

# Which men need genetic counselling and/or testing?

Prof. Ros Eeles

Oncogenetics Team,

The Institute of Cancer Research &

Royal Marsden NHS Foundation Trust, London UK

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# What are the questions?

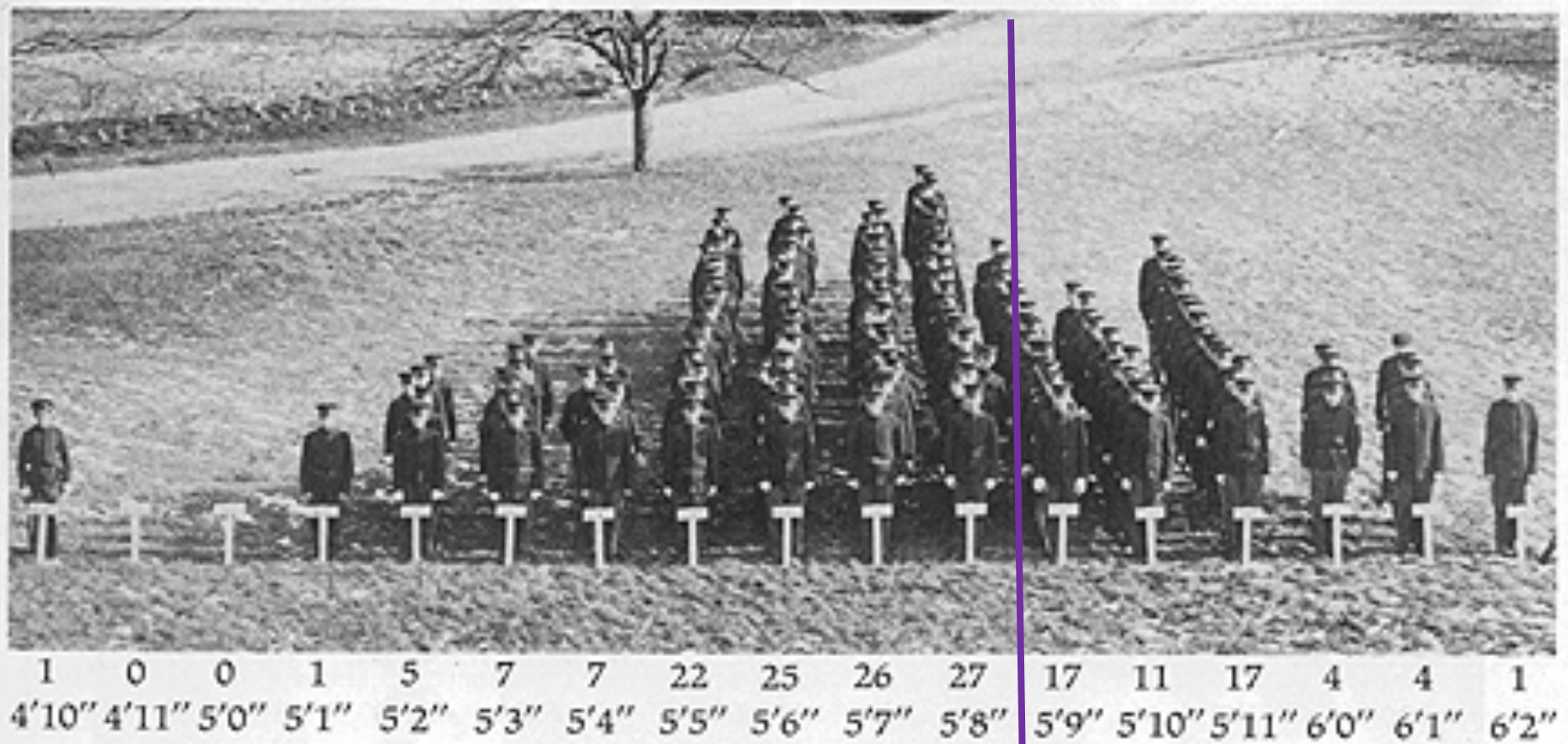
*What is the spectrum of genetic predisposition that we currently know?*

*How should we use this? Who should be tested? Are there international discrepancies in the guidelines?*

*How do we manage men who are at higher risk?*

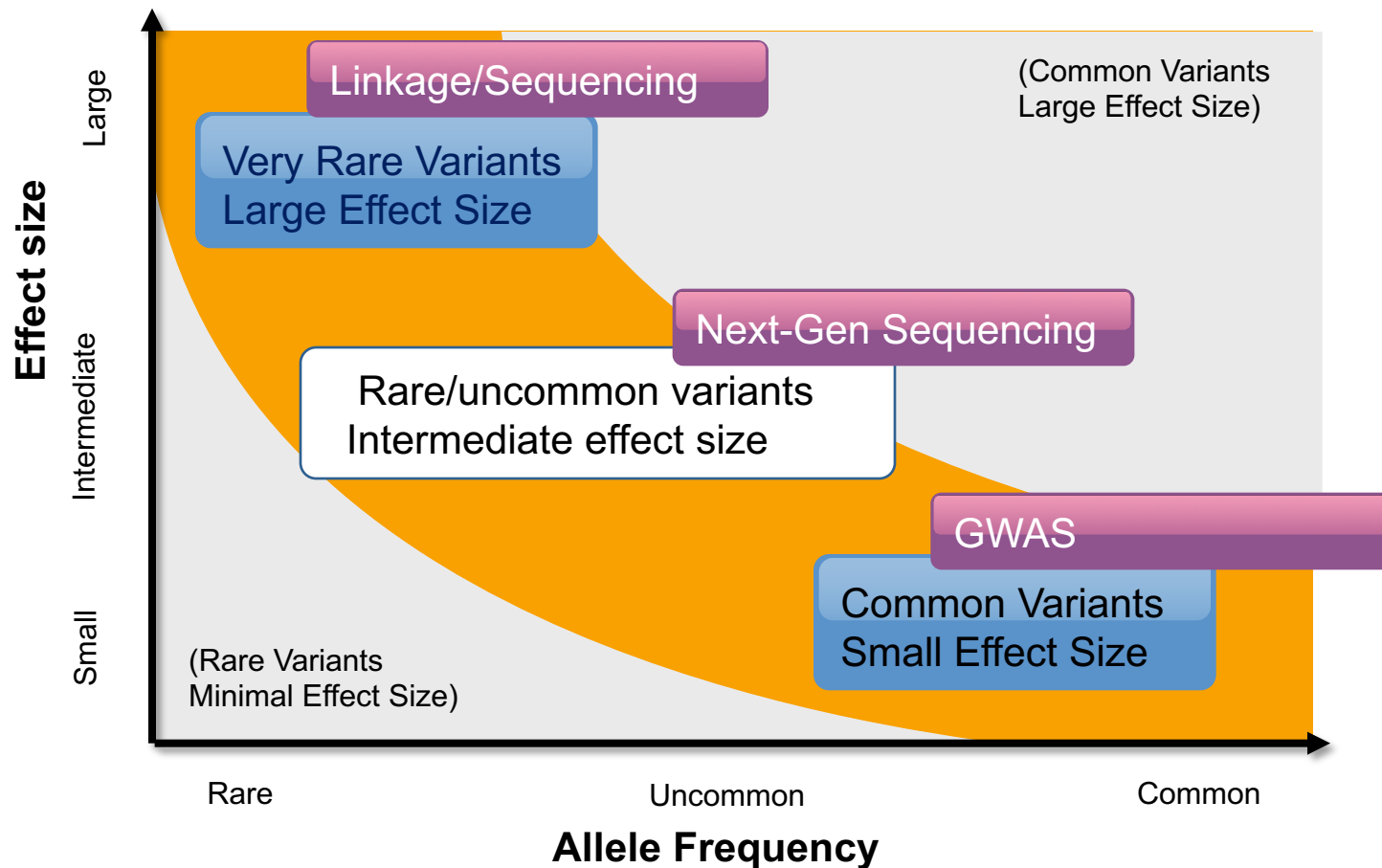
*What will the future look like?*

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Prostate cancer risk distribution has similar pattern

# Finding the Full Spectrum of Genetic Variants in Complex Disease

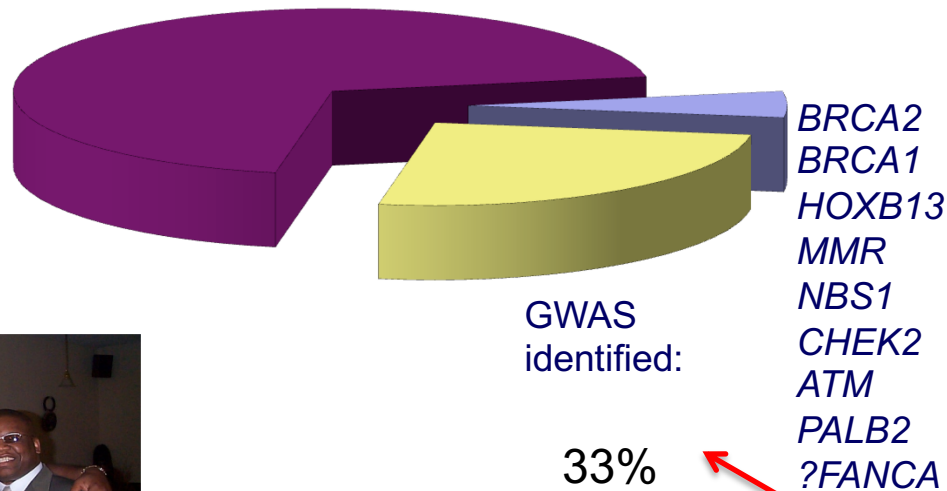


# Excess Familial Risk

## Prostate Cancer

When should we do panel testing?

Unexplained: ~60%



>80 new variants

Now 170  
When should we do  
population mass testing?

$\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$

Europe (31)  
Australia (2)

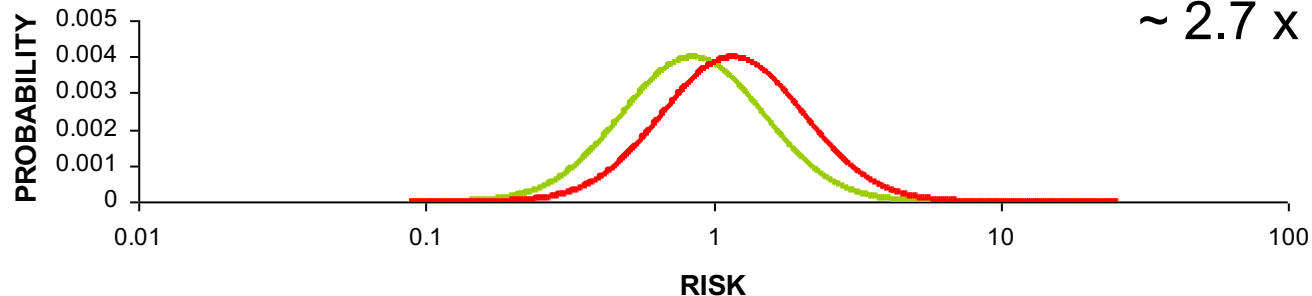
Analysis of 98 500 European samples  
170 SNPs

# Prostate cancer risk prediction

170 common loci

Top 1%  
~ 5.7 x risk

Top 10%  
~ 2.7 x risk



Now a total of 27 loci are also associated with aggressive and early onset <55 years disease (Gleason score  $\geq 8$ ; PSA > 100; death from prostate cancer)

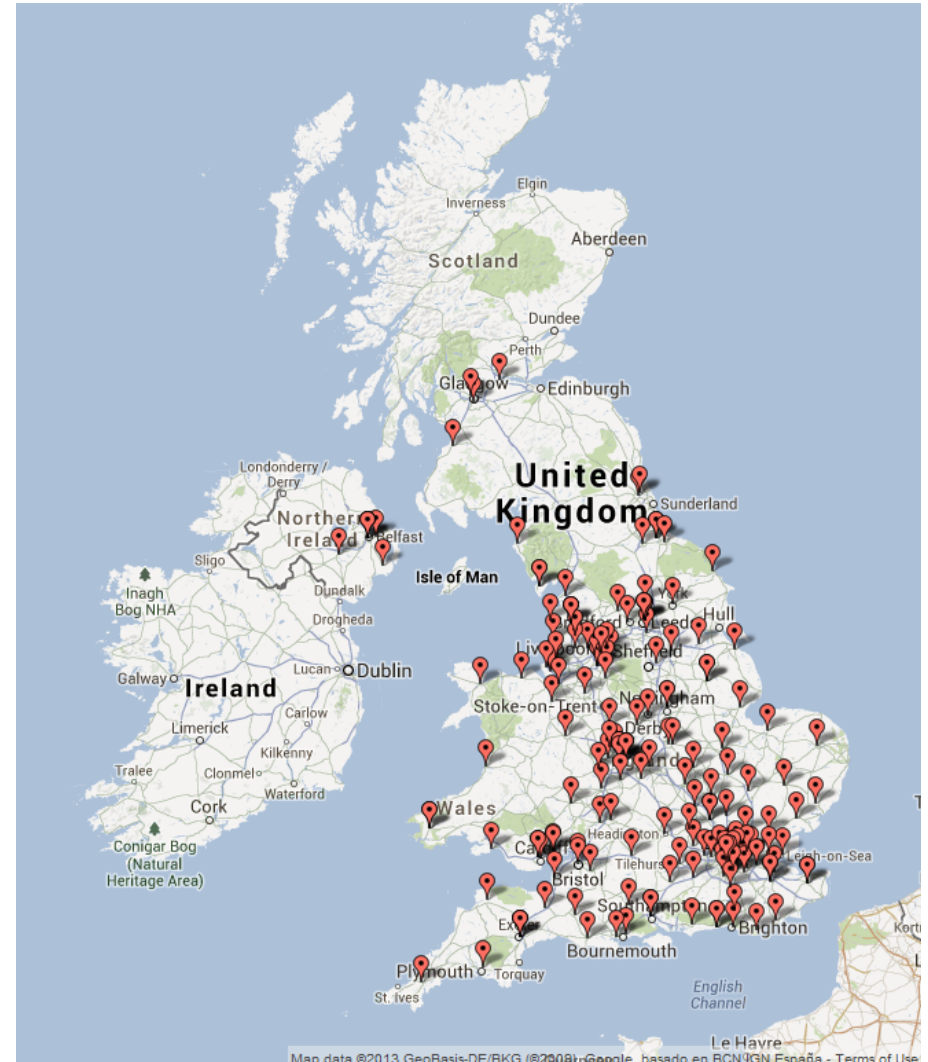


# What is the incidence of DNA repair gene mutation if +ve FH?

All men selected from UK Genetic Prostate Cancer Study(UKGPCS)

191 prostate cancer cases

3+ cases in family any age





# Methods

## Target genes

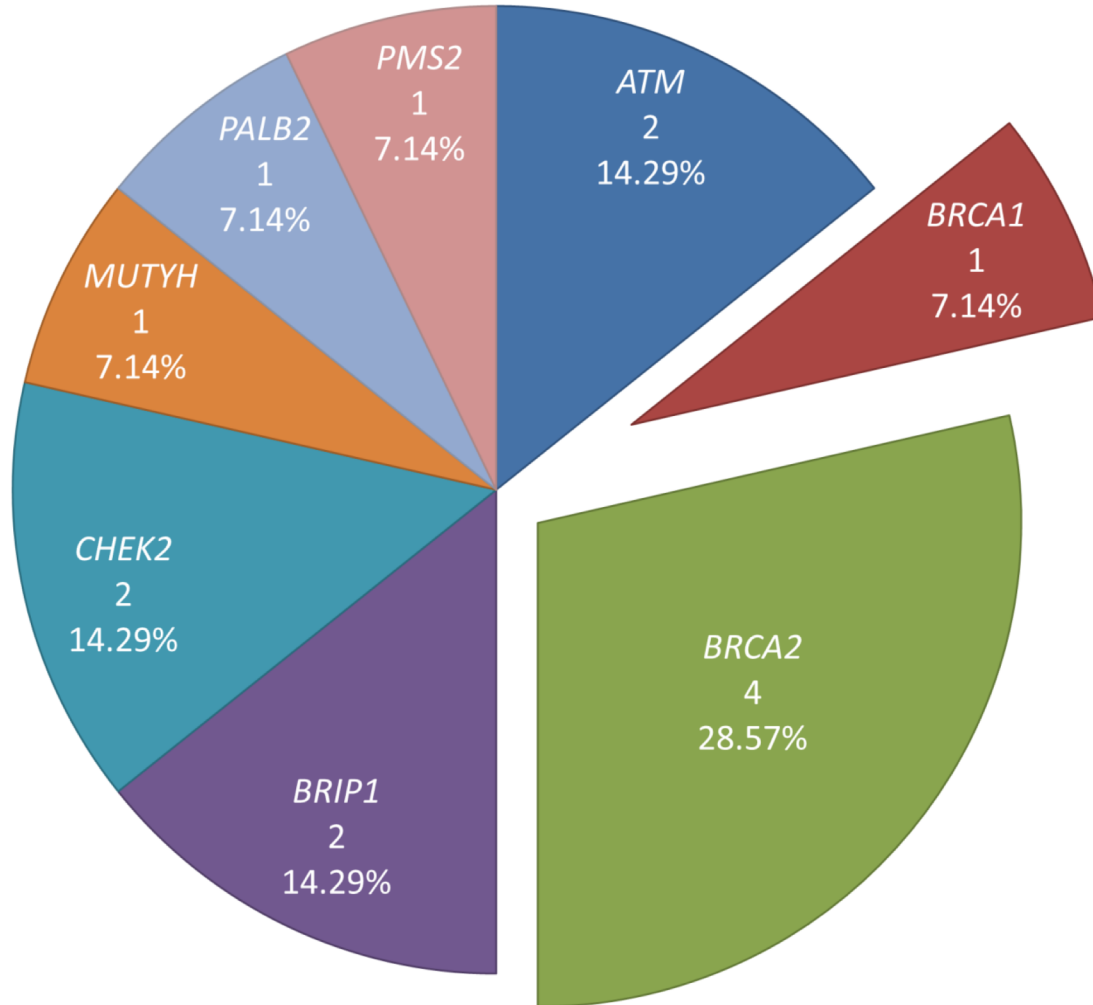
- “BROCA” target capture set, 22 tumour suppressor genes (Walsh *et al.*, 2010)

High risk	Moderate risk	Rare multi-organ cancer syndromes
<b>BRCA1*</b>	PALB2*	TP53 (Li-Fraumeni)
<b>BRCA2*</b>	CHEK2*	CDH1 (Hereditary gastric cancer)
	BRIP1*	PTEN (Cowdens)
	NBS1*	STK11 (Peutz Jeghers)
	RAD50	MLH1 (Lynch )
	MRE11	MLH3 (Lynch)
	ATM	MSH2 (Lynch)
	BARD1	MSH6 (Lynch)
	RAD51C	PMS1 (Lynch)
		PMS2 (Lynch)
		MUTYH (Lynch)

\*Genes implicated previously in PrCa

# Results

## 14 putative LoF mutations in 8 genes



- *BRCA2* most frequent
- *BRIP1* only repeat variant
- 6/13 unique variants novel (1KG, ESP)
- All known variants MAF  $\leq 0.5\%$
- No subject carried more than one LoF mutation
- 7.3% men were carriers

# Results

## LoF status and clinical features

Clinical characteristic		LoF (n=14)		Non-carriers (n=140)		LoF vs non-carriers (P value)
		No	%	No	%	
Age, years	Median	58.5	-	59	-	0.334
	Range	41-71	-	47-82	-	
Gleason	Gleason ≤6	5	35.71%	62	44.29%	0.599
	Gleason 7	2	14.29%	27	19.29%	
	Gleason ≥ 8	3	21.43%	15	10.71%	
	Unknown	4	28.57%	36	25.71%	
Tumour Stage	T1	3	21.43%	38	27.14%	0.776
	T2	4	28.57%	45	32.14%	
	T3	2	14.29%	24	17.14%	
	T4	1	7.14%	2	1.43%	
	Tx	4	28.58%	31	22.14%	
Nodal stage	N0	4	28.57%	76	54.29%	0.00142**
	N1	3	21.43%	1	0.71%	
	Nx	7	50.00%	63	45.00%	
Metastasis	M0	7	50.00%	74	52.86%	0.0431*
	M1	3	21.43%	5	3.57%	
	Mx	41	28.57%	61	43.58%	
PSA at diagnosis, ng/ml	Median	11.1	-	8.25	-	0.156
	Range	3.09-91.12	-	0.04-259	-	

## DNA repair gene mutations in young onset prostate cancer cases in the UK

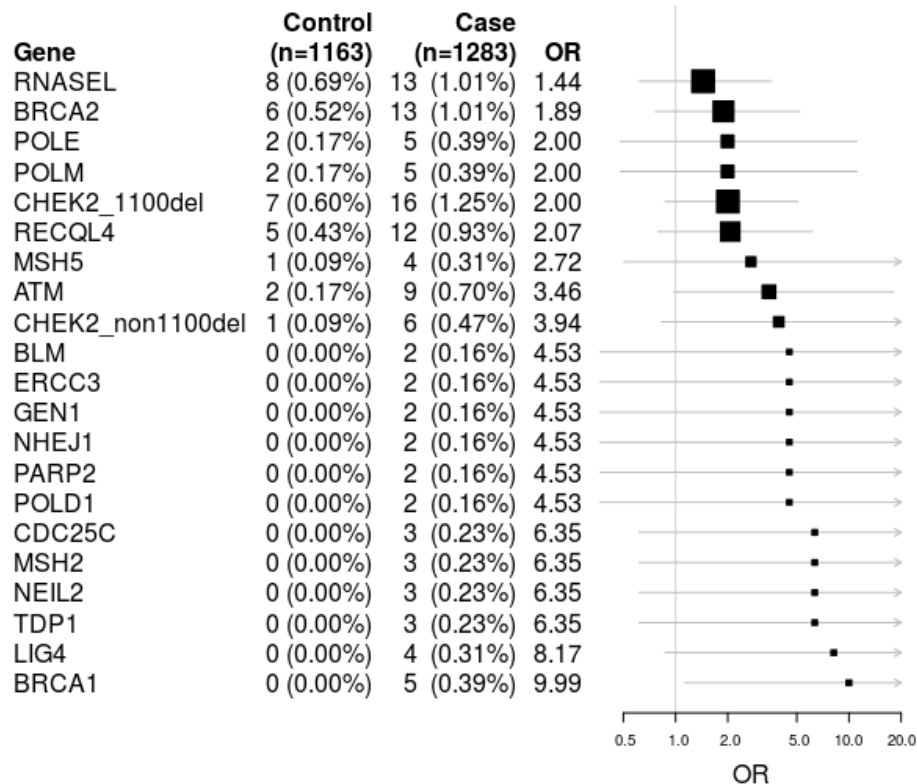
- To investigate the role of rare variants in a large set of young onset (<65 years) PrCa, no selection for family history
- To capture a comprehensive gene set in the DNA repair and damage response pathways including 175 genes
- Design: a case - control study to allow a more comprehensive assessment of all variants compared to UK population frequencies

# Results

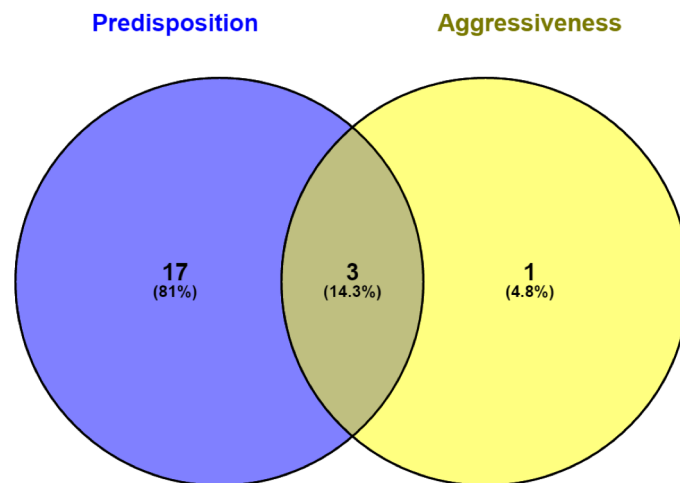
- 2,448 samples  
1,285 cases and 1,163 controls
- The total proportion of PTV carriers in cases was higher than in controls;  
14.5% vs. 11.6%,  $P = 0.036$ ; OR = 1.29, 95% CI 1.01-1.64
- This enrichment was greater within the previously reported BROCA gene set of 22 tumour suppressor genes; 4.5% vs. 2.2%,  $P = 2.5 \times 10^{-3}$ ;  
OR = 2.07, 95% CI 1.28-3.34

# Forest plot of 20 genes selected by ADA case-control analysis

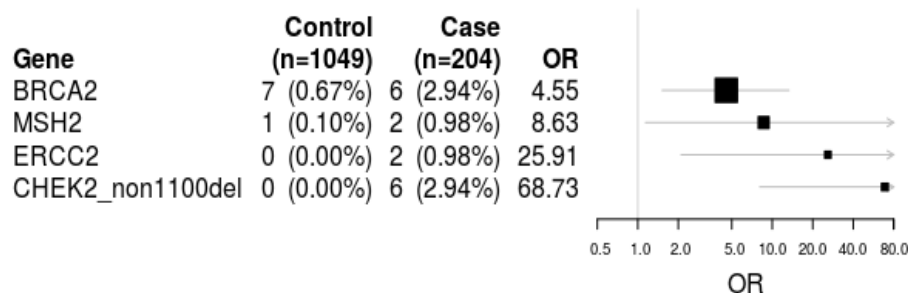
OR estimated by Firth's logistic regression



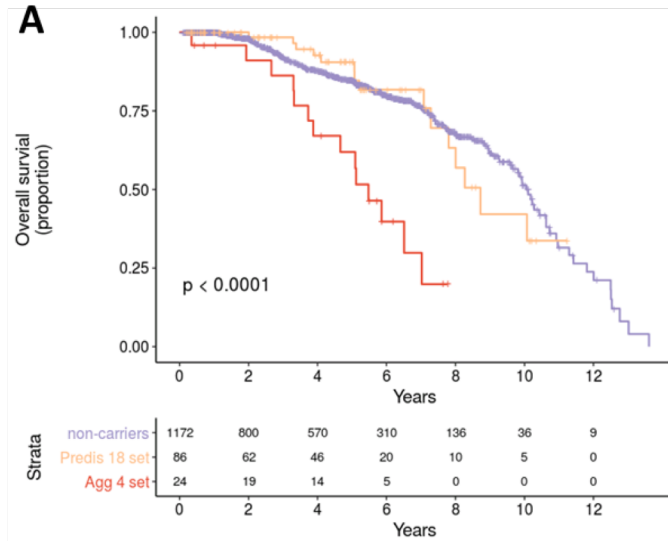
Venn diagram shows the overlap of gene set showing final grouping of Predis 18 and Agg 4 candidate gene sets



4 genes selected by ADA in the aggressive phenotype analysis

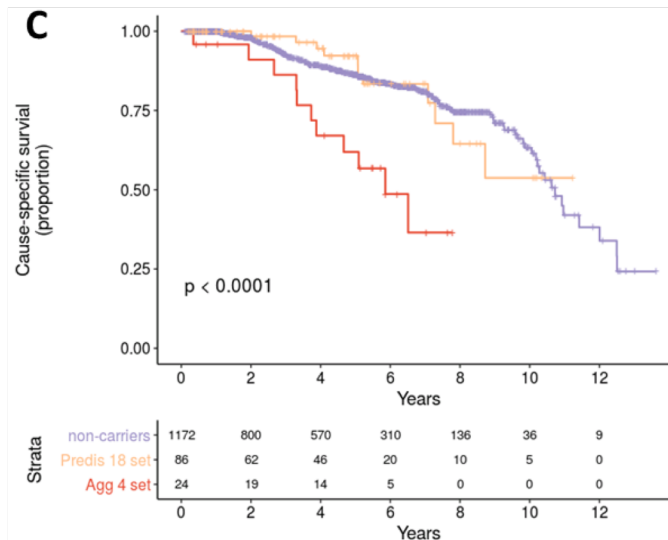


# Gene-set Overall survival (A), multivariate analysis of (OS) (B) Cause-specific survival (C), multivariate analysis of (CSS) (D)



**B**

Variable	OS Events = 236	n	Hazard ratio (95%CI)	p
<b>Geneset carrier status</b>	non-carrier	563		
	Predis 18	39	1.02 (0.40, 2.59)	0.96
	Aggressive 4	15	2.73 (1.24, 6.02)	0.01
<b>Age at diagnosis</b>	Clinical symptoms	617	1.01 (0.94, 1.08)	0.83
<b>Method of detection</b>	Screen Detected	394		
	No	223	0.75 (0.43, 1.32)	0.32
<b>PCa 1° Family history</b>	Yes	492		
	No	125	0.98 (0.45, 2.11)	0.95
<b>PSA</b>	≤10	346		
	>10	271	1.44 (0.88, 2.37)	0.14
<b>Gleason</b>	≤6	268		
	7	247	1.85 (0.99, 3.45)	0.05
	≥8	102	2.09 (1.03, 4.21)	0.04
<b>T stage</b>	T1	151		
	T2	292	0.78 (0.39, 1.55)	0.48
	T3	153	1.08 (0.52, 2.26)	0.84
	T4	21	0.89 (0.34, 2.35)	0.82
<b>N stage</b>	N0	574		
	N1	43	1.50 (0.80, 2.82)	0.20
<b>M stage</b>	M0	584		
	M1	33	7.45 (3.82, 14.53)	<0.001
<b>PRS</b>		617	0.76 (0.56, 1.03)	0.08

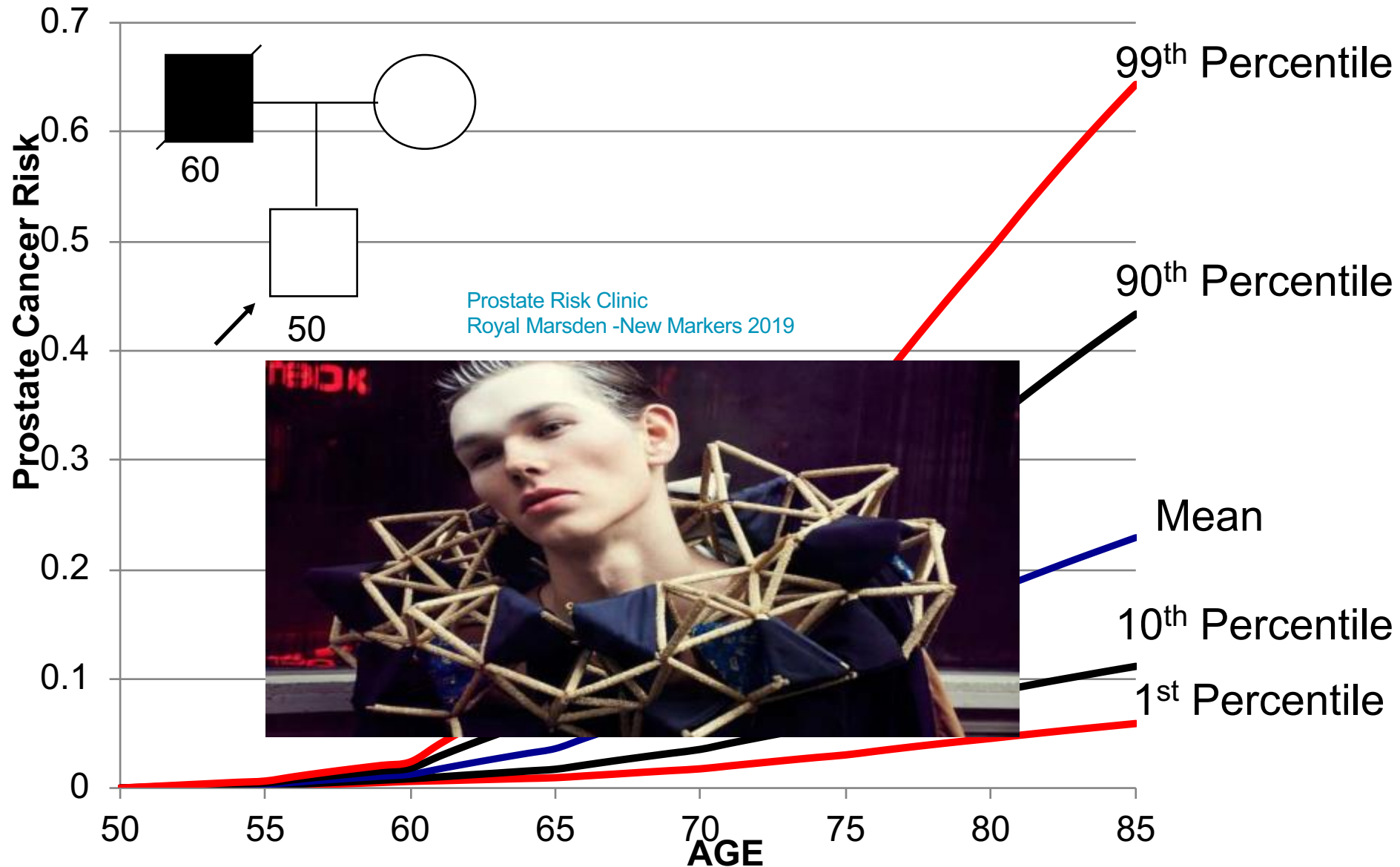


**D**

Variable	CSS Events = 181	n	Hazard ratio (95% CI)	p
<b>Geneset carrier status</b>	non-carrier	563		
	Predis 18	39	1.01 (0.31, 3.36)	0.98
	Aggressive 4	15	1.67 (0.63, 4.38)	0.30
<b>Age at diagnosis</b>	Clinical symptoms	617	0.96 (0.89, 1.03)	0.25
<b>Method of detection</b>	Screen Detected	394		
	No	223	0.50 (0.23, 1.08)	0.08
<b>PCa 1° Family history</b>	Yes	492		
	No	125	0.67 (0.20, 2.24)	0.51
<b>PSA</b>	≤10	346		
	>10	271	1.63 (0.89, 2.98)	0.11
<b>Gleason</b>	≤6	268		
	7	247	3.42 (1.35, 8.67)	0.01
	≥8	102	3.97 (1.48, 10.68)	0.01
<b>T stage</b>	T1	151		
	T2	292	1.09 (0.39, 3.01)	0.87
	T3	153	1.78 (0.64, 4.96)	0.27
	T4	21	1.53 (0.45, 5.19)	0.50
<b>N stage</b>	N0	574		
	N1	43	1.39 (0.70, 2.76)	0.35
<b>M stage</b>	M0	584		
	M1	33	7.01 (3.37, 14.59)	<0.001
<b>PRS</b>		617	0.66 (0.46, 0.96)	0.03



# Predicted Prostate Cancer Risk by SNP profile distribution in addition



# The Interim results from the IMPACT study: evidence for PSA screening in *BRCA2* carriers

Page EC, Bancroft EK, Brook MN, et al

Accepted for Publication in European Urology 14 Sept 2019

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**PLEASE DO NOT TWEET**

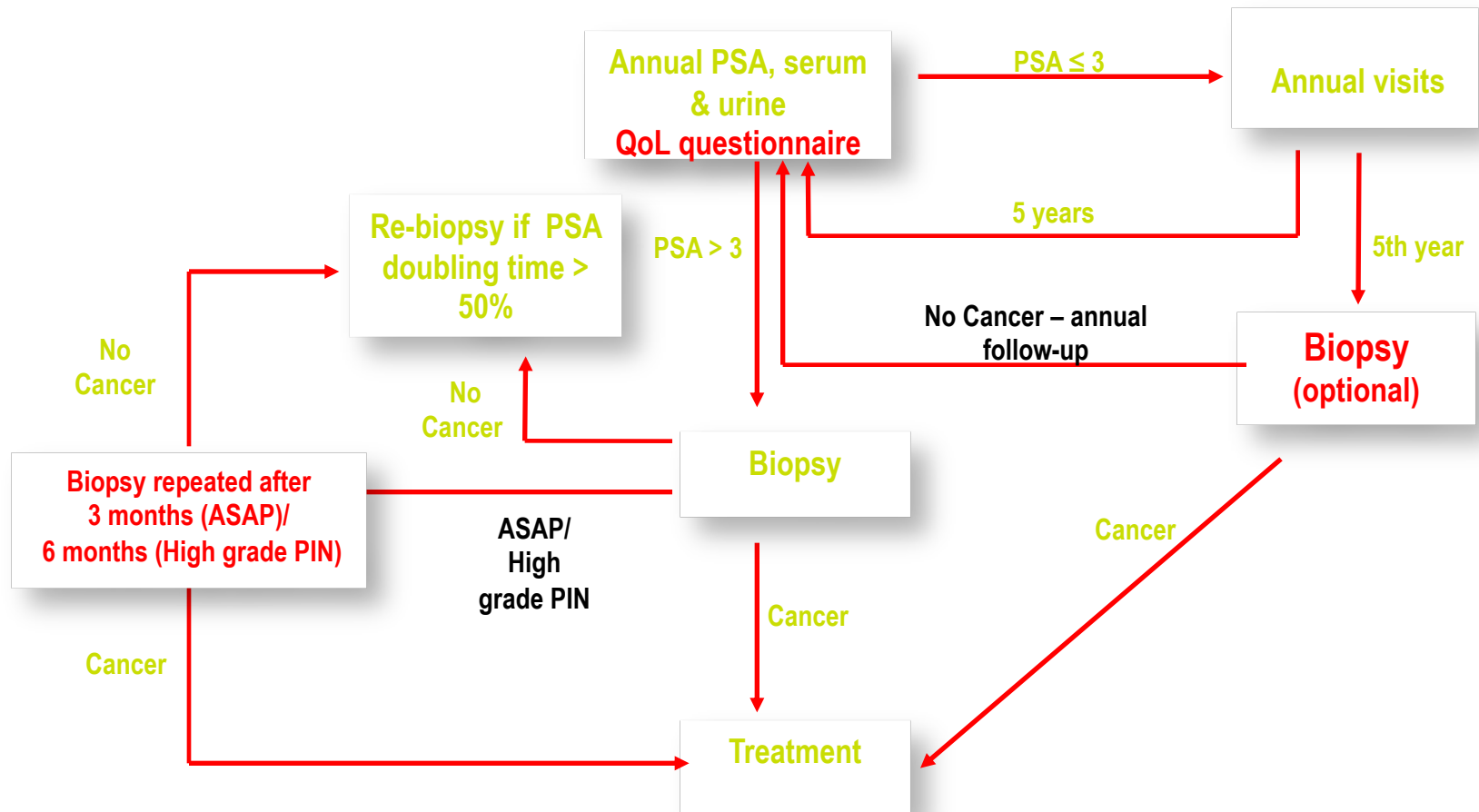
# The IMPACT Study

*Identification of **M**en with a genetic predisposition to **P**rostate  
**C**ancer: **T**argeted screening in men at high genetic risk and  
controls*

**Professor Ros Eeles**

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# Algorithm

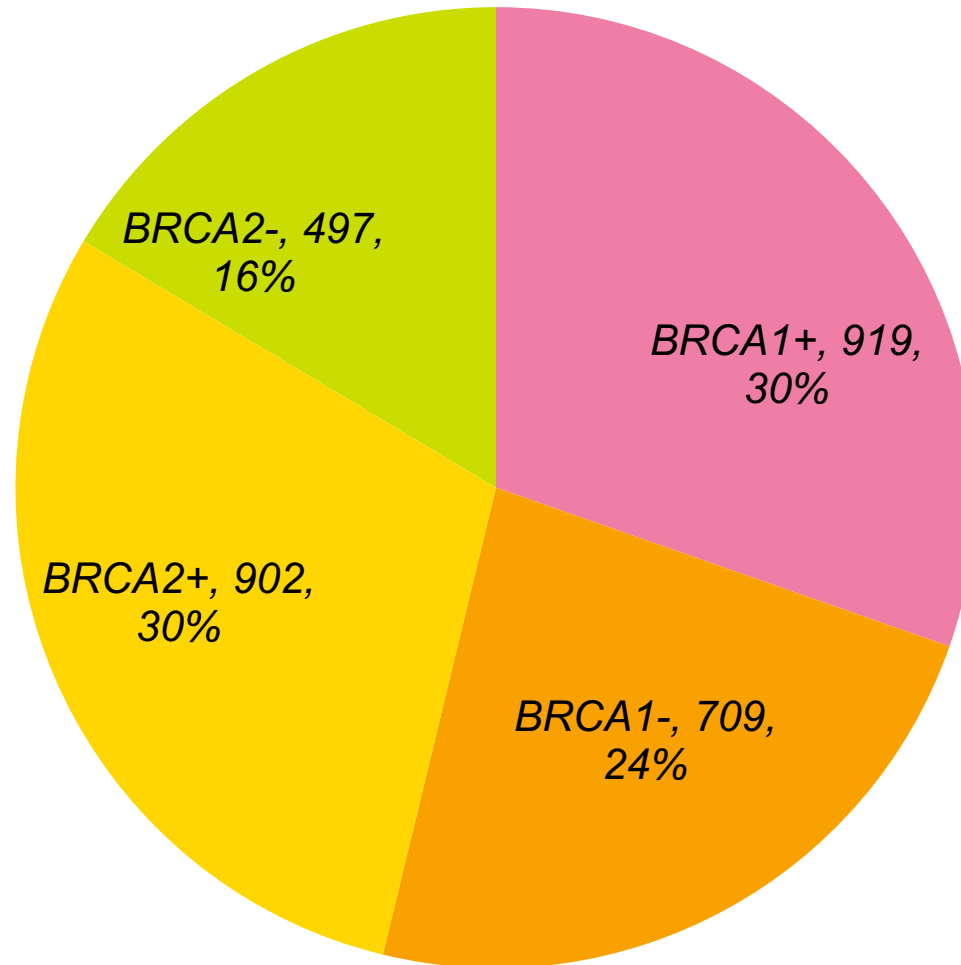


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## 65 recruitment centres in 20 countries

# BRCA Recruitment Population (n=2932)

21



\*An additional 95 BRCA2 controls BRCA1 mutation tested to enable them to be BRCA1 and BRCA2 controls

# Prostate cancer detection rates

## 4 rounds of screening

After 4 rounds of screening:

- 2932 subjects (9363 Total PSAs taken)
- Biopsy frequency 5%
- 112 cancers

Positive Predictive Value of  
Biopsy for *BRCA2* carriers: 31%

*BRCA2* controls: 18% ( $p=0.025$ )

Cancer Incidence Rate (per 100  
years) for

*BRCA2* carriers: 19

*BRCA2* Controls: 12

Incidence Rate Ratio (IRR) for  
*BRCA2 carriers vs controls*

1.95 ( $p= 0.031$ )



# IMPACT data age restricted (50-64 at entry) to match ERSPC Goteborg Study

	Goteborg	IMPACT				
		Overall	<i>BRCA2+</i>	<i>BRCA2-</i>	<i>BRCA1+</i>	<i>BRCA1-</i>
No. Cancers	1396	85	37	11	21	16
No. Biopsies	4654	256	90	32	78	63
PPV of biopsy, (%)	30.00	33.20	41.11	34.38	26.92	25.40
p-value comparison with Goteborg		0.276	0.023	0.590	0.557	0.429

	Goteborg	IMPACT				
		Overall	<i>BRCA2+</i>	<i>BRCA2-</i>	<i>BRCA1+</i>	<i>BRCA1-</i>
No. Cancers	1396	85	37	11	21	16
No. of PSA >3ng/ml requiring action	5365	353	99	57	94	84
PPV of PSA >3ng/ml requiring action, (%)	26.02	24.08	37.37	19.30	22.34	19.05
p-value comparison with Goteborg		0.769	0.004	0.340	0.588	0.227

## Cancer characteristics of PSA detected Cancers

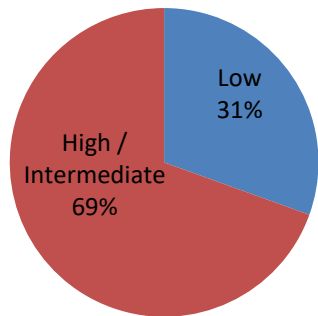
Genetic Status	BRCA2+ (n=48)	BRCA2- (n=15)	p-value	BRCA1+ (n=33)	BRCA1- (n=20)	p-value
Median Age at Diagnosis (IQR) (years)	61 (56, 64)	64 (60, 66)	0.044	62 (57, 66)	61 (58, 62)	0.3
Median PSA at Diagnosis (IQR) (ng/ml)	4.5 (3.6, 5.5)	4.2 (3.4, 6.1)	0.9	4.4 (3.8, 5.9)	4.4 (3.6, 5.3)	0.7
Gleason Score 6	18 (38%)	11 (73%)	0.019**	18 (55%)	13 (65%)	0.6**
Gleason Score 7 (3+4)	15 (31%)	1 (7%)		9 (27%)	4 (20%)	
Gleason Score 7 (4+3)	9 (19%)	2 (13%)		4 (12%)	3 (15%)	
Gleason Score 8+	6 (12%)	1 (7%)		2 (6%)	0	
T stage- T1/T2a	16 (35%)	8 (57%)	0.2**	9 (31%)	8 (40%)	0.6**
T Stage - T2b	2 (4%)	2 (14%)		0	1 (5%)	
T Stage -T2c/T3	28 (61%)	4 (29%)		20 (69%)	11 (55%)	
Risk Category* - Low	11 (23%)	9 (60%)	0.011**	10 (30%)	4 (20%)	0.5**
Risk Category* - Intermediate	7 (14.5%)	1 (7%)		3 (9%)	6 (30%)	
Risk Category* - High	30 (62.5%)	5 (33%)		20 (61%)	10 (50%)	
Screening Round diagnosed -1	25 (52%)	7 (47%)		23 (70%)	13 (65%)	
Screening Round diagnosed -2	7 (14.5%)	1 (7%)		3 (9%)	3 (15%)	
Screening Round diagnosed -3	9 (19%)	5 (33%)		6 (18%)	2 (10%)	
Screening Round diagnosed -4	7 (14.5%)	2 (13%)		1 (3%)	2 (10%)	
Active Surveillance	8 (17%)	7 (47%)		5 (17%)	6 (30%)	
Radical Prostatectomy	32 (70%)	6 (40%)		22 (76%)	12 (60%)	
Only non-surgical Treatment	6 (13%)	2 (13%)		2 (7%)	2 (10%)	

\*Using NICE guidelines, risk category classification system (<https://www.nice.org.uk/guidance/cg175/chapter/recommendations>)

\*\*p-values calculated on difference between clinically significant disease and non-clinically significant disease

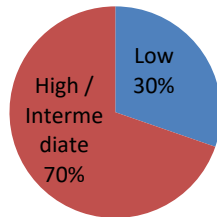
# Results using NICE guidelines

## Overall Risk Category - All Cancers



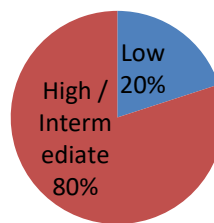
### Overall Risk Category - BRCA1 mutation carrier

+



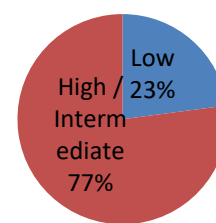
### Overall Risk Category - BRCA1 mutation non carrier

-



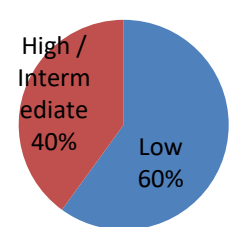
### Overall Risk Category - BRCA2 mutation carrier

+



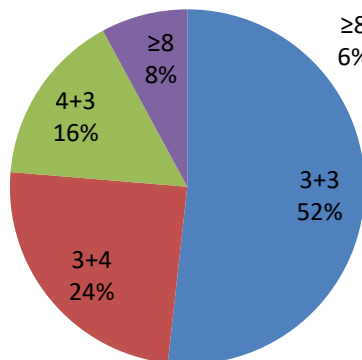
### Overall Risk Category - BRCA2 mutation non carrier

-



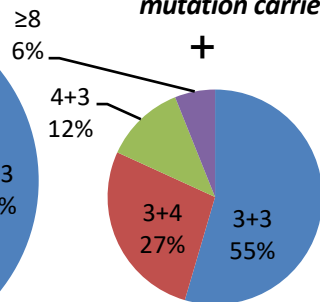
## Final Gleason Score

### Overall Gleason Score - All Cancers



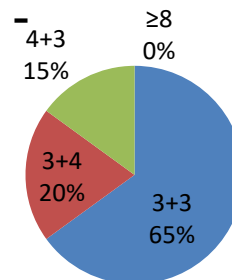
### Overall Gleason Score - BRCA1 mutation carrier

+



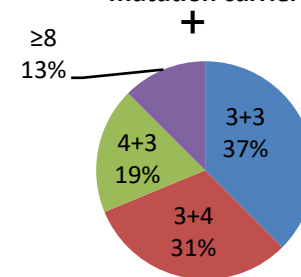
### Overall Gleason Score - BRCA1 mutation non carrier

-



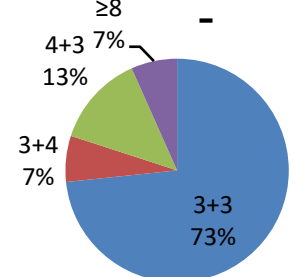
### Overall Gleason Score - BRCA2 mutation carrier

+



### Overall Gleason Score - BRCA2 mutation non carrier

-



# Interim Analysis Summary

After four annual PSA screening rounds *BRCA2* mutation carriers:

- Cancer incidence rate per 1,000 person years was higher in *BRCA2* carriers than non-carriers (19.4 vs 12.0;  $p=0.03$ )
  - Younger at diagnosis median age 61 vs 64 years ( $p=0.04$ ) in *BRCA2* carriers vs non carriers
  - have significantly more aggressive tumours than non-carriers. 77% vs 40% ( $p=0.011$ ) intermediate and high risk disease in *BRCA2* carriers vs non carriers
- Systematic PSA screening is indicated in men carrying a *BRCA2* mutation

Not seen in *BRCA1* but more follow up needed

## What is here and what is coming?

Men with prostate cancer and a family history of breast/ovarian cancer  
-BRCA1/2 germline testing



Panel testing for men with young onset disease, FH prostate cancer  
and mCRPC                      ?AS



PP/  
US



-Testing at diagnosis - mainstreaming in prostate cancer in those on AS and castrate resistant cases

-Testing for common variants to stratify populations and modify risk of those with a family history

-Associated screening programmes stratified by risk

[ros.eeles@icr.ac.uk](mailto:ros.eeles@icr.ac.uk)

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## CNIO

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## The IMPACT study



The ROYAL MARSDEN  
NHS Foundation Trust



PRACTICAL

