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). The majority of patients (85%) have NSCLC, which can be further subdivided into types: adenocarcinoma (most common), squamous cell carcinoma, and large cell (rare). 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 and RNA 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. From September 2023, AWMGS offer the same DNA and RNA-based testing to patients with both adenocarcinomas and squamous cell carcinomas.

Around 10-15% of NSCLC tumours have activating variants within the EGFR TK domain (exons 18-21), with these variants being more common in adenocarcinomas. A variety of NICE-approved EGFR TKIs are available to treat NSCLC patients [(1)]. Patients progressing on treatment with 1st or 2nd generation EGFR TKIs may be tested for the resistance EGFR variant p. (Thr790Met) prior to embarking on treatment with 3rd generation EGFR TKIs [(2,3)].

BRAF variants occur in 2-5% of patients with NSCLC, with the highest prevalence seen in adenocarcinomas. The most common activating variant in BRAF is p.(Val600Glu) within the kinase domain. The BRAF-targeted therapies dabrafenib and trametinib have been approved by NICE for NSCLCs harbouring the BRAF p.(Val600Glu) variant[(4)].

Approximately 32% of patients with lung adenocarcinomas, and 4% of squamous cell lung cancer patients harbour a KRAS p.(Gly12Cys) variant. NSCLC patients with locally advanced or metastatic disease harbouring this KRAS variant may benefit from Sotorasib therapy[(5)].

NSCLC patients may also be tested for the existence of structural variants, such as gene rearrangements (fusions). ALK and ROS1 gene rearrangements occur in approximately 5% and 1-2% of adenocarcinomas respectively, and in <1% of squamous cell carcinomas. Presence of an ALK or ROS1 gene rearrangement in a NSCLC patient indicates the patient should be considered for treatment with TKI therapies such as crizotinib [(6,7)].

NTRK gene rearrangements are found in 0.2-3.3% of NSCLC. Lung tumours that harbour NTRK gene fusions are highly sensitive to selective TRK TKIs, including larotrectinib and entrectinib [(8,9)]. RET gene fusions are found in 1-2% of NSCLC [(10)]. Evidence indicates that patients with RET-fusion positive NSCLC may benefit from treatment

with selpercatinib, and this drug is now NICE approved for use in this patient group [10, 11].

Other structural variants occurring within NSCLC include; MET exon 14 skipping alterations and EGFRvIII gene rearrangements. Approximately 3-5% of patients with NSCLC have tumours harbouring MET exon 14 skipping alterations [12 13]. NSCLC patients showing MET exon 14 skipping may benefit from treatment with the MET inhibitor tepotinib [12, 13]. The EGFRvIII gene rearrangement occurs in 0-1% of NSCLC [14]. There are no currently approved treatments targeting EGFRvIII rearrangements in NSCLC.

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.

ctDNA testing on blood sample is available for NSCLC patients at diagnosis and progression. More information on this service 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).

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.

Table 2. NSCLC RNA Gene Panel

Genes Covered			
ALK	RET	MET	NTRK2
ROS1	EGFR	NTRK1	NTRK3

Note: if <30ng RNA is obtained, the FISH salvage pathway will be used in place of RNA-based NGS. Should this salvage pathway be

required and insufficient material be available to perform all relevant analyses, tests will be performed in accordance with the published gene fusion frequencies within the tumour type, with the most frequently rearranged gene being the first to be tested.

A fully interpreted report will be issued for lung adenocarcinoma and squamous samples; if the primary site of the tumour is uncertain a non-interpretative 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 lung request form Microsoft Word - PD-GEN-ReqTumAn Lung (medicalgenomicswales.co.uk) and complete all fields.

Links for further information

Cancer Research UK www.cancerresearchuk.org
https://www.nice.org.uk/guidance

All Wales Genetics Laboratory (AWGL)
Phone: 02920 742 641 Fax: 029 2074 4043
Email: lab.genetics@wales.nhs.uk Website:
http://www.medicalgenomicswales.co.uk

References

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