



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1602 – Testing for neurotrophic tropomyosin receptor kinase (NTRK) gene fusion status, in patients with locally advanced or metastatic solid tumours, to determine eligibility for larotrectinib (Vitrakvi) – codependent

Applicant: Bayer Australia Ltd

Date of MSAC consideration: MSAC 80th Meeting, 26-27 November 2020

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

The integrated codependent submission (or applicant-developed assessment report (ADAR)) was received from Bayer Australia Limited by the Department of Health. The submission requested:

- Medicare Benefits Schedule (MBS) listing of FISH and NGS testing for the evaluation of the presence of a neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusion to determine eligibility for treatment with larotrectinib in patients with locally advanced or metastatic solid tumours of any origin; and
- Pharmaceutical Benefits Scheme (PBS) Section 100 Authority Required listing of larotrectinib for the treatment of *NTRK* fusion positive solid tumours that are unresectable locally advanced, or metastatic, or locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support Medicare Benefits Schedule (MBS) funding for *NTRK* fusion testing primarily because the Pharmaceutical Benefits Advisory Committee (PBAC) had deferred its decision regarding larotrectinib, the codependent targeted medicine. MSAC foreshadowed that it would expedite a reconsideration of *NTRK* fusion testing in paediatric patients if the PBAC recommends larotrectinib for this population, but advised there are additional issues requiring reconsideration for adult patients.

Consumer summary

Bayer Australia Ltd applied for public funding via the Medicare Benefits Schedule (MBS) for genetic testing for neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusion status in all patients with locally advanced or metastatic solid tumours to help determine if they could benefit from the medicine larotrectinib.

This was a codependent application, meaning that the genetic test is needed to identify patients who might benefit from the medicine. The application for larotrectinib was first considered by the Pharmaceutical Benefits Advisory Committee (PBAC), which deferred its decision on larotrectinib.

There are three *NTRK* genes, *NTRK1*, *NTRK2* and *NTRK3*. They instruct cells in the body to produce specific proteins, called Trk proteins. In some types of cancer, *NTRK* genes can be fused with other genes in a way that causes more of the Trk proteins to be made in the cancer cells, making the cancer cells survive longer.

Larotrectinib is a medicine that targets cancer cells that have a lot of Trk protein, and can help destroy these cells. The application stated that testing for *NTRK* gene fusions can help doctors decide if that patient is likely to benefit from larotrectinib.

Overall, *NTRK* gene fusions are rare, found in less than 1% of all solid tumours. However, these fusions are more common in certain types of rare cancer. In these “high frequency” tumours, *NTRK* fusions are found in 80% or more of these tumours.

This application was for *NTRK* gene fusion testing across four subgroups:

- children with advanced cancers that have a high frequency of *NTRK* gene fusions
- children with advanced cancers that have a low frequency of *NTRK* gene fusions
- adults with advanced cancers that have a high frequency of *NTRK* gene fusions
- adults with advanced cancers that have a low frequency of *NTRK* gene fusions, but only if the result of another type of test (immunohistochemistry, or IHC) suggests that an *NTRK* fusion is involved.

MSAC considered that genetic testing of cancers in children is more commonly performed than in adults. Children usually get a panel of genetic tests to characterise their cancer as soon as possible, to reduce the delay in finding the most appropriate treatment. It is also best to avoid radiation and less targeted chemotherapy in children, as these can have long-term effects. This means it would be preferable for the doctor treating a child with an advanced cancer to know that the tumour has an *NTRK* fusion to inform a decision about starting larotrectinib.

For adults, MSAC advised that *NTRK* testing would likely most benefit those with cancers that have a high frequency of *NTRK* fusions. MSAC also advised that there were issues with the economic model that needed more work before MSAC could decide whether *NTRK* fusion testing was good value for money in adults with cancers that have a low frequency of *NTRK* fusions.

MSAC’s advice to the Commonwealth Minister for Health

MSAC did not support testing for *NTRK* gene fusion status in patients with locally advanced or metastatic solid tumour to help determine eligibility for larotrectinib. This was mainly because the PBAC had deferred its recommendation on larotrectinib. MSAC advised that it could speedily reconsider the application for children, but that more detailed information would be needed to reconsider the application for adults.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted the purpose of the application was testing for *NTRK* gene fusions in patients with unresectable locally advanced or metastatic solid tumours, to determine eligibility for larotrectinib. Testing mostly uses fluorescence *in situ* hybridisation (FISH), or next-generation sequencing (NGS) using either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). MSAC accepted that the comparator was “no testing”. Four separate subgroups were proposed in the application:

1. paediatric patients with locally advanced or metastatic solid tumours with high-frequency of *NTRK* fusions (first-line testing)
2. adult patients with locally advanced or metastatic solid tumours with high-frequency of *NTRK* fusions (first-line testing)
3. paediatric patients with locally advanced or metastatic solid tumours with low-frequency *NTRK* fusions (first-line testing)
4. adult patients with locally advanced or metastatic solid tumours with low-frequency *NTRK* fusions, who have relapsed/refractory disease and after prior immunohistochemistry [IHC] testing returns a positive result.

MSAC noted that the application was considered at a joint meeting of the Economics Sub-Committee of the Pharmaceutical Benefits Advisory Committee (PBAC) and the Evaluation Sub-Committee of MSAC (the ESCs) in October 2020. The application for larotrectinib was deferred by the PBAC at its November 2020 meeting. MSAC noted that the PBAC had concluded that the potential comparative treatment benefit of larotrectinib would mostly be in the subgroups of paediatric patients and adult patients with high-frequency tumours, but was seeking a suitable price reduction from the applicant and advice from MSAC before completing its consideration of these subgroups.

MSAC noted that the diagnostic pathway for paediatric patients is different from adults. Although prior IHC testing was not proposed for children with low-frequency *NTRK* fusions due to the potential delay in selecting treatment that may follow a false negative IHC result, MSAC also noted that paediatric patients, usually managed as public patients in (tertiary) public hospitals, undergo a wide range of tests (including IHC, FISH and NGS) as standard practice, and that the full range of these tests would be conducted even if the IHC result is negative. MSAC also noted the ongoing PRISM study ([NCT03336931](https://clinicaltrials.gov/ct2/show/study/NCT03336931)) in which the Australian and New Zealand Children's Oncology Group conducts molecular testing on fresh frozen samples from paediatric tumours (funded under the Medical Research Future Fund [MRFF]). Results from this study are expected to add to the evidence base for paediatric patients.

For IHC testing in the low- and high-frequency adult populations, MSAC considered that more information was needed on the false negative rate for IHC and the reasons for this, as well as a definition of a positive IHC result (e.g. whether this would include weak positivity, or would be better defined as “non-negative”).

MSAC considered the differences between using FISH or DNA-NGS or RNA-NGS for *NTRK* fusion testing. MSAC noted that RNA-NGS is more sensitive and specific and provides more functional information than DNA-NGS or FISH, but also that RNA is more difficult to extract from tumours, requires a greater amount of tumour sample (80 nanograms rather than 40 nanograms), and should be done early in the diagnosis pathway because it degrades relatively easily, including in paraffin-embedded samples. RNA-NGS for *NTRK* fusions can be done as stand-alone tests or as part of a panel. MSAC advised that RNA-NGS is preferable to FISH, mostly because it can identify different types of *NTRK* fusions which

have different prognostic values across different cancer types and therefore potentially different predictive values for the effectiveness of larotrectinib. However, MSAC considered that FISH is more widely available than RNA-NGS across pathology laboratories, whilst NGS is likely to become more available in the future. MSAC therefore considered that FISH testing could be supported in the shorter-term to allow greater patient access whilst clinicians collecting samples from potentially suitable patients are trained to do so in a way that optimises their storage as fresh frozen samples and, if necessary, their transport for RNA-NGS.

MSAC responded to the key concerns raised by the ESCs:

- Clinical utility of *NTRK* testing and the proposed test sequencing for this application – MSAC considered that the clinical utility would depend on access to larotrectinib, it would be reasonable to allow populations with high-frequency tumour types to have direct access to FISH/NGS without a prior IHC test, and it would be reasonable for paediatric patients with low-frequency tumour types have direct access to FISH/NGS without a prior IHC test because of the small numbers of these patients and the likelihood of their cancer being oncogenically driven by a detected *NTRK* fusion is high.
- Test performance and quality assurance – MSAC noted that a quality assurance program is available and that, given the level of expertise required, testing would likely be restricted to National Association of Testing Authorities (NATA) accredited laboratories whose scope of practice includes somatic FISH testing on fresh or paraffin-embedded tissue, and somatic NGS testing using DNA or RNA.

MSAC discussed the three multicentre, open-label single-arm clinical studies of larotrectinib (LOXO-001, NAVIGATE, and SCOUT) involving adult and paediatric patients with *NTRK*-fusion positive, locally advanced or metastatic solid tumours. MSAC noted that the data for larotrectinib was pooled across these studies, which limited the ability to demonstrate whether efficacy was similar or different across specific cancer types; and was also compared with standard of care using historical data, which may not reflect current contemporary standard of care. However, MSAC also considered that it is generally desirable to avoid radiotherapy and standard chemotherapy in paediatric patients (which would occur for the comparator of no genetic testing + standard of care) because of late-term effects, particularly on cognition and fertility and risk of second malignancy.

MSAC noted the economic model was based on naive indirect comparisons, leading to uncertain incremental benefits, and high and uncertain incremental cost-effectiveness ratios (ICERs). The model inappropriately assumed that testing across all the options in regular Australian practice would perform as well as the evidentiary standard, given that test performance was also shown to vary depending on whether DNA or RNA is used for NGS, and FISH performance was uncertain due to lack of data. The model structure did not allow for the implications of either false positive or false negative results from testing (such as inappropriate treatment and delayed appropriate treatment), both of which tend to overestimates the quality-adjusted life years (QALYs) gained and thus to underestimate the ICERs. The model submitted in the application also included the applicant's proposed risk-sharing arrangement (RSA), which would reduce the effective price of larotrectinib, but which the Department considered to be excessively burdensome to administer and so should not be included in the base case analysis. MSAC also noted that the ESCs had had considerable concerns relating to the sponsor's proposed RSA. When this RSA component was removed by the assessment group before the MSAC meeting, the base case ICER increased to \$155,000 to < \$255,000 per QALY, and the relative order of the population groups changed (i.e. when the RSA is included, ICERs were lower for the paediatric or high-

frequency population subgroups than the adult or low-frequency subgroups, but removing the RSA reverses this order so the adult or low-frequency subgroups have lower ICERs). MSAC considered that this reflected the different projected durations of larotrectinib therapy across these subgroups. MSAC agreed with the PBAC that a larotrectinib price reduction would be essential to result in more acceptable ICERs.

MSAC agreed with the ESCs consideration that, for adults with advanced cancers that have a low frequency of *NTRK* gene fusions, it was likely that there would be a substantial increase in utilisation of existing MBS items for pan-Trk IHC tests and thus their financial costs. The financial estimates would also need to be adjusted for MSAC’s recommended reduced fees for both types of *NTRK* testing.

MSAC noted the pre-MSAC response, but considered that it was not sufficient to address satisfactorily all of the ESCs’ key issues.

MSAC foreshadowed that any MSAC-supported MBS item descriptors should specify solid tumour cancer which is locally advanced or metastatic as aligned with the TGA-approved indication for larotrectinib, specify that the fusions relate to *NTRK1*, *NTRK2* and *NTRK3*, and list which tumour types are eligible for patients aged 18 years or over. MSAC considered that the proposed fee for RNA-NGS should be aligned with Alport testing (fee: \$1,200; 75% benefit: \$900). Alport testing analyses four genes, rather than the three genes analysed for *NTRK* fusions, but MSAC considered that this fee would be appropriate given the additional complexity associated with using RNA. MSAC noted that the current fee for FISH testing for two or three sarcoma genes is considered to be low, and considered that reimbursement for *NTRK* testing should not be separate for each of the three *NTRK* tests. MSAC also noted that the proposed fee does not consider the Greatest Permissible Gap, which might be more relevant for adults with low frequency tumours, but considered that the service would not be provided in an outpatient setting for children. MSAC noted that the applicant would accept MSAC’s recommendations on the fees, as outlined in its pre-MSAC response.

The foreshadowed MBS items reflecting MSAC discussions are as follows:

Item number: AAAA	Category 6 (Pathology services) – Group P7 Genetics
<p>Fluorescence in-situ hybridisation (FISH) test of tumour tissue from a patient aged 18 years or over with:</p> <ul style="list-style-type: none"> • solid tumour cancer of one of the following types [list here would identify MSAC-accepted low frequency <i>NTRK</i> fusion cancers which are yet to be specified], • which is metastatic OR is locally advanced where surgical resection is likely to result in severe morbidity, • and with documented evidence of tropomyosin receptor kinase (TrkA, TrkB or TrkC) immunoreactivity by immunohistochemical (IHC) examination, <p>requested by a specialist or consultant physician to determine if requirements relating to neurotrophic tropomyosin receptor kinase (<i>NTRK1</i>, <i>NTRK2</i> or <i>NTRK3</i>) fusions for access to a Trk inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</p> <p>This item cannot be claimed if MBS items BBBB, CCCC or DDDD have been claimed for the same patient. Applicable only once per cancer diagnosis.</p> <p>Fee: \$400.00. Benefit: 75% = \$300.00 85% = \$340.00 for 1 <i>NTRK</i> fusion test, Fee: \$533.00. Benefit: 75% = \$400.00 85% = \$453.00 for 2 <i>NTRK</i> fusion tests, Fee: \$667.00. Benefit: 75% = \$500.00 85% = \$566.00 for 3 <i>NTRK</i> fusion tests</p>	

Item number: BBBB	Category 6 (Pathology services) – Group P7 Genetics
<p>Fluorescence in-situ hybridisation (FISH) test of tumour tissue from a patient:</p> <ul style="list-style-type: none"> with solid tumour cancer which is metastatic OR is locally advanced where surgical resection is likely to result in severe morbidity, and who is either aged less than 18 years OR is aged 18 years or over and has either mammary analogue secretory carcinoma of the salivary gland or secretory breast cancer, <p>requested by a specialist or consultant physician to determine if requirements relating to neurotrophic tropomyosin receptor kinase (<i>NTRK1</i>, <i>NTRK2</i>, or <i>NTRK3</i>) fusions for access to a tropomyosin receptor kinase (Trk) inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</p> <p>This item cannot be claimed if MBS items AAAA, CCCC or DDDD have been claimed for the same patient. Applicable only once per cancer diagnosis.</p> <p>Fee: \$400.00. Benefit: 75% = \$300.00 85% = \$340.00 for 1 <i>NTRK</i> fusion test, Fee: \$533.00. Benefit: 75% = \$400.00 85% = \$453.00 for 2 <i>NTRK</i> fusion tests, Fee: \$667.00. Benefit: 75% = \$500.00 85% = \$566.00 for 3 <i>NTRK</i> fusion tests</p>	
Item number: CCCC	Category 6 (Pathology services) – Group P7 Genetics
<p>Next generation sequencing (NGS) test of tumour tissue from a patient aged 18 years or over with:</p> <ul style="list-style-type: none"> solid tumour cancer of one of the following types [list here would identify MSAC-accepted low frequency <i>NTRK</i> fusion cancers which are yet to be specified], which is metastatic OR is locally advanced where surgical resection is likely to result in severe morbidity, and with documented evidence of tropomyosin receptor kinase (TrkA, TrkB or TrkC) immunoreactivity by immunohistochemical (IHC) examination <p>requested by a specialist or consultant physician to determine if requirements relating to neurotrophic tropomyosin receptor kinase (<i>NTRK1</i>, <i>NTRK2</i> or <i>NTRK3</i>) fusions for access to a Trk inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</p> <p>This item cannot be claimed if MBS items AAAA, BBBB or DDDD have been claimed for the same patient. Applicable only once per cancer diagnosis.</p> <p>Fee: \$1,200.00 Benefit: 75% = \$900.00 85% = \$1,115.30</p>	
Item number: DDDD	Category 6 (Pathology services) – Group P7 Genetics
<p>Next generation sequencing (NGS) test of tumour tissue from a patient:</p> <ul style="list-style-type: none"> with solid tumour cancer which is metastatic OR is locally advanced where surgical resection is likely to result in severe morbidity, and who is either aged less than 18 years OR is aged 18 years or over and has either mammary analogue secretory carcinoma of the salivary gland or secretory breast cancer, <p>requested by a specialist or consultant physician to determine if requirements relating to neurotrophic tropomyosin receptor kinase (<i>NTRK1</i>, <i>NTRK2</i> or <i>NTRK3</i>) fusions for access to a Trk inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</p> <p>This item cannot be claimed if MBS items AAAA, BBBB or CCCC have been claimed for the same patient. Applicable only once per cancer diagnosis.</p> <p>Fee: \$1,200.00 Benefit: 75% = \$900.00 85% = \$1,115.30</p>	

Note: Text in red font indicates MSAC-proposed amendments to the proposed listings.

MSAC foreshadowed that it would expedite a reconsideration of *NTRK* fusion testing in paediatric patients if the PBAC recommends larotrectinib for this population. However, MSAC advised there are additional issues requiring reconsideration for adult patients, including an evidentiary basis to assess whether *NTRK* fusion type predicts variation in larotrectinib response rates to better justify the recommended fee difference between RNA-NGS and FISH testing, a revised economic model and revised financial estimates, to be addressed in any integrated codependent resubmission.

4. Background

Table 1 Key components of the clinical issue addressed by the submission

Component	Description
Population	<p>Test: locally advanced or metastatic solid tumour patient subpopulations:</p> <ol style="list-style-type: none"> Paediatric patients newly diagnosed with locally advanced or metastatic solid tumours with high frequency NTRK gene fusions; Adult patients newly diagnosed with locally advanced or metastatic solid tumours with high frequency NTRK gene fusions; Paediatric patients newly diagnosed with locally advanced or metastatic solid tumours with low frequency NTRK gene fusions; Adult patients with locally advanced or metastatic solid tumours with low frequency NTRK gene fusions who have progressed following one or more standard of care therapies. <p>Treatment: patients with locally advanced or metastatic solid tumours with confirmed <i>NTRK</i> gene fusions who would become eligible for Trk inhibitor treatment (first-line for Populations 1, 2 and 3 and second- or later-line for Population 4)</p>
Intervention	<p>Tests: IHC (triage for Populations 1, 2 and 3), FISH or NGS (diagnostic for all four Populations)</p> <p>Treatment: larotrectinib 100 mg BID for adults or 100 mg/m² BID with a maximum of 100 mg BID administered for paediatric patients</p>
Comparator	No test + SoC
Outcomes	<p>Test: sensitivity, specificity, PPV, NPV, NNT</p> <p>Treatment: overall response rate, duration of response, overall survival, progression-free survival, safety</p>
Clinical claim	In patients with a locally advanced or metastatic solid tumour with confirmed <i>NTRK</i> fusion, larotrectinib + <i>NTRK</i> gene fusion testing (FISH or NGS +/- IHC) is superior in terms of efficacy and safety when compared to no <i>NTRK</i> gene fusion testing + SoC

Source: Table 1.1 (page 19) and section 1.1.2.5 (page 26) of the submission

BID = "bis in die" or twice a day; FISH = fluorescence *in situ* hybridisation; IHC = immunohistochemistry; NGS = next generation sequencing; NNT = number needed to treat; NPV = negative predictive value; *NTRK* = neurotrophic tropomyosin receptor kinase; PPV = positive predictive value; SoC = standard of care

Alignment with agreed PICO confirmation

The alignment between the PICO confirmation ratified by PASC and the submission is presented in Table 2.

Table 2 Compliance with PICO Confirmation

PASC-approved (ratified) PICO Confirmation item	Compliance	Change and justification provided in submission
Proposed MBS listing	No	The submission has added two new MBS items that were not included in the ratified PICO Confirmation. These allow for FISH and NGS testing without prior IHC testing. The submission has proposed that the fee for NGS should be \$2,100 based on MBS item 73358 for whole genome sequencing. This is higher than the \$980 proposed in the ratified PICO. This increase was not adequately justified in the submission.
Population / clinical indication	No	The ratified PICO Confirmation indicates larotrectinib for first-line therapy in all patient populations, but the submission indicates that, in Population 4, larotrectinib treatment would be for second- or third-line treatment after disease progression.
Comparator	No	The PICO Confirmation indicated that the comparator would be untargeted chemotherapy and/or immunotherapies, based on tumour histology. The submission was inconsistent with the PICO Confirmation as it did not include SoC immunotherapies.
Reference/evidentiary standard	Yes	No reference standard was identified for the detection of <i>NTRK</i> fusions in the ratified PICO Confirmation. However, the current literature and ESMO recommendations indicate that RNA-NGS is the gold standard provided that RNA quality is optimal.
Clinical management algorithm	No	The proposed clinical algorithm in the submission differs from the algorithm in the ratified PICO Confirmation. The submission disagreed with PASC's advice that to "include IHC testing for all proposed subpopulations would be beneficial.
Clinical outcomes assessed	Yes	The clinical outcomes assessed were in-line with those proposed in the ratified PICO Confirmation

ESMO = European Society for Medical Oncology; FISH = fluorescence *in situ* hybridisation; IHC = immunohistochemistry; NGS = next generation sequencing; *NTRK* = neurotrophic tropomyosin receptor kinase; PASC = PICO Confirmation Advisory Sub-Committee; PICO = Population, Intervention, Comparator, Outcome; RNA = ribonucleic acid; SoC = standard of care;

Source: Constructed during evaluation

The submission addressed the thirteen recommendations that were reported in the January 2020 MSAC [Discussion paper](#), which are presented in Table 3.

Table 3 MSAC concerns and how these were addressed in the submission

Recommendations	How/where this submission addresses the recommendation?	Was the issue addressed adequately in the submission?
1. A biological plausibility analysis to give the rationale as to why a therapeutic response to the treatment could be expected across diverse sites or organs.	Larotrectinib demonstrates consistent response across different tumour types.	The biological plausibility of the <i>NTRK</i> fusion being the oncogenic driver was not fully covered in the submission.
2. Any other biomarkers that may have predictive value for the proposed treatment should be discussed.	Given that the presence of <i>NTRK</i> fusion is generally mutually exclusive of other biomarkers and when present, <i>NTRK</i> fusion is the main oncogenic driver, it is not expected that other biomarkers would have predictive value for larotrectinib.	The submission did not fully address the co-occurrence of MSI-H, TMB and PD-L1 expression in <i>NTRK</i> fusion positive tumours, and the possible implications for targeted treatment options.
3. The biomarker prevalence in the overall population should be reported, along with its prevalence in	A comprehensive review of <i>NTRK</i> fusion prevalence was provided in the submission.	The prevalence rate for paediatric STS used by the submission was not verifiable and likely inaccurate due to the inclusion of IFS, a

Recommendations	How/where this submission addresses the recommendation?	Was the issue addressed adequately in the submission?
as many specific tumour types as possible.		known high frequency <i>NTRK</i> cancer in the paediatric STS cohort.
4. The biomarker prevalence may change during the course of disease, especially if the biomarker is unstable, or has a prognostic effect (as for dMMR in CRC). Thus, the prevalence rate of the biomarker should be considered in the specific stage(s) of disease being targeted for testing and treatment.	<i>NTRK</i> fusions are primary oncogenic drivers and as such, the prevalence rate would not be expected to change at different disease stages.	The stability and/or persistence of <i>NTRK</i> fusions with tumour progression is largely unknown, and was not well covered in the submission.
5. The reference standard test and the evidentiary standard test should be nominated, see Section B3.1 and Item 5 in Appendix 7, respectively, of the MSAC Technical Guidelines for Investigative Services (MSAC 2017).	RNA-NGS is the reference standard as recommended by ESMO. NGS was the main test for patients enrolled in the trial (RNA or DNA not specified) and is the evidentiary standard.	Well covered in the submission.
6. If the proposed test is not the evidentiary standard test used in the supportive clinical trials assessing treatment efficacy, then bridging data should be provided to assess the comparability of the performance of the proposed test to the evidentiary standard test. Key differences that may affect or alter the eligibility/selection of patients for the proposed treatment should be identified, e.g., for pan-tumour use, this comparison would be dMMR as determined by IHC vs MSI-H as determined by either the PCR-based MSI test or, in the near future, a next generation sequencing (NGS) MSI computational algorithm.	The proposed testing algorithm includes IHC screening before confirmatory NGS/FISH testing in adults with low frequency <i>NTRK</i> tumours. As such, the diagnostic accuracy of this testing strategy was assessed in the submission. The diagnostic evidence for DNA-NGS is also assessed. The submission noted that there was a lack of evidence assessing FISH for <i>NTRK</i> fusions.	The diagnostic accuracy of IHC and DNA-NGS was covered by the submission.
7. Data on the accuracy of the test across tumour types should be provided in Section B3 of the assessment to demonstrate that the test performance is consistent, or if not, to identify when other testing measures are required, e.g. varying diagnostic thresholds, at-risk patient populations etc.	Diagnostic accuracy of IHC and DNA-NGS vs the reference standard RNA-NGS was provided in the submission.	Diagnostic accuracy of IHC across different tumour types was discussed by the submission.
8. Test reproducibility is particularly important for pan-tumour assessments to demonstrate testing equivalence across different tumour types and for different diagnostic laboratories.	NGS has high reproducibility.	This was not fully covered in the submission. However, if the IHC, FISH, or NGS tests are performed in a NATA-accredited laboratory with a quality assurance program in place, test reproducibility should not be an issue.
9. It is important that the positive predictive value (PPV) and negative predictive value (NPV) for the biomarker test versus its reference standard is provided over the relevant biomarker prevalence range for the tumours being targeted to	The PPV and NPV were calculated taking into account the prevalence range of <i>NTRK</i> fusions across different tumour types.	This was well covered in the submission. However the economic analysis assumes 100% test performance of NGS and FISH. The model structure does not allow false positives to be modelled, and so the implications of inappropriate

Recommendations	How/where this submission addresses the recommendation?	Was the issue addressed adequately in the submission?
enable an assessment of the ratio of correct to incorrect test results.		treatment and delayed appropriate treatment for these patients has not been considered.
10. MSAC/PBAC may consider it prudent to ensure that testing for access to a pan-tumour medication is not undertaken before other viable treatment options are considered. Alternatively, each patient could be individually triaged for either standard of care or the pan-tumour medicine, based on the prevalence of the biomarker in that tumour type and/or the population level evidence supporting a potential treatment effect of the therapy in that patient.	The proposed clinical algorithm in the submission was developed in consultation with clinicians. It considered the current available evidence as well as ethical considerations and clinical need.	The clinical algorithm proposed by the submission differed from that in the ratified PICO Confirmation.
11. For tumour types with very low prevalence rates, MSAC could consider the use of sequential testing to reduce the number of false positive patients who would be eligible for targeted treatment.	Sequential testing for this population was considered appropriate only for adults patients with advanced stage cancer.	The submission recommended triage IHC testing for adults with low frequency <i>NTRK</i> fusion cancers but not for paediatric patients.
12. Should the prevalence of the biomarker change during the course of disease and in response to treatments such as chemotherapy or radiotherapy, a re-biopsy may be necessary which will have implications for patient safety, test uptake and costs.	The prevalence of the biomarker is not expected to change in response to prior treatments.	This was not well covered in the submission. The prevalence of the biomarker may or may not change in response to treatment. However, resistance mutations are expected to occur.
13. The evidence is likely to consist of single-arm phase II trials in pan-tumour applications. Thus, demonstrating a therapeutic benefit will rely on the use of a reference case (most common cancer) of the effect size of the treatment in biomarker positive patients over the current standard of care. In the absence of randomised controlled trials, the comparison could be made using prognostic data from a historical data set with subgroup cohorts defined by having different test results (e.g. dMMR and proficient MMR), against which the results of single-arm trials across a pan-tumour population can be benchmarked.	The submission proposed an approach to assessing the therapeutic benefit of larotrectinib.	The submission used a naïve comparison between the single-arm larotrectinib trials compared with historical SoC trials.

Source: Table 1.7 (page 43 of the submission)

5. Prerequisites to implementation of any funding advice

The availability of testing, the TGA status and NATA-accreditation for the FISH and NGS tests was not discussed in the submission.

IHC testing for Trk fusion proteins is currently conducted in NATA-accredited laboratories and is reimbursed under the MBS items: 72846, 72847, 72849, and 72850.

Limited *NTRK* gene fusion testing in a small number of tumour types also occurs in NATA-accredited laboratories and is reimbursed under the MBS (e.g. Sarcoma (MBS item 73374), mammary analogue secretory carcinoma (MASC) of the salivary gland (73381) and secretory carcinoma of the breast (73379). However, the type of testing conducted by accredited laboratories was not discussed in the submission. The tests used for reimbursement under these MBS items are not specified and involve a fee of \$340. These three items may represent a more appropriate benchmark for the proposed fee for a FISH test.

The currently available DNA-NGS panels was also not discussed. Both the MSK-IMPACT and FoundationOne CDx panels are commonly used to detect *NTRK* fusions in the literature. However, the TGA Clinical Evaluation Report for larotrectinib reported that the FoundationOne DNA-NGS panel is currently not available in Australia.

PASC noted that access to RNA-NGS could be an issue, because few laboratories are currently performing this technique in Australia (compared with more widely used DNA-NGS methods) and training is required.

6. Proposal for public funding

The submission proposed four MBS items as listed in Table 4, with modifications in coloured text suggested during the evaluation.

Table 4 Applicant-proposed MBS listings, with modifications in coloured text added during the evaluation

Item number: AAAA	Category 6 (Pathology services) – Group P7 Genetics
	<p>Fluorescence in-situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic cancer, with documented evidence of tropomyosin receptor kinase (Trk) A, TrkB or TrkC immunoreactivity by immunohistochemical (IHC) examination, requested by a specialist or consultant physician to determine if requirements relating to <i>neurotrophic tropomyosin receptor kinase (NTRK)</i> fusions for access to a Trk inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</p> <p>Up to 3 tests per patient per cancer diagnosis (one each for <i>NTRK1</i>, <i>NTRK2</i> and <i>NTRK3</i>)</p> <p>This item cannot be claimed if MBS items BBBB, CCCC or DDDD have been claimed for the same patient.</p> <p>Fee: \$400.00. Benefit: 75% = \$300.00 85% = \$340.00</p>
Item number: BBBB	Category 6 (Pathology services) – Group P7 Genetics
	<p>Fluorescence in-situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic cancer requested by a specialist or consultant physician to determine if requirements relating to neurotrophic tropomyosin receptor kinase (<i>NTRK</i>) fusion for access to a tropomyosin receptor kinase (Trk) inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</p> <p>For patients aged under 18 years, must be diagnosed with a unresectable locally advanced or metastatic solid tumour OR For patients aged 18 years or over, must be diagnosed with a unresectable locally advanced or metastatic solid tumour type that harbours <i>NTRK</i> gene fusions at high frequency ($\geq 75\%$).</p> <p>Up to 3 tests per patient per cancer diagnosis (one each for <i>NTRK1</i>, <i>NTRK2</i> and <i>NTRK3</i>)</p> <p>This item cannot be claimed if MBS items AAAA, CCCC or DDDD have been claimed for the same patient.</p> <p>Fee: \$400.00. Benefit: 75% = \$300.00 85% = \$340.00</p>
Item number: CCCC	Category 6 (Pathology services) – Group P7 Genetics
	<p>Next generation sequencing (NGS) test of tumour tissue from a patient with locally advanced or metastatic cancer, with documented evidence of tropomyosin receptor kinase (Trk) A, TrkB or TrkC immunoreactivity by immunohistochemical (IHC) examination, requested by a specialist or consultant physician to determine if requirements relating to <i>neurotrophic tropomyosin receptor kinase (NTRK)</i> fusions for access to a Trk inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</p> <p>One test per cancer diagnosis.</p> <p>This item cannot be claimed if MBS items AAAA, BBBB or DDDD have been claimed for the same patient.</p> <p>Fee: \$2,100. Benefit: 75% = \$1,575.00 85% = \$2,015.30</p>

Item number: DDDD	Category 6 (Pathology services) – Group P7 Genetics
Next generation sequencing (NGS) test of tumour tissue from a patient with locally advanced or metastatic cancer requested by a specialist or consultant physician to determine if requirements relating to neurotrophic tropomyosin receptor kinase (<i>NTRK</i>) fusion for access to a tropomyosin receptor kinase (Trk) inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	
For patients aged under 18 years, must be diagnosed with a unresectable locally advanced or metastatic solid tumour OR For patients aged 18 years or over, must be diagnosed with a unresectable locally advanced or metastatic solid tumour type that harbours <i>NTRK</i> gene fusions at high frequency ($\geq 75\%$).	
One test per cancer diagnosis.	
This item cannot be claimed if MBS items AAAA, BBBB or CCCC have been claimed for the same patient.	
Fee: \$2,100. Benefit: 75% = \$1,575.00 85% = \$2,015.30	

Text in red or blue added during the evaluation.

Source: Tables 1.9, 1.10, 1.11 and 1.12 (pages 54-55) of the submission

Item AAAA is consistent with item AAAA in the ratified PICO. Item CCCC is similar to item BBBB in the ratified PICO except that NGS is not limited to RNA-NGS in item CCCC.

The submission suggested two new items that were not included in the ratified PICO that allow for FISH (Item BBBB) and NGS (Item DDDD) testing without prior IHC testing. To be eligible for testing using these two items, patients aged under 18 years must be diagnosed with a solid tumour and patients aged 18 years or over must be diagnosed with a solid tumour that harbours *NTRK* gene fusions at high frequency ($\geq 75\%$).

The wording of these two items left the exact nature of the testing population open to misinterpretation. Although the item descriptors initially state testing “of tumour tissue from a patient with locally advanced or metastatic cancer,” the description of eligible patients makes no mention of cancer stage. The addition of the words highlighted in red in the item descriptors for BBBB and DDDD would remove any ambiguity about the testing population.

The submission proposed that the fee for NGS should be \$2,100 based on MBS item 73358 for whole genome sequencing. This is higher than the \$980 proposed in the ratified PICO, which was based on a brief literature search¹. The submission justified this cost on the basis that it is expected that running an NGS panel would incur a similar cost to whole genome sequencing (WGS). No further information was provided to justify a comparison of costs between *NTRK* fusion testing and WGS.

This was likely to be an inaccurate assumption, even if a large commercially available 400-500 gene panel is used. The MBS item descriptor requests only analysis of the *NTRK1/2/3* genes and not the entire 400-500 gene panel. A large part of the cost for NGS would likely be due to the analysis of the sequence variants. Analysis of variants identified in all 400-500 genes sequenced would be much more time consuming (and therefore more expensive) than analysis of variants identified in just three genes.

The current fee for FISH under the MBS is \$400 (i.e. MBS items: 73341 and 73344). It was assumed that FISH to confirm *NTRK* fusion would incur the same cost. However, FISH *NTRK* fusion testing may require up to three tests to identify the presence of a *NTRK* fusion in one of the three *NTRK* genes. Wording to this effect was added in blue to the item descriptors. Tests should also be sequenced to initially test for the most likely *NTRK* gene to be involved according to cancer type. For example, infantile fibrosarcoma (IFS), MASC and secretory breast carcinoma (SBC) almost always involve rearrangement of the *NTRK3* gene.

¹ The search identified a French costing study of NGS testing for cancer diagnosis, using targeted gene panels. The mean total cost of NGS analysis of somatic cells was estimated to be 607€ ± 207€. The conversion rate used for the MBS item estimate is 1€=\$1.614 AUD (as at 4 November 2019).

7. Summary of public consultation feedback/consumer Issues

Consultation feedback was received from one organisation, which was in general supportive of the application, and agreed with the PASC-ratified PICO which requested the proposed items be amended to ‘Trk inhibitors’ as a generic term, rather than larotrectinib. However, the organisation:

- noted there was potential for substantial number of IHC tests, which may represent a financial burden to pathology providers given the current reimbursement for pan-Trk IHC testing; a potential solution could be a separate MBS item to reflect the increased relative cost of the test and the complexity of pan-Trk IHC testing
- considered that confirmatory NGS sequencing method should also not be specific to RNA-sequencing.

8. Proposed intervention’s place in clinical management

The overall proposed population for *NTRK* fusion testing was all patients with locally advanced or metastatic solid tumours that are either unresectable or require disfiguring surgery or limb amputation.

NTRK gene fusions occur in less than 5% of most solid tumour types. However, in some rare solid tumour types, such as MASC, SBC, IFS and congenital mesoblastic nephroma (CMN; cellular or mixed histotype), *NTRK* gene fusions are found at frequencies above 75%. Due to the differences between the paediatric and adult subpopulations and the low versus high frequency *NTRK* fusion tumours, PASC recommended “a disaggregated approach” to the paediatric and adult populations. Therefore, the overall population considered in the submission is divided into four sub-populations based on age (adult and paediatric patients) and *NTRK* fusion frequency².

The proposed subpopulations and the representative tumour types were as follows:

1. Paediatric patients with locally advanced or metastatic solid tumours with high frequency *NTRK* fusions

In the larotrectinib trials, most paediatric patients were categorised as having either IFS (n=32) or paediatric soft tissue sarcoma (STS; n=19).

IFS was considered as the main representative tumour type for this subpopulation. For this tumour type, complete resection is curative in the majority of patients, however, the large size of the lesion frequently makes resection difficult and results in major functional consequences. Given its overall rarity and the lack of adequate comparator data, paediatric STS was also included as an additional representative subtype. Paediatric STS is a rare, heterogeneous group of malignant neoplasms arising within embryonic mesenchymal tissues during the process of differentiation into muscle, fascia and fat. IFS is a distinct subgroup of paediatric STS.

However, paediatric STS does not align with the *NTRK* fusion frequency classification scheme preferred by PASC. The study used by the submission to classify STS as a high frequency *NTRK* fusion cancer did not report the source of its information and included patients with IFS in the analysis³. It has likely been wrongly classified as a high frequency *NTRK* cancer type because it is estimated that only 20-30% of these cancers

² Hsiao SJ, Zehir A, Sireci AN, Aisner DL. Detection of Tumor *NTRK* Gene Fusions to Identify Patients Who May Benefit from Tyrosine Kinase (TRK) Inhibitor Therapy. *The Journal of Molecular Diagnostics*. 2019;21(4):553-71

³ Assi T, Rassy E, Nasserredine H, Farhat F, Karak FE, Kattan J, et al. TRK inhibition in soft tissue sarcomas: A comprehensive review. *Seminars in Oncology*. 2020;47(1):73-84.

have a recognised oncogenic driver mutation⁴. Table 5 lists the most common oncogenic driver mutations associated with various paediatric STS histological subtypes. This table indicates that the prevalence of the *NTRK* fusion oncogenic driver mutations is likely to be low in all but two of these histological subtypes.

Table 5 Histologic subtypes of soft tissue sarcomas in paediatric patients and the most common oncogenic driver mutation associated with them

Paediatric STS subtype	Most common oncogenic driver mutation
Alveolar rhabdomyosarcoma	<i>AX3/7-FKHR</i> gene fusion
Desmoplastic round cell tumour	<i>EWSR1-WT1</i> gene fusion
Spindle cell rhabdomyosarcoma	<i>VGLL2</i> rearranged
Undifferentiated round cell sarcoma	<i>CIC-DUX4</i> gene fusion
Infantile fibrosarcoma	<i>ETV6-NTRK3</i> gene fusion
Clear cell sarcoma	<i>EWSR1-ATF1</i> gene fusion
Infantile myofibromatosis	<i>PDGFRB</i> missense variant
Malignant fibrous histiocytoma	Unknown
Dermatofibrosarcoma protuberans	<i>COL1A1-PDGFB</i> gene fusion
Malignant peripheral nerve sheath tumour	<i>HuR-ELAVL1</i> gene fusion
Kaposi's sarcoma	Herpesvirus cyclin
Ewing's sarcoma	<i>EWSR1-FLI1/ERG</i> , <i>FUS-ERG</i> gene fusions
Liposarcoma	<i>FUS-DDIT3</i> gene fusion
Leiomyosarcoma	<i>KANK2-ALK</i> gene fusion
Synovial sarcoma	<i>SS18-SSX1</i> gene fusion
Spindle cell sarcoma	<i>MLL4-GPS2</i> gene fusion
Epithelioid hemangioendothelioma	<i>WWTR1-CAMTA1</i> gene fusion
Malignant hemangiopericytoma	<i>YAP-TAZ</i> gene fusion
Alveolar soft part sarcoma	<i>ASPSR1-TFE3</i> gene fusion
Chondrosarcoma	<i>EWS-WT1/CHN</i> gene fusion
Undifferentiated sarcoma	<i>COL1A1-PDGFB</i> ; <i>CIC-DUX4</i> ; <i>EWSR1-COL1A1</i> ; <i>BCOR-CCNB3</i> ; <i>KIAA1549-BRAF</i> gene fusions
Tumours with myopericytic or myofibromatous differentiation	<i>LMNA-NTRK1</i>; <i>TPM3-NTRK1</i> gene fusions

Tumour types in which *NTRK* gene fusions are commonly identified are highlighted in boldface.

Source: Loeb et al. (2008)⁵; Dupain et al. (2017)⁶; Suurmeijer et al. (2019)⁷

2. Adult patients with locally advanced or metastatic solid tumours with high frequency *NTRK* fusions

The representative tumour type for this subpopulation was MASC, which was the most represented high frequency *NTRK* fusion cancer occurring in adults who participated in the larotrectinib trials.

⁴ Dupain C, Harttrampf AC, Urbinati G, Georger B, Massaad-Massade L. Relevance of Fusion Genes in Pediatric Cancers: Toward Precision Medicine. *Molecular Therapy - Nucleic Acids*. 2017;6:315-26.

⁵ Loeb DM, Thornton K, Shokek O. Pediatric soft tissue sarcomas. *Surg Clin North Am*. 2008;88(3):615-vii.

⁶ Dupain C, Harttrampf AC, Urbinati G, Georger B, Massaad-Massade L. Relevance of Fusion Genes in Pediatric Cancers: Toward Precision Medicine. *Molecular Therapy - Nucleic Acids*. 2017;6:315-26.

⁷ Suurmeijer AJH, Kao Y-C, Antonescu CR. New advances in the molecular classification of pediatric mesenchymal tumors. *Genes, Chromosomes and Cancer*. 2019;58(2):100-10.

3. Paediatric patients with locally advanced or metastatic solid tumours with low frequency *NTRK* fusions

The representative tumour type for this subpopulation was primary central nervous system (CNS)/glioma. Tumours of the CNS (mainly brain tumours) account for the largest number of cancer deaths for children in Australia, with the frequency of *NTRK* fusions in CNS/glioma tumours being estimated at 2.2%. In the larotrectinib trials, 24 patients had a primary CNS tumour of which 20 were aged < 18 years. Of these, the most commonly diagnosed tumour subtype was glioblastoma multiforme (GBM), which is a grade IV tumour.

4. Adult patients with locally advanced or metastatic solid tumours with low frequency *NTRK* fusions

The submission considered two representative tumour types for this patient population: adult STS and CRC.

Adult STS is a rare cancer with a *NTRK* fusion frequency of approximately 1.4% in adults. In the larotrectinib trials, there were 17 adults with STS, which was the second most common low frequency *NTRK* fusion cancer type for adults.

In Australia, CRC is the second most common cancer, and is the second highest *NTRK* fusion cancer subtype. Although the frequency of *NTRK* fusion is very low (approximately 0.3%), 8 patients in the larotrectinib studies had CRC. *NTRK* fusions have been extensively characterised in this cancer type and it is likely that *NTRK* fusion testing may be higher in this cancer type.

The submission claimed that *NTRK* fusions are known to be oncogenic driver mutations, and as *NTRK* fusion cancers are less likely to have a second mutation suitable for a targeted therapy, treatment needs to be directed against the Trk fusion kinase in these patients. This may be reasonable in some cases. However, other biomarkers such as PD-L1 expression, MSI-H and high TMB are expressed in some *NTRK* fusion cancers⁸. There is a possibility that the *NTRK* gene fusion detected in these patients is not the only (or even the primary) oncogenic driver mutation.

Targeted therapies directed against these other biomarkers are either currently funded by the PBS (e.g. high PD-L1 expression in NSCLC for treatment with pembrolizumab) or are likely to become available at some time in the future (e.g. pembrolizumab is currently registered (provisional approval pathway) for the treatment of unresectable or metastatic MSI-H or mismatch repair deficient (dMMR) tumours that have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan). Therefore, it is highly likely that some patients may become eligible for more than one targeted therapy at the same time. Some guidance as to which targeted therapy to select first, based on its comparative effectiveness, may be required.

In the proposed clinical management algorithm, all four populations would be tested on diagnosis of advanced disease. Testing would require fresh or formalin-fixed, paraffin-embedded (FFPE) tumour tissue. Currently, IHC testing and limited *NTRK* gene fusion testing in a small number of tumour types is reimbursed under the MBS.

⁸ Pietrantonio F, Di Nicolantonio F, Schrock AB, Lee J, Tejpar S, Sartore-Bianchi A, et al. ALK, ROS1, and *NTRK* Rearrangements in Metastatic Colorectal Cancer. *JNCI: Journal of the National Cancer Institute*. 2017;109(12); Gatalica Z, Xiu J, Swensen J, Vranic S. Molecular characterization of cancers with *NTRK* gene fusions. *Modern Pathology*. 2019;32(1):147-53; Solomon JP, Linkov I, Rosado A, Mullaney K, Rosen EY, Frosina D, et al. *NTRK* fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. *Modern Pathology*. 2020;33(1):38-46

The submission proposed that Populations 1, 2 and 3 would be directly tested for *NTRK* fusion using FISH or NGS, whereas Population 4 would first receive a pan-Trk IHC test. Only those with positive results would then receive a confirmatory FISH or NGS test.

This differed from the ratified PICO Confirmation, which recommends pan-Trk IHC testing for all patients. Adult and paediatric patients with high frequency *NTRK* fusion cancers would receive a FISH or RNA-NGS test, regardless of the IHC result, i.e. in these populations IHC would not be used to triage use of a confirmatory testing but, rather, as the basis to instigate treatment prior to confirmatory testing. However, adult and paediatric patients with low frequency *NTRK* fusion cancers would be triaged, with only those patients with positive pan-Trk IHC test results receiving a FISH or RNA-NGS test.

The proposed change to directly test for patients with high frequency *NTRK* fusion cancers may be reasonable if RNA-NGS is used in practice.

It was less certain if this change is reasonable if FISH testing were used instead of RNA-NGS. One premise for using both pan-Trk IHC testing and FISH testing would be due to the inability of FISH testing to distinguish between an active and an inactive gene fusion. The addition of the IHC test would detect the expression of the fusion protein.

The change for paediatric patients with low frequency *NTRK* fusion cancers was not justified in the submission and may not be reasonable, as the number of patients that require testing to identify one true positive (TP) is high (number needed to test [NNT] = 192).

Patients from Populations 1, 2 or 3 who test positive would then be eligible for first-line treatment with larotrectinib, whereas positive patients from Population 4 will not be eligible for treatment with larotrectinib until they have failed one or more SoC treatments.

9. Comparator

The nominated comparator to *NTRK* fusion testing was “no testing” for all adult and paediatric advanced stage cancer patients. This was in agreement with the ratified PICO.

10. Comparative safety

Adverse events from testing

The pan-Trk IHC, and FISH or NGS *NTRK* fusion tests all use FFPE tissue samples and therefore there are no safety issues associated with these tests unless a new biopsy is required.

Any procedure where the skin is penetrated carries a risk of bleeding or infection or other complications. Re-biopsy rates in advanced lung cancer have previously been considered by MSAC to be up to 12% in lung cancer⁹, but these rates are likely to vary by tumour type and other contextual considerations.

Adverse events from changes in management

The summary of overall adverse events (AEs) pooled from the single-arm larotrectinib studies (regardless of *NTRK* fusion status) is presented in the table below. The safety profiles for the SoC chemotherapy regimens are well established.

⁹ Public Summary Document Application No. 1293 – Epidermal Growth Factor Receptor (EGFR) testing to determine eligibility for afatinib treatment in patients with locally advanced or metastatic non-small-cell lung cancer

Table 6 Summary of adverse events in larotrectinib studies (Overall Safety Analysis Set regardless of fusion status)

TEAE	Overall safety set n = 279
Patients with TEAE	275 (99%)
Patients with TEAE related to larotrectinib	216 (77%)
Patients with TEAE Grade 3 or 4	148 (53%)
Patients with TEAE Grade 3 or 4 and related to larotrectinib	43 (15%)
Patients with TEAE and action taken of larotrectinib permanently discontinued	26 (9%)
Patients with TEAE and action taken of larotrectinib permanently discontinued and related to larotrectinib	6 (2%)
Patients with serious TEAE	96 (34%)
Patients with serious TEAE and related to larotrectinib	15 (5%)
Patients with fatal TEAE ^a	16 (6%)

Larotrectinib July 2019 data-cut

^a Refers to TEAEs both related and unrelated to larotrectinib treatment

TEAEs are defined as adverse events that start on or after the first administration of Larotrectinib. Related events are those judged by the Investigator as related to Larotrectinib. Severity grade assignment based on CTCAE (v4.03): Grade 3 (severe), Grade 4 (life-threatening). Percentages are calculated based on the number of patients in the column heading as the denominator.

TEAE, treatment emergent adverse event; CTCAE, Common Terminology Criteria for Adverse Events

Source: Table 2.93, p229 of the submission

Forty three (15%) of patients had Grade 3/4 treatment emergent adverse events (TEAEs), that were considered to be related to larotrectinib. Of these, 26 patients (9%) had TEAEs that led to permanent treatment discontinuation.

The TGA Delegate’s Overview for larotrectinib presented pooled safety data for three paediatric subgroups: infants/toddlers (aged 28 days to 23 months), children (aged 2 to 3 years), and adolescents (aged 12 to <18 years). For the majority of TEAEs, the incidence was higher in the infants/toddler subgroup compared to children. AEs in paediatric patients were assessed to be serious by the investigator for 12 (36%) infants/toddlers, 10 (26%) children and 7 (33%) adolescents.

11. Comparative effectiveness

Overview of the evidence base

The approach taken in the submission was to present evidence that has been linked to support the contention that the targeting of *NTRK* gene fusions with larotrectinib will improve patient outcomes.

Table 7 Summary of the linked evidence approach for all four population groups

	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in clinical studies
Accuracy and performance of the test (analytical validity)	DNA- vs RNA-NGS: 3 comparative studies FISH vs RNA-NGS: 1 comparative study IHC vs RNA-NGS: 1 comparative study 2 case-control studies IHC vs DNA-NGS: 1 case-control study	<input checked="" type="checkbox"/> k=3; n=34,450 <input checked="" type="checkbox"/> k=1; n=44 <input checked="" type="checkbox"/> k=3; n=4,603 <input checked="" type="checkbox"/> k=1; n=78	High Low Low High
Prognostic evidence	2 prospective cohort studies and 1 retrospective cohort study	<input checked="" type="checkbox"/> k=3 n=696	Low
Change in patient management	No evidence provided	<input type="checkbox"/> k=0	-
Treatment effectiveness			
Predictive effect (treatment effect variation)	[Comparison of outcomes in patients with and without the biomarker who receive the medicine or its comparator]	<input type="checkbox"/> k=0 n=0	
Treatment effect (enriched)	[Single randomised controlled trial of medicine vs usual care in patients that are test positive in both arms]	<input type="checkbox"/> k=0 n=0	
Naïve indirect comparison	[<i>NTRK</i> fusion positive patients from 3 single-arm larotrectinib studies and SoC patients, regardless of <i>NTRK</i> status, from single arms of 7 historical studies]	<input checked="" type="checkbox"/> k=3 n=164 <input checked="" type="checkbox"/> k=7 n=919	High

^a reference standard available

k = number of studies, n = number of patients.

Source: Constructed during evaluation

The submission presented evidence to address parts of the analytic framework as outlined in Table 8.

Table 8 Data availability to inform comparisons

Proposed test vs no test	No evidence presented	
Proposed test vs alternative test	DNA- vs RNA-NGS: 3 comparative studies FISH vs RNA-NGS: 1 comparative study IHC vs RNA-NGS: 1 comparative study; 2 case-control studies IHC vs DNA-NGS: 1 case-control study	
	Proposed medicine	Comparator medicine
Biomarker test positive	LOXO-001, NAVIGATE, SCOUT single-arm studies	No evidence presented
Biomarker test negative	LOXO-001 and SCOUT single-arm studies	No evidence presented
Biomarker untested	No evidence presented	Sandler 2001, Mascarenhas 2010, Airoldi 2001, Grill 2018, Wick 2017, Schöffski 2016, Mayer 2015

Source: Sections 2B and 2D of the submission

The study populations, tests and treatment regimens were not always transferrable across the evidence linkages, as they varied considerably.

Similarly, the evidence to support the comparative clinical benefit of larotrectinib was based on a naïve indirect comparison between pooled data from single-arm larotrectinib studies and single-arm SoC data from historical studies. The three larotrectinib studies had different design/objectives, patient/disease characteristics, and there was also an indication of heterogeneity of treatment effects by tumour type. Limitations of the efficacy data for SoC mainly involve the heterogeneity of response to SoC therapies by tumour type, treatment line, and agents used, and the inclusion of historical data that are unlikely to represent current SoC data. The two bodies of evidence, therefore, do not appear to be transitive. All these comparator issues contribute to the uncertainty of the incremental benefit of larotrectinib.

Effectiveness (based on linked evidence)

Prognostic evidence

Three studies (four publications) were included from the literature search conducted by the submission as providing prognostic evidence. All three studies provided a Kaplan-Meier analysis to generate overall survival curves in cancer patients with or without *NTRK* fusions.

All three studies reported that there was a shorter survival time for patients with *NTRK* fusion tumours compared to patients with *NTRK* wild type tumours. However, the difference only reached statistical significance in the studies by Park et al. (2016)¹⁰ and Pietrantonio et al. (2017)¹¹, which included only patients with CRC. The only study that included patients with cancers other than CRC did not show a statistically significant difference in overall survival for patients with and without *NTRK* fusion cancer¹².

Predictive evidence

Given the single-arm nature of the supporting studies, evidence of any larotrectinib treatment effect variation by *NTRK* fusion status could not be directly isolated from any prognostic effects of *NTRK* fusion status.

Comparative analytical performance

The median sensitivity and specificity of pan-Trk IHC, and FISH or DNA-NGS *NTRK* fusion testing compared with RNA-NGS, as the reference standard, to detect *NTRK* gene fusions in solid tumours of any origin are summarised in Table 9.

Table 9 Median sensitivity and specificity for pan-Trk IHC, FISH or DNA-NGS *NTRK* fusion testing compared with RNA-NGS, as the reference standard, to detect *NTRK1*, 2 or 3 gene fusions

Test	Number of studies	Median sensitivity	Median specificity
IHC: NTRK1-3	3 (N=4,603)	87.9%	95.6%
NTRK1	1 (N=27)	96.3%	NR
NTRK2	1 (N=5)	100%	NR
NTRK3	1 (n=34)	79.4%	NR
FISH (for <i>NTRK3</i> only)	1 (N=44)	95.8%	75.0%
RS with good quality RNA	(n=23)	100%	100%
RS with poor quality RNA	(n=21)	87.5%	61.5%
DNA-NGS (<i>NTRK1-3</i>)	2 (N=34,432)	77.5%	99.9%

DNA = deoxyribonucleic acid; FISH = fluorescence *in situ* hybridisation; IHC = immunohistochemistry; NGS = next generation sequencing; *NTRK* = neurotrophic tropomyosin receptor kinase; RNA = ribonucleic acid; RS = reference standard

Source: Constructed during evaluation.

Several shortcomings for these methods should be noted:

- Being the reference standard, RNA-NGS was considered to be the most accurate methodology for identifying functional *NTRK* gene fusions. It is able to detect all previously known and unknown *NTRK1*, 2 or 3 gene fusion pairs. However, its accuracy decreases when the RNA is extracted from the FFPE tumour samples older than 5 years, as the RNA is of poorer quality.

¹⁰ Park DY, Choi C, Shin E, Lee JH, Kwon CH, Jo H-J, et al. *NTRK1* fusions for the therapeutic intervention of Korean patients with colon cancer. *Oncotarget*. 2016;7(7):8399-412.

¹¹ Pietrantonio F, Di Nicolantonio F, Schrock AB, Lee J, Tejpar S, Sartore-Bianchi A, et al. ALK, ROS1, and *NTRK* Rearrangements in Metastatic Colorectal Cancer. *JNCI: Journal of the National Cancer Institute*. 2017;109(12).

¹² Bazhenova L, Jiao X, Lokker A, Snider J, Castellanos E, Nanda S, et al. Abstract 09: Cancers with *NTRK* gene fusions: Molecular characteristics and prognosis. *Clinical Cancer Research*. 2020;26(12 Supplement 1):09.

- IHC, using a pan-Trk antibody, has reduced sensitivity for detecting *NTRK3* fusions compared to detecting *NTRK1* and *NTRK2* fusions. The reason for this is not known.
- Some *NTRK3* introns are extremely long (up to 193KB) that make them infeasible to cover or they contain repetitive elements, which cannot be tiled with unique probes, reducing the sensitivity of DNA-NGS (but not RNA-NGS).
- The accuracy of the FISH test is uncertain mostly due to the results being limited to a single study – using break-apart FISH to detect *NTRK3* fusions – which was identified during the evaluation.

Summary of the clinical validity of pan-Trk IHC, and FISH or NGS *NTRK* fusion testing

The clinical validity of pan-Trk IHC, and FISH or NGS testing to detect *NTRK* fusions in each of the four population groups indicated in the ratified PICO Confirmation is summarised in Table 10.

Table 6 Summary of the clinical validity of pan-Trk IHC, FISH and NGS testing to detect *NTRK* fusions in the four distinct population groups

	Population 1	Population 2	Population 3	Population 4
Patients	Paediatric	Adult	Paediatric	Adult
NTRK fusion frequency	High	High	Low	Low
Example tumour types	IFS, CMN, MASC, SBC NOTE Inclusion of paediatric STS by the submission was likely not appropriate for this population	MASC, SBC	STS (non-IFS), glioma, thyroid, bone sarcoma, Spitzoid melanoma. Many of the other cancer types occurring in Population 4	STS, thyroid, lung, CRC, melanoma, Spitzoid melanoma, GIST, glioblastoma, cholangiocarcinoma, appendiceal, bone sarcoma, pancreatic, cervical, uterine, breast
Number of advanced stage patients	21	8	192	33,227
TRK gene(s) most frequently involved(see Section 1.1.2.2)	<i>NTRK3</i>	<i>NTRK3</i>	<i>NTRK1</i> and <i>NTRK2</i>	<i>NTRK1</i> and <i>NTRK2</i>
Reference standard	RNA-NGS PPV and NPV = 100% if good quality RNA is available if RNA is degraded, false negatives will occur	RNA-NGS PPV and NPV = 100% if good quality RNA is available if RNA is degraded, false negatives will occur	RNA-NGS PPV and NPV = 100% if good quality RNA is available if RNA is degraded, false negatives will occur	RNA-NGS PPV and NPV = 100% if good quality RNA is available if RNA is degraded, false negatives will occur
The most accurate alternative test method compared to the reference standard	FISH <i>NTRK3</i> • PPV 96-98% • NPV 62-72%	FISH <i>NTRK3</i> • PPV 98-99% • NPV 52-54%	DNA-NGS, if NTRK fusion frequency is above 1% • PPV 89-99% • NPV 96-100%	DNA-NGS, if NTRK fusion frequency is above 1% • PPV 89-99% • NPV 96-100%
Inappropriate diagnostic tests	DNA-NGS ^a : • Does not detect all <i>NTRK3</i> fusions	DNA-NGS: • Does not detect all <i>NTRK3</i> fusions	FISH <i>NTRK3</i> : • Most <i>NTRK</i> fusions will involve <i>NTRK1</i> or <i>NTRK2</i>	FISH <i>NTRK3</i> : • Most <i>NTRK</i> fusions will involve <i>NTRK1</i> or <i>NTRK2</i>

	Population 1	Population 2	Population 3	Population 4
Number of NTRK fusion positive patients	20	8	1	164
Number needed to test with RNA-NGS to identify 1 true positive patient	1.05	1.00	192	203
False positives (when using the most accurate testing method)	2-4% of positive test results are predicted to be falsely positive. These patients would receive inappropriate treatment No patient would be falsely positive.	1-2% of positive test results are predicted to be falsely positive. These patients would receive inappropriate treatment No patient would be falsely positive.	1-11% of positive test results are predicted to be falsely positive. These patients would receive inappropriate treatment No patient would be falsely positive.	1-11% of positive test results are predicted to be falsely positive. These patients would receive inappropriate treatment 33 (20%) positive patients would be falsely positive.
False negatives (when using the most accurate testing method)	28-38% of negative test results are predicted to be falsely negative. These patients would not receive targeted treatment 1 out of 21 patients will be falsely negative likely due to the small number of patients.	46-48% of negative test results are predicted to be falsely negative. These patients would not receive targeted treatment No patient will be falsely negative likely due to the small number of patients.	0-4% of negative test results are predicted to be falsely negative. These patients would not receive targeted treatment No patient would be falsely negative.	0-4% of negative test results are predicted to be falsely negative. These patients would not receive targeted treatment 36 (0.1%) of negative patients would be falsely negative.
Subgroups for whom the test is not useful	None	None	Tumour types with <i>NTRK</i> fusion frequency below 0.5% • PPV 44-80% • NPV 99-100% 20-56% of positive test results will be falsely positive. These patients would receive inappropriate treatment.	Tumour types with <i>NTRK</i> fusion frequency below 0.5% • PPV 44-80% • NPV 99-100% 20-56% of positive test results will be falsely positive. These patients would receive inappropriate treatment.
Is pan-Trk IHC useful as a triage test?	No: • High false negative rate as it does not detect all <i>NTRK3</i> gene fusions NPV 47-77% 23-53% of negative test results are falsely negative. These patients would not receive targeted treatment	No: • High false negative rate as it does not detect all <i>NTRK3</i> gene fusions NPV 32-47% 53-68% of negative test results are falsely negative These patients would not receive targeted treatment	Yes, as a rule out test • There would be very few patients with a negative test result who are falsely negative. NPV 98-100%	Yes, as a rule out test • There would be very few patients with a negative test result who are falsely negative. NPV 98-100%
Number with pan-Trk IHC triage negative tests who would not receive further testing or targeted treatment	NA	NA	0/142 (0%) negative patients would be falsely negative	20/29,825 (<0.001%) negative patients would be falsely negative

	Population 1	Population 2	Population 3	Population 4
Uncertainties	<p>Reliability of the estimated accuracy of FISH <i>NTRK3</i> testing is uncertain</p> <ul style="list-style-type: none"> • Only one small study was identified <p>No information about the value of sequential FISH testing:</p> <ul style="list-style-type: none"> • Should FISH <i>NTRK1</i> and FISH <i>NTRK2</i> be done sequentially in those who are FISH <i>NTRK3</i> negative to detect rare non-<i>NTRK3</i> cases? 	<p>Reliability of the estimated accuracy of FISH <i>NTRK3</i> testing is uncertain</p> <ul style="list-style-type: none"> • Only one small study was identified <p>No information about the value of sequential FISH testing:</p> <ul style="list-style-type: none"> • Should FISH <i>NTRK1</i> and FISH <i>NTRK2</i> be done sequentially in those who are FISH <i>NTRK3</i> negative to detect rare non-<i>NTRK3</i> cases? 	<p>The accuracy of FISH testing could not be determined:</p> <ul style="list-style-type: none"> • No data available on the accuracy of FISH for detecting <i>NTRK1</i> or <i>NTRK2</i> fusions <p>The accuracy of DNA-NGS as a confirmatory test after pan-Trk IHC triage is uncertain:</p> <ul style="list-style-type: none"> • As RNA-NGS is the most accurate method, testing should be limited to RNA-NGS 	<p>The accuracy of FISH testing could not be determined:</p> <ul style="list-style-type: none"> • No data available on the accuracy of FISH for detecting <i>NTRK1</i> or <i>NTRK2</i> fusions <p>The accuracy of DNA-NGS as a confirmatory test after pan-Trk IHC triage is uncertain:</p> <ul style="list-style-type: none"> • As RNA-NGS is the most accurate method, testing should be limited to RNA-NGS

^a Due to the size of some *NTRK* exons and the presence of repeat elements, not all *NTRK3* gene fusions can be detected using DNA-NGS

DNA = deoxyribonucleic acid; CMN = congenital mesoblastic nephroma; CRC = colorectal cancer; FISH = fluorescence *in situ* hybridisation; GIST = gastrointestinal stromal tumour; IFS = infantile fibrosarcoma; IHC = immunohistochemistry; MASC = mammary analogue secretory carcinoma; NGS = next generation sequencing; NPV = negative predictive value; *NTRK* = neurotrophic tropomyosin receptor kinase; PPV = positive predictive value; RNA = ribonucleic acid; SBC = secretory breast carcinoma; STS = soft tissue sarcoma
Source: Constructed during evaluation.

The submission proposed that paediatric patients with low frequency *NTRK* fusion cancers (Population 3) should not be screened first with pan-Trk IHC, as recommended for the equivalent adult population, but should be tested directly with NGS or FISH. The submission did not give a reason for this, other than to suggest that this was in response to expert opinion.

The number needed to treat results presented above suggest that pan-Trk IHC triage testing in the paediatric population with low frequency *NTRK* fusion cancers (Population 3) could be as effective in ruling out the presence of an *NTRK* fusion as for the low frequency adult population for which it is proposed (Population 4). Pan-Trk IHC triaging would reduce greatly the number of NGS tests required, and if RNA-NGS is used, few of the pan-Trk IHC positive patients should be wrongly diagnosed.

Prevalence

The *NTRK* fusion prevalence rates were combined to determine the median prevalence rates (and range) for the various tumour types. These results, shown in Table 11, were compared with the *NTRK* fusion prevalence rate used by the submission. The prevalence estimate used by the submission was reasonable for all tumour types, except paediatric STS. The paediatric STS population from which the 80% prevalence rate was derived included an unknown proportion of patients with IFS, a known high frequency *NTRK* fusion cancer type.¹³

The tumour types among the 19 paediatric patients with STS enrolled in the larotrectinib studies included infantile myofibromatosis, spindle cell sarcomas, undifferentiated sarcoma,

¹³ Assi T, Rassy E, Nassereddine H, Farhat F, Karak FE, Kattan J, et al. TRK inhibition in soft tissue sarcomas: A comprehensive review. *Seminars in Oncology*. 2020 2020/02/01/;47(1):73-84.

and tumours with myopericytic or myofibromatous differentiation.¹⁴¹⁵ As very few STS types have *NTRK* gene fusions, their inclusion in Population 1 was inappropriate. They are more likely to be representative of paediatric patients with low frequency *NTRK* fusion cancers (Population 3).

Table 7 Median prevalence of *NTRK* fusions estimated from the literature during evaluation, prevalence used by the submission and proportion of tumour types included in the trials

Tumour type	Proportion of patients enrolled in trials	Proportion of patients per population group	Median prevalence (range)	Prevalence used by the submission
Population 1: Paediatric high frequency <i>NTRK</i> fusion cancers				
IFS	17.0% (32/188)	61.5% (32/52)	87.2% (50–93.8)	90%
Paediatric STS	10.1% (19/188)	36.5% (19/52)	0.68% (0.21–1.17)	80%
CMN	0.5% (1/188)	1.9% (1/52)	67.6% (38.9–83.3)	90%
SBC	0%	0%	93.8% (92–95.5)	90%
Population 2: Adult high frequency <i>NTRK</i> fusion cancers				
Salivary gland (MASC)	11.2% (21/188)	80.8% (21/26)	94.3% (66.7–100)	90%
SBC	2.7% (5/188)	19.2% (5/26)	93.8% (92–95.5)	90%
Population 3: Paediatric low frequency <i>NTRK</i> fusion cancers				
Paediatric CNS High grade glioma Glioma	11.2% (21/188)	100% (21/21)	6.7% (5.3–22) 2.5%	2.2%
Thyroid	0%	0%	–	3.65%
Paediatric bone sarcoma	0%	0%	–	1.24%
Spitzoid melanoma	0%	–	11.1%	–
Population 4: Adult low frequency <i>NTRK</i> fusion cancers				
Thyroid	14.4% (27/188)	30.7% (27/88)	2.31% (2.2–15.2)	3.65%
Adult STS	9.0% (17/188)	19.3% (17/88)	0.68% (0.21–1.17)	1.4%
Lung	6.9% (13/188)	14.8% (13/88)	0.19% (0.01–3.3)	0.23%
CRC	4.3% (8/188)	9.1% (8/88)	0.64% (0.16–3.8)	0.30%
Melanoma	3.7% (7/188)	8.0% (7/88)	0.32% (0.21–0.54)	0.34%
Stomach (GIST)	2.1% (4/188)	4.5% (4/88)	0.46% (0–0.92)	2.2%
Adult CNS (Glioblastoma)	1.6% (3/188)	3.4% (3/88)	0.58% (0.16–2.6)	2.2%
Pancreatic	1.1% (2/188)	3.4% (3/88)	0.3% (0.34–0.56)	0.75%
Adult bone sarcoma	1.1% (2/188)	3.4% (3/88)	–	1.24%
Cholangiocarcinoma	1.1% (2/188)	3.4% (3/88)	0.36% (0.25–3.6)	0.26%
Appendiceal	0.5% (1/188)	1.1% (1/88)	1.34% (0.48–2.1)	0.58%
Hepatic	0.5% (1/188)	1.1% (1/88)	0%	1.24%
Prostate	0.5% (1/188)	1.1% (1/88)	0%	0.24%
Spitzoid melanoma	0%	0%	16.4%	–
Salivary gland (not MASC)	0%	0%	5.19% (5.08–5.29)	–
Cervical	0%	0%	0.89% (0.3–1.47)	–

¹⁴ Hong DS, DuBois SG, Kummar S, Farago AF, Albert CM, Rohrberg KS, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *The Lancet Oncology*. 2020;21(4):531-40.

¹⁵ Laetsch TW, DuBois SG, Mascarenhas L, Turpin B, Federman N, Albert CM, et al. Larotrectinib for paediatric solid tumours harbouring *NTRK* gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. *The Lancet Oncology*. 2018;19(5):705-14.

Tumour type	Proportion of patients enrolled in trials	Proportion of patients per population group	Median prevalence (range)	Prevalence used by the submission
Uterine	0%	0%	0.68% (0–4.1)	–
Head and neck	0%	0%	0.45% (0.4–0.5)	–
Breast	0%	0%	0.13% (0.01–0.18)	0.2%
Bladder urothelial	0%	0%	0%	–
Kidney	0%	0%	0%	–
Ovarian	0%	0%	0%	–
Unknown population group				
Cancer of unknown primary	0.5% (1/188)	–	–	–

Source: Table 3 in Section 1.1.2.3 of the evaluation; Table 1.2 (page 24) of the submission and Attachment 4.1 NTRK frequency
 CMN = congenital mesoblastic nephroma; CNS = central nervous system; CRC = colorectal cancer; GIST = gastrointestinal stromal tumour; IFS = infantile fibrosarcoma; MASC = mammary analogue secretory carcinoma; *NTRK* = neurotrophic tropomyosin receptor kinase; SBC = secretory breast carcinoma; STS = soft tissue sarcoma

Change in management in practice

The submission proposed that patients with locally advanced or metastatic solid tumours who are found to have a *NTRK* fusion positive cancer would receive targeted treatment with larotrectinib instead of SoC as per the proposed clinical management algorithm.

Patients who are *NTRK* fusion negative would not have a change in management and would receive SoC as per the current clinical management algorithm.

Claim of codependence

Larotrectinib is a highly selective tropomyosin receptor kinase (Trk) inhibitor that binds to the Trk fusion proteins and competitively inhibits the binding of ATP to the ATP-binding site. This interferes with autophosphorylation of the kinase domain of Trk and thereby prevents downstream signalling and blockage of the oncogenic pathways.

The submission claimed that, as *NTRK* fusions are known to be oncogenic driver mutations, treatment directed against the Trk fusion kinase in these patients is likely to inhibit tumour proliferation and growth.

The commentary indicated that this may not be correct in all cases as other biomarkers such as PD-L1 expression, MSI-H and high TMB do occur frequently in some types of *NTRK* fusion cancers. There is a possibility that the *NTRK* gene fusion detected in these patients is not the only (or even the primary) oncogenic driver mutation.

The MSI-H phenotype was present in 77-86% of *NTRK* fusion positive colorectal carcinomas (CRC). Targeted therapies directed against MSI-H CRC are not currently available on the PBS. Pembrolizumab is currently registered (provisional approval pathway) for the treatment of unresectable or metastatic MSI-H or mismatch repair deficient (dMMR) CRC and non-CRC tumours that have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

The commentary therefore concluded that it is highly likely that some patients may become eligible for more than one targeted therapy at the same time. Some guidance as to which targeted therapy to select first, based on its comparative effectiveness, may be required.

Furthermore, the assessment and quantification of treatment effect variation, by *NTRK* fusion status, was not feasible given that the available evidence was based on single-arm

larotrectinib studies. Consequently, the clinical utility of the proposed tests could not be determined from the evidence provided.

12. Economic evaluation

The submission presented a modelled economic evaluation based on a naïve indirect comparison of nonrandomised studies (comparing larotrectinib and SoC). The types of economic evaluation presented were a cost-effectiveness analysis and a cost-utility analysis, measuring outcomes in terms of life-years (LYs) gained and quality-adjusted life years (QALYs) gained, respectively. This was consistent with the submission's clinical claim of superiority of *NTRK* fusion testing and larotrectinib treatment in patients with *NTRK* fusion positive solid tumours.

Patients enter the model at the point of treatment, and so the number and cost of *NTRK* fusion testing was back-calculated using estimates of prevalence and test performance for each of the representative tumour types.

Different testing strategies were proposed based on patient age and the frequency of *NTRK* fusions within that tumour type. Tumour types that are associated with a high frequency of *NTRK* fusions and paediatric patients with tumours that have a low frequency of *NTRK* fusions were proposed to receive either NGS or FISH testing. The testing strategies proposed differed from those in the Ratified PICO, notably the absence of IHC triage in paediatric patients with a low frequency of *NTRK* fusions, and no additional IHC test with NGS/FISH in tumour types that have a high frequency of *NTRK* fusions. Sensitivity analyses were conducted during the evaluation regarding these.

NGS and FISH were considered to be the evidentiary standard, and so the impact of inaccurate testing by the evidentiary standard was considered to be incorporated in the larotrectinib study results. Little detail was provided regarding the test methodology used in the larotrectinib studies. The performance of NGS in detecting *NTRK* fusions varies depending on the NGS methodology (i.e. DNA or RNA) and the performance of FISH is uncertain due to a paucity of data. Therefore, the assumption that NGS and FISH in practice would reflect the performance of the test in the larotrectinib studies may not be reasonable. While the model structure allowed for the implications of false negative results to be considered, it did not allow for the implications of false positive results to be examined.

Adults with low frequency *NTRK* fusion tumours were proposed to receive IHC testing first, with confirmatory NGS or FISH testing only in those who are found to be IHC-positive. The back-calculations used to estimate the number of tests required to identify one *NTRK* fusion positive patient accounted for the cost implications of IHC false positive test results, but did not account for IHC false negative results.

The test parameters used in the economic evaluation base case analysis and the estimated number of IHC (where applicable) and NGS/FISH tests required to identify one *NTRK* fusion positive patient are presented in Table 12. These are presented for all subgroups with and without IHC triage – the submission assumed IHC triage would only apply in adults with low frequency *NTRK* tumour types (i.e. represented by colorectal and adult STS tumour types).

Table 8 Test parameters used in the economic evaluation

	Paediatric STS and IFS	Paediatric CNS/glioma	Salivary	Colorectal	Adult STS
Prevalence	0.86 ^a	0.022	0.90	0.003	0.014
IHC sensitivity	80.0%	100%	88.9%	87.5%	80%
IHC specificity	74.4%	20.8%	52.0%	100%	74.4%
IHC PPV ^b	95.0%	2.8%	94.3%	100%	4%
NGS/FISH sensitivity	100%	100%	100%	100%	100%
NGS/FISH specificity	100%	100%	100%	100%	100%
No. tests to identify one <i>NTRK</i> fusion positive patient – with IHC triage					
No. IHC tests ^c	1.16	45.45	1.11	333.33	71.43
<i>Revised</i> ^d	1.45		1.25	380.95	89.29
No. NGS/FISH tests ^e	1.05	36.21	1.06	1.00	23.54
No. tests to identify one <i>NTRK</i> fusion positive patient – without IHC triage					
No. NGS/FISH tests ^c	1.16	45.45	1.11	333.33	71.43

Source: Constructed during the evaluation from Table 3.23 and Table 3.24, p296 of the submission and the 'A3.1_Larotrectinib_PBACMSAC_CEA_June2020.xlsm' workbook.

CNS = central nervous system; IFS = infantile fibrosarcoma; IHC = immunohistochemistry; NGS/FISH = next generation sequencing or fluorescence *in situ* hybridisation; *NTRK* = neurotrophic tropomyosin receptor kinase; PPV = positive predictive value; STS = soft tissue sarcoma

Note: The number of IHC tests required to identify one *NTRK* fusion positive patient was revised during the evaluation to take into account the impact of IHC false negative results.

^a Weighted 62.7% IFS (0.90), 37.3% STS (0.80)

^b $(\text{prevalence} \times \text{sensitivity of IHC}) / [(\text{prevalence} \times \text{sensitivity of IHC}) + (1 - \text{prevalence}) \times (1 - \text{specificity of IHC})]$

^c $1 / \text{prevalence}$

^d $1 / (\text{prevalence} \times \text{sensitivity of IHC})$

^e $1 / \text{IHC PPV}$

As described in 'Prevalence' above, the source used to inform the estimate in paediatric STS included an unknown proportion of patients with IFS, which are known to have a high frequency of *NTRK* fusions, and so the frequency of *NTRK* fusions in paediatric patients with STS in this study is unknown. The best estimate of *NTRK* fusion frequency estimated during the evaluation was 0.68%. This alternate estimate was tested in sensitivity analysis conducted during the evaluation. This increased the number of patients needed to test, using NGS or FISH, from 1.25 to 147.

The submission did not consider whether there were implications for retesting of unevaluable test results or whether there are any adverse events associated with testing (including of rebiopsy should an additional sample be required).

The submission did not propose alternate listing scenarios, however in addition to the overall analysis across all solid tumour types, analyses by subgroup were presented.

The revised economic evaluation excluding the applicant's proposed RSA rebate is summarised in Table 13.

Table 13 Results of the economic evaluation, tumour type analyses (excluding proposed RSA rebate)

	Larotrectinib	SoC	Increment
Paediatric high <i>NTRK</i> frequency fusion tumour types (represented by paediatric IFS and STS)			
Total cost	\$redacted	\$redacted	\$redacted
<i>Revised</i>	<i>\$redacted</i>	<i>\$redacted</i>	<i>\$redacted</i>
Total QALYs	7.764	3.168	4.596
Incremental cost/extra QALY gained			\$redacted¹
<i>Revised</i>			<i>\$redacted¹</i>
Adult high <i>NTRK</i> frequency fusion tumour types (represented by MASC)			
Total cost	\$redacted	\$redacted	\$redacted
<i>Revised</i>	<i>\$redacted</i>	<i>\$redacted</i>	<i>\$redacted</i>
Total QALYs	7.137	0.898	6.239
Incremental cost/extra QALY gained			\$redacted²
<i>Revised</i>			<i>\$redacted²</i>
Paediatric low <i>NTRK</i> frequency fusion tumour types (represented by paediatric glioma)			
Total cost	\$redacted	\$redacted	\$redacted
<i>Revised</i>	<i>\$redacted</i>	<i>\$redacted</i>	<i>\$redacted</i>
Total QALYs	5.388	2.990	2.398
Incremental cost/extra QALY gained			\$redacted³
<i>Revised</i>			<i>\$redacted³</i>
Adult low <i>NTRK</i> frequency fusion common tumour types (represented by colorectal cancer)			
Total cost	\$redacted	\$redacted	\$redacted
<i>Revised</i>	<i>\$redacted</i>	<i>\$redacted</i>	<i>\$redacted</i>
Total QALYs	1.871	0.629	1.242
Incremental cost/extra QALY gained			\$redacted³
<i>Revised</i>			<i>\$redacted³</i>
Adult low <i>NTRK</i> frequency fusion rare tumour types (represented by adult STS)			
Total cost	\$redacted	\$redacted	\$redacted
<i>Revised</i>	<i>\$redacted</i>	<i>\$redacted</i>	<i>\$redacted</i>
Total QALYs	5.519	0.988	4.530
Incremental cost/extra QALY gained			\$redacted³
<i>Revised</i>			<i>\$redacted³</i>

Source: Table 3.37, p309 of the submission.

IFS = infantile fibrosarcoma; MASC = mammary analogue secretory carcinoma; *NTRK* = neurotrophic tropomyosin receptor kinase; QALY = quality adjusted life year; SoC = standard of care; STS = soft tissue sarcoma.

Note: Analyses in italics were also revised during the evaluation to: account for IHC false negative test results, use the efficient price for the average dispensed dose of infusible chemotherapies, apply per pack costing of temozolomide (rather than cost on a per mg basis), and update PBS fees as of July 1, 2020.

The redacted values correspond to the following ranges:

¹ \$135,000 to < \$155,000

² \$115,000 to < \$135,000

³ \$95,000 to < \$115,000

13. Financial/budgetary impacts

The submission presented an epidemiological approach to estimate the use and financial impact of listing larotrectinib treatment. The submission did not explicitly provide an epidemiological approach to estimate the number of patients eligible for *NTRK* fusion testing. Rather, the submission applied the number of tests required to identify one patient with *NTRK* fusions to the number of patients estimated to receive larotrectinib. This approach implicitly assumed that the rate of uptake of both testing and treatment is the same; and that testing occurs at the time at which treatment decisions regarding larotrectinib are being taken. In adult patients with low frequency *NTRK* tumour types, this may not be a reasonable approach, given that *NTRK* fusion testing can occur on diagnosis of advanced disease before initiation of first-line treatment, and that not all patients tested would be eligible for larotrectinib treatment on disease progression.

The submission assumed that, for each adult patient with a low frequency *NTRK* tumour type that exhibited *NTRK* fusions and received larotrectinib treatment, 8.04 IHC tests were required to identify that one patient. This was based on the weighted number of NGS/FISH tests required in this patient group to identify one patient with *NTRK* fusions after IHC testing. This was not correct. Based on the submission's assumptions of *NTRK* fusion prevalence and IHC performance, approximately 290 IHC tests would be required in this subgroup to identify one patient with an *NTRK* fusion (see Table 14). The number of IHC tests assumed in the submission financial implications was therefore substantially underestimated. The number of IHC tests may be even higher in practice, as it has been implicitly assumed (through the back-calculations to estimate the number of patients eligible for larotrectinib treatment) that testing would occur after failure of earlier lines of treatment, whereas testing could occur at diagnosis of advanced disease.

Table 9 IHC and NGS/FISH testing in adults with low frequency *NTRK* tumour types

	To find 1 <i>NTRK</i> fusion positive patient			Scaled across the eligible population
	Adult STS	Colorectal	Weighted ^a	
Prevalence	1.4%	0.3%		0.41% ^b
IHC sensitivity	80%	87.5%		85.0% ^b
IHC specificity	74.4%	100%		97.6% ^b
No. IHC tests ^c	89.29	380.95	289.85	10,442
Outcomes of IHC testing (tests required)				
IHC TP (IHC and NGS/FISH)	1.00	1.00	1.00	36
IHC TN (IHC only)	65.50	379.81	281.64	10,146
IHC FP (IHC and NGS/FISH)	22.54	0.00	7.04	254
IHC FN (IHC only)	0.25	0.14	0.18	6
No. NGS/FISH tests required (in IHC TP and IHC FP)	23.54	1.00	8.04	290
No. <i>NTRK</i> fusion positive patients identified	1.00	1.00	1.00	36

Source: Constructed during the evaluation from the 'A4.2 Larotrectinib_PBACMSAC_Section4_June2.xlsx' workbook included in the submission.

IHC = immunohistochemistry; NGS/FISH = next generation sequencing or fluorescence *in situ* hybridisation; *NTRK* = neurotrophic tropomyosin receptor kinase; STS = soft tissue sarcoma

^a IHC testing outcomes were weighted 68.8% colorectal cancer, 31.2% adult STS.

^b The weighted parameters were estimated from the weighted IHC testing outcomes. Weighted prevalence was estimated by: (IHC TP + FN)/No. IHC tests; sensitivity: IHC TP/(IHC TP + FN); and specificity: IHC TN/(IHC TN + FP).

^c 1 / (prevalence × sensitivity)

The submission assumed that pan-Trk IHC testing would occur within the same patient episode as part of an IHC panel to identify a number of other oncogenic biomarkers, and as such, the cost of this IHC panel would apply in the absence of *NTRK* testing. The submission therefore assumed that, with the introduction of *NTRK* fusion testing, the incremental cost for an increase in IHC panel size from 7–10 to 11 or more would apply in one-third of patients. This was not justified. No information was provided to support a minimum number of relevant oncogenic biomarkers broadly across tumour types (and whether these would be tested at the same time as testing for *NTRK* fusions). The incremental cost of IHC testing may be higher if no IHC testing is assumed in the comparator, or if the panel size increases from 1–3 to 4–6 antibodies with *NTRK* fusion testing.

The submission assumed that 50% of patients would, on average would either receive two FISH tests (at a proposed MBS fee of \$400 each) or receive one NGS test (at a proposed fee of \$2,100). The estimated cost per NGS test was not reasonable as assessment of the sequence variants of only three genes would be required. The PICO ratified by PASC suggested that the fee could be \$980. Further, the split of test use was not justified, despite acknowledgement in the submission that use of NGS is likely to increase over time. The weighted MBS fee was assumed to be \$1,450. With the 80% level of MBS rebate applied, the cost to the MBS of *NTRK* fusion testing would be \$1,160. This approach did not take into account the implications of the Greatest Permissible Gap, which would increase the MBS rebate payable above 85% in the outpatient setting for items costing \$565.00 or more.

Given that the estimated use and cost of IHC have been underestimated, the cost of NGS to the MBS has been underestimated and cost-offsets related to a reduction in infusion and radiotherapy MBS items have been overestimated, the net costs to the MBS are likely to be underestimated at the proposed NGS fee.

The estimated cost of *NTRK* fusion testing to the MBS may be an underestimate at the proposed NGS fee, as the use and cost of IHC testing was underestimated and the cost of NGS to the MBS did not take into account the implications of the Greatest Permissible Gap.

Table 10 Estimated use and financial implications of *NTRK* fusion testing to the MBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Increased use of IHC testing						
Adults with low frequency <i>NTRK</i> tumours who receive larotrectinib	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
No. IHC tests required (8.04 per patient)	redacted ¹	redacted ¹	redacted ²	redacted ²	redacted ²	redacted ²
Revised (290 per patient)	redacted ³	redacted ³	redacted ³	redacted ⁴	redacted ⁴	redacted ⁴
No. patients that increase IHC testing from 7–10 antibodies to 11+ (33%)	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
Revised	redacted ²	redacted ²	redacted ⁵	redacted ⁵	redacted ⁵	redacted ⁵
Incremental cost of IHC testing (\$11.92)	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶
Revised	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶
Increased use of NGS/FISH testing						
Paediatric patients with high frequency <i>NTRK</i> tumours who receive larotrectinib	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
No. NGS/FISH tests required (1.24 per patient)	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
Adults with high frequency <i>NTRK</i> tumours who receive larotrectinib	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
No. NGS/FISH tests required (1.11 per patient)	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
Paediatric patients with low frequency <i>NTRK</i> tumours who receive larotrectinib	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
No. NGS/FISH tests required (45.4 per patient)	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
Adults with low frequency <i>NTRK</i> tumours who receive larotrectinib	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
No. NGS/FISH tests required (8.04 per patient)	redacted ¹	redacted ¹	redacted ²	redacted ²	redacted ²	redacted ²
No. NGS/FISH tests	redacted ¹	redacted ¹	redacted ²	redacted ²	redacted ²	redacted ²
Cost of NGS/FISH testing (\$1,160 per test)	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶
Revised (\$1,217.58 per test)^a	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶
Total cost to the MBS	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶
Revised	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶
Changes in use of other MBS items						
Reduction in MBS item 13915	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
Revised	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
Reduction in MBS item 13918	redacted ²	redacted ²	redacted ²	redacted ²	redacted ²	redacted ²
Revised	redacted ²	redacted ²	redacted ²	redacted ²	redacted ²	redacted ²
Reduction in MBS item 15100	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
Revised	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹	redacted ¹
Total cost offsets	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶
Revised	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶
Net cost to the MBS	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶
Revised	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶	\$redacted⁶

Source: Constructed during the evaluation from Table 4.21-23, p326-7 of the submission and the 'A4.2 Larotrectinib_PBACMSAC_Section4_June2.xlsx' workbook.

To construct the PSD, the Department added in data from Table 105, p303 of the Commentary

IHC = immunohistochemistry; MBS = Medicare Benefits Schedule; NGS/FISH = next generation sequencing or fluorescence *in situ* hybridisation; *NTRK* = neurotrophic tropomyosin receptor kinase

^a Assuming 50% undertake FISH testing, with the 80% benefit (\$640), and 25% undertake NGS, at the 75% benefit (\$1,575) and 25% undertake NGS at the 85% benefit, which increases above 85% due to the Greatest Permissible Gap (\$2,015.30)

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 10,000 to < 20,000

⁴ 20,000 to < 30,000

⁵ 5,000 to < 10,000

⁶ \$0 to < \$10 million

14. Key issues from the ESCs for MSAC

ESCs key issue	ESCs advice to MSAC
Clinical utility of NTRK fusion testing	The submission was based on naïve comparison between data from single-arm larotrectinib studies and standard of care (SoC) data from historic studies. Given the absence of a concurrent SoC control arm in the <i>NTRK</i> fusion positive population, any treatment effect variation by <i>NTRK</i> gene fusion status could not be clearly differentiated from the prognostic effects of <i>NTRK</i> gene fusion status and consequently, the extent of clinical utility of <i>NTRK</i> fusion testing is unclear.
Analytical performance of NTRK fusion testing	The evidence base for the analytical performance of the proposed tests to detect <i>NTRK</i> fusions was limited with a small number of studies (only 1 study for FISH) consisting of small patient numbers. There was also a lack of information in the studies presented particularly around blinding of the results between tests. The economic model assumed that NGS and FISH performed as per the evidentiary standard (i.e. 100% sensitivity and 100% specificity). The ESCs considered this was unlikely as NGS performance was dependant on methodology and the performance of FISH in detecting <i>NTRK</i> fusions was unknown.
Proposed fee for NGS	The proposed fee of \$2,100 for NGS testing was based on the cost of whole genome sequencing. The ESCs considered this was not reasonable as the analysis of sequence variants of only three genes is required. The ESCs considered that the complexity of analysing three gene variants would likely be similar to characterisation of germline gene mutations and variants reimbursed under MBS items 73296 and 73354 and suggested that the fee of \$1,200 for these items could be applied for NGS sequencing for <i>NTRK</i> gene fusion status.
Item descriptor	<p>The ESCs supported the suggestion that the proposed MBS item descriptors for FISH testing should restrict the number of FISH tests per patient per cancer diagnosis to one for each of the three <i>NTRK</i> genes to help to prevent unnecessary re-testing of samples.</p> <p>The ESCs supported the suggestion that the proposed MBS item descriptors for NGS and FISH should explicitly state that testing is for patients with unresectable locally advanced or metastatic disease to make clear the eligible testing population.</p> <p>The ESCs suggested that the proposed MBS item descriptors for NGS and FISH should be reworded to explicitly state the gene fusions being identified and to list the specific tumour types under high and low frequency <i>NTRK</i> tumours to minimise use beyond the intended population and ensure that the appropriate MBS item is billed for a patient's tumour type.</p>
Pan-Trk IHC	The submission proposed pan-Trk triage IHC only for adult patients with low frequency <i>NTRK</i> fusion cancers. The ESCs considered that pan-Trk IHC should also be used as a triage test for paediatric patients with low <i>NTRK</i> fusion cancers in addition to adult patients with low frequency <i>NTRK</i> tumours. The ESCs considered that pan-Trk triage would be useful for patients with low frequency <i>NTRK</i> cancers in reducing the number of more expensive NGS tests required as the number of patients that require testing to identify one true positive patient is large.
Test performance in economic evaluation	The assumption that test performance would equal that in the larotrectinib case series studies is unlikely as this depends on the different test method(s) used.
Financial estimates	<p>The financial estimates were considered by DUSC. The ESCs considered the assumption that patients would receive either two FISH tests on average or one NGS test was uncertain. The ESCs considered that in clinical practice, additional NGS testing may be required to confirm the results of negative FISH test results. Further, the ESCs noted that the estimated cost to the MBS for NGS did not account for the Greatest Permissible Gap and as such, the costs of NGS in the submission were underestimated in this regard.</p> <p>The ESCs considered that the costs of pan-Trk IHC testing were underestimated in the submission. The ESCs noted that the submission assumed this IHC testing would be reimbursed under existing MBS items for IHC and that most patients would have already received pan-Trk IHC testing via an IHC panel to identify a number of oncogenic biomarkers. The ESCs considered this was not adequately justified as no information was provided to support pan-Trk IHC testing at the same time as testing for other oncogenic biomarkers.</p>

ESCs discussion

The ESCs noted that up to three FISH tests (one for each of *NTRK1*, *NTRK2* and *NTRK3*) may be required per patient to determine the presence of an *NTRK* fusion in one of the three *NTRK* genes. The ESCs advised that the proposed MBS items should be limited to once per cancer diagnosis per patient and to referral by a specialist or consultant physician. The ESCs

agreed with the evaluation that the proposed MBS item descriptors for FISH testing should be amended to restrict the number of FISH tests per patient to one for each *NTRK* gene. The ESCs considered this would help to prevent unnecessary re-testing of samples. The ESCs also agreed with the evaluation that the proposed MBS item descriptors for NGS and FISH should be amended to explicitly state that testing is for patients with unresectable locally advanced or metastatic disease to make clear the eligible testing population. The ESCs noted that the pre-ESCs response indicated the applicant accepted these amendments to the proposed MBS item descriptors.

The ESCs considered that the fee of \$2,100 proposed for NGS based on MBS item 73358 for whole genome sequencing was not adequately justified and likely to be an overestimate given a large part of the cost of NGS would likely be due to sequence analysis and analysis of three gene variants only is required. The ESCs considered that the complexity of analysing three gene variants would likely be similar to characterisation of germline gene mutations and variants reimbursed under MBS items 73296 and 73354 and suggested that the fee of \$1,200 for these items could be applied for NGS sequencing for *NTRK* gene fusion status. The ESCs noted that a fee of \$1,200 is similar to the \$980 proposed in the ratified PICO which was based on a brief literature search.

The ESCs suggested that the proposed MBS item descriptors for NGS and FISH should be reworded to explicitly state the gene fusions being identified and list the specific tumour types under high and low frequency *NTRK* tumours to minimise use beyond the intended population and ensure that the appropriate MBS item is billed for a patient's tumour type.

The ESCs noted that RNA-NGS was nominated as the reference standard based on European Society for Medical Oncology (ESMO) recommendations and information in the literature. The ESCs noted there was limited evidence of the analytical performance for the proposed tests (i.e. NGS, FISH and IHC) given the small number of studies presented with small patient numbers, lack of information within the studies, high risk of bias across studies, an uncertain reference standard, and varying clinical validity according to the population/cancer type. Overall, the ESCs considered that the performance of *NTRK* fusion testing in clinical practice was uncertain. The ESCs noted that, based on the available evidence, the sensitivity of pan-Trk IHC was similar to RNA-NGS with the exception of the detection of *NTRK3* fusions for which a pan-Trk antibody has reduced sensitivity. The ESCs noted that the accuracy of FISH testing is uncertain as only one study on the performance of FISH in detecting *NTRK3* fusions with RNA-NGS as the reference standard was available. However, the ESCs noted that the available data indicated a high rate of false negative FISH test results with NPV ranging from 62%-72% for population 1 and 52%-54% for population 2. Given this, the ESCs considered that, in clinical practice, NGS might also be used in those with a negative FISH test as confirmatory testing, which could affect both the economic evaluation and the financial estimates.

The ESCs noted that, although RNA-NGS is considered the most accurate for detecting functional *NTRK* gene fusions, there are instances where DNA-NGS may be the preferred methodology such as when the quality of the RNA sample is poor. Further, the ESCs noted that many laboratories in Australia currently do not have the expertise to perform RNA-NGS. The ESCs suggested that the proposed MBS item descriptors could specify the NGS methodology to be used under certain circumstances.

The ESCs considered that NGS and FISH was unlikely to perform as per the evidentiary standard in clinical practice as assumed by the submission particularly given the performance of NGS was dependent on the methodology used and RNA-NGS would unlikely be used in all cases.

The ESCs considered that maintaining an adequate supply of tumour specimens for the validation of RNA-NGS or FISH test results may be an issue for laboratories given a high throughput of tumour specimens and panels of positive and negative samples may be required to serve on a validation panel for optimal test performance and *NTRK* fusions are only common in rare tumour types.

The ESCs noted the submission proposed and modelled a testing strategy where pan-Trk IHC triage is only used for adult patients with low frequency *NTRK* fusion tumours. This differed from that of the ratified PICO, which proposed that pan-Trk-IHC triage be used for all patients. As such, the cost-effectiveness of pan-Trk IHC triage for the other three patient population types is unknown. The ESCs considered that pan-Trk IHC should be used as a triage test for paediatric patients with low frequency *NTRK* fusion cancers (Population 3) in addition to adult patients with low frequency *NTRK* fusion cancers. This would reduce the number and cost of NGS tests required as the number of patients that require testing to identify one true positive patient is large. Although the ESCs considered not requiring pan-Trk IHC triage in high frequency *NTRK* fusion cancers may be reasonable, this would depend on RNA-NGS being used widely in practice, which is uncertain. The pre-ESCs response indicated that the applicant was willing to accept a recommendation from MSAC for pan-Trk IHC triage in paediatric patients with low frequency *NTRK* fusion tumours.

The ESCs noted that the submission claimed that *NTRK* fusion testing plus larotrectinib was superior to no *NTRK* testing plus standard of care (SoC) in terms of efficacy and safety, in the proposed testing and treatment populations. The ESCs noted that, based on the limited clinical evidence (i.e. single-arm uncontrolled studies) and absence of a concurrent SoC control arm in the *NTRK* fusion positive population, any treatment effect variation by *NTRK* gene fusion status could not be clearly differentiated from the prognostic effects of *NTRK* gene fusion status and consequently, the extent of clinical utility of *NTRK* fusion testing is unclear.

The ESCs noted that the estimated cost to the MBS for NGS did not account for the Greatest Permissible Gap which increases the MBS rebate payable above 85% of the MBS fee for items with a fee of \$565.00 or more in the outpatient setting. In this regard, the costs for NGS are likely to be underestimated in the submission.

The ESCs considered that the numbers and costs of pan-Trk IHC testing were underestimated in the submission. The ESCs noted that the submission assumed IHC testing would be reimbursed under existing MBS items for IHC and that most patients would have already received pan-Trk IHC testing via an IHC panel to identify a number of oncogenic biomarkers. The ESCs considered this was not adequately justified as no information was provided to support pan-Trk IHC testing at the same time as testing for other oncogenic biomarkers.

The ESCs considered it likely that there would be a substantial increase in utilisation of existing MBS items (72846, 72847, 72849 and 72850) for pan-Trk IHC tests. The ESCs also noted the consultation feedback received from one organisation proposing a separate MBS item to reflect the complexity of pan-Trk IHC testing.

The ESCs noted that the estimated extent of use and financial implications are discussed in the DUSC advice on this application.

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

Bayer will continue to work collaboratively with the MSAC, the Department of Health and Federal Government to help ensure that patients with an NTRK fusion cancer in Australia receive access to NTRK fusion testing through the MBS at the earliest opportunity.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](#)