Australian Government

Department of Health

Consultation Survey on MSAC Application 1660

Diagnostic testing for mesenchymal-epithelial transition (MET) Exon 14 (METex14) skipping alterations in non-small cell lung cancer (NSCLC) to determine Pharmaceutical Benefits Scheme eligibility for tepotinib treatment

This feedback survey relates to the application form and Population, Intervention, Comparator and Outcome (PICO) Confirmation for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)).

Please use this template, to prepare your feedback on the application form and/or the PICO Confirmation. You are welcome to provide feedback from either a personal or group perspective for consideration by the Department of Health when the application is being reviewed.

The data collected will be used to inform the Medical Services Advisory Committee (MSAC) process to ensure that when proposed healthcare interventions are assessed for public funding in Australia, they are patient focused and seek to achieve best value.

This feedback survey should take approximately 15 minutes to complete.

You may also wish to supplement your responses with further documentation or diagrams or other information to assist the Department in considering your feedback.

Thank you for taking the time to provide valuable feedback.

Responses may be provided to the MSAC, its subcommittees, a health technology assessment group and the applicant. Should you require de-identification please contact the HTA team (details below).

While stakeholder feedback is used to inform the application process, you should be aware that your feedback may be used more broadly by the applicant.

Please reply to the HTA Team:

Email: HTA@health.gov.au

Postal: MDP 959 GPO 9848 ACT 2601

PART 1 – PERSONAL AND ORGANISATIONAL INFORMATION

1. Respondent details

Name: Michael Quinn on behalf of Australian Genomics

Email: Australian.genomics@mcri.edu.au

Phone No: 07 3646 0185

2. (a) Is the feedback being provided on an individual basis or by a collective group? (please select)

☐ Individual
☒ Collective Group

(b) If individual, specify the name of the organisation you work for

(c) If collective group, specify the name of the group

Australian Genomics

3. How would you best identify yourself?

☐ General Practitioner
☐ Specialist
☐ Researcher
☐ Consumer
☐ Care giver
☒ Other

(a) If other, please specify

Project Officer for Australian Genomics, in consultation with senior program administrators, clinicians and researchers from Australian Genomics.

PART 2 – CLINICAL NEED AND PUBLIC HEALTH SIGNIFICANCE

4. Describe your experience with the medical condition (disease) and/or proposed intervention and/or service relating to the application form

Australian Genomics is an Australian Government initiative supporting genomic research and its translation into clinical practice. Through broad engagement and a national collaborative approach, it achieves two key objectives: to improve efficiency, reach and timeliness of genomic research projects, and to support Commonwealth, State and Territory health departments in the implementation of genomics research outcomes by refining and communicating evidence to inform policy development.

Australian Genomics engages with current and emerging government policy and priorities to identify gaps and opportunities, to support policy and action for integrating genomic technologies into the health system. By interfacing with consumers, government, industry and global genomics initiatives, Australian Genomics drives change and growth in the sector.

Australian Genomics has investigated clinical implementation of genomic testing into a range of rare disease and cancer diseases. This had included a Somatic flagship, that investigated clinically actionable variants in a range of cancer types using the Comprehensive Cancer Panel (391 cancer gene panel) at the Peter MacCallum Cancer Centre. This study, on non-resectable solid tumours (including non-small cell lung cancer (NSCLC)) also investigated the implementation of treatment changes in patients after their genomic result.

Additionally, an Australian Genomics Lung Cancer Diagnosis flagship has investigated the methodology of endobronchial ultrasound lymph node aspirates for nucleotide extraction and whole genome / whole exome sequencing technologies, to guide lung cancer treatment.

5. What do you see as the benefit(s) of the proposed medical service, in particular for the person involved and/or their family and carers?

Without the proposed medical service, this subset of patients would not be identified as being suitable for targeted tepotinib treatment.

Additionally, for those with a MetEx14 confirmation, the proposed treatment offers a maintenance in quality of life, and response rate of up to 50% (Paik *et al*., 2020). Although the dataset is not mature, anecdotal evidence suggests a prolonged survival in NSCLC after tepotinib treatment (Roth *et al*., 2020). Although patients with NSCLC with MET mutations are generally older (eg median age 74, Paik *et al*., 2020), trials have indicated a maintenance in quality of life during drug administration (stable symptoms of dyspnea, reduced cough symptoms) (Paik *et al*., 2020). The adverse event profile (for example peripheral edema) was comparable to similar studies of tepotinib (discontinuation in 11% of patients, Paik *et al*., 2020).

As METex14 is usually detected in patients older than 70 years, the targeted treatment (typically taken as a daily oral dose as per the VISION trial (Paik *et al*., 2020)) has a great advantage over more generic chemotherapies, which have associated adverse side-effects and toxicity.

Taken together, we believe the proposed service and treatment will provide considerable hope for respective patient's family, carers and offer stabilisation of quality of life.

6. **What do you see as the disadvantage(s) of the proposed medical service, in particular for the person involved and/or their family and carers?**

The Paik *et al*., (2020) study, found that adverse effects were found in 28% of patients, including peripheral edema in 7% of patients (deemed to be grade 3 or higher). Other adverse events of treatment included pleural effusion and dyspnea. The risk of adverse effects would have to be explained to patients prior to consenting to treatment.

Relevant counselling and support services for patient and other family members should be available as standard of care through respective oncology services.

It is also noted that in there is a risk of acquired resistance when using a targeted therapy. Although there is limited testing of tepotinib resistance in NSCLC, acquired resistance has been documented in lung cancer driver oncogene targeted treatment. This acquired resistance risk would need to be incorporated into any treatment plan.

7. **What other benefits can you see from having this intervention publically funded on the Medicare Benefits Schedule (MBS)?**

Generally, there would be considerable reduction in financial burden to the family. Additionally, there may be a reduction in financial cost to the health system / potential increase in QALYs (quality-adjusted life years), however there is a lack in data for these metrics due to the recent approval of the drug.

8. **What other services do you believe need to be delivered before or after this intervention, eg Dietician, Pathology etc?**

We understand this service will mainly be delivered through oncology services, in conjunction with sample collection by a respiratory physician.

PART 3 – INDICATION(S) FOR THE PROPOSED MEDICAL SERVICE AND CLINICAL CLAIM

9. Do you agree or disagree with the proposed population(s) for the proposed medical service as specified in Part 6a of the application form?

- [x] Strongly Agree
- [ ] Agree
- [ ] Disagree
- [ ] Strongly Disagree

(a) Specify why or why not:

The frequency of Exon 14 MET skipping is estimated in the literature (3-5%). As outlined in the application, based on the literature and a local laboratory internal audit estimate, the higher estimate of a 5% frequency of the METex14 alteration has been assumed.

10. Have all the associated interventions been adequately captured in Part 6b of the application form?

- [x] Yes
- [ ] No

(b) Please explain:

We have two general comments in the intervention description.

Firstly, more detail around the nature of the diagnostic test would be informative. For example, it is not clear which technology the test will be based on (Real-time PCR, NGS (Illumina) or NGS (Thermo Fisher). Additionally, when RNA sequencing will be used is not clear. Finally, potential validation of the assay by IHC is not defined. Such details are important to ensure national consistency between testing laboratories. We note these details may appear in the summary dossier.

Secondly, for clarity it would be useful if Figure 1 / Figure 2 was modified to clearly indicate where testing would stop and when treatment would be administered.

11. Do you agree or disagree that the comparator(s) to the proposed medical service as specified in Part 6c of the application form?

- [x] Strongly Agree
- [ ] Agree
- [ ] Disagree
- [ ] Strongly Disagree

The comparator of “no test” is appropriate.

12. Do you agree or disagree with the clinical claim made for the proposed medical service as specified in Part 6d of the application form?

☒ Strongly Agree
☐ Agree
☐ Disagree
☐ Strongly Disagree

(a) Specify why or why not:

The test will offer targeted treatment currently not offered as standard of care.

PART 4 – COST INFORMATION FOR THE PROPOSED MEDICAL SERVICE

13. Do you agree with the proposed MBS item descriptor, as specified in Question 53 of the application form?

- ☐ Strongly Agree
- ☒ Agree
- ☐ Disagree
- ☐ Strongly Disagree

(b) Specify why or why not:

We agree with the item descriptor in general. We note it is described as Category 6 or 7 (Pathology or genetic services). The possible involvement of genetic services in some cases is covered by the wording "requested by or on behalf of, a specialist or consultant physician".

We also assume that more details about the diagnostic test (eg DNA/RNA, nature of NGS instrumentation and sequencing depth) will be provided in the 'full submission dossier'

14. Do you agree or disagree with the proposed MBS fee, as specified in Question 53 of the application form?

- ☐ Strongly Agree
- ☐ Agree
- ☐ Disagree
- ☐ Strongly Disagree

(c) Specify why or why not:

PART 5 – ADDITIONAL COMMENTS

15. Do you have any additional comments on the proposed intervention and/or medical condition (disease) relating to the proposed medical service?

As mentioned above, we assume that additional detail about the diagnostic test (eg DNA/RNA, nature of NGS instrumentation and sequencing depth) will be provided in the 'full submission dossier'. This is particularly important due to the documented breadth of deletions/variants that can lead to exon 14 skipping (Frampton *et al*., 2015 reported 130 unique variants). The event can also occur at a variety of locations (eg deletion at splice acceptor and donor site, mutation at splice donor site). As outlined in Cortot *et al*., 2017, if WES is utilized, intronic sequences will not be well covered. Similarly, the use of RNA sequencing to detect exon14 skipping presents challenges in terms of securing RNA samples of suitable quality in clinical practice. Such detail is important to provide guidance to laboratories pursuing NATA accreditation for the test.

Additionally, from the application, it is not clear how many laboratories would be capable of delivering the service, although it is mentioned that there is no 'single sponsor' for detection METex14 alternations (Part 5). Part 6b also mentioned that although the test is not routinely performed, the test is offered in select Australian laboratories. In Part 3, it is also mentioned that there is an expectation that laboratories will develop an in-house test, accredited through NATA. If the test is provided in a range of laboratories across Australia, this should allow for good equity of access.

It is not clear if MET IHC be used as a validation technique if necessary (Passinen-Sohns *et al*., 2017). Vuong *et al*., (2018) found a strong correlation between-MET overexpression and MET exon 14 mutations. Cortot *et al*., (2017) indicate that IHC could be used as a low-cost pre-screening step.

Although not directly related to this application, we also note that there is no mention of the possibility of using a liquid biopsy in the future. This technique is non-obtrusive and offers the ability to monitor the patient drug response also the opportunity to follow longitudinal on-treatment biomarker data (Paik *et al*., 2020).

Survey Reference List

Cortot, A. B., Z. Kherrouche, C. Descarpentries, M. Wislez, S. Baldacci, A. Furlan, and D. Tulasne. 2017. 'Exon 14 Deleted MET Receptor as a New Biomarker and Target in Cancers', *J Natl Cancer Inst*, 109.

Frampton, G. M., S. M. Ali, M. Rosenzweig, J. Chmielecki, X. Lu, T. M. Bauer, M. Akimov, J. A. Bufill, C. Lee, D. Jentz, R. Hoover, S. H. Ou, R. Salgia, T. Brennan, Z. R. Chalmers, S. Jaeger, A. Huang, J. A. Elvin, R. Erlich, A. Fichtenholtz, K. A. Gowen, J. Greenbowe, A. Johnson, D. Khaira, C. McMahon, E. M. Sanford, S. Roels, J. White, J. Greshock, R. Schlegel, D. Lipson, R. Yelensky, D. Morosini, J. S. Ross, E. Collisson, M. Peters, P. J. Stephens, and V. A. Miller. 2015. 'Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors', *Cancer Discov*, 5: 850-9.

Paasinen-Sohns, A., V. H. Koelzer, A. Frank, J. Schafroth, A. Gisler, M. Sachs, A. Graber, S. I. Rothschild, A. Wicki, G. Cathomas, and K. D. Mertz. 2017. 'Single-Center Experience with a Targeted Next Generation Sequencing Assay for Assessment of Relevant Somatic Alterations in Solid Tumors', *Neoplasia*, 19: 196-206.

Paik, P. K., E. Felip, R. Veillon, H. Sakai, A. B. Cortot, M. C. Garassino, J. Mazieres, S. Viteri, H. Senellart, J. Van Meerbeeck, J. Raskin, N. Reinmuth, P. Conte, D. Kowalski, B. C. Cho, J. D. Patel, L. Horn, F. Griesinger, J. Y. Han, Y. C. Kim, G. C. Chang, C. L. Tsai, J. C. Yang, Y. M. Chen, E. F. Smit, A. J. van der Wekken, T. Kato, D. Juraeva, C. Stroh, R. Bruns, J. Straub, A. Johne, J. Scheele, J. V. Heymach, and X.

Le. 2020. 'Tepotinib in Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations', *N Engl J Med*, 383: 931-43.

Roth, K. G., I. Mambetsariev, and R. Salgia. 2020. 'Prolonged survival and response to tepotinib in a non-small-cell lung cancer patient with brain metastases harboring MET exon 14 mutation: a research report', *Cold Spring Harb Mol Case Stud*, 6.

Vuong, H. G., A. T. N. Ho, A. M. A. Altibi, T. Nakazawa, R. Katoh, and T. Kondo. 2018. 'Clinicopathological implications of MET exon 14 mutations in non-small cell lung cancer - A systematic review and meta-analysis', *Lung Cancer*, 123: 76-82.

16. Do you have any comments on this feedback survey? Please provide comments or suggestions on how this process could be improved.

More structured questions around 6a and 6b are suggested – for example if sufficient evidence is given for various points (eg health benefits, effectiveness of treatment etc).

Also, there are some cases where agree/disagree as a response is not applicable – for example where information is redacted and an informed decision cannot be reached.

Again, thank you for taking the time to provide valuable feedback.