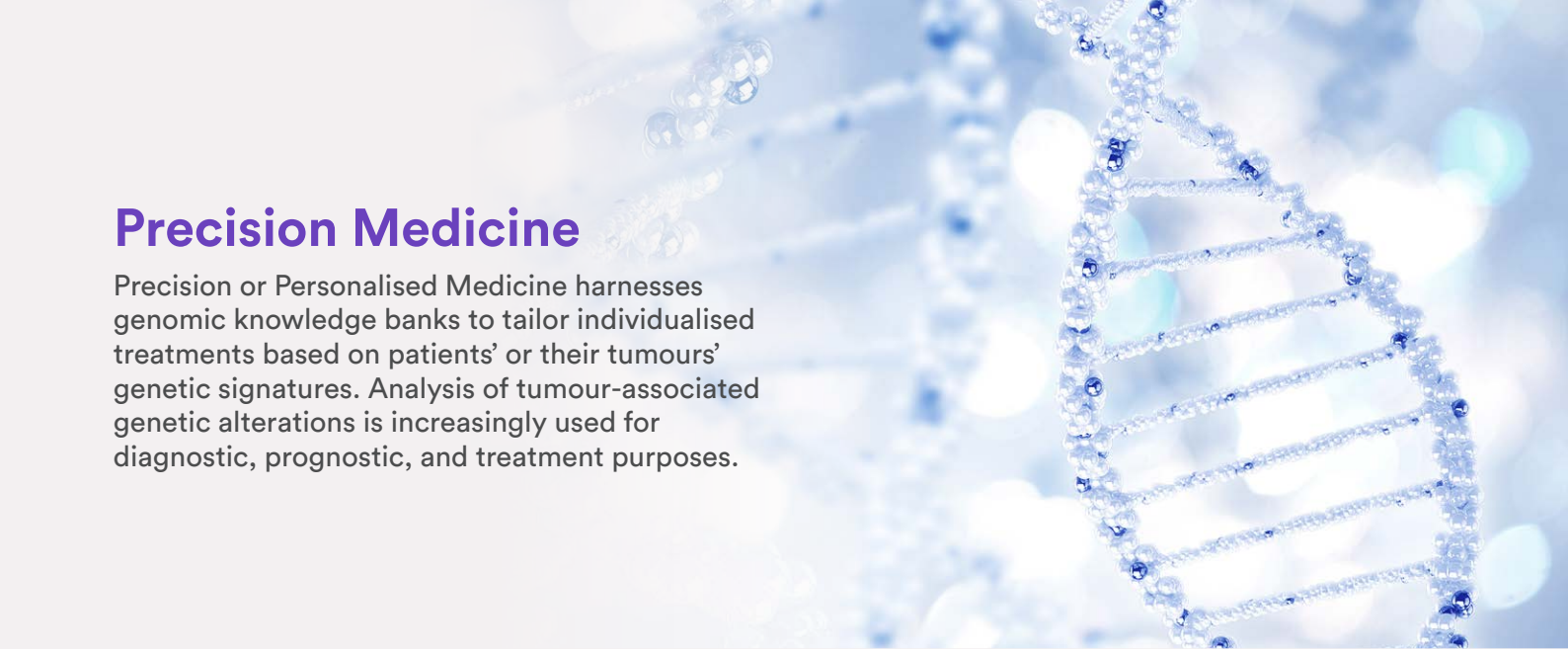
AUSTRALIAN Clinicallabs

Somatic Mutation Testing in Solid Tumours

Supporting treatment decisions and improving outcomes for cancer patients

3 NEW pathology MBS items for NSCLC from 1st November 2023



Precision Medicine

Precision or Personalised Medicine harnesses genomic knowledge banks to tailor individualised treatments based on patients' or their tumours' genetic signatures. Analysis of tumour-associated genetic alterations is increasingly used for diagnostic, prognostic, and treatment purposes.

Somatic Mutation and Targeted Therapy in Cancer

The advent of molecular profiling overcame the limitations of morphological solid tumour classification methods. The presence or absence of activated therapeutic driver mutations or gene targets is currently employed to guide treatment decisions.

Genetic profiling in tumours can identify resistant mutations in response to therapy and may predict a poor prognosis in cancer.

Next Generation Sequencing at Clinical Labs

Clinical Labs uses a high-quality genomic analysis, such as Next Generation Sequencing (NGS) testing panels designed to investigate multiple relevant actionable mutations in formalin-fixed paraffin-embedded (FFPE) tumour samples.

The efficiency of NGS of DNA and RNA has led to an increasing number of large, targeted multi-gene somatic mutation panels that provide a more efficient, cost- and tissue-saving tumour analysis. They confer greater depth of coverage in selected areas of interest (e.g., hotspot regions with known actionable mutations, rarer mutations and tumour sub-clones), faster turnaround, and more clinically relevant data. However, despite the high sensitivity of NGS, there are limitations and caveats to consider for each test type that vary by biomarker and tumour type.

What Do We Test?

An FFPE sample of 5-10 µm thickness from the tumour tissue. NGS can detect variants using inputs of ~20ng of FFPE-extracted DNA/RNA and from specimens with a tumour cell content less than 50%, for which, when possible, we recommend micro-dissection.

"Precision medicine has already transformed cancer care: both common and rare malignancies can be targeted by specific therapies to improve clinical outcomes in patients."

MBS Update

From 1 November 2023, three new pathology items will be included in the MBS to test for genetic variants in patients with non-squa¬mous (or histology not otherwise specified) non-small cell lung cancer. MBS items will include broader actionable gene variants along with fusion genes to access specific therapies relevant to these variants listed on the PBS.

Somatic Mutation Testing Panels available at Clinical Labs

Comprehensive Oncomine Precision Assay (OPA) Gene Panel (ThermoFisher Scientific)

Local and International Guidelines (NCCN & ASCO) strongly recommend comprehensive multi-gene panel– based genomic sequencing for cancer patients with the goal of identifying rare driver mutations for which effective drugs may already be available. Comprehensive tumour profiling aids clinicians in selecting the most appropriate treatment for their cancer patients, avoiding unnecessary toxic therapy, resistance, or overtreatment, or in suggesting potential synergistic drug combinations (e.g., combination of *BRAF* and *MEK* inhibitors in *BRAF* mutant melanoma)[25]. This approach is also of valuable use if the tumour is poorly differentiated or of unknown origin.

Genes sequenced in this panel include:

- *AKT1*
- *AKT2*
- *AKT3*
- *ALK*
- *AR*
- *ARAF*
- *BRAF*
- *CDK4*
- *CDKN2A*
- *CHEK2*
- *CTNNB1*
- *EGFR*
- *ERBB2*
- *ERBB3*
- *ERBB4*
- *ESR1*
- *FGFR1*
- *FGFR2*
- *FGFR3*
- *FGFR4*
- *FLT3*
- *GNA11*
- *GNAQ*
- *GNAS*
- *HRAS*
- *IDH1*
- *IDH2*
- *KIT*
- *KRAS*
- *MAP2K1*
- *MAP2K2*
- *MET*
- *MTOR*
- *NRAS*
- *NTRK1*
- *NTRK2*
- *NTRK3*
- *PDGFRA*
- *PIK3CA*
- *PTEN*
- *RAF1*
- *RET*
- *ROS1*
- *SMO*
- *TP53*

Please note: No Medicare rebate available.

Lung Cancer Gene Panel (DNA)

Mutation in *EGFR* occurs in ~35% of NSCLC patients of East Asian origin and ~16% in Western populations[8,9,10]. *EGFR* mutations are predictive biomarkers of treatment response to tyrosine kinase inhibitors (TKIs), Gefitinib, and Erlotinib[11,12]. A third-generation *EGFR* TKI and is effective in patients with tumours harbouring the resistance p.*T790M EGFR* mutation (~50-60% of lung cancer patients[13,14,15]) following progression on *EGFR* TKIs[16,17]. Detection of *KRAS* or *BRAF* mutations (observed in 2-4% of NSCLC patients) is considered a negative predictor of response to anti-*EGFR* treatment and is associated with poorer survival[20,22,24].

Genes sequenced in this panel include:

- *EGFR*
- *KRAS*
- *NRAS*
- *BRAF*
- *PIK3CA*
- *AKT1*

Please check ALK (IHC) and ALK (FISH) Medicare eligibility criteria on page 5.
Test cost: Medicare rebate available if criteria are met.

MET Exon 14 skipping (RNA) in lung cancer

From November 2022, testing for *MET* exon 14 skipping mutation (3-4%) should be performed for patients with all types of NSCLC to determine the eligibility for *MET* inhibitors capmatinib and tepotinib[25].

MET exon 14 skipping (RNA) testing

MET Exon 14 skipping (RNA testing) is now available.*
**Provided suitability of sample for testing.*

Test cost: Medicare rebate available if criteria are me.

RNA Fusion Test Panel in Solid Tumours

RNA-based fusion testing is recommended for patients with no other oncogenic driver detected by DNA. Approximately 5% of NSCLC patients display a rearrangement in *ALK* (2-5%), while *ROS* proto-oncogene 1 (*ROS1*) and *RET* proto-oncogene (*RET*) rearrangements are observed in 1-2% of patients. With variable prevalence, the presence of neurotrophic tyrosine receptor kinase (*NTRK*) fusions provides a rationale for genomic testing for all solid tumours for patients who may be candidates for *TRK*-inhibitor therapy. *NTRK1-3* fusion is described in 90- 100% of secretory salivary gland carcinomas (also known as MASC). They may also be present in 2-15% of papillary thyroid carcinomas and in less than 1% of other head and neck tumours[25].

Genes sequenced in the RNA Fusion Panel include:

- *RET*
- *ALK*
- *ROS-1*
- *NTRK1* or *NTRK2* or *NTRK3*

Test cost: Medicare-rebatable for lung cancer only.

Colorectal Cancer Gene Panel

Mutations in proto-oncogene *KRAS* are detected in up to 40% of CRC[5], which can confer resistance to treatment with *EGFR* antibodies, and only patients with wild-type *KRAS* tumours obtain benefit from these agents[6,7]. It is, therefore, vital that the *KRAS* mutation status of a patient's colorectal tumour can be detected to allow patients access to treatment.

Genes sequenced in this panel include:

- *KRAS*
- *NRAS*
- *BRAF*
- *PIK3CA*
- *PTEN*
- *AKT1*

Test cost: Medicare rebate available if criteria are met.

Melanoma Gene Panel

Targeted therapy with Anti-*BRAF* (vemurafenib or dabrafenib) remains the first-line treatment for melanoma tumours which harbour a *BRAF* mutation, particularly in Australia[18]. In cutaneous melanoma, the *BRAF* gene is mutated in ~60% of cases and *p.V600E (c.1799TA)* accounts for more than 90% of *BRAF* mutations[19]. Detection of *cKIT* mutations may guide the selection of *KIT* TKIs (imatinib and sunitinib) for melanoma treatment[21, 23] and may lead to better outcomes compared to *BRAF* melanoma patients treated with *BRAF* inhibitors[23].

Genes sequenced in this panel include:

- *BRAF*
- *NRAS*
- *cKIT*

Test cost: Medicare rebate available if criteria are met.

Breast Cancer Gene Panel

In breast cancer, oncogenic mutations in *PIK3CA* or *ERBB2* amplification (along with *TP53* mutations) occur in ~25% of cases[1,2]. As such, mutated *PI3K* has become an attractive therapeutic target in breast cancer therapy, and a number of agents targeting the *PI3K* pathway are currently in clinical development[25].

Genes sequenced in this panel include:

- *PIK3CA*
- *AKT1*
- *ERBB2*
- *TP53*
- *PTEN*

Test cost: No Medicare rebate available.

Thyroid Cancer Test Panel (DNA)

In anaplastic thyroid cancer (ATC), *BRAF* p.*V600E* mutation occurs in ~40% of patients with papillary thyroid carcinoma (PTC) and is associated with a more aggressive disease[3,4].

Genes sequenced in this panel include:

- *BRAF*
- *NRAS*
- *KRAS*
- *RET*

Test cost: No Medicare rebate available.

Medullary Thyroid Cancer (MTC) Panel

Medullary thyroid cancer (MTC) is associated with oncogenic mutations in *RET* (40-60%) that can be targeted by therapeutic treatments[25].

Genes sequenced in this panel include:

- Oncogenic mutations in *RET*

Test cost: No Medicare rebate available.

Medicare Eligibility Criteria

***EGFR* Mutation Test Funding Information**

Medicare Eligibility Criteria (Item 73337)

A test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician, to determine if the requirements relating to epidermal growth factor receptor (*EGFR*) gene status for access to erlotinib or gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

***MET* Exon 14 skipping Test Funding Information**

Medicare Eligibility Criteria (Item 73436)

A test of tumour tissue from a patient diagnosed with locally advanced or metastatic non-small cell lung cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to *MET* proto-oncogene, receptor tyrosine kinase (*MET*) exon 14 skipping alterations (*METex14sk*) status for access to tepotinib are fulfilled under the Pharmaceutical Benefits Scheme.

***KRAS* Mutation Test Funding Information**

Medicare Eligibility Criteria (Item 73338)

A test of tumour tissue from a patient with metastatic colorectal cancer (stage IV), requested by a specialist or consultant physician, to determine if the requirements relating to rat sarcoma oncogene (RAS) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled, if:

(a) The test is conducted for all clinically relevant mutations on *KRAS* exons 2, 3 and 4 and *NRAS* exons 2, 3 and for; or

(b) A RAS mutation is found

***BRAF* Mutation Test Funding Information**

Medicare Eligibility Criteria (Item 73336)

A test of tumour tissue from a patient with unresectable stage III or stage IV metastatic cutaneous melanoma, requested by, or on behalf of, a specialist or consultant physician, to determine if the requirements relating to *BRAF* V600 mutation status for access to dabrafenib under Pharmaceutical Benefits Scheme (PBS) are fulfilled.

***ALK* Rearrangement Test Funding Information**

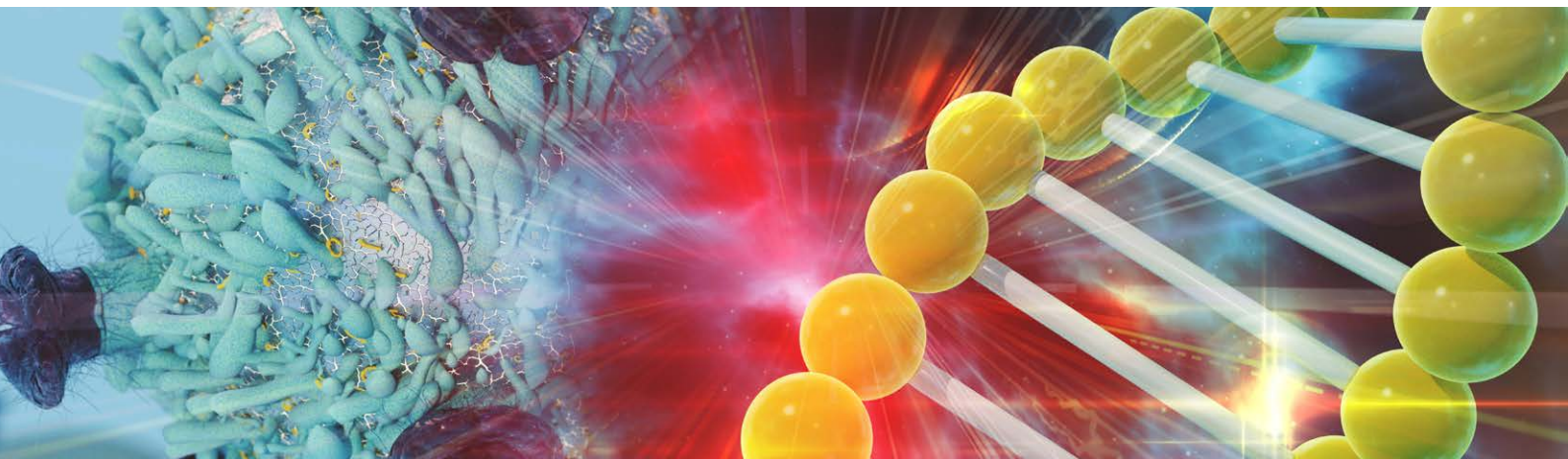
*ALK IHC – Medicare Rebate/Private Payment ***

ALK IHC will be available as a screening test for samples that return a negative *EGFR* mutation result. This test may be rebated by Medicare; a separate request will be required following *EGFR* reporting. If the test is not rebated by Medicare, a private fee of $75 may be applied. If *ALK* over expression is detected by IHC, confirmation of an *ALK* rearrangement by FISH is recommended.

** Private Payment Fees are correct as at 15/08/17 and may be subject to change.

ALK (FISH) – Medicare Eligibility Criteria (Item 73341) (referred out test)

Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of anaplastic lymphoma kinase (*ALK*) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score > 0, and with documented absence of activating mutations of the epidermal growth factor receptor (*EGFR*) gene, requested by a specialist or consultant physician to determine if requirements relating to *ALK* gene rearrangement status for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.



Ordering Somatic Mutation with Clinical Labs

1. Fill out our Somatic Mutation Testing Request Form.
2. Tick the Somatic Mutation test panel required.
3. Send to our lab along with Fresh FFPE (of 5-10 µm thickness from the tumour tissue).
4. Results will be available 5-7 business days after the receipt of the patient's sample.

For further information about Somatic Mutation testing available at Clinical Labs, including gene panels, pricing, and request forms, please visit clinicallabs.com.au/cancer-services.

About the author

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