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 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 off 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 adecarcinomas.. 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 NSCLC 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 or 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 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.

Approximately 20 to 25% of patients who receive a diagnosis of NSCLC have resectable disease, however, 30 to 55% of patients who undergo curative surgery have recurrence. Standard care for resectable (stage IB (≥4 cm) to IIIA) NSCLC is surgical resection. Treatment options in addition to surgery are limited. Neoadjuvant chemoradiotherapy or adjuvant chemotherapy may be considered with the aim of improving long-term outcomes [15].

CheckMate-816 trial showed neoadjuvant nivolumab (an anti–PD-1 antibody) plus chemotherapy is more effective for stage 1B to 3A resectable NSCLC compared with neoadjuvant chemotherapy alone. For the trial, patients with known ALK rearrangements or EGFR variants were excluded [16]. In order for patients to be eligible for this treatment actionable EGFR variants and ALK fusions must be excluded.

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

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.

Patients for which neoadjuvant nivolumab (an anti–PD-1 antibody) plus chemotherapy is being considered, are able to have testing to assess eligibility by assessing whether an ALK rearrangement or EGFR variant is present usually using the RNA Gene panel and DNA Gene panel outlined above.

FISH slides for ALK analysis will also be requested on these cases in case of a salvage pathway being required after RNA gene panel failure or if an RNA NGS result is unavailable in the required turnaround time.

Please see specimen requirements section and request form for further information

Specimen Requirements

For information on sending FFPE samples refer to the CYSGODI service information sheet.
Please use the 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

1) https://www.nice.org.uk/guidance/ta654/resources/osimertinib-for-untreated-egfr-mutationpositive-nonsmallcell-lung-cancer-pdf-82609198655173; Riely et al (2021) Cancer Discov. 11(7):1688-1699 (Mobocertinib reference); https://www.nice.org.uk/guidance/ng122/chapter/Treatment#systemic-anti-cancer-therapy-sact-for-advanced-non-small-cell-lung-cancer.
2) Hirsch et al. 2006; Journal of Clinical Oncology 24(31): 5034-5042; Lynch et al. 2004; New England Journal of Medicine 350(21):2129-2139.
3) Cross et al. 2014 Cancer Disc 4(9) 1046-61; Liao et al. 2015 Curr Opin Oncol 27(2) 94-101.
4) https://www.nice.org.uk/guidance/TA898.
5) Li et al. (2020) CodeBreak 100: Registrational phase 2 trial of sotorasib in KRAS p.G12C mutated non-small cell lung cancer. 2020 World Conference on Lung Cancer. Abstract PS01.07.
6) Hallberg, B., and Palmer, R.H. (2011) F1000 Medicine Reports 3:21.
7) Shaw, A.T., et al (2014). N Engl J Med. 20; 371(21): 1963-1971.
8) Drilon, A. et al. (2018) The New Eng J of Med 378,8: 731-739.
9) Doebele, R.C. et al. (2020) Lancet Oncology 21 (2): 271-282.
10) Subbiah, V. et al. (2021) Clin Cancer Res. 2021 Jun 4.
11) https://www.nice.org.uk/guidance/TA911
12) Paik, P.K., et al., (2020). The New Eng J of Med, 383 (10), 931–943; Heist, R.S. et al. (2016) The Oncologist 21(4):481-486.
13) https://www.nice.org.uk/guidance/ta789/resources/tepotinib-for-treating-advanced-nonsmallcell-lung-cancer-with-met-gene-alterations-pdf-82611565234117
14) Gan, H.K., et al. (2013) The FEBS Journal 280(21):5350-5370

15) NICE technology appraisal TA876 Overview | Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer | Guidance | NICE
16) Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. Forde et al. N Engl J Med 2022; 386:1973-1985 DOI: 10.1056/NEJMoa2202170