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***Application 1602.1 – NTRK fusion testing in patients with locally advanced or metastatic solid tumour to determine eligibility for larotrectinib (Vitrakvi)***

**Applicant: Bayer Australia Ltd**

**Date of MSAC consideration:** **83rd MSAC Meeting, 25-26 November 2021**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](http://www.msac.gov.au/)

# Purpose of application

The resubmission was received from Bayer Australia Limited by the Department of Health. It comprised an integrated codependent submission for:

* Medicare Benefits Schedule (MBS) listing of immunohistochemistry (IHC), fluorescence *in situ* hybridisation (FISH) and next generation sequencing (NGS) testing. These were for the evaluation of a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion to determine eligibility for treatment with larotrectinib in paediatric patients with locally advanced or metastatic solid tumours of any origin and in adult patients with locally advanced or metastatic mammary analogue secretory carcinoma (MASC), secretory breast carcinoma (SBC) colorectal cancer (CRC), soft tissue sarcoma (STS), non-small cell lung cancer (NSCLC) or thyroid cancer
* Pharmaceutical Benefits Scheme (PBS) Section 100 Authority Required listing of larotrectinib for the treatment of *NTRK* fusion positive solid tumours (as listed above) 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.

# 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 supported the creation of new MBS items for NTRK fusion testing to determine eligibility for treatment with larotrectinib in all paediatric patients, and adult patients with high-frequency NTRK fusion cancer types. Separate items would be required for separate methodologies due to their differing costs and performance and the need to allow time for pathology laboratories to develop the capacity to provide NGS-based services. MSAC did not support public funding for adult patients with any type of tumour harbouring NTRK fusion at low frequency due to poorer test performance and in alignment with the Pharmaceutical Benefits Advisory Committee’s (PBAC’s) intention to not recommend listing larotrectinib in this population on the PBS.

MSAC supported the following item descriptors:

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| **Item number AAAA Category 6 (Pathology services) – Group P7 Genetics** |
| Fluorescence in-situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic neurotrophic solid tumour at risk of being caused by a tropomyosin receptor kinase (*NTRK*) gene fusion as determined by either:   * occurring in a child less than 18 years of age, OR * being mammary analogue secretory carcinoma of the salivary gland, OR * being secretory breast cancer,   requested by a specialist or consultant physician to determine if requirements relating to neurotrophic tropomyosin receptor kinase (*NTRK1, NTRK2, or NTRK3*) fusions for access to a tropomyosin receptor kinase (Trk) inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.  This item cannot be claimed if MBS item BBBB has been claimed for the same patient.  Applicable only once per cancer diagnosis.  **Fee:** $400.00. **Benefit:** 75% = $300.00 85% = $340.00 for 1 *NTRK* fusion test |
| **Two tests described in item AAAA**  **Fee:** $533.00. **Benefit:** 75% = $400.00 85% = $453.00 |
| **Three or more tests described in item AAAA**  **Fee:** $667.00. **Benefit:** 75% = $500.00 85% = $579.10a |

a Accounting for Greatest Permissible Gap

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| **Item number BBBB Category 6 (Pathology services) – Group P7 Genetics** |
| Next generation sequencing (NGS) test for neurotrophic tropomyosin receptor kinase (*NTRK1*, *NTRK2*, *NTRK3*) fusions by RNA or DNA in tumour tissue from a patient with locally advanced or metastatic neurotrophic solid tumour at risk of being caused by an *NTRK* gene fusion as determined by either:   * occurring in a child less than 18 years of age, OR * being mammary analogue secretory carcinoma of the salivary gland, OR * being secretory breast cancer,   requested by a specialist or consultant physician to determine if requirements relating to neurotrophic tropomyosin receptor kinase (*NTRK1, NTRK2 or NTRK3*) fusions for access to a Trk inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.  This item cannot be claimed if MBS item AAAA has been claimed for the same patient.  Applicable only once per cancer diagnosis.  **Fee:** $1,000.00 **Benefit**: 75% = $750.00 85% = $912.10a |

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**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 children and some adult patients with locally advanced or metastatic solid tumours to help determine if they could benefit from the medicine larotrectinib. This was a resubmission.

This was a codependent application, meaning that genetic testing is needed to identify patients who might benefit from the medicine. The application for larotrectinib was considered by the Pharmaceutical Benefits Advisory Committee (PBAC), which deferred its decision on larotrectinib pending MSAC’s advice on the funding of *NTRK* testing.

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 show if a 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 some advanced cancers that have a high frequency of *NTRK* gene fusions
* adults with some 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 untargeted 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 whether 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’s advice to the Commonwealth Minister for Health**

MSAC supported testing for *NTRK* gene fusion status in all children with locally advanced or metastatic solid tumours, and in adults with some locally advanced or metastatic solid tumours that have a high frequency of *NTRK* fusion, to help determine eligibility for larotrectinib. MSAC determined that this testing is safe, effective and cost-effective. MSAC did not support *NTRK* gene fusion testing for adults with tumours that have a low frequency of *NTRK* fusions, because it was not likely to provide value for money.

# Summary of consideration and rationale for MSAC’s advice

MSAC noted the purpose of this integrated codependent submission was to request MBS listing of *NTRK* fusion testing to determine eligibility for treatment with larotrectinib in patients with locally advanced or metastatic solid tumours; and to request PBS listing of larotrectinib for the treatment of the same conditions.

MSAC noted the proposed populations in the application:

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

MSAC noted that, for the original submission in November 2020, the PBAC had deferred its decision regarding larotrectinib, and MSAC did not support listing the test because of this deferral. MSAC instead 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 ([Application 1602 Public Summary Document](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1602-public), page 1).

MSAC noted the application was considered at a joint meeting of the Economics Sub-Committee of the PBAC and the Evaluation Sub-Committee of MSAC (the ESCs) in October 2021. MSAC noted that the PBAC, at its November 2021 meeting, was of a mind to recommend listing larotrectinib for paediatric patients and adult patients with tumours harbouring *NTRK* fusions at high frequency on the basis that the incremental cost-effectiveness ratio (ICER) in these populations was acceptable at the proposed price, pending MSAC advice on the funding of the codependent *NTRK* testing. The PBAC also considered there was a high clinical need for effective treatments for patients with *NTRK* fusion tumours in these populations. The PBAC did not recommend listing larotrectinib for adult patients with any type of tumour harbouring *NTRK* fusions at low frequency because the ICER for this population remained unacceptably high and uncertain. Further, the PBAC was uncertain of the clinical need within this patient population.

MSAC noted the proposed clinical management algorithm in which all paediatric and adult patients with high frequency *NTRK* fusion tumour types are tested directly with either FISH or NGS (using either DNA or RNA) and adult patients with low-frequency *NTRK* fusion tumour types are triaged with pan-Trk IHC with only those testing positive proceeding to access FISH or NGS testing. MSAC considered the comparator of no genetic testing and standard of care was appropriate.

MSAC considered the evidence for diagnostic accuracy of pan-Trk IHC in adult patients with low-frequency *NTRK* gene fusion cancer types. MSAC noted the results from a single case control study showed that *NTRK1* and *NTRK2* fusions are better detected with IHC than *NTRK3* fusions (see Table 6). MSAC agreed with the ESCs which noted many uncertainties associated with this study, including multiple domains at high risk of bias, which resulted in little confidence in the estimates of effect size and thus the true test performance in this population is unknown. MSAC discussed the issue of false positives with IHC, also noting the results from a patient cohort with lung cancer from Strohmeier et al 2021[[1]](#footnote-1), which none of the 12 IHC-positive tumors (using a definition of 1% IHC-positivity threshold) were positive on RNA testing when it could be done.

MSAC considered the evidence for diagnostic accuracy of *NTRK* testing with FISH or NGS. MSAC agreed with the ESCs and considered that FISH is not 100% sensitive and specific in usual pathology practice and noted that RNA-NGS is more sensitive than DNA-NGS, providing that RNA quality is optimal.

Overall, MSAC agreed with the ESCs and considered that there continued to be limited evidence of the analytical performance of the proposed tests (i.e. NGS, FISH and IHC). In particular MSAC did not support this testing of adult patients with low-frequency *NTRK* gene fusion cancer types because the evidence for these patients was highly uncertain and there was no study data presented that was generalisable to the requested adult low-frequency population in Australia. However, based on the limited evidence, MSAC also concluded that, although analytical performance varied across RNA-NGS, DNA-NGS and FISH, this was within acceptable limits for paediatric patients or adult patients with high-frequency *NTRK* gene fusion cancer types.

MSAC considered that the test was likely to be comparatively safe if the rates of false positives and false negatives are sufficiently small, and noted the desire to avoid chemotherapy or radiotherapy in paediatric patients.

MSAC noted that, while the modelled economic evaluation presented in the resubmission was restructured to allow the implications of false positive and false negative results to be analysed, the base case retained the assumption that NGS and FISH performed with 100% sensitivity and 100% specificity. For adult patients with low-frequency *NTRK* gene fusion cancer types who require IHC testing, MSAC noted that the resubmission assumed 100% specificity, which was inconsistent with the clinical evidence. Reducing the specificity would result in more false positives in the low-frequency population, meaning more patients would be treated inappropriately, which would increase the ICER. MSAC also noted that the ICER in adult patients with low-frequency *NTRK* gene fusion cancer types was less favourable and highly sensitive to changes in test performance (see Table 11).

MSAC noted the financial and budgetary impacts, based on approximately < 500 eligible patients per year. MSAC noted the net cost to government (PBS and MBS) of approximately $10 to < $20 million to $10 to < $20 million per year, and the net cost to the MBS of $0 to < $10 million in Year 1 to $0 to < $10 million in Year 6. However, MSAC considered that the resubmission’s predicted number of NGS or FISH tests for paediatric patients with low-frequency tumours relative to adult patients with low-frequency tumours (< 500 vs. < 500 per patient) seemed to be erroneously high, and this also affected the financial estimates.

MSAC noted the consultation feedback received from the Children’s Cancer Institute (who lead the Zero Childhood Cancer research program), which supported not requiring IHC triage in paediatric patients, and advocated for use of NGS over FISH testing. However, MSAC noted that not all laboratories routinely perform NGS, and only a few laboratories in Australia perform NGS with RNA. MSAC therefore considered that FISH testing should be retained as an option, as testing is likely to occur outside those centres with NGS capability. MSAC noted that NGS is likely to become more available in the future. In addition, MSAC noted the pre-MSAC response, which also acknowledged the uncertainty of utilisation of FISH vs NGS and the likelihood of this changing over time.

MSAC considered the proposed fees for *NTRK* gene fusion testing. MSAC recalled that, in its consideration of the original submission, MSAC had considered that the fee for RNA-NGS should be aligned with that for Alport testing (fee: $1,200; 75% benefit: $900) ([Application 1602 Public Summary Document](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1602-public), page 5). However, MSAC advised that, because the item descriptor allows either DNA-NGS or RNA-NGS at the laboratories’ discretion, an appropriate weighted fee for the NGS item would be $1,000, noting that few laboratories would perform RNA-NGS in the near future. MSAC noted that separate FISH probes are required for fusions in each of the *NTRK1*, *NTRK2* and *NTRK3* genes and that the marginal costs reduce for using additional probes, which was consistent with the fee structure in the proposed MBS item. MSAC also noted the current fees for *NTRK* testing in patients with sarcoma ranged from $340 for 1 gene and $800 for ≥4 genes (method agnostic MBS items 73374, 73375, 73376) and for characterisation of *ETV6‑NTRK3* gene rearrangement was $340 (method agnostic MBS items 73379, 73381). MSAC considered that this level of reimbursement would not be suitable for NGS. MSAC supported the proposed fees for FISH testing on the basis that the benchmark fee of $340 may not reflect real-world costs for laboratories conducting FISH testing.

MSAC considered the proposed MBS item descriptors for *NTRK* gene fusion testing. MSAC advised that separate MBS items should be created for the two separate methodologies due to their differing costs and performance and the need to allow time for pathology laboratories to develop the capacity to provide NGS-based services:

* One item for FISH testing in a patient who is either aged less than 18 years, or has a tumour type at high risk of being caused by a *NTRK* fusion, with a fee of $400 for one test, $533 for two tests or $667 for three tests
* One item for NGS testing, using either DNA or RNA, in a patient who is either aged less than 18 years, or has a tumour type at high risk of being caused by a *NTRK* fusion, with a fee of $1,000.

MSAC also considered that the two cancer types with high frequency of *NTRK* fusion in adults: mammary analogue secretory carcinoma of the salivary gland or secretory breast cancer, should be specified in the item descriptor.

MSAC advised that only one item can be claimed per cancer diagnosis (for either FISH or NGS), not both, and that this would be decided by the testing laboratory.

Overall, MSAC supported MBS funding of *NTRK* fusion testing for all paediatric patients, and adult patients with high-frequency *NTRK* fusion cancer types. MSAC did not support public funding for adult patients with any type of tumour harbouring NTRK fusions at low frequency due to poorer test performance and in alignment with the PBAC’s intention to not recommend listing larotrectinib in this population on the PBS. Thus, MSAC advised that the proposed MBS item for IHC testing prior to *NTRK* fusion testing (see Table 2) was not required. However MSAC foreshadowed that, in the event there was a satisfactory basis to change this advice, then with testing at the time of initial diagnosis of metastatic or locally advanced disease and 1% staining being considered positive (included as an explanatory note), the lower of the two current sets of IHC fees should apply.

**Other discussion**

Redacted.

# Background

MSAC has previously considered *NTRK* fusion testing for access to larotrectinib for the treatment of *NTRK* fusion positive locally advanced or metastatic solid tumours of any histology. The original application was considered by MSAC at its November 2020 meeting.

The resubmission addressed the concerns of MSAC, with respect to the thirteen recommendations that were reported in the MSAC [Discussion paper](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/Additional-Resources), which are presented in Table 1.

**Table 1 MSAC concerns and how these were addressed in the resubmission**

| **Recommendations** | **MSAC, PBAC and ESCs comments about the original submission** | **How the resubmission addressed the recommendation** | **Was the issue addressed adequately in the resubmission?** |
| --- | --- | --- | --- |
| 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. | The biological plausibility of the *NTRK* fusion being the oncogenic driver was not fully covered in the submission. | Results highlight the consistent treatment response of larotrectinib across different tumour types for the latest data cut (ePAS5; July 2020, Figure 2.60). This is consistent with the results presented in the original submission. | None of the 14 adult patients with low frequency NTRK fusion cancer types: Cholangiocarcinoma, pancreatic, appendiceal, hepatic, prostate or CNS cancers responded to treatment with larotrectinib, suggesting NTRK fusions may not be the primary oncogenic drivers in some of these tumour types. |
| 1. Any other biomarkers that may have predictive value for the proposed treatment should be discussed. | The submission did not fully address the co-occurrence of MSI-H, TMB and PD-L1 expression in *NTRK* fusion positive tumours, and the possible implications for targeted treatment options. | Although co-occurrence of PD-L1, MSI-H and high TMB are expressed in some *NTRK* fusion cancers such as CRC, PBS-listing for larotrectinib in CRC is proposed in R/R disease with no remaining suitable alternate therapy. Therefore, it is assumed patients with cancers such as CRC would have failed other targeted therapies before being eligible for larotrectinib. | This means that all NSCLC patients with *NTRK* gene fusion tumours would receive treatment with checkpoint inhibitors pembrolizumab (if PD-L1 expression levels are high) or nivolumab prior to receiving larotrectinib.  This is likely to affect the number of eligible patients, as delayed treatment may result in patients being too ill to receive larotrectinib (ECOG >2). |
| 1. The biomarker prevalence in the overall population should be reported, along with its prevalence in as many specific tumour types as possible. | The prevalence rate for paediatric STS used by the submission was not verifiable and likely inaccurate due to the inclusion of IFS, a known high frequency *NTRK* cancer in the paediatric STS cohort. | Paediatric STS *NTRK* prevalence was amended to 0.68% as recommended by the ESCs and PBAC. | This is reasonable. |
| 1. 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. | The stability and/or persistence of *NTRK* fusions with tumour progression is largely unknown, and was not well covered in the submission. | No new data from the larotrectinib trials or literature review was identified in the resubmission and thus no further updates were included.  Testing for *NTRK* fusion is proposed for patients with advanced disease and therefore the biomarker prevalence is not expected to change. | Testing is to occur at diagnosis of locally advanced or metastatic R/R disease, with no other suitable treatment options.  As noted by the resubmission, stability of the biomarker only becomes an issue if testing was to occur earlier (at diagnosis of earlier stage disease). |
| 1. The reference standard test and the evidentiary standard test should be nominated. | Well covered in the submission. | No further updates. | No further information was required. |
| 1. 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. | The diagnostic accuracy of IHC and DNA-NGS was covered by the submission. | No further updates. | There is still a lack of evidence for assessing the accuracy of FISH for detecting *NTRK1* and *NTRK2* fusions.  An additional study that compared pan-Trk IHC and FISH *NTRK* fusion testing provides only concordance data |
| 1. Data on the accuracy of the test across tumour types should be provided 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 across different tumour types was discussed by the submission.  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”) | Data relating to the diagnostic accuracy of IHC was updated, including 3 additional studies comparing IHC and RNA-NGS. However, overall conclusions relating to diagnostic performance for IHC remain consistent with the original submission. | Two of the three additional studies were identified during the previous evaluation. The third study provides diagnostic accuracy of IHC compared to RNA-NGS in paediatric patients with CMN (a paediatric high frequency *NTRK* fusion cancer type). The overall conclusions remain consistent with the previous commentary.  The false negative rate for IHC and the definition of a positive IHC result were not discussed in the resubmission |
| 1. Test reproducibility is particularly important for pan-tumour assessments to demonstrate testing equivalence across different tumour types and for different diagnostic laboratories. | 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. | The resubmission agreed with PBAC/MSAC that test reproducibility should not be an issue given IHC, FISH and NGS tests are expected to be performed in NATA-accredited laboratories.  Additional data relating to test reproducibility was presented: a multinational ring study analysed FISH and NGS for the detection of *NTRK* gene fusions in various FFPE cancer tissues found inter-laboratory reproducibility was strong for both evaluated methodologies. | The resubmission highlighted that the study by Kirchner et al (2020) found that both FISH and NGS for the detection of *NTRK* gene fusions in various FFPE cancer tissues showed strong inter-laboratory reproducibility. This was reasonable. |
| 1. 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 enable an assessment of the ratio of correct to incorrect test results. | 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 treatment and delayed appropriate treatment for these patients has not been considered. | The economic analysis was amended to a test-treat model for this resubmission which allows the implications of false FISH/NGS results to be considered. | While the model presented in the resubmission was restructured to allow the implications of false positive and false negative results to be analysed, the base case retains the assumption of 100% test performance of NGS (DNA and RNA) and FISH. This was not reasonable  The ICER is sensitive, particularly in the low frequency populations, to changes in the specificity of NGS/FISH testing. |
| 1. 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 clinical algorithm proposed by the submission differed from that in the ratified PICO Confirmation. | MSAC considered that 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 to 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 (MSAC application 1602 2020 PSD p.4).  Adult patients with low-frequency *NTRK* fusion tumour types are triaged with pan-Trk IHC prior to access to FISH/NGS in proposed clinical algorithm. | MSAC’s advice has been incorporated into the clinical management algorithm. However, according to the proposed clinical management algorithm, IHC testing has been delayed until the patient has failed all other treatment options. This should be amended so that testing still occurs at diagnosis of advanced disease but treatment is delayed until no viable options are available. |
| 1. 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. | The submission recommended to triage adults with low frequency *NTRK* fusion cancers using IHC testing for but not for paediatric patients. | As discussed directly above, MSAC considered it appropriate to directly test all paediatrics and adult high frequency tumours with FISH/NGS directly (without IHC triage). | Triage testing with pan-Trk IHC has been recommended for adult patients with low frequency *NTRK* fusion cancer types in the resubmission |
| 1. 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. | 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. | Although it is possible the biomarker could change during the course of disease, given the proposed PBS restriction criteria where patients are no longer eligible for PBS-subsidised larotrectinib following disease progression, this is unlikely to be an issue.  In addition, patients must not have received prior treatment with a Trk inhibitor to be eligible for PBS-subsidised larotrectinib. | As testing is to occur at the diagnosis of advanced disease, the stability of the biomarker should not be an issue. A rebiopsy should only be necessary if insufficient tumour material is available for *NTRK* fusion testing. |
| 1. 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 used a naïve comparison between the single-arm larotrectinib trials compared with historical SoC trials. | The approach to assessing the therapeutic benefit of larotrectinib remains unchanged for this resubmission.  The latest larotrectinib trial data across the three pivotal trials as well as updated SoC comparators was included for this resubmission. | Updated ePAS5 and SAS3 datasets were used in the resubmission.  Updated SoC comparator studies were included for adults with low frequency *NTRK* fusion tumour types: CRC, NSCLC, STS or thyroid cancer. |
| 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. | Not addressed | The previous submission reported a higher objective response rate for *NTRK3* fusions (85%), which includes most patients with high frequency *NTRK* fusion cancers, than for *NTRK1* and *NTRK2* fusions (63% and 50%, respectively). |

Source: Table MSAC.3 pp 17-21 of the commentary

# Prerequisites to implementation of any funding advice

The resubmission noted that both the MSK-IMPACT and FoundationOne CDx panels are commonly used to detect *NTRK* fusions in the literature and that both panels are now available in Australia (MSAC application 1602 Public Summary Document [PSD] 2020, p11).

MSAC previously noted that a quality assurance program is available and that 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 application 1602 PSD 2020, p4). Thirteen NATA-accredited Australian laboratories currently have RNA-NGS capabilities, but only two laboratories are currently validated to perform *NTRK* fusion testing.

The accreditation of pan-Trk IHC testing is yet to be developed.

# Proposal for public funding

To address the financial burden to pathology providers and the utilisation estimates and financial impact uncertainties in regard to IHC triage testing in adult low frequency tumours, a new MBS listing was proposed for pan-Trk IHC testing for adult low frequency *NTRK*-fusion tumours as presented in the resubmission (Table 2).

The commentary proposed amendments are in coloured text, noting the first dot point amendment was to list the cancer types eligible for testing in the item descriptor rather than listing them in a footnote; and the third dot point amendment was to allow pan-Trk IHC testing for adults with high frequency *NTRK* fusion cancer types (MASC of the salivary gland or SBC) if FISH or DNA-NGS methods are used instead of RNA-NGS to detect *NTRK* fusions. This was due to the inability of FISH and DNA-NGS to distinguish between an active and an inactive gene fusion.

**Table 2 Proposed MBS listing for IHC testing in adult low frequency tumours, with modifications in coloured text added during the evaluation**

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| **Item number: TBC Category 6 (Pathology services) – Group P5 Tissue Pathology** |
| Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with antigenic specificity for tropomyosin receptor kinase (Trk).  Immunohistochemistry (IHC) examination of tumour tissue from a patient aged 18 years or over with:   * solid tumour cancer of one of the following types: soft tissue sarcoma, colorectal, *non-small cell lung*\* or thyroid cancer * which is metastatic OR is locally advanced where surgical resection is likely to result in severe morbidity, * solid tumour cancer of one of the following types: mammary analogue secretory carcinoma of the salivary gland or secretory breast cancer if *NTRK* gene fusion testing was conducted using fluorescence in-situ hybridisation (FISH) or DNA-based next generation sequencing (NGS) methods and a *NTRK* gene fusion was detected.   Applicable only once per cancer diagnosis. |
| Fee: $74.50 Benefit: 75% = $55.90 85% = $63.35 |

\*Lung cancer was specified in the resubmission but this should be changed to non-small cell lung cancer to align with the PBS restriction and the population in the clinical trials

Source: Table 1.14 p80 of the resubmission

The MBS items requested for *NTRK* fusion testing using FISH (AAAA or BBBB; see Table 3) or NGS (DNA or RNA not specified; CCCC or DDDD; see Table 3) in the resubmission have taken into account the advice from MSAC and are listed below (see MSAC application 1602 PSD 2020, pp5-6).

The red text indicates MSAC-proposed amendments to the proposed listings. The blue text is an amendment suggested during the evaluation to list the cancer types eligible for testing in the item descriptor rather than as a footnote (consistent with pan-Trk IHC MBS item).

The resubmission specified lung cancer in the MBS listings, which is broader than the proposed PBS listing that specified NSCLC. All patients with lung cancer in the larotrectinib studies had NSCLC.

The resubmission also specified MASC of the salivary gland in the MBS descriptor whereas salivary gland tumour (a broader term) was specified in the PBS restriction. MASC was the most commonly represented high frequency *NTRK* cancer occurring in adults in the larotrectinib studies, but accounts for approximately only 4.5% of all salivary gland tumours.

**Table 3 Proposed MBS listings for FISH and NGS testing, with modifications in coloured text added (red text indicates previous MSAC-proposed amendments (Nov 2020); blue text indicates commentary-proposed amendment)**

|  |
| --- |
| **Item number: AAAA Category 6 (Pathology services) – Group P7 Genetics** |
| Fluorescence in-situ hybridisation (FISH) test of tumour tissue from a patient aged 18 years or over with:   * solid tumour cancer of one of the following types: soft tissue sarcoma, colorectal, *non-small cell lung*\* or thyroid cancer * 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,   requested by a specialist or consultant physician to determine if requirements relating to neurotrophic tropomyosin receptor kinase (*NTRK1, NTRK2 or NTRK3*) fusions for access to a Trk inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.  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.  **Fee:** $400.00. **Benefit:** 75% = $300.00 85% = $340.00 for 1 *NTRK* fusion test,  **Fee:** $533.00. **Benefit:** 75% = $400.00 85% = $453.00 for 2 *NTRK* fusion tests,  **Fee:** $667.00. **Benefit:** 75% = $500.00 85% = $566.00 for 3 *NTRK* fusion tests |
| **Item number BBBB Category 6 (Pathology services) – Group P7 Genetics** |
| Fluorescence in-situ hybridisation (FISH) test of tumour tissue from a patient:   * 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,   requested by a specialist or consultant physician to determine if requirements relating to neurotrophic tropomyosin receptor kinase (*NTRK1, NTRK2, or NTRK3*) fusions for access to a tropomyosin receptor kinase (Trk) inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.  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.  **Fee:** $400.00. **Benefit:** 75% = $300.00 85% = $340.00 for 1 *NTRK* fusion test,  **Fee:** $533.00. **Benefit:** 75% = $400.00 85% = $453.00 for 2 *NTRK* fusion tests,  **Fee:** $667.00. **Benefit:** 75% = $500.00 85% = $566.00 for 3 *NTRK* fusion tests |
| **Item number CCCC Category 6 (Pathology services) – Group P7 Genetics** |
| Next generation sequencing (NGS) test of tumour tissue from a patient aged 18 years or over with:   * solid tumour cancer of one of the following types: soft tissue sarcoma, colorectal, *non-small cell lung*\* or thyroid cancer * 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   requested by a specialist or consultant physician to determine if requirements relating to neurotrophic tropomyosin receptor kinase (*NTRK1, NTRK2 or NTRK3*) fusions for access to a Trk inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.  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.  **Fee:** $1,200.00 **Benefit:** 75% = $900.00 85% = $1,115.30 |
| **Item number DDDD Category 6 (Pathology services) – Group P7 Genetics** |
| Next generation sequencing (NGS) test of tumour tissue from a patient   * 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,   requested by a specialist or consultant physician to determine if requirements relating to neurotrophic tropomyosin receptor kinase (*NTRK1, NTRK2 or NTRK3*) fusions for access to a Trk inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.  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.  **Fee:** $1,200.00 **Benefit**: 75% = $900.00 85% = $1,115.30 |

\*Lung cancer was specified in the resubmission but this should be changed to non-small cell lung cancer to align with the PBS restriction and the population in the clinical trials

Source: Tables 1.15, 1.16, 1.17 and 1.18 (pp 82-84) of the resubmission

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

# Summary of public consultation feedback/consumer issues

No new consultation feedback was received for the resubmission before ESC. Following ESC, consultation feedback was received from the Children’s Cancer Institute which was supportive of the application. This feedback support not requiring IHC triage in paediatric patients, given the rare status of these tumours and the high prevalence of fusion partner genes that are not the more common *ETV6-NTRK3* fusion, and noted the NGS method be agnostic.

For the previous submission, consultation feedback was received from one organisation, which:

* 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 (see [MSAC application 1602 PSD 2020, p13](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/5128EFED7C5AC114CA25848200015CD5/$File/1602%20Final%20PSD_Nov%202020_redacted.docx)).

PASC had previously noted the letters of support received as part of consultation feedback to it (Ratified [PICO Confirmation 1602, 2020, p22](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/5128EFED7C5AC114CA25848200015CD5/$File/1602%20Ratified%20PICO.docx)).

# Proposed intervention’s place in clinical management

The resubmission proposed four subpopulations with metastatic or locally advanced (where surgical resection is likely to result in severe morbidity) tumours based on age (adult and paediatric patients) and *NTRK* fusion frequency:

1. Paediatric patients newly diagnosed with solid tumours with high-frequency *NTRK* gene fusions that are metastatic or locally advanced
2. Adult patients newly diagnosed with solid tumours with high-frequency *NTRK* gene fusion cancer types: MASC or SBC that are metastatic or locally advanced
3. Paediatric patients newly diagnosed solid tumours with low-frequency *NTRK* gene fusions that are metastatic or locally advanced
4. Adult patients with solid tumours with low-frequency *NTRK* gene fusion cancer types: CRC, STS, NSCLC or thyroid cancer that are metastatic or locally advanced and have relapsed/refractory disease with no suitable alternate therapy.

The proposed paediatric populations were unchanged in the resubmission; however, the adult populations were redefined to only include specific tumour types.

For paediatric and adult patients with high frequency *NTRK* fusion cancer types and paediatric patients with low frequency *NTRK* fusion cancer types, the proposed clinical management algorithms were unchanged from the previous submission. The proposed clinical management algorithm for adults with low frequency *NTRK* fusion cancer types: CRC, NSCLC, STS or thyroid cancer was changed in the resubmission, primarily to delay testing until patients have relapsed/refractory disease with no satisfactory alternate therapy.

The proposed clinical management algorithms in the resubmission also indicated that treatment with larotrectinib only occurs once patients have failed multiple-line treatment options until no suitable options remain. The commentary considered that the term ‘no suitable alternate therapy available’ could be misinterpreted to mean that treatment with larotrectinib is considered more “suitable” than a standard of care (SoC) chemotherapy regimen. It would be clearer as pertaining to last line treatment if it was worded as ‘having failed or been contraindicated to all other treatment options’.

# Comparator

The nominated comparator to *NTRK* fusion testing was “no testing” for all adult and paediatric advanced stage cancer patients. This was unchanged from the original submission.

# Comparative safety

*Adverse events from testing*

No new evidence was provided for this section.

*Adverse events from changes in management*

The key issues related to comparative safety have not changed from the previous submission.

# Comparative effectiveness

*Overview of the evidence base*

Consistent with the previous submission, the approach taken in the resubmission 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 4). New literature searches identified additional studies and two new drug comparators were added for adults with low frequency *NTRK* fusion cancer types*.*

**Table 4 Summary of the linked evidence approach**

|  | **Type of evidence supplied** | **Extent of evidence supplied** | **Overall risk of bias in clinical trials** |
| --- | --- | --- | --- |
| Accuracy and performance of the test (analytical validity) | DNA- vs RNA-NGS: 4 comparative studies  FISH vs RNA-NGS: 1 comparative study  IHC vs FISH: 2 comparative studies  IHC vs RNA-NGS: 3 comparative studies  2 case-control studies  IHC vs DNA-NGS: 1 case-control study  IHC positive vs RNA-NGS or FISH: 6 cohort studies | ☒ k=4; n=34,807  ☒ k=1; n=44  ☒ k=2; n=75  ☒ k=5; n=4,982  ☒ k=1; n=78  ☒ k=6; n=13,470 | High  Low  High  Low  High  High |
| Prognostic evidence | *NTRK* fusion positive cancers: 2 prospective case-control studies, 2 retrospective cohort studies and 1 retrospective case-control study | k=5 n=5,345 | Low |
|  | Trk IHC positive cancers: 3 retrospective cohort studies and 1 retrospective case-control study | k=4 n=858 | Low |
| Change in patient management | No evidence provided | 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] | 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] | k=0 n=0 |  |
| Naïve indirect comparison | [*NTRK* fusion positive patients from 3 single-arm larotrectinib studies and SoC patients, regardless of *NTRK* fusion status, from single arms of 11 historical studies] | k=3 n=225  k=11 n=2,356  Population 1: n= 62 vs 199  Population 2: n= 23 vs 20  Population 3: n= 26 vs 208  Population 4: n= 74 vs 1,929 | High |

k = number of studies, n = number of patients; Population 1=Paediatric high frequency; Population 2=Adult high frequency; Population 3=Paediatric low frequency; Population 4=Adult low frequency.

Source: Constructed during evaluation

The resubmission presented evidence to address parts of the analytic framework as outlined in Table 5. The new evidence provided in the resubmission or during evaluation has been underlined.

**Table 5 Data availability to inform comparisons**

|  |  |  |
| --- | --- | --- |
| Proposed test vs alternate test | DNA-NGS vs RNA-NGS: 3 (plus 1 new) comparative studies  FISH vs RNA-NGS: 1 comparative study  IHC vs FISH: 2 comparative studies  IHC vs RNA-NGS: 1 (plus 2 new) comparative studies, 2 case-control studies  IHC vs DNA-NGS: 1 case-control study  IHC positive vs RNA-NGS or FISH: 6 cohort studies | |
|  | **Proposed medicine** | **Comparator medicine** |
| Biomarker test positive | LOXO-001, NAVIGATE, SCOUT single-arm studies (updated data from NAVIGATE and SCOUT; July 2020 data cutoff).  Updated pooled data across the LOXO-001, NAVIGATE, and SCOUT studies bases on new July 2020 cutoff (ePAS5 and “SAS New”) | *Exploratory analysis in* NTRK *fusion patients (N=29) from a genomic database (VOYAGER) were presented but did not inform the economic evaluation* |
| Biomarker test negative | LOXO-001 and SCOUT single-arm studies (updated data from NAVIGATE and SCOUT; July 2020 data cutoff). | No evidence presented |
| Biomarker untested | No evidence presented | Sandler et al. (2001), Mascarenhas et al. (2010), Airoldi et al. (2001), Grill et al. (2018), Wick et al. (2017), Schöffski et al. (2016), van der Graaf et al. (2012), Mayer et al. (2015), Borghaei et al. (2015), Shepherd et al. (2005), Schlumberger et al. (2015) |

Source: Sections 2B and 2D of the previous submission and the resubmission, as well as additional data identified during evaluation. New data sources in the resubmission and the commentary have been underlined.

ePAS5 includes paediatric and adult tumour types other than primary CNS with documented *NTRK* fusion (N=192, median follow-up for overall survival 24 months compared to 15.8 months for the ePAS4 (N=164) in the previous submission; SAS New includes paediatric and adult primary CNS patients with documented *NTRK* fusion tumours (N=33; median follow-up for overall survival 16.5 months compared to 6 months for the SAS3 (N=24) in the previous submission)

ePAS = extended primary analysis set; k=number of studies, n=number of patients; SAS = supplementary analysis set.

The commentary noted that 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 SoC data from historical single-arm 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.

*Prognostic evidence*

Seven new studies were identified that provided new prognostic evidence.

The commentary noted that all except two studies found at least a trend towards a poorer prognosis in *NTRK* fusion positive and/or Trk IHC positive cancers than *NTRK* wild type and/or Trk IHC negative cancers of various types. One study suggested that *NTRK* fusions did not affect the prognosis of glioblastoma patients and another study reported opposite results for different head and neck squamous cell carcinoma subtypes.

The additional studies strengthen the conclusions reached in the previous submission and commentary: the prognostic impact of *NTRK* fusions was inconclusive, as it cannot be determined if the effect size differs between cancer types, or indeed, if *NTRK* fusion cancers have a poorer prognosis in all cancer types.

*Predictive evidence*

The commentary considered that given the single-arm studies used as evidence, the treatment effect variation by *NTRK* fusion status could not be isolated from the prognostic effects or quantified in the data presented.

*Comparative analytical and clinical performance*

*NTRK* fusion testing in paediatric and adult high frequency populations

MSAC previously accepted that all paediatric patients with solid tumours and adults with high frequency *NTRK* fusion solid tumour types, MASC and SBC, should be tested using either FISH or NGS, with RNA-NGS the preferred test (MSAC application 1602 PSD 2020, pp3-4).The commentary noted that the test accuracy results and any consequences with respect to false positive and false negative test results for these patients do not differ from that reported in the previous commentary.

In summary:

* RNA-NGS performed with good quality RNA will have few false positive or false negative results and is considered to be the reference standard
* NTRK3 FISH was 100% sensitive and specific compared to RNA-NGS performed with good quality RNA in one study
  + No data are available to assess the accuracy of *NTRK1* and *NTRK2* FISH testing
  + However, some false positives will occur as the FISH test cannot distinguish between active and inactive *NTRK* gene fusions.
* DNA-NGS is less sensitive (median 90.55%) compared with RNA-NGS but is highly specific (median 99.9%)
  + The false positives are due to the *NTRK* fusions being inactive
  + The false negatives are due to the inability of the DNA-NGS test to detect all *NTRK3* fusions due to probe design limitations.

*NTRK* fusion testing in adult low frequency population

The median sensitivity and specificity values for pan-Trk IHC testing compared to RNA-NGS *NTRK* fusion testing in pan-tumour populations remain unchanged from that calculated during the previous evaluation. However, it is unlikely that these studies are appropriate for providing the benchmark accuracy for IHC triage testing in the revised population of adults with low frequency population *NTRK* fusion cancers as only 50-60% of the pan-tumour samples were from the tumour types now included: CRC, STS, NSCLC or thyroid cancer.

The commentary considered that the approach taken by the resubmission to use the sensitivity and specificity values reported in one study (Solomon et al. 2020) for the specific cancer types included in this subpopulation was flawed. While it may be reasonable to use the sensitivity values comparing pan-Trk IHC with RNA-NGS (80-87.5%; see Table 6) as they represent the testing of all positive patients included in the study cohort, it was not reasonable to use the specificity value of 100% for CRC, NSCLC and thyroid cancer as only 1.0% (76/7,493) of all RNA-NGS *NTRK* fusion negative samples from the three tumour types were tested with pan-Trk IHC. Additionally, other studies have reported false positive results in these tumour types.

Table 6 Diagnostic accuracy of pan-Trk IHC compared to RNA-NGS

| **Study ID** | **Patients/samples** | **TP** | **FP** | **FN** | **TN** | **Sens/Spec** |
| --- | --- | --- | --- | --- | --- | --- |
| Gatalica et al. (2019) | N=4,136 FFPE tissue samples of various solid cancer types from adult patients  Tumour types relevant to the resubmission.  Low frequency NTRK fusion cancers included in Population 4: 51% of all samples; NSCLC (35%), CRC (11%), STS (4%), thyroid carcinoma (0.6%)  Tumours were considered IHC positive if ≥1% of tumour cells exhibited positivity at any intensity above background. Different subcellular staining patterns were considered positive (cytoplasmic, membranous, nuclear, and perinuclear) | 21  NTRK1  7  NTRK2  8  NTRK3  6 | 166 | 7  1  1  5 | 3,942 | Sens: 75.0%  Spec: 95.6%  Sens: 87.5%  Sens: 88.9%  Sens: 54.5% |
| Hechtman et al. (2017) | N=23 patients with NTRK1, 2 or 3 rearrangements detected by MSK-IMPACT.  Tumour types relevant to the resubmission.  High frequency NTRK fusion cancers: 22% of all cases; MASC (n=4) and SBC (n=1)  Low frequency NTRK fusion cancers: 43% of all cases; CRC (n=5), lung (n=3) and sarcoma (n=2)  N=20 consecutive tumours (not described) without evidence of NTRK fusion on Archer RNA-NGS  IHC positivity was not defined but all IHC positive cases displayed cytoplasmic staining. | 21  NTRK1  8  NTRK2  2  NTRK3  6 | 0 | 1  0  0  1 | 20 | Sens:95.5%  Spec 100%  Sens: 100%  Sens: 100%  Sens: 85.7% |
| Solomon et al. (2020) | N=66 cases with NTRK structural variants identified by MSK-IMPACT  N=317 NTRK fusion negative cases  Tumour types relevant to the resubmission.  Low frequency NTRK fusion cancers: 40% of all cases; thyroid (10%), sarcoma (13%), lung (8%), colon (9%).  Positive IHC staining was defined as staining above background in at least 1% of tumour cells in any pattern including membranous, cytoplasmic, perinuclear, or nuclear. | 58  NTRK1  26  NTRK2  5  NTRK3  27  Thyroid  9  CRC  7  Lung  7  Sarcoma  8 | 60  0  0  0  10 | 8  1  0  7  2  1  1  2 | 257  27  25  24  29 | Sens:87.9%  Spec:81.9%  Sens: 96.3%  Sens: 100%  Sens: 79.4%  Sens:81.8%  Spec:100%  Sens:87.5%  Spec:100%  Sens:87.5%  Spec:100%  Sens:80.0%  Spec:74.4% |
| Zhao et al (2021) | N=357 lung adenocarcinomas that were EGFR, ALK, ROS1, KRAS, BRAF, ERBB2, RET and MET mutation negative  IHC staining was graded according to the percentage of stained tumour cells and staining intensity. The staining pattern was also identified.  13 showed cytoplasmic staining of any intensity  4 had strong-moderate cytoplasmic staining | 4 | 9 | 0 | 344 | Sens: 100%  Spec: 97.5% |
| Zhao et al (2020) | N=22 archival CMN cases (12 classic, five cellular, and five mixed)  IHC positivity was defined as moderate or strong staining. Non-specific, weak and blush-like staining was considered to be negative. | 5 | 1 | 0 | 17 | Sens: 100%  Spec: 94.4% |

CMN = FFPE = formalin-fixed paraffin-embedded; FN = false negative; FP = false positive; IHC = immunohistochemistry; MASC = mammary analogue secretory carcinoma; NGS = next generation sequencing; NTRK = Neurotrophic Tropomyosin-Related Kinase; RNA = ribonucleic acid; SBC = secretory breast carcinoma; TN = true negative; TP = true positive

*Source: Constructed during evaluation*

The commentary considered that, as both RNA-NGS and FISH have been nominated as confirmatory tests after pan-Trk IHC triage testing, the negative percent agreement (NPA) for pan-Trk IHC compared with FISH *NTRK* fusion testing could be used to estimate the proportion of IHC positive tests that are expected to be false positive (i.e. 1-NPA).

All additional studies that reported pan-Trk IHC accuracy in patients with CRC, NSCLC, STS or thyroid cancer compared with RNA-NGS or FISH were combined for each cancer type to provide a more accurate estimate for the proportion of false positive and false negative tests expected from pan-Trk IHC testing.

The commentary stated that proportion of positive IHC results that are false positive and the proportion of negative IHC results that are false negative were recalculated during the evaluation using inputs derived from the included studies and the inputs presented by the resubmission (Table 7).

**Table 7 The proportion of positive IHC results that are false positive and the proportion of negative IHC results that are false negative (true positives) in the resubmission and in the commentary**

| **Tumour type** | ***Proportion of positives IHC results that are false positive*** | | ***Proportion of negative IHC results that are false negative*** | |
| --- | --- | --- | --- | --- |
| **Resubmission** | **Recalculation during evaluation** | **Resubmission** | **Recalculation during evaluation** |
| CRC  No. to be tested = 9,766 | Prevalence = 0.3%  TP:FP = 25:0  0% are false positive | Prevalence = 0.64%  TP:FP = 59:1,213  95.39% are false positive | FN:TN = 4:9,737  0.04% are false negative | FN:TN = 4:8,490  0.05% are false negative |
| NSCLC  No. to be tested = 7,307 | Prevalence = 0.23%  TP:FP = 15:0  0% are false positive | Prevalence = 0.19%  TP:FP = 13:88  87.05% are false positive | FN:TN = 2:7,290  0.03% are false negative | FN:TN = 1:7,205  0.01% are false negative |
| Thyroid cancer  No. to be tested = 1,046 | Prevalence = 3.65%  TP:FP = 31:0  0% are false positive | Prevalence = 2.31%  TP:FP = 17:41  29.27% are false positive | FN:TN = 7:1,008  0.68% are false negative | FN:TN = 7:981  0.73% are false negative |
| STS  No. to be tested = 781 | Prevalence = 1.4%  TP:FP = 9:197  95.75% are false positive | Prevalence = 0.68%  TP:FP = 4:31  86.91% are false positive | FN:TN = 2:573  0.38% are false negative | FN:TN = 1:745  0.09% are false negative |

*Source: Constructed during evaluation*

The proportion of negative IHC results that were calculated to be false negative calculated using the inputs reported in the resubmission and derived from the included studies during evaluation were similar. Both indicated a very low proportion of false negative test results; this is due to the small number of true positive patients and the large number of true negative patients. When the proportion of false negatives compared with true positives is considered, the false negative rate is quite high (see below).

The calculated proportion of false positives using the inputs reported in the resubmission and the commentary differed greatly for CRC, NSCLC and thyroid cancer. This was largely due to the resubmission assuming 100% specificity for the pan-Trk IHC test compared to RNA-NGS in these tumour types.

Falsenegativerateforpan***-***TrkIHCtesting

MSAC considered that more information was needed on the false negative rate for IHC and the reasons for this (MSAC application 1602 PSD 2020, p3). This was not discussed in the resubmission.

It is reported in the literature that most tumours with false negative results had *NTRK3* fusions and that the pan-Trk antibody, EPR17341, which is the best-characterised and most commonly used antibody, is not sensitive enough to detect all *NTRK3* gene fusions.

The proportion of tumours that have *NTRK* fusions likely to be false negative was calculated using the estimated proportion of *NTRK* fusions likely to be *NTRK1*, *NTRK2* or *NTRK3* and the median sensitivity for that fusion type (Table 8). Approximately 40% of all adults with low frequency *NTRK* fusions have *NTRK3* fusions, and around 22% (95% confidence interval [CI] 12.5, 34.6) of all *NTRK3* fusions are likely to be the false negative.

**Table 8 Proportion of *NTRK*1/2/3 fusions in adult low frequency *NTRK* fusion cancers**

| **Tumour type** | **Proportion *NTRK1*** | **Proportion *NTRK2*** | **Proportion *NTRK3*** |
| --- | --- | --- | --- |
| CRC (k=8) | 51 (83.6%) | 1 (1.6%) | 9 (14.8%) |
| NSCLC (k=5) | 15 (57.7%) | 3 (11.5%) | 8 (30.8%) |
| Thyroid cancer (k=4) | 9 (20.5%) | 0 (0%) | 35 (79.5%) |
| STS (k=3) | 5 (62.5%) | 0 (0%) | 3 (37.5%) |
| Overall | 76 (58.0%; 95% CI 49.5, 66.1) | 4 (3.1%; 95% CI 1.2, 7.6) | 51 (38.9%; 95% CI 31, 47.5) |
| Median sensitivity of pan-Trk IHC test | 96.3% (range 87.5-100; k=3) | 100% (range 88.9-100; k=3) | 79.4% (range 54.5-85.7; k=3) |
| Proportion that would be false negative | 3/76 (3.9% of all *NTRK1*)  [95% CI 1.4, 11.0] | 0/4 (0% of all *NTRK2*)  [95% CI 0, 49] | 11/51 (21.6% of all *NTRK3*)  [95% CI 12.5, 34.6] |

Source: Table 25 of Section 2B.6.7 of the commentary

A published guideline on the diagnostic, clinical, and therapeutic aspects of *NTRK*-fusion tumours[[2]](#footnote-2), developed by three Spanish medical societies , reported that when IHC is used as a screening method, maximum sensitivity must be achieved, because once a report of IHC negativity is issued, it is unlikely that this patient will undergo another test for the detection of *NTRK* fusions. This would be the case for Australian adults with low frequency *NTRK* fusion cancers.

Definition of a positive pan-Trk IHC test result

MSAC considered that more information was needed on the definition of a positive IHC result (MSAC application 1602 PSD 2020, p3). This was not discussed in the resubmission.As there appears to be no universally accepted scoring method, the definition of IHC positivity in the included studies was checked during the evaluation to determine which was the most common.

In nine out of thirteen studies that used an IHC staining method, positive IHC staining was defined as staining above background in at least 1% of tumour cells in any pattern including membranous, cytoplasmic, perinuclear, or nuclear. In two studies, IHC positivity was defined as moderate to strong diffuse staining (i.e. in >50% of tumour cells).

There is uncertainty about the definition of a pan-Trk IHC positive tumour used in Australian laboratories. This definition used will affect the number of confirmatory tests likely to be performed:

* If IHC positivity is defined as any staining above background in <1% of tumour cells, there will be more positive test results requiring a confirmatory test, but potentially there will be fewer patients with false negative IHC results who would miss out on treatment with larotrectinib
* If IHC positivity is defined as moderate to strong staining in at least 50% of tumour cells, there will be fewer positive test results requiring a confirmatory test, but potentially more patients with NTRK fusions showing weaker staining, especially those with NTRK3 fusions, will be false negative.

*Prevalence*

The prevalence rates for all adult and paediatric high frequency and low frequency *NTRK* fusion cancer types did not change in the resubmission, except that paediatric STS was correctly reclassified as a low frequency *NTRK* fusion cancer type with a prevalence rate of 0.68%.

*Change in management in practice*

This section was unchanged from the previous submission.

*Claim of codependence*

The claim of codependence was unchanged from the previous submission.

# Economic evaluation

The resubmission presented an updated modelled economic evaluation, based on a naïve indirect comparison of single-arm studies. This compared *NTRK* testing and larotrectinib treatment in patients identified with *NTRK* fusions and SoC treatment in those without, to no testing, where all patients were treated with 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.

The structure of the model has changed since the previous submission. Previously, entry into the model was at the point of treatment, whereas in the resubmission, entry is at the point of testing. As a result, the average cost of testing across the tested population is applied, rather than the average cost to identify one *NTRK*-positive patient. The commentary considered this change was reasonable; however, the new testing component of the model was structured to allocate patients by test result (e.g. true negative, false positive, etc.) where tumour type costs and outcomes were weighted within each of these test outcome points. Regardless of the testing outcome, tumour types were weighted by the distribution of *NTRK*-positive patients which was not appropriate. Rather, costs and outcomes should have been weighted according to the distribution of tumour types in those that are found to have that test result. For example, as perfect test performance has been assumed for some tumour type groups, no false results are expected in these tumour types and so their costs and outcomes should not be included.

The test parameters (i.e. prevalence of *NTRK* fusions and test performance) used in the resubmission were generally unchanged from the previous submission (Table 9). While the lower prevalence estimate, 0.68%, was applied in paediatric STS, the modelled prevalence in the paediatric high subgroup was also weighted by the distribution of tumour types in the treated population (i.e. *NTRK*-positives) rather than the distribution of tumour types in the tested population, which the commentary considered was not appropriate.

**Table 9 Test parameters used in the economic evaluation**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Paediatric high | Paediatric low | Adult high | CRC | STS | NSCLC | Thyroid |
| Prevalence | 55.6% a | 2.2% | 90.0% | 0.3% | 1.4% | 0.2% | 3.7% |
| IHC sensitivity | − | − | − | 88.0% b | 80.0% | 87.5% | 81.8% |
| IHC specificity | − | − | − | 100.0% | 74.0% | 100.0% | 100.0% |
| IHC PPV c | − | − | − | 100.0% | 4.2% | 100.0% | 100.0% |
| NGS/FISH sensitivity | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| NGS/FISH specificity | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| Overall test performance | | | | | | | |
| Sensitivity d | 100.0% | 100.0% | 100.0% | 88.0% | 80.0% | 87.5% | 81.8% |
| Specificity e | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |

Source: Constructed during the evaluation from the ‘A3.1\_Larotrectinib\_PBACMSAC\_CEA\_June21\_resub\_6June21.xlsx’ workbook included in the resubmission*.*

Note: Shaded cells denote inputs unchanged from the previous submission.

a Weighted 61.5% IFS (90%), 38.5% STS (0.68%). A revised estimate of 34.2% is applied in analyses conducted during the evaluation. This was derived from dividing the total number of *NTRK* positives expected in this group in practice by the number of tests required to identify these patients.

b IHC sensitivity was 87.5% in the previous submission.

c (prevalence × sensitivity of IHC)/[(prevalence × sensitivity of IHC + (1 – prevalence) × (1 − specificity of IHC)]

d IHC sensitivity (if relevant) × NGS/FISH sensitivity

e NGS/FISH specificity

CRC = colorectal cancer; IHC = immunohistochemistry; NGS/FISH = next generation sequencing or fluorescence *in situ* hybridisation; NSCLC = non-small cell lung cancer; *NTRK* = neurotrophic tropomyosin receptor kinase; PPV = positive predictive value; STS = soft tissue sarcoma

The commentary noted the issues raised during the previous evaluation regarding the performance of testing remain. IHC test performance remained based on one study with small patient numbers such that the specificity reported in some tumour types (i.e. 100%) is unlikely to be reproducible in clinical practice. Given the low prevalence estimates – particularly for colorectal cancer and NSCLC – small reductions in the specificity of IHC testing will lead to substantial increases in the number of NGS/FISH tests required. The assumption of 100% test performance for NGS/FISH also remains inadequately justified, given that differences in test performance between NGS modalities have been observed and the limited data available on the performance of FISH. However the analyses were not overly sensitive to the use of plausible alternatives in these estimates.

As for the previous submission, the resubmission has not considered whether there are 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 resubmission has proposed that the timing of testing be on diagnosis of advanced or metastatic disease. In adults with low *NTRK* fusion frequency tumour types, larotrectinib treatment is not proposed for use until the later-line setting, and so some patients who are found to be *NTRK*-positive may not be eligible for larotrectinib once they progress to the later-line setting (such as poor performance status). This has not been considered in the resubmission’s model.

The results of the economic evaluation are presented for the following tumour type groups:

* Adult high *NTRK* frequency and all paediatric patients
* Specified adult low frequency *NTRK* tumour types combined
* Overall population proposed for larotrectinib treatment.

The resubmission’s base case analysis was based on the overall pooled larotrectinib data set, and so included tumour types more broadly (such as adults with low *NTRK* frequency tumour types). The commentary considered as this has limited applicability to the proposed setting, analyses are presented based on the tumour types subgroup analyses, weighted as expected in practice, and include revisions to the model, such as weighting the distribution of tumour types to reflect the tested rather than treated population (Table 10).

**Table 10 Results of the economic evaluation**

|  | ***NTRK* testing + larotrectinib in *NTRK+* and SoC in *NTRK−*** | **No testing +  SoC** | **Increment** |
| --- | --- | --- | --- |
| **Adult high *NTRK* frequency and all paediatric patients combined**  *Relevant tumour type subgroup analyses* (*weighted as per the distribution in Australian clinical practice) - revised a* | | | |
| Cost | *$redacted* | *$64,593* | *$redacted* |
| QALY gained | *3.623* | *2.712* | *0.910* |
| **Incremental cost/extra QALY gained** |  |  | ***$redacted1*** |
| **Specified adult low *NTRK* frequency tumour types combined**  *Relevant tumour type subgroup analyses* (*weighted as per the distribution in Australian clinical practice) - revised a* | | | |
| Cost | *$redacted* | *$78,294* | *$redacted* |
| QALY gained | *0.812* | *0.804* | *0.008* |
| **Incremental cost/extra QALY gained** |  |  | ***$redacted1*** |
|  |  |  |  |
| **Overall population proposed for larotrectinib treatment**  *Relevant tumour type subgroup analyses* (*weighted as per the distribution in Australian clinical practice) - revised a* | | | |
| Cost | *$redacted* | *$78,170* | *$redacted* |
| QALY gained | *0.838* | *0.821* | *0.016* |
| **Incremental cost/extra QALY gained** |  |  | ***$redacted1*** |

Source: Constructed during the evaluation from the ‘A3.1\_Larotrectinib\_PBACMSAC\_CEA\_June21\_resub\_6June21.xlsx’ workbook included in the resubmission

a The distribution of tumour types was revised to reflect the distribution in the tested population (rather than the treated population). The most conservative OS and PFS parametric models were also applied for the high *NTRK* fusion frequency tumour types. Other minor revisions to treatment costs modelled and SoC STS data.

*NTRK* = neurotrophic tropomyosin receptor kinase; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; SoC = standard of care.

*The redacted values correspond to the following ranges:*

*1 $75,000 to < $95,000*

The commentary performed sensitivity analyses on arbitrary variation in test parameters in the specified adult low frequency *NTRK* tumours combined:

* Decrease in sensitivity and specificity by 20%: ICER = $115,000 to < $135,000
* Decrease NGS/FISH specificity by 10%: ICER = $$255,000 to < $355,000.

The commentary considered that while the analyses were observed to be highly sensitive to alternative test performance assumptions explored in the resubmission, there is a low risk of these being realised in practice. Analyses were conducted during the evaluation on plausible alternate values, and the ICER was not found to be overly sensitive to these (Table 11).

**Table 11 Selected univariate sensitivity analyses performed on testing parameters and costs: specified adult low *NTRK* frequency tumour types combined**

|  | **Inc. cost** | **Inc. QALYs** | **ICER** | **%** |
| --- | --- | --- | --- | --- |
| **Base case- *commentary*** | ***$redacted*** | ***0.008*** | ***$redacted****1* |  |
| Test parameters |  |  |  |  |
| *NGS/FISH performance, median DNA-NGS performance:* 90.55% sensitivity and 99.9% specificity *(base case: 100% test performance)* | *$redacted* | *0.007* | *$redacted2* | *4%* |
| *IHC sensitivity, 88%, 96% specificity  (base case: varies by tumour type)* | *$redacted* | *0.008* | *$redacted1* | *2%* |
| Decrease adult low IHC sensitivity and specificity by 20% | *$redacted* | *0.006* | *$redacted3* | *32%* |
| Increase adult low IHC sensitivity and specificity by 20% | *$redacted* | *0.009* | *$redacted1* | *–2%* |
| Decrease NGS/FISH sensitivity and specificity by 10% | *$redacted* | *0.007* | *$redacted4* | *269%* |
| *Decrease NGS/FISH sensitivity by 10%* | *$redacted* | *0.007* | *$redacted1* | *1%* |
| *Decrease NGS/FISH specificity by 10%* | *$redacted* | *0.008* | *$redacted4* | *241%* |
| Cost of testing |  |  |  |  |
| *IHC test cost, $59.60 (base case: $74.50)* | *$redacted* | *0.008* | *$redacted1* | *–2%* |
| *FISH tests, average 3 (base case: average 2)* | *$redacted* | *0.008* | *$redacted1* | *0%* |
| Proportion of NGS tests, 0% (base case: 50%) | *$redacted* | *0.008* | *$redacted1* | *–1%* |
| Proportion of NGS tests, 100% (base case: 50%) | *$redacted* | *0.008* | *$redacted1* | *1%* |
| Cost of NGS, $600 (base case: $1,200) | *$redacted* | *0.008* | *$redacted1* | *–1%* |
| Cost of NGS, $300 (base case: $1,200) | *$redacted* | *0.008* | *$redacted1* | *–1%* |
| No cost of testing in paediatric patients | *$redacted* | *0.008* | *$redacted1* | *0%* |

Source: Compiled from Table 160, p430-432 of the commentary

*The redacted values correspond to the following ranges:*

*1 $75,000 to < $95,000*

*2 $95,000 to < $115,000*

*3 $115,000 to < $135,000*

*4 $255,000 to < $355,000*

# Financial/budgetary impacts

The resubmission presented an updated epidemiological approach to estimate the use and financial impact of listing *NTRK* fusion testing and larotrectinib treatment. The commentary noted that, as per the previous submission, the resubmission does not explicitly provide an epidemiological approach to estimate the number of patients eligible for *NTRK* fusion testing. Rather, the number of tests required to identify one patient with *NTRK* fusions has been applied 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 *NTRK* fusion 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 approach used to estimate the number of IHC tests required was generally unchanged from the previous submission, in that for each adult patient with a low *NTRK* fusion frequency tumour type who exhibited *NTRK* fusions and received larotrectinib treatment, the number of IHC tests required to identify that one true positive patient was applied. The commentary considered that this approach 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 can occur on diagnosis of advanced disease. Thus the estimates presented are likely to be underestimated. For each patient treated with larotrectinib, the resubmission estimated that 217 IHC tests were required. This was based on the *NTRK* frequency for each of the specified tumour types, weighted by the expected distribution of the tumour types in the treated population. This approach did not take into account IHC sensitivity, and so more IHC tests are required to identify one true positive patient. The MBS schedule fee applied per IHC test was $74.50 (which may not be reasonable), with an 80% level of MBS rebate assumed.

As for IHC testing, the resubmission applied an estimated number of NGS/FISH tests required to identify one *NTRK* fusion positive patient for each subgroup to the number of patients who take up larotrectinib treatment. The commentary considered that the estimates used were reasonable for the paediatric subgroups and the adults with high *NTRK* fusion frequency tumour types. For adults with low *NTRK* fusion frequency types, IHC test performance (i.e. 100%) was unlikely to be reproducible in clinical practice. Given the low prevalence estimates – particularly for colorectal cancer and NSCLC – small reductions in the specificity of IHC testing would lead to substantial increases in the number of NGS/FISH tests required. Further, as for IHC testing, as the item descriptors allow for NGS and FISH testing on diagnosis of advanced stage disease, the number of NGS/FISH tests in this subgroup may be underestimated.

Costing of NGS and FISH was consistent with the economic model, with 50% of patients receiving, on average, two FISH tests (at a proposed MBS fee of $533) or 50% receiving one NGS test (at a proposed fee of $1,200). The commentary considered that the assumption that patients would receive on average two FISH tests may not be reasonable, particularly for low frequency tumour types, where the majority of people tested would require all three genes tested. This would remain the case, even with IHC triage in adults (assuming more plausible estimates of IHC specificity). The weighted MBS fee was assumed to be $866.50. With the 80% level of MBS rebate applied, the cost to the MBS of *NTRK* fusion testing was $693.20. 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 high cost items.

The estimated use and financial impact of *NTRK* fusion testing to the MBS is summarised in Table 12.

**Table 12 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** | | | | | | |
| Adult low *NTRK* fusion frequency patients who receive larotrectinib | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| No. IHC tests required  (Redacted1per patient) | Redacted2 | Redacted2 | Redacted2 | Redacted2 | Redacted2 | Redacted2 |
| *Revised (Redacted1per patient)a* | *Redacted2* | *Redacted2* | *Redacted2* | *Redacted2* | *Redacted2* | *Redacted2* |
| No. IHC tests estimated in the November 2020 submission  (8.04 per patient) | Redacted1 | Redacted1 | Redacted3 | Redacted3 | Redacted3 | Redacted3 |
| *Revised (Redacted1 per patient)* | *Redacted4* | *Redacted4* | *Redacted4* | *Redacted5* | *Redacted5* | *Redacted5* |
| Cost of IHC testing ($59.60) | $Redacted6 | $Redacted6 | $Redacted6 | $Redacted6 | $Redacted6 | $Redacted6 |
| *Revised* | *$Redacted6* | *$Redacted6* | *$Redacted6* | *$Redacted6* | *$Redacted6* | *$Redacted6* |
| **Increased use of NGS/FISH testing** | | | | | | |
| Paediatric high *NTRK* fusion frequency patients who receive larotrectinib | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| No. NGS/FISH tests required  (Redacted1per patient) | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| Adult high *NTRK* fusion frequency patients who receive larotrectinib | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| No. NGS/FISH tests required  (Redacted1per patient) | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| Paediatric low *NTRK* fusion frequency patients who receive larotrectinib | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| No. NGS/FISH tests required  (Redacted1per patient) | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| Adults low *NTRK* fusion frequency patients who receive larotrectinib | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| No. NGS/FISH tests required  (Redacted1per patient) | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| No. NGS/FISH tests | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| No. NGS/FISH tests estimated in the November 2020 submission | Redacted1 | Redacted1 | Redacted3 | Redacted3 | Redacted3 | Redacted3 |
| Cost of NGS/FISH testing  ($693.20 per test)b | Redacted6 | Redacted6 | Redacted6 | Redacted6 | Redacted6 | Redacted6 |
| *Revised ($717.03 per test)c* | *$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 MBS item 13950** | | | | | | |
| Total infusions | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| Reduction in MBS item 13950 | Redacted3 | Redacted3 | Redacted3 | Redacted3 | Redacted3 | Redacted3 |
| *Revised d* | *Redacted1* | *Redacted1* | *Redacted1* | *Redacted1* | *Redacted1* | *Redacted1* |
| Cost offset ($89.12) | Redacted6 | Redacted6 | Redacted6 | Redacted6 | Redacted6 | Redacted6 |
| *Revised* | *$Redacted6* | *$Redacted6* | *$Redacted5* | *$Redacted6* | *$Redacted6* | *$Redacted6* |
| **Changes in use of MBS item 15100** | | | | | | |
| No. radiotherapy sessions  (28.5 per patient) | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| Reduction in MBS item 15100 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| *Revised e* | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 | Redacted1 |
| Cost offset ($39.36) | Redacted6 | Redacted6 | Redacted6 | $Redacted6 | $Redacted6 | $Redacted6 |
| *Revised* | *$Redacted6* | *$Redacted6* | *$Redacted6* | *$Redacted6* | *$Redacted6* | *$Redacted6* |
| **Total cost offsets** | **$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*** | ***$Redacted6*** |
| **Net cost to the MBS  (November 2020 submission)** | **$Redacted6** | **$Redacted6** | **$Redacted6** | **$Redacted6** | **$Redacted6** | **$Redacted6** |
| ***Revised*** | ***$Redacted6*** | ***$Redacted6*** | ***$Redacted6*** | ***$Redacted6*** | ***$Redacted6*** | ***$Redacted6*** |

Source: Constructed during the evaluation from Table 4.24, Table 4.25 and Table 4.26, pp474−475 and the ‘A4.2\_larotrectinib\_PBACMSAC\_Section4\_June21\_3June21’ workbook included in the resubmission.

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

a 1 / (weighted prevalence × weighted IHC sensitivity), where weighted prevalence was derived by dividing Redacted1 patients estimated with NTRK fusions by the Redacted4 patients eligible for later-line treatment, and weighted sensitivity was 84.6%.

b Assuming 50% undertake FISH testing, with the 80% benefit ($426.40) and 50% undertake NGS testing with the 80% benefit ($960)

c Assuming 50% undertake FISH testing, with the 80% benefit ($426.40), and 25% undertake NGS, at the 75% benefit ($900) and 25% undertake NGS at the 85% benefit, which increases above 85% due to the Greatest Permissible Gap ($1,115.30)

d The resubmission assumed that a reduction in the use of MBS item 13950 was twice the number of chemotherapy agents administered. Further, the resubmission did not consider that item 13950 can only be claimed once each time a patient presents for treatment (so irrespective of the number of agents administered or the time taken).

e The resubmission multiplied the number of services offset by two without any justification

*The redacted values correspond to the following ranges:*

*1 < 500*

*2 5,000 to < 10,000*

*3 500 to < 5,000*

*4 10,000 to < 20,000*

*5 20,000 to < 30,000*

*6 0 to < $10 million*

The net costs to the MBS were most sensitive to the incidence estimates applied, the tumour types included, the timing of *NTRK* testing, IHC specificity and cost and the split of NGS and FISH testing (Table 13).

**Table 13 Key sensitivity analyses around net financial implications analysis to the MBS**

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| --- | --- | --- | --- | --- | --- | --- |
| **Net cost to MBS** | ***$Redacted1*** | ***$Redacted1*** | ***$Redacted1*** | ***$Redacted1*** | ***$Redacted1*** | ***$Redacted1*** |
| Include all adult low frequency tumour types  (base case: only specified) | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* |
| *Allow IHC testing on diagnosis of advanced disease (base case: after failure to first-line therapy)* | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* |
| *Allow IHC and NGS/FISH testing on diagnosis of advanced disease (base case: after failure to first-line therapy)* | *$Redacted1* | *$$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* |
| *IHC specificity, maximum 96%  (base case: maximum 100%)* | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* |
| 100% patients receive NGS  (base case: 50%) | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* | *$Redacted1* |

Source: Constructed during the evaluation from the ‘A4.2\_larotrectinib\_PBACMSAC\_Section4\_June21\_3June21.xlsx’ workbook included in the resubmission.

IHC = immunohistochemistry; FISH = fluorescence in situ hybridisation; NGS = next generation sequencing

*The redacted values correspond to the following ranges:*

*1 0 to < $10 million*

# Key issues from ESCs to MSAC

| **ESCs key issue** | **ESCs advice to MSAC** |
| --- | --- |
| Evidence for diagnostic accuracy of pan-Trk IHC is weak. | The ESCs considered there were many uncertainties with the single case control study (Solomon et al. 2020) including multiple domains at high risk of bias. This resulted in little confidence in the estimates of effect size and thus the true test performance in adult patients with low-frequency *NTRK* gene fusion cancer types is unknown. |
| Assumption of perfect test performance of pan-Trk IHC is unachievable. | The ESCs noted that the resubmission assumed 100% specificity in the economic analysis which was inconsistent with the clinical evidence for some cancer types included in adult patients with low-frequency *NTRK* gene fusion cancer types. The ESCs considered that small reductions in specificity, and thereby including more false positives, would substantially increase costs of confirmatory NGS/FISH testing as it translates to large absolute numbers for the low prevalence estimates such as CRC and NSCLC. |
| Generalisability of study data | The ESCs noted that there was no study data presented for adult patients with low-frequency *NTRK* gene fusion cancer types that was generalisable to the Australian population. Thus, the ESCs considered that this meant that the PPV and NPV were unable to be calculated with validity. |
| New MBS item for pan-Trk IHC- higher fee relative to standard IHC | The ESCs considered that no clear justification was provided for the higher proposed fee for pan-Trk IHC than the standard fee for IHC using 1-3 antibodies. If MSAC supports the pan-Trk IHC positivity defined as staining above background in at least 1% of tumour cells, than the cheaper fee may be acceptable. |
| Assumption of perfect test performance of FISH and NGS is unachieveable | The ESCs noted that the comparison of FISH vs. RNA-NGS (gold standard, providing that RNA quality is optimal) was limited to 1 study (Church et al. 2018) with significant concerns with false positives and false negatives, due to worse test performance when test failures were included. The ESCs considered that FISH is not 100% sensitive and specific in usual pathology practice and noted that for RNA-NGS, the lability of RNA precludes 100% test performance. |
| Test parameters in the model | The ESCs considered that the base case estimates for test performance (i.e. NGS, FISH and IHC) were unachievable and noted that the ICER was highly sensitive to changes in test performance in adult patients with low-frequency *NTRK* gene fusion cancer types. |
| Data on prognostic effects of *NTRK* gene fusion status remains to be inconclusive | The ESCs noted that the assessment of the prognostic impact of *NTRK* fusions was inconclusive, as it cannot be determined if the effect size differs between cancer types, or indeed, if *NTRK* fusion cancers have a poorer prognosis in all cancer types. In addition, the ESCs also noted that the prognostic role of *NTRK* fusions in low prevalence cancers, such as NSCLC and CRC are unknown. |

**ESCs discussion**

The ESCs noted that the purpose of this resubmission was testing for neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions to determine eligibility for treatment with larotrectinib.

The ESCs noted that four distinct populations were proposed, the paediatric population was unchanged in the resubmission; however, the adult population was redefined to include specific tumour types:

1. Paediatric patients newly diagnosed with solid tumours with high-frequency *NTRK* gene fusions that are metastatic or locally advanced
2. Adult patients newly diagnosed with solid tumours with high-frequency *NTRK* gene fusion cancer types: mammary analogue secretory carcinoma (MASC) or secretory breast carcinoma (SBC that are metastatic or locally advanced
3. Paediatric patients newly diagnosed solid tumours with low-frequency *NTRK* gene fusions that are metastatic or locally advanced
4. Adult patients with solid tumours with low-frequency *NTRK* gene fusion cancer types: colorectal cancer (CRC), soft tissue sarcoma (STS), non-small cell lung cancer (NSCLC) or thyroid cancer that are metastatic or locally advanced and have relapsed/refractory disease with no suitable alternate therapy.

The ESCs noted several issues with the new MBS item for pan-Trk immunohistochemistry (IHC) item for adult low frequency *NTRK* gene fusion cancer types (Table 2):

* The ESCs considered that no clear justification was provided for the higher proposed fee for pan-Trk IHC ($74.50) than the standard fee for IHC using 1-3 antibodies of $59.60 (MBS item 72846). The ESCs noted that the appropriateness of the increased fee would depend on the scoring algorithm for Trk IHC positivity. If positivity is defined as any staining above background in at least 1% of tumour cells, then the cheaper fee may be more appropriate.
* The ESCs queried if ‘thyroid cancer’ needed to be more tightly defined given it is a common cancer with variable prognosis.
* The ESCs also queried the linkage between the first and second sentences and also if the Boolean logic flowed correctly and clearly across the entire item descriptor.

The ESCs considered the new MBS items for *NTRK* fusion testing using FISH or NGS for paediatric or adults with metastatic or locally advanced high-frequency tumours MASC or SBC (BBBB; DDDD, see Table 3). The ESCs noted the descriptions of the paediatric and adult populations should be in separate dot points to improve clarity.

The ESCs queried the appropriateness of the proposed fee for the new MBS items (CCCC or DDDD; see Table 3) for *NTRK* fusion testing using NGS (DNA or RNA not specified). The ESCs noted that although the proposed fee of $1,200 was consistent with previous MSAC advice (see MSAC application 1602 PSD 2020, pp5-6), this fee was higher than the suggested fee of $980 from a costing study in the Ratified PICO (see Ratified PICO Confirmation 1602, 2020, p24). In addition, the ESCs considered that the cost per NGS test may not be reasonable as only three genes need to be assessed for sequence variants.

The ESCs noted that many of the concerns of MSAC were not addressed in the resubmission, including the biological plausibility for impact of *NTRK* fusions across multiple cancer types, *NTRK* fusion prevalence across different populations, change in *NTRK* fusion prevalence as disease progresses, and establishing the prognostic value of *NTRK* fusion cancer.

The ESCs considered the seven new studies identified by the resubmission to provide prognostic evidence. The ESCs considered that the assessment of the prognostic impact of *NTRK* fusions remained inconclusive, as it cannot be determined if the prognostic effect size differs between cancer types, or indeed, if *NTRK* fusion cancers have a poorer prognosis in all cancer types. The ESCs also considered that the prognostic role of NTRK fusions in low prevalence *NTRK* fusion cancers, such as NSCLC and CRC is unknown. In addition, the ESCs queried whether the clinical place of testing and treatment was supported in these low prevalence cancer types with alternative treatment options.

The ESCs considered the evidence of analytical validity of pan-Trk IHC in adult patients with low-frequency *NTRK* gene fusion cancer types. The ESCs noted that consistent with the previous submission, IHC test performance was informed by a single case-control study with small patient numbers (Solomon et al. 2020). The ESCs noted that sensitivity was 79% for *NTRK3*, 96-100% for *NTRK1* and *NTRK2* and specificity was 100% for CRC and lung cancer but 74% for STS (see Table 6). The key uncertainty was that the risk of bias was high in multiple domains due to: patient selection was unclear, the index test was not applied to all cases and was not blinded, the reference standard was not applied to all cases and included different tests, the control group was highly selected and included cases with the reference standard, there was high drop out with results only reported from 66/87 cases, and the risk of bias due to it being an applicant-sponsored study. Due to these concerns, the ESCs considered that the risk of bias for this study was higher than as assessed by the commentary. Overall, the ESCs considered that the true test performance in this population is unknown and that the study data from an enriched US centre was not generalisable to the intended low prevalence population in Australia.

The ESCs also noted further uncertainty that IHC test performance in usual pathology practice would be affected by other issues such as different monoclonal antibodies used, different dilution titres used, test performance in subgroups of the population according to patient characteristics that may influence results is unknown, and test concordance between different laboratories is unknown.

In addition, the ESCs noted that MSAC had requested more information on the definition of a positive IHC result and the false negative rate for IHC and the reasons for this. The ESCs noted that 9/13 studies used a definition of 1% positivity threshold, 2/13 did not state a threshold, and 2/13 used a 50% positivity threshold. The ESCs noted that the weight of the evidence used a 1% positivity threshold, but considered that there was uncertainty about the definition of an IHC-positive tumour used in Australian laboratories. The ESCs also noted that the threshold of positivity could significantly impact false results; the lower 1% threshold would result in more positive test results requiring a confirmatory test, but potentially there will be fewer patients with false negative IHC results who would miss out on treatment with larotrectinib.

The ESCs noted that the evidence underpinning the diagnostic performance of FISH was limited to a single study (Church et al. 2018) with small numbers (level IV evidence) in paediatric patients with infantile fibrosarcoma. The ESCs noted that there were significant concerns with estimates for false positives and false negatives, due to worse test performance when test failures were included. The ESCs considered that FISH is not 100% sensitive and specific in usual pathology practice and noted that for RNA-NGS, the lability of RNA precludes 100% test performance. In addition, the ESCs also considered that the study population was not genersalisable to adult patients with low-frequency *NTRK* gene fusion cancer types.

Overall, the ESCs noted that, consistent with the previous submission, there continued to be limited evidence of the analytical performance of the proposed tests (i.e. NGS, FISH and IHC), in particular the evidence for adult patients with low-frequency *NTRK* gene fusion cancer types was highly uncertain and there was no study data presented that was generalisable to the intended low prevalence population in Australia. Thus, the ESCs considered that this meant that the PPV and NPV were unable to be calculated with confidence.

The ESCs noted that the resubmission 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 considered that, based on the updated data, it remained difficult to assess comparative benefits and harms from the limited clinical evidence of single-arm studies with naïve, unanchored indirect comparisons. As concluded previously, 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 while the modelled economic evaluation presented in the resubmission was restructured to allow the implications of false positive and false negative results to be analysed, the base case retained the assumption that NGS and FISH performed with 100% sensitivity and 100% specificity, which was considered unachievable in usual pathology practice. For adult patients with low-frequency *NTRK* gene fusion cancer types who require IHC testing, the ESCs noted that the resubmission assumed 100% specificity which was inconsistent with the lower estimates reported for some cancer types in Solomon et al. (2020), and was also considered unachievable. The ESCs noted that the ICER in adult patients with low-frequency *NTRK* gene fusion cancer types was highly sensitive to changes in test performance (see Table 11). In addition, the ESCs considered that small reductions in specificity of IHC testing, and thereby including false positives, would substantially increase costs of confirmatory NGS/FISH testing as it translates to large absolute numbers for the low prevalence estimates such as CRC and NSCLC.

The ESCs considered that due to the approach taken to back-calculate the number needed to test (NNT) rather than using a true epidemiological approach, the numbers and costs of pan-Trk IHC testing and NGS/FISH remained underestimates in the resubmission. The ESCs noted that, consistent with the economic analysis, the NNT to detect one pan-Trk positive case is very high in the adult low frequency *NTRK*-gene fusion cancer types which was driving up the relative cost of testing across the codependency (e.g. number needed to test could be up to 500 in NSCLC). The ESCs also noted that the net costs to the MBS were most sensitive to the incidence estimates applied, the tumour types included, the timing of *NTRK* testing, IHC specificity and the assumptions around the cost and the split of FISH testing and NGS.

The ESCs noted the National Pathology Accreditation Advisory Council (NPAAC) advice to MSAC raised several implementation issues, including: the major concern regarding quality of testing is that these mutations are rare and small laboratories may not accumulate enough positive samples to permit validation of the assay or demonstrate continuing competence in this testing; the antibodies for IHC need to be standardised and an IHC external quality assessment (EQA) program is needed, and the confirmatory testing (FISH or reverse transcription polymerase chain reaction [PCR]) must again be validated as an in house IVD, although an EQA is available locally and internationally.

The ESCs noted no consumer feedback was received for the resubmission. The ESCs recalled the previous consultation feedback received from one organisation (see Section 5).

Overall, the ESCs considered that there remained high uncertainty regarding the proposal for *NTRK* fusion testing in the resubmission, with greater consequences for adult patients with low-frequency *NTRK* gene fusion cancer types. The ESCs queried whether the proposed pan-Trk IHC testing would be feasible in Australia. The ESCs considered that most of the uncertainty related to the types of clinical evidence observed for these rare tumours such as single-arm studies with naïve, unanchored indirect comparisons, which had flow on consequences for the interpretation of the modelled ICER results.

# Other significant factors

The resubmission allowed a number of alternate funding scenarios to be considered, however all include *NTRK* testing for access to larotrectinib treatment. On the basis of previous MSAC and PBAC consideration, the main scenarios include:

* Adult high *NTRK* frequency and all paediatric patients (NGS/FISH testing);
* Specified adult low frequency *NTRK* tumour types combined (IHC followed by NGS/FISH in those that are IHC-positive); and the
* Overall population proposed for larotrectinib treatment (with proposed testing as described above).

# Applicant comments on MSAC’s Public Summary Document

Bayer welcomes the MSAC’s decision to support NTRK fusion testing to determine eligibility for treatment with larotrectinib in paediatric patients and adult patients with high-frequency NTRK fusion cancer types. Bayer will continue to work collaboratively with the MSAC, the Department of Health and Government to ensure that patients with an NTRK fusion cancer in Australia receive access to NTRK fusion testing through the MBS at the earliest opportunity.

# Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:   
[visit the MSAC website](http://www.msac.gov.au/)s

1. Strohmeier S, Brcic I, Popper H, Liegl-Atzwanger B, Lindenmann J, Brcic L. Applicability of pan-TRK immunohistochemistry for identification of NTRK fusions in lung carcinoma. Sci Rep. 2021 May 7;11(1):9785. doi: 10.1038/s41598-021-89373-3. PMID: 33963267; PMCID: PMC8105314. [↑](#footnote-ref-1)
2. Garrido P, Hladun R, de Álava E, Álvarez R, Bautista F, López-Ríos F, et al. Multidisciplinary consensus on optimising the detection of *NTRK* gene alterations in tumours. Clinical and Translational Oncology. 2021;23(8):1529-41 [↑](#footnote-ref-2)