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# Regulatory Approval and Economic Evaluation of Tumor-Agnostic Therapies: A Comparative Study of Larotrectinib and Entrectinib

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**KEYWORDS**

Tumor-agnostic therapy, Larotrectinib, Entrectinib, Health technology assessment, Economic evaluation, Basket trial, Real-world data, Cross-country comparison

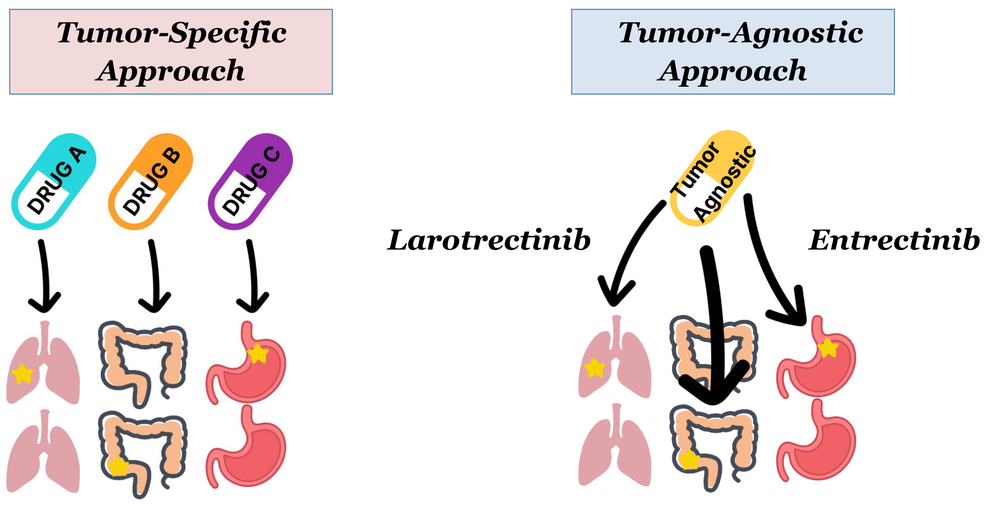
## BACKGROUND

### Concept of Tumor-Agnostic Therapies

- **Tumor-agnostic therapies** are approved based on **specific molecular alterations**, rather than the tumor's anatomical origin.
- The **neurotrophic tyrosine receptor kinase (NTRK) gene fusion** is one of the most representative biomarkers, detected across multiple solid tumors such as lung, thyroid, and soft-tissue sarcoma, though its overall **prevalence is <1%**.
- **NTRK fusions lead to constitutive activation of TRK signaling pathways, promoting uncontrolled cell proliferation and survival**, which drives oncogenesis regardless of tissue type.
- **Larotrectinib** and **entrectinib**, both selective **tropomyosin receptor kinase (TRK) inhibitors**, were the **first tumor-agnostic targeted therapies** approved globally between **2018 to 2020** for **NTRK fusion–positive solid tumors**.

### Challenges for HTA and Economic Evaluation

- Evidence for these therapies originates from **single-arm basket trials** (*NAVIGATE, SCOUT, STARTRK-1/2*) involving **small and heterogeneous patient populations**.
- The **rarity of NTRK fusions** makes it difficult to generate comparative or long-term survival data, leading to **high uncertainty in ICER estimation**.
- Traditional **HTA and economic evaluation (EE) frameworks**, developed for tumor-specific indications with larger populations, are poorly suited to assess such rare biomarker-defined therapies.




## OBJECTIVES

To compare **regulatory approval and reimbursement strategies** for **larotrectinib** and **entrectinib** in **United Kingdom, Australia, Canada, and Republic of Korea** focusing on **EE approaches** and **HTA decision-making frameworks** applied to tumor-agnostic therapies.

## METHODS

| Country | Regulatory Agency | Reimburesment Agency |
|---|---|---|
| United Kingdom | MHRA Regulating Medicines and Medical Devices | NICE National Institute for Health and Care Excellence |
| Australia | TGA Health Safety Regulation | PBS The Pharmaceutical Benefits Scheme — Accessed by PBAC |
| Canada | Health Canada | cadth Canada's Drug and Health Technology Agency |
| Republic of Korea | Ministry of Food and Drug Safety | HIRA HEALTH INSURANCE REVIEW & ASSESSMENT SERVICE |

- Regulatory, HTA, and reimbursement information for **larotrectinib** and **entrectinib** were collected from official publications of major agencies across eight countries.
- Sources included **regulatory approvals, HTA assessment reports, and reimbursement databases**.
- A **comparative analysis** was conducted focusing on **approval pathways, HTA interpretation, EE approach, and reimbursement outcomes.**

## RESULTS

| Country | Pro-duct | Regulatory authorization | HTA recommendation | EE approach | Indication scope | Time gap (approval → reimbursement) |
|---|---|---|---|---|---|---|
| UK | L | MHRA (adopting EMA-authorized, Sep 2019) | NICE TA630 (May 2020) | • Basket-trial evidence used for cost-utility analysis, ICER highly uncertain, **real-world data collection included under CDF managed access**. | Adult + Pediatric: NTRK fusion–positive solid tumors | 8 months |
| | E | MHRA (adopting EMA-authorized, Jul 2020) | NICE TA644 (Aug 2020) | | | 1 month |
| Australia | L | TGA provisional approval (Sep 2020) | PBAC (Jul 2022) | • Basket-trial evidence used, surrogate-based cost-utility analysis, ICER uncertainty noted. | Adult + Pediatric: solid tumors with confirmed NTRK fusion | 22 months |
| | E | TGA provisional approval (May 2020) | PBAC (2020-22) multiple evaluations | • Basket-trial evidence used, cost-utility analyses **re-evaluated multiple times**, ICER remained very uncertain. | Adult only: ROS1-positive NSCLC (**NTRK fusion tumor-agnostic not listed**) | > 2 years; restricted indication only |
| Canada | L | Health Canada NOC/c (Jul 2019) | CADTH (Sep 2021) | • Model-based EE using basket-trial inputs, ICER considered non-interpretable, conditional reimbursement with **major price reduction**. | Adult + Pediatric: NTRK fusion–positive solid tumors | 26 months |
| | E | Health Canada NOC/c (Feb 2020) | CADTH (Nov 2022) | | Adult only: NTRK fusion–positive solid tumors | 33 months |
| Korea | L | MFDS approval (May 2020) | HIRA (Apr 2022) | • **EE exemption** under ultra-rare disease policy, **ICER not calculated**, reimbursement based on clinical need and budget impact. | Adult + Pediatric: NTRK fusion–positive solid tumors | 23 months |
| | E | MFDS approval (Apr 2020) | | | | 24 months |

**Note:** L, Larotrectinib; E, Entrectinib. (Information verified as of October 2025)

## CONCLUSION

- **Larotrectinib** and **Entrectinib** were approved on **small, single-arm basket trials**, resulting in substantial **uncertainty in cost-effectiveness**.
- Despite relying on the same evidence, countries adopted **different HTA approaches** and reached **divergent reimbursement outcomes**.
- The UK applied managed access via the CDF, Australia listed only larotrectinib for tumor-agnostic use after formal cost-utility evaluation, Canada implemented conditional reimbursement with major price reductions, and Korea granted coverage under EE exemption for ultra-rare disease.
- These findings reveal **methodological limitations** of current HTA systems in evaluating **tumor-agnostic therapies**.
- As new **biomarker-driven therapies** such as RET, BRAF, MSI-H, and TMB-H continue to emerge, it will be increasingly important to **establish clear and consistent evaluation methodologies** to ensure fair and sustainable access across health systems.