



**Australian Government**  
**Department of Health**

# **Application Form**

**(New Request for Public Funding)**

**(Version 2.4)**

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: [hta@health.gov.au](mailto:hta@health.gov.au)

Website: [www.msac.gov.au](http://www.msac.gov.au)

# PART 1 – APPLICANT DETAILS

## 1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): N/a

Corporation name: BAYER AUSTRALIA LTD

ABN: 22 000 138 714

Business trading name: BAYER AUSTRALIA LTD

**Primary contact name:** 'REDACTED'

Business: 'REDACTED'

Mobile: 'REDACTED'

Email: 'REDACTED'

**Alternative contact name:** 'REDACTED'

Primary contact numbers

Business: 'REDACTED'

Mobile: 'REDACTED'

Email: 'REDACTED'

## 2. (a) Are you a lobbyist acting on behalf of an Applicant?

- Yes  
 No

## (b) If yes, are you listed on the Register of Lobbyists?

- Yes  
 No

## PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

### 3. Application title

Testing for Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion status in patients with locally advanced or metastatic solid tumours to determine eligibility for larotrectinib.

### 4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

NTRK gene fusions have been reported across a wide range of solid tumour types as the primary oncogenic driver in both the adult and paediatric patient populations. Although considered a rare occurrence, overall incidence and prevalence of NTRK-fusions in the population are currently unknown. It has been reported that frequency of NTRK gene fusions varies by tumour localisation, from <1% to 3% in common tumour histologies (such as lung cancer and colorectal) to approaching 100% in rare histologies such as mammary analogue secretory carcinoma and paediatric cancers such as infantile fibrosarcoma [1]. Current evidence suggests that NTRK gene fusions are implicated in <1% of all solid tumours [2-5].

NTRK-fusion cancer currently has no effective therapy targeting the primary oncogenic driver leading to the pathogenesis of this malignancy. As a result, overall survival for patients with advanced NTRK-fusion cancer is poor. Current standard of care for patients with unresectable or metastatic cancer includes cycling through multiple lines of untargeted, cytotoxic chemotherapy where efficacy decreases. In addition, chemotherapy can be associated with significant toxicity potentially causing secondary tumours and reduced quality of life.

Thus, there is a high unmet need for an effective, well-tolerated, targeted therapy for adults and children with advanced NTRK gene fusion cancer.

### 5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

This application requests new MBS items for NTRK-fusion testing, in patients with locally advanced or metastatic solid tumour to determine eligibility for larotrectinib. The proposed testing population is discussed in further detail in Part 7 of this MSAC application.

To identify NTRK-fusions, screening can be performed using immunohistochemistry under MBS items 72846, 72847, 72849 and 72850. Positive IHC results must be followed with confirmatory testing using a molecular method to verify the presence of a fusion, as overexpression of wildtype TRK proteins may also be detected using IHC [6]. There are currently two appropriate molecular testing methods that are recommended to validate positive results: fluorescence in-situ hybridisation (FISH) and RNA-based next-generation sequencing (RNA-NGS) [6, 7]. FISH is currently reimbursed under MBS items 73341 and 73344 to determine eligibility for crizotinib, ceritinib or alectinib for patients with non-small cell lung cancer. NGS is currently not MBS-funded.

### 6. (a) Is this a request for MBS funding?

- Yes  
 No

### (b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

- Amendment to existing MBS item(s)  
 New MBS item(s)

### (c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

Screening for NTRK-fusions can be routinely performed using IHC under items 72846, 72847, 72849 and 72850. New items are sought for NTRK-fusion testing using FISH and RNA-NGS.

**(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?**

- i.  An amendment to the way the service is clinically delivered under the existing item(s)
- ii.  An amendment to the patient population under the existing item(s)
- iii.  An amendment to the schedule fee of the existing item(s)
- iv.  An amendment to the time and complexity of an existing item(s)
- v.  Access to an existing item(s) by a different health practitioner group
- vi.  Minor amendments to the item descriptor that does not affect how the service is delivered
- vii.  An amendment to an existing specific single consultation item
- viii.  An amendment to an existing global consultation item(s)
- ix.  Other (please describe below):

**(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?**

- i.  A new item which also seeks to allow access to the MBS for a specific health practitioner group
- ii.  A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
- iii.  A new item for a specific single consultation item
- iv.  A new item for a global consultation item(s)

**(f) Is the proposed service seeking public funding other than the MBS?**

- Yes
- No

No other source of public funding for NTRK-fusion testing other than the MBS will be sought. However, this application will be part of a co-dependent submission where public funding on the PBS for larotrectinib will be sought for eligible patients.

**(g) If yes, please advise:**

PBS funding will be sought for larotrectinib for the treatment of adult and paediatric patients with locally advanced or metastatic solid tumours harbouring an NTRK gene fusion.

**7. What is the type of service:**

- Therapeutic medical service
- Investigative medical service
- Single consultation medical service
- Global consultation medical service
- Allied health service
- Co-dependent technology
- Hybrid health technology

**8. For investigative services, advise the specific purpose of performing the service (which could be one or more of the following):**

- i.  To be used as a screening tool in asymptomatic populations
- ii.  Assists in establishing a diagnosis in symptomatic patients
- iii.  Provides information about prognosis
- iv.  Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- v.  Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

**9. Does your service rely on another medical product to achieve or to enhance its intended effect?**

- Pharmaceutical / Biological
- Prosthesis or device
- No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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(b) If yes, please list the relevant PBS item code(s):

N/A

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

<input type="checkbox"/> Yes (please provide PBAC submission item number below) <input checked="" type="checkbox"/> No
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(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name: VITRAKVI Generic name: Larotrectinib
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11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

<input type="checkbox"/> Yes <input type="checkbox"/> No <b>Not applicable for this application.</b>
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**(b) If yes, please provide the following information (where relevant):**

Billing code(s): N/A  
Trade name of prostheses: N/A  
Clinical name of prostheses: N/A  
Other device components delivered as part of the service: N/A

**(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?**

- Yes  
 No

**Not applicable for this application.**

**(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?**

- Yes  
 No

**Not applicable for this application**

**(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):**

N/A

**12. Please identify any single and / or multi-use consumables delivered as part of the service?**

Immunohistochemistry (IHC)

The Sponsor believes that single and multi-use consumables required to screen NTRK-fusions via IHC will not change (see Q46 in Part 7 of this application).

Fluorescence in-situ hybridisation (FISH)

The Sponsor believes that the single use consumables required to conduct an NTRK FISH test would be similar as those required for the existing ROS-1 and ALK FISH testing.

Ribonucleic acid-Next-Generation Sequencing (RNA-NGS)

Single-use kits are required for preparation, processing and analysis.

Details of these consumables will be confirmed by seeking feedback from the identified pathology laboratories and presented in the full submission dossier.

## PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: Pharmaceutical product: VITRAKVI<sup>®</sup> (larotrectinib)  
Manufacturer's name: BAYER AUSTRALIA LTD  
Sponsor's name: BAYER AUSTRALIA LTD

Type of therapeutic good: IHC, FISH and RNA-NGS testing  
Manufacturer's name: N/a  
Sponsor's name: Various.

The proposed medical services for NTRK-fusion testing include: IHC, FISH and RNA-NGS.

As previously mentioned in Part 2 of this MSAC application, NTRK-fusion screening can be performed using IHC under the following MBS items: 72846, 72847, 72849 and 72850.

- (b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

Class III  
 AIMD  
 N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

Yes (If yes, please provide supporting documentation as an attachment to this application form)  
 No

- (b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

'REDACTED'

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

Yes (please provide details below)  
 No

'REDACTED'

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

Yes (please provide details below)  
 No

Currently, there are no TGA approved tests for NTRK-fusions. NTRK-fusion testing items would be regulated by the TGA as in-vitro diagnostic medical devices (IVDs). NGS Instrument/analyser IVDs are listed on the ARTG via Illumina Incorporated - Instrument/analyser IVDs.<sup>1</sup>

1

[https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=82F3B6842765289BCA257FA8004221F2&agid=\(PrintDetailsPublic\)&actionid=1](https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=82F3B6842765289BCA257FA8004221F2&agid=(PrintDetailsPublic)&actionid=1)

## PART 4 – SUMMARY OF EVIDENCE

17. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1.	Single arm, pooled analysis of the three pivotal trials (see table below).	<p>Drilon A et al. Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children</p> <p>N Engl J Med. 2018 February 22; 378(8): 731–739.</p> <p>doi:10.1056/NEJMoa1714448.</p> <p>NCT02122913 (LOXO-TRK-14001), NCT02637687 (NAVIGATE), and NCT02576431 (SCOUT).</p>	<p><b>Design:</b> Patients with consecutively and prospectively identified TRK fusion–positive cancers were enrolled into one of three protocols: a phase 1 study involving adults, a phase 1–2 study involving children, or a phase 2 study involving adolescents and adults.</p> <p><b>Intervention:</b> Larotrectinib</p> <p><b>Population:</b> Adults and paediatric patients with confirmed NTRK fusionpositive cancers, n=55</p> <p><b>Results:</b></p> <p>The median duration of response and progression-free survival had not been reached. At a median follow-up of 9.4 months, 86% of the patients with a response (38 of 44 patients) were continuing treatment or had undergone surgery that was intended to be curative.</p> <p><b>Interim data cut-off 17 July 2017</b></p>	<p><a href="https://www.nejm.org/doi/pdf/10.1056/NEJMoa1714448?articleTools=true">https://www.nejm.org/doi/pdf/10.1056/NEJMoa1714448?articleTools=true</a></p>	22 February 2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
2.	Single arm, pooled analysis of the three pivotal trials (see table below).	<p>Lassen U et al. Larotrectinib efficacy and safety in TRK fusion cancer: an expanded clinical dataset showing consistency in an age and tumor agnostic approach.</p> <p>European Society for Medical Oncology (ESMO) 2018 Congress</p> <p>NCT02122913 (LOXO-TRK-14001), NCT02637687 (NAVIGATE), and NCT02576431 (SCOUT).</p>	<p>Larotrectinib, the first selective TRK inhibitor, has demonstrated an overall response rate of 75% with a favourable safety profile in the first 55 consecutively enrolled adult and paediatric patients with TRK fusion cancer (see Dilon 2018 above). Here the clinical activity of larotrectinib is reported in an additional 35 TRK fusion cancer patients and provides updated follow-up of the primary analysis set (PAS) of 55 patients as of 19<sup>th</sup> February 2018.</p> <p><b>Interim data cut-off February 2018</b></p>	<p><a href="https://oncologypro.esmo.org/Meeting-Resources/ESMO-2018-Congress/Larotrectinib-efficacy-and-safety-in-TRK-fusion-cancer-an-expanded-clinical-dataset-showing-consistency-in-an-age-and-tumor-agnostic-approach">https://oncologypro.esmo.org/Meeting-Resources/ESMO-2018-Congress/Larotrectinib-efficacy-and-safety-in-TRK-fusion-cancer-an-expanded-clinical-dataset-showing-consistency-in-an-age-and-tumor-agnostic-approach</a></p>	21 October 2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
3.	Single arm, pooled analysis of the three pivotal trials (see table below).	<p>Lassen U et al. Larotrectinib efficacy and safety in TRK fusion cancer: an expanded clinical dataset showing consistency in an age and tumor agnostic approach.</p> <p>ESMO Congress Munich 2018</p> <p>NCT02122913 (LOXO-TRK-14001), NCT02637687 (NAVIGATE), and NCT02576431 (SCOUT)</p>	<p>Data from 30 July 2018 data cut-off from the three pivotal trials, namely LOXO-TRK-14001, NAVIGATE and SCOUT presented at ESMO Congress in Munich 2018. These findings follow on from Drilon 2018.</p> <p><b>Interim data cut-off 30 July 2018</b></p>	<p><a href="https://www.loxooncology.com/docs/presentations/Lassen_Laro_ESMO2018.pdf">https://www.loxooncology.com/docs/presentations/Lassen_Laro_ESMO2018.pdf</a></p>	19-23 October 2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
4.	Single arm, multi-centre, open-label, phase I dose escalation study.	<p>Hong D et al. Larotrectinib in adult patients with solid tumours: a multi-centre, open-label, phase I dose escalation study.</p> <p>Annals of Oncology, Volume 30, Issue 2, February 2019, Pages 325–331</p> <p><a href="https://doi.org/10.1093/annonc/mdy539">https://doi.org/10.1093/annonc/mdy539</a></p> <p>NCT02122913 (LOXO-TRK-14001).</p>	<p>Adult patients, at least 18 years of age, with a locally advanced or metastatic solid tumour refractory to standard therapies were eligible.</p> <p>Of the 67 patients who were assessable for objective response, 8 had cancers that harbour NTRK gene fusion. Following independent, central radiology review, eight (100%) of eight patients with tumours harbouring NTRK gene fusions were deemed to have had an objective response, including two with complete responses and six with partial responses.</p> <p>Median duration of response was not reached.</p>	<a href="https://academic.oup.com/annonc/article/30/2/325/5280725">https://academic.oup.com/annonc/article/30/2/325/5280725</a>	8 January 2019
5.	Summary of regulatory milestones for larotrectinib.	<p>Scott L. Larotrectinib: First Global Approval.</p> <p>Drugs (2019) 79:201–206</p> <p><a href="https://doi.org/10.1007/s40265-018-1044-x">https://doi.org/10.1007/s40265-018-1044-x</a>.</p>	<p>This article summarises the milestones in the development of larotrectinib leading to its first approval for the treatment of adult and paediatric patients with solid tumours that have NTRK gene fusion.</p>	<a href="https://link.springer.com/article/10.1007%2Fs40265-018-1044-x">https://link.springer.com/article/10.1007%2Fs40265-018-1044-x</a>	11 January 2019

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
6.	Literature review of NTRK testing methods and recommendations.	<p>Marchio C et al. ESMO recommendations on the standard methods to detect NTRK-fusions in daily practice and clinical research</p> <p>Annals of Oncology, mdz204</p> <p>doi:https://doi.org/10.1093/annonc/mdz204</p>	The European Society for Medical Oncology (ESMO) Translational Research and Precision Medicine Working Group (TR and PM WG) launched a collaborative project to review the available methods for the detection of NTRK gene fusions, their potential applications, and strategies for the implementation of a rational approach for the detection of TRK1/2/3 fusion genes in human malignancies. This paper presents recommendations for the routine clinical detection of targetable NTRK1/2/3 fusions.	<a href="https://academic.oup.com/annonc/advance-article/doi/10.1093/annonc/mdz204/5527752">https://academic.oup.com/annonc/advance-article/doi/10.1093/annonc/mdz204/5527752</a>	3 July 2019
7	Literature review of NTRK testing methods and recommendations.	<p>Penault-Llorca F et al. Testing algorithm for identification of patients with TRK fusion cancer</p> <p>J Clin Pathol 2019;72:460–467</p> <p>doi:10.1136/jclinpath-2018-205679.</p>	Testing algorithm to aid detection of these gene fusions in clinical practice and guide treatment decisions.	<a href="https://jcp.bmj.com/content/jclinpath/72/7/460.full.pdf">https://jcp.bmj.com/content/jclinpath/72/7/460.full.pdf</a>	9 May 2019

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
8.	Literature review of NTRK testing methods.	Wong D et al. Methods for Identifying Patients with Tropomyosin Receptor Kinase (TRK) Fusion Cancer  Pathology & Oncology Research  <a href="https://doi.org/10.1007/s12253-019-00685-2">https://doi.org/10.1007/s12253-019-00685-2</a> .	Literature review highlighting current testing methods including FISH, RT-PCR, IHC and NGS to inform response for small molecule TRK inhibitors such as larotrectinib.	<a href="https://link.springer.com/content/pdf/10.1007/s12253-019-00685-2.pdf">https://link.springer.com/content/pdf/10.1007/s12253-019-00685-2.pdf</a>	11 June 2019
9.	Literature review of NTRK testing methods and recommendations.	Hsiao SJ et al. Detection of Tumor NTRK Gene Fusions to Identify Patients Who May Benefit from Tyrosine Kinase (TRK) Inhibitor Therapy  J Mol Diagn 2019, 21: 553e571  doi: <a href="https://doi.org/10.1016/j.jmoldx.2019.03.008">https://doi.org/10.1016/j.jmoldx.2019.03.008</a> ).	Review of the structure of the three NTRK genes and the nature and incidence of NTRK gene fusions in different solid tumour types, and summary of the clinical data showing the importance of identifying tumours harbouring such genomic events. laboratory techniques that can be used to diagnose NTRK gene fusions in clinical samples is also outlined. Diagnostic algorithm is also proposed for solid tumours to facilitate the identification of patients with TRK fusion cancer.	<a href="https://jmd.amjpathol.org/article/S1525-1578(18)30595-6/pdf">https://jmd.amjpathol.org/article/S1525-1578(18)30595-6/pdf</a>	4 July 2019

\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.

\*\*\* If the publication is a follow-up to an initial publication, please advise.

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1.	Single arm, multi-centre, open-label Phase 1 study conducted in two parts: an initial dose escalation phase of larotrectinib in patients with advanced solid tumours will be followed by an expansion phase in patients with solid tumours having a NTRK-fusion.	LOXO-TRK-14001 NCT02122913	<p><b>Intervention:</b> Larotrectinib</p> <p><b>Population:</b></p> <ul style="list-style-type: none"> <li>• <b>Dose escalation phase:</b> patients with advanced solid tumours</li> <li>• <b>Expansion phase:</b> patients with advanced solid NTRK-fusion tumours</li> </ul> <p><b>Estimated enrolment:</b> 74</p> <p><b>Study stage:</b> Active, not recruiting</p>	<a href="https://clinicaltrials.gov/ct2/show/NCT02122913?term=LOXO-TRK-14001&amp;rank=1">https://clinicaltrials.gov/ct2/show/NCT02122913?term=LOXO-TRK-14001&amp;rank=1</a>	<b>Estimated study completion date:</b> 'REDACTED'

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
2.	Single arm, multi-centre, open-label Phase 2 study in patients with advanced solid tumours harbouring NTRK-fusion.	NAVIGATE NCT02576431	<p><b>Intervention:</b> Larotrectinib</p> <p><b>Population:</b> Patients with advanced tumours harbouring NTRK1/2/3 gene fusion who have received prior standard therapy</p> <p><b>Estimated enrolment:</b> 320 patients</p> <p><b>Study stage:</b> Recruiting</p>	<a href="https://clinicaltrials.gov/ct2/show/NCT02576431?term=Larotrectinib&amp;rank=4">https://clinicaltrials.gov/ct2/show/NCT02576431?term=Larotrectinib&amp;rank=4</a>	Estimated study completion date: 'REDACTED'
3.	Single arm, multi-centre, open-label Phase 1/2 study in patients with advanced solid or primary CNS tumours.	SCOUT NCT02637687	<p><b>Intervention:</b> Larotrectinib</p> <p><b>Population:</b></p> <ul style="list-style-type: none"> <li>• <b>Phase 1:</b> patients with advanced solid tumours</li> <li>• <b>Phase 2:</b> patients with advanced solid NTRK-fusion tumours</li> </ul> <p><b>Estimated enrolment:</b> 104</p> <p><b>Study stage:</b> Recruiting</p>	<a href="https://clinicaltrials.gov/ct2/show/NCT02637687?term=Larotrectinib&amp;rank=5">https://clinicaltrials.gov/ct2/show/NCT02637687?term=Larotrectinib&amp;rank=5</a>	Estimated study completion date: 'REDACTED'

\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

\*\*\*Date of when results will be made available (to the best of your knowledge).

## PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

**19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

- Peter MacCallum Cancer Centre
- Garvan Institute of Medical Research
- The Royal College of Pathologists of Australasia (RCPA)
- QML Pathology
- The Medical Oncology Group of Australia (MOGA)
- Australian Genomics Health Alliance

A letter of support has been requested from the above organisations and will be provided during the development of the PICO.

**20. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

RCPA; MOGA

**21. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

- Rare Cancers Australia
- The Australia and New Zealand Sarcoma Association (ANZSA)

A letter of support has been requested from the above organisation and will be provided during the development of the PICO

**22. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

N/A

**23. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

Name of expert 1: 'REDACTED'  
Telephone number(s): 'REDACTED'  
Email address: 'REDACTED'  
Justification of expertise: 'REDACTED'

Name of expert 2: 'REDACTED'  
Telephone number(s): 'REDACTED'  
Email address: 'REDACTED'  
Justification of expertise: 'REDACTED'

*Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.*

# PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

## **PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION**

### **24. Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease in terms of both morbidity and mortality:**

The *NTRK* gene family encodes for 3 TRK transmembrane proteins that hold an essential role in the development and function of the nervous system through activation of neurotrophins [8]. Under normal physiologic conditions, the TRK receptor family comprises 3 transmembrane proteins: TRKA, TRKB, and TRKC; these transmembrane proteins are encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively [8]. Currently, *NTRK* gene fusions are the best characterized abnormalities among all *NTRK* alterations occurring in cancers; therefore, they represent the main molecular alterations with known oncogenic and transforming potential [8]. With the advent of therapies available that target these *NTRK* gene fusion protein products, these gene fusions have come to be recognized as important oncogenic drivers across multiple tumour histologies [8].

The fusion of *NTRK* occurs when the gene is broken apart and the portion of the gene encoding for the kinase domain is fused back adjacent to a different gene [9]. In all reported *NTRK* gene fusions, the 3' region of the *NTRK* gene (encoding the kinase domain) is joined with a 5' sequence of a fusion partner gene by an intrachromosomal or interchromosomal rearrangement, and the resultant oncoprotein is typically a constitutively activated or overexpressed kinase, leading to activation of downstream oncogenic pathways. This constitutively active downstream signalling leads to unchecked cellular proliferation and growth through the TRK pathway, making *NTRK* gene fusions oncogenic drivers [1, 9].

There are currently no approved targeted therapies for TRK fusion cancers leading to the pathogenesis of this malignancy, and treatment recommendations regarding TRK fusion cancer have not been included within guidelines to date. Therefore, patients with known *NTRK* gene fusions are currently treated per treatment guideline recommendations for the specific tumour histology, often involving multiple lines of chemotherapy. As these patients relapse, they are moved through subsequent lines of therapy with a “one-size-fits-all” approach that provides the same treatment options to patients with that histology progressing through their disease. The major drawback to this approach is that efficacy decreases with each subsequent line of therapy. Additionally, tumours that are exposed to various ineffective therapies are likely to develop resistance mechanisms and alternate pathways to escape cell death, leading to tumour cells that are more difficult to kill. Multiple lines of therapy also increase the risk of toxicity from exposure to medications, risk of developing secondary cancers, and increased cost [10]. There is considerable room for improvement in both response rates and survival for patients with *NTRK*-fusion positive cancers, highlighting the need for *NTRK*-fusion testing and effective and safe targeted therapies.

### **25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:**

The three larotrectinib pivotal trials (LOXO-TRK-14001, NAVIGATE and SCOUT) included *NTRK* fusion positive patients spanning multiple different solid tumour types. Patients were included if they had locally advanced or metastatic disease and were relapsed/refractory (R/R) to one or more prior treatments. In addition patients were included if no standard or available curative therapy exists or would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy. An overall Response Rate of 75% was reported with high responses observed regardless of tumour type, age or TRK fusion characteristics [2] indicating the tumour-agnostic value of larotrectinib. Larotrectinib also appeared to be well-tolerated with 93% of all adverse events (AEs) being of grade 1 or 2 severity [2]. The Sponsor acknowledges the available data is based on single arm, non-comparative studies. However, conducting an RCT for this patient population would not be feasible due to the rarity of some cancers. Indeed, the FDA has stated that “Due to limited numbers of patients with *NTRK* fusion positive solid tumors, lack of equipoise in settings without available therapies, and expectations for patient cross-over (if a randomized clinical trial were conducted) it does not

appear feasible or appropriate to conduct a randomized trial of larotrectinib to demonstrate that larotrectinib improves the overall survival (OS) in patients with NTRK-fusion-positive solid tumors<sup>2</sup>.”.

The proposed testing/treatment algorithm (Figure 1) was developed in consultation with local clinicians. The Sponsor proposes NTRK-fusion testing/larotrectinib treatment in a tumour-agnostic (i.e. pan-tumour) population. This is aligned with the pivotal trial populations, proposed TGA listing and is appropriate given the rarity of NTRK gene fusions. The algorithm then considers three patient populations based on the line of therapy which takes into account differences in NTRK incidence, clinical need and currently available treatment options across different solid tumours:

1. Adult and paediatric patients with locally advanced or metastatic solid tumours with high-frequency NTRK-fusions;
2. Paediatric patients with locally advanced or metastatic solid tumours with low-frequency NTRK-fusions;
3. Adult patients with locally advanced or metastatic solid tumours with low-frequency NTRK-fusions.

In addition, the proposed testing methodology differs for tumours with high or low NTRK-fusion frequency. The testing methodology is based on the ESMO [7] and Penault-Llorca, Rudzinski [6] algorithms for NTRK-fusion testing. The algorithm also takes into account test accuracy, cost, as well as availability of currently available testing methodologies.

1. Adult and paediatric patients with locally advanced or metastatic solid tumours with high-frequency NTRK-fusion tumours

Based on the available evidence, Australian clinicians have advised that larotrectinib should be used as a first-line treatment for patients with locally advanced or metastatic cancer. This is due to the considerable efficacy and safety benefit of larotrectinib compared to current SoC chemotherapy in tumours with high NTRK fusion frequency, particularly in paediatric patients.

In order to identify patients who will benefit from larotrectinib treatment, NTRK-fusion status of the tumour needs to be identified. According to the above mentioned guidelines and the advice from Australian clinicians, NTRK-fusion testing for adult and paediatric patients with high-frequency NTRK-fusion tumours should be tested via NGS or FISH. If confirmed NTRK-fusion positive, these patients would be treated with larotrectinib. If negative, patients would receive SoC treatment.

2. Paediatric patients with locally advanced or metastatic solid tumours with low-frequency NTRK-fusion tumours

Paediatric patients with low-frequency NTRK-fusion tumours should be initially screened using IHC, as treatment of paediatric population with cytotoxic chemotherapy might be considered unethical if more effective and safe targeted therapy alternative, such as larotrectinib, is available. Clinicians have therefore advised that paediatric patients with locally advanced or metastatic cancer harbouring NTRK-fusion need to be identified and these patients should be treated first-line with larotrectinib. IHC as a screening tool for tumours with low NTRK-fusion frequency is recommended by ESMO [7] and Penault-Llorca, Rudzinski [6] in jurisdictions (such as Australia) that do not currently use NGS routinely in patients with advanced cancer.

Paediatric patients who are negative for NTRK-fusion using IHC would be treated with current SoC treatment whereas NTRK-fusion positive patients are to be subsequently tested using confirmatory NGS or FISH. Patients who are negative for NTRK-fusion via NGS or FISH would be treated with current SoC whereas positive patients should be treated with larotrectinib.

3. Adult patients with locally advanced or metastatic solid tumours with low-frequency NTRK-fusion tumours

For this sub-population, the proposed line of therapy for larotrectinib is in patients that are relapsed or refractory (R/R) to prior SoC treatment which aligns with the inclusion criteria of the pivotal trials. The Sponsor would like to seek feedback from PASC on how an acceptable (i.e. would derive clinically meaningful benefit) prior SoC treatment could be defined before larotrectinib would be considered, particularly given the

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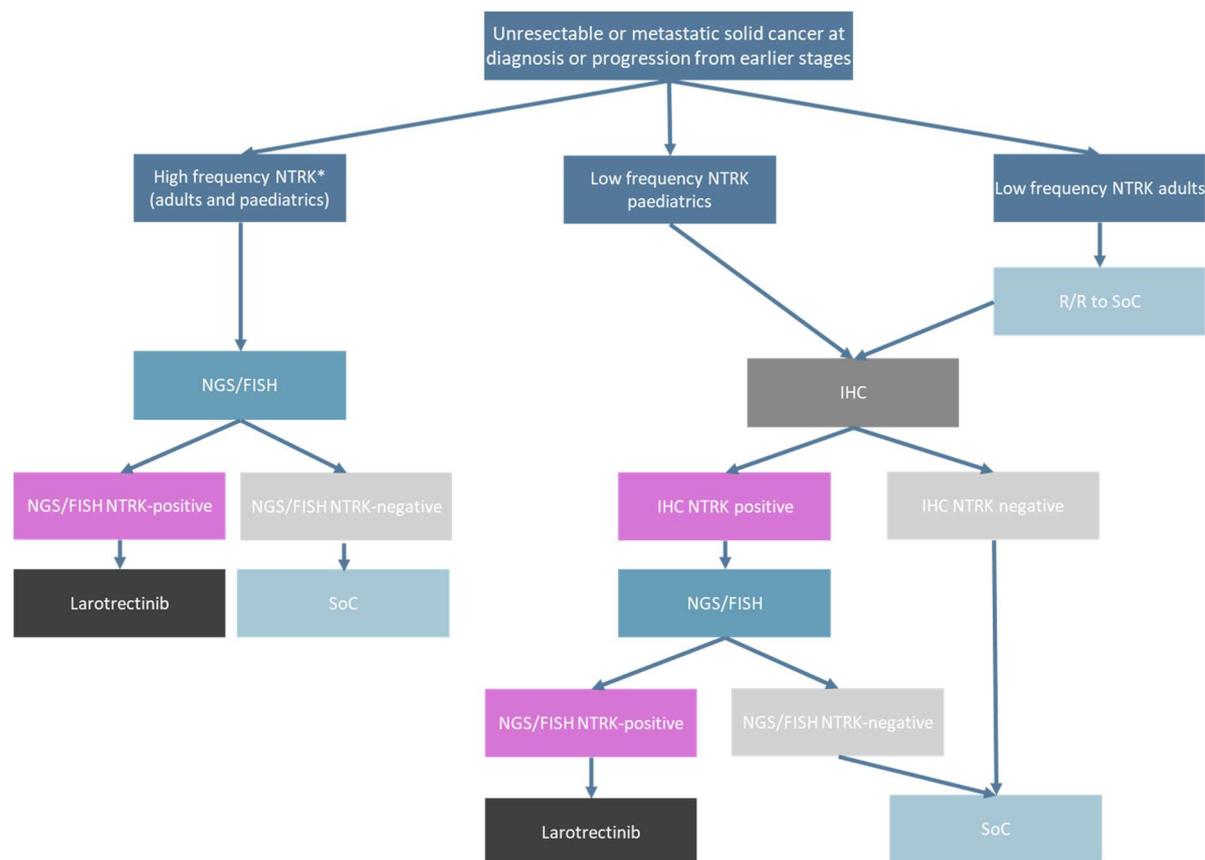
2

[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/210861Orig1s000\\_211710Orig1s000Multidisciplinary.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210861Orig1s000_211710Orig1s000Multidisciplinary.pdf)

multitude of different treatment options across different tumour types. For example, clinicians suggested that this could be based on a response rate threshold (e.g. >20%).

Patients who experience lack of response to current SoC treatment should be screened for NTRK with IHC. As with paediatric patients with low-frequency NTRK-fusion cancers, patients who are negative for NTRK-fusion using IHC should be treated with current SoC treatment whereas NTRK-fusion positive patients are to be tested using NGS or FISH. Patients who are negative for NTRK-fusion via NGS or FISH should be managed with SoC whereas positive patients should be treated with larotrectinib.

**Figure 1 Proposed testing and treatment algorithm**



\* High-frequency for the purposes of this application is defined as frequency of 80% or greater [6].

Abbreviations: FISH, fluorescence in-situ hybridisation; IHC, immunohistochemistry; NGS, next-generation sequencing; NTRK, Neurotrophic Tyrosine Receptor Kinase; R/R, relapsed or refractory; SoC, standard of care.

**26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):**

As described in Q25, newly diagnosed or patients (adults and paediatrics) with high-frequency NTRK-fusion solid tumours who have progressed to unresectable or metastatic stage undergo first-line genetic testing. Similarly, paediatrics with low-frequency NTRK-fusion solid tumours will also undergo first-line genetic testing. In contrast, adults with low-frequency of NTRK-fusion solid tumours are treated with first-line SoC treatment and only those who experience lack of response will undergo subsequent genetic testing.

The clinical management of patients prior to progression to unresectable or metastatic stage remains the same.

## **PART 6b – INFORMATION ABOUT THE INTERVENTION**

### **27. Describe the key components and clinical steps involved in delivering the proposed medical service:**

#### *NTRK-fusion testing*

##### Immunohistochemistry (IHC)

Different antibodies are available to detect TRK expression in tissue samples. There are antibodies directed against specific NTRK proteins (TRKA or TRKB) [11-13], antibodies targeting an amino acid sequence common to TRKA, TRKB, and TRKC (pan-TRK antibodies) [35-38] or a pan-TRK antibody cocktail [14]. Positive controls for IHC include the cell lines KM12 (TPM3-NTRK1) [33], MO-91 (ETV6-NTRK3) and CUTO-3.29 (MPRIIP-NTRK1) [15], and formalin-fixed, paraffin-embedded (FFPE) cell pellets can be used as external controls in immunohistochemical runs [16]. Peripheral nerves can serve as internal control, if present in the stroma. Nonneoplastic tissues (skin, blood vessels, inflammatory cells) serve as negative internal controls [17].

##### Fluorescent in-situ Hybridisation (FISH)

FISH is a commonly used method for detecting chromosomal rearrangements, and has been effectively used to detect ALK, ROS1 and RET fusions in solid tumours [7]. Either fusion or break-apart probes can be used screen for NTRK1, NTRK2 or NTRK3 fusions; nevertheless, split-apart fusion probes are invariably easier in FFPE samples. Similar to IHC, FISH cannot ascertain the 5' partner or whether the fusion results in a productive in-frame chimeric transcript [7]. Given that a multiplex FISH requires a great deal of experience in its interpretation, three separate FISH assays would have to be run in parallel, which becomes expensive and time consuming. FISH, however, can be very effective at identifying the presence of the ETV6-NTRK3 fusion gene in the tumour types where it is highly prevalent [7].

##### Next-Generation Sequencing (NGS)

NGS provides a precise method to detect NTRK gene fusions, with high sensitivity and specificity compared with other testing methods [18]. An advantage of NGS is that multiple oncogenic events in addition to NTRK gene fusions can be identified from a single tumour sample [18]. A wide variety of NGS-based approaches are available for fusion testing with the primary distinguishing factor being whether they are RNA- or DNA-based [19]. Access to NGS in a clinical setting may be limited as availability of this technique varies between states in Australia.

#### *VITRAKVI® (larotrectinib) treatment*

Larotrectinib is an orally bioavailable, ATP-competitive, potent, and highly selective TRK inhibitor that was rationally designed to avoid activity with off-target kinase. The target for larotrectinib is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by NTRK1, NTRK2, and NTRK3 genes, respectively.

In-frame gene fusion events resulting from chromosomal rearrangements of the human genes NTRK1, NTRK2, and NTRK3 lead to the formation of oncogenic TRK fusion proteins. These resultant novel chimeric oncogenic proteins are aberrantly expressed, driving constitutive kinase activity and subsequently activating downstream cell signalling pathways involved in cell proliferation and survival leading to TRK fusion cancer. Larotrectinib demonstrated potent inhibition of TRK proteins and inhibition of proliferation of tumour cells in a concentration-dependent manner.

Eligibility for PBS treatment with larotrectinib is proposed in solid-tumour patients, both adults and paediatrics with confirmed NTRK-fusions. This is in line evidence across the three clinical trials (LOXO-TRK-14001, NAVIGATE and SCOUT).

Larotrectinib is administered as capsules unless patients could not swallow capsules, in which case a liquid formulation will be available. The proposed dosage is 100mg for adults and paediatrics with body surface area (BSA)  $\geq 1 \text{ m}^2$  or 100 mg/m<sup>2</sup> for paediatrics with BSA  $< 1 \text{ m}^2$  administered orally twice a day until disease progression or the occurrence of unacceptable AEs.

### **28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?**

Registered trademarks may be held by various commercial kits used at stages of the testing process for example for DNA extraction, quality assurance, quantification, PCR amplification, as well as the NGS platform itself.

**29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?**

The tumour testing approach to identify NTRK-fusions via NGS, FISH or IHC is a new approach for solid tumours. However, clinicians routinely test for other oncogenic drivers such as EGFR.

**30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):**

Each patient would only require one NGS or FISH test to identify the NTRK-fusion status of their tumour. It is unlikely that a patient would require more than one NTRK-fusion test over their life.

**31. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:**

No other medical services or healthcare resources need to be delivered at the same time as NTRK-fusion testing.

**32. If applicable, advise which health professionals will primarily deliver the proposed service:**

NGS testing to identify NTRK-fusions should be conducted and the results interpreted and reported by suitably qualified and trained molecular pathologists. Testing should be conducted in specialist laboratories holding the appropriate accreditation i.e. NATA and registration for this diagnostic testing procedure.

**33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:**

N/A

**34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:**

Testing to identify NTRK-fusions in patients with advanced solid tumour should be based on a referral request from a specialist or consultant physician i.e. specialist oncologist or paediatrician.

**35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:**

Testing to NTRK-fusions via NGS should be conducted by NATA-accredited laboratories and the results interpreted and reported by suitably qualified and trained pathologists.

**36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):**

<input type="checkbox"/> Inpatient private hospital (admitted patient)
<input type="checkbox"/> Inpatient public hospital (admitted patient)
<input type="checkbox"/> Private outpatient clinic
<input type="checkbox"/> Public outpatient clinic
<input type="checkbox"/> Emergency Department
<input type="checkbox"/> Private consulting rooms - GP
<input type="checkbox"/> Private consulting rooms – specialist
<input type="checkbox"/> Private consulting rooms – other health practitioner (nurse or allied health)
<input type="checkbox"/> Private day surgery clinic (admitted patient)
<input type="checkbox"/> Private day surgery clinic (non-admitted patient)
<input type="checkbox"/> Public day surgery clinic (admitted patient)
<input type="checkbox"/> Public day surgery clinic (non-admitted patient)
<input type="checkbox"/> Residential aged care facility
<input type="checkbox"/> Patient’s home
<input checked="" type="checkbox"/> Laboratory
<input type="checkbox"/> Other – please specify below

**(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:**

N/A
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**37. Is the proposed medical service intended to be entirely rendered in Australia?**

<input checked="" type="checkbox"/> Yes
<input type="checkbox"/> No – please specify below

**PART 6c – INFORMATION ABOUT THE COMPARATOR(S)**

**38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):**

The nominated comparator is 'no test' + SoC administered to all patients.

Given the multitude of comparators and treatment settings, the Sponsor would like to seek feedback from PASC on a practical and pragmatic way of making this comparison, in light of the single arm nature of the studies, number of comparators/settings, etc.

There is unlikely to be trial evidence relating to the clinical utility of larotrectinib in this patient population i.e. change in clinical practice after PBS listing. However, it is expected the uptake rate of larotrectinib will be high given the considerable benefit of larotrectinib in this patient population in regards to efficacy and safety compared to SoC chemotherapy.

There is also limited efficacy evidence in NTRK-negative patients, making this comparison difficult and the Sponsor would like to seek PASC advice on how to address this limitation. It should be noted that during the phase I LOXO-TRK-14001 trial, following independent review, it was found that all patients with tumours harbouring NTRK gene fusion were deemed to have an objective response whereas patients with tumours that did not harbour NTRK gene fusion did not show response to larotrectinib [20]. In addition, an argument of biological plausibility should also be considered i.e. larotrectinib targets aberrantly expressed, TRKA, TRKB and TRKC proteins which drive constitutive kinase activity and subsequently activating downstream cell signalling pathways involved in cell proliferation and survival and thus leading to TRK fusion cancer. Since this activity is not present in NTRK-fusion negative cancers, it is plausible to infer that larotrectinib will be an ineffective treatment.

The Sponsor is also aware that the TRK inhibitor entrectinib is under consideration by the FDA. Of note, entrectinib has broader TRK inhibitory activity (ROS1, ALK, NTRK) and therefore, likely have a different efficacy and safety profile.

**39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?**

Yes (please list all relevant MBS item numbers below)

No

**40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):**

The nominated comparator is 'no NTRK-fusion test' and SoC treatment. The clinical management pathway of this patient population (newly diagnosed or patients with solid tumours who have progressed to unresectable or metastatic stage) from testing to treatment is described in Q25 and shown in Figure 1.

Broadly, the SoC for newly diagnosed or patients with solid tumours who have progressed to unresectable or metastatic disease stage is radiotherapy or systemic chemotherapy, commonly in combinations. For some tumour types, immunotherapies are recommended. The choice of treatment is also dependent on prior treatment, and the ability of the patient to tolerate treatment. SoC treatment may not be well established for some rare cancers.

In addition to drug and drug administration cost, healthcare resources associated with treatment may include the management of drug-related toxicities, ongoing disease management costs.

**41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?**

- In addition to (i.e. it is an add-on service)
- Instead of (i.e. it is a replacement or alternative)

**(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:**

All eligible patients (see Q25) will be tested for NTRK-fusion instead of not being tested. After confirmed NTRK-fusion, larotrectinib will be used instead of standard of care treatment in these patients. Patients who are confirmed NTRK-fusion negative will be treated with standard of care therapy.

**42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):**

If patients are found to be NTRK-fusion positive, they would receive treatment with larotrectinib (100mg for adults and paediatrics with BSA  $\geq 1 \text{ m}^2$  or 100 mg/m<sup>2</sup> for paediatrics with BSA  $< 1 \text{ m}^2$ ) administered orally twice a day until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs (see Appendix for further detail on dosage regimen. All other patients would receive SoC.

Based on the available evidence, treatment with larotrectinib may delay disease progression, offer high response rates and potential opportunity for curative surgery and reduce overall mortality with a superior safety profile. Therefore, healthcare resource utilisation in the following areas could potentially be reduced:

- Adverse event related treatment;
- Ongoing disease management resource utilisation;
- Post-progression therapy; and
- Palliative care costs.

**PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME**

**43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):**

The overall clinical claim is that the proposed co-dependent technologies, namely NTRK-fusion testing and larotrectinib are superior in terms of comparative effectiveness versus the main comparator, no testing with SoC treatment in patients with locally advanced or metastatic NTRK-fusion solid tumours.

**44. Please advise if the overall clinical claim is for:**

- Superiority
- Non-inferiority

**45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:**

**Safety Outcomes**

Safety and tolerability of larotrectinib treatment assessed by AEs, physical examinations, laboratory findings, and vital signs.

**Clinical Effectiveness Outcomes**

**Drug outcomes**

Objective response rate (ORR)

Overall survival (OS)

Progression-free survival (PFS)

Partial response (PR)

Complete response (CR)

Health-related quality of life (HRQoL)

**Test outcomes**

*Trial based (evidentiary standard) analytical performance:*

Sensitivity

Specificity

Positive predictive value (PPV)

Negative predictive value (NPV)

*Clinical utility of test:*

Prognostic effect of NTRK-fusion in patients with locally advanced or metastatic solid tumours.

Treatment effect modification of larotrectinib in patients with locally advanced or metastatic confirmed NTRK-fusion solid tumours.

*Other test-related considerations:*

Re-biopsy rates

Test turn-around time

Estimated number of patients being tested

Number needed to test

Cost of testing per patient

## PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

### 46. Estimate the prevalence and/or incidence of the proposed population:

As it is assumed that all solid tumour patients who have confirmed NTRK-fusion will be eligible for larotrectinib, the following epidemiological estimates refer to the eligible testing population. The Sponsor acknowledges that there are high levels of uncertainty associated with these estimates and will provide more robust estimates for the MSAC/PBAC co-dependent submission. These current estimates are intended to be indicative.

Due to the lack of this data across all different solid tumour types, late-stage cancer (locally advanced or metastatic) is approximated by using yearly cancer deaths as a proxy as sourced from the Cancer in Australia 2019 Australian Institute of Health and Welfare report [21]. Estimated mortality for all solid cancers combined is reported to be 46,225 in 2019 [21]. The prevalence of NTRK-fusions varies according to cancer type from 0.31% for more common cancer types (Okamura et al 2019) to 90-100% in some rare cancers. TRK-fusions were observed in 0.31% of adult cancers and 0.34% of paediatric cancers. Assuming an overall prevalence of 1% NTRK fusion positive tumours, it is estimated that there will be 462 late-stage, NTRK-fusion cancer patients annually that would be eligible to be treated with larotrectinib (i.e. 462 patients are confirmed true-positive NTRK-fusion cancer patients).

To estimate the number of patients that would be tested for NTRK-fusion, it is also necessary to estimate the number of patients that are eligible for testing that would have tested negative and not be eligible for larotrectinib treatment (i.e. number needed to test).

The estimated 163 patients that are confirmed NTRK fusion positive consist of patients with tumour types with high NTRK fusion frequency (defined as occurring in  $\geq 80\%$  tumours by Penault-Llorca, Rudzinski [6]) and tumour types with low NTRK-fusion frequency. This is relevant as the testing algorithm differs according to the patient's cancer and its frequency of NTRK-fusion (details regarding NTRK testing algorithm is provided as an attachment).

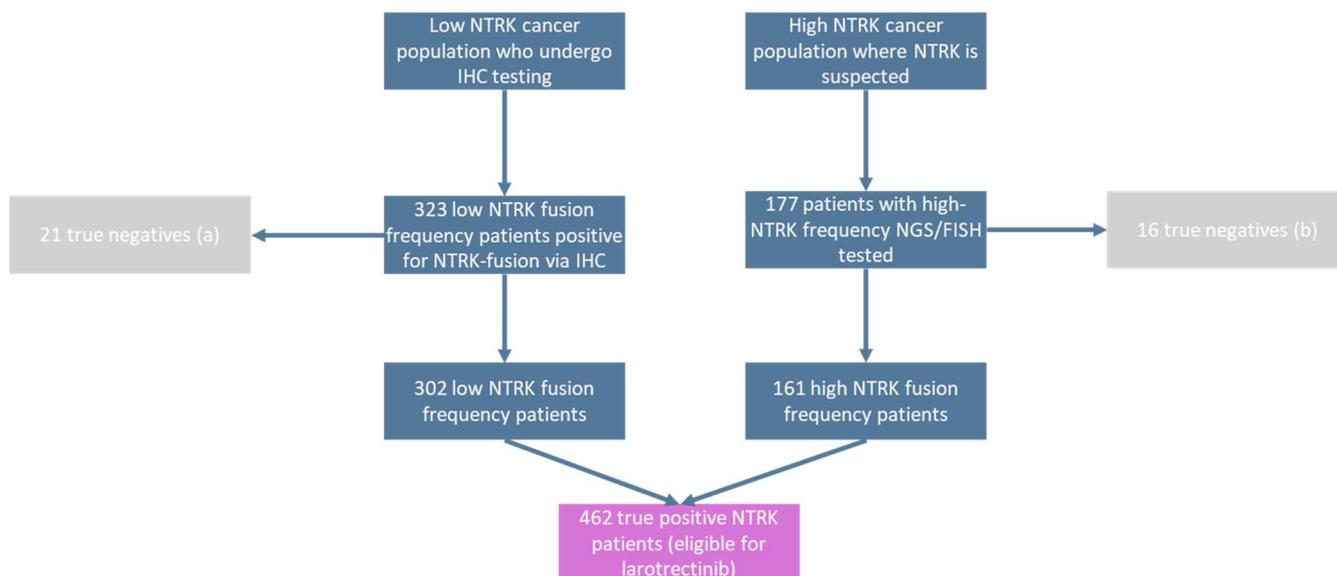
In the extended primary analysis set across the three pivotal larotrectinib trials (LOXO-TRK-14001, NAVIGATE and SCOUT), approximately 35% of the NTRK-fusion cancer patients had cancers with high-frequency of NTRK-fusions with the remaining 65% had cancers with low-frequency of NTRK-fusion. Using this distribution, it is estimated that there will be 161 NTRK-fusion cancer patients have cancers with high NTRK frequency, and 302 NTRK-fusion cancer patients have cancers with low NTRK-frequency per year in Australia.

Across all cancers of high-frequency of NTRK-fusion, it is proposed that patients are tested up-front with NGS or FISH. If it is assumed that approximately 90% of these patients would test positive for NTRK-fusion and be eligible for larotrectinib patients, then an additional 10% of patients would have been tested for NTRK-fusion with a negative result. Therefore, it is estimated that 177 patients in with high-frequency NTRK-fusion tumours would be tested with NGS or FISH – 161 would be NTRK-fusion positive and are eligible for larotrectinib and 16 would be NTRK-fusion negative and are not eligible for larotrectinib.

Across all cancers with low-frequency of NTRK-fusion, all patients are initially screened using IHC, and only those who are positive using this test are subsequently tested using NGS. It is estimated that the false positive rate for IHC may as high as 7% (lower-bound specificity reported at 93% [22]). Therefore, in addition to the 302 confirmed positive patients that would be eligible for larotrectinib patients, there would be an additional 21 patients that would be subsequently tested for NTRK-fusion with NGS/FISH and have a negative result. Therefore, it is estimated that 323 patients with low-frequency NTRK-fusion tumours would be tested with NGS or FISH– 302 would be NTRK-fusion positive and are eligible for larotrectinib and 21 would be NTRK-fusion negative and are not eligible for larotrectinib. Therefore, a total of approximately 499 suspected NTRK-fusion positive patients require NGS/FISH testing to determine true-positives and thus eligibility for larotrectinib per year. A summary of the methodology discussed above is shown in Figure 2.

The number of patients screened with IHC has not been estimated given that IHC testing is currently reimbursed on the MBS. It is not expected that IHC utilisation will significantly change if screening is introduced for NTRK-fusions. This is because it is expected that patients who have late-stage cancer are already been screened for different types of mutations using IHC. IHC screening for NTRK-fusion would simply involve adding TRK specific antibodies to the IHC testing panel.

**Figure 2 Testing and treatment utilisation estimates**



- a) False positive rate of IHC NTRK testing estimated at 7% (1 minus specificity of 93% [22])
- b) Assuming 10% of high frequency NTRK fusion tumour patients collectively are NTRK-negative

Individual components may not sum to the total amount due to rounding errors

**47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:**

It is expected that testing to determine NTRK-fusion status would be conducted only once per patient.

**48. How many years would the proposed medical service(s) be required for the patient?**

Tissue testing to determine NTRK-fusion status is not required for routine monitoring of a patient. It is expected that all patients should only require testing once to detect NTRK-fusion.

**49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:**

See question 46.

**50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of ‘leakage’ to populations not targeted by the service:**

It is not anticipated that there would be any supply or demand issues as the overall number of patients requiring testing to detect NTRK-fusions is manageable even if the number of laboratories conducting testing does not increase. Risk of leakage is expected to be low given the specific details of the proposed item descriptor.

A more detailed utilisation analysis will be presented in the co-dependent MSAC/PBAC submission.

## PART 8 – COST INFORMATION

### 51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

The current cost of IHC ranges from \$59.60 to \$101.35 per test, depending on the number of antibodies. This figure is not anticipated to change with the addition of eligibility screening for larotrectinib for patients with NTRK-fusion.

The current cost of FISH is \$400 (MBS items: 73341 and 73344).

NGS is not currently listed on the MBS. The cost of NGS can vary significantly depending on the number of targets included. The Sponsor would like PASC to advise on how to appropriately cost NGS for NTRK gene fusion.

### 52. Specify how long the proposed medical service typically takes to perform:

For a standard EGFR mutation test, the time taken in a laboratory to perform the test is shown below.

- FISH: 1-2 days
- NGS: 5-7 Days

### 53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Due to the differences in testing algorithm for this patient population (see Q25), 2 item descriptors for each type of test are proposed.

#### FISH

#### Category 6 – Pathology services

**Proposed item descriptor:** The following draft MBS item descriptor is based on the proposed testing algorithm for NTRK-fusion, in which adults with tumours harbouring NTRK-fusion at low-frequency have an IHC pre-screen, followed by confirmatory NTRK FISH testing:

Fluorescence in-situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic NTRK-fusion cancer, with documented evidence of TRK-A/B or C immunoreactivity by immunohistochemical (IHC) examination, requested by a specialist or consultant physician to determine if requirements relating to NTRK-fusion for access to larotrectinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Fee: \$400.00 Benefit: 75% = \$300.00 85% = \$340.00

#### Category 6 – Pathology services

**Proposed item descriptor:** The following draft MBS item descriptor is based on the proposed testing algorithm for NTRK-fusion, in which adults and paediatrics with tumours harbouring NTRK-fusion at high-frequency or paediatrics with tumours are tested with NTRK FISH:

Fluorescence in-situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic NTRK-fusion cancer, requested by a specialist or consultant physician to determine if requirements relating to NTRK-fusion for access to larotrectinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Fee: \$400.00 Benefit: 75% = \$300.00 85% = \$340.00

**Category 6 – Pathology services**

**Proposed item descriptor:** The following draft MBS item descriptor is based on the proposed testing algorithm for NTRK-fusion, in which adults with tumours harbouring NTRK-fusion at low-frequency have an IHC pre-screen, followed by confirmatory NGS testing:

RNA Next-generation Sequencing test of tumour tissue from a patient with locally advanced or metastatic NTRK-fusion cancer, with documented evidence of TRK-A/B or C immunoreactivity by immunohistochemical (IHC) examination, requested by a specialist or consultant physician to determine if requirements relating to NTRK-fusion for access to larotrectinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Fee: \$TBC Benefit: 75% = \$TBC 85% = \$TBC

**Category 6 – Pathology services**

**Proposed item descriptor:** The following draft MBS item descriptor is based on the proposed testing algorithm for NTRK-fusion, in which adults and paediatrics with tumours harbouring NTRK-fusion at high-frequency are tested with RNA-NGS:

RNA Next-generation Sequencing (RNA-NGS) test of tumour tissue from a patient with locally advanced or metastatic NTRK-fusion cancer, requested by a specialist or consultant physician to determine if requirements relating to NTRK-fusion for access to larotrectinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Fee: \$TBC Benefit: 75% = \$TBC 85% = \$TBC

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# Appendix

## **Dosage regimen**

### Adults

The recommended dose of Vitrakvi in adults is 100 mg taken orally, twice daily until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

### Paediatric

Dosing in paediatric patients is based on body surface area (BSA). The recommended dose of Vitrakvi in paediatric patients (1 month to 18 years) is 100 mg/m<sup>2</sup> taken orally, twice daily with a maximum of 100 mg per dose until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

### Administer Vitrakvi with or without food.

If the patient vomits after taking a dose, the patient should not take an additional dose to make up for vomiting. If a dose is missed, the patient should not take two doses at the same time to make up for a missed dose. Patients should take the next dose at the next scheduled time.