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Genetic risk modeling using machine learning to predict radiotherapy complications and identify key biological correlates

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Acknowledgement

GWAS Study
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Part 1. Genome-wide association studies

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Background

- Our goal in GWAS is to predict how the risk of radiation toxicity varies between patients, based on germ line genome characteristics
- Previous single-SNP models suffer from multiple-testing correction due to a large number of SNPs being evaluated
  - Important SNPs may fail to achieve genome-wide significance
- Therefore, we have taken a **many-SNP** approach to developing predictive models, using machine learning methods

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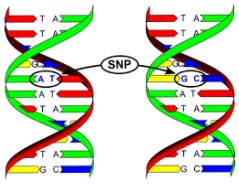
Single nucleotide polymorphisms (SNPs)



https://www.tubascan.eu

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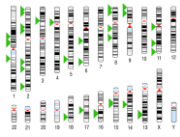
Genome-wide association studies (GWAS)

Patient 1 …CAAGGTA…
Patient 2 …CAATGTA…
Patient 3 …CAATGTA…
Patient 4 ...CAAGGTA…

Single Nucleotide Polymorphism (SNP) is genetic variation at **one location** in a DNA sequence.



Genome-Wide Association Studies (GWAS) find associations between a disease and such variations across **the whole genome**.

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Coding

- Wild type homozygous: 0
- Heterozygous: 1
- Mutant homozygous: 2

- Coded as the number of rare alleles

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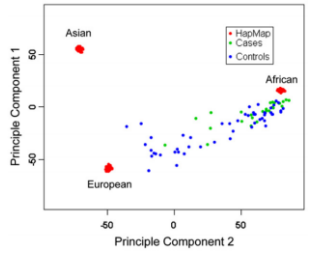
Population structure



Kerns 2010, Int. Rad. Onc. Biol. Phys

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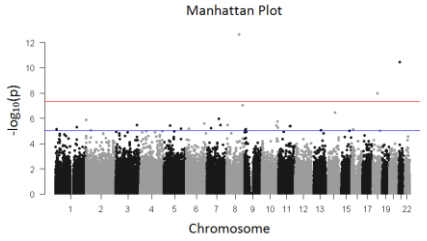
Statistical analysis



❖ Genome-wide significance level = 5×10^{-8}

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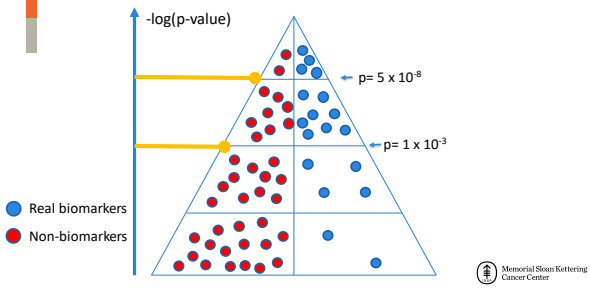
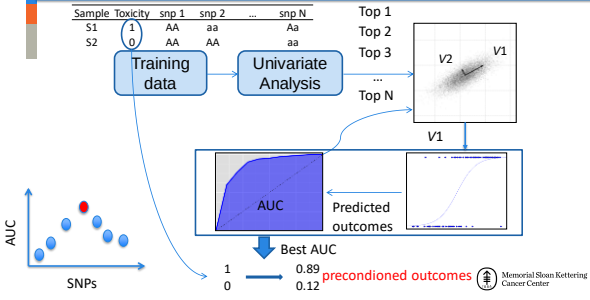
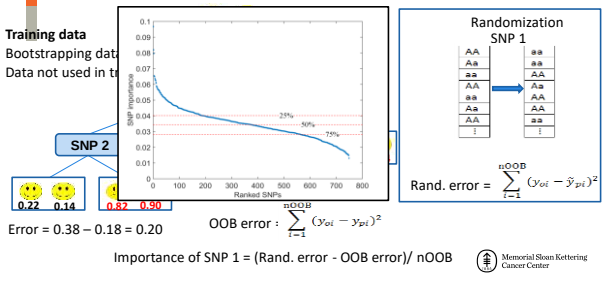
Filtering



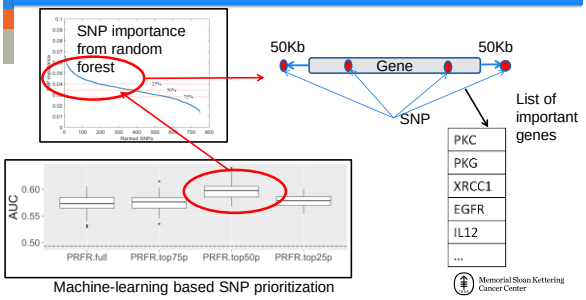
Preconditioning



SNP importance



A subset of features



Machine-learning based SNP prioritization

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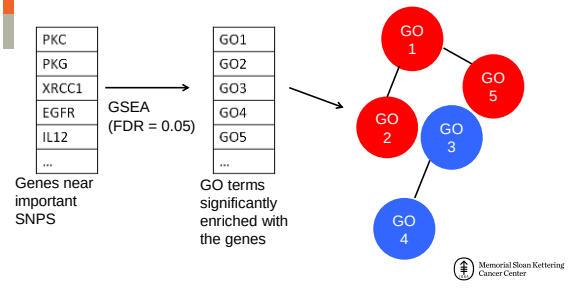
Gene ontology analysis



Genes near important SNPS

GO terms significantly enriched with the genes

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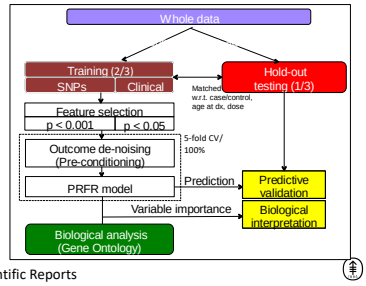
Preconditioning Random Forest Regression (PRFR)



Oh et al., 2017. Scientific Reports

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Data

- 368 patients with prostate cancer
  - DNA was genotyped using Affymetrix genome wide array (v6.0)
- Quality control
  - Missing rate > 5% of samples
  - MAF < 5%
  - Hardy-Weinberg equilibrium (p-value < 10^{-5})
  - 613,496 SNPs remained

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Rectal bleeding

Oh et al., 2017. Scientific Reports

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Data preprocessing

- Outcome: rectal bleeding
  - RTOG ≤ 1 (coded 0) vs RTOG ≥ 2 (coded 1)
- Data split: rectal bleeding
  - Training dataset
    - 243 samples
    - 49 events
    - 749 SNPs (p< 0.001; Chi-square test)
  - Validation dataset
    - 122 samples
    - 25 events
- 5-fold cross validation with 100 iterations

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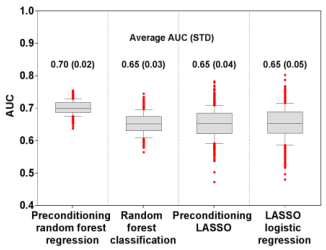
Performance



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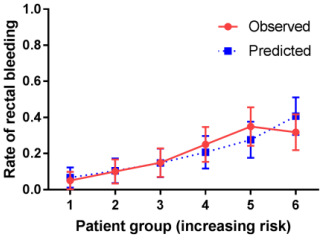
Performance



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Biological analysis

#	GO Processes/Genes
1	Regulation of ion transport CACNA1D,CCL13,DPP6,GCK,GNB4,GPR63,HOMER1,IL1RAPL1,JDP2, KCNIP4,KCNJ6,NLGN1,NOS1AP,PDE4D,PRKCB,PRKG1,VDR
5	Regulation of transmembrane transporter activity CACNA1D,GNB4,HOMER1,NLGN1,NOS1AP,PDE4D,PRKCB,PRKG1

GASTROENTEROLOGY 2005;129:591–608

Epidermal Growth Factor Partially Restores Colonic Ion Transport Responses in Mouse Models of Chronic Colitis

DECLAN F. McCOLE, GERHARD ROGLER, NISSI VARKI, and KIM E. BARRETT
Department of Medicine, School of Medicine, University of California, San Diego, San Diego, California

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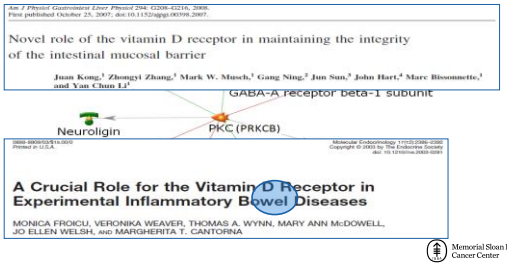
Protein-protein network



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Erectile dysfunction toxicity

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Data preprocessing

- Outcome: erectile dysfunction
  - SHIM ≤ 7 (coded 1) vs SHIM ≥ 16 (coded 0)
- Data split
  - Training dataset
    - 157samples
    - 88 events
    - 367 SNPs (p< 0.001; Chi-square test)
  - Validation dataset
    - 79 samples
    - 45 events

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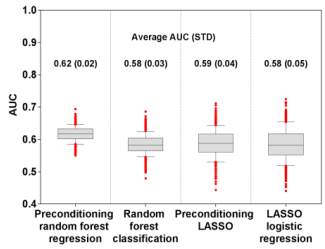
Performance



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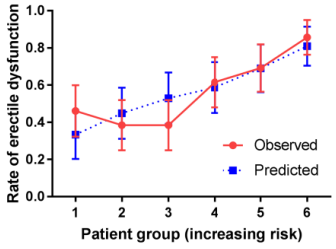
Performance



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Biological analysis

Ranking	GO Processes	FDR
1	negative regulation of heart contraction	8.376E-10
2	negative regulation of blood circulation	2.180E-08
3	neutrophil chemotaxis	5.026E-08
4	neutrophil migration	5.883E-08
5	granulocyte chemotaxis	9.684E-08
6	granulocyte migration	1.300E-07
7	positive regulation of locomotion	2.631E-07
8	regulation of muscle system process	5.510E-07
9	regulation of muscle contraction	5.510E-07
10	positive regulation of cell migration	8.960E-07

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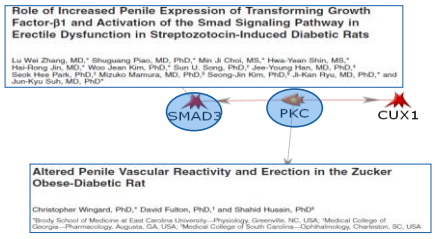
Protein-protein network



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Genitourinary Toxicity

Lee et al., 2018. Int J Rad Oncol Biol Phys

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GU symptoms

Symptom Category*	Symptom Name	Training Set Size	Testing Set Size	Event Rate (%)	Modeled?
Irritative (Storage)	Frequency	119	60	23	O
	Urgency	161	81	16	O
	Nocturia	111	56	17	O
Obstructive (Voiding)	Intermittency	164	82	10	X
	Weak Stream	149	75	18	O
	Straining	196	98	5	X
Post-micturition	Incomplete Emptying	168	84	10	X

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GU modeling

Symptom Name	Training Set Size	Event rate	# SNPs p<0.001	#clinical p<0.05	PRFR Performance	
					AUC	P-value
Frequency	119	0.23	539	0	0.64	0.06
Urgency	161	0.16	758	0	0.53	0.38
Nocturia	111	0.17	977	1	0.55	0.33
Weak stream	149	0.18	823	0	0.70	0.01

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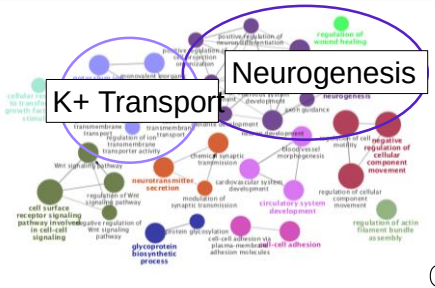
Gene ontology analysis



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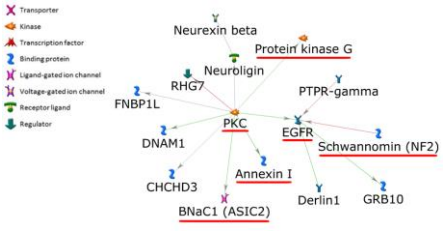
Protein-protein network



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Summary

- We developed a promising method using whole-genome data for deriving predictive risk models for predicting late radiation-induced toxicites
- SNP -> Gene -> Pathway analysis
- Found that biological correlates are tissue specific
- Other studies
  - Secondary contralateral breast cancer
  - Fatigue in breast cancer
  - Weight gain in breast cancer

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Part 2. Radiogenomics

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Data

- **Imaging data:**
  - Pre-treatment CT scans in head and neck cancer were downloaded from the TCIA
  - 77 CT scans were analyzed
  - Using CERR, 104 radiomic features were evaluated
    - Apte, 2018. Medical Physics
  - Feature stability test
  - Volume dependent features were removed
  - 67 features were analyzed

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Data

- **Biological data:**
  - **Recurrent gene mutations**
    - cBioPortal (https://www.cbioportal.org/)
  - **Tumor subtypes**
    - Broad Institute FireBrowse (http://firebrowse.org/)
  - **Immune infiltrates**
    - Thorsson, 2018. Immunity
  - **HPV status**
    - Nulton, 2017. Oncotarget

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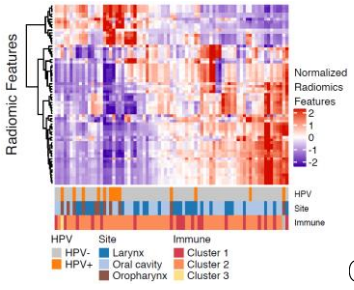
Clustering



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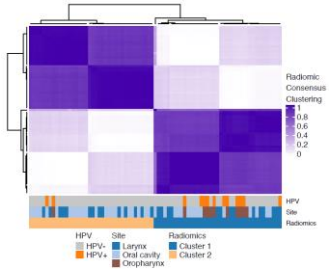
Consensus clustering



Subsite	Cluster 1	Cluster 2
Oral cavity	15	23
Larynx	14	14
Oropharynx	10	1
P-value	**0.0096**	

HPV	Cluster 1	Cluster 2
Positive	11	2
Negative	28	36
P-value	**0.0127**	

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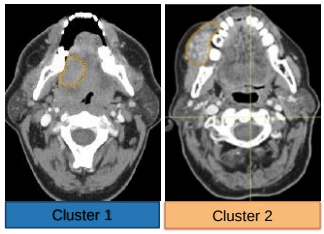
Representative scans



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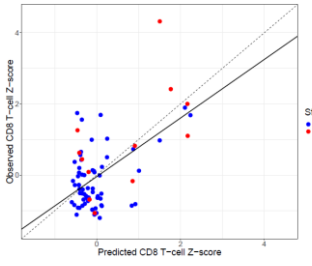
CD8 Prediction using Random Forest



	R^2	P-value
All	0.3	**<0.0001**
HPV+	0.36	**0.0405**
HPV-	0.16	**0.0012**

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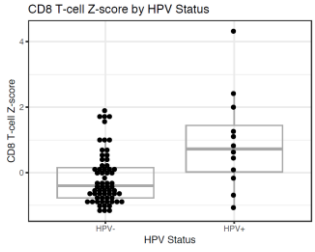
HPV status vs CD8 T-cell



P-value = **0.0061**

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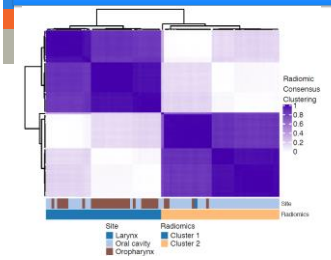
Validation



Subsite	Cluster 1	Cluster 2
Oral cavity	14	37
Larynx	0	1
Oropharynx	27	4
P-value	1.3×10^{-7}	

HPV	Cluster 1	Cluster 2
Positive	24	3
Negative	17	39
P-value	4.0×10^{-7}	

- 83 cases (MSKCC)
- Oral cavity: 51, Larynx: 1, Oropharynx: 31

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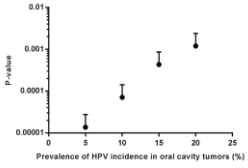
Difference of HPV status

- **Sensitivity test**
  - Randomly select 5%, 10%, 15%, and 20% of samples in oral cavity tumors
  - Assign them to HPV-positive
  - Iterate 1000 times



- **Prevalence of HPV incidence: 5%**
  P=1.4×10^{-5} (95% CI: 1.3×10^{-5}-1.5×10^{-5})

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Summary

- Found clearly separable radiomic clusters
- The differences in subsite and HPV status between the two radiomic clusters were statistically significant
- Built a machine learning model to predict CD8 T-cell
- Validation using an independent dataset

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Thank you

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