ORACLE (Outcome Risk Associated Clonal Lung Expression)

ORACLE is a diagnostic and prognostic 23-transcript biomarker technology developed from the flagship TRACERx NSCLC study that harnesses AI and addresses sampling bias to distinguish between high- and low-risk lung tumours with high accuracy. The underlying ORACLE methodology has broader applicability in identifying biomarker signatures in other cancer-types

Unmet Need and Clinical Impact

Transcriptomic intra-tumour heterogeneity (ITH) and chromosome instability within NSCLC hinder accurate diagnosis and prognosis.

- Single biopsies fail to capture ITH, with 30–40% of tumours yielding disparate prognostic scores depending on where the biopsy needle was place.
- No attempts to derive a prognostic gene expression signature for patients with lung adenocarcinoma (LUAD) has been successfully adopted in clinical practice due to poor reproducibility in independent patient cohorts or failure to provide molecular information beyond existing clinicopathological risk factors.

Sampling bias and unreliable biomarker assessments therefore limit the identification of high-risk patients who would benefit from early intervention, reflecting the low 5-year mortality rate of 15% in population where surgical resection was performed with curative intent in patients with stage I disease.

ORACLE leverages homogeneously (clonally) expressed markers from solid tumour biopsies to sample and test one biopsy per tumour to:

- address sampling bias
- improve diagnostic precision in lung cancer
- stratify patients into disease subtypes predictive of outcome

Unique Value

- Clonal transcriptomic biomarkers overcome tumour sampling bias: novel calculations of mean intra-tumour and mean inter-tumour heterogeneity scores (**Fig 1**)
- Demonstrated improved diagnostic precision compared to current Tumour, Node, Metastasis (TNM) substaging criteria (**Fig 2**)
- Pan-cancer prognostic relevance: RNA heterogeneity quadrants (Q4) underpins survival outcomes in multiple cancer types independent of clinicopathological risk factors (**Fig 3**)

Stage of Development

- Prospective validation using TRACERx cohorts (n=158): ORACLE outperformed six other RNA-seq-based prognostic signatures for LUAD across four metrics for tumour sampling bias and demonstrated superior predictive power for lung-cancer-specific survival in stage I LUAD
- Currently undergoing advanced retrospective study validation in international cohorts (n>1000)

Intellectual Property Status:

Patents filed for both the LUAD gene panel and the underlying methodology to generate new biomarker signatures

- PCT filed in 2020 (PCT/GB2020/050221) with N/R phase entry in US, CA, EP and AU in 2021 for biomarker gene signature
- Divisional applications filed in 2024 in EP and US to cover ORACLE methodology

Commercial Strategy:

- Looking for commercial partners with global reach to enable further clinical validation, market access and broad implementation
- Collaborative development or straight licensing interest are welcome

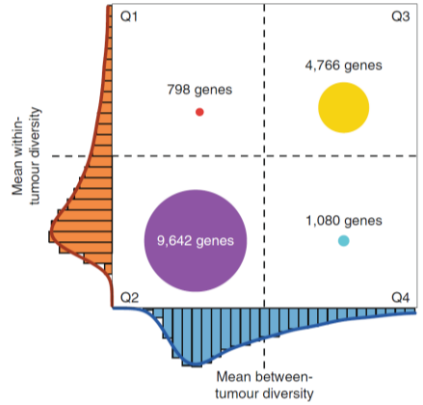

Fig 1: RNA heterogeneity quadrants calculated with RNA intratumor (y axis) and intertumor heterogeneity (x axis) plotted as density curves

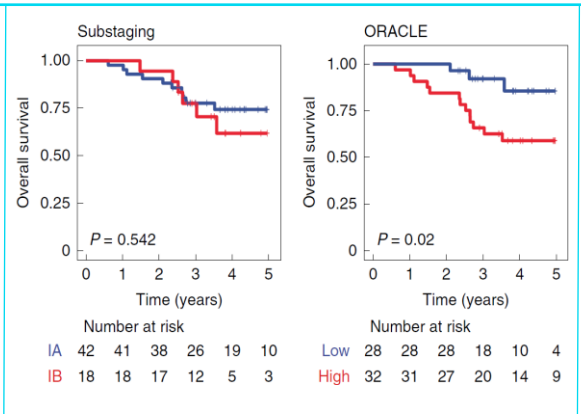

Fig 2: Prognostic value of substaging criteria (left) vs. ORACLE (right) in patients with stage I disease

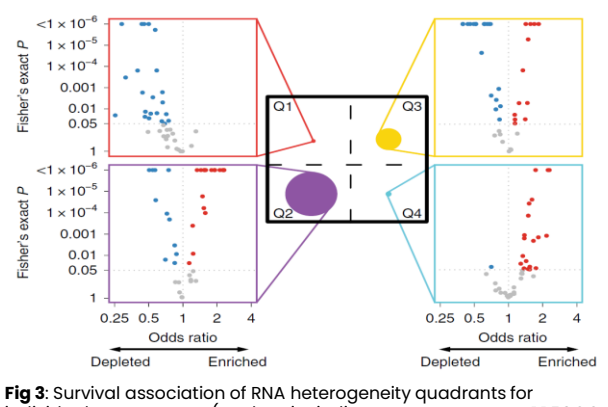

Fig 3: Survival association of RNA heterogeneity quadrants for individual cancer types (each point indicates a cancer type; PRECOG database). Prognostically significant genes per quadrant for each cancer type is shown as non-significant (gray), enriched (red) or depleted (blue).

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