External Quality Assessment of Non-Small Cell Lung Carcinoma Panel Testing – A Pilot Study

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Introduction

The Australian Medicare Benefits Schedule (MBS) provides coverage for a wide range of medical services including pathology testing where eligible individuals can receive subsidised medical services from participating healthcare providers.

In November 2023, a new MBS item was introduced for the testing of genetic variants in newly diagnosed patients with non-small cell lung carcinoma (NSCLC), using a nucleic acid-based multi-gene panel test to detect variants in at least *EGFR, BRAF, KRAS* and *MET* exon 14, and to determine the fusion status of at least *ALK, ROS1, RET, NTRK1, NTRK2* and *NTRK3*. The purpose of the test is to determine patient access to specific therapies relevant to these variants listed on the Pharmaceutical Benefits Scheme (PBS).

Method

A questionnaire to gauge laboratory interest and testing capacity for a single multi-gene assay covering the above genes was distributed in May 2023. The questionnaire was sent to laboratories actively participating in the RCPAQAP NSCLC programs listed below:

- ALK Translocation in NSCLC
- ROS1 Translocation in NSCLC
- Mutation Detection in Lung Cancer

Based on the questionnaire responses, 7 laboratories (6 Australian, 1 overseas) with current capacity for such testing were invited to participate in the first pilot EQA study. A single case of high-grade adenocarcinoma positive for a *MET* c.3082G>A variant (c.3028G>A, VAF 43%) was sourced from the Hunter Cancer Biobank. Each participating laboratory received 5 x 6µm FFPE tissue sections for testing. All participants submitted a copy of their pathology reports for assessment. For this study, participating laboratories were assessed for their genotyping results on the core genes above.

Results

Questionnaire Responses

There was a low 21% response rate to the questionnaire (Australian, 69%; Hong Kong, 19%; New Zealand, 13%). Key questions and laboratory responses are listed in Table 1.

Table 1. Laboratory responses to questionnaire on NSCLC testing capacity.

Q1. Does your laboratory perform single gene or gene panel DNA testing for NSCLC?	
Single gene	25%
Gene panel	44%
Both	31%
Q2. Does your laboratory currently test for gene rearrangements in NSCLC?	
Yes, by IHC and/or FISH testing only	50%
Yes, by IHC/FISH or molecular testing	44%
No	6%
Q3. If Medicare rebate becomes available for nucleic acid-based single nucleotide variant and fusion/rearrangement testing in newly diagnosed NSCLC (ALK, ROS1, RET, NTRK1/2/3), do you currently have the capacity to provide such testing? If no, do you plan to develop this capacity in the next 6 months?	
Yes	44%
In development	19%
Will consider if funding available	13%
No	13%
Not applicable	13%
Q4. Is your laboratory currently involved in a quality assurance program for NSCLC gene panel testing (beyond EGFR, KRAS, BRAF)?	
Yes (RCPAQAP, EMQN, GenQA)	47%
No	53%

Pilot EQA Results

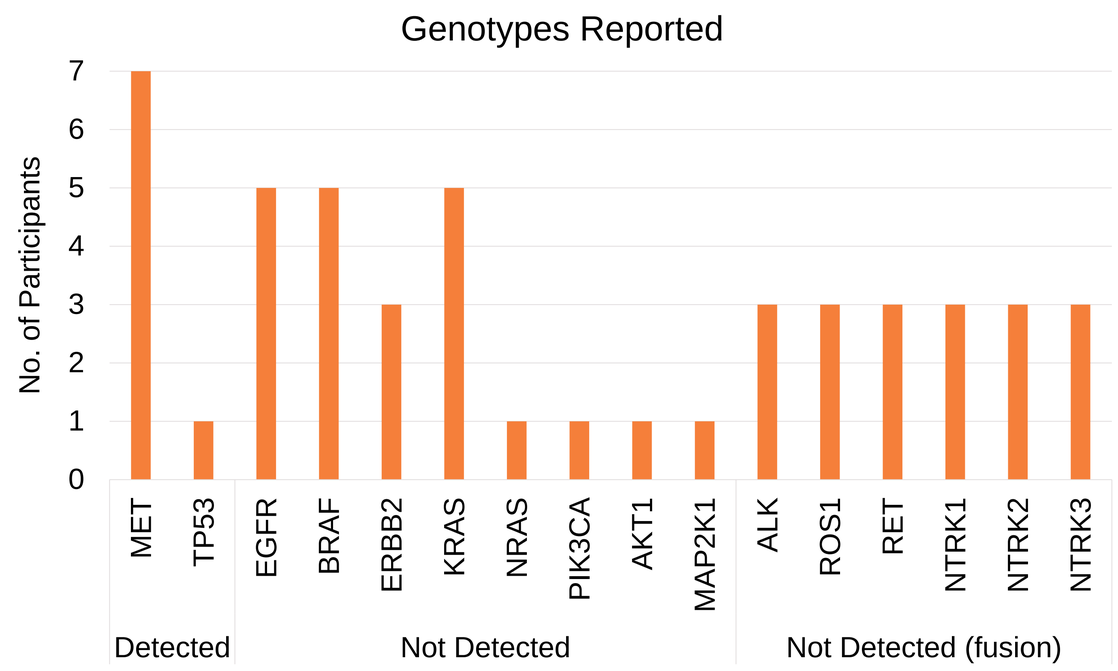
Methods used by participating laboratories in the pilot study are listed in Table 2.

Table 2. Methods used in the RCPAQAP NSCLC Gene Panel EQA.

Analytical Principal	Assay	nParts / %
NGS	Oncomine Precision Assay	3 (43%)
	Illumina Trusight Tumor 15	1 (14%)
	Oncomine Focus Assay	1 (14%)
	Custom Gene Panel	1 (14%)
	Somatic Tumour Targeted Sequencing OCP52	1 (14%)
RT-PCR	Biocartis Idylla GeneFusion Panel	1 (14%)

All participating laboratories included *EGFR, KRAS, BRAF, MET, ALK, ROS1 and RET* in their assays; NTRK1/2/3 were not included in one laboratory's panel.

Figure 1. Genotypes reported for the NSCLC Gene Panel pilot EQA.



All laboratories correctly identified the expected *MET* exon 14 variant c.3082G>A, with a median variant allele frequency (VAF) of 46.15%. One laboratory reported a *TP53* c.578A>T variant at VAF 14.1%.

Key clinical advice and therapeutic implications reported for this case are presented in Table 3.

Table 3. Key clinical advice reported.

Clinical advice	nParts / %
Worse prognosis	1 (14.3%)
May benefit from:	
Anti-MET therapy	3 (42.9%)
capmatinib	3 (42.9%)
tepotinib	4 (57.1%)
crizotinib	2 (28.6%)
cabozantinib	1 (14.3%)
glesatinib	1 (14.3%)

Conclusion

- As the majority of the laboratories participating in the RCPAQAP NSCLC programs are Anatomical Pathology laboratories performing either immunohistochemistry (IHC) or fluorescence in situ hybridisation (FISH) testing only, a multi-target molecular test may not be relevant hence the low response rate to the questionnaire.
- The pilot EQA study was a success and program will be offered in 2024, in conjunction with the Mutation Detection in Lung Cancer program.