Prediction of normal tissue radiosensitivity from polymorphisms in candidate genes

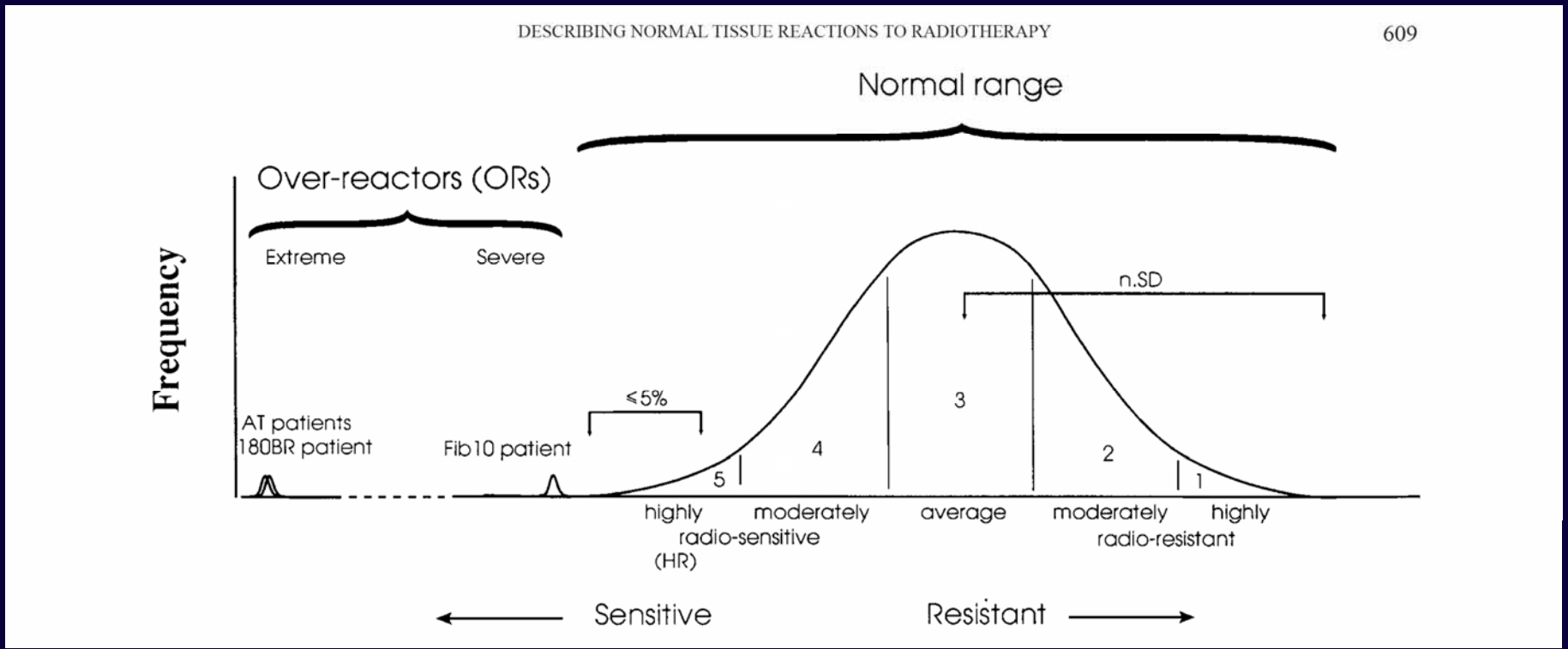
C. Nicolaj Andreassen

MD, PhD

Department of Experimental Clinical Oncology
Aarhus University Hospital, Denmark

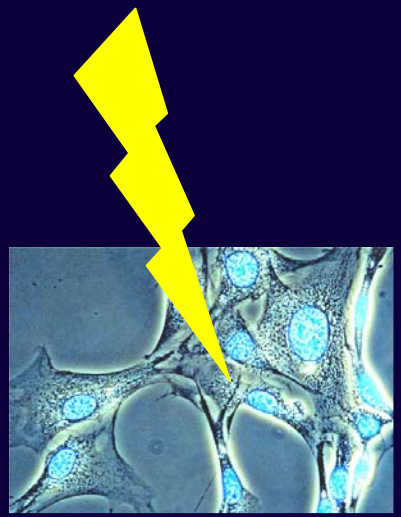
nicolaj@oncology.dk

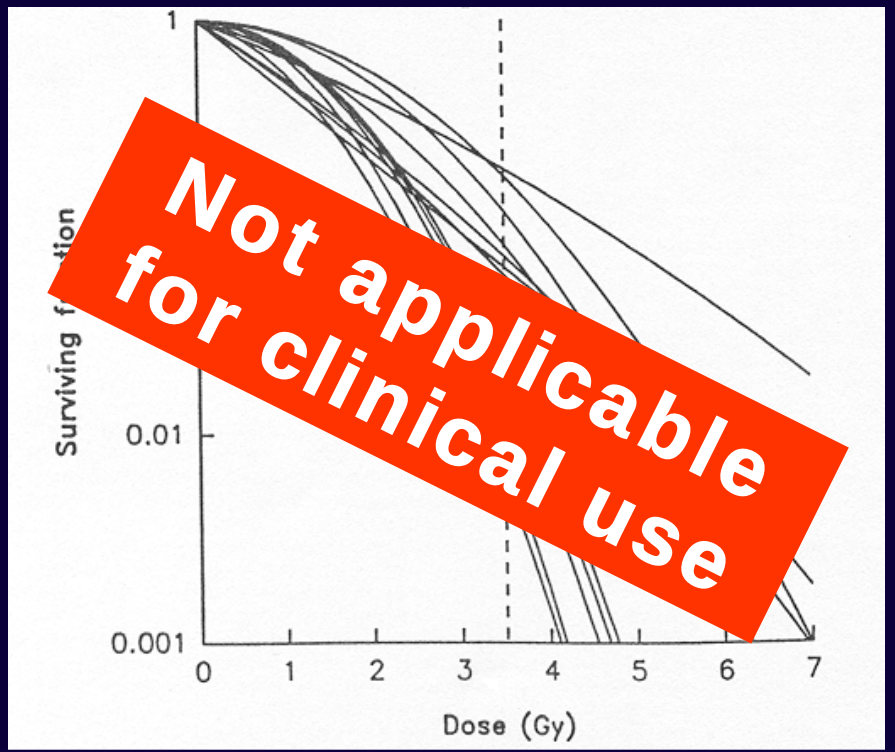
Variation in normal tissue response



Burnet et al. 1998

Prediction of normal tissue response



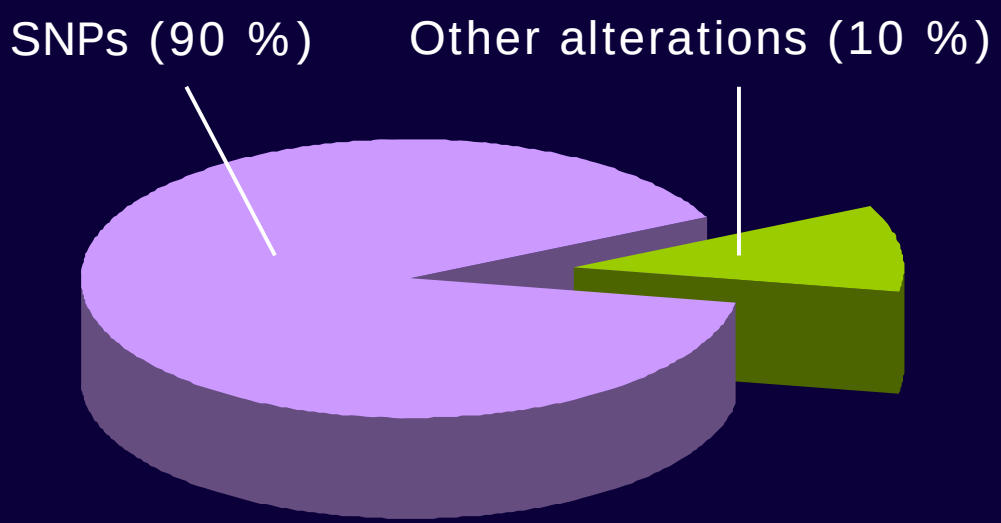


Human genome

3 billion bases

25.000 genes

11 million SNPs

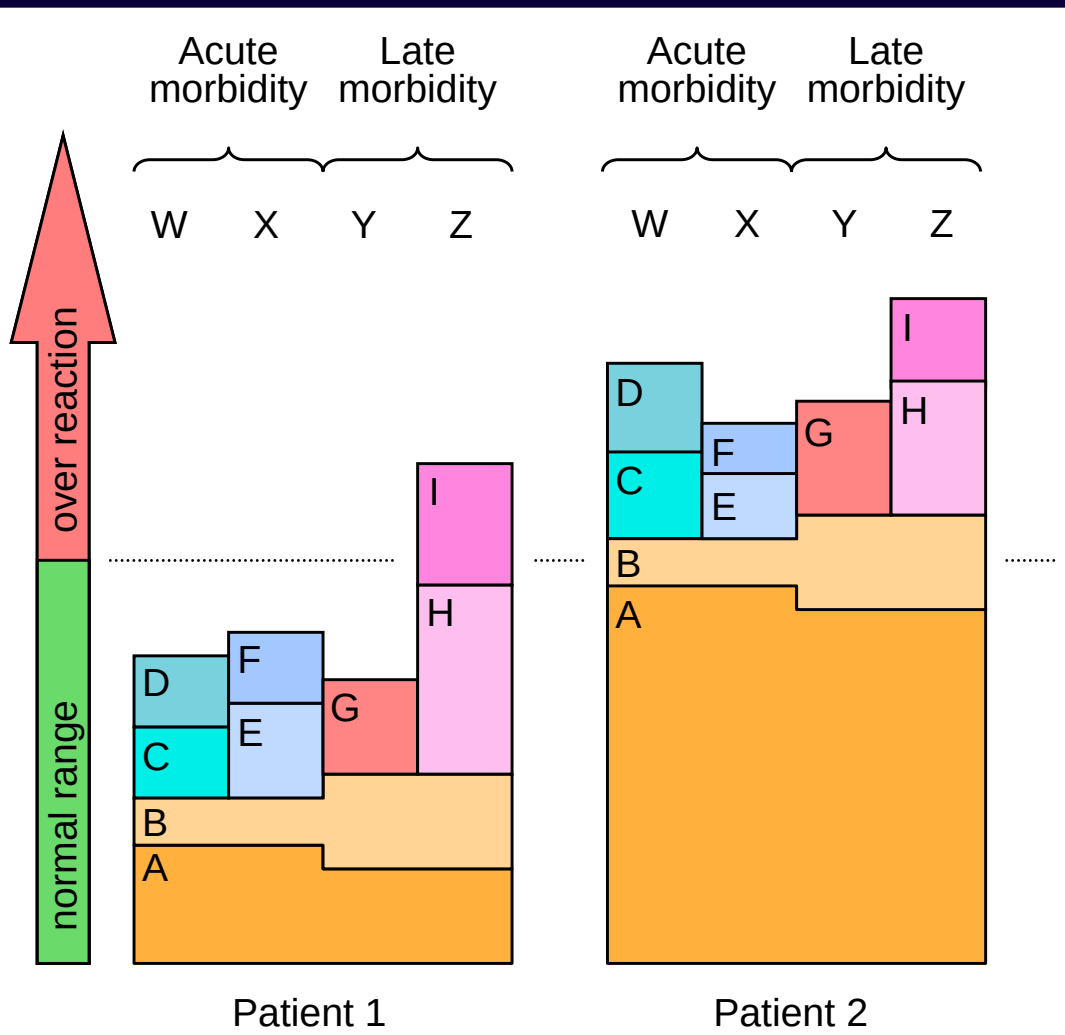


And a possibly much higher number of different rare sequence alterations

Three basic assumptions

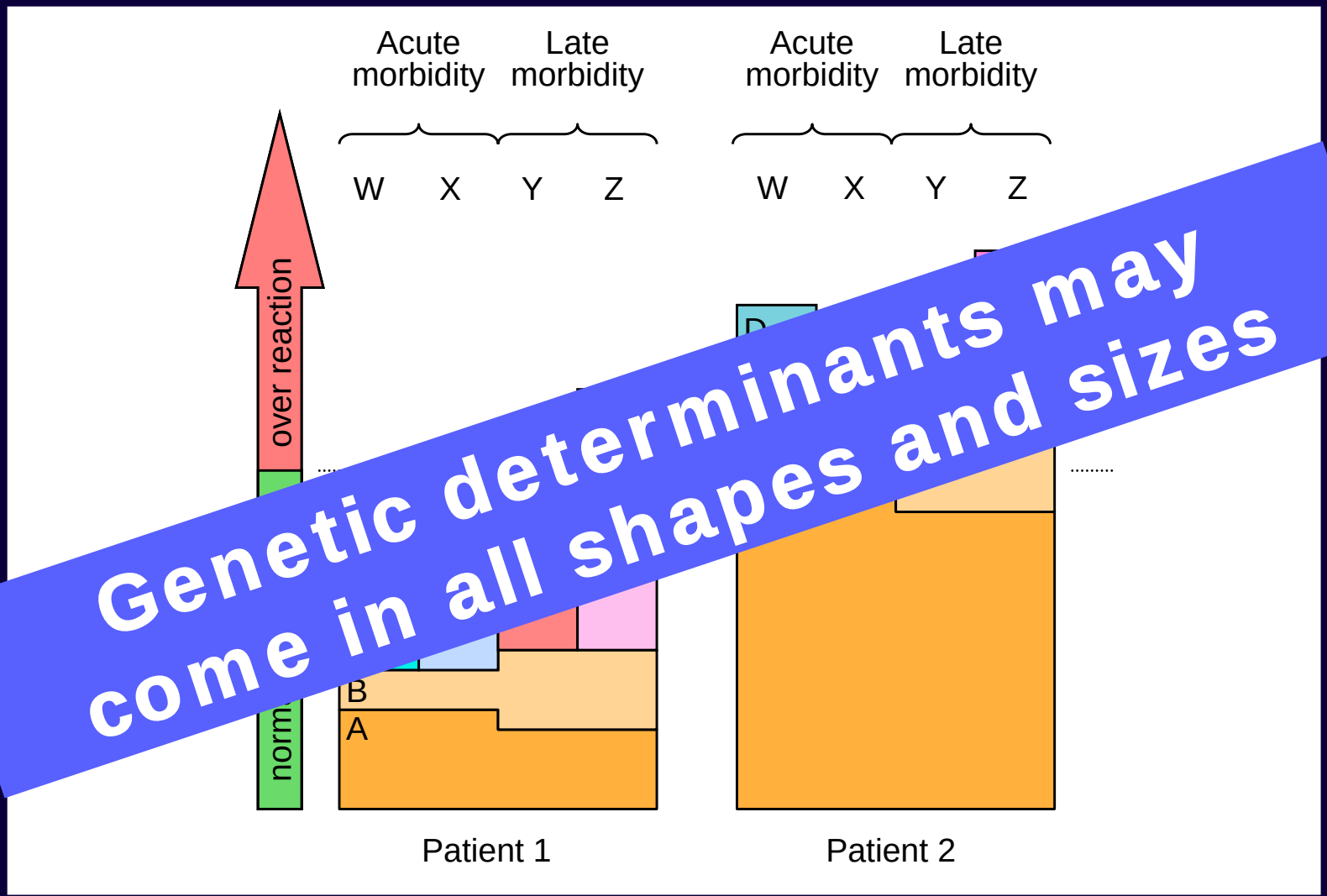
- Clinical radiosensitivity should be regarded as a 'complex trait' dependent on the combined influence of genetic alterations in several genes
- Single nucleotide polymorphisms constitute a proportion of such genetic determinants
- Some genetic determinants selectively affect certain types of normal tissue reactions whereas others exhibit a general impact on radiosensitivity

A putative model



Andreassen, Acta Oncol 44; 801-815 (2005)

A putative model



Genetic determinants may come in all shapes and sizes

Andreassen, Acta Oncol 44; 801-815 (2005)

Overview of clinical studies

39 studies

Sample size 5 – 446 Median 78 pts.

21 studies on SNPs

18 studies on other types of variation

Overview of clinical studies

46 genes

TGFB1

ATM BCL2 BRCA1 BRCA2 XRCC1 XRCC2 XRCC3 XRCC5 APEX OGG1 XPF XPD hHR21 RAD50 RAD51 RAD52 NBS MRE11 DNA lig IV ERCC2 ERCC4 ESR1 NBN MSH6 NR3C1

GSTP1 GSTM1 GSTT1 GSTA1 SOD2 CAT MPO eNOS

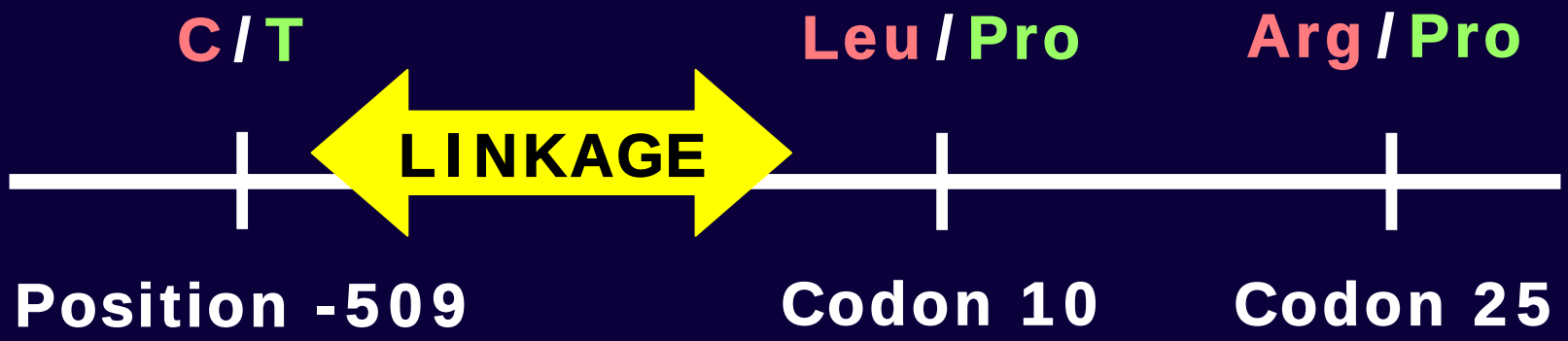
CYP1A1 CYP2C9 CYP2C19 CYP3A5 CYP2D6 CYP11B2 CYP17A1 DHFR CX3CR1 Hyl-1 MS HTHFR

Toma Suga et al. 2007: 999 SNPs in 137 genes. N=399

TGFB1 SNPs

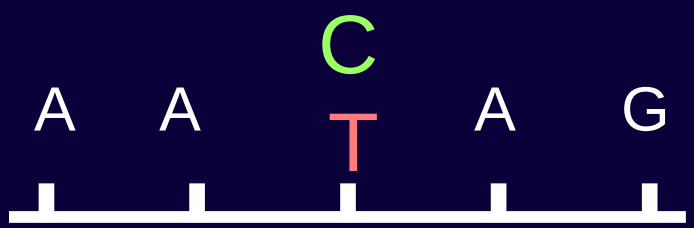
'Master switch'

Martin M et al 2000



Protein secretion rate

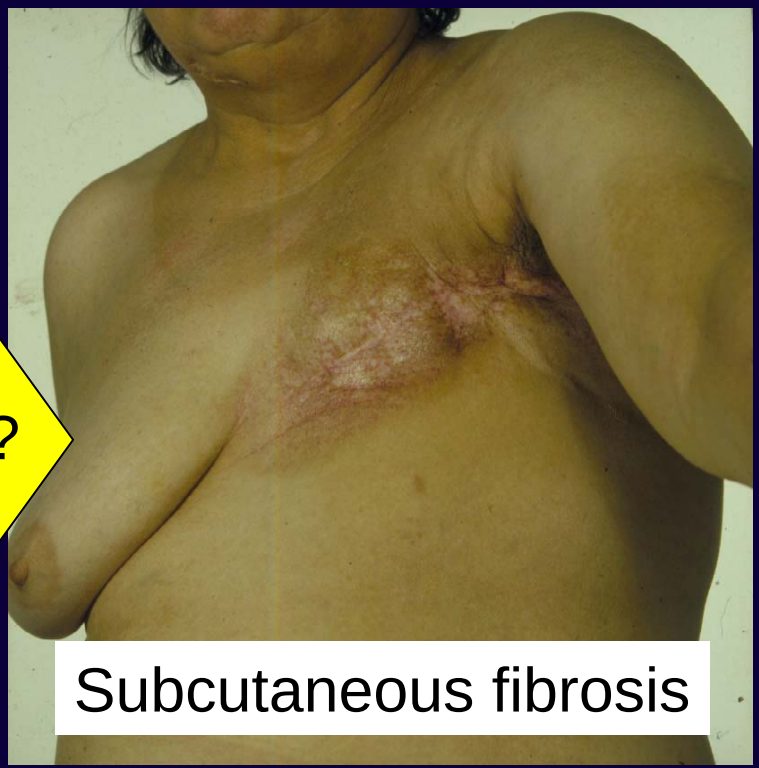
TGF beta 1 SNPs



RISK

- TGFB1 codon 10
- TGFB1 codon 25
- TGFB1 position –509

Association ?



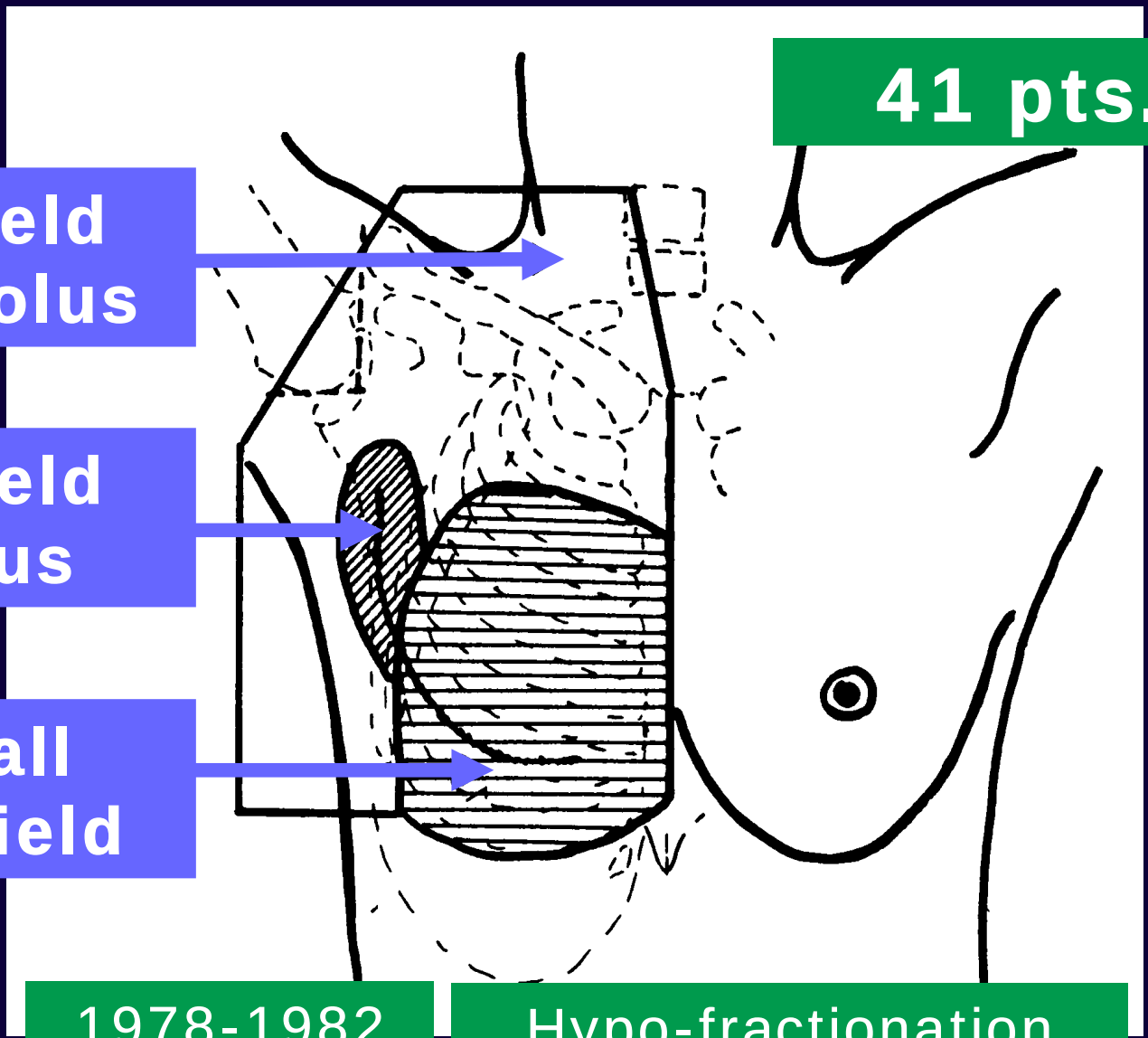
Subcutaneous fibrosis

41 pts.

Photon field without bolus

Photon field with bolus

Chest wall electron field



1978-1982

Hypo-fractionation

Clinical data

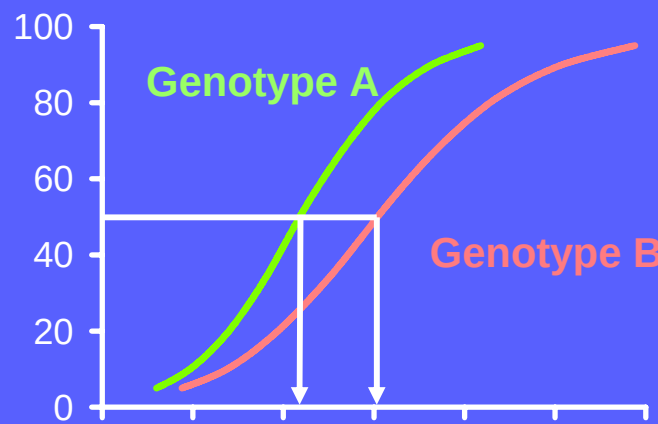
Response

Dosimetry

Dose

Biological material

Genotype

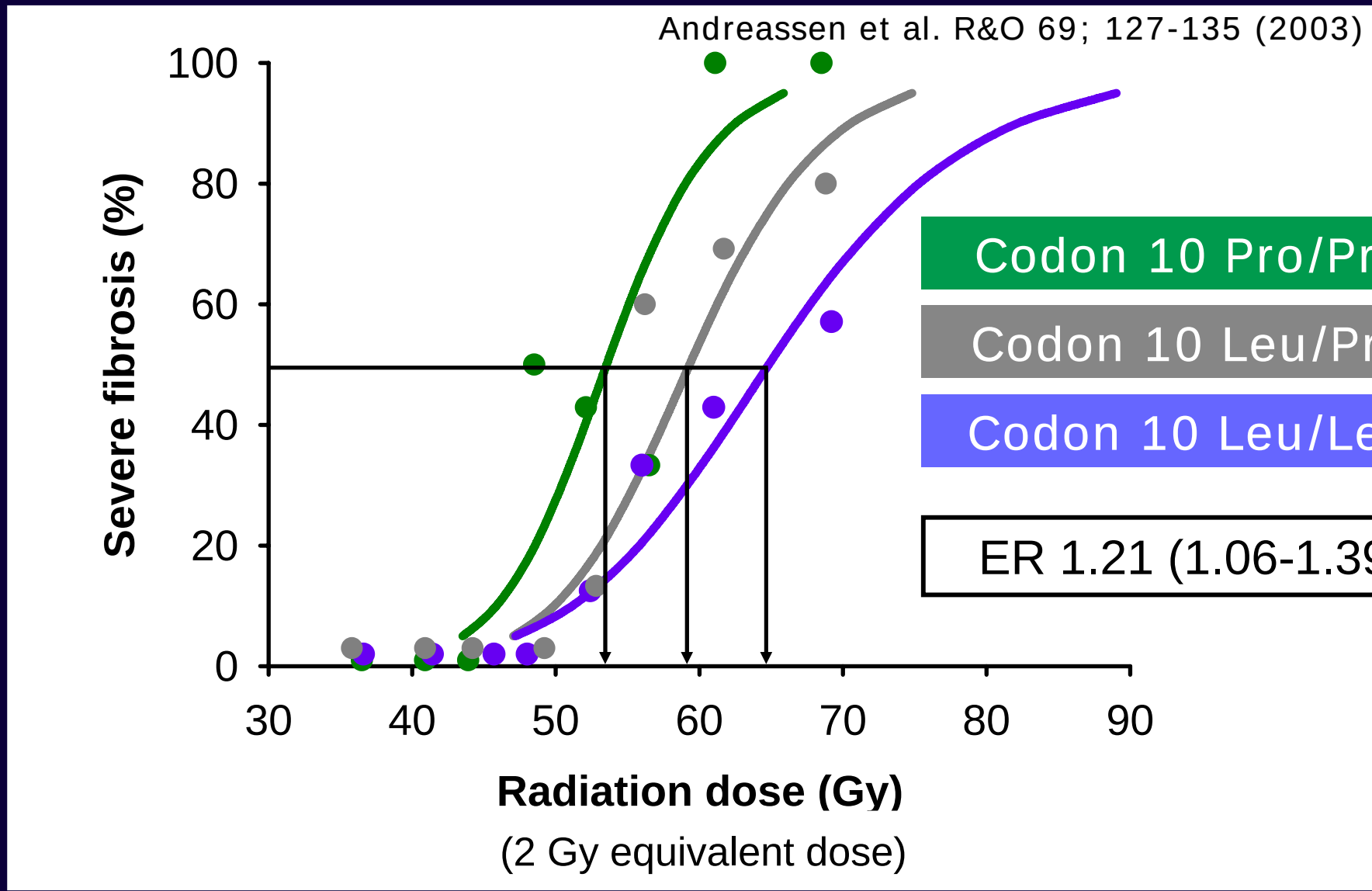


ED_{50}

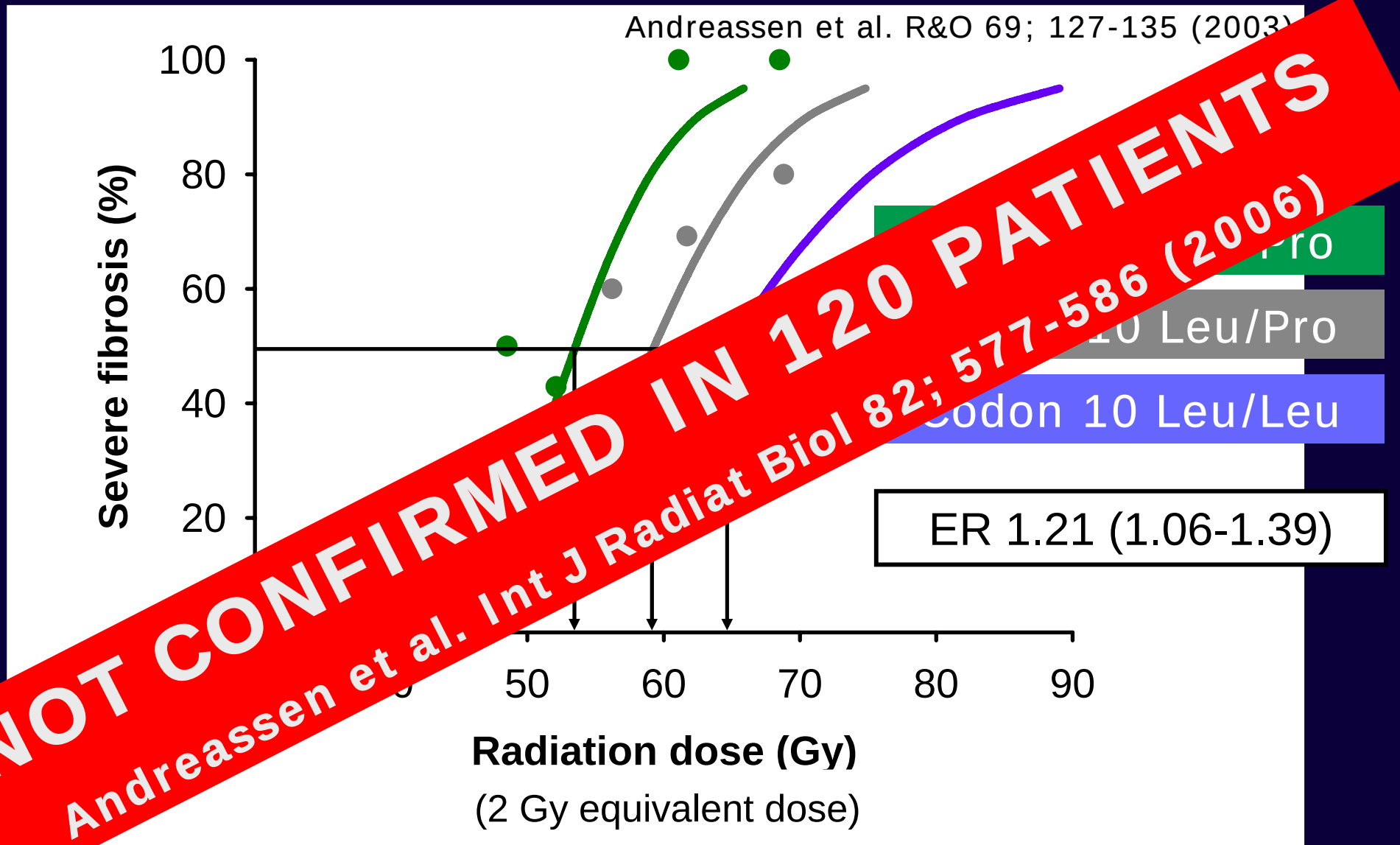
Enhancement ratios

41 pts / 123 radiation fields

TGF-B1 codon 10 genotype and fibrosis risk



TGF-B1 codon 10 genotype and fibrosis risk



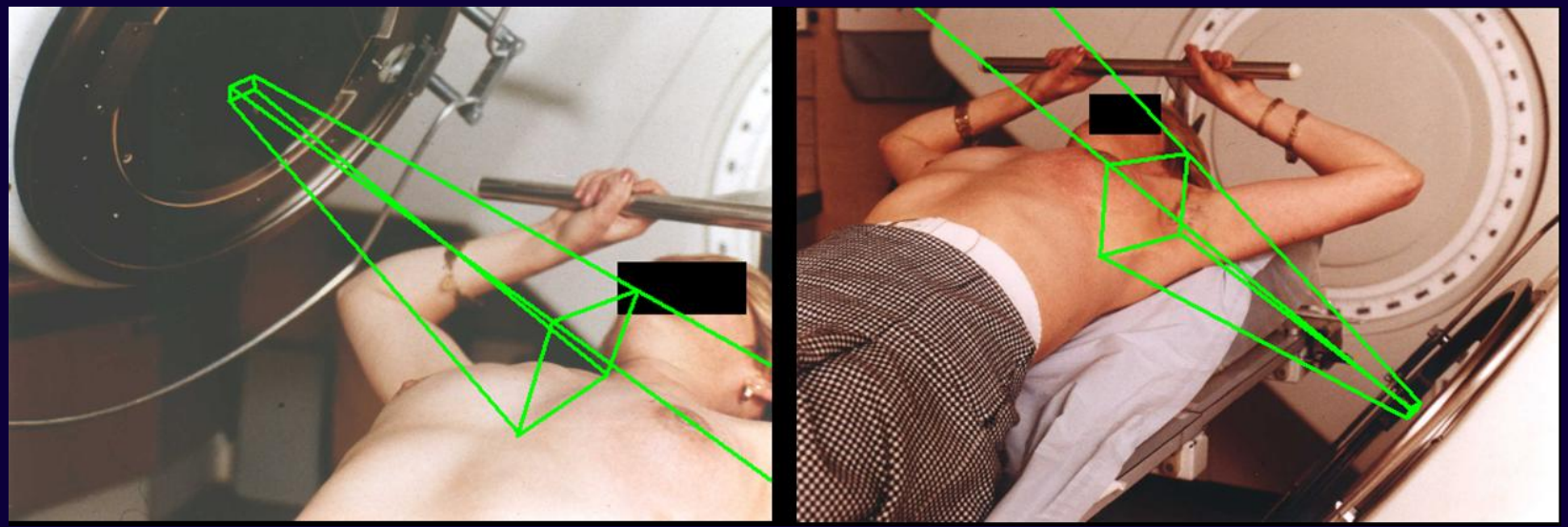
NOT CONFIRMED IN 120 PATIENTS

Andreassen et al. Int J Radiat Biol 82; 577-586 (2006)

MATERIAL

1986-1994

935 Early stage breast cancer patients

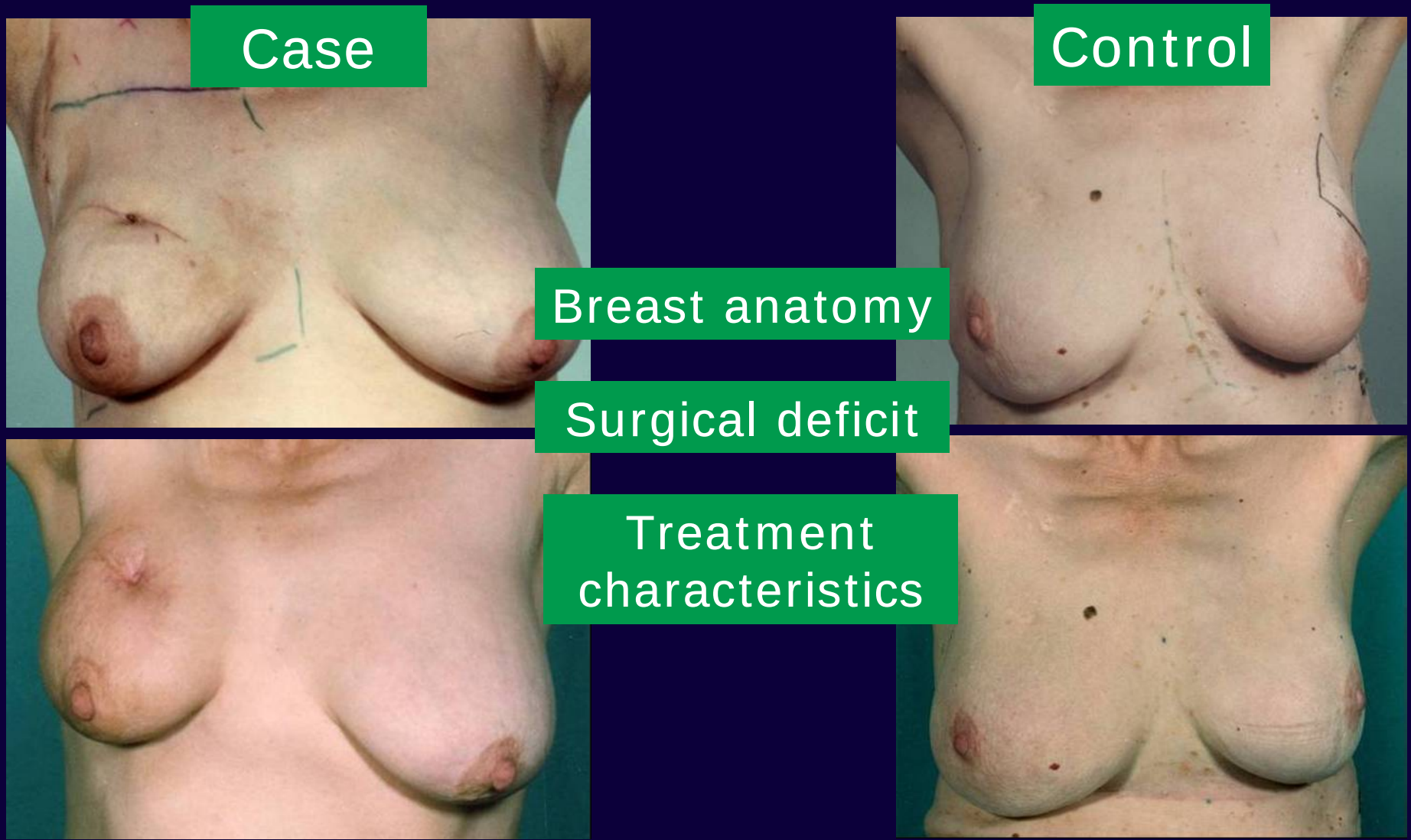


Radiotherapy fractionation trial
(”Pre START trial’)

Royal Marsden Hospital

Gloucestershire Oncology Centre

26 matched case-control pairs



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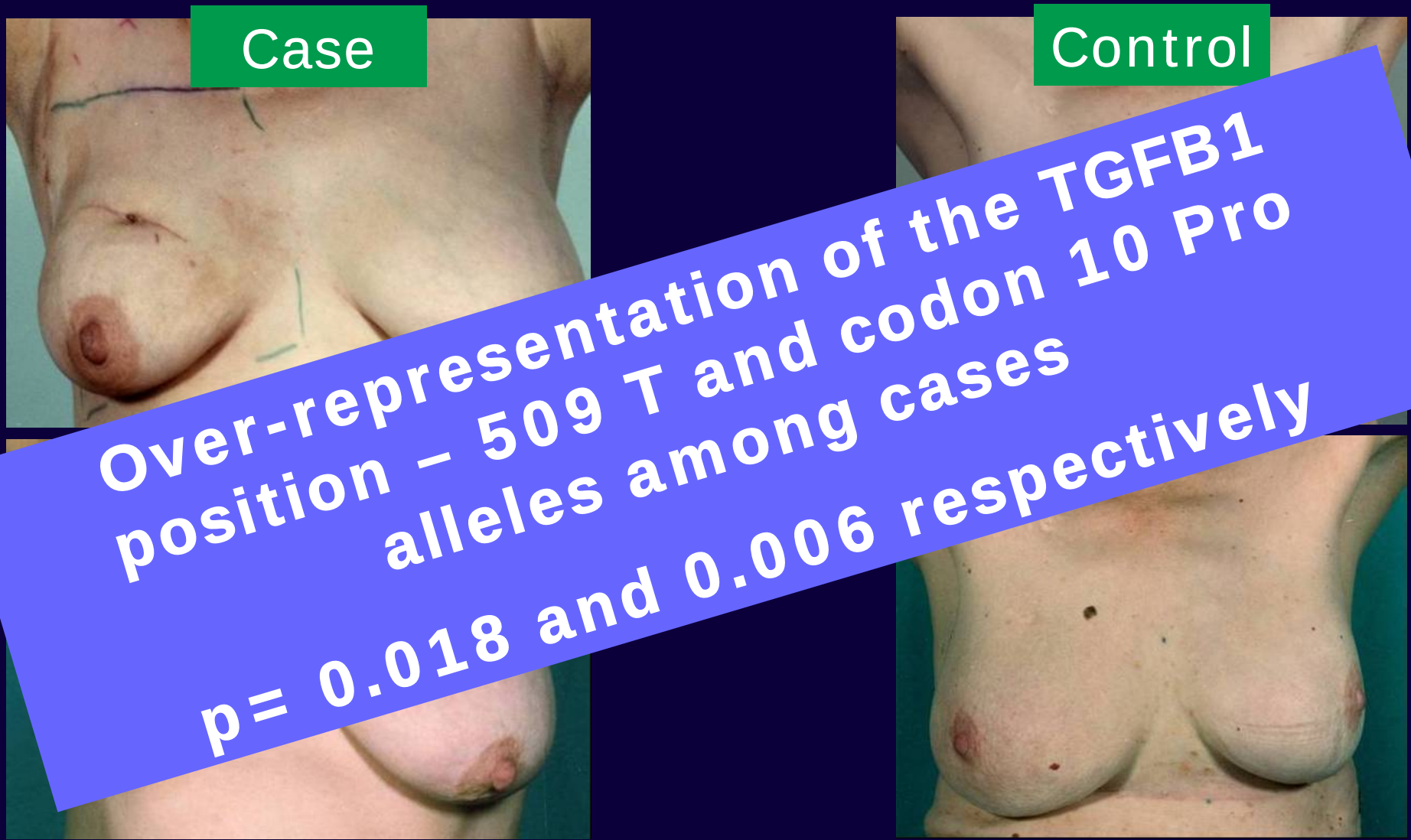


Over-representation of the TGFB1 position – 509 T and codon 10 Pro alleles among cases

p= 0.018 and 0.006 respectively

Head and neck patients from the DAHANCA trials

Presented at ECCO 14

DAHANCA 6&7

- N=99
- Treated in 1992-1999
- Dose 66–68 Gy, 2 Gy per fraction, 5 or 6 fx per week
- Median length of follow up 59 months

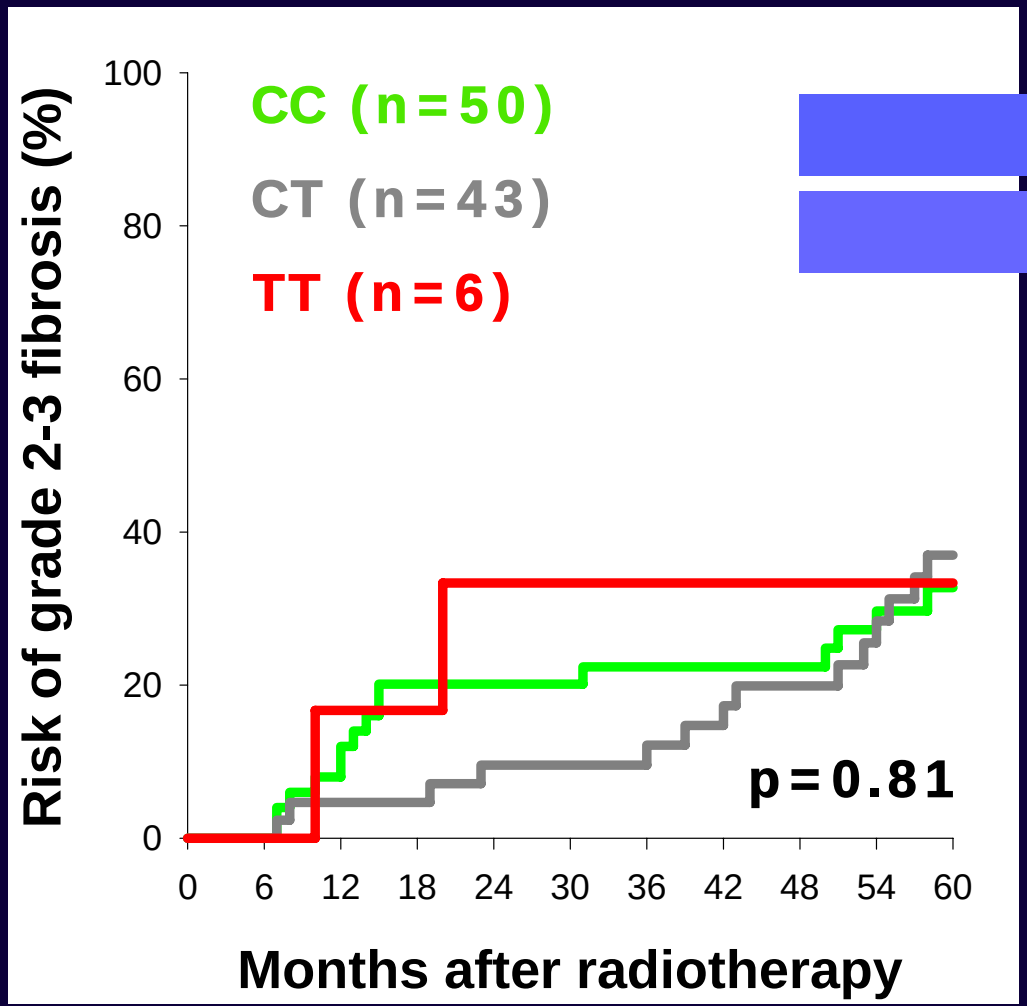
- N=304
- Treated in 2000-2006
- Dose 66–68 Gy, 2 Gy per fraction, 6 fx per week
- Median length of follow up 41 months

Abstract #900

Scored for subcutaneous fibrosis at a four point ordinal scale

(grades 0-3) as part of rutine follow up

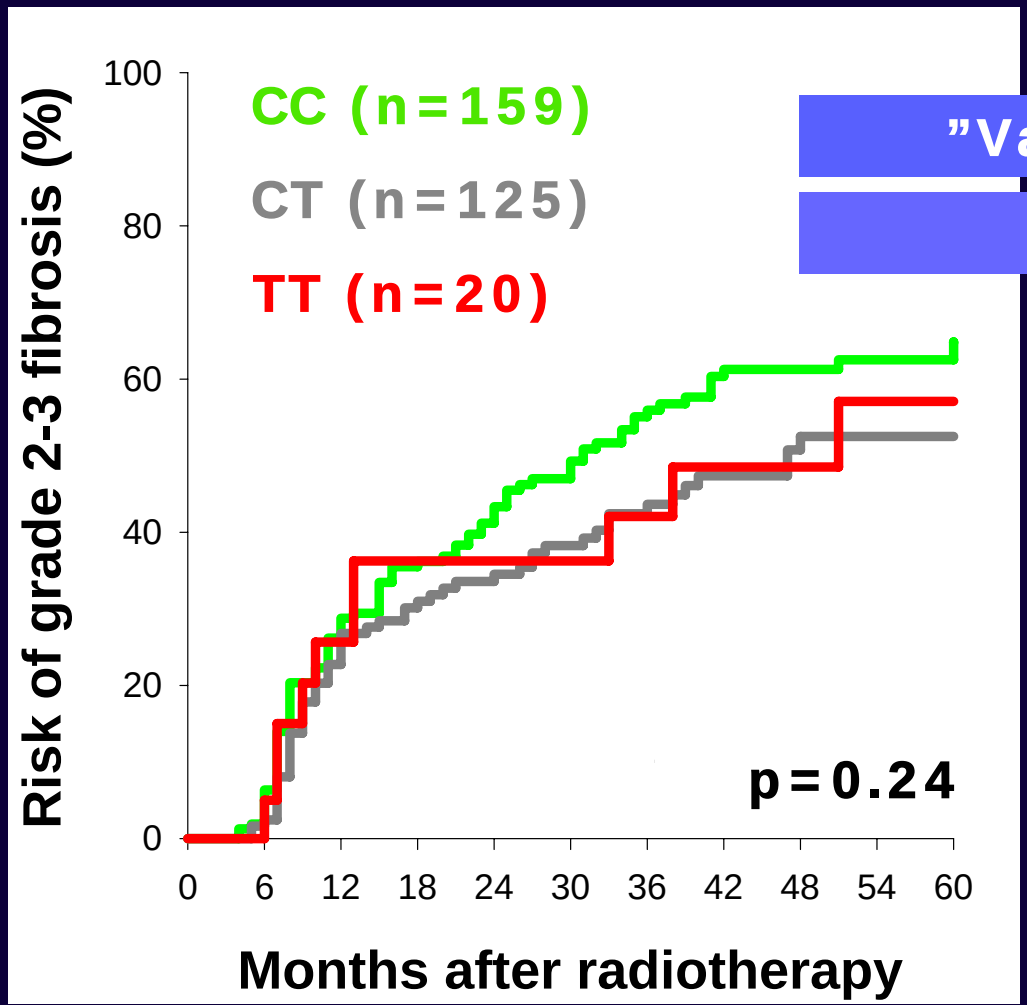
Cumulative fibrosis risk according to TGFB1 position -509 genotype



"Test set"

N=99

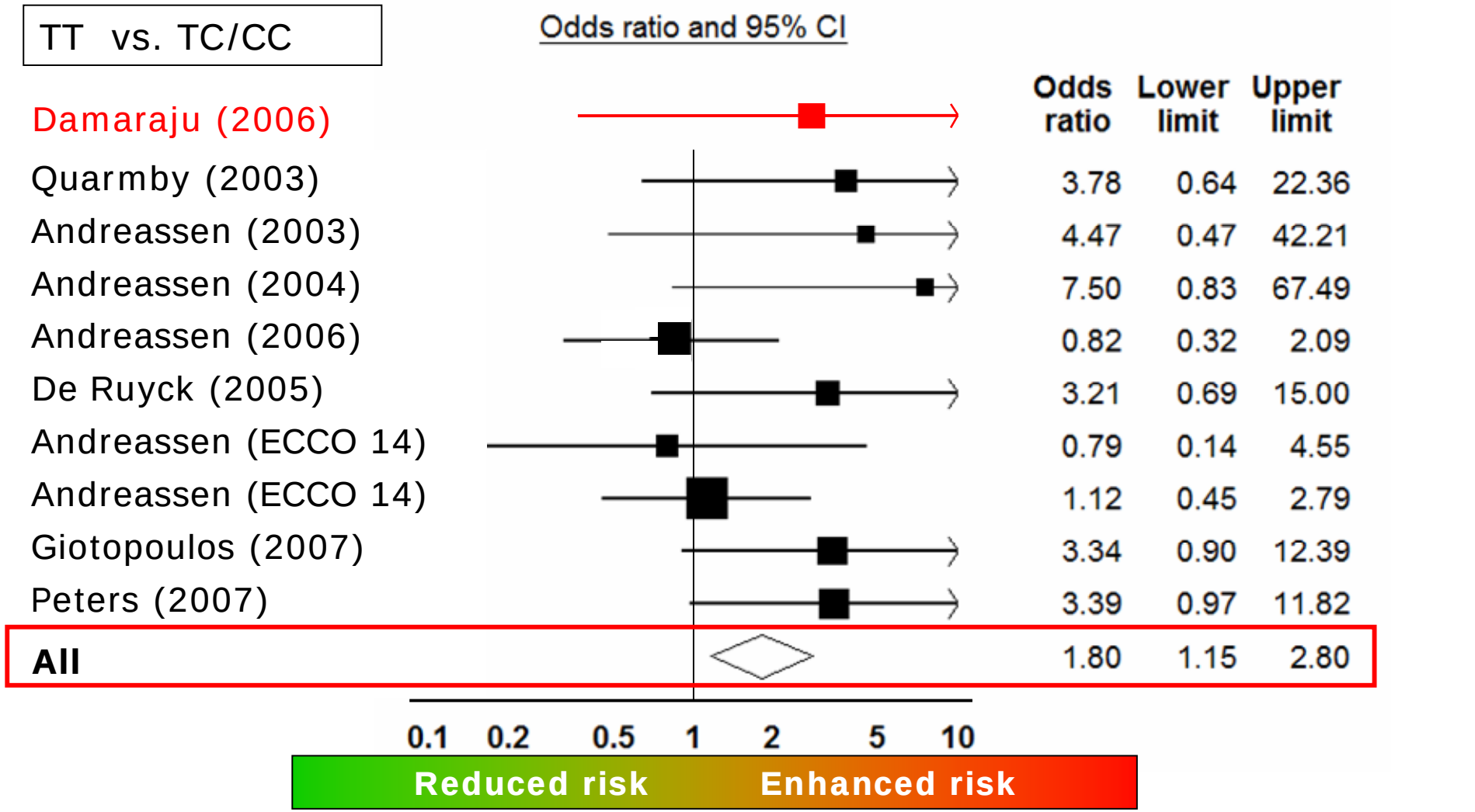
Cumulative fibrosis risk according to TGFB1 position -509 genotype



”Validation set”

N=304

Meta analysis:
TGFB1 position -509 T allele and late toxicity risk



Meta analysis:
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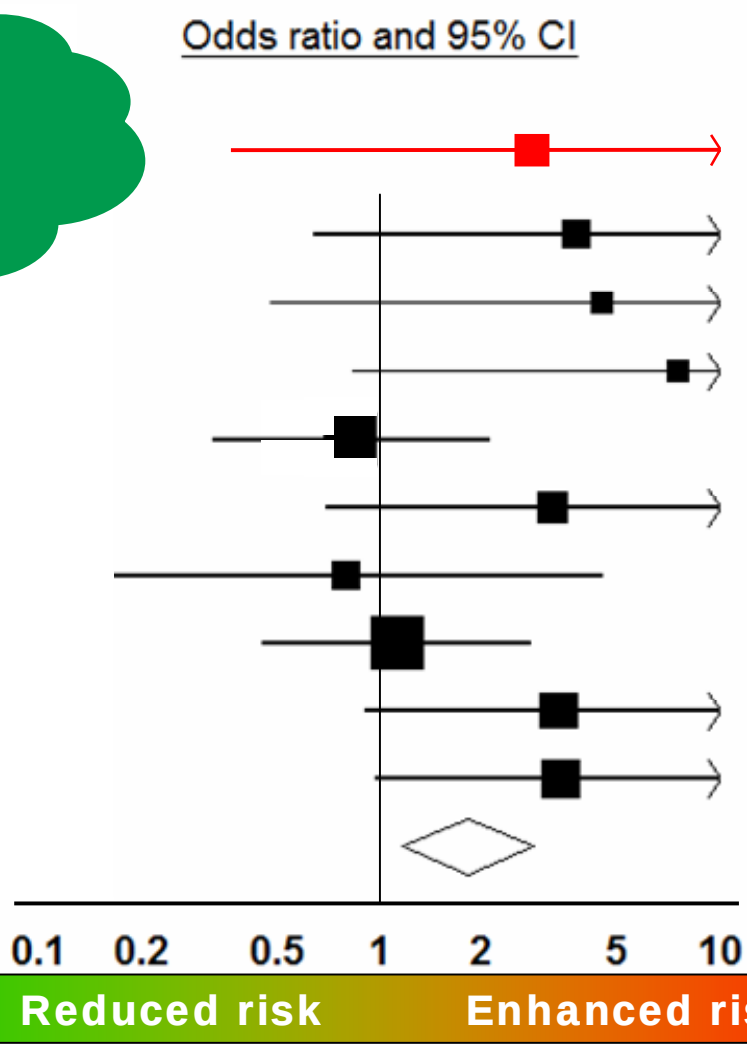
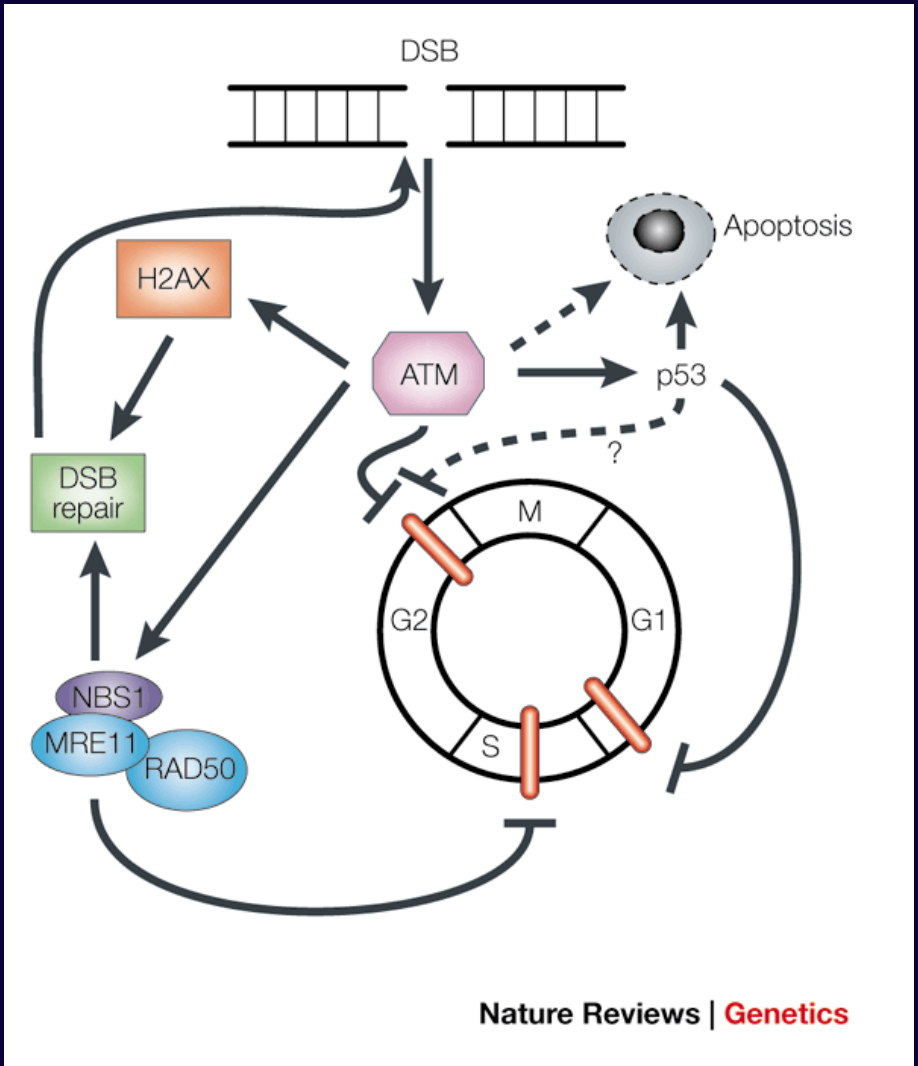
Proof of association !



Indication of publication bias?

ATM



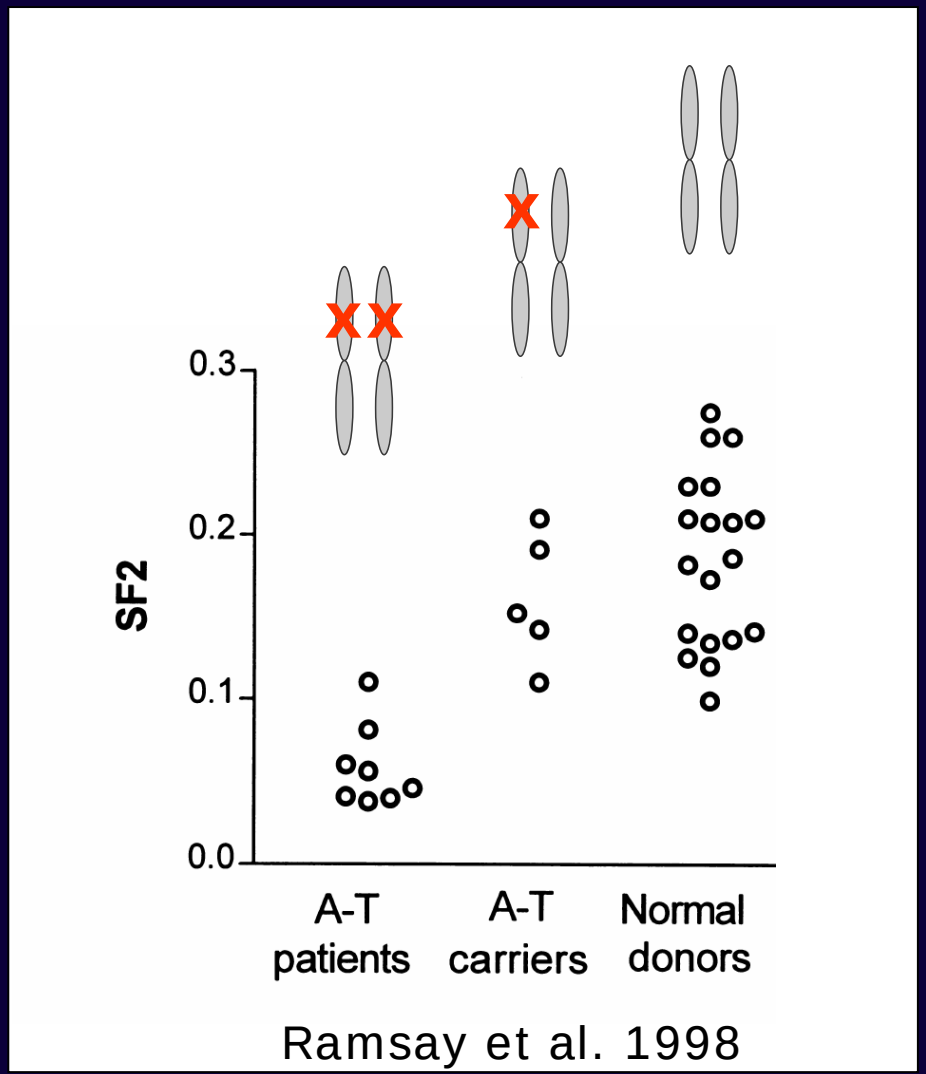
DETECTION OF DNA DSB

INDUCTION OF CELL CYCLE ARREST

DNA REPAIR

APOPTOSIS

ATM



DETECTION OF DNA DSB

INDUCTION OF CELL CYCLE ARREST

DNA REPAIR

APOPTOSIS

AT heterozygosity and clinical radiosensitivity

Author (year)	N=	
Appleby JM et al. (1997)	23	No significant accumulation of AT heterozygocity among 'overreactors'
Clarke RA et al. (1998)	9	
Ramsey J et al. (1998)	15	
Shayeghi M et al. (1998)	80	
Hall EJ et al. (1998)	17	
Oppitz U et al. (1999)	20	
Weissberg JB et al. (1998)	13	
Bremer M et al. (2003)	10	

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Bremer M et al. (2003)	10

No evidence of excessive radiation reactions in AT heterozygotes

DHPLC

Association between the possession of 2 *ATM* single base alterations and enhanced risk of fibrosis after radiotherapy for breast cancer (N=46)

p=0.001

Iannuzzi CM et al. IJROBP 52: 606-613 (2002)

Association between the possession single base *ATM* alterations and enhanced risk of late toxicity after bracytherapy for prostate cancer (N=37)

p=0.005

Cesaretti et al. JA. IJROBP 61: 196-202 (2005)

DHPLC

Association between the possession of *ATM* single base alterations and enhanced risk of late skin or subcutaneous toxicity after radiotherapy for breast cancer (N=131)

OR 2.4 (95% CI 1.1-5.2)

Ho AY et al. IJROBP 69: 677-684 (2007)

Association between the possession single base *ATM* alterations and enhanced risk of late toxicity after bracytherapy for prostate cancer (N=108)

p=0.04 – 0.05

Cesaretti JA et al. IJROBP 68: 1406-1410 (2007)

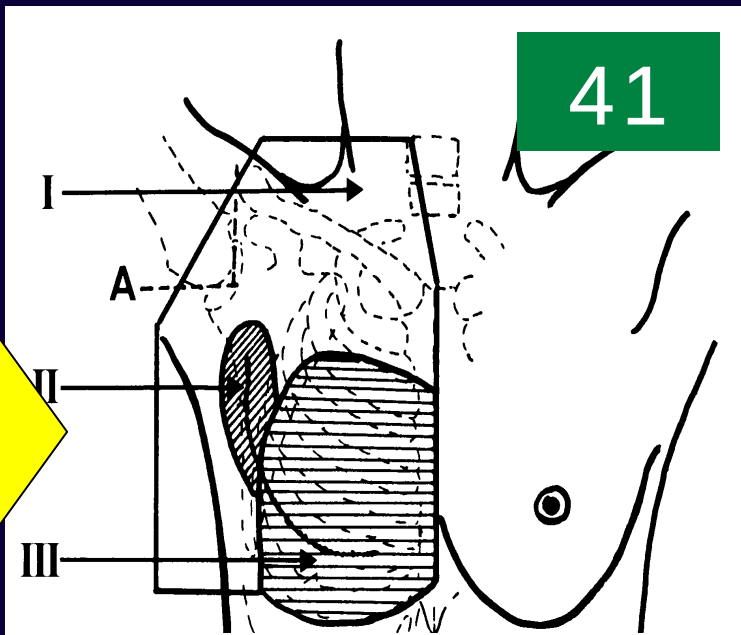
METHOD

RISK

ATM variations

DHPLC

Association



Subcutaneous fibrosis

RESULTS

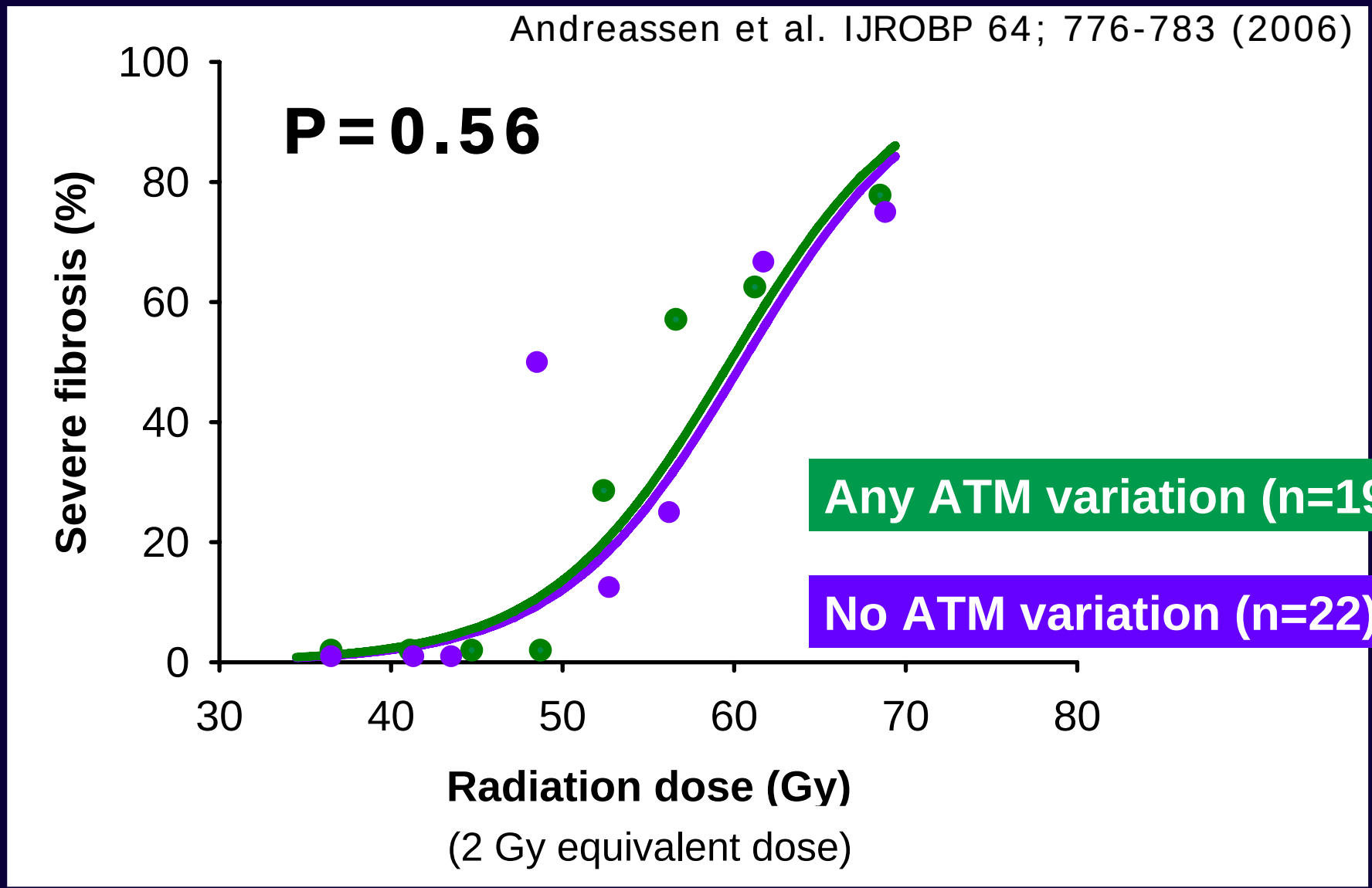
22 patients had a total of 28 genetic alterations

9 patients had 2 alterations each

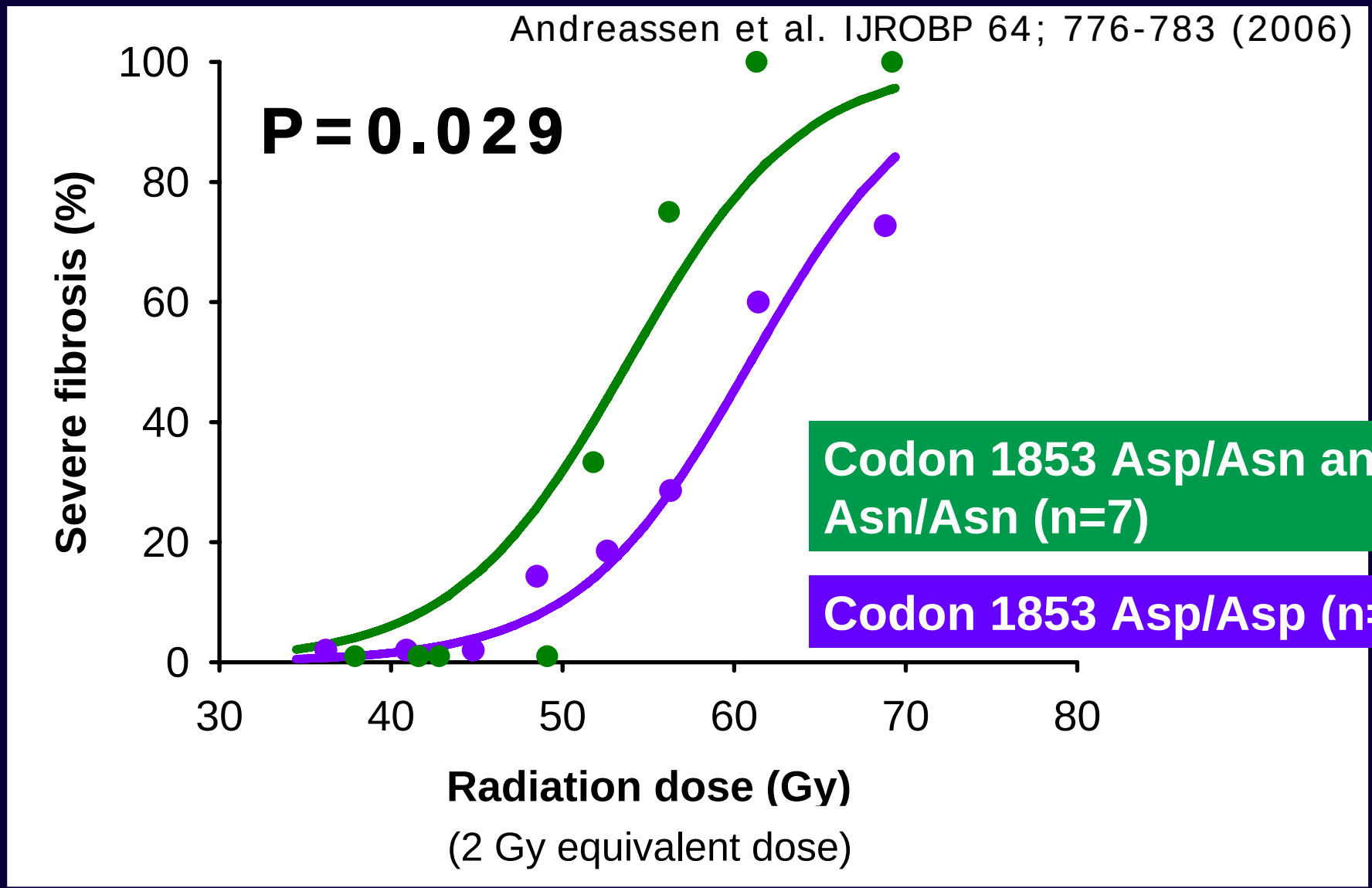
All alterations were single base substitutions

10 caused amino acid change

ATM genotype and risk of subcutaneous fibrosis



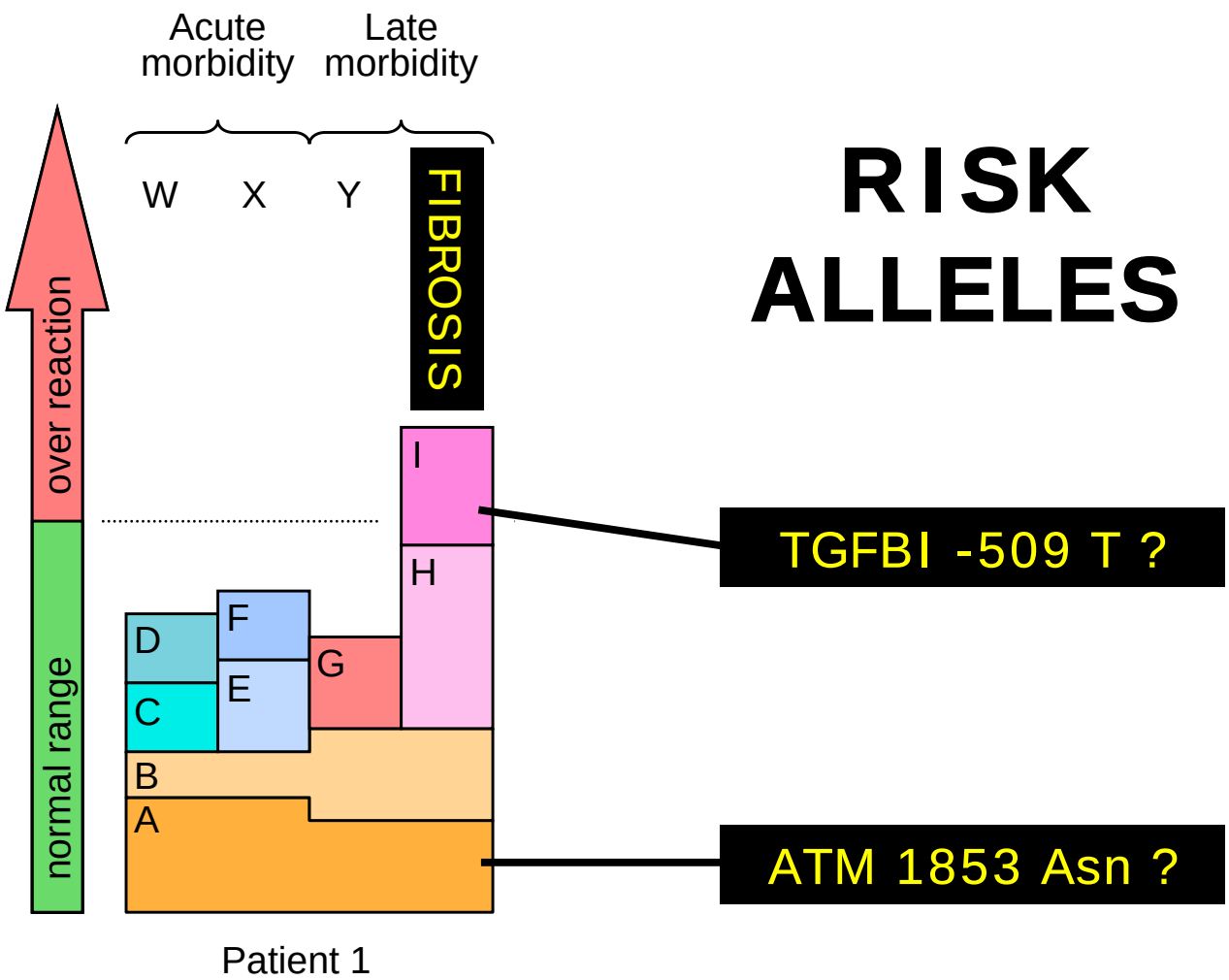
ATM genotype and risk of subcutaneous fibrosis



Overview:
ATM codon 1853 Asn allele and toxicity risk

Author (year)	N=	Significant association
Hall E et al. (1998)	17	”TREND”
Angele S et al. (2003)	254	**YES**
Andreassen CN et al. (2003)	41	**YES**
Andreassen CN et al. (2004)	52	”TREND”
Andreassen CN et al. (2006)	120	TREND (ER 1.04 (0.99-1.10))
Damaraju S et al. (2006)	124	TREND (OR 2.12 (O.81-5.59))
Ho AY et al. (2007)	131	**YES**
Tomo Suga MS et al. (2007)	399	ATM 1853 not polymorphic

A putative model



How to proceed?

Consolidation of previous findings

Broad-based candidate gene approach

Whole genome association studies??

Gene expression profiling

RNA interference

Animal models

Studies addressing onco-genesis and tumour biology

How to proceed?

Consolidation of previous findings

Broad-based candidate gene approach

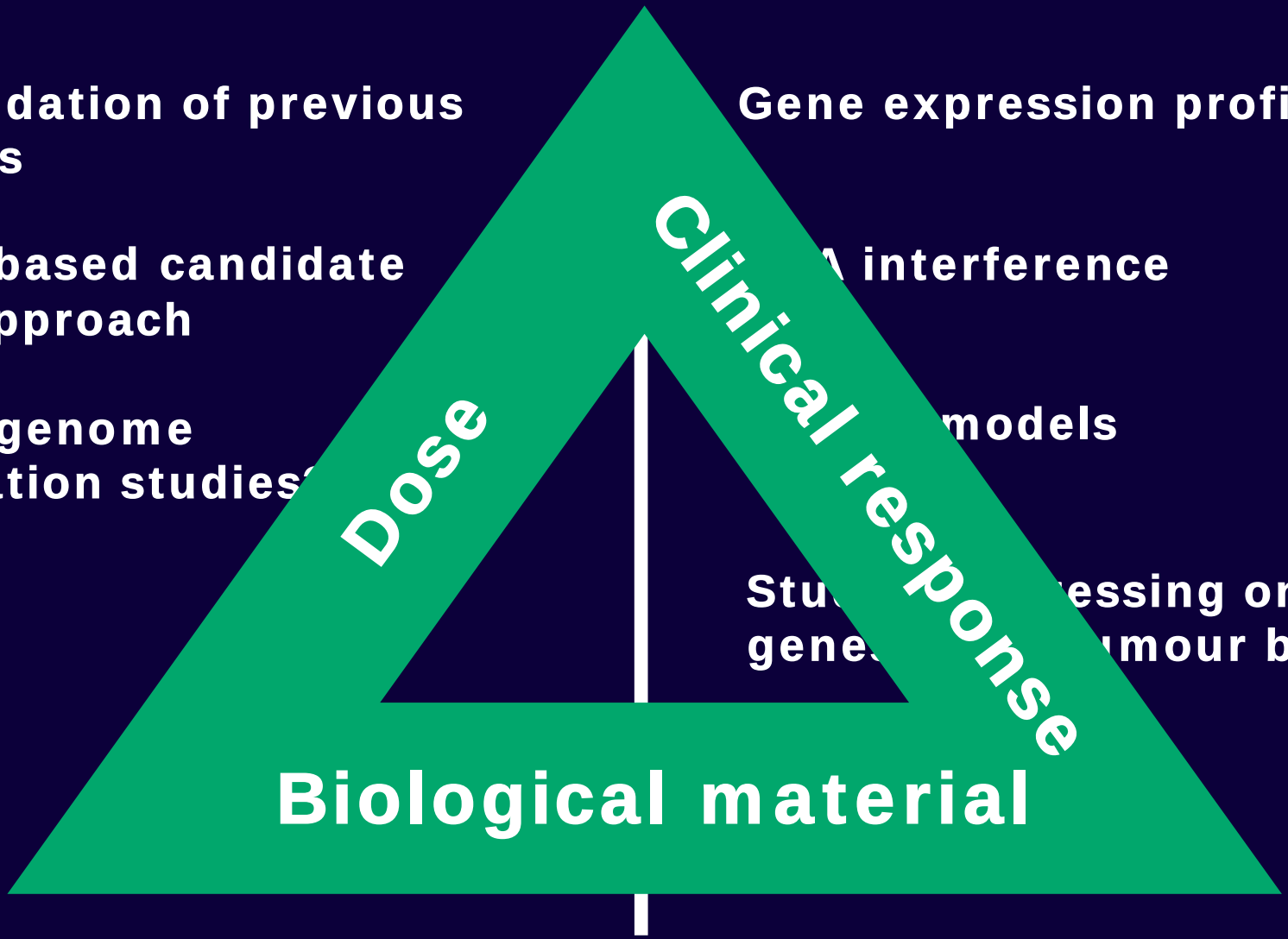
Whole genome association studies

Gene expression profiling

A interference

models

Stu essing onco-
gene umour biology



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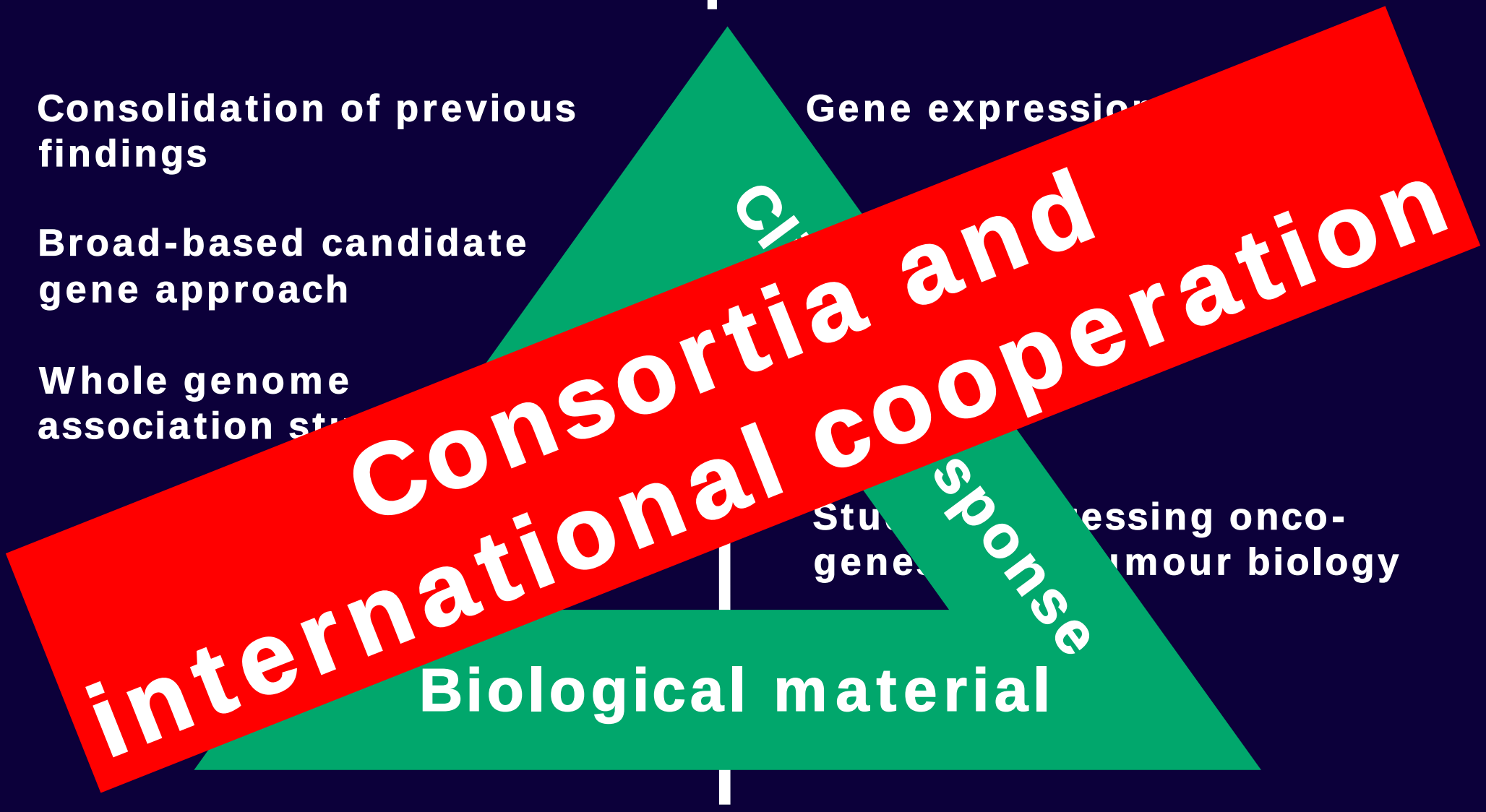

Conclusion

- A number of relatively small and methodologically heterogeneous studies have investigated possible associations between SNPs in candidate genes and clinical normal tissue radiosensitivity
- Indications exist that that SNPs in TGFB1 and ATM may affect normal tissue complication risk
- We are still far from having a comprehensive understanding of the genetics that may underlie radiosensitivity
- Recent advances in molecular biology provide new opportunities to gain insight in the mechanisms underlying radiation-induced normal tissue damage

The persuit for the holy grail

Thank you

for your attention

nicolaj@oncology.dk