/how-to-perform-genome-wide-association-analysis-gwas-for-absolute-beginners-from-raw-variants-to-disease-associated-loci-using-

GWAS: *genome wide association studies*

Genome-wide association studies (GWAS) estimate the effect size of individual genetic variants associated with a phenotype or disease.

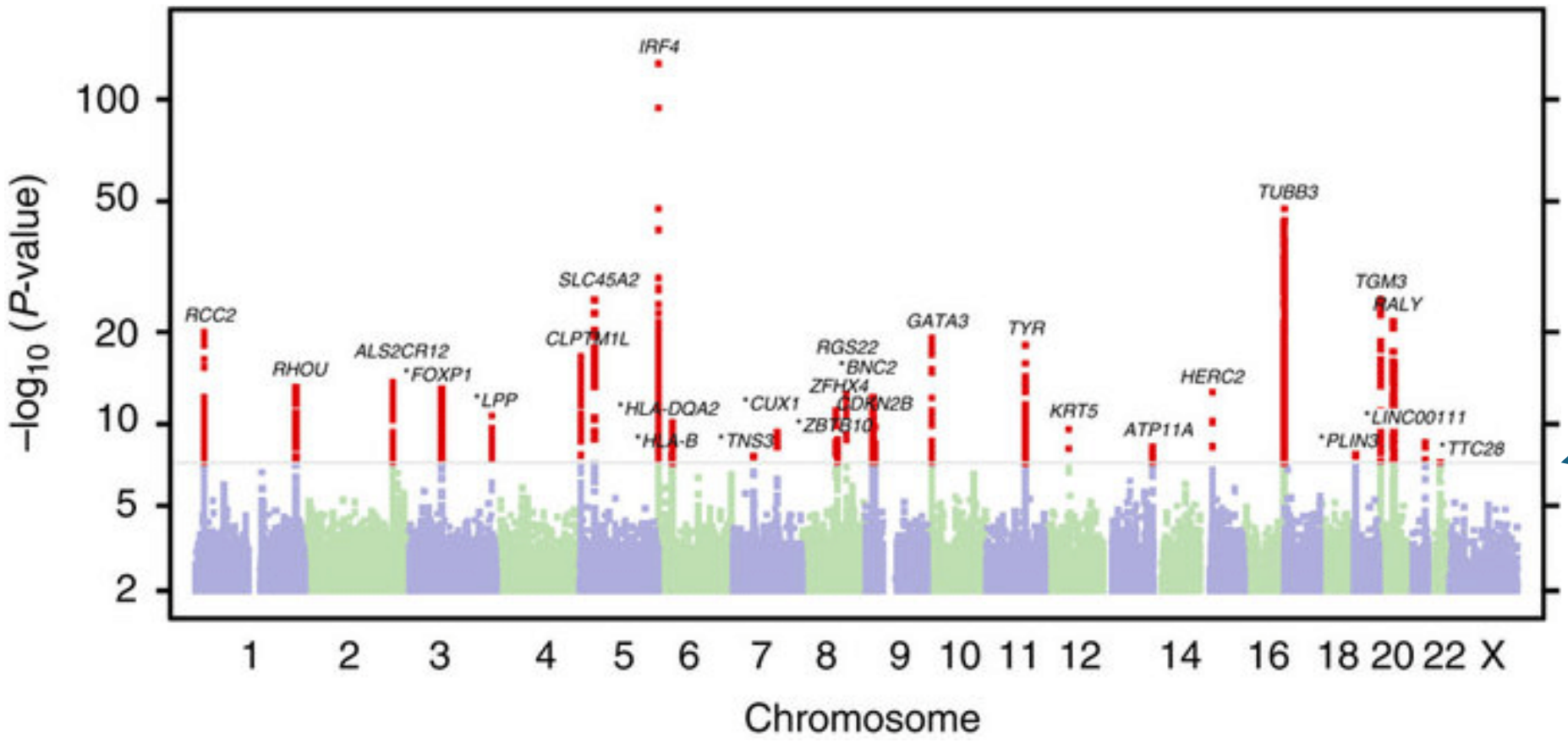


Significance threshold after Bonferroni correction for multiple testing: 5×10^{-8}

Adapted from a slide kindly shared by Laura Duran.

Graphical GWAS outcome

Manhattan plot



Significance threshold after Bonferroni correction for multiple testing: 5×10^{-8}

Adapted from a slide kindly shared by Laura Duran.

GWAS Summary statistics:

SNP	SNP chr	SNP pos	Other Allele	Effect Allele	MAF	Beta	SE	P
1:900730_G_A	1	900730	G	A	0.1070	-0.5229	0.0598	2.31e-18
1:846808_C_T	1	846808	C	T	0.1980	1.1701	0.0424	7.41e-168
1:846078_C_T	1	846078	C	T	0.1900	1.2671	0.0340	3.88e-304
1:846864_G_C	1	846864	G	C	0.1970	1.1873	0.0327	4.09e-288
1:901023_T_C	1	901023	T	C	0.0635	0.3909	0.0677	7.96e-9
1:845635_C_T	1	845635	C	T	0.1880	-0.5095	0.0445	2.39e-30
1:853239_A_G	1	853239	A	G	0.1970	-0.8584	0.0435	1.48e-86
1:848456_A_G	1	848456	A	G	0.2050	-0.6497	0.0431	2.90e-51

Adapted from a slide kindly shared by Laura Duran.

https://www.ebi.ac.uk/gwas/

GWAS Catalog

elixir Core Data Resource GBC GLOBAL CORE BIODATA RESOURCE

The NHGRI-EBI Catalog of human genome-wide association studies

Search the catalog

Examples: Parkinson disease, rs3093017, Yao, 2q37.2, HBS1L, 6:167120000-167130000, GCST90132222, PMID:35241825

Are you accessing the GWAS catalog programmatically? The newly designed REST API v2.0 is here! Find out more in our blog post.

Download

Download a full copy of the GWAS Catalog in spreadsheet format as well as current and older versions of the GWAS diagram in SVG format.

Summary statistics

Documentation and access to full summary statistics for GWAS Catalog studies where available.

Submit

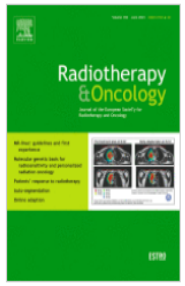
Submit summary statistics to GWAS Catalog.

ORIGINAL ARTICLE · Volume 159, P241-248, June 2021 · *Open Access*

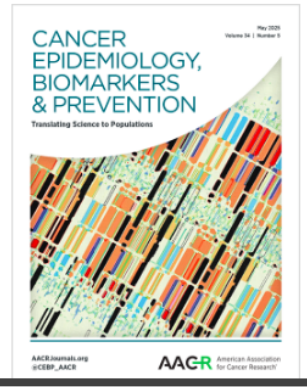
Download Full Issue

Development of a method for generating SNP interaction-aware polygenic risk scores for radiotherapy toxicity

Nicola Rares Franco [a,1] · Michela Carlotta Massi [a,b,1] · Francesca Ieva [a,b,c] · Andrea Manzoni [a] · Anna Maria Paganoni [a,b,c] · Paolo Zunino [a] · Liv Veldeman [d,e] · Piet Ost [d,e] ·



Volume 34, Issue 5
1 May 2025



RESEARCH ARTICLES | MAY 02 2025

A Polygenic Risk Score for Late Bladder Toxicity Following Radiotherapy for Non-Metastatic Prostate Cancer

Manzur Farazi; Xin Yang; Carson J. Gehl; Gillian C. Barnett; Neil G. Burnet; Jenny Chang-Claude; Christopher C. Parker; Alison M. Dunning; David Azria; Ananya Choudhury; Tiziana Rancati; Dirk De Ruysscher; Petra Seibold; Elena Sperk; Christopher J. Talbot; Liv Veldeman; Adam J. Webb; Rebecca Elliott; Miguel E. Aguado-Barrera; Ana M. Carballo; Olivia Fuentes-Ríos; Antonio Gómez-Caamaño; Paula Peleteiro; Ana Vega; Harry Ostrer; Barry S. Rosenstein; Shiro Saito; Matthew Parliament; Nawaid Usmani; Brian Marples; Yuhchyau Chen; Gary Morrow; Edward Messing; Michelle C. Janelsins; William Hall; Catharine M.L. West; Paul L. Auer; Sarah L. Kerns

Genetics and Genomics

A genome-wide association study of radiotherapy induced toxicity in head and neck cancer patients identifies a susceptibility locus associated with mucositis

Line M. H. Schack, Elnaz Naderi, Laura Fachal, Leila Dorling, Craig Luccarini, Alison M. Dunning, The Head and Neck Group of the Radiogenomics Consortium, The Danish Head and Neck Cancer Group (DAHANCA), Enya H. W. Ong, Melvin L. K. Chua, Johannes A. Langendijk, Behrooz Z. Alizadeh, Jens Overgaard, Jesper Grau Eriksen, Christian Nicolaj Andreassen & Jan Alsner

British Journal of Cancer **126**, 1082–1090 (2022) | Cite this article

ELSEVIER

Radiotherapy and Oncology
Volume 187, October 2023, 109806

Original Article

Genome-wide association study of treatment-related toxicity two years following radiotherapy for breast cancer

Harkeran K. Jandu [a], Colin D. Veal [a], Laura Fachal [b], Craig Luccarini [c], Miguel E. Aguado-Barrera [d e],

nature communications

Article | Open access | Published: 22 April 2026

Genetic determinants of fatigue up to 2 years after radiotherapy in prostate cancer patients

Philipp Heumann, Miguel E. Aguado-Barrera, Harkeran K. Jandu, David Azria, Erik

What is a Polygenic Risk Score (PRS)?

- A PRS is a weighted combination of multiple common genetic variants, each contributing modestly to an individual's risk of a trait, disease, or treatment response

Adapted from a slide kindly shared by Laura Duran.

Estimation of the polygenic risk score (PRS)

A PRS is a weighted combination of multiple common genetic variants, each contributing modestly to an individual's risk of a trait, disease, or treatment response

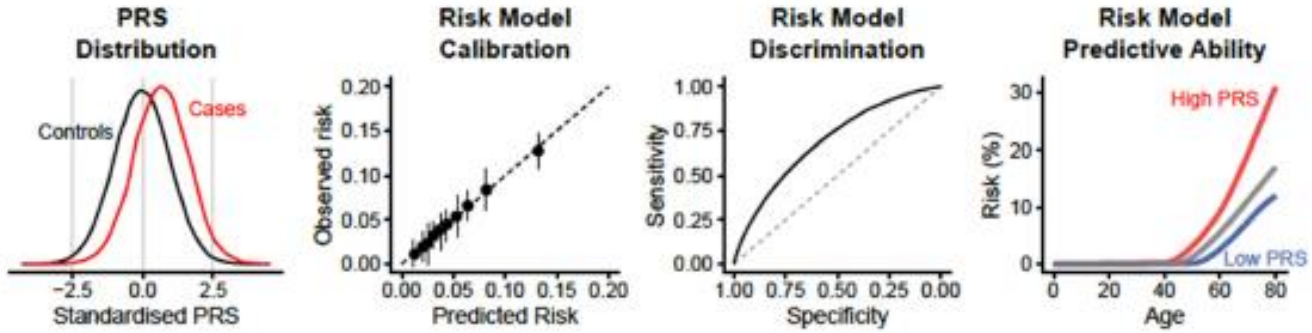
$$PRS=\beta_1 x_1 + \beta_2 x_2 +...+ \beta_k x_k + \beta_n x_n$$

β_k = **estimated effect** (risk coefficient) of SNP k
X_k = **number of risk alleles** carried by the individual at SNP k (0, 1, or 2)
n = number of SNPs included in the PRS

Adapted from a slide kindly shared by Laura Duran.

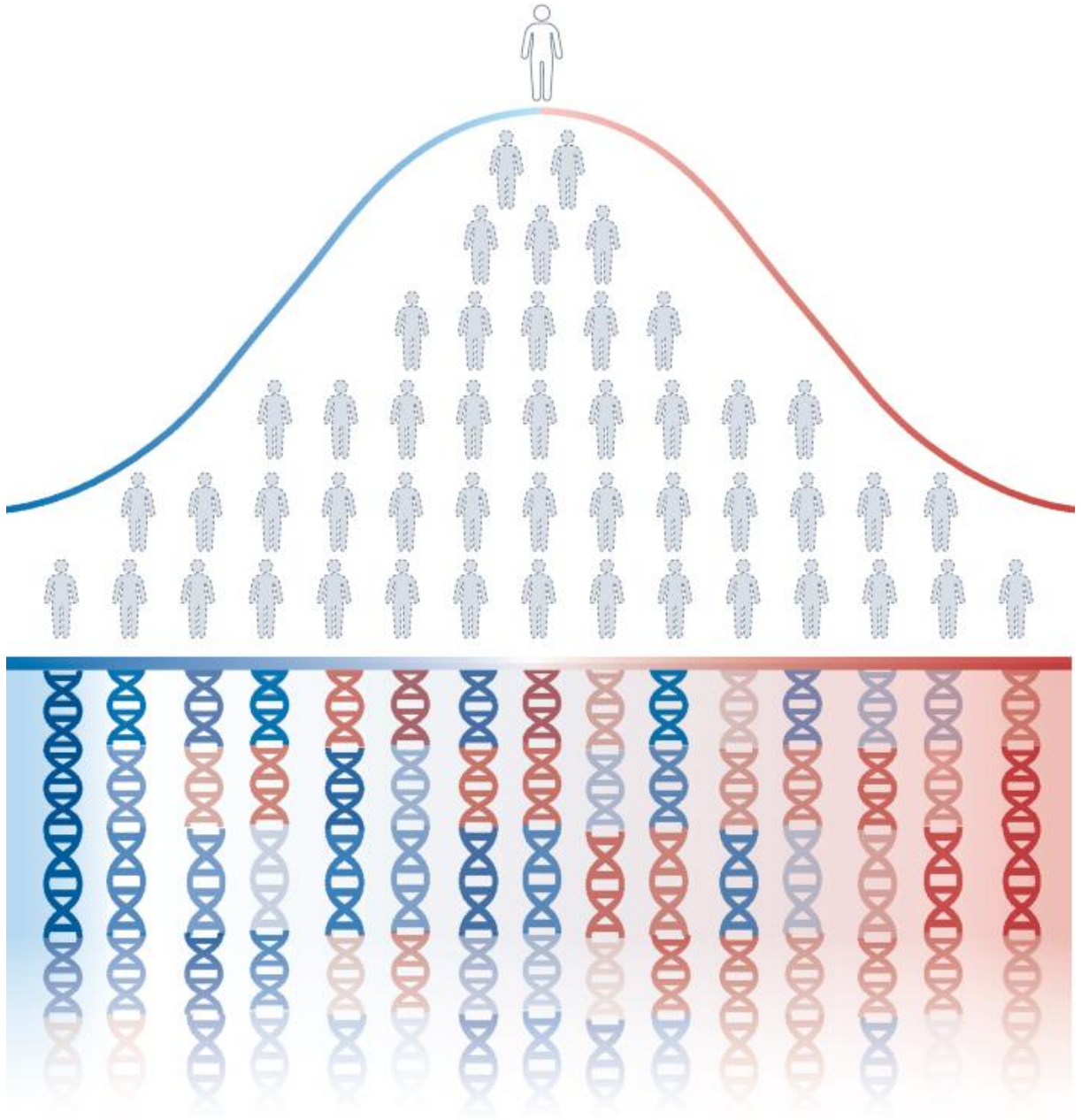
From GWAS to PRS: Development Steps

- **Genetic association study (GWAS) for the phenotype of interest → generates summary statistics** (list of variants, p-values of association, and effect sizes/weights for each variant)
- **Model development:** construction of the PRS using clearly defined methodologies (e.g., LASSO regression, LDpred)
- **Validation:** confirmation of PRS association and calibration with the phenotype in an independent cohort
- **(Potential) integration into a multivariable risk model** combining genetic and non-genetic factors
- **Model evaluation:** assessment of predictive performance (e.g., discrimination, calibration, and clinical utility)



Adapted from a slide kindly shared by Laura Duran.

$$PRS_i = \sum_{j=1}^{M} (\log OR_j) G_{ij}$$



Furrer et al., 2026, Nat Hum Behaviour
https://doi.org/10.1038/s41562-026-02475-8

Stage	What GWAS/PRS can tell us	What they cannot tell us by themselves
Discovery	Variants statistically associated with a trait, disease, or treatment outcome	Whether the variant is causal
Biology	Candidate genes, loci, and pathways for investigation	The underlying molecular mechanism without functional validation
Risk Stratification	Relative genetic risk compared with others	Certainty of disease/toxicity, absolute risk, or timing of onset/progression
Clinical Use	One component of a broader prediction model	Clinical decisions without integration of other genetic, clinical, and environmental factors

https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores

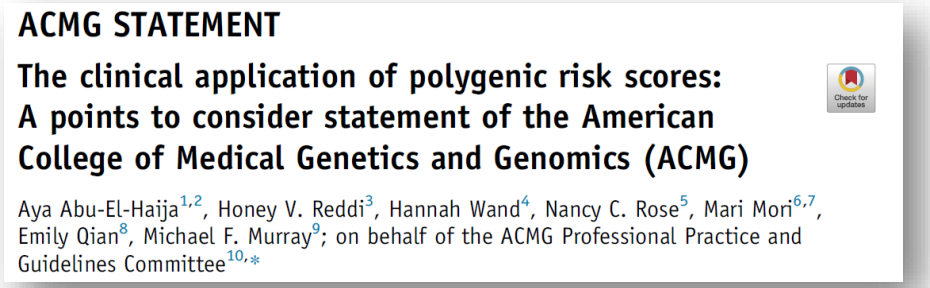
Wrap-up

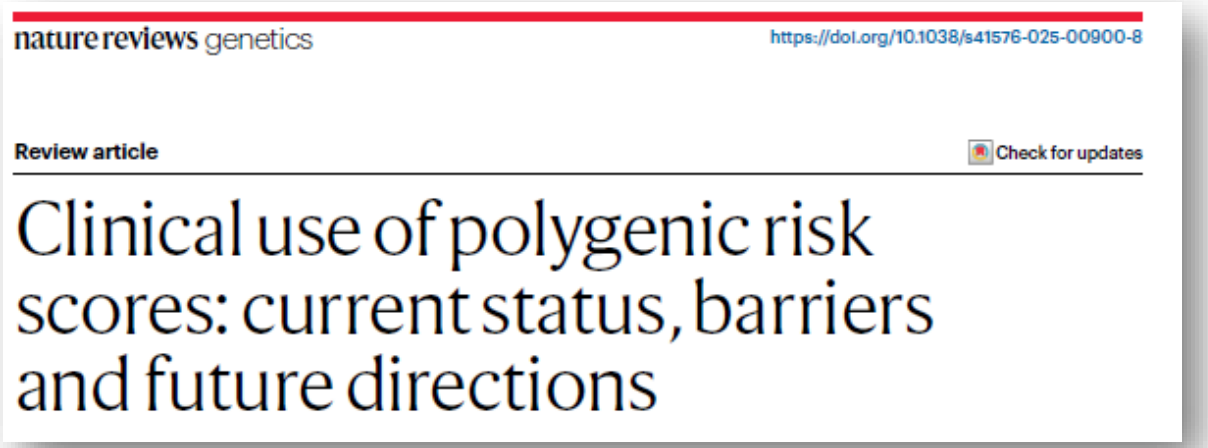
GWAS and PRS are powerful tools for risk stratification and biological discovery, but they identify associations rather than causation. Their clinical value depends on functional validation and integration with clinical and environmental information.

Recommended bibliography

Tutorial: a guide to performing polygenic risk score analyses

Shing Wan Choi[1,2], Timothy Shin-Heng Mak[3] and Paul F. O'Reilly[1,2]✉





Adapted from a slide kindly shared by Laura Duran.

WP4: Genomic Markers

Sara Gutiérrez-Enríquez, Antón Vega Méndez, Carmen Moreno Aldomà, Jacqueline S. Penaloza, Victoria Reyes and Goretti Mallorquí, Vall d'Hebron Institute of Oncology (VHIO), Barcelona Spain

tetris

Risk assessment *T*ools for severe side *E*ffects after *breasT R*adiotherapy: radiation safety through biological extended models and *dIgital twinS*

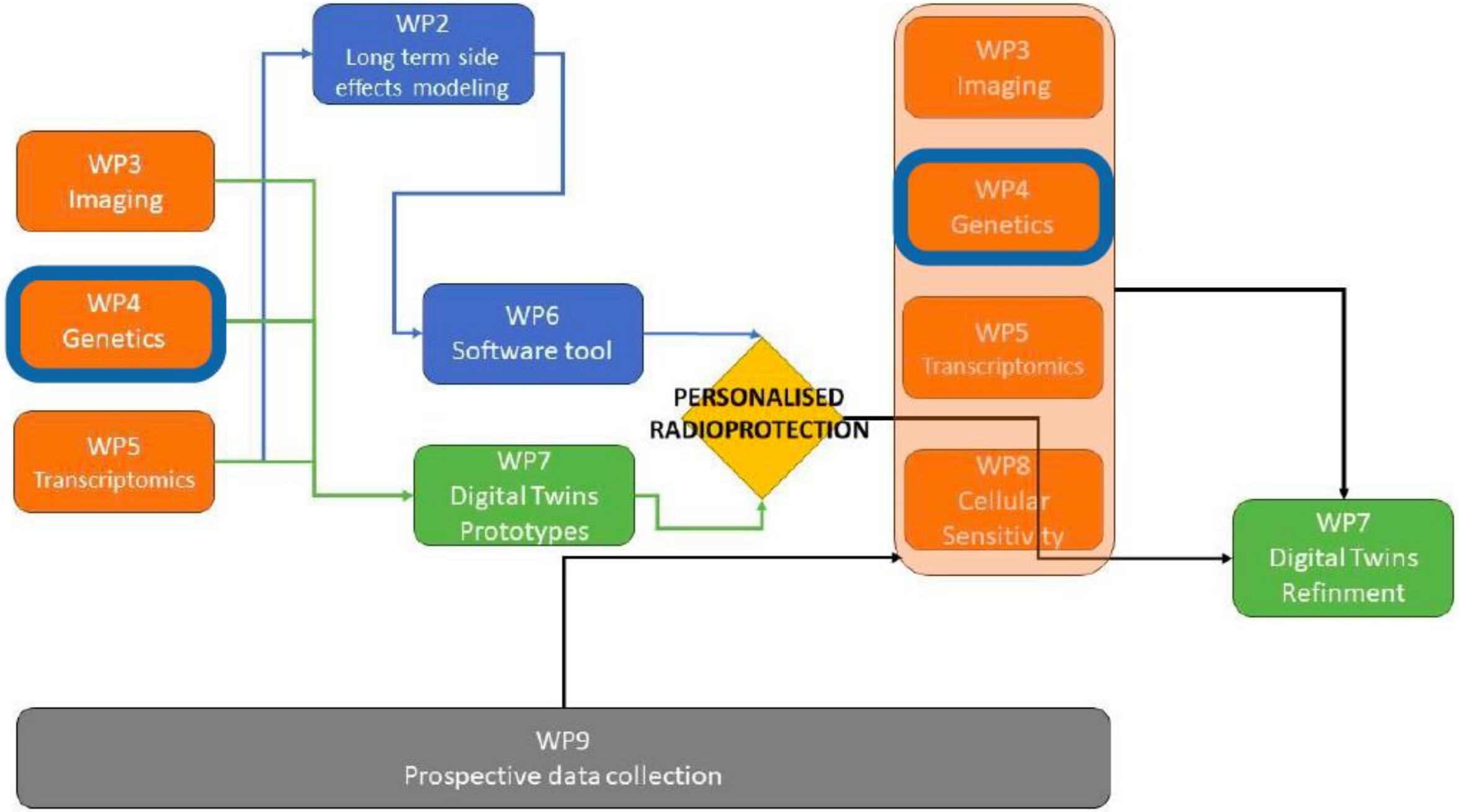
This project has received funding under Euratom Research and Training Programme (EURATOM) Grant ID 101166699

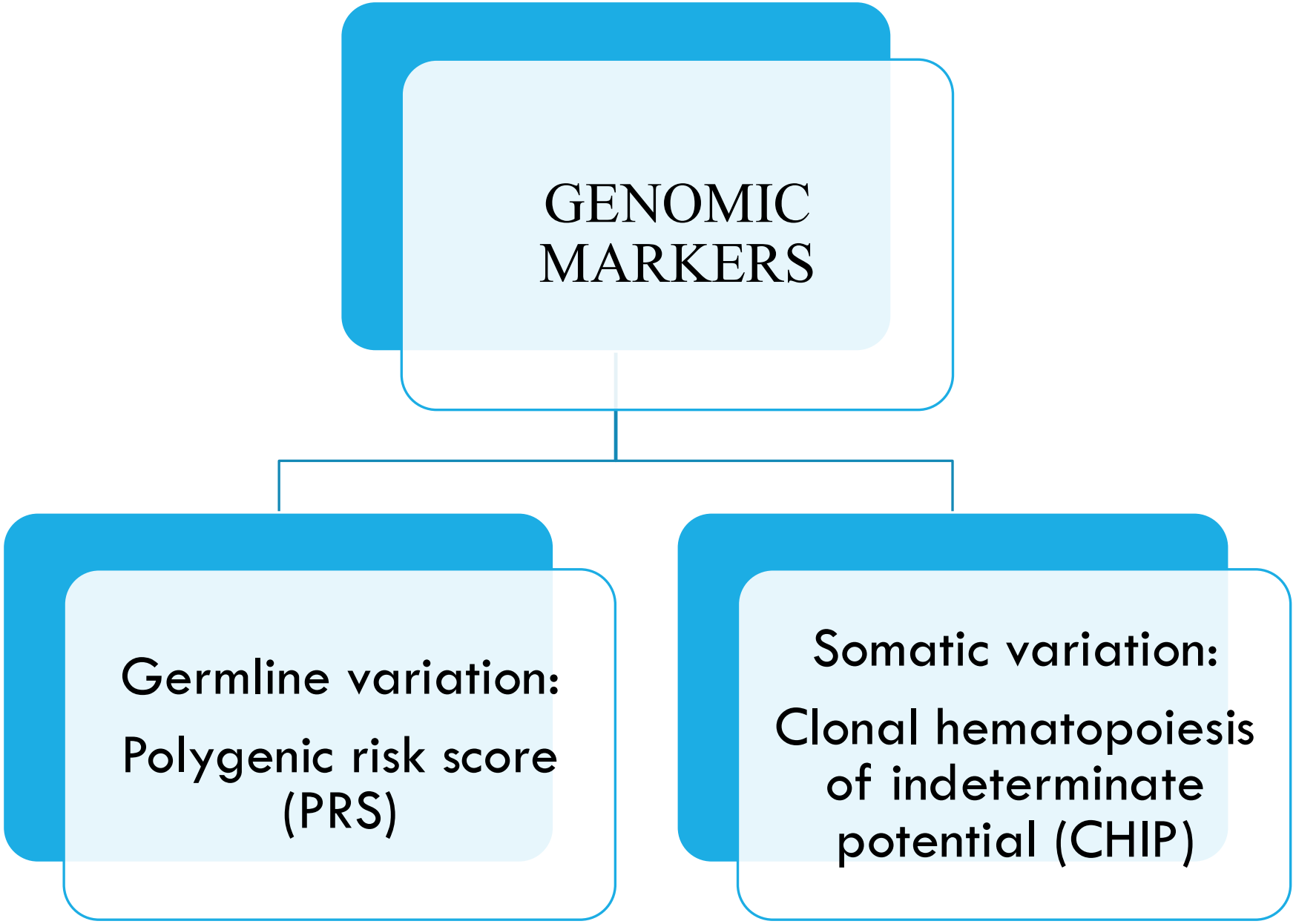
EU Grant Agreement n. 101166699

Objectives

WP4 aims at:

- Estimating genetic markers to be included in the risk scores developed in WP2 and in the CE-marked software tool (WP6).
- The same biomarkers will also be considered in prototyping digital twins (WP7).


WP2
Long term side effects modeling
WP3
Imaging
WP4
Genetics
WP5
Transcriptomics
WP6
Software tool
WP7
Digital Twins
Prototypes
PERSONALISED
RADIOPROTECTION
WP3
Imaging
WP4
Genetics
WP5
Transcriptomics
WP8
Cellular
Sensitivity
WP7
Digital Twins
Refinment
WP9
Prospective data collection

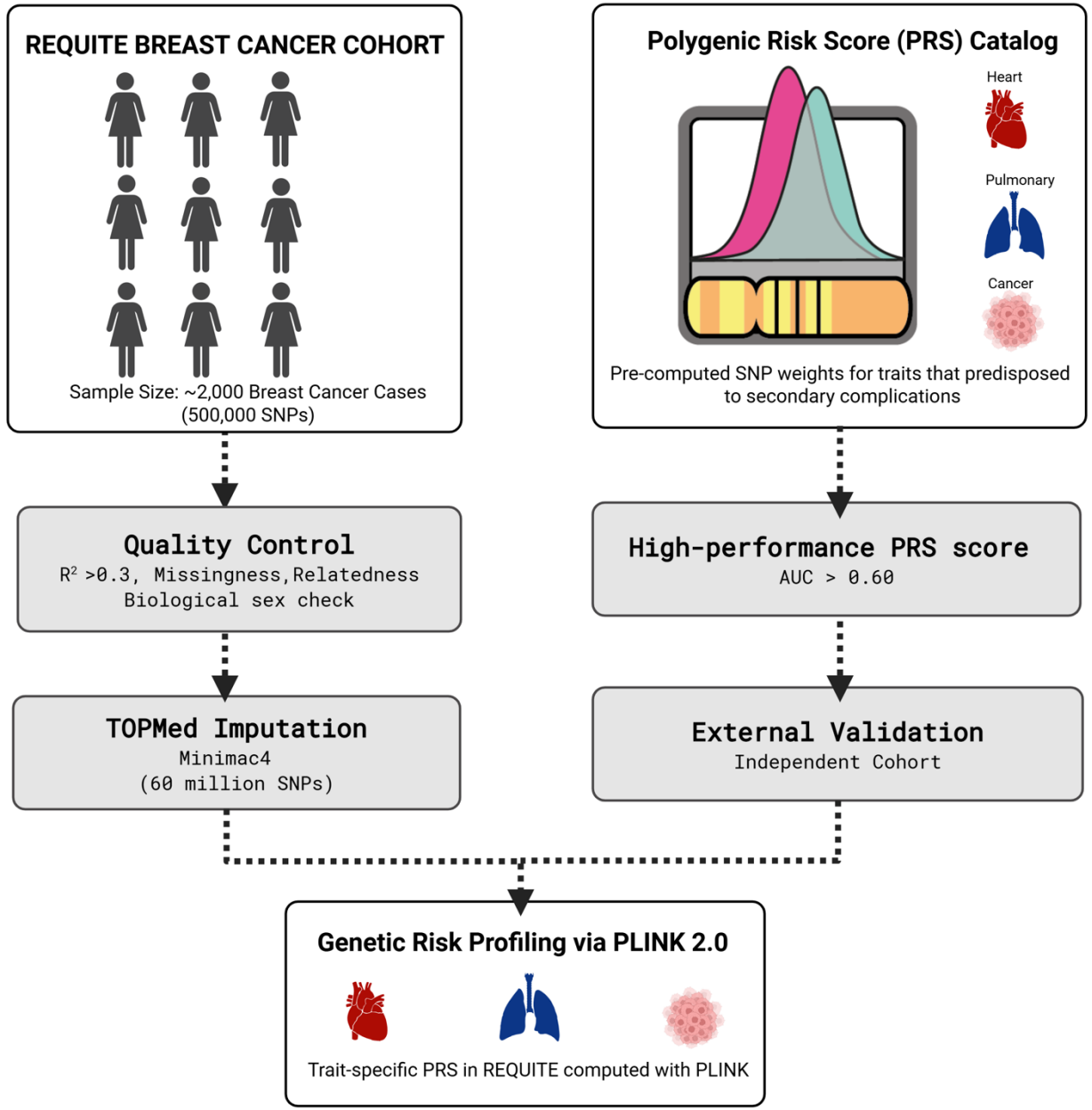

GENOMIC MARKERS
Germline variation:
Polygenic risk score (PRS)
Somatic variation:
Clonal hematopoiesis of indeterminate potential (CHIP)

Workflow for developing PRS

- Part I: Processing of REQUITE Breast Cancer Variants
    1) Starting variants ~ 600,000 SNPs, Oncoarray
    2) Imputation ~ 60 million SNPs

- Part II: Selection of the published SNP weights
    1) Traits of Interest were selected
    2) Review of performance scores
    3) Review of study design of publication

- Part III: Compute PRS score using PLINK 2.0



Baseline patient phenotypes for PRS development: 21 baseline traits that may predispose to late radiotherapy complications

Pulmonary

- Asthma
- Chronic obstructice pulmonary disease (COPD)
- Idiopathic pulmonary fibrosis
- Pneumonitis

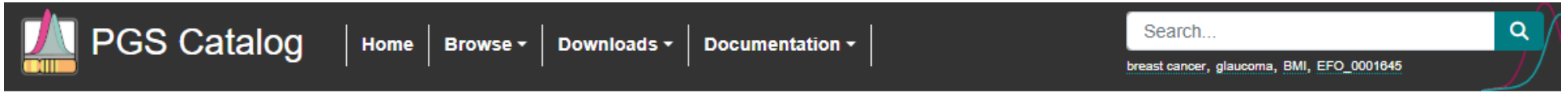
Heart

- Heart failure
- Stroke (vascular disease)
- Venous thromboembolism (vascular disease)
- Angeina pectoris
- Atrial fibrillation
- Hypertension
- Myocardial infarction
- Coronary artery disease
- Dilated cardiomyopathy

Cancer

- Breast cancinoma
- Lymphoid Leukemia
- Non-hodgkins lymphoma
- Thyroid cancer
- Esophageal adenocarcinoma
- Cutaneous Melanoma
- Lung carcinoma
- Sarcoma

PGS catalog



Score Details

Score Construction	
PGS Name	**PRS313_BC**
Development Method	
Name	Hard-Thresholding Stepwise Forward Regression
Parameters	p < 10^-5
Variants	
Original Genome Build	**GRCh37**
Number of Variants	313
Effect Weight Type	**NR**

PGS Source	
PGS Catalog Publication (PGP) ID	PGP000002
Citation (*link to publication*)	Mavaddat N *et al. Am J Hum Genet* (2018)

Ancestry Distribution

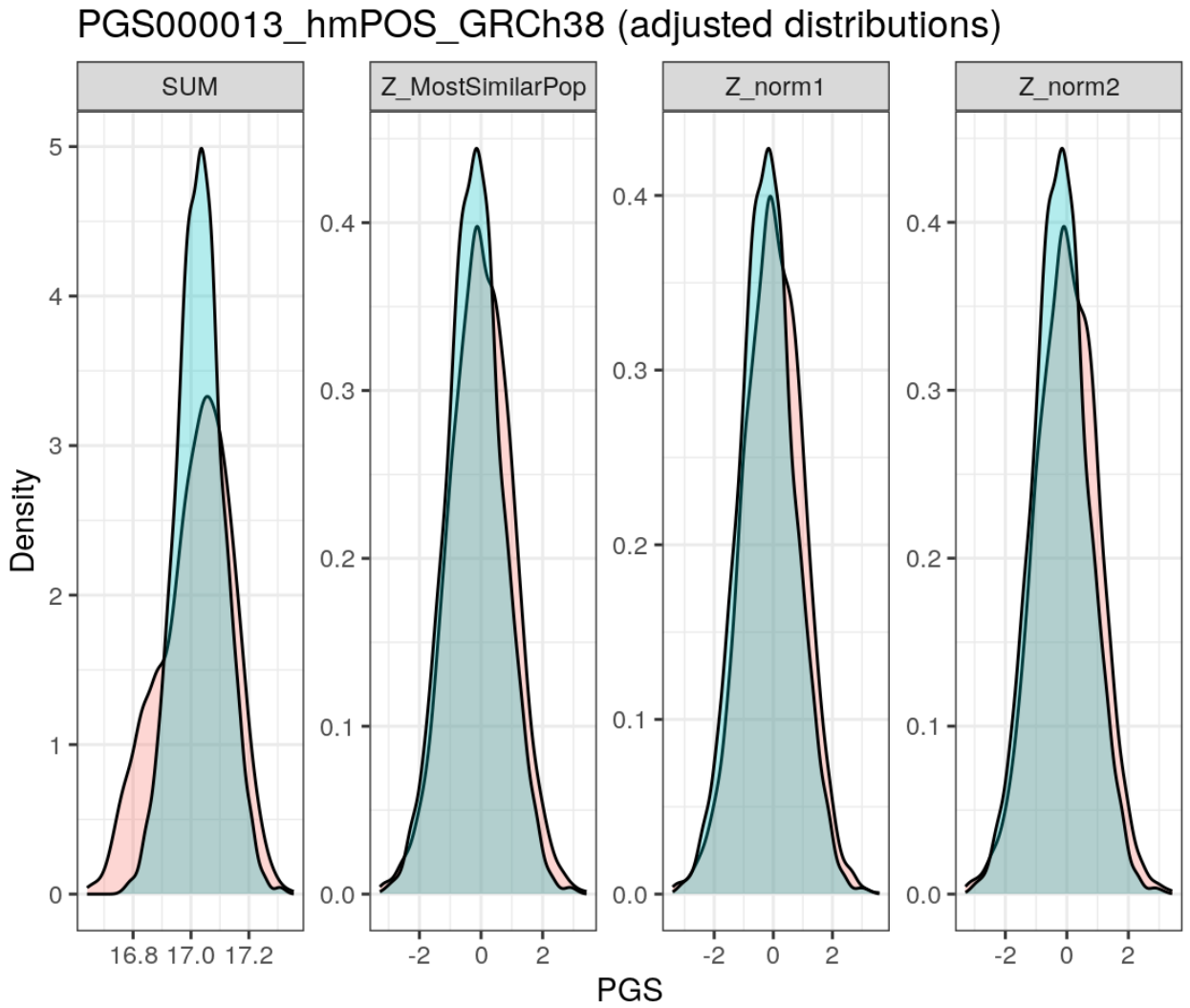
Source of Variant Associations (**G**WAS)	European: 100% 158,648 individuals (100%)
Score **D**evelopment/Training	European: 100% 10,444 individuals (100%)
PGS **E**valuation	European: 74.6% Multi-ancestry (including European): 6.8% African: 5.1% Additional Asian Ancestries: 5.1% Not Reported: 3.4% Hispanic or Latin American: 1.7% East Asian: 1.7% Multi-ancestry (excluding European): 1.7% 59 Sample Sets

https://www.pgscatalog.org/score/PGS000004/

21 baseline traits that may predispose to late radiotherapy complications

Scoring file	Number of variants	Match %	Total matched	Total unmatched
PGS000004_hmPOS_GRCh37	313	87.5	274	39
PGS000013_hmPOS_GRCh37	6630150	99.5	6595104	35046
PGS000016_hmPOS_GRCh37	6730541	99.4	6689857	40684
PGS000703_hmPOS_GRCh37	183692	90.1	165465	18227
PGS000706_hmPOS_GRCh37	186726	90.1	168255	18471
PGS000710_hmPOS_GRCh37	183566	90.1	165349	18217
PGS000788_hmPOS_GRCh37	75	90.7	68	7
PGS000791_hmPOS_GRCh37	19	84.2	16	3
PGS000797_hmPOS_GRCh37	12	75	9	3
PGS001784_hmPOS_GRCh37	911440	99.9	910907	533
PGS001787_hmPOS_GRCh37	909990	99.9	909481	509
PGS001788_hmPOS_GRCh37	910082	99.9	909569	513
PGS001790_hmPOS_GRCh37	910146	99.9	909629	517
PGS001791_hmPOS_GRCh37	910439	99.9	909913	526
PGS001793_hmPOS_GRCh37	910099	99.9	909589	510
PGS001796_hmPOS_GRCh37	910337	99.9	909781	556
PGS003382_hmPOS_GRCh37	672	97.5	655	17
PGS003388_hmPOS_GRCh37	356743	95.4	340216	16527
PGS003391_hmPOS_GRCh37	133	82	109	24
PGS004862_hmPOS_GRCh37	709534	100	709184	350
PGS004911_hmPOS_GRCh37	374114	99.9	373775	339

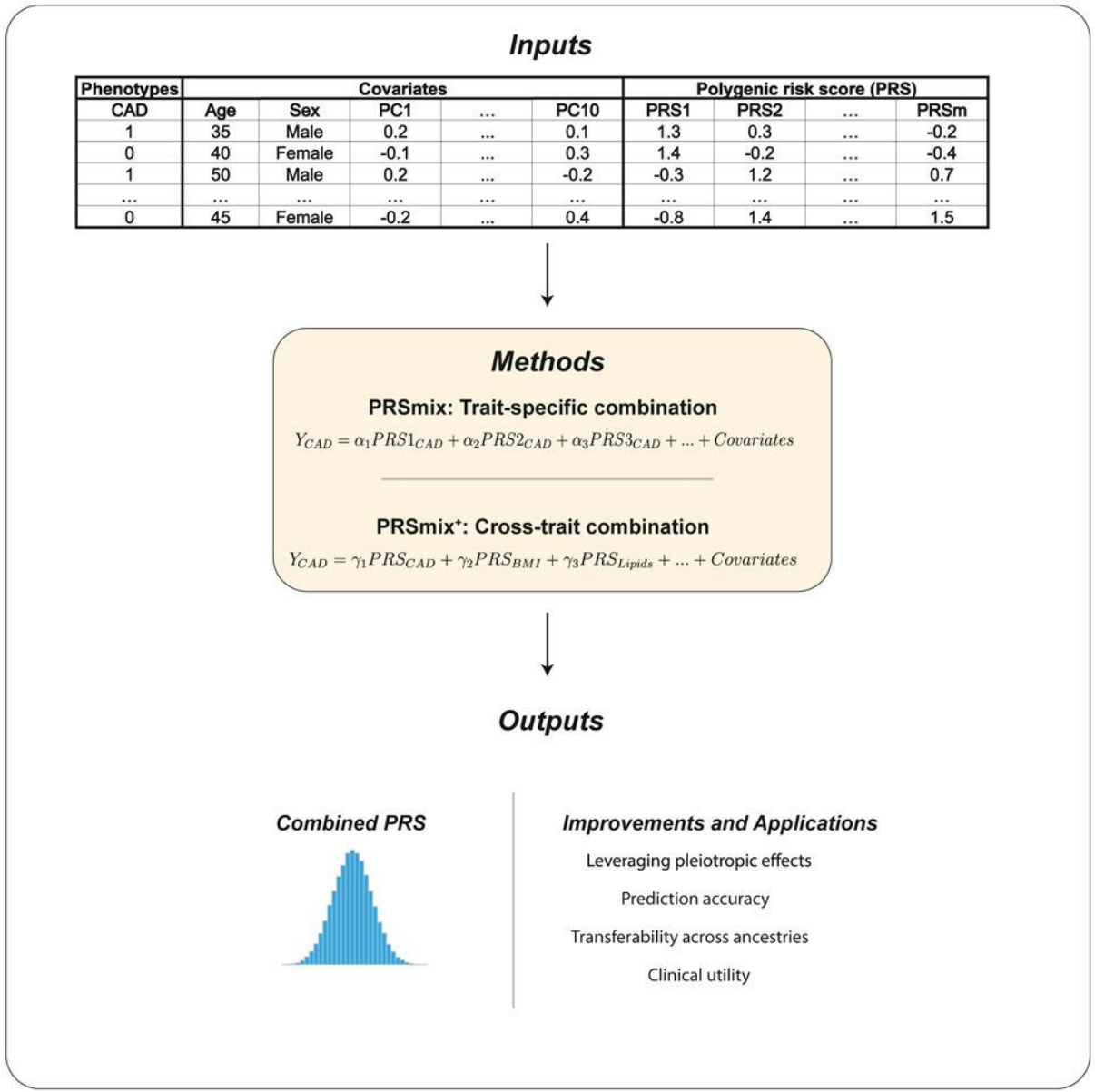
21 baseline traits that may predispose to late radiotherapy complications



Coronary artery disease

Ongoing and future work

PRS

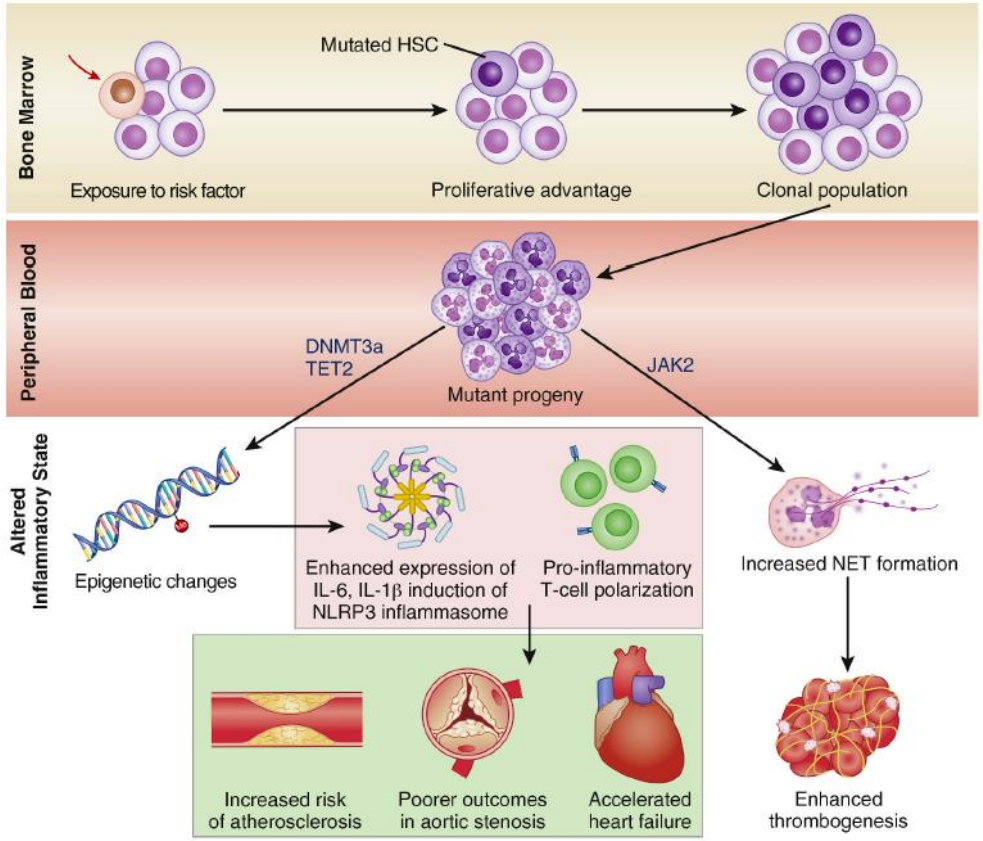


Truong et al Integrative polygenic risk score improves the prediction accuracy of complex traits and diseases. Cell Genom. 2024. PMID: 38508198

Ongoing and future work

Somatic variation in blood normal cells:

Clonal hematopoiesis of indeterminate potential (CHIP)



Hereditary Cancer Genetics Group, 2026

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tetris

Risk assessment *Tools* for severe side *Effects* after breas*T* *R*adiotherapy:
radiation safety through biological extended models and *d*igital *twin*S

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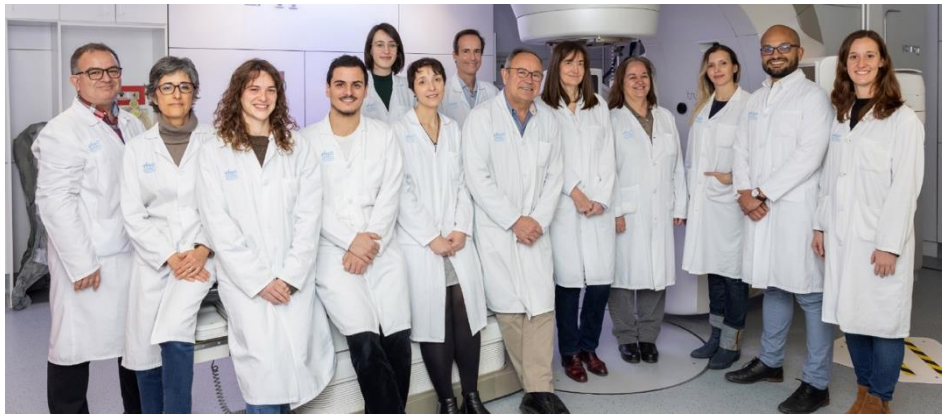

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THANK YOU

TETRIS - Risk assessment *Tools* for severe side *Effects* after *breasT Radiotherapy*: radiation safety through biological extended models and *dIgital twinS*

EU Grant Agreement n. 101166699

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