Use of GWAS to predict individual patient response

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ICRP Workshop on Individual Response to Ionizing Radiation

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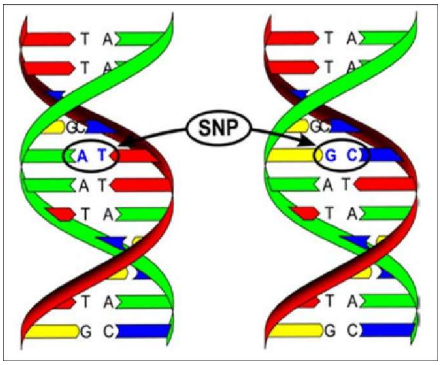
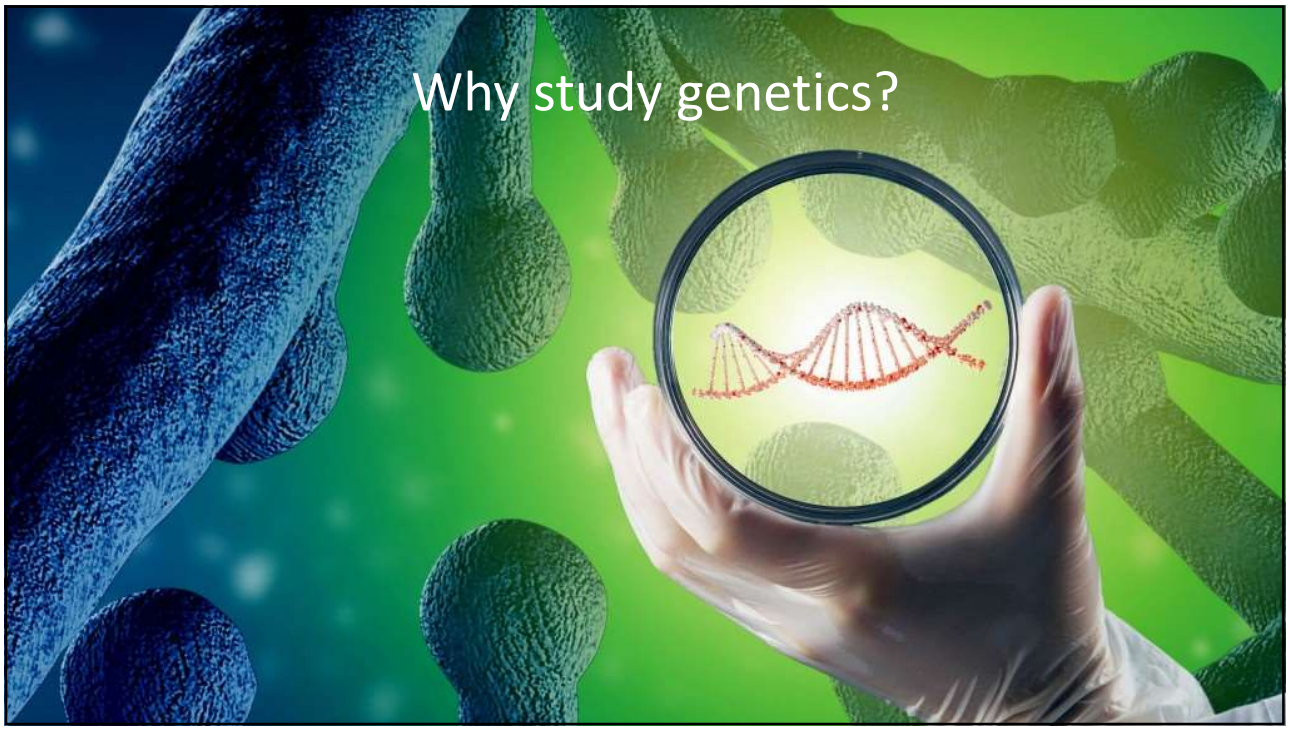
Genome wide association study (GWAS)

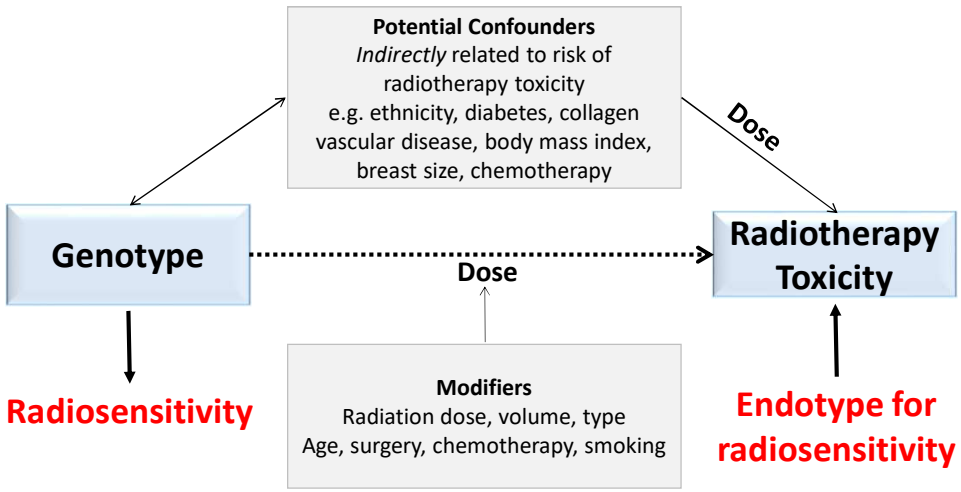
- An observational study of a genome-wide set of genetic variants
- Identify variants associated with a trait or disease
- Usually focus on single-nucleotide polymorphisms (SNPs)
- Identifying genetic variants (SNPs) associated with radiotherapy toxicity





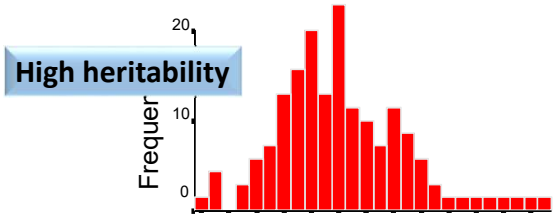
Genetics *contributes* to risk of toxicity

A test based on genetics alone is unlikely to predict for risk of toxicity



The genetic trait of *intrinsic* radiosensitivity as a continuous variable

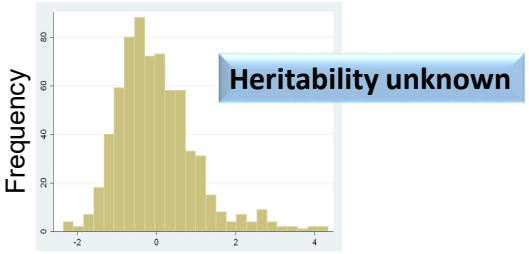
Distribution of cellular radiosensitivity for 122 individuals



Cellular radiosensitivity – surviving fraction at 2 Gy

West & Barnett 2012 Gen Med 3:52

Distribution of radiotherapy toxicity in ~900 breast cancer patients



Residuals - toxicity after allowing for known modifiers

Barnett et al 2011; IJROBP 82:1065-74

Phenotype → Endotype

Genetics contributes to risk of toxicity. Rare mutations have large effects. Common variants will account for some of the risk. If we can find enough variants it would be clinically useful.

GWAS to predict risk of toxicity

Radiogenomics Consortium

REQUITE

Radiogenomics Consortium Prostate GWAS

OncoArray-500K, ~7 million SNPs
Time to grade 2/3 toxicity, n=3,874

	RAPPER n=2,010	RADIOGEN n=658	GenePARE n=495	UGhent n=311	CCI-BT n=252	CCI-EBRT n=148
Median age (yr)	68	72	65	65	65	68
Intermed/high risk	60%	81%	53%	74%	38%	92%
Prior surgery	0%	20%	0%	31%	0%	0%
Hormones	100%	70%	51%	64%	22%	49%
Median BED (Gy)	120	123	204	136	158	153

CCI=Cross Cancer Institute; BED=biological effective dose

Sarah Kerns et al 2020, JNCI

Three new SNPs identified

p-values must be <5 x 10^{-8}

SNP	MAF	Toxicity	HR (95% CI)	P	BFDP
rs17055178	0.09	Rectal bleeding	1.95 (1.58, 2.43)	**$6.2x10^{-10}$**	0.09%
rs10969913	0.05	Decreased stream	3.92 (2.50, 5.83)	**$2.9x10^{-10}$**	1.07%
rs11122573	0.06	Haematuria	1.92 (1.53, 2.42)	**$1.8x10^{-8}$**	1.96%

MAF = minor allele frequency; BFDP = Bayesian false discovery probability

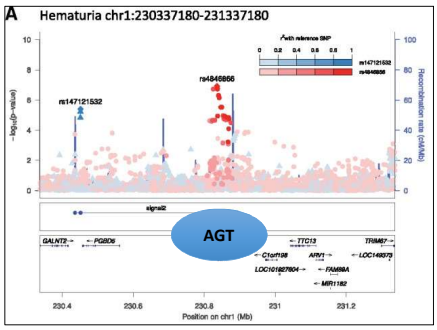
Rs10969913 validated in a Japanese cohort

Kerns *et al* 2020 JNCI

Ongoing analyses: includes REQUITE cohort and multi-ethnicities

Identifies credible causal variants (CCVs)

- CCVs associated with regulation of *AGT*
- *AGT* encoding angiotensinogen - converted to angiotensin II by angiotensin converting enzyme (ACE)
- Angiotensin maintains blood pressure and fluid balances - too much causes vasoconstriction and increases in blood pressure
- Angiotensin signaling may influence radiation-induced blood vessel wall injury and interstitial fibrosis



Fine mapping identifies another variant, less common but higher HR 4.43 (95% CI 2.35 - 8.33)

GWAS to mitigate risk of toxicity

- Tested the hypothesis that patients taking angiotensin converting enzyme inhibitors (ACEi) have a reduced risk of late hematuria
- Two observational cohorts: Rochester (n=256) and REQUITE (n=1,437)
- Patients assessed pre-radiotherapy and prospectively for up to four years
- Cumulative probability of haematuria estimated using multivariable relative risk models to assess the effect of ACEi on time to hematuria adjusting for clinical factors
- A polygenic risk score (PRS) for blood pressure was tested for association with hematuria in REQUITE and in the Radiogenomics Consortium GWAS


Radiotherapy and Oncology

Original Article

Use of angiotensin converting enzyme inhibitors is associated with reduced risk of late bladder toxicity following radiotherapy for prostate cancer

ACEi use during radiotherapy protects against risk of late haematuria (n=1,372)

	Characteristic	Adjusted HR (95% CI)	P-value
ACEi use during radiotherapy	No Yes	Ref. **0.51 (0.28 to 0.94)**	- **0.030**
Heart disease	No Yes	Ref. 0.32 (0.15 to 0.67)	- 0.003
Prior transurethral resection	None TURB only TURP only TURP and TURB	Ref. 4.03 (0.96 to 17.0) 4.05 (2.28 to 7.18) 5.17 (1.23 to 21.8)	- 0.058 <0.001 0.025
Pelvic radiotherapy	No Yes	Ref. 0.55 (0.32 to 0.96)	- 0.037
Bladder V70Gy, percent		1.13 (1.04 to 1.22)	0.004

Kerns *et al* 2022

Polygenic risk score for blood pressure predicts for risk of hypertension but not radiotherapy toxicity

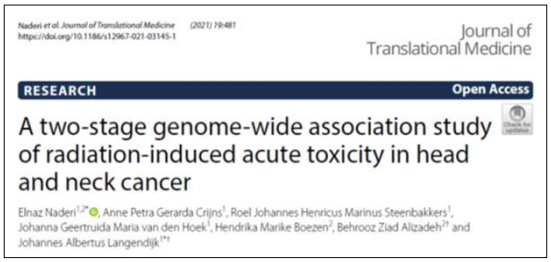
	Hypertension (N = 5,288)	Haematuria (N = 5,126)	Rectal bleeding (N = 4,592)
Odds radio	1.38	0.96	1.03
95% CI	1.31 to 1.46	0.87 to 1.06	0.95 to 1.11
***P*-value**	<0.001	0.41	0.51

The protective effect of ACEi use is not related to its effect on reducing blood pressure

- **First study showing a radioprotective effect of ACEi on bladder**
- **Mechanistic studies needed to understand how targeting the angiotensin pathway protects the bladder**

Kerns *et al* 2022

Head and neck cancer GWAS



Nadeni et al. Journal of Translational Medicine (2021) 19:481
https://doi.org/10.1186/s12967-021-03145-1

Journal of Translational Medicine

RESEARCH Open Access

A two-stage genome-wide association study of radiation-induced acute toxicity in head and neck cancer

Elnaz Nadeni[1,2*], Anne Petra Gerarda Crijns[1], Roel Johannes Henricus Marinus Steenbakkers[1], Johanna Geertruida Maria van den Hoek[1], Hendrika Marike Boezen[2], Behrooz Ziad Alizadeh[2†] and Johannes Albertus Langendijk[1*†]

www.nature.com/bjc British Journal of Cancer

ARTICLE OPEN

Genetics and Genomics

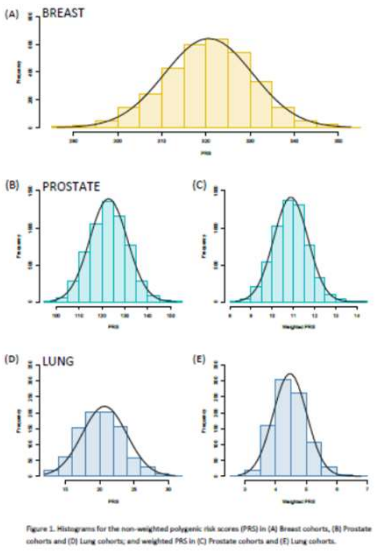
A genome-wide association study of radiotherapy induced toxicity in head and neck cancer patients identifies a susceptibility locus associated with mucositis

Line M. H. Schack[1,2✉], Elnaz Nadeni[3,4], Laura Fachal[5,6], Leila Dorling[7], Craig Luccarini[5], Alison M. Dunning[5], The Head and Neck Group of the Radiogenomics Consortium*, The Danish Head and Neck Cancer Group (DAHANCA)*, Enya H. W. Ong[8], Melvin L. K. Chua[9,10], Johannes A. Langendijk[3], Behrooz Z. Alizadeh[3,4], Jens Overgaard[1], Jesper Grau Eriksen[1,2], Christian Nicolaj Andreassen[1,2] and Jan Alsner[1]

- In 1,780 patients, an association between a locus on chromosome 5 and mucositis with a pooled OR for rs1131769 in meta-analysis of 1.95 (95% CI 1.48–2.41; p=4.34 × 10^{-16})
- In 1,298 patients, a region on 5q21.3 contained 16 SNPs was significant for xerostomia (p≤3.78× 10^{-9}). SNPs located within three genes (EFNA5, FBXL17, FER). In-silico functional analysis showed the genes may be involved in DNA damage response and co-expressed in minor salivary glands.

Radiotherapy is safe in patients with high polygenic risk scores for cancer

- Barnett *et al*, Int J Radiat Oncol Biol Phys, in press
- RGC and REQUITE cohorts
- 9,717 patients with breast (n=3,078), prostate (n=5,748) or lung (n=891) cancer
- PRS generated by summing cancer susceptibility risk alleles: 352 breast, 136 prostate, 24 lung
- Patients with increased polygenic predisposition to breast, prostate or lung cancer have no increased risk of early or late toxicity
- Secondary analyses identified rs138944387 associated with breast pain (OR=3.05; 95%CI 1.86- 5.01; P=1.09x10^{-5}) and rs17513613 with oedema (OR=0.94; 95%CI 0.92- 0.97; P=1.08 x1 0^{-5}).



Int J Radiat Oncol Biol Phys. 2022 Nov 1;114(3):494-501.

Patients with an increased polygenic risk of cancer have no increased risk of toxicity (STATlate)

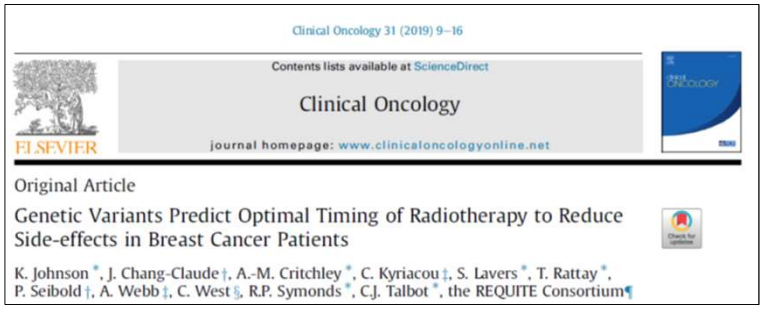
Cancer	Univariable analysis		Multivariable analysis	
	Beta (95%CI)	P	Beta (95%CI)	P
Breast n=3,133	PRS:-0.0002 (-0.0021, 0.0017)	0.83	PRS:-0.0005 (-0.0026, 0.0016)	0.67
Prostate n=4,861	PRS: -0.0003 (-0.0018, 0.0012)	0.70	PRS: -0.0002 (-0.0016, 0.0013)	0.82
	wPRS: -0.0074 (-0.0220, 0.0071)	0.31	wPRS: -0.0060 (-0.0203, 0.0083)	0.38
Lung n=621	PRS: -0.0123 (-0.0245, -0.0001)	**0.05**	PRS: -0.0139 (-0.0259, -0.002)	**0.02**
	wPRS: -0.0739 (-0.1453, -0.0025)	**0.04**	wPRS: -0.0847 (-0.1544, -0.015)	**0.02**

Breast covariates: breast volume, age, cardiovascular disease, smoker, tumour weight, cosmesis after surgery, post-operative haematoma or infection, breast volume receiving >107% prescribed dose, radiotherapy boost, acute toxicity, tamoxifen and chemotherapy use.
Prostate covariates: age, BED, use of androgen deprivation therapy, prior prostatectomy
Lung: study, gender, age, smoker, concurrent chemotherapy, radiotherapy technique, FEV1, V20 lung and V35 esophagus

Int J Radiat Oncol Biol Phys. 2022 Nov 1;114(3):494-501.

Treatment time and circadian genotype interact to influence the severity of radiotherapy side-effects

- Circadian rhythm affects biological processes including response to cancer treatment
- Evidence conflicts on whether treatment time affects risk of radiotherapy side-effects
- Johnson, Talbot *et al* showed an interactive effect of time and genotype of circadian rhythm genes on late toxicity after breast radiotherapy.



Treatment time and circadian genotype interact to influence the severity of radiotherapy side-effects

- Clinical and genotype data from 1690 REQUITE breast cancer patients with erythema (acute) and breast atrophy (two years post-radiotherapy) as primary endpoints.
- Local date times for each fraction were converted into solar times as continuous predictors.
- Genetic chronotype markers were included in logistic regressions to identify predictors of toxicity.
- Significant predictors for erythema included BMI, radiation dose and *PER3* genotype.
- Effect of treatment time on acute toxicity was inconclusive, with no interaction between time and genotype.

Webb, Talbot et al, EBioMedicine, in press

Treatment time and circadian genotype interact to influence the severity of radiotherapy side-effects

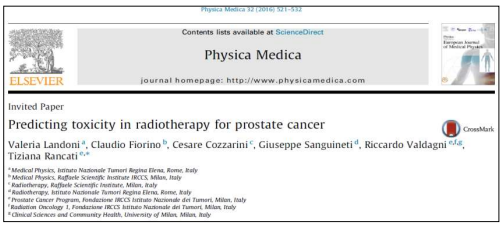
- BMI, radiation dose, surgery type, mean treatment time and SNPs in *CLOCK* (rs1801260), *PER3* (rs2087947) and *RASD1* (rs11545787) genes predicted for breast atrophy ($p<0{\cdot}05$).
- Significant interaction between time and the genotypes of the circadian rhythm genes (p=0.005-0.02), with peak time for toxicity determined by genotype.
- Late atrophy can be mitigated by selecting optimal treatment time according to genotypes of circadian genes.
- *PER3* rs2087947C/C genotypes should be treated in the morning; T/T in the afternoon).
- Estimated triple-homozygous patients (14%) reduce their chance of atrophy from 70% to 33% by treating in the morning as opposed to mid-afternoon.

Webb, Talbot et al, EBioMedicine, in press

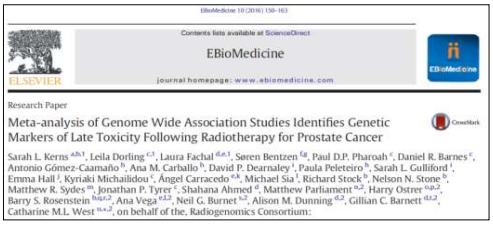
Unlikely to be radiosensitivity test alone

Late rectal bleeding following radiotherapy for prostate cancer

Clinical & dosimetric



Validated SNPs

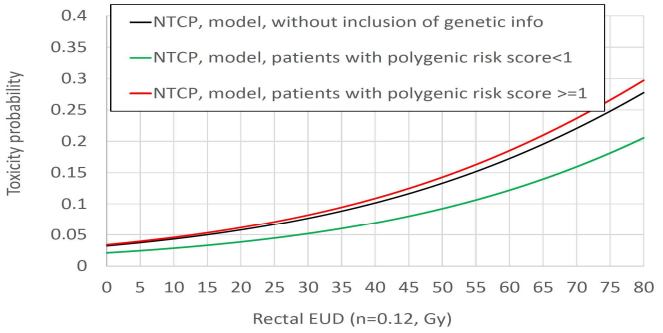


1,359 prostate cancer patients recruited into REQUITE
2-year follow-up

Tiziana Rancati & Petra Seibold

Effect of adding a polygenic risk score

NTCP model for late rectal bleeding ≥grade 2 at 2 years



Late rectal bleeding grade ≥ 2	
Rectal EUD (per 1Gy increase)	OR=1.06
Polygenic risk score*	**OR=1.34**
Cardiovascular diseases	OR=1.91
Abdominal surgery	OR=1.91

*3 SNPs

Tiziana Rancati & Petra Seibold

Risk prediction modelling

Finding new ways of adding genetic information to risk modelling

	Urinary Frequency ≥grade 2
AUC PRS	0.65
AUC PRSi	0.78


Radiotherapy and Oncology 159 (2021) 241–248

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

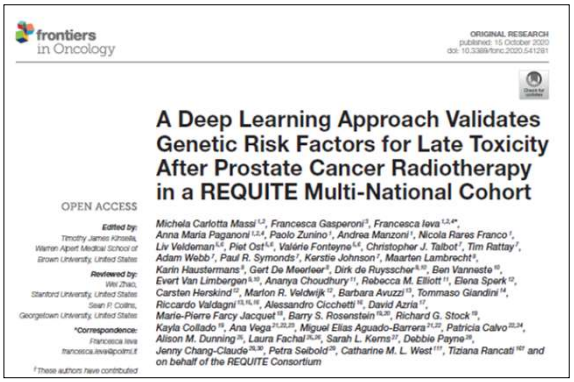
Development of a method for generating SNP interaction-aware polygenic risk scores for radiotherapy toxicity

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], Valérie Fonteyne [d,e], Christopher J. Talbot [f], Tim Rattay [f], Adam Webb [f], Kerstie Johnson [f], Maarten Lambrecht [g], Karin Haustermans [g], Gert De Meerleer [g], Dirk de Ruysscher [h,i], Ben Vanneste [j], Evert Van Limbergen [h,i], Ananya Choudhury [l], Rebecca M. Elliott [l], Elena Sperk [k], Marlon R. Veldwijk [k], Carsten Herskind [k], Barbara Avuzzi [l], Barbara Noris Chiorda [l], Riccardo Valdagni [l,m,n], David Azria [o], Marie-Pierre Farcy-Jacquet [p], Muriel Brengues [q], Barry S. Rosenstein [q,r], Richard G. Stock [q], Ana Vega [s,t,u], Miguel E. Aguado-Barrera [s,t], Paloma Sosa-Fajardo [s,t,v], Alison M. Dunning [w], Laura Fachal [w,x], Sarah L. Kerns [y], Debbie Payne [z], Jenny Chang-Claude [aa,ab], Petra Seibold [aa], Catharine M.L. West [l,2], Tiziana Rancati [n,2], REQUITE Consortium [3]

- 1,401 REQUITE prostate patients
- 43 published SNPs
- PRS = sum of risk alleles
- PRSi= accounts for co-inherited SNPs and epistasis

Deep learning approach to validate SNPs as predictors of radiotherapy toxicity

- 1,401 REQUITE prostate patients
- Deep Sparse AutoEncoders trained to recognise features (SNPs) identifying patients with no toxicity and tested on a independent mixed population of patients without and with toxicity
- 24 of the 43 SNPs that were associated with the toxicity endpoints were validated as identifying patients with toxicity
- Twenty of the 24 SNPs were associated with the same toxicity endpoint as reported in the literature


frontiers in Oncology

ORIGINAL RESEARCH

A Deep Learning Approach Validates Genetic Risk Factors for Late Toxicity After Prostate Cancer Radiotherapy in a REQUITE Multi-National Cohort

OPEN ACCESS

Michela Carlotta Massi, Francesca Gasperoni, Francesca Ieva, Anna Maria Paganoni, Paolo Zunino, Andrea Manzoni, Nicola Rares Franco, Liv Veldeman, Piet Ost, Valérie Fonteyne, Christopher J. Talbot, Tim Rattay, Adam Webb, Paul R. Symonds, Kerstie Johnson, Maarten Lambrecht, Karin Haustermans, Gert De Meerleer, Dirk de Ruysscher, Ben Vanneste, Evert Van Limbergen, Ananya Choudhury, Rebecca M. Elliott, Elena Sperk, Carsten Herskind, Marlon R. Veldwijk, Barbara Avuzzi, Tommaso Giandini, Riccardo Valdagni, Alessandro Cicchetti, David Azria, Marie-Pierre Farcy Jacquet, Barry S. Rosenstein, Richard G. Stock, Kayla Collado, Ana Vega, Miguel Elias Aguado-Barrera, Patricia Calvo, Alison M. Dunning, Laura Fachal, Sarah L. Kerns, Debbie Payne, Jenny Chang-Claude, Petra Seibold, Catharine M. L. West, Tiziana Rancati and on behalf of the REQUITE Consortium

Summary

- Genetic will *contribute* to an individual patient's risk of toxicity
- GWAS can identify common genetic variants that increase risk of toxicity
- GWAS data can be used to investigate polygenic risk scores for other traits
- Future toxicity risk prediction is likely to involve models include dosimetric, clinical and genetic information
- There are likely to be multiple models for multiple endpoints

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