MANCHESTER 1824

The University of Manchester

The Role of Genetics in Personalised Radiotherapy

Catharine West

The University of Manchester

16th April 2015

15-18 April 2015, Geneva, Switzerland

Organisers

IASLC International Association for the Study of Lung Cancer

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

Partners

ESTRO European Society for RADIOTHERAPY & ONCOLOGY

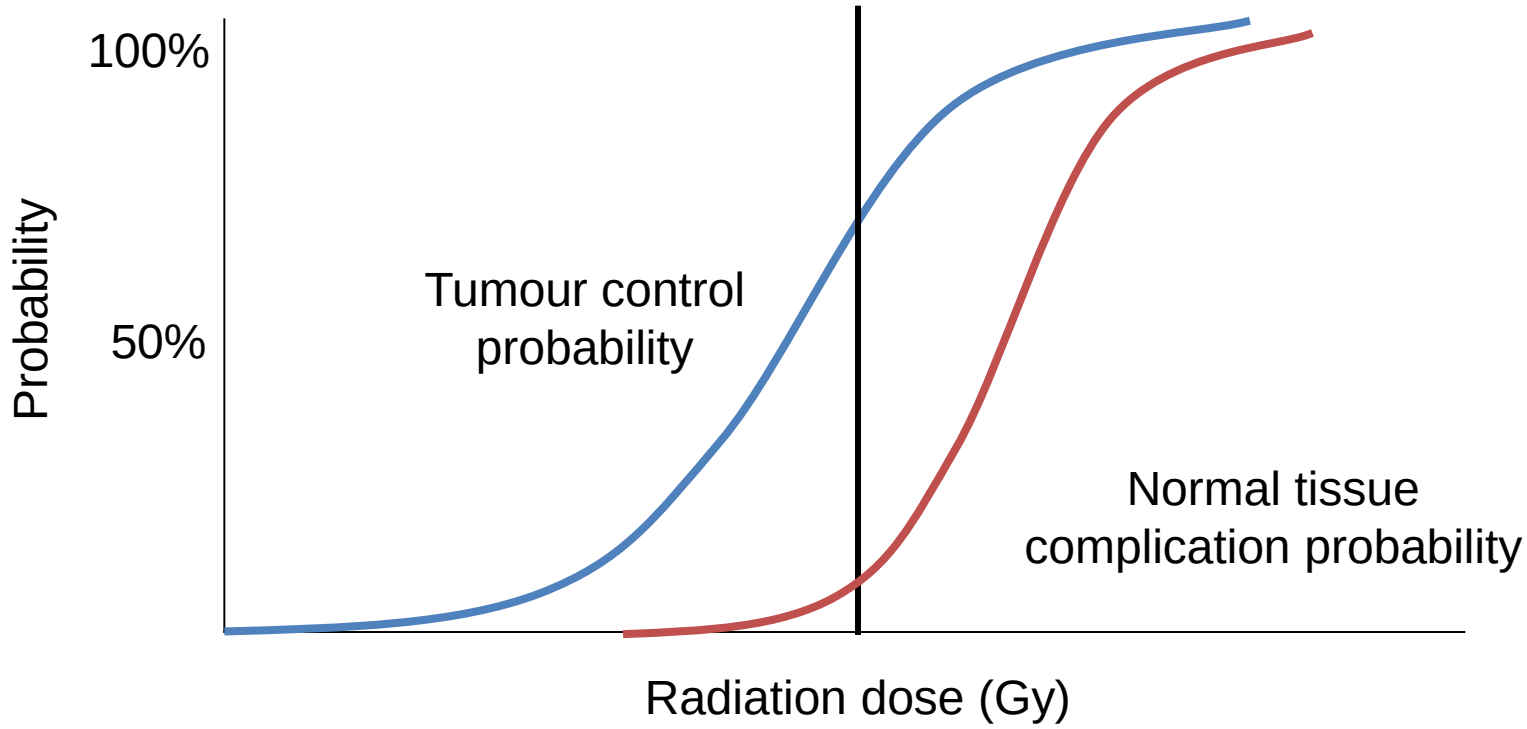
European Society of Thoracic Surgeons 1993

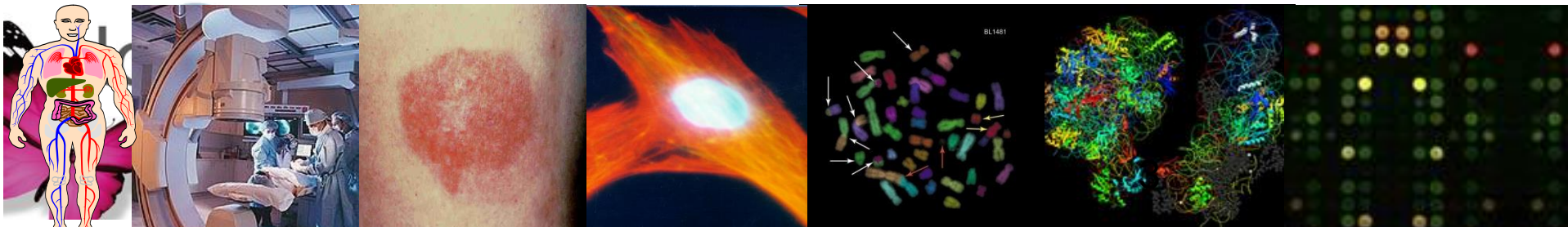
etop Information | Research

Disclosure slide

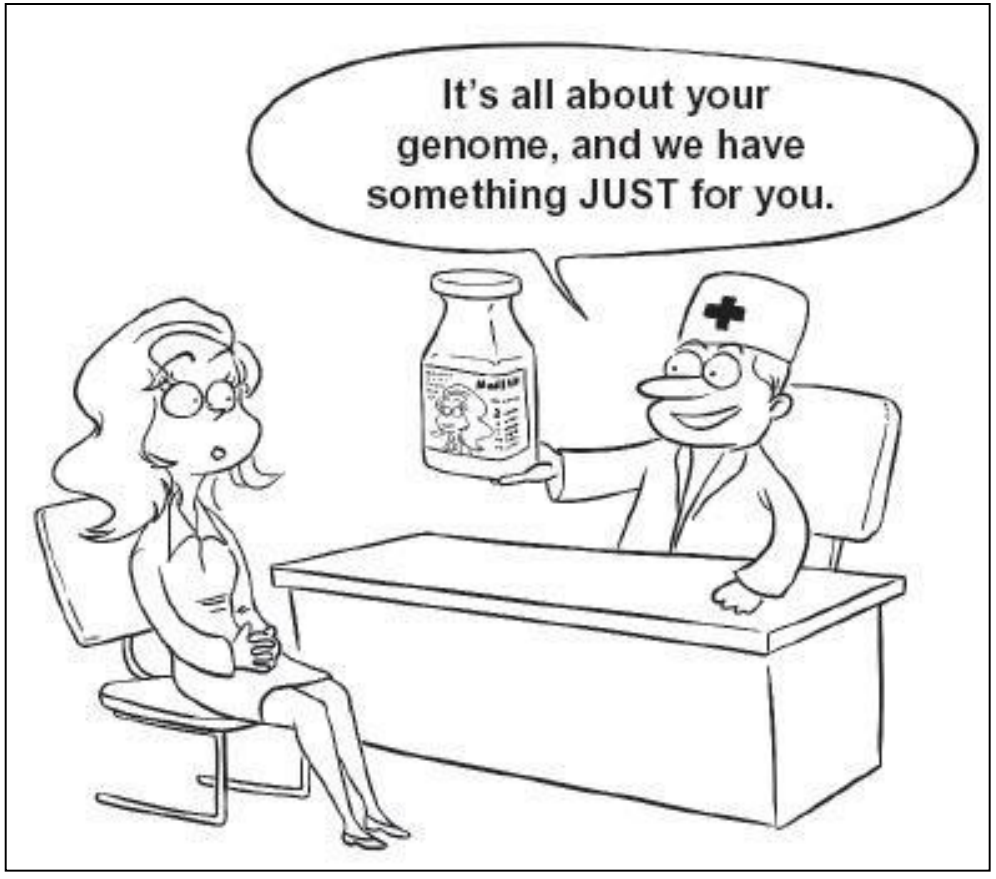
- No financial interest in, or arrangement with, a company whose products or services are discussed in the lecture
- No financial interest in, or arrangement with, a competing company
- No other financial connections that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated

Personalising radiotherapy to optimise therapeutic ratios





Deciding the right dose for individual patients requires biological optimisation



Breast cancer risk test devised in 77-gene analysis

By James Gallagher
Health editor, BBC News website

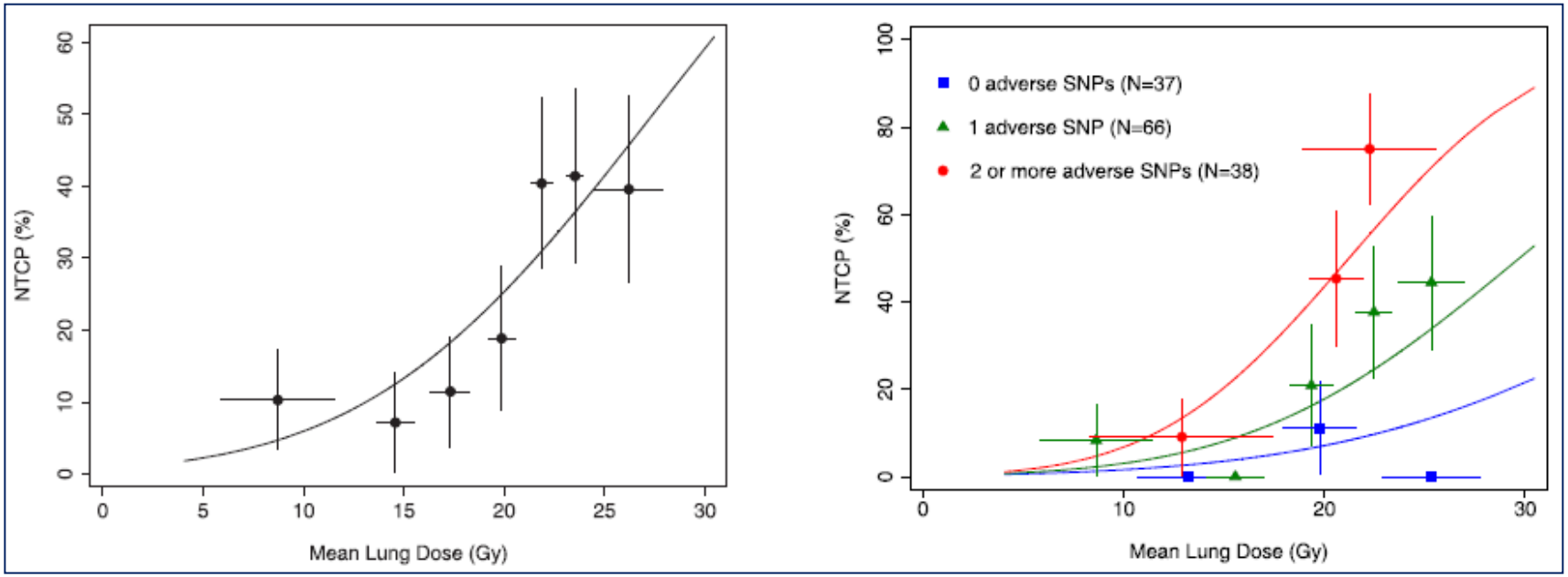
9 April 2015 | Health

Mavaddat et al 2015 JNCI 107(5)

Author	n	Toxicity	SNPs	HR
Pu 2014	421	Toxicity	11,930 SNPs	sig
Zhang 2014	301	Lung injury	21 SNPs	3.59
Wen 2014	362	Pneumonitis	8 SNPs	2.97
Li 2014	168	Pneumonitis	*APEX1*	5.98
Kelsey 2013	39	Lung perfusion	33 SNPs	sig
Pang 2013	271	Pneumonitis	*HSPB1*	sig
Xiong 2013	362	Pneumonitis	*ATM*	0.49
Yin 2012				1.96
Niu 2012				2.29
Guerra 2012				5.46
Voets 2012				ns
Tucker 2012				sig
Mak 2012				0.22
Kelsey 2012				sig
Guerra 2011	301	Esophagitis	*HSPB1*	0.29
Yin 2011	165-228	Pneumonitis	*RAD51, XRCC1, APEX1, LIG4*	0.35-3.61
Yang 2011	253	Pneumonitis	*TP53, ATM*	2.62-6.17
Hildebrandt 2010	173	Pneumonitis	6 SNPs	69.4
Zhang 2010	253	Pneumonitis	*ATM, TP53*	sig
Yuan 2009	164	Pneumonitis	*TGFB1*	0.39

- ~20 studies
- 39 – 421 patients
- Under powered
- No correction for multiple testing

The potential for using genetic analysis



Tucker et al 2013; Int J Radiat Oncol Biol Phys 85:252

16 SNPs in:
XRCC1, XRCC3, APEX1, MDM2, TGFB1,
TNF, TNFR, MTHFR, MTRR, VEGF

Genome wide association studies

- No assumptions about which genes are important
- Common variants with small effects
- Breast cancer GWAS (>120,000 cases & controls) identified 94 variants. The top 1% of the polygenic risk score have a 3-fold increased risk of breast cancer.
- Prostate cancer GWAS (~25,000 cases & 25,000 controls) identified 74 variants responsible. The top 1% of the risk distribution have a 4.7-fold increased risk prostate cancer.

Independent validation of genes and polymorphisms reported to be associated with radiation toxicity: a prospective analysis study

Gillian C Barnett, Charlotte E Coles, Rebecca M Elliott, Caroline Baynes, Craig Luccarini, Don Conroy, Jennifer S Wilkinson, Jonathan Tyrer, Vivek Misra, Radka Platte, Sarah L Gulliford, Matthew R Sydes, Emma Hall, Søren M Bentzen, David P Dearnaley, Neil G Burnet, Paul D P Pharoah, Alison M Dunning, Catharine M L West

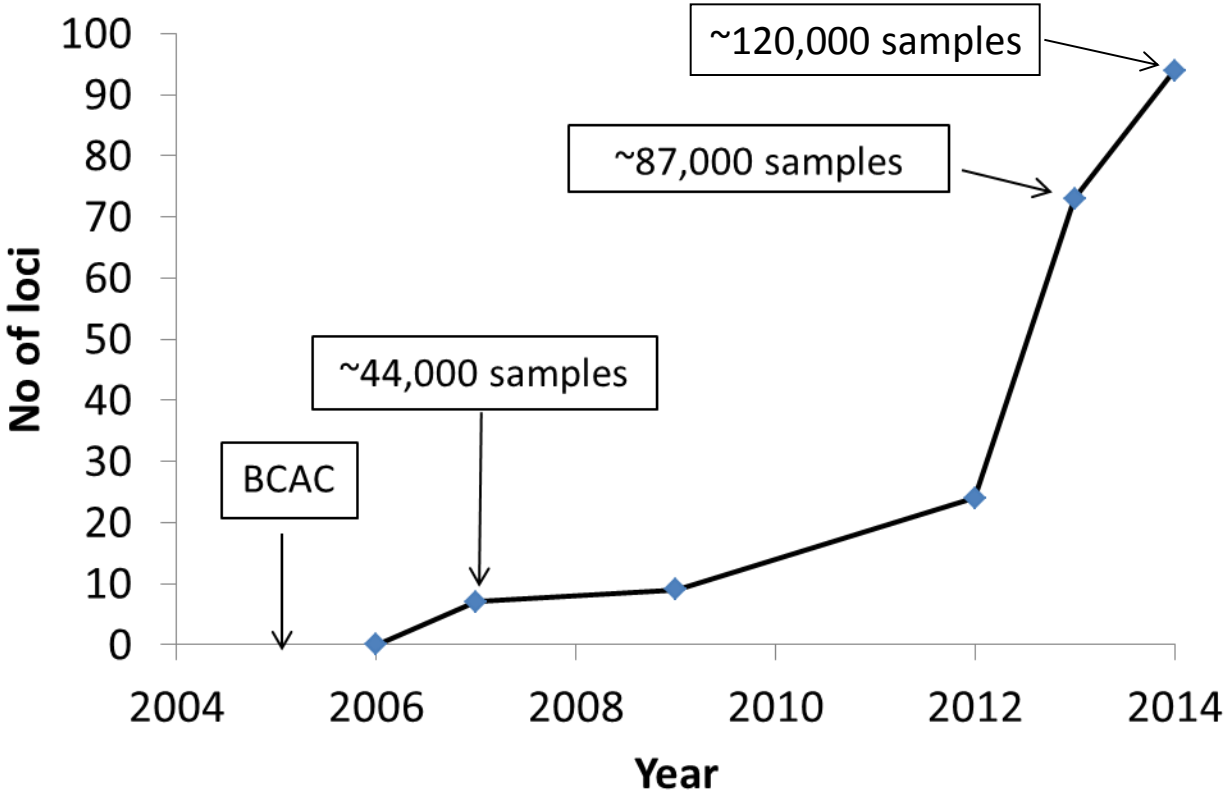
Summary

Background Several studies have reported associations between radiation toxicity and single nucleotide polymorphisms (SNPs) in candidate genes. Few associations have been tested in independent validation studies. This prospective study aimed to validate reported associations between genotype and radiation toxicity in a large independent dataset.

Lancet Oncol 2012; 13: 65-77
Published Online
December 13, 2011
DOI:10.1016/S1470-

- 92 SNPs in 1,613 radiotherapy patients
- Previously reported associations were not replicated, showing published SNPs do not *individually* exert a clinically relevant effect
- Effect size is small

Need for a consortium approach



The Radiogenomics Consortium

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 5, pp. 1295–1296, 2010

0360-3016/10/$–see front matter

doi:10.1016/j.ijrobp.2009.12.017

REPORT

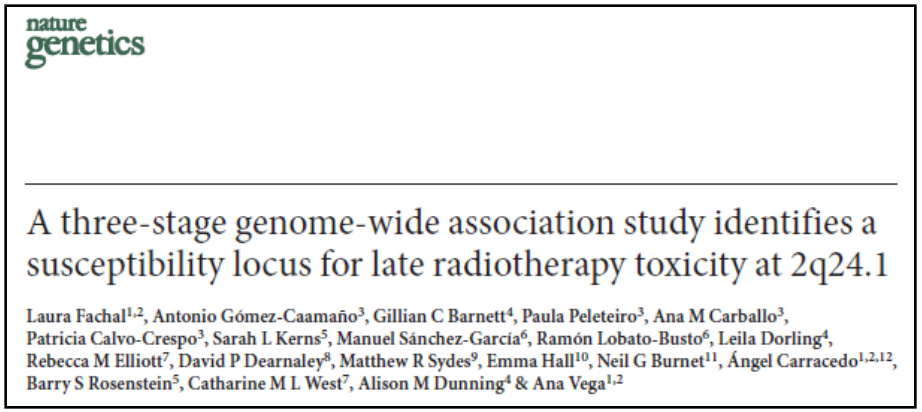
ESTABLISHMENT OF A RADIOGENOMICS CONSORTIUM

CATHARINE WEST* AND BARRY S. ROSENSTEIN† ON BEHALF OF: JAN ALSNER, DAVID AZRIA, GILLIAN BARNETT, ADRIAN BEGG, SØREN BENTZEN, NEIL BURNET, JENNY CHANG-CLAUDE, ERIC CHUANG, CHARLOTTE COLES, KIM DE RUYCK, DIRK DE RUYSSCHER, ALISON DUNNING, REBECCA ELLIOTT, LAURA FACHAL, JANET HALL, KARIN HAUSTERMANS, CARSTEN HERSKIND, TOBIAS HOELSCHER, TAKASHI IMAI, MAYUMI IWAKAWA, DON JONES, CECILIA KULICH ON BEHALF OF EQUAL-ESTRO, JAN-HANS LANGENDIJK, PETER O'NEILL, MAHMUT OZSAHIN, MATTHEW PARLIAMENT, ANDRZEJ POLANSKI, BARRY ROSENSTEIN, DANIELA SEMINARA, PAUL SYMONDS, CHRIS TALBOT, HUBERT THIERENS, ANA VEGA, CATHARINE WEST, & JOHN YARNOLD.

* School of Cancer and Imaging Sciences, The University of Manchester, The Chrisite Hospital, Wilmslow Road, Withington, Manchester, M20 4BX, United Kingdom and † Department of Radiation Oncology, Mount Sinai School of Medicine, New York, NY

184 members from 106 institutions in 23 countries

GWAS identify novel genes

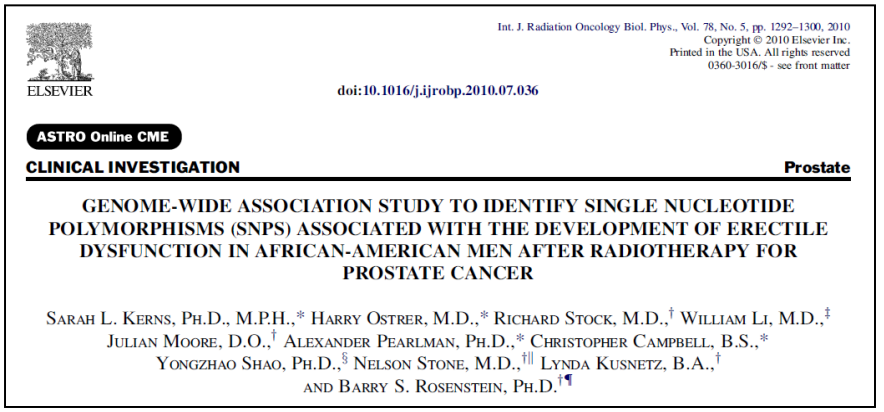


nature genetics

A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1

Laura Fachal[1,2], Antonio Gómez-Caamaño[3], Gillian C Barnett[4], Paula Peleteiro[3], Ana M Carballo[3], Patricia Calvo-Crespo[3], Sarah L Kerns[5], Manuel Sánchez-García[6], Ramón Lobato-Busto[6], Leila Dorling[4], Rebecca M Elliott[7], David P Dearnaley[8], Matthew R Sydes[9], Emma Hall[10], Neil G Burnet[11], Ángel Carracedo[1,2,12], Barry S Rosenstein[5], Catharine M L West[7], Alison M Dunning[4] & Ana Vega[1,2]

Gene involved in muscle cell regeneration with overall toxicity



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Int. J. Radiation Oncology Biol. Phys., Vol. 78, No. 5, pp. 1292–1300, 2010
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0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.07.036

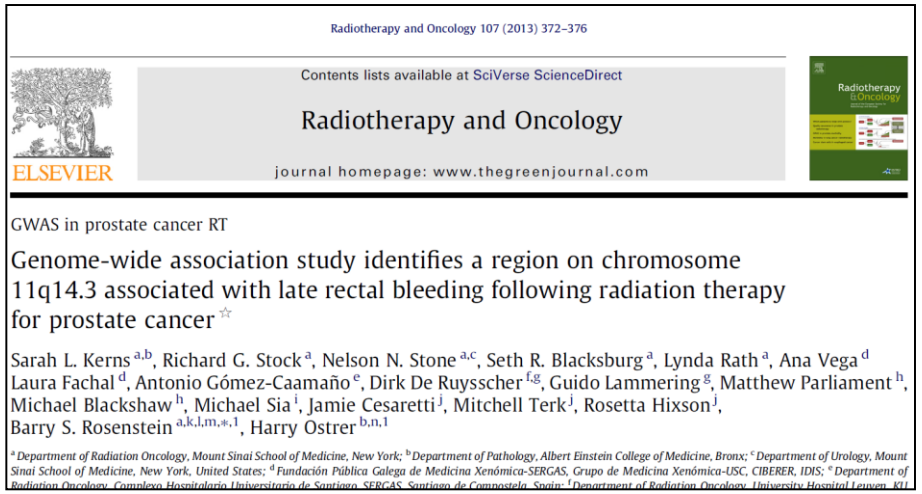
ASTRO Online CME

CLINICAL INVESTIGATION — Prostate

GENOME-WIDE ASSOCIATION STUDY TO IDENTIFY SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) ASSOCIATED WITH THE DEVELOPMENT OF ERECTILE DYSFUNCTION IN AFRICAN-AMERICAN MEN AFTER RADIOTHERAPY FOR PROSTATE CANCER

Sarah L. Kerns, Ph.D., M.P.H.,* Harry Ostrer, M.D.,* Richard Stock, M.D.,† William Li, M.D.,‡ Julian Moore, D.O.,† Alexander Pearlman, Ph.D.,* Christopher Campbell, B.S.,* Yongzhao Shao, Ph.D.,§ Nelson Stone, M.D.,†‖ Lynda Kusnetz, B.A.,† and Barry S. Rosenstein, Ph.D.†¶

Gene involved in erectile function with erectile dysfunction



Radiotherapy and Oncology 107 (2013) 372–376

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

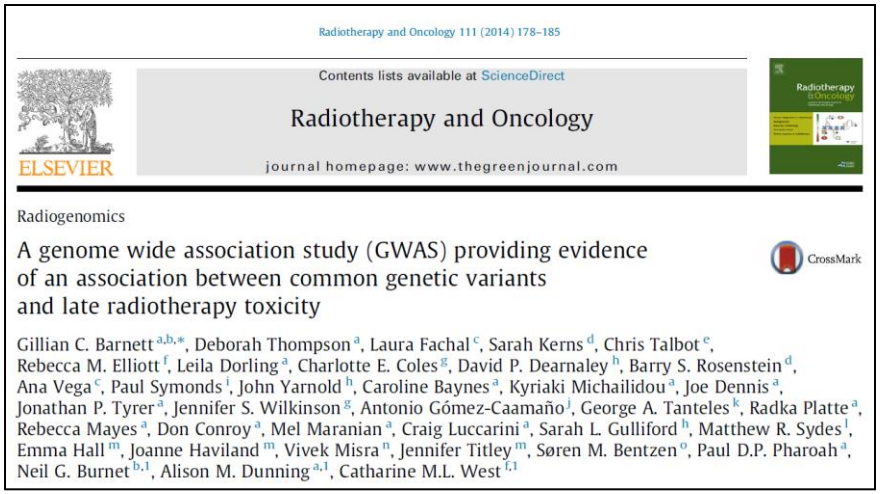
GWAS in prostate cancer RT

Genome-wide association study identifies a region on chromosome 11q14.3 associated with late rectal bleeding following radiation therapy for prostate cancer ☆

Sarah L. Kerns[a,b], Richard G. Stock[a], Nelson N. Stone[a,c], Seth R. Blacksburg[a], Lynda Rath[a], Ana Vega[d] Laura Fachal[d], Antonio Gómez-Caamaño[e], Dirk De Ruysscher[f,g], Guido Lammering[g], Matthew Parliament[h], Michael Blackshaw[h], Michael Sia[i], Jamie Cesaretti[j], Mitchell Terk[j], Rosetta Hixson[j], Barry S. Rosenstein[a,k,l,m,*,1], Harry Ostrer[b,n,1]

[a] Department of Radiation Oncology, Mount Sinai School of Medicine, New York; [b] Department of Pathology, Albert Einstein College of Medicine, Bronx; [c] Department of Urology, Mount Sinai School of Medicine, New York, United States; [d] Fundación Pública Galega de Medicina Xenómica-SERGAS, Grupo de Medicina Xenómica-USC, CIBERER, IDIS; [e] Department of Radiation Oncology, Complexo Hospitalario Universitario de Santiago, SERGAS, Santiago de Compostela, Spain; [f] Department of Radiation Oncology, University Hospital Leuven, KU

Gene involved in regulation of angiogenesis and rectal bleeding



Radiotherapy and Oncology 111 (2014) 178–185

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

Radiogenomics

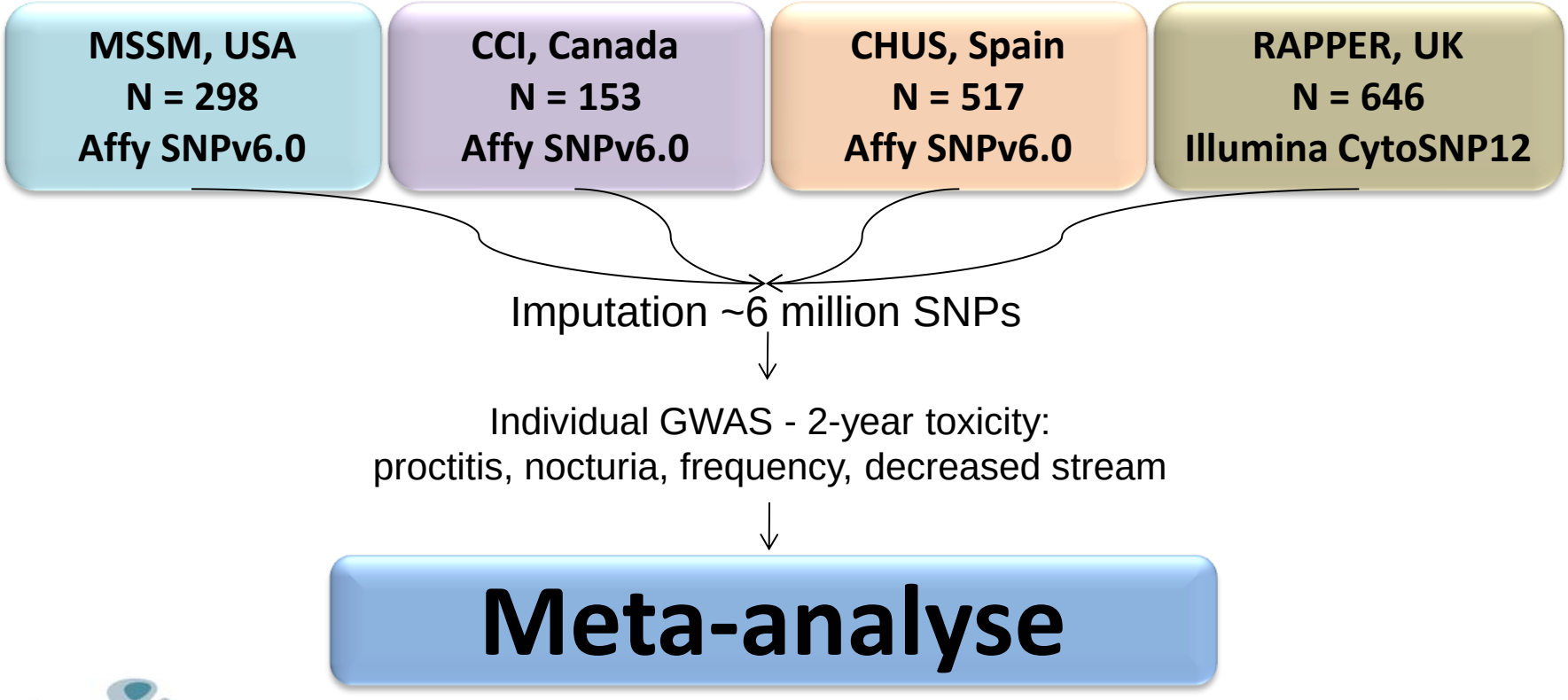
A genome wide association study (GWAS) providing evidence of an association between common genetic variants and late radiotherapy toxicity

CrossMark

Gillian C. Barnett[a,b,*], Deborah Thompson[a], Laura Fachal[c], Sarah Kerns[d], Chris Talbot[e], Rebecca M. Elliott[f], Leila Dorling[a], Charlotte E. Coles[g], David P. Dearnaley[h], Barry S. Rosenstein[d], Ana Vega[c], Paul Symonds[i], John Yarnold[h], Caroline Baynes[a], Kyriaki Michailidou[a], Joe Dennis[a], Jonathan P. Tyrer[a], Jennifer S. Wilkinson[g], Antonio Gómez-Caamaño[j], George A. Tanteles[k], Radka Platte[a], Rebecca Mayes[a], Don Conroy[a], Mel Maranian[a], Craig Luccarini[a], Sarah L. Gulliford[h], Matthew R. Sydes[l], Emma Hall[m], Joanne Haviland[m], Vivek Misra[n], Jennifer Titley[m], Søren M. Bentzen[o], Paul D.P. Pharoah[a], Neil G. Burnet[b,1], Alison M. Dunning[a,1], Catharine M.L. West[f,1]

Gene involved in smooth muscle contraction and rectal incontinence

Radiogenomics Consortium prostate GWAS meta-analysis



Meta-analysis of 1,638 patients

- Identified three SNPs:
  - rs17599026 with urinary frequency (OR 3·17, 95%CI 2·10-4·77, p= $3{\cdot}3 \times 10^{-8}$)
  - rs7720298 with decreased urine stream (OR 2·71, 95%CI 1.90-3·85, p=$3{\cdot}4 \times 10^{-8}$)
  - rs11230328 with overall toxicity (Beta 0·31, 95%CI 0·21-0·40, p=$6{\cdot}8 \times 10^{-10}$)

- Heterogeneous radiotherapy cohorts can be pooled/meta-analysed to increase sample size and identify low-penetrance genetic variants associated with radiotherapy toxicity

Kerns, Fachal, Dorling, Barnett, Dunning, Rosenstein et al

How many SNPs?

- Sufficient for a useful polygenic risk score
- 10 alleles with a RR=1.15
- 5% of cases in the sensitive tail of this distribution would have a RR>2 for developing a specific toxicity endpoint
- If the prevalence of an endpoint is not low, say 0.2, a study of 10,000 patients has >99% power to detect a signature

Bentzen & Pharaoh

Author	n	Toxicity	SNPs	HR
Pu 2014	421	Toxicity	11,930 SNPs	sig
Zhang 2014	301	Lung injury	21 SNPs	3.59
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Pang 2013	271	Pneumonitis	*HSPB1*	sig
Xiong 2013	362	Pneumonitis	*ATM*	0.49
Yin 2012	261	Pneumonitis	*LIG4*	1.96
Niu 2012	307	Pneumonitis	*TGFB1*	2.29
Guerra 2012	198	Esophagitis	*TGFB1*	5.46
Voets 2012	209	Dyspnoea	*TGFB1*	ns
Tucker 2012	141	Pneumonitis	5 SNPs	sig
Mak 2012	136	Pneumonitis	*MTHFR*	0.22
Kelsey 2012	39	Lung perfusion	*TGFB1*	sig
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Yuan 2009	164	Pneumonitis	*TGFB1*	0.39

OncoArray

- Illumina Infinium® OncoArray-500K BeadChips
- 499,170 markers
- Specific variants for 5 cancers
- ~45,000 lung cancer variants

Clinical Oncology xxx (2014) 1–4

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

The REQUITE Project: Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-effects and Improve Quality of Life in Cancer Survivors

C. West *, D. Azria †, J. Chang-Claude ‡, S. Davidson §, P. Lambin ¶, B. Rosenstein ||, D. De Ruysscher **, C. Talbot ††, H. Thierens ‡‡, R. Valdagni §§, A. Vega ¶¶, M. Yuille *

1. Perform a multi-centre, cohort study collecting: blood samples, epidemiology and treatment data, and longitudinal side-effect and quality-of-life data (before and after treatment, years 1 & 2) in 5,300 patients with prostate, breast or lung cancer

2. Produce a centralised biobank of DNA and a centralised database including radiotherapy plans

3. Validate published biomarkers of radiosensitivity – genetic and apoptosis assay, PAXgene tubes

4. Validate clinical predictive models of radiotherapy toxicity in breast, prostate and lung cancer and incorporate biomarker data

5. Design interventional trials to reduce long-term side-effects

REQUITE

Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-Effects and Improve Quality-of-Life in Cancer Survivors

REQUITE

L2a

LUNG PATIENT FACTORS – BASELINE

(to be completed pre-radiotherapy)

Study Number RQ☐☐☐☐☐-☐

Patient Initials ☐☐☐

Date of Birth (dd/mm/yyyy) ☐☐/☐☐/☐☐☐☐

Date Completed (dd/mm/yyyy) ☐☐/☐☐/☐☐☐☐

Name + Signature of Person completing the CRF _____

Patient Information

Gender ☐ 1=Male 2=Female

Height (cm) ☐☐☐

Weight at cancer diagnosis (kg) ☐☐☐

Age at start of radiotherapy (yrs) ☐☐

Smoker ☐ 0=Never 1=Ex before cancer diagnosis 2=Ex since cancer diagnosis 3=Current 7=Do not wish to answer

If ever smoker
Duration of smoking (yrs) ☐☐
No. of tobacco products a day ☐☐☐

If ex smoker before cancer diagnosis: Time since quitting smoking (yrs) ☐☐

Tobacco product _____

Alcohol intake ☐ 0=Never 1=Previously consumed alcohol, but stopped BEFORE cancer diagnosis 2=Previously consumed alcohol, but stopped AT cancer diagnosis 3=Current 7=Do not wish to answer

Previous alcohol consumption: Approximate number of alcoholic drinks a week ☐☐☐ 777=Do not wish to answer 888=Not applicable

Current alcohol consumption: Approximate number of alcoholic drinks a week ☐☐☐ 777=Do not wish to answer 888=Not applicable

If female:

Menopausal status at time of cancer diagnosis ☐ 1=Pre 2=Post 3=Peri

If postmenopausal, age of menopause (yrs) ☐☐

If postmenopausal, use of menopausal hormone replacement therapy? ☐ 0=No 1=Yes

Radiotherapy

Date radiotherapy started (dd/mm/yyyy) ☐☐/☐☐/☐☐☐☐

Date radiotherapy finished (dd/mm/yyyy) ☐☐/☐☐/☐☐☐☐

Radiotherapy technique ☐ 1=3D CRT 2=ARC therapy (eg VMAT, RapidARC) 3=IMRT 4=Tomotherapy 5=Stereotactic body radiation therapy/stereotactic ablative radiotherapy

Treatment planning system algorithm ☐ 1=Pencil beam 2=Collapsed cone 3=Monte Carlo 4=Accuros or similar 5=Other _____

Total Dose (Gy)	☐☐•☐☐	Number of Fractions	☐☐
GTV (tumour & nodes if applicable (cm^3))	☐☐☐•☐	Mean Lung* Dose (Lung - GTV) (Gy)	☐☐•☐☐
PTV (tumour & nodes if applicable (cm^3))	☐☐☐•☐	V5 (%) Lung* - PTV	☐☐•☐
CTV (tumour & nodes if applicable (cm^3))	☐☐☐•☐	V20 (%) Lung* - PTV	☐☐•☐
V35 (%) Oesophagus	☐☐•☐	V5 (%) Heart	☐☐•☐
V50 (%) Oesophagus	☐☐•☐	V30 (%) Heart	☐☐•☐
V60 (%) Oesophagus	☐☐•☐	V40 (%) Heart	☐☐•☐
Max dose to 1cc Oesophagus (Gy)	☐☐•☐☐	V50 (%) Heart	☐☐•☐
Mean Oesophageal dose (Gy)	☐☐•☐	Max dose to 1cc of Heart (Gy)	☐☐•☐☐
		Mean Heart dose (Gy)	☐☐•☐

Definition for heart delineation:
The heart should be outlined along with the pericardial sac. The pericardial sac surrounds the heart and extends superiorly to encompass the main pulmonary artery, the ascending aorta and the superior vena cava. Outlining should extend superiorly to the inferior limit of the aortic arch (the aortopulmonary window) and the superior limit of the trunk of the pulmonary artery if it can be identified on the radiotherapy planning CT scan.

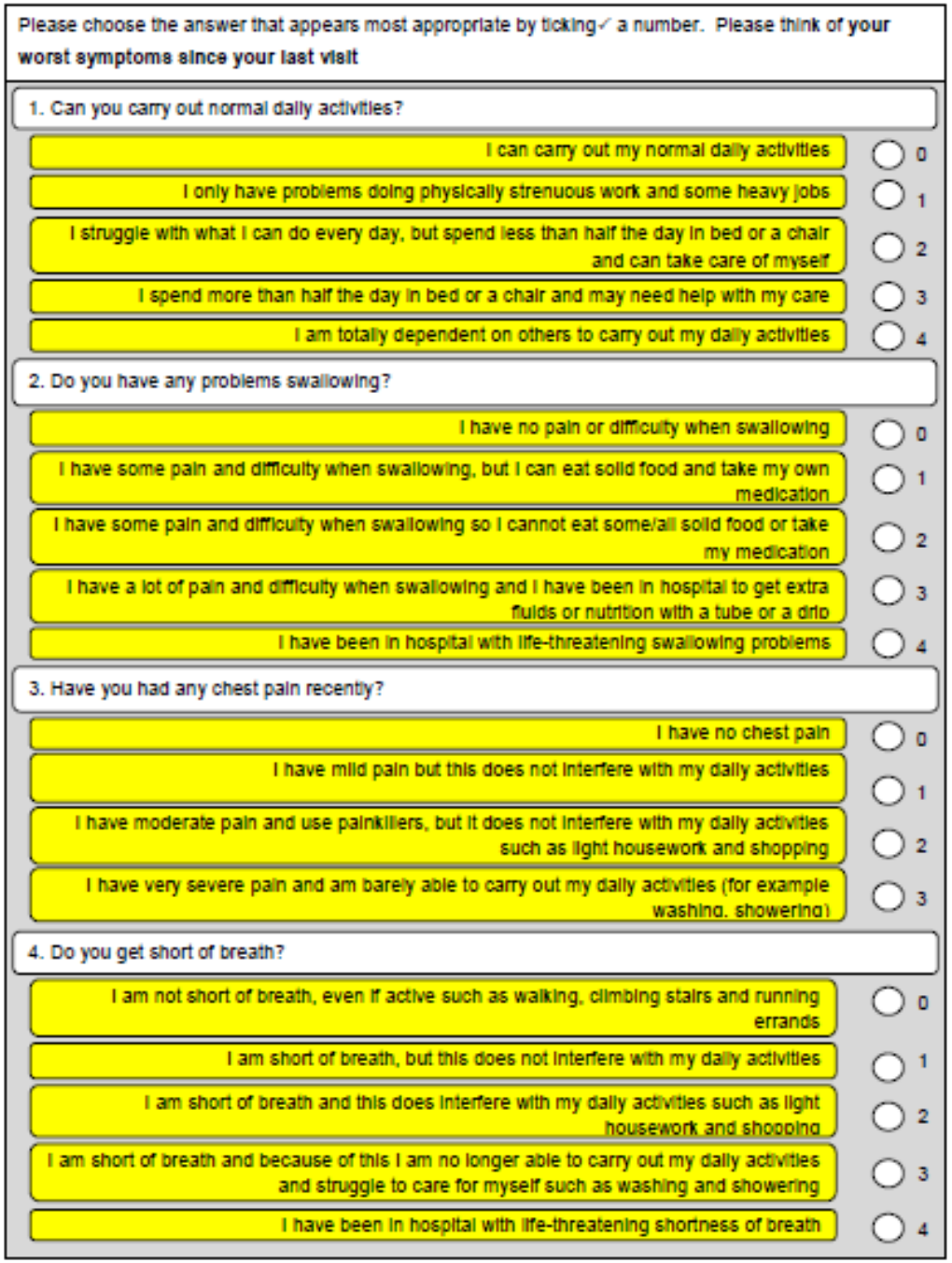
Heart delineation ☐ 1=As defined 2=Left ventricle only 3=Others _____

Radiotherapy interrupted for more than 3 days ☐ 0=No 1=Yes 9=Not known

If yes, reason _____

*Lung = both lungs together

http://www.requite.eu/



Please choose the answer that appears most appropriate by ticking✓ a number. Please think of **your worst symptoms since your last visit**

1. Can you carry out normal daily activities?

I can carry out my normal daily activities	0
I only have problems doing physically strenuous work and some heavy jobs	1
I struggle with what I can do every day, but spend less than half the day in bed or a chair and can take care of myself	2
I spend more than half the day in bed or a chair and may need help with my care	3
I am totally dependent on others to carry out my daily activities	4

2. Do you have any problems swallowing?

I have no pain or difficulty when swallowing	0
I have some pain and difficulty when swallowing, but I can eat solid food and take my own medication	1
I have some pain and difficulty when swallowing so I cannot eat some/all solid food or take my medication	2
I have a lot of pain and difficulty when swallowing and I have been in hospital to get extra fluids or nutrition with a tube or a drip	3
I have been in hospital with life-threatening swallowing problems	4

3. Have you had any chest pain recently?

I have no chest pain	0
I have mild pain but this does not interfere with my daily activities	1
I have moderate pain and use painkillers, but it does not interfere with my daily activities such as light housework and shopping	2
I have very severe pain and am barely able to carry out my daily activities (for example washing, showering)	3

4. Do you get short of breath?

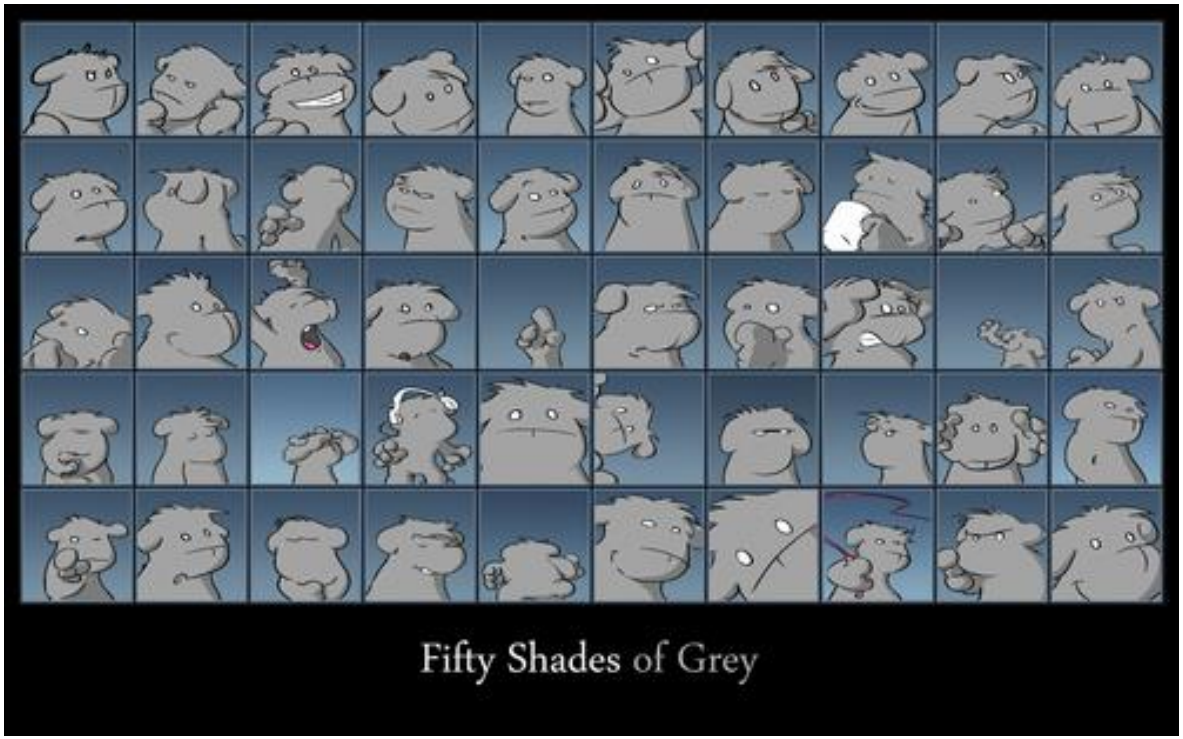
I am not short of breath, even if active such as walking, climbing stairs and running errands	0
I am short of breath, but this does not interfere with my daily activities	1
I am short of breath and this does interfere with my daily activities such as light housework and shopping	2
I am short of breath and because of this I am no longer able to carry out my daily activities and struggle to care for myself such as washing and showering	3
I have been in hospital with life-threatening shortness of breath	4

Lung questionnaire

- Nederlands
- English
- Français
- Deutsch
- Italiano
- Español

http://www.requite.eu/

Genetics has potential for the biological optimisation of radiotherapy



Shades of gray