CANCER RESEARCH HORIZONS

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ECLIPSE: A NOVEL, HIGH-SENSITIVITY LIQUID BIOPSY TOOL TO TRACK CANCER EVOLUTION

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OPPORTUNITY OVERVIEW

- **Technology:** ECLIPSE (Extraction of Clonality from LIquid bioPSiEs) is a novel informatic method developed to track tumour evolution over time by using low circulating tumour DNA (ctDNA) fraction plasma samples (>0.1%).
- **Unique value:** ECLIPSE is much more sensitive than existing liquid biopsy approaches for estimating tumour clonal composition. This high level of sensitivity means the methodology can detect mutations in plasma, which can be compared longitudinally to detect clonal evolution of tumours, identify clones that are likely to metastasise, and eventually inform treatment of a patient over time.
- **Validation:** The methodology has been validated in a cohort of non-small cell lung cancer patients and is expected to be applicable to all solid tumour oncology indications.
- **The Team:** Alexander Frankell, Chris Abbosh and Charles Swanton at UCL and The Francis Crick Institute.
- **Intellectual Property status:** A PCT application for the ECLIPSE methodology has been filed (PCT/EP2022/077987 October 2022).
- **Seeking:** We are seeking a co-development/licensing partner with liquid biopsy expertise to validate the methodology in a clinical setting and/or in additional oncology indications.

ECLIPSE OVERCOMES THE CHALLENGES OF LOW TUMOUR CONTENT PLASMA SAMPLES

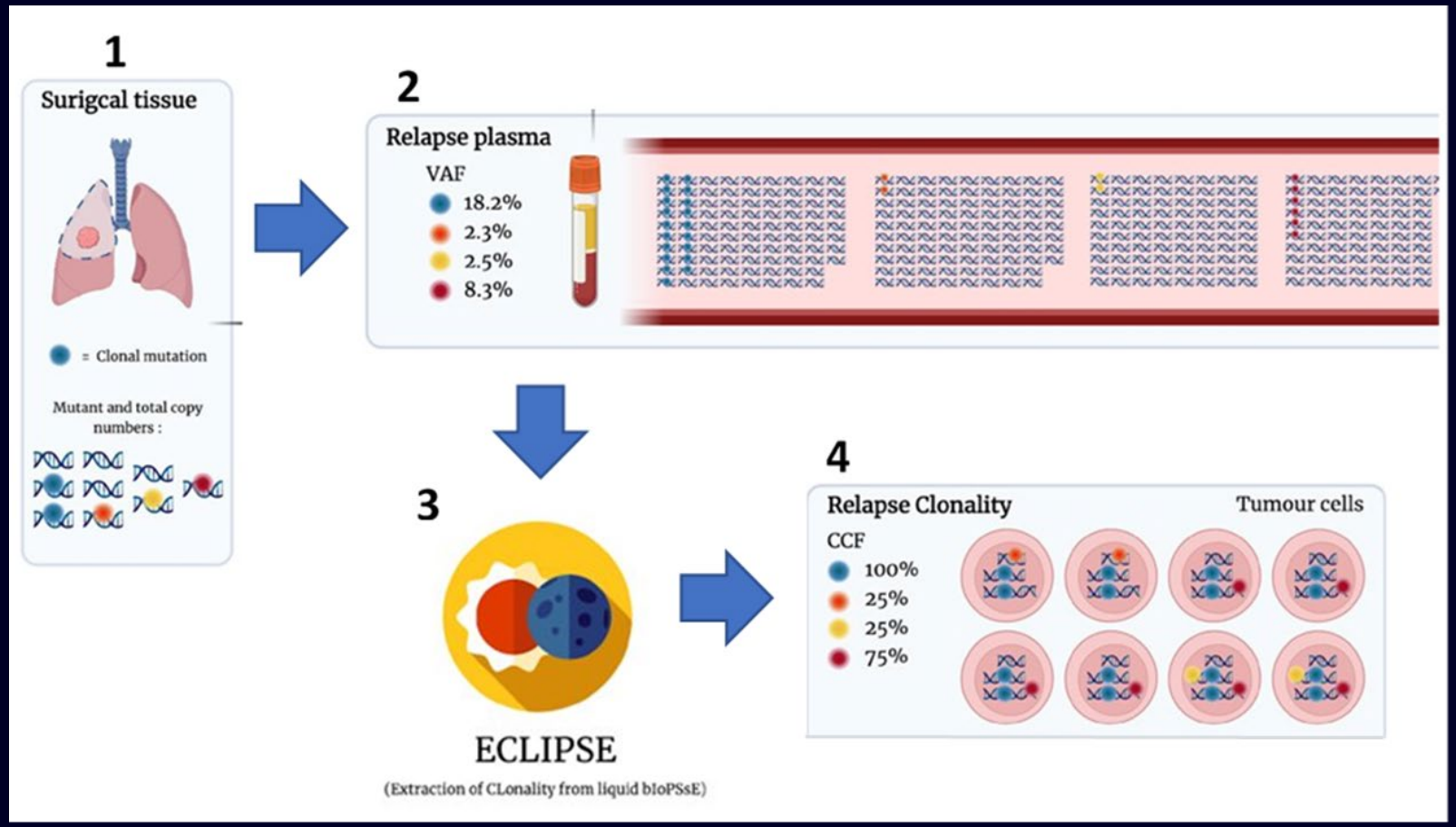
- Understanding tumour heterogeneity is clinically important for patient prognosis, targeting therapy resistance, and predictions of immuno-oncology response.

- Dense longitudinal and multiregional sampling across sites of disease is not possible using tumour tissue, particularly in standard-of-care clinical settings. Sampling of tumour DNA in circulation, using liquid biopsy, may provide unbiased sampling of the total tumour mass through time without requiring multiregional sampling.

- Standard liquid biopsy methods are limited to ctDNA samples with over 10% tumour content because they rely on whole exome sequencing or whole genome sequencing. However most pre-operative, minimal residual disease or early metastatic settings samples contain less than 1% ctDNA, which means that standard liquid biopsy techniques cannot be used to measure clonality of the tumour in these conditions.

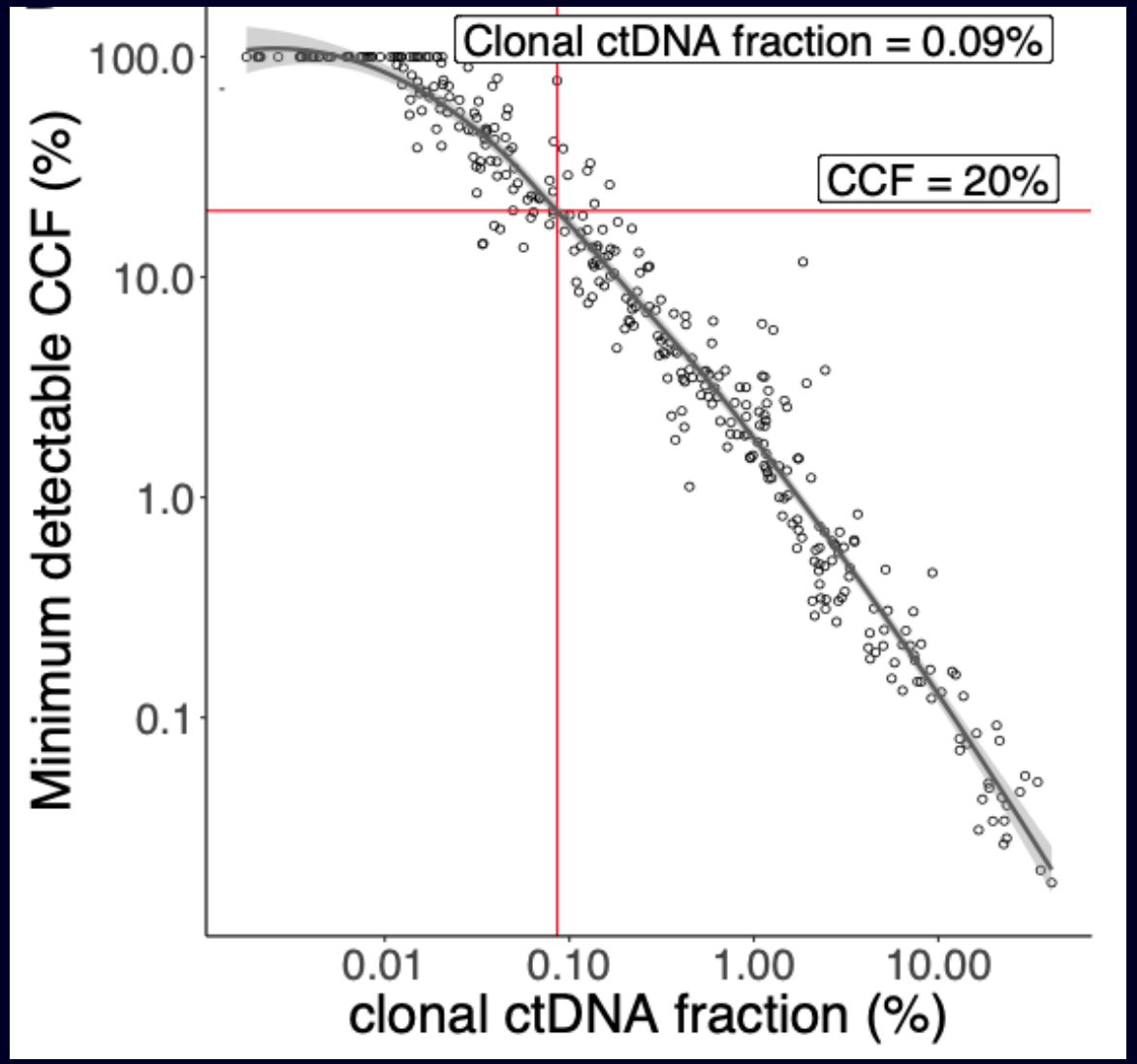
- ECLIPSE allows for tumour clonality to be tracked in plasma samples with ctDNA present at as low as 0.1%, by leveraging genomic information for each mutation from a matched tumour tissue sample.

ECLIPSE METHODOLOGY



1. Biopsies taken from different regions of the primary tumour are sequenced to identify the mutations present and their copy number.
2. The same mutations are sequenced in plasma DNA, at high depth, to measure the variant allele frequency (VAF) of these mutations in the sample. (Steps 1 and 2 are performed routinely by many tumour-informed Minimal Residual Disease tests).
3. ECLIPSE combines these data and corrects for noise.
4. The output is the cancer cell fraction (CCF) for each mutation: the proportion of cancerous cells in the tumour that contains each mutation detected in step 1.

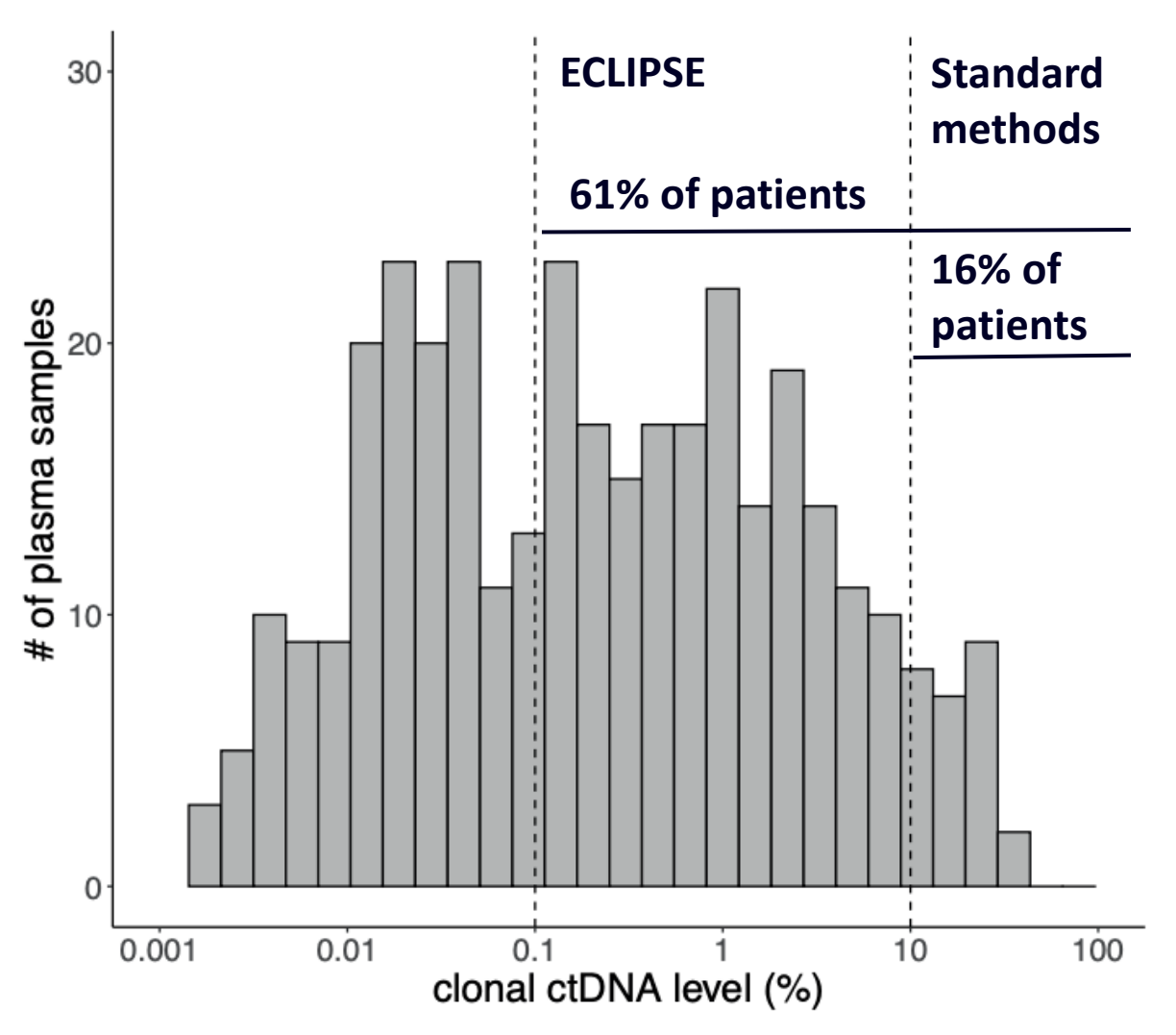
ECLIPSE HAS HIGH DETECTION POWER



- All ctDNA positive samples in a cohort of non small-cell lung cancer (NSCLC) patients within the TRACERx (TRAcking Cancer Evolution through therapy (Rx)) trial were analysed in silico using ECLIPSE to estimate the cancer cell fraction (CCF) for each mutation (subclone).
- Plasma samples with clonal ctDNA levels greater than 0.1% had a minimally detectable CCF of 20% for a representative subclone.
- This enabled ECLIPSE's threshold to be estimated at 0.1% ctDNA (this was also validated in *in vitro* spike-in experiments.)

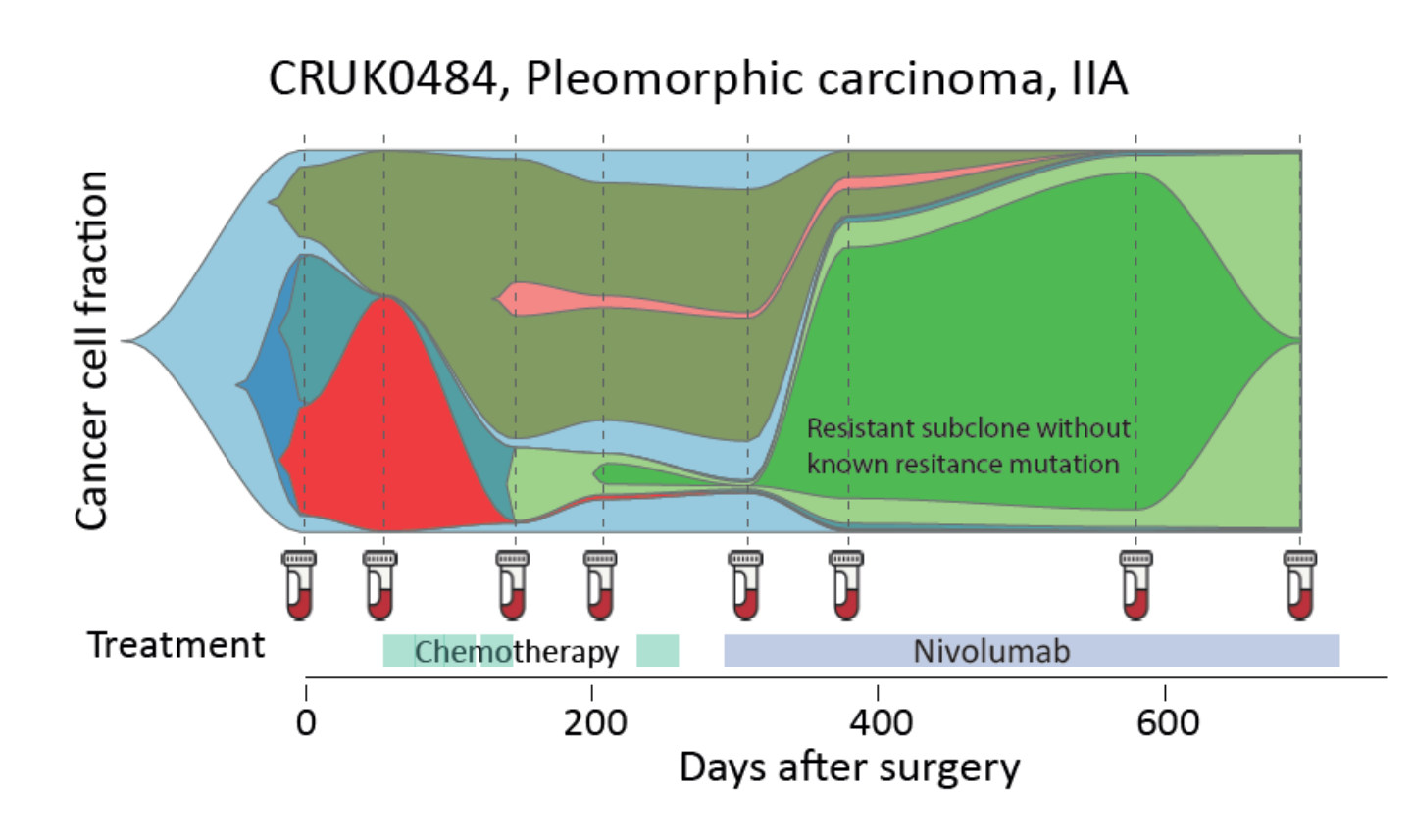
ECLIPSE HAS HIGHER SENSITIVITY THAN STANDARD METHODS

ECLIPSE sensitivity vs standard methods



- This histogram includes all ctDNA positive samples in a cohort of 197 patients longitudinally tracked within the TRACERx study.
- The ctDNA thresholds of ECLIPSE (~0.1%) and of standard liquid biopsy techniques (~10%) were plotted against the cohort ctDNA levels.
- ECLIPSE detects clonal ctDNA in 61% of patients, while standard liquid biopsy methods detects clonal ctDNA in only 16% of patients.

ECLIPSE CAN DETECT RESISTANCE BY TRACKING SUBCLONAL EVOLUTION



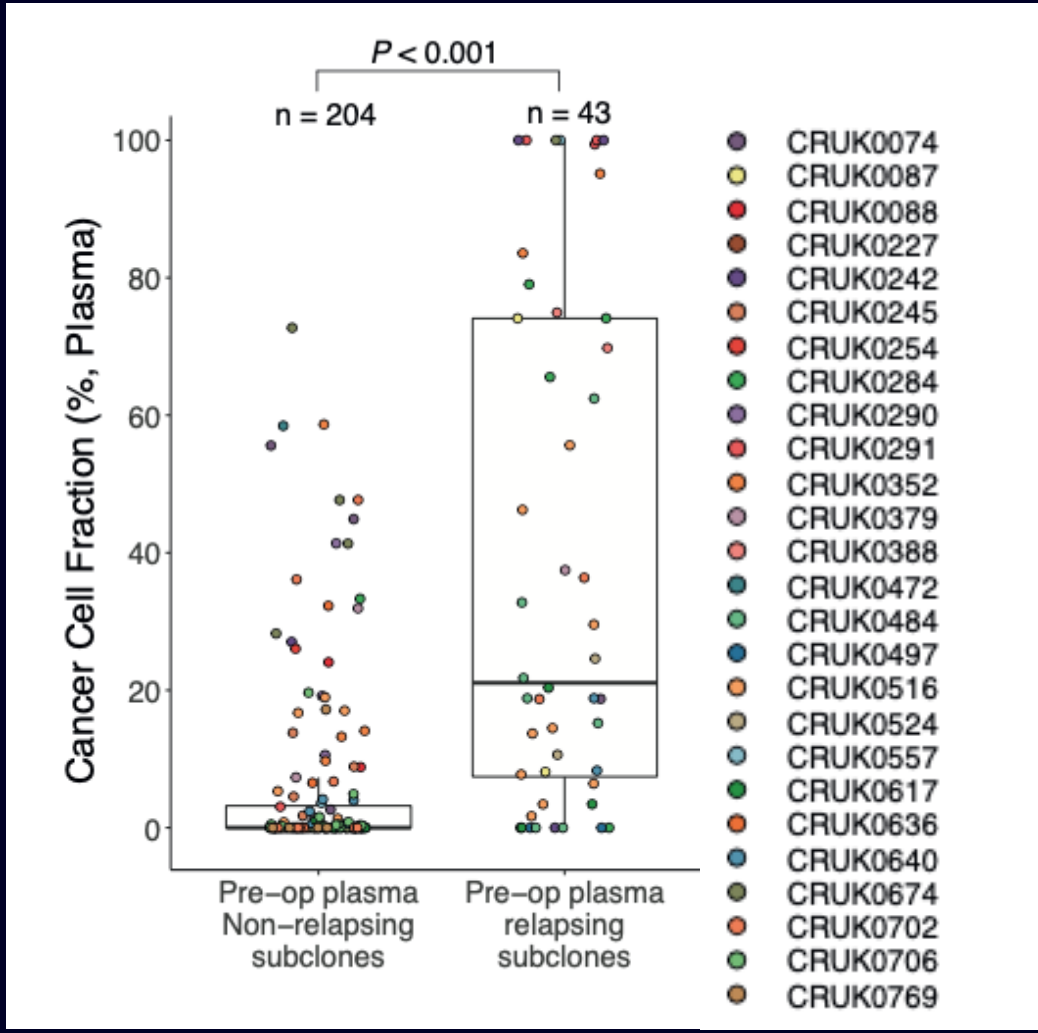
Plasma samples were collected over the course of treatment, and the cancer cell fraction for various subclones was measured using ECLIPSE (different subclones are depicted by different colours). After chemotherapy, a resistant subclone (green), without a known resistance mutation, expanded.

- The team applied ECLIPSE to post-surgical plasma samples to assess the clonal structure of cancers over time from surgery through treatment and relapse.
- The figure shows the ECLIPSE readout from an example patient (CRUK0484) with a clonally complex relapse who underwent several rounds of therapy.
- Subclonal evolution was observed over time, with shifts in clonal structure (indicated by different colours in the figure) concurrent with Nivolumab (anti PD-1) therapy.
- Looking at clonal composition in this way enables detection of resistance to therapy even if there are no known resistance mechanisms.

ECLIPSE can detect the presence of subclones that drive resistance to therapy.

ECLIPSE IDENTIFIES METASTATIC SUBCLONES PRIOR TO SURGERY

Subclone size (CCF) measured by ECLIPSE predicts metastasis



- Metastatic NSCLC TRACERx patient samples were analyzed using ECLIPSE (each patient represented by a circle on the graph).
- The figure shows the cancer cell fraction (subclone size) detected by ECLIPSE for one subclone, in pre-operative samples of non-relapsing and relapsing patients.
- The size of each subclone (CCF) was found to be associated with the likelihood of that subclone metastasizing.
- Subclone size can also be measured using multiregional primary tumour sampling. However, such multiregional sequencing of primary tumours is not practical in the clinic. Using the ECLIPSE methodology on plasma is therefore more applicable to a clinical setting.
- ECLIPSE can identify which subclonal genetic alterations are likely to metastasize.

ECLIPSE may enable guidance of neoadjuvant/adjuvant targeted therapies and in turn the eradication of clones before they metastasize.

NEXT STEPS

- Analysis of CT and PET scans alongside ECLIPSE to see if ECLIPSE can warn of clinical recurrence at specific sites of disease.

- Analysis of other cancer types with ECLIPSE (the researchers are currently applying for access to data from a study of 4 cancer types in a total of 100 patients).

- *In vitro* sequencing experiments with clonal admixtures to detect the lower limit of detection of ECLIPSE.

We are seeking an industry co-development partner and/or licensee to help validate the programme in a clinical setting and /or in additional oncology indications.

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THANK YOU

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