Clinical Guidelines for Polygenic Risk Score in Predicting Radiation Toxicity in Breast Cancer

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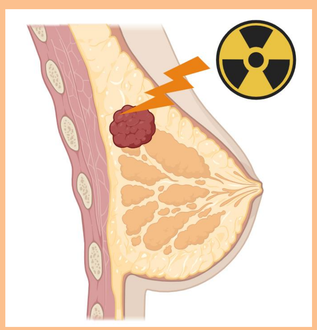
INTRODUCTION

Breast Cancer (BCa) is a Global Public Health Concern



- **Breast Cancer (Bca)** is the leading cause of cancer death in women.
- **Worldwide 1 in 6** cancer deaths is due to Bca.
- Leading cause of death in European women.
- **Radiotherapy** has increased survival, but there are risk involved
- **Severe side effects from treatment:**
  - Cardiovascular toxicity
  - Pulmonary toxicity
  - Secondary cancers
- ***Radiation safety tools are necessary to personalize treatment for patients.***

Predicting Risk is Key for Personalizing Radiation Treatment for BCa patients

Objective: We will use the REQUITE genetic data to calculate the PRS for traits associated with severe side effects from radiotherapy. Our results will be one feature to build the digital-twin for European BCa patients.

- **What are the three components required for risk prediction for Bca patients?**

REQUITE Genotype Data → Target Phenotypes for PRS → Published GWAS: Pre-computed SNPs & Effect Weights

PRS: quantifies the cumulative effect of numerous genetic variants associated with disease susceptibility

METHODS

Fig 1: REQUITE Genotype Data

Feature	Description
Total number of markers	499,170
Number of tag SNPs*	275,691
Cancer-specific variants†	
Breast	~120,000
Colorectal	~40,000
Lung	~45,000
Ovarian	~50,000
Prostate	~80,000
Headroom for additional custom markers	120,000
Number of samples per OncoArray BeadChip	24
DNA requirement	200 ng
Assay	Infinium HTS
Instrument support	iScan or HiScan
Sample throughput‡	5,760 samples / week
Scan time / Sample	2.5 minutes
Spacing	**Mean**
Spacing (Kb)	1 marker / 5.4 Kb

* Defined by SNPs that overlap in position with those on the HumanOmniExpress-24 BeadChip.
† Overlap may exist between variants in some cancer types.
‡ Estimate assumes one dual iScan system, one AutoLoader 2.x, one Tecan robot, and a five-day work week.

Fig 2: Target Phenotypes for PRS

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

Fig 3: How is PRS calculated using the PLINK software?

For an individual, the PRS is calculated as:

$$PRS_i = \sum_{j=1}^{M} \beta_j G_{ij}$$

Where:

M= number of SNPs used in the score

β_j=effect size (weight) of SNP j, typically from GWAS

G_{ij}=genotype dosage for individual i and j

Genotype one patient

SNP ID	Genotype	Dosage (G)
rs1	AA	0
rs2	AG	1
rs3	GG	2

GWAS weights

SNP ID	Effect Allele	Beta (β)
rs1	A	0.10
rs2	G	-0.20
rs3	G	0.05

rs1: AA → Dosage of A = 0
0.10 x 0 = 0

rs2: AG → Dosage of G = 1
-0.20 x 1 = -0.20

rs3: GG → Dosage of G = 2
0.05 x 2 = 0.10

PRS = 0 + -0.20 + 0.10
= -0.10

Patient for this trait PRS is -0.10

Fig 4A: Resulting Pipeline for PRS Calculation

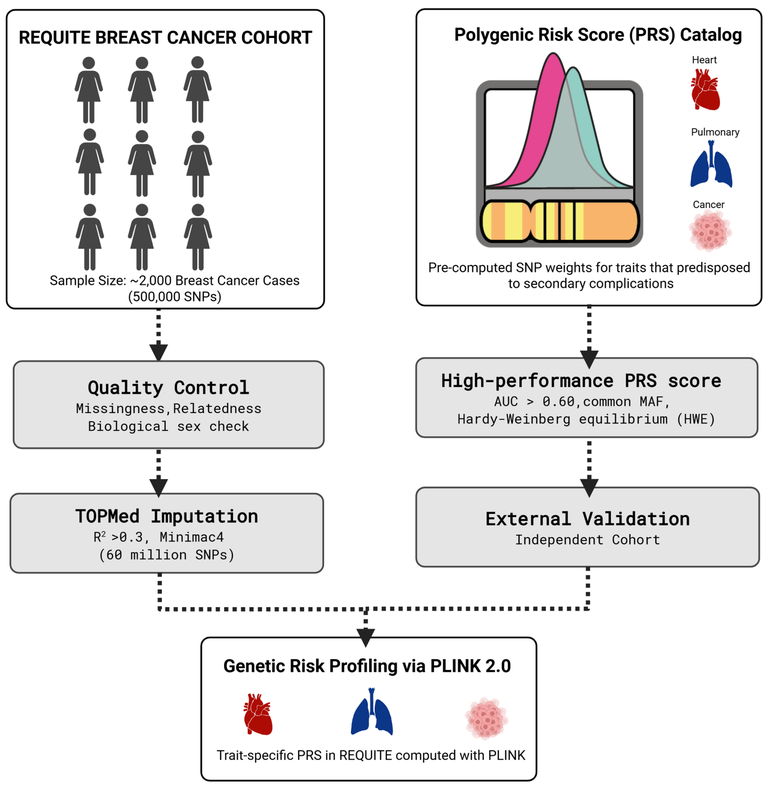


Fig 4B. PRS Curves for select traits

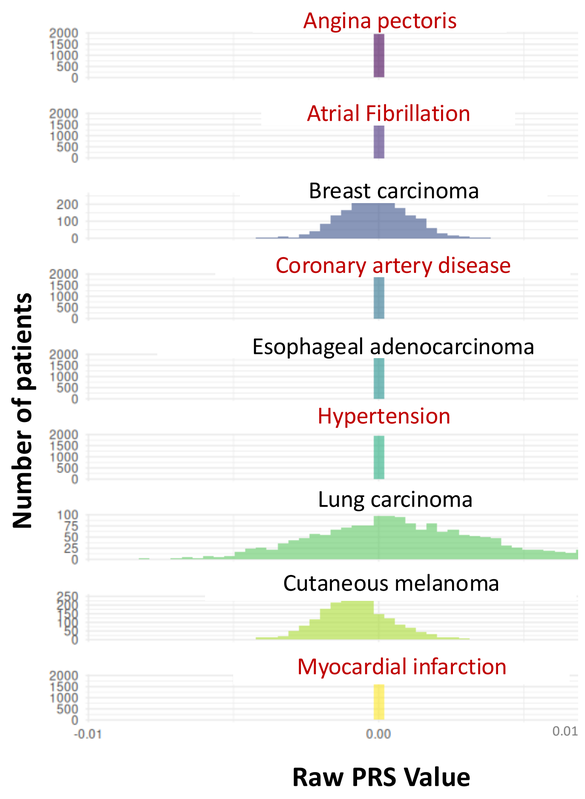


Fig 5: Clinical Guidelines for PRS Application

****This symbol indicates missing steps of analysis**

1. Selection of appropriate PRS
2. Population Matching**
3. Quality Control

   SNPs QC:
   - MAF filter
   - poor imputation
   - HWE derivation

   Sample QC:
   - Sex discordance
   - imputation filter
   - extreme heterozygosity
   - relatedness
4. Dosage calculation
5. PRS transformation for clinical use**

Collister 2022 et al., Frontier Genetics

Fig 6: Population Matching to remove non-European patients

Principle component analysis using 1000 genomes as the truth set

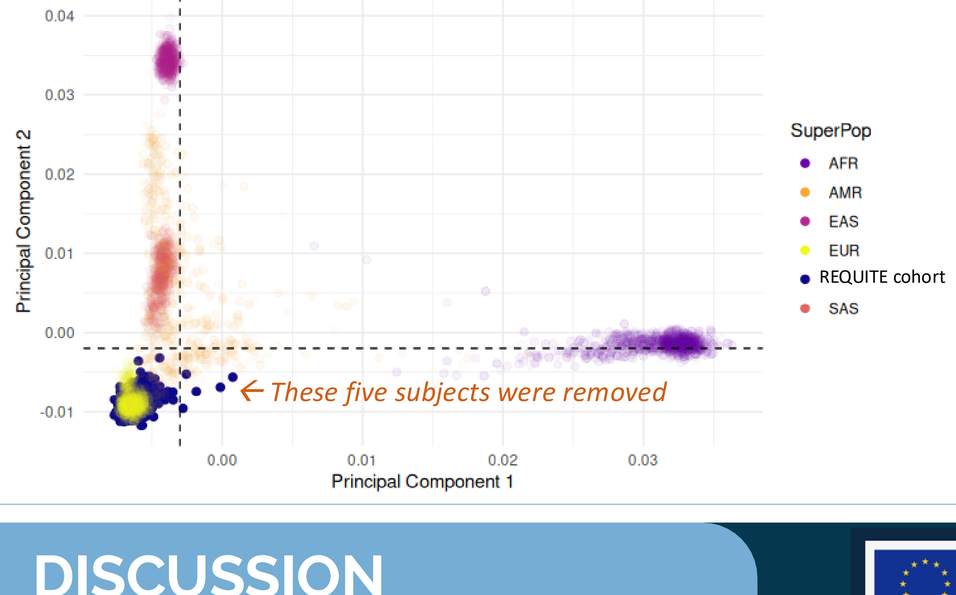
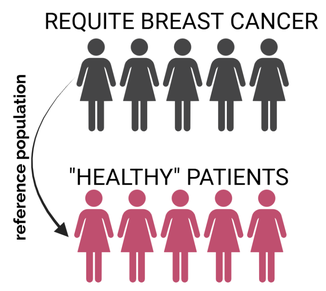


Fig 7: Potential Application of 1000 Genomes as Reference Population

$$PRS_z = \frac{PRS_{raw} - \mu}{\sigma}$$



Where:
μ is the mean in a **reference population**
σ is the **standard deviation** in that population

The PRS is centered around 0 relative to the ***reference population*** and is scaled, where 1 unit is equal to 1 σ from the μ.

Would it be possible to use 1000 Genomes as a reference population?

DISCUSSION

The incorporation of PRS into clinical workflows enables earlier surveillance and personalized prevention strategies, potentially improving patient outcomes across all cancers treated with radiotherapy. Challenges remain in finding an appropriate reference population to transform the PRS value. Overall, our findings support the translational value of PRS in Radiation Oncology and highlight its relevance for public health initiatives globally.

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