Clinical utility of cell-free DNA analysis in matching patients with advanced cancer to early phase drug trials

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BACKGROUND

- Early phase clinical trials are often cancer patients' 'last chance' of treatment but response rates are low. Matching patients to targeted trial drugs based on predictive biomarkers improves patient response and trial success[1, 2].
- Predictive biomarkers are detected by molecular profiling of tumour tissue but tumour tissue acquisition is often invasive and challenging. Liquid biopsies offer a non-invasive alternative by analysing biomarkers in bodily fluids, such as cell-free DNA (cfDNA) which is released from cells into the circulation. In patients with cancer, tumour cells also release cfDNA, termed circulating tumour DNA (ctDNA).
- FoundationOne liquid (FOL) is a FDA-approved liquid biopsy that analyses cfDNA in patients' blood using hybrid-based next generation sequencing to detect tumour-related genomic findings, including gene alterations and genomic signatures, in ctDNA. FOL reports list genomic findings, highlight 'actionable' findings and list matched therapies including trials.
- FOL may provide an alternative to solid tumour profiling to genotype-match patients with advanced solid cancer to early phase trials but clinical utility in trial matching is unknown.

AIMS

- Determine the clinical utility of FOL in matching patients with advanced solid cancer to targeted, early phase clinical trials.
- Identify reasons for the failure of FOL tests to result in patients commencing matched, targeted early phase clinical trials.

METHODS

- All FOL tests performed in the Newcastle Experimental Cancer Medicine Centre (ECMC) for trial matching in patients with advanced solid cancer over a two-year period were analysed.
- During this period, two versions of FOL were used as 'FOL' was expanded and replaced by 'FOL CDx'[3, 4]. FOL detected alterations in 70 genes and Microsatellite Status (MS). FOL CDx detects alterations in 324 genes, MS, Blood Tumour Mutational Burden (bTMB) and Tumour Fraction (TFx). Results are presented for all FOL tests including FOL and FOL CDx.
- Electronic patient records of all patients who had FOL tests were systematically reviewed and followed-up for at least 90 days (unless patient died < 90 days). Data gathered from patient records included patient demographics, FOL test results including detection of gene alterations and genomic signatures (MS, bTMB and TFx) and the impact of FOL test results on matching patients to trials.
- Data were analysed to assess clinical utility of FOL in matching patients to trials.
- 'Actionable' is used to describe genomic findings detected by FOL that were targeted in a trial(s) listed on the FOL report.

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RESULTS

PATIENT DEMOGRAPHICS (n = 131)

- 144 FOL tests were performed in 131 patients (11 patients had repeat tests)
- 61.8% of patients were female and 38.2% were male
- Median age at first FOL test was 59 years old (range 20 to 84)
- Patients had a range of 18 cancer types, as shown in Figure 1
- Median follow-up was 304 days
- Median survival was 211 days

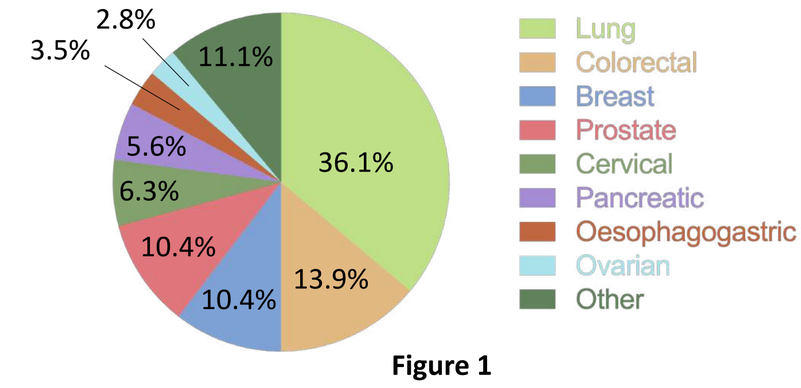


Figure 1

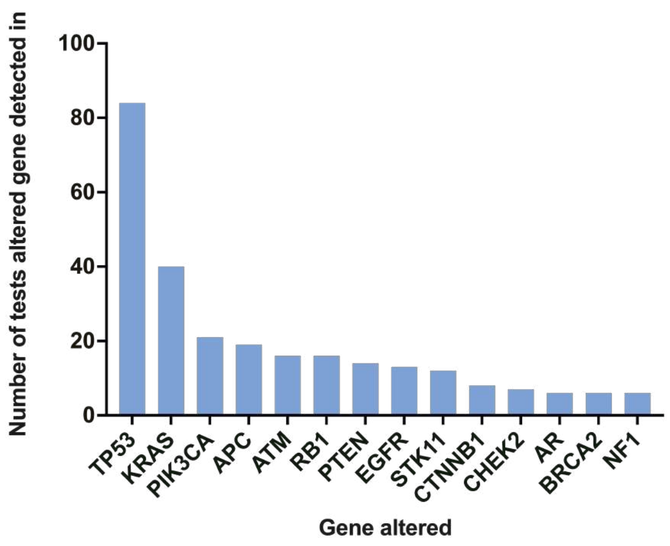


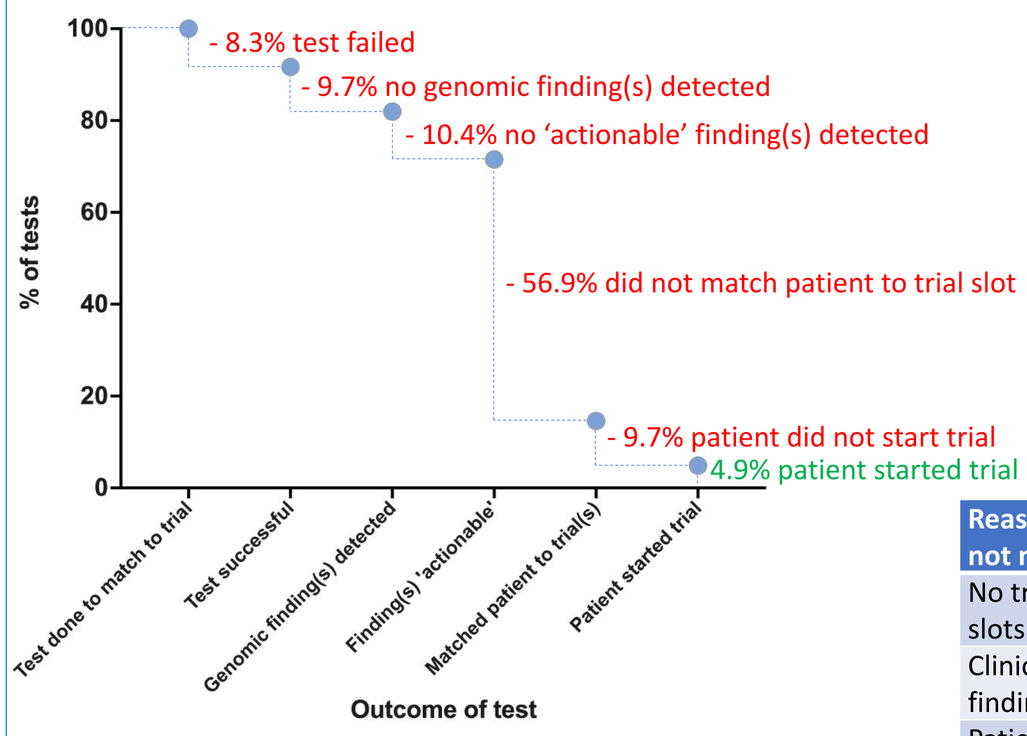
Figure 2

GENOMIC FINDINGS IN SUCCESSFUL FOL TESTS (132 tests)

- Median number of altered genes detected in each test was 3 (range 0-14)
- Total number of altered genes detected in 132 tests was 414
- Alterations were detected in 110 different genes, the most frequently altered genes are shown in Figure 2
- Genomic signatures detected were bTMB and TFx
- 206 (49.8%) of 414 altered genes detected were 'actionable'
- Median number of 'actionable' altered genes detected in each test was 1 (range 0-6)
- Only 'actionable' genomic signature detected was high bTMB (10+)

CLINICAL UTILITY

Figure 3: Clinical utility of FOL in trial matching



The greatest loss of clinical utility, as shown in Figure 3, was in the **56.9%** of all tests that had 'actionable' results but did not match patients to available trial slots for reasons outlined in Table 1.

Of 144 FOL tests:

- 91.7% were successful
- 81.9% detected tumour-related genomic findings
- 71.5% detected 'actionable' findings
- 14.6% matched patients to a trial slot
- 4.9% resulted in the patient starting a matched trial
- No adverse physical outcomes of the FOL test procedure were reported

Table 1

Reason 'actionable' test result did not match patient to trial slot	Number of tests
No trial slot available for patient – no slots and/or patient ineligible	50
Clinicians deemed 'actionable' findings poor therapeutic targets	18
Patient deteriorated	6
Specific finding not detected	3
Patient died	3
Patient cancelled appointment	1
Low quality test - unreliable	1

7 (4.9%) of 144 FOL tests resulted in 7 patients starting a matched, targeted trial; 5 had progressive disease at their first response evaluation, 1 had progressive disease at their second response evaluation and 1 patient remains on trial with stable disease.

DISCUSSION

- 4.9% of FOL tests led to patients starting a matched trial, similar to the success rates of broad-panel solid tumour assays[2, 5].
- FOL utility was limited by few trial slots, strict eligibility criteria and uncertain efficacy of targeting some 'actionable' findings.
- Limitations of the analysis included the lack of a comparator arm, retrospective data collection and an insufficient number of patients starting FOL-matched trials to draw conclusions about the efficacy of targeting FOL-detected alterations.

CONCLUSIONS

FOL achieved similar success in trial matching as solid tumour assays. FOL is clinically validated in detecting predictive biomarkers in patients with advanced cancer and biomarker-stratification in early phase trials improves drug efficacy and trial success. When considered together, these findings support the clinical utility of FOL in matching patients with advanced cancer to targeted, early phase trials with a higher chance of response than unmatched trials, all without the challenges and risks of solid biopsies.

FUTURE WORK

- Ongoing data collection about FOL involving the use of a proforma for each test performed in the ECMC.
- Health economics analysis to determine cost-efficacy of FOL in matching patients to early phase trials in NHS cancer services.
- Creation of a database of patients' cfDNA profiles and trial outcomes to establish the efficacy of targeting genomic findings.
- Larger, prospective trials to compare the outcomes in patients matched to targeted trials by FOL or solid tumour profiling.