CANCER RESEARCH HORIZONS

Germline Panel for Prostate Cancer **Biochemical Recurrence Prediction**

Non-confidential summary, 2024

FURTHER FASTER TOGETHER
We are beating cancer

Our mission

We are a cancer-focused diagnostic and drug discovery, development and commercialisation organisation that fast-tracks scientific breakthroughs for patient benefit.

INNOVATION ENGINE

A powerful innovation engine, built to complement and realise the full potential of CRUK's network of exceptional investigators and cancer centres, and ~$500M annual R&D spend.

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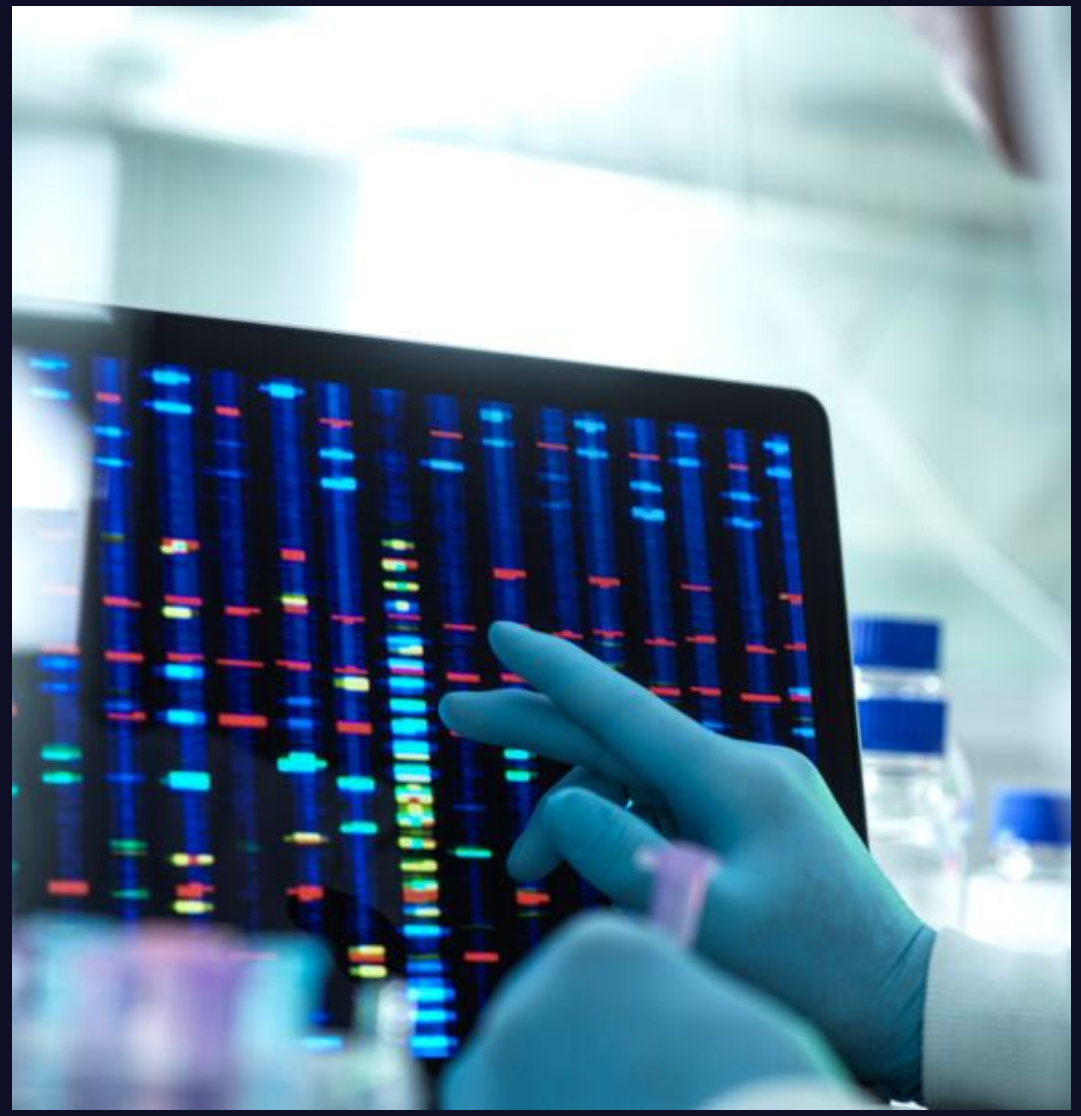
We are currently seeking co-development and/or licensing interest in the Prostate Cancer Germline Panel to translate this technology into the clinic.

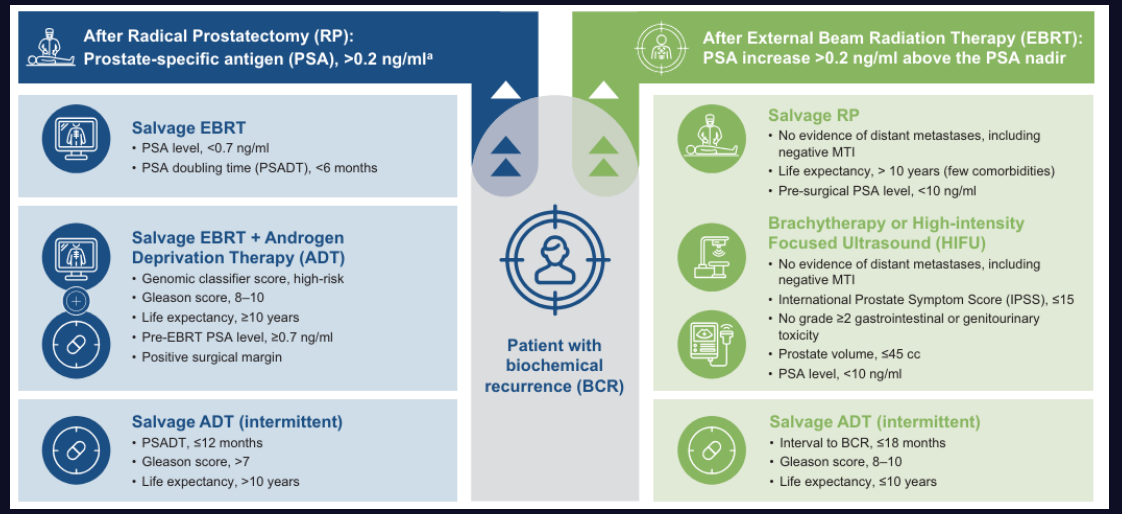


Opportunity overview

- **Technology:** A germline panel to stratify patients with higher chances of biochemical recurrence after radical prostatectomy.
- **Unmet need:** Effective management of patients after radical prostatectomy requires that physicians evaluate PSA levels, as well as clinical and radiologic indicators, to balance the efficacy of proposed treatments against the risks of recurrence and metastatic progression. Current tests on the market informing on somatic changes are effective for determining progression, but not after radical surgery, as they need a large tumour load to be positive.
- **Solution:** A predictive germline test which can be done without any obvious tumour being present. The research team have shown that rare deleterious coding germline variants are robustly associated with time to recurrence after radical treatment.
- **Unique Value:** Germline signatures have the advantage to help stratify patients in both pre- and post- operative settings and follow up strategies as they don't rely on tumour-based analysis.
- **Stage of Development:** The panel has been derived using whole-genome sequencing data of blood DNA from 850 prostate cancer patients with radical treatment from the Pan Prostate Cancer Group (PPCG). The findings were validated with 383 patient samples from The Cancer Genome Atlas (TCGA) dataset and further validation is ongoing.
- **Clinical Impact:** A germline test presents the possibility to triage treatment intensification. Identifying patients more likely to relapse post-radical prostatectomy can help putting them on a different clinical treatment plan comprising more radical / earlier intervention or more frequent follow-up.
- **Team**: Prof. Rosalind Eeles & Dr. Zsofia Kote-Jarai, The Institute of Cancer Research.
- **Intellectual Property Status:** Patent covering the biomarker panel for detecting the germline variants and predicting a patient's prognosis of prostate cancer; PCT filed April 2023; (WO2023209401A1).
- **Publication:** *European Urology,* Volume 82, Issue 2, 2022, https://doi.org/10.1016/j.eururo.2022.05.007.

30% of patients present biochemical recurrence after radical prostatectomy

- **Radical prostatectomy is the default primary treatment** for patients diagnosed with clinically localised prostate cancer[1]
- However, **radical prostatectomy fails in 30% patients**, presenting biochemical recurrence (BCR)[2]
- **Effective management of patients after radical prostatectomy is logistically complex**, requiring multiple clinical and radiologic indicators[3]



Effective monitoring of BCR can be resource demanding and logistically complex [4]

1. Pessoa RR, et al. Transl Androl Urol. 2021 May;10(5):2158-2170.
2. Tourinho-Barbosa R, et al. Int Braz J Urol. 2018 Jan-Feb;44(1):14-21.
3. Burns, D, et al. Eur. Urol. 2022, 82, 201–211.
4. Shore, N.D, et al. Prostate Cancer Prostatic Dis 27, 192–201 (2024).

A more sensitive diagnostic tool is needed for effective management of patients after radical prostatectomy

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Unmet clinical need

Current prostate cancer patient monitoring tests informing on somatic changes are effective for determining progression, but not after radical surgery, as they need a large tumour load to be positive[1]

Ideal state for post-radical prostatectomy cancer care

Triaging treatment intensification using a sensitive diagnostic tool to effectively balance the efficacy of proposed treatments against the risks of recurrence and metastatic progression.

1. Burns, D, et al. Eur. Urol. 2022, 82, 201–211.

The germline-based approach can enable effective patient stratification at the key clinical decision points

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Our Solution: A diagnostic test based on rare germline variants that can predict time to biochemical recurrence (BCR) after prostatectomy.

Unique Value:

Identifying patients more likely to relapse post-radical prostatectomy will enable:

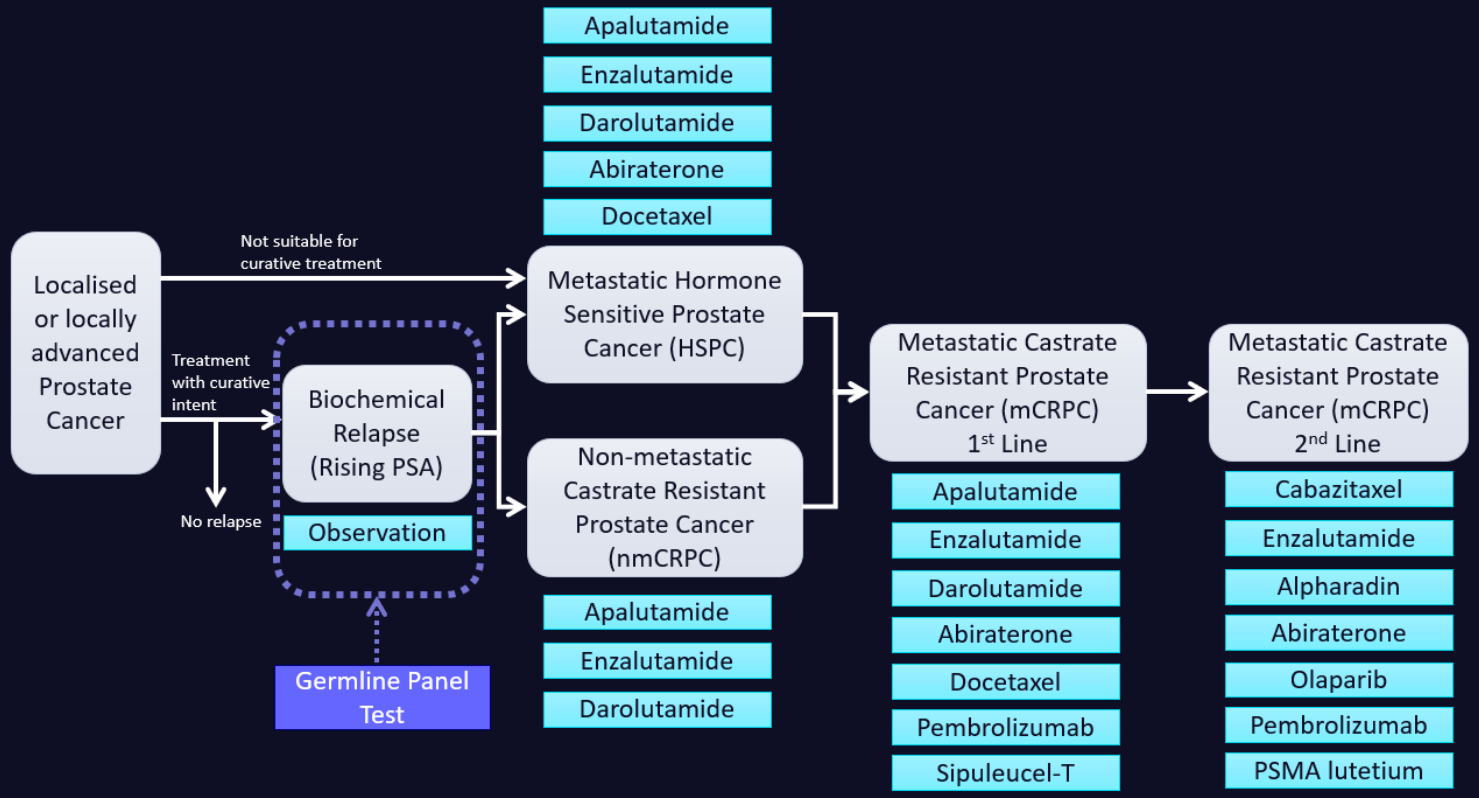
- Adapting the clinical treatment plan to comprise more radical treatment
- Earlier intervention / radiotherapy
- More frequent follow-up and monitoring

Advantages:

- Germline testing can be done without any obvious tumour being present, so it can overcome the limitations of the standard of care somatic tests.
- Germline signatures can help stratify patients in both pre- and post- operative settings and follow up strategies as they do not rely on tumour-based analysis.

The test has potential to enable effective patient stratification in the clinical journey

*Our optimised germline panel will be applied following local treatment with curative intent (post radiotherapy or post radical prostatectomy), with the potential to help **30% of patients** get the right intervention at the right time.*



The panel has been validated on TCGA patient samples and further validation is ongoing

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Methodology and completed validation

- The panel has been derived using whole-genome sequencing data of blood DNA from 850 prostate cancer patients with radical treatment from the Pan Prostate Cancer Group (PPCG).
- The findings were validated with 383 patient samples from The Cancer Genome Atlas (TCGA) dataset.

Gene-sets used for panel validation:

- Hypoxia
- PI3K/ AKT/mTOR signalling
- TNFA signalling via NFKB
- KRAS signalling
- Inflammatory response

Ongoing validation and future plans

- Develop a model to predict outcome in clinical trials using germline variants.
- Analyse germline-somatic interactions and their impact on prostate cancer progression.
- Determine whether a profile can predict response to radiotherapy.

The technology is developed by world leading experts in Prostate Cancer Oncogenetics

CRUK and ICR have a strong track record in developing Prostate Cancer therapeutics (e.g. Zytiga®), new forms of radiotherapy, and diagnostic tools

Prof. Rosalind Eeles is a Professor of Oncogenetics at the Institute of Cancer Research and clinician at the Royal Marsden NHS Foundation Trust. She is a leader in the field of genetic susceptibility to prostate cancer, and is known for the discovery of 14 genetic variants involved in prostate cancer predisposition.

Dr Zsofia Kote-Jarai is a senior staff scientist in the Division of Genetics and Epidemiology. Dr Kote-Jarai has led and supported numerous research projects with the aim of identifying key elements of genetic predisposition to prostate cancer.

Find out more about ICR's research into prostate cancer. Find out more about CRH's/ CRUK's work in prostate cancer.

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