Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the leading cause of cancer death worldwide. There are two main types – small cell and non-small cell (NSCLC) – and the majority of patients (85%) have NSCLC. Depending upon the disease type and progression, treatment can involve surgery, radiotherapy and combined chemotherapy.

Genetic testing informs diagnosis, prognosis and treatment options. In particular, analysis focuses on DNA changes linked to the effectiveness of targeted tyrosine kinase inhibitor (TKI) therapies. TKI treatments slow or stop the cancer growth by blocking chemical messengers that promote cell growth and division.

Around 10-15% of NSCLC tumours have activating variants within the EGFR TK domain (exons 18-21). NICE recommends the use of EGFR TKIs for NSCLC patients with EGFR sensitising mutations; 3rd generation EGFR TKIs are recommended for locally advanced or metastatic NSCLC patients with an EGFR T790M variant [1,2].

BRAF variants occur in 2-4% of patients with lung adenocarcinoma. The most common activating variant in BRAF is V600E within the kinase domain. NSCLC patients with BRAF variants have a decreased likelihood of response to EGFR TKIs but may benefit from combined targeted therapy strategies [3,4].

Approximately 13% of patients with lung adenocarcinomas harbour a KRAS G12C variant. Patients with locally advanced or metastatic disease harbouring a KRAS G12C variant may benefit from Sotorasib therapy [5].

NSCLC patients may also be tested for the existence of gene rearrangements (fusions). ALK or ROS1 gene rearrangements occur in approximately 5% and 1-2% of adenocarcinomas respectively. Presence of an ALK or ROS1 gene rearrangement indicates the patient should be considered for treatment with TKI therapies such as crizotinib[6,7]. NTRK gene rearrangements (fusions) are found in 0.2%-3.3% of NSCLC. Lung tumours that harbour NTRK gene rearrangements are highly sensitive to selective TRK tyrosine kinase inhibitors (TKIs), including larotrectinib and entrectinib [8,9].

Within patients with NSCLC, other structural variants occurring at lower frequencies (shown in brackets) include; EGFRvIII (0-1%), MET exon 14 skipping events (1.5-6%) and RET fusions (0.9%) [10-12]. There are no currently approved treatments targeting MET exon 14 skipping variant, EGFRvIII or RET rearrangements in NSCLC. However, the presence of a RET gene fusion indicates the patient may benefit from Selpercatinib, which is not currently NICE approved [12].

Test Information

The All Wales Genomics Laboratory utilises the Illumina TruSight Oncology 500 High Throughput DNA/RNA assay for next generation sequencing using the Illumina NovaSeq 6000™ to identify nucleotide variants and gene rearrangements (fusions) in patients with solid tumours. More information on this service is available here.

Table 1. NSCLC DNA Gene Panel

Gene	Hotspot/Screen	Regions Covered
EGFR	Hotspots	Exons 18, 19, 20 and 21 (covers 95% of known EGFR TKI variants).
KRAS	Hotspots	Exon 2, 3, and 4 (covers: p.12, p.13, p.59, p.61, p.117, p.146).
BRAF	Hotspots	Exons 11 and 15 (covers: p.599, p.600 and p.601 mutations, accounting for 98% of known BRAF variants).

Table 2. NSCLC RNA Gene Panel

Genes Covered			
ALK	RET	MET	NTRK2
ROS1	EGFR	NTRK1	NTRK3

Note: if <40ng of DNA is obtained from the FFPE sample provided, an alternative NGS panel will be utilised for testing, which provides hotspot analysis of all clinically actionable genes relevant to the tumour type but overall a less comprehensive gene analysis.

A fully interpreted report will be issued.

Please be aware that variants of uncertain significance (VUS) may be identified with this test, these will be further investigated if they are in clinically relevant gene regions and reported as appropriate.

This test is performed to evaluate somatic variants within tumour samples and is not designed to assess for germline variants within the targeted genes.

Specimen Requirements

For information on sending FFPE samples refer to the CYSGODI service information sheet.
Please use the FFPE solid tumour request form and complete all fields.

Links for further information

Orphanet www.orpha.net
EDDNAL www.eddnal.com
OMIM www.omim.org
Genetic Test Registry www.ncbi.nlm.nih.gov/gtr Cancer Research UK
www.cancerresearchuk.org
https://www.nice.org.uk/guidance

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