THE IMPORTANCE OF *BRAF* TESTING IN NSCLC

Incidence of *BRAF* mutations

- ***BRAF* mutations are rare,** occurring in around 2–4% of patients with NSCLC[1]
- **Around 50% of *BRAF* mutations are *BRAF*^{V600E} mutations,**[1-3] which mostly occur in lung adenocarcinoma[1]
- ***BRAF*^{V600} mutations are actionable therapeutic targets in advanced NSCLC,** with effective treatment options[2,4-11]
- **International guidelines** for advanced/metastatic *BRAF*^{V600}-mutant NSCLC recommend *BRAF/MEK* inhibitor combinations for first-line treatment, or second-line treatment in patients with disease progression after first-line chemotherapy or immunotherapy[12]
- **Early *BRAF* testing could help identify appropriate treatment pathways** for patients with *BRAF*^{V600}-mutant NSCLC[4,12,13]

European and international guidelines recommend testing for *BRAF* mutations in advanced and metastatic disease[12,14,15]

ESMO[12]	SEAP/ SEOM[16]	ASCO[15]	CAP/IASLC/ AMP[16]
✓	✓	✓	✓

✓ Testing recommended ✓ Expanded panel testing recommended

Which mutations to test for?

- ESMO guidelines recommend testing for all targetable oncogenic gene mutations in metastatic NSCLC[12]
- Broad biomarker testing could support early drug access[12]

Recommended gene mutation testing

ESMO[12]	*EGFR*	*ALK*	*ROS1*	*BRAF*	*NTRK*
	KRAS	*MET*	*RET*	*HER2*	*NRG1*

NGS is the preferred testing method for *BRAF*^{V600} mutations[1-3,12,13]

	NGS	RT qPCR	IHC
Sensitivity	High	High (for known targets)	Moderate–high
Specificity	High	High	Moderate (83–100%)
Scope	*BRAF*^{V600} & non-*BRAF*^{V600}, multiplex	*BRAF*^{V600} allele-specific	Detects *BRAF*^{V600} mutant protein only
Other	▪ Multiple testing is cost-effective ▪ Analysis of ctDNA in liquid biopsy is possible	▪ Wide range of use ▪ Reproducible	▪ Cost-effective ▪ Fast turnaround

Despite guideline recommendations, real-world testing is not consistently implemented in metastatic and advanced NSCLC[17-20]

Key barriers include:

Long turnaround times that can delay treatment

Opportunities[18,20,21]

- Multiplex testing using NGS panels within a single sample for optimised testing efficiency (i.e. more rapid than sequential testing)
- Optimise tissue sample use and cost-effectiveness

Insufficient sample (repeat biopsy challenging)

Opportunities[18,20]

- Ensure enough tissue is obtained at diagnosis
- Optimise tissue handling
- Liquid biopsy is a less invasive option for repeat sampling

Best practices to achieve timely and accurate genetic testing

- **Close co-ordination** between pathologists, oncologists, surgeons, and radiologists[22]
- **Multidisciplinary collaboration** to quickly and accurately procure tissue samples[20]
- **Testing of multiple biomarkers** for concurrent testing with a faster turnaround and better sample management[20,22]
- **Standardisation of testing protocols** with the goal of improving patient outcomes and cost-effectiveness[22]
- **Reflex testing and open dialogue** between pathologists and oncology teams to prioritise the sample, simplify preparations, and minimise waiting time[14,16,18]

Abbreviations: *ALK,* anaplastic lymphoma kinase; AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; *BRAF,* V-Raf murine sarcoma viral oncogene homolog B; CAP, College of American Pathologists; ctDNA, circulating tumour DNA; *EGFR,* epidermal growth factor receptor; ESMO, European Society for Medical Oncology; *HER2,* human epidermal growth factor receptor 2; IASLC, International Association for the Study of Lung Cancer; IHC, immunohistochemistry; *KRAS,* Kirsten rat sarcoma viral oncogene; *MET,* mesenchymal-epithelial transition factor; *MEK,* meiotic chromosome-axis-associated kinase; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; *NRG1,* neuregulin 1; NSCLC, non-small cell lung cancer; *NTRK,* neurotrophic tyrosine receptor kinase; *RET,* rearranged during transfection; *ROS1,* ROS proto-oncogene 1; RT qPCR, real-time quantitative polymerase chain reaction; SEAP, Spanish Society of Pathological Anatomy; SEOM, Spanish Society of Medical Oncology

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