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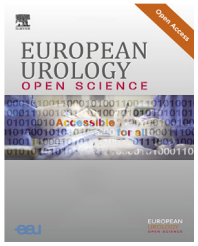

European Association of Urology

Letter to the Editor

Re: Bernard Pope, Gahee Park, Edmund Lau, et al. Ultrasensitive Detection of Circulating Tumour DNA enriches for Patients with a Greater Risk of Recurrence of Clinically Prostate Cancer. Eur Urol 2024;85:407–10

The recent study by Pope et al [1] used the integration of variant reads (INVAR) method for detection of circulating tumour DNA (ctDNA) and highlights its potential as a biomarker for predicting higher risks of disease recurrence in localised prostate cancer (LPC) [1]. This is an important advance considering the inability of conventional detection methods to capture the low abundance of ctDNA in early-stage PC.

Hennigan et al [2] had previously highlighted the challenges in detecting ctDNA in LPC via ultra-low-pass whole-genome sequencing and targeted sequencing of allele-specific alterations. Similarly, our earlier study involving a cohort of 24 patients with LPC detected ctDNA in only 8.3% of cases using targeted sequencing with a 66-gene panel [3]. The low detection rate accentuates the necessity for more sensitivity methods in identifying the scarce ctDNA present in LPC. Studies using targeted sequencing equipped with unique molecular identifiers (UMIs) have improved detection rates and unveiled tumour variants in ctDNA in patients with clinically LPC [4,5]. The INVAR method applied in this study, which integrates error-suppression and signal-enrichment strategies to analyse hundreds of patient-specific mutated loci, has significantly enhanced ctDNA detection in LPC, achieving a success rate of 16% in the patient cohort. This enhancement suggests a substantial step forward in ctDNA analytical technology.

This study establishes a crucial correlation between the presence of ctDNA and more aggressive disease characteristics, along with shorter biochemical recurrence–free and metastasis-free survival. These findings, corroborated by observations from targeted sequencing with UMIs, highlight the association between ctDNA variants and a higher risk of rapid disease progression [4]. Further exploration and validation of the INVAR method for new applications in LPC, such as monitoring minimal residual disease, is essential for clinical implementation.

Despite these advances, integration of the INVAR method into clinical practice faces several hurdles. Future research needs to clearly demonstrate the advantages of INVAR over existing prognostic biomarkers. In addition, the substantial costs associated with whole-genome sequencing of the primary tumour pose a considerable barrier to broader application. A comprehensive cost-benefit analysis comparing INVAR with traditional methods would provide critical insights to facilitate its clinical adoption.

In summary, the INVAR method, noted for its high sensitivity in detecting ctDNA, offers compelling evidence supporting the clinical utility of ctDNA analysis in the management of LPC. This paves the way for further research and the eventual integration of more sensitive and accurate ctDNA detection methods into routine practice. It is anticipated that such advances will be facilitated by the decreasing costs of sequencing technologies, which could potentially revolutionise the field of oncology by enhancing early detection and tailored treatment strategies.

Conflicts of interest: The authors have nothing to disclose.

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