Ensuring more men at high risk of prostate cancer are diagnosed early

-considerations of family history and genetics

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What do we currently know?

- The risks are higher in:

-men with a family history (2-10 fold depending on the strength of the family history)

-men of African/Black African-Caribbean ancestry

-those with higher genetic risk (single gene variants and a combination of common variants)

ICR The Institute of Cancer Research

The UK Genetic Prostate Cancer Study

PROSTATE CANCER UK

CANCER RESEARCH UK

NIHR | National Institute for Health Research

in partnership with

The ROYAL MARSDEN NHS Foundation Trust

UK data
16430
men
Mainly
European
origin

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European Association of Urology

Prostate Cancer

Family History of Prostate Cancer and Survival Outcomes in the UK Genetic Prostate Cancer Study

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Article info

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Abstract

Background: A family history (FH) of prostate cancer (PrCa) is associated with an increased likelihood of PrCa diagnosis. Conflicting evidence exists regarding familial PrCa and clinical outcomes among PrCa patients, including all-cause mortality/overall survival (OS), PrCa-specific survival (PCSS), aggressive histology, and stage at diagnosis.
Objective: To determine how the number, degree, and age of a PrCa patient's affected relatives are associated with OS and PCSS of those already diagnosed with PrCa.

Results

- A FH of PrCa in patients with a diagnosis of PrCa was associated with a decreased risk of death from all cause
- This association was greater in those with an increasing number (p-trend = $1.1x10^{-5}$) and increasing closeness (p-trend = $6.2x10^{-4}$) of the diagnosed relatives.

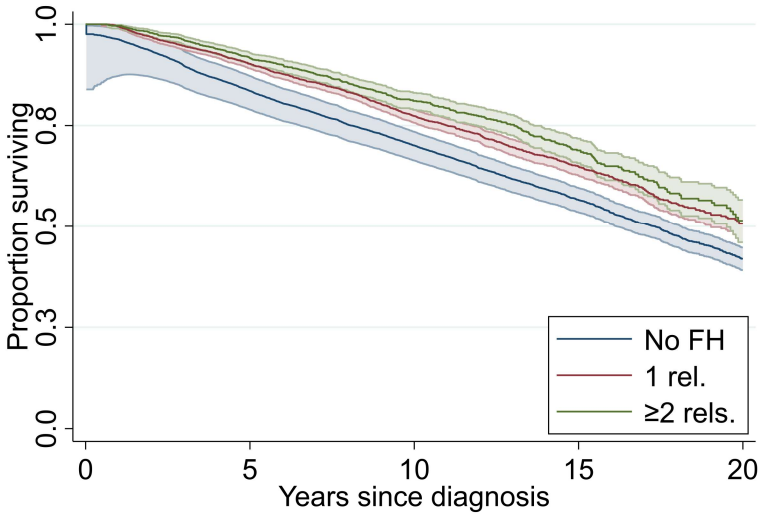


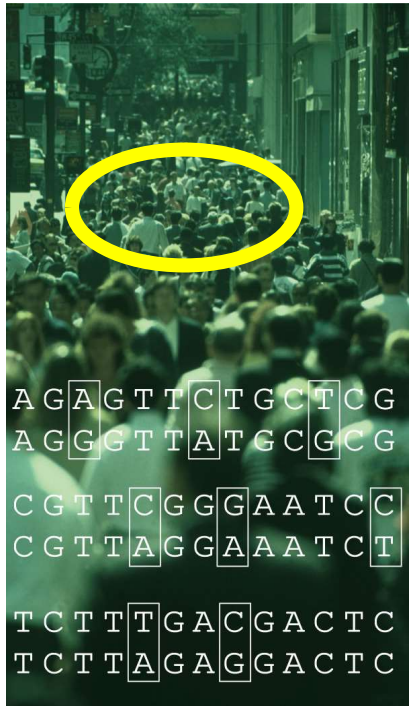
Fig. 1: Overall survival by number of affected relatives

	Censored, N	Deaths, N	Total, N	Person-years of follow-up, N (%)	Haz. Ratio	(95% C.I.)	P	P-trend
No FH	7,278	3,059	10,337	81,609 (63.4)		Ref.		
1 Rels	3,071	910	3,981	31,015 (24.1)		0.85 (0.79, 0.93)	$1.5x10^{-4}$	
2+ Rels	1,611	411	2,022	16,125 (12.5)		0.80 (0.71, 0.90)	$3.2x10^{-4}$	$1.1x10^{-5}$

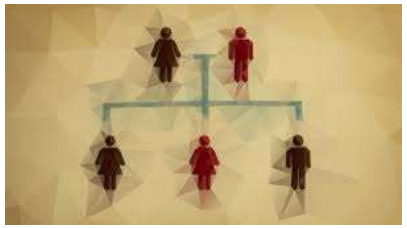
The genetic alterations we can currently find

Common
Variation
20% of individuals
have ≥2 fold risk

Polygenic risk score



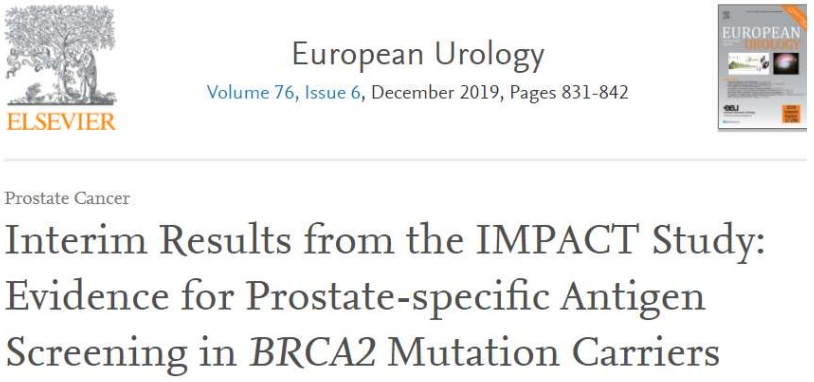
Rare genetic variants



Results from the IMPACT studies of targeted PSA screening in *BRCA1/2* and Lynch Syndrome mutation carriers

These papers showed we should do

- Yearly PSA in carriers of *BRCA2* mutations from 40
- *BRCA2* is now EAU guideline but not in UK

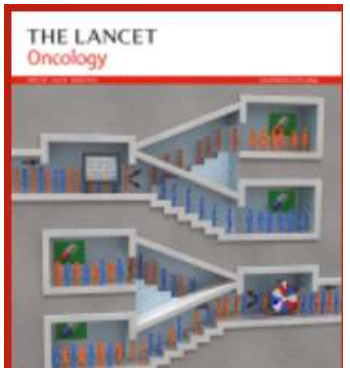


Those with gene mutations are more likely to have aggressive disease

- *BRCA2* 77% (versus 40%)

Baseline data at the moment for MSH2/6 so too early for guideline

- *MSH2* 85% (11 of 13)
- *MSH6* 75% (3 of 4)



Page EC, Bancroft EK, Brook MN, et al. Interim results from the IMPACT study: evidence for prostate-specific antigen screening in BRCA2 mutation carriers. Eur Urol 2019; 76: 831–42

Bancroft E, Page EC, Brook MN, et al. A prospective prostate cancer screening programme for men with pathogenic variants in mismatch repair genes (IMPACT): initial results from an international prospective study. Lancet Oncol 2021; 22 (11) :1618-1631

Prostate screening

- Currently no prostate cancer general population screening programme
- PSA screening debate
  - What is a 'normal' PSA?
  - What screening interval?
  - Optimal imaging?
  - When to biopsy?
- Overdiagnosis / overtreatment
- Screening high-risk individuals
  - benefit outweigh potential harms?
  - Research ongoing internationally

Research focussed on stratifying screening for higher-risk men using genetics

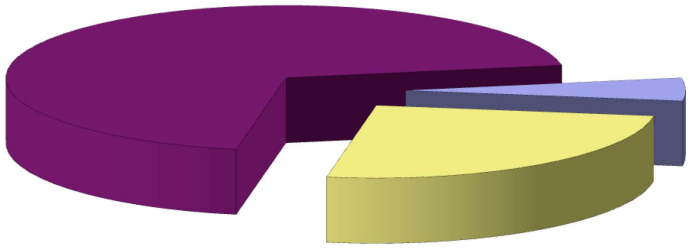
	General Population screening	Screening in men with a Family History	Screening in Black men	Screening in *BRCA2* carriers
American Urological Association	No	Yes from 40 years	Yes from 40 years	Not specified
American Cancer Society	No	Yes from 40-45 years	Yes from 40-45 years	Not specified
European Association of Urology	No	Yes from 45 years	Yes from 45 years	Yes from 40 years
NICE / NSC	No	Not specified	Not specified	Not specified

Excess Familial Risk

Prostate Cancer

Panel of genes – mainly DNA repair

451 SNP score
applicable to Black men



What do we not know?

1. FH has 2-fold risk - this is also the risk to those with other DNA repair gene mutations and higher PRS and in Black men -we know the risks but apart from *BRCA2,* not the outcomes of implementing screening in these groups
2. Do men with other rare genetic variants have the same risks as *BRCA2* mutation carriers and should they therefore have annual PSA screening from 40?
3. We do have PSA data reducing mortality in Europeans at 15 -22 years (20%) CAP/ERSPC but not in diverse groups
4. Should men at higher risk have MRI or PSA or biopsy?
5. BARCODE 1 PRS study (NEJM in press McHugh, Bancroft et al and Eeles 2025) of PRS and biopsy found 40% had cancer and 55% of those were Gleason 7 and above and 21% needed radical treatment – MRI did not see 66% of cancers in more favourable disease and 17% of aggressive cancers – is PRS associated disease therefore different?
6. Will PRS deliver for diverse groups?

PROSTATE CANCER UK
TRANSFORM

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Prostate health checks

Arm 1: PSA 3 + MRI

PSA ≥ **3**ng/ml

↓

Prostagram™

↓

Targeted biopsy

Arm 2: PSA 1 + MRI

PSA ≥ **1**ng/ml

↓

Prostagram™

↓

Targeted biopsy

Arm 3: MRI-only

Any PSA level

↓

Prostagram™

↓

Targeted biopsy

Arm 4: PRS

PRS ≥ **3.5%**

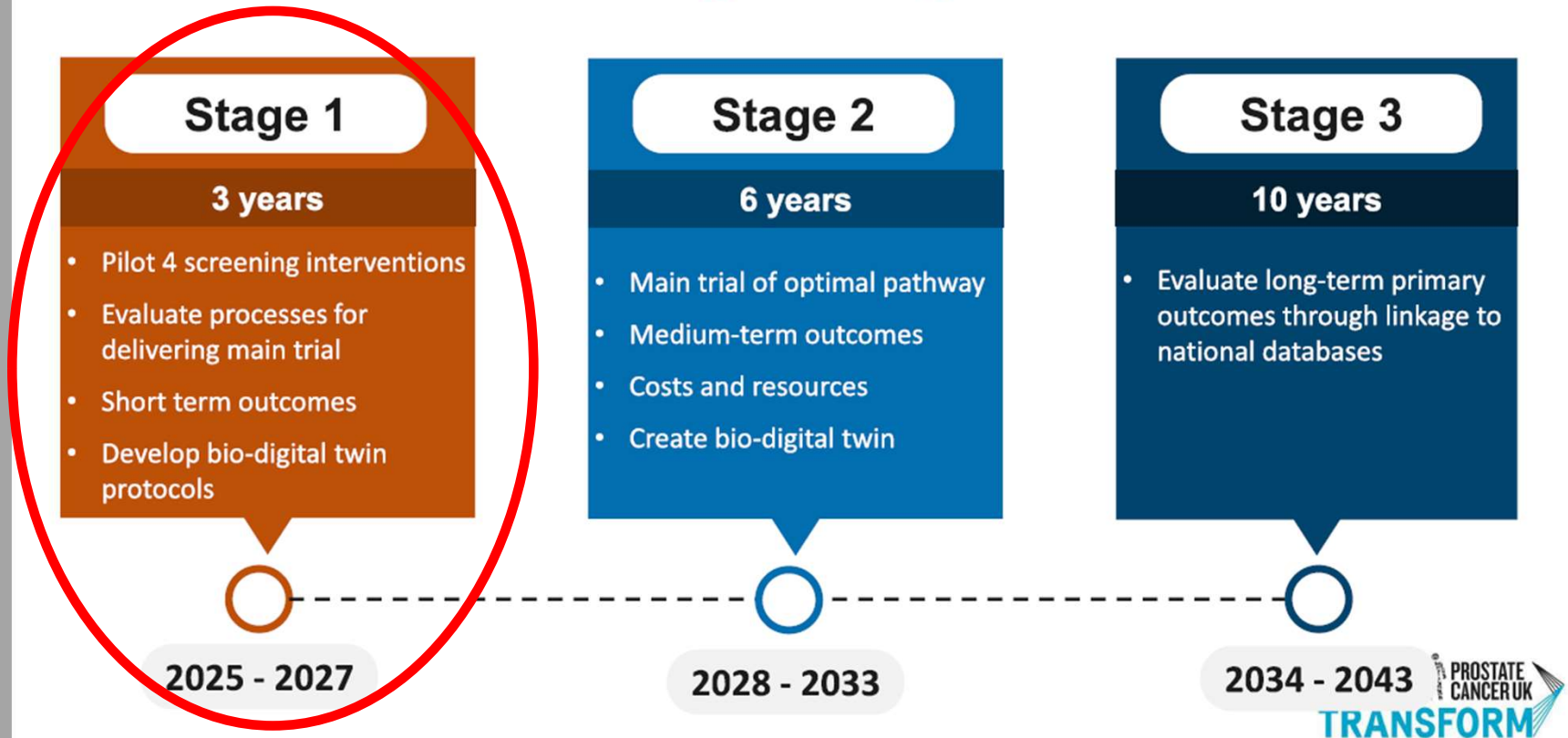
↓

Prostagram™

↓

Targeted biopsy

TRANSFORM – 3 stage design



So what should we do?

1. FH of prostate cancer and cancer in Black men has at least a 2-fold risk and a GP can currently discuss PSA screening
2. We should consider implementation of the EAU guideline for carriers of *BRCA2* mutations
3. Research needs to continue in higher risk groups to find the optimal pathways for screening
4. We need the TRANSFORM study to deliver (early results by 2027) and it has an inbuilt biobanking design