PATHWAYS TO PRECISION

# A global landscape analysis of access to tumour-agnostic therapies

CONTRACT RESEARCH REPORT
December 2025

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# List of acronyms and abbreviations

**AEMPS:** Agencia Española de Medicamentos y Productos Sanitarios

**AIFA:** Agenzia Italiana del Farmaco

**ANS:** National Agency of Supplementary Health

**ANVISA**: Agência Nacional de Vigilância Sanitária

**BHM:** Bayesian Hierarchical Model

**C2H**: Center for Outcomes Research and Economic Evaluation for Health

**C-CAT:** Centre for Cancer Genomics and Advanced Therapeutics

**CDA-AMC**: Canada's Drug Agency-L'Agence des médicaments du Canada

**CDF:** Cancer Drugs Fund

**CEESP**: Committee of Economic Evaluation and Public Health

**CGP:** Comprehensive Genome Profiling

**CONITEC:** Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde

**dMMR:** Mismatch Repair-deficient

**EMA:** European Medicines Agency

**ESMO:** European Society for Medical Oncology

**ETAC-S:** ESMO Tumour-Agnostic Classifier and Screener

**FDA:** Food and Drug Administration

**FISH:** Fluorescent In-situ Hybridisation

**G-BA:** Gemeinsamer Bundesausschuss

**HAS:** Haute Autorité de Santé

**HTA:** Health Technology Assessment

**ICER**: Institute for Clinical and Economic Review

**IDF:** Innovative Drugs Fund

**IHC:** Immunohistochemistry

**INESSS:** Institut national d'excellence en santé et en services sociaux

**IQWIG:** Institute for Quality and Efficiency in Healthcare

**ISH:** In-situ Hybridisation

**ITC:** Indirect Treatment Comparisons

**JCA:** Joint Clinical Assessment

**MEA:** Managed Entry Agreement

**MHLW:** Ministry of Health, Labour and Welfare

**MSAC:** Medical Services Advisory Committee

**MSI-H:** Microsatellite Instability-High

**NGS:** Next Generation Sequencing

**NHI:** National Health Insurance

**NHS:** National Health Service

**NHSA:** National Healthcare Security Administration

**NICE:** National Institute for Health and Care Excellence

**NMPA:** National Medicinal Products Administration

**NSCLC:** Non-small cell lung cancer

**NRDL:** National Reimbursement Drug List

**NTRK:** Neurotrophic Tyrosine Receptor Kinase

**OBA:** Outcomes-based Agreement

**ORR**: Objective Response Rate

**OS:** Overall Survival

**P&R:** Pricing and Reimbursement

**PBAC:** Pharmaceutical Benefits Advisory Committee

**PBS:** Pharmaceutical Benefits Scheme

**PICO:** Patient, Intervention, Comparator, Outcome

**PMDA:** Pharmaceuticals and Medical Devices Agency

**QALY:** Quality-adjusted Life Year

**RCT:** Randomised Control Trial

**RSA:** Risk Sharing Agreement

**RWE:** Real World Evidence

**SoC:** Standard of Care

**STA:** Single Technology Assessment

**TA:** Tumour-agnostic

**TC:** Transparency Committee

**TGA:** Therapeutic Goods Agency

# Executive Summary

## Key points

- Tumour-agnostic (TA) therapies disrupt conventional oncology paradigms by targeting molecular alterations rather than tumour histology. The path from regulatory approval to patient access remains highly variable and complex across jurisdictions.
- Regulatory, health technology assessment (HTA) and reimbursement approaches vary widely across key national health systems. Diagnostic access also remains uneven, further limiting patient identification and uptake.
- To unlock the full potential of TA therapies, stakeholders must evolve evidence standards, HTA methodologies and payment models. National coverage for molecular testing and international collaboration are also critical enablers.

"To realise the full potential of TA therapies, stakeholders must confront the inherent tension between innovation and traditional assessment requirements."

Tumour-agnostic (TA) therapies represent a paradigm shift in oncology by targeting molecular alterations regardless of tumour histology. Since the landmark approval of pembrolizumab for microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumours by the US Food and Drugs Administration (FDA) in 2017, the number of TA therapies has grown substantially. Despite this scientific progress, TA therapies face a combination of challenges, including the reliance on evidence from basket trials, small and heterogeneous patient populations, scarcity or lack of tumour-specific comparator evidence, the use of surrogate endpoints like objective response rate (ORR) and availability of molecular testing, making it difficult to assess, reimburse, pay and adopt them in clinical practice. Consequently, the path from regulatory approval to patient access remains highly variable and complex across jurisdictions.

This report provides a landscape analysis of access to TA therapies across 11 countries - Australia, Brazil, Canada, China, France, Germany, Italy, Japan, Spain, the UK, and the US. It focuses on three TA therapies - pembrolizumab, larotrectinib, and entrectinib - to assess regulatory, health technology assessment (HTA), and reimbursement outcomes and identify barriers and possible solutions along the access pathway.

The key findings are:

- **Regulatory Variability:** While all countries have approved at least one TA therapy, regulatory approaches vary. Neurotrophic tyrosine receptor kinase (NTRK) inhibitors have been widely accepted due to their consistent clinical response, whereas MSI-H/dMMR therapies have faced more scrutiny. The FDA has led with early approvals of TA therapies, while others like the European Medicines Agency (EMA) have adopted a more cautious approach, requiring additional evidence to support TA-based indications and restricting indications when considerable treatment heterogeneity was observed.

- **HTA Challenges:** TA therapies challenge traditional HTA frameworks, which are designed for organ-specific treatments. Key challenges include their reliance on single-arm trials, surrogate endpoints like objective response rate, and limited comparative effectiveness data. Some HTA bodies, like Canada's Drug Agency (CDA-AMC), have begun to issue TA-specific guidance and considered Bayesian statistical approaches, but are under review by most other agencies.

- **Reimbursement Gaps:** Reimbursement remains inconsistent across and within countries. While TA therapies targeting ultra-rare biomarkers (e.g., NTRK fusions) often gain conditional coverage, other therapies (e.g., MSI-H/dMMR) face greater hurdles. Differences in payment models, HTA frameworks, and regional-level decision-making further complicate access.

- **Diagnostic Access Is Critical:** Adoption of advanced diagnostic infrastructure is essential to identifying eligible patients. Testing access is uneven and often depends on the targeted therapies available in the clinical setting, with significant disparities in funding, infrastructure, and clinical integration, especially in lower-resourced settings.

- **Emerging Policy Trends:** Key developments include FDA and CDA-AMC guidance on TA-specific evidence generation and assessment, the European Society for Medical Oncology's (ESMO) screening framework for TA potential, and early signs of

HTA reform in jurisdictions like Australia. International efforts, such as Project Orbis, may support greater alignment and efficiency.

Our analysis identified evidence gaps in some countries - particularly Brazil, China, and Japan - where published information on evidence assessment and decision-making approaches remains limited.

## Implications

To realise the full potential of TA therapies, stakeholders must confront the inherent tension between innovation and traditional assessment requirements. Novel trial designs, improved biomarker validation, adaptive reimbursement models, and molecular testing that align with clinical recommendations will all be critical. The findings underscore a need for systemic alignment between developers and decision-makers to support timely and equitable access to these paradigm-shifting therapies.

For systems where limited evidence was found, further research is needed to better understand decision-makers' positions on TA therapies, clarify evidence requirements, and identify ways to improve current systems - particularly by making them more structured and transparent to external stakeholders.

The key recommendations are:

- **Tailor evidence-generation strategies** and analytical approaches to accommodate tumour heterogeneity and small populations, leveraging real-world data and Bayesian methods in supporting trial data.
- **Evolve HTA methodologies** to increase acceptance of surrogate endpoints and methods for indirect comparisons, including situations where only observational data are available.
- **Increase the implementation of innovative payment models** that can facilitate conditional reimbursement and continue evidence development to address uncertainties.
- **Ensure national coverage for molecular testing,** co-evaluating diagnostics and therapies, and integrating testing into cancer pathways.
- **Promote cross-stakeholder and cross-border collaboration,** including joint guidance on basket trials and coordinated post-marketing data collection.

## Study limitations and recommendations for next steps

This analysis was scoped to draw on publicly available sources to examine regulatory, HTA, and reimbursement pathways for TA therapies across 11 countries across the globe. This approach ensures transparency and consistency. It also comes with inherent limitations.

Not all the reasoning behind regulatory and payer decisions is made public, and informal practices or behind-the-scenes factors are often not documented. As such, while findings reflect the state of play based on accessible evidence, they may not capture the full complexity of each system.

Future work should consider qualitative methods - such as interviews with decision-makers and stakeholders - to uncover the context behind the decision and better understand evolving thinking around TA therapies. Additionally, a more detailed analysis of individual HTA

reports could reveal patterns in how uncertainties are managed, and which methodological flexibilities are (likely) being accepted.

# 1. Introduction and Objectives

## 1.1. Background

Advances in precision medicine and cancer molecular biology have transformed the way malignancies are classified and treated. The identification of molecular alterations as therapeutic targets, enabled by novel diagnostic technologies, has paved the way for tumour-agnostic (TA) therapies, also known as histology-independent therapies. Unlike traditional treatments guided by tumour histology or organ origin, TA therapies target specific molecular alterations regardless of tumour type (NCI, 2025). This molecular-guided approach represents a paradigm shift from the conventional "one size fits all" strategy to precision medicine (Horgan et al., 2021), offering the potential for more effective and less toxic interventions in the fight against cancer.

The approval of pembrolizumab for its TA indication in the treatment of adult and paediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumours in 2017 by the US Food and Drug Administration (FDA) marked the advent of TA therapies (Westphalen et al., 2024). This milestone was soon followed by other targeted agents, including the neurotrophic tyrosine receptor kinase (NTRK) fusion inhibitors larotrectinib and entrectinib, both approved by the end of 2020 by the FDA and the European Medicines Agency (EMA) (Westphalen et al., 2024). By 2024, nine TA therapies had been approved by the FDA and three by the EMA for their TA indications (Westphalen et al., 2024).

These approvals by regulatory agencies address significant unmet needs and highlight the clinically meaningful benefits of TA therapies. However, notable differences exist in the overall degree of and timelines to access around the world, reflecting differences in evidence acceptance, and mechanisms to support access to these innovations. Timely access also depends on the integration of diagnostic testing in health systems to identify patients that are most likely to benefit from these therapies.

As the number of TA treatment approvals grows, significant advancements in diagnostic tools, such as molecular profiling technologies, have driven TA therapy advancements (Vranic et al., 2022). With ongoing progress in cancer biology and biomarker research, the pipeline of TA therapies is expected to expand. To ensure that scientific progress fosters meaningful transition towards precision medicine, challenges in providing timely access to TA therapies need to be addressed.

## 1.2. Objectives

The objectives of this report are:

- To describe the current state of play in relation to the access pathway of TA oncology treatment, including regulatory guidance, HTA TA-specific considerations, and medical and clinical research societies' views from the published literature.
- To identify and articulate the barriers and solutions as proposed by various stakeholders, and reflect on potential further opportunities for improvement along the patient access pathway.

This report provides key insights from our analyses and comparisons across the regions considered, while the Appendix presents more detailed country profiles.

## 1.3. Scope and methodology

### Scope

The scope of this landscape analysis is to provide a high-level overview **across regulatory, HTA, reimbursement, and payment mechanisms** for **eleven countries** and **three case studies.**

The geographical scope includes: Australia, Brazil, Canada, China, France, Germany, Italy, Japan, Spain, the UK, and the US.

Within those, we analyse three TA therapy case studies to illustrate key outcomes in regulatory, HTA and reimbursement processes, and payment mechanisms. These include:

- **Entrectinib and larotrectinib**, indicated for NTRK fusion-positive solid tumours.
- **Pembrolizumab,** indicated for MSI-H or dMMR solid tumours, which is approved in only certain tumour types in the regulatory label of some jurisdictions.

These therapies were selected due to their relatively established presence as well as their approval status in key regulatory bodies across the countries examined by this report.[1] Entrectinib and larotrectinib received TA approval from both the FDA and EMA for the treatment of NTRK fusion-positive solid tumours. While their approvals are relatively recent, sufficient time has passed to allow for an assessment of subsequent HTA evaluations, reimbursement decisions, and patient access considerations in multiple geographies.

Similarly, pembrolizumab received a TA indication approval from the FDA in 2017 (Westphalen et al., 2024), enabling an analysis of its impact on patient access. In Europe, pembrolizumab was approved for various tumour-specific indications (EMA, 2022). In Canada, pembrolizumab first received regulatory approval from Health Canada for a multi-tumour indication in dMMR/MSI-H cancers in April 2019 (Health Canada, 2019a). In August 2024, the label was updated to a TA indication based on additional data demonstrating a sustained duration of response in adult and paediatric patients (Health Canada, 2024). This regulatory divergence presents a compelling contrast for further exploration.

### Targeted literature review

The targeted literature review aimed to provide an updated description of the broader global **landscape for TA therapies** since the publication of the previous OHE report in 2020 on this topic (Rodes Sanchez, Henderson and Steuten, 2020), including challenges and ongoing developments. To that end, we searched peer-reviewed and grey literature to gather information on the regulatory and HTA processes, evidence requirements, methodologies, and decision-making practices for TA therapies in the 11 selected countries.

[1] *Selpercatinib was excluded from this analysis as it remains too early to evaluate its impact, particularly regarding HTA and payer decisions across different countries. Similarly, other emerging TA agents introduced between 2020 and 2022, prior to selpercatinib, were approved only in the US, limiting their relevance for a multi-region access analysis.*

The literature search was conducted using the PubMed database for articles published between 2018 to November 2024. This was supplemented with manual searches of relevant regulatory, HTA, and medical society websites to identify official guidance documents, white papers, access schemes, and organisational positions. Data were systematically extracted using a standardised Excel form.

## Case studies

For the case studies, HTA decision outcomes and reimbursement statuses were collected from official HTA and payer websites as of February 2025. Where necessary, translation services were used to extract information from non-English documents. In the following sections, we present how the case studies have been assessed by decision-makers along the access pathways in each country under review.

# 2. Key developments and challenges in TA therapy access

## 2.1. Challenges in evidence generation

Challenges in evidence generation that are unique to TA therapies include the use of basket trials to evaluate therapies across multiple cancer types simultaneously and the heterogeneity of tumour types and patient populations targeted. Other challenges faced by TA therapies are similar to other oncology therapies for rare cancers, such as the reliance on single-arm trials and small sample sizes. We explain challenges in evidence generation and assessment below, using the PICO (patient, intervention, comparator, outcome) framework, which is often used in HTA and research contexts (HTACG, 2024):

**Population:** TA therapies often target small, heterogeneous populations with unmet clinical needs, due to a lack of effective treatment options. The prognostic value of biomarkers (such as MSI-H, which could improve understanding of the disease course while predicting a positive response to immunotherapy) often remains uncertain (Huyghe et al., 2022).

**Intervention:** These therapies may have prior tumour-specific approved indications, which can build confidence in safety and clinical use, but raise challenges around pricing across different indications and uses.

**Comparator:** As some tumour types covered do not have an effective treatment option, trials often lack comparative evidence, with many being single-arm studies. When an active treatment exists, the presence of multiple standard-of-care treatments across tumour types and across countries can complicate the generation of robust evidence. It also highlights the need for indirect comparative evidence through indirect treatment comparisons (ITC) to demonstrate relative effectiveness. In these cases, comparator evidence can come from historical data or prospective data to assess long-term clinical outcomes.

**Outcome:** TA studies often use objective response rate (ORR), which provides a quantifiable measure of how effectively a treatment can shrink or eliminate tumours across multiple cancer types with the same molecular characteristic. ORR is often used as a primary endpoint, complemented by duration of response (Tateo et al., 2023). On the one hand, there are concerns among academics that surrogate endpoints may not fully reflect clinical benefit, as it does not indicate whether the response will lead to long-term survival (Briggs et al., 2022); on the other hand, regulatory and medical stakeholders recognise the role of ORR in treatment development and for screening therapies with TA potential (Westphalen et al., 2024). Variability in response rates across tumour types further complicates efficacy assessment. Differences in natural histories, progression, and baseline prognoses of tumours can impact the threshold of what constitutes a clinically meaningful response.

## 2.2. Patient access pathway overview

Considering the entire patient access pathway – from regulatory approval to reimbursement and adoption – is essential for identifying recent advancements in TA therapies and addressing remaining barriers to patient access. Figure 1 shows the key decision-makers along the access pathways and recent impactful publications or policy developments relevant for each:

## Regulators

Regulatory agencies, which assess efficacy and safety of new interventions for market approval decisions, are challenged by tumour heterogeneity, especially when patient populations vary in disease severity and treatment response. Limited evidence on the prognostic value of certain biomarkers can also complicate the assessment (FDA, 2022b).

To date, the FDA is the only regulatory agency to have issued guidance specifically focused on TA therapies, while the EMA has acknowledged the use of basket trials for such therapies in its broader guidance on evaluating anti-cancer treatments (FDA, 2022b; EMA, 2019a).

## HTA agencies

A survey of European HTA organisations identified TA therapies as the most challenging therapies to assess (Hogervorst et al., 2022) due to uncertainty in clinical and cost-effectiveness. Cost-effectiveness analyses can be complicated by the lack of comparative evidence from clinical trials and the need to assess clinical effectiveness across multiple tumour types with varying standards of care (SoC), costs, and outcomes (Hogervorst et al., 2022). Additionally, molecular testing requirements, while identifying appropriate treatments for patients, introduce additional costs that need to be taken into account in value for money estimations and health system considerations (Murphy et al., 2021).

In 2021, CDA-AMC (formerly CADTH) issued guidance on the economic evaluation of TA therapies. The guidance briefly outlines considerations for selecting patient population and comparators, cost-effectiveness assessments and handling uncertainty, while highlighting the need for additional guidance (CDA-AMC, 2021a). Other HTA agencies have not released TA-specific guidance, but a recent review of the Australian HTA methods recommended the development of TA-specific methods (Department of Health and Aged Care, 2024b). In 2024, the EU member state coordination group on HTA released guidance on the validity of clinical studies as part of the methodological requirements for conducting joint clinical assessments (JCA); it provides requirements for reporting basket trials (HTACG, 2024). Finally, in Canada, the Quebec HTA agency, Institut national d'excellence en santé et en services sociaux (INESSS), has introduced defined threshold criteria for TA therapies (INESSS, 2025).

## Medical societies

Medical societies play a crucial role in shaping oncology practice and driving research, both regionally and internationally. Their clinical guidelines and biomarker testing recommendations can help bridge the gap between regulatory approval, broader clinical acceptance, and integration into routine care.

Among medical societies, the European Society for Medical Oncology (ESMO) has been particularly active, by developing the ESMO Tumour-Agnostic Classifier and Screener (ETAC-S) tool, introducing a set of minimum criteria for demonstrating TA potential (Westphalen et al., 2024).

## Payment and access mechanisms

Existing payment models were not created with the complexity of TA therapies in mind, where value can vary across different tumour types and, in some cases, previously approved indications of the drug. Early access and coverage with evidence development schemes, which enable timely patient access while addressing uncertainty, exist in some jurisdictions but are not specific to TA therapies or systematically implemented. Examples of access mechanisms used for TA therapies include the National Institute for Health and Care

Excellence (NICE) Cancer Drugs Fund (CDF) in the UK and the AIFA Innovative Medicines Fund in Italy.

## Figure 1 Access pathway and key developments by decision makers in the context of assessing tumour-agnostic therapies

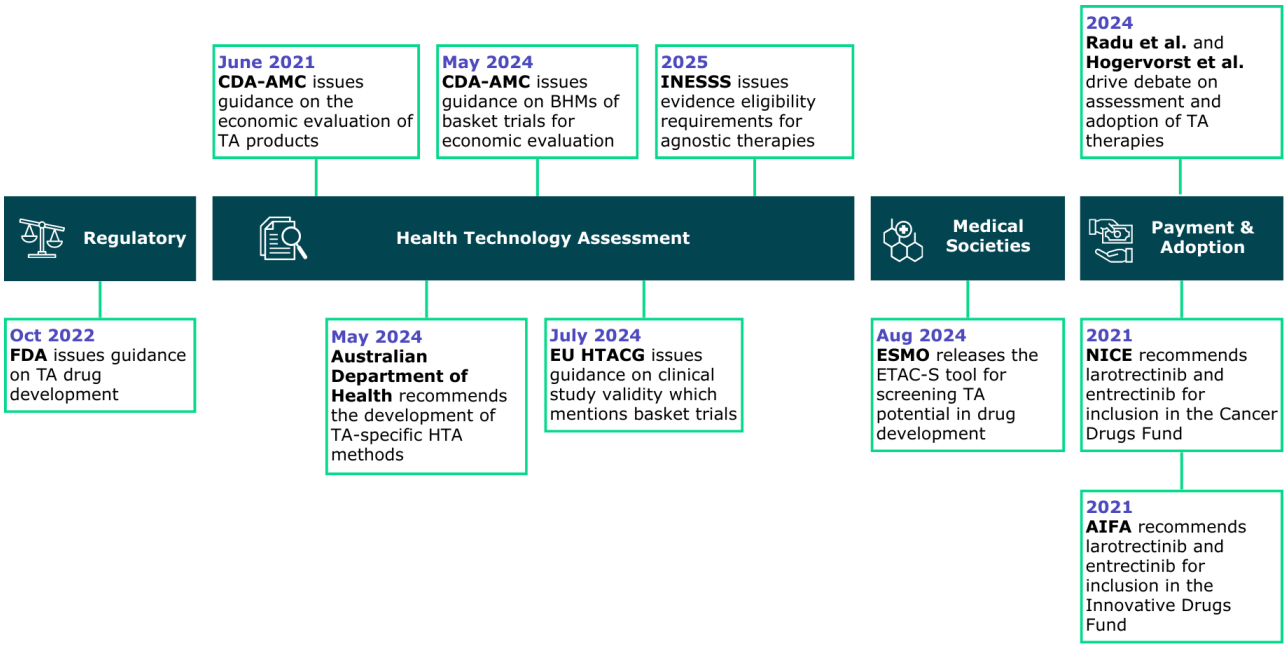



Figure presents information from decisions makers as of September 2025 *(AIFA, 2021b; a; CDA-AMC, 2021a, 2024b; Department of Health and Aged Care, 2024b; FDA, 2022b; HTACG, 2024; INESSS, 2025; Radu et al., 2024; Westphalen et al., 2024; NICE, 2020a; b)*

Finally, **academic and policy research,** mainly from a European perspective, has driven the debate regarding the assessment and adoption of TA therapies to improve approaches for decision-making and, ultimately, improve patient outcomes. Notably, Radu et al. and Hogervorst et al. highlight challenges and solutions for evidentiary requirements, value assessments, payment models, and policy alignment (Radu et al., 2024; Hogervorst et al., 2024).

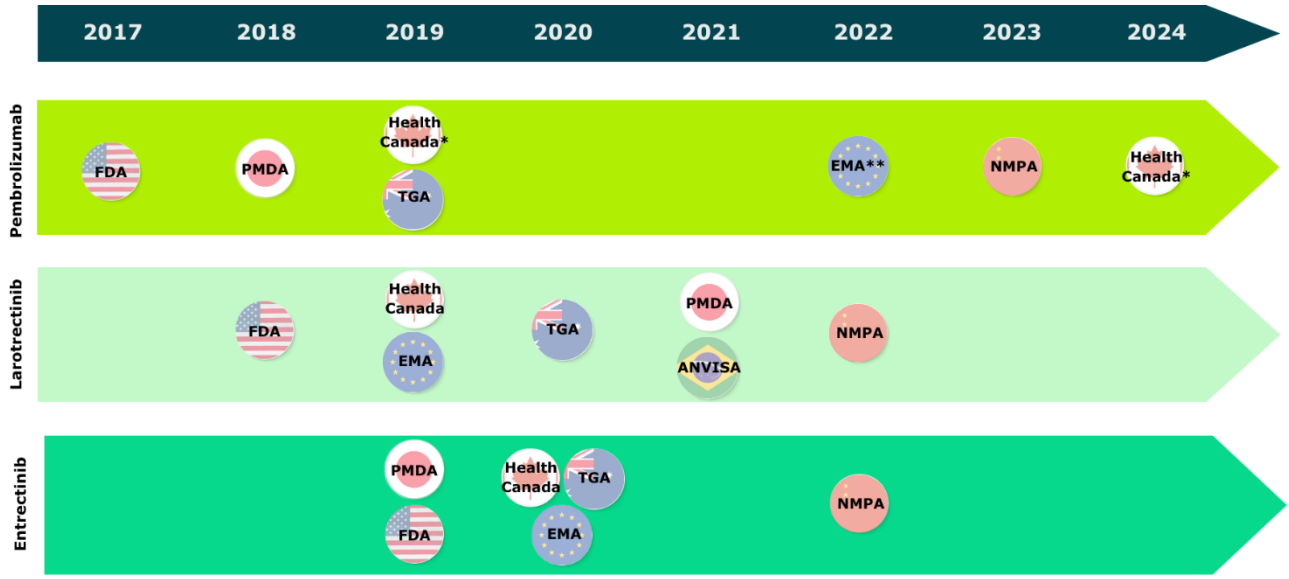
## 2.3. Regulatory trends and approaches
## Timelines of regulatory approvals

As shown in Figure 2, larotrectinib and entrectinib have widely received TA approvals in the selected regions, although entrectinib was not reviewed by Brazil's Agência Nacional de Vigilância Sanitária (ANVISA) at the time of the report (CONITEC, 2022).

Comparatively, the TA indication of pembrolizumab is less established internationally. In Canada, it was approved for a multi-tumour indication in April 2019 (Health Canada, 2019a), but its label was updated to a TA indication in August 2024 (Health Canada, 2024), significantly later compared to other regions. In the EU, pembrolizumab is not approved for any TA indications but was instead granted a series of tumour-specific indications (EMA, 2022).

The approval timelines can also be influenced by factors such as the timing of the developer submission and/or regional differences in regulatory approval pathways or processes.

## Figure 2 Tumour-agnostic approval timelines across different regulators




ANVISA: Brazilian Health Regulatory Agency (Brazil); EMA: European Medicines Agency (EU); FDA: Food and Drug Administration (USA); NMPA: National Medical Products Administration (China); PMDA: Pharmaceuticals and Medical Devices Agency (Japan); TGA: Therapeutic Goods Administration (Australia).
*In Canada, pembrolizumab initially received approval for multiple MSI-H/dMMR tumour types in 2019 before transitioning to a full TA indication in 2024.
** In Europe, pembrolizumab was granted a multi-tumour label in the EU, covering five specific tumour types with MSI-H/dMMR biomarkers.
Missing countries for the regulatory approval of the three case studies indicate that the product or its TA indication was either 1) not evaluated or 2) was evaluated but rejected; but the two are not able to be distinguished.

Figure presents information from decisions makers as of September 2025 *(Bayer, 2022; Cube, 2023; CONITEC, 2021; Health Canada, 2019b, 2024, 2020; NMPA, 2022; PMDA, 2018, 2019, 2021; TGA, 2019, 2020b; a; Westphalen et al., 2024)*

## Differences in regulatory approaches

The FDA has been at the forefront of approving TA therapies, demonstrating openness to granting approvals based on early efficacy signals and surrogate endpoints across histology-independent populations. The FDA's approach underscores its responsive stance by using innovative and collaborative processes to expedite access to medicines addressing unmet medical needs. In all case studies, ORR was the primary endpoint (Mulder et al., 2022; Tateo et al., 2023).

The FDA's approval of TA indications for NTRK inhibitors highlights a broader readiness to approve such therapies when they target rare genomic alterations (Mulder et al., 2022). The FDA is the only regulatory agency that has released TA-specific guidance (albeit draft) (FDA, 2022b); this is supplemented by further guidance on master protocols published in the same year and the previous guidance on clinical trial endpoints for cancer drugs (FDA, 2018a, 2022a).

In comparison, the EMA has adopted a more cautious approach compared to the FDA, placing greater emphasis on the need for robust tumour-specific evidence. Pembrolizumab was granted standard marketing authorisation in 2022 for the treatment of cancers with MSI-H/dMMR biomarkers, five years after the FDA's TA approval (EMA, 2022). The EMA required more comprehensive data, including an expanded dataset with 30 additional patients (EMA, 2022; Mulder et al., 2022), and approved pembrolizumab only for five specific tumour types: colorectal, endometrial, gastric, small intestine, and biliary tract cancers. Pancreatic cancer was excluded due to insufficient evidence of clinical benefit.

In the case of larotrectinib and entrectinib, both were approved for their TA indications but were restricted to patients with no satisfactory treatment options (EMA, 2019b, 2020b). Notably, the EMA did acknowledge the TA nature of NTRK gene fusions as a valid biomarker, due in part to the rarity of these genomic alterations and the consistently high response rates observed across diverse tumour types (EMA, 2019b).

Regulatory approaches in other countries generally span a spectrum in terms of evidence requirements and openness to emerging methodologies, from FDA's innovative and adaptable stance to EMA's preference for more traditional evidence. For example, in Health Canada's assessment of pembrolizumab, there were initial concerns about evidence meaning that the original indication was multi-tumour. However in 2024, the regulatory label was updated to include a TA indication for solid tumours supported by additional efficacy data (Health Canada, 2019a, 2024). The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan requires local population-specific data but efforts are underway to reduce the delay in patient access caused by these additional study requirements, such as developing guidelines to promote multiregional clinical trials (Otsubo, 2024). In addition, the PMDA recently released guidance on utilising master protocol trials offering recommendations for designing, conducting, and analysing non-traditional clinical trials, such as basket trials commonly used for TA therapies (PMDA, 2024). The Therapeutic Goods Agency (TGA) in Australia has granted provisional approvals for TA therapies based on single-arm trial data, but continued approval of all three case studies depends on confirmatory trials verifying clinical benefits (TGA, 2019, TGA, 2020a, TGA, b). In Brazil, ANVISA's evidence requirements align closely with those of other regulatory agencies, owing to its involvement in various regulatory harmonisation forums (Ivama-Brummell et al., 2023).

### Evidence accepted

An analysis of the evidence supporting the approvals by regulators of the three case studies indicates that most regulators have accepted pooled or integrated analyses (Mulder et al., 2022). Pooled analysis combines individual patient data from multiple trials into a single dataset, whereas integrated analysis incorporates both individual patient and aggregate data to assess treatment effects comprehensively (FDA, 2015).

Pooled efficacy and safety data were assessed by the FDA, EMA and TGA for the 3 case studies (See Appendix A). Pooled efficacy data were assessed by Health Canada and ANVISA for larotrectinib. PMDA in Japan assessed separately presented trial data for the case studies and no data was found for National Medicinal Products Administration (NMPA) in China.

## Key takeaways

The TA therapies considered in the case studies are recognised to some extent by all regulatory agencies within the scope of this analysis. These agencies all provide mechanisms (although with potentially different impact) to foster and grant early access to innovative therapies. The acceptance of TA indications for NTRK inhibitors across multiple regions highlights a broader willingness to approve therapies targeting rare genomic drivers

with biological rationale whereas approvals for MSI-H/dMMR cancers have been more varied due to concerns over variability in treatment effect. The case of pembrolizumab for MSI-H/dMMR cancers demonstrates that regulatory agencies do not act in a harmonised way but can take varied approaches to TA approvals, reflecting differences in evidence requirements, risk tolerance, and reliance on biomarker-driven data for accepting TA-based indications.

The FDA is the most willing to grant TA approvals based on early efficacy signals for TA indications. The EMA, Health Canada and TGA have adopted more cautious approaches, requiring additional evidence to support TA-based indications and, as a result, restricting indications when treatment heterogeneity was observed. Japan has granted TA approvals for all case studies, although limited information is available on TA-specific regulatory criteria. In China, NMPA have granted regulatory approval for TA indications across the NTRK inhibitors and checkpoint inhibitors, but evidence around TA evaluations remains limited. Brazil's ANVISA has approved larotrectinib TA indication but has not evaluated entrectinib and pembrolizumab in their TA indications.

Moving forward, regulatory harmonisation and real-world evidence can play a crucial role in refining TA approval pathways and addressing uncertainties surrounding safety and efficacy across diverse tumour types. In addition, continued cross-agency collaboration and guidance evolution will be crucial to ensure consistent and equitable access to TA therapies.

## 2.4. HTA methods and reimbursement approaches

### Key HTA challenges

The challenges highlighted in the regulatory context are further exacerbated in the HTA and reimbursement stages.

First, comparative effectiveness assessment is particularly problematic. Traditional HTA relies on direct comparisons with existing treatments, but TA therapies often lack a clear comparator. This requires the use of ITCs or novel statistical methods, which can introduce methodological biases and reduce confidence in relative effectiveness estimates if not conducted and interpreted with due consideration.

Another concern is available endpoints. Basket trials frequently rely on surrogate endpoints such as ORR. While useful for early efficacy signals, ORR may not reliably predict longer-term outcomes such as overall survival (OS). Where OS is available, these trials are unlikely to have sufficient power. Additionally, the heterogeneity of included cancers can also result in variable response rates, further complicating the interpretation and generalisation of clinical benefit.

These clinical uncertainties also impact cost-effectiveness and value assessments. The limited data on long-term outcomes and the broad application of these therapies across diverse tumour types introduce additional uncertainty into health economic models. In addition, traditional cost-utility analysis may not fully capture the value offered by TA therapies, particularly when used in rare populations or when there is no alternative treatment.

Finally, reimbursement systems tend to be structured around organ-specific pathways, making it administratively and financially challenging to accommodate a TA indication that spans multiple cancer types (Weymann et al., 2023). Payers may question the sustainability of funding high-cost therapies for broadly defined patient groups, without outcomes data for each tumour site, leading to potential uncertainty in the expected budget impact.

# Comparison of HTA methodologies

This section provides an overview of HTA methodologies and processes across the countries under consideration, with a focus on the adaptability of their approach for topics relevant to the assessment of TA therapies. When referring to 'adaptability', we consider explicit methods and processes as well as the HTA body's receptiveness to considering novel approaches, leading to striking a balance between robust methods and keeping pace with medical innovation. A full description of HTA methods in this context can be found in Appendix B. The USA is omitted from this section, given the absence of a government HTA body.

## An evolving approach: Canada and the UK

CDA-AMC in Canada and NICE in the UK are considered to be methodologically advanced and relatively adaptable in terms of evidence requirements. Both are open to the consideration of Real World Evidence (RWE) (as outlined in their respective frameworks), accepting surrogate endpoints if sufficiently justified and have acknowledged the rationale for basket trials while highlighting the potential challenges associated (CDA-AMC, 2021a, 2023; NICE, 2022, 2025). CDA-AMC has issued TA-specific economic evaluation guidelines, whereas NICE have not issued formal documentation (CDA-AMC, 2021a). NICE's method innovations, such as its severity modifier and CDF, have been used to support the assessment of TA therapies (NICE, 2020a; b).

In Canada, Quebec's HTA agency INESSS has stipulated eligibility requirements for TA therapies to specify a minimum level of evidence needed (INESSS, 2025). The number of patients is at least 35 per tumour site evaluated, but may come from different studies or data sources. For each tumour site to be evaluated, ORR ≥ 60% or ORR ≥ 20% AND duration of response ≥ 9 months. While this framework offers some guidance for the evaluation of TA therapies, the rationale behind it is unclear and, in addition, it could pose additional barriers to access, particularly when compared to the more flexible approach adopted by CDA-AMC.

## Moderate adaptability: Australia, Spain, Italy and Brazil

HTA agencies in Australia (Pharmaceutical Benefits Advisory Committee (PBAC)), Spain (Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)), Italy (Agenzia Italiana del Farmaco (AIFA)), and Brazil (Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde (CONITEC)) have elements of flexibility but may not be explicitly outlined in methods guidance, or they may be inconsistently applied. Despite being considered in some circumstances, an overall hesitancy to accept RWE, surrogate endpoints and basket trials remains a barrier to the assessment of TA therapies in these countries. This can be explained by the lack of formal guidance on the topics, as seen in Australia, Spain and Brazil, or limited guidance as in Italy. Generally, inclusion of non-randomised control trial (RCT) evidence in HTA submissions may lead to uncertainties being reflected in pricing and reimbursement (P&R) decisions. Over time, progress towards the acceptance of non-RCT evidence has been slow but promising; producing explicit and detailed guidance could accelerate improvements.

## Relatively less adaptable approach: France and Germany

HTA agencies in France (Haute Autorité de santé (HAS)) and Germany (Gemeinsamer Bundesausschuss (G-BA) have a stronger focus on the demonstration of clinical benefits. The consideration of RWE, surrogate endpoints and basket trials is limited compared to the countries described above. The G-BA can request prospective generation of RWE under specific circumstances and is assessed according to a methodological framework to ensure

that studies meet high methodological standards (IGES, 2021). HAS' RWE requirements are similarly strict. Likewise, surrogate endpoints are only accepted by G-BA or HAS if they have been sufficiently validated (HAS, 2020; IQWIG, 2023). HAS does not accept the use of basket trials which has limited access to TA therapies (HAS, 2020). G-BA does not have any explicit guidance on the use of basket trials or single-arm studies.

### HTA not routinely conducted: China and Japan

HTA is conducted by the National Healthcare Security Administration (NHSA) in China, which reviews the list of drugs available for reimbursement and only requires an in-depth analysis for those selected for price negotiation. Published evidence on HTA and reimbursement decision-making remains limited.

HTA in Japan is conducted by the Centre for Outcomes Research and Economic Evaluation for Health (C2H) for a small number of drugs annually to aid price adjustments for innovative or high-cost therapies. The HTA guidelines refer to RWE, asking for sufficient detail on the quality of the evidence (C2H, 2024). No TA therapies have been subjected to HTA evaluation.

## Reimbursement mechanisms

For most health systems considered, a positive HTA decision will generally lead to the availability of a TA therapy, often supported by agreements between payers and developers, such as managed entry agreements (MEA) (Australia, Brazil, France, the UK). However, positive HTA recommendations are not a guarantee of reimbursement in some countries where final reimbursement decisions are made at a regional level (Canada, Spain and Italy). In other countries, reimbursement is granted regardless of whether a full HTA is conducted (Japan) or the outcome of the assessment (Germany). In China, reimbursement decisions are less transparent but likely driven by a combination of factors, including HTA outcome and price negotiations. In the US, reimbursement decisions are made by private and public insurers.

Overall, the TA therapies included as case studies are reimbursed to some extent in most of the countries under consideration, but the mechanisms and processes used to achieve this access vary widely and depend on local context. This is shown in Table 1, which provides a summary of the current regulatory, HTA and reimbursement outcomes for the selected case study therapies across key markets. For detailed country profiles, see Appendix B.

Our analysis suggests that reimbursement for TA therapies is more likely in systems that incorporate formal mechanisms to manage uncertainty (also known as coverage with evidence development schemes), such as the CDF in the UK, or dedicated funds to facilitate the introduction of innovative therapies, such as the Innovative Drug Fund in Italy. This can be seen in the case of entrectinib and larotrectinib for both countries.

In cases where the available evidence was deemed to have unacceptable levels of uncertainty or the medicine was deemed cost-effective for a subgroup only, reimbursement may be restricted compared to the marketing indication. This can be seen in the case of entrectinib in Australia and larotrectinib in Australia and France.

MEAs can be instrumental in ensuring access to innovative therapies, whether that be financial-based or performance-based risk-sharing arrangements. The only example of a financial risk sharing agreement (RSA) found was for larotrectinib in Australia, where there

is a subsidy cap and Commonwealth payment[2] in place (PBAC, 2024). The details of the RSA are not publicly available.

Although no evidence of performance-linked reimbursement arrangements in the context of TA therapies was identified within the scope of this project, they present an opportunity to enhance patient access to TA therapies by sharing risks between the developer and payer (Koleva-Kolarova et al., 2022). Outcomes-based agreements (OBA) could be employed to help distribute the financial risk as payments are tied to the therapy's effectiveness, ensuring that payers only pay for successful outcomes. OBAs are particularly useful when there is uncertainty in survival-related outcomes, as in the case of TA therapies.

Indication-based pricing, which allows prices to vary depending on the use or the indication of therapy, can also be relevant for TA therapies, as they can be approved for other tumour types in addition to a TA indication (such as in the case of pembrolizumab). These payment models can create a more flexible and sustainable approach to funding TA therapies, but they are not without challenges. These challenges involve data management, legal and financial hurdles, and the need for stakeholder coordination-issues that extend beyond TA therapies. To note, a TA indication may challenge the concept of use-specific pricing as the price might combine variable levels of clinical effectiveness across tumour types and can result in some tumour types with a price either above or below the population-specific value.

There are examples of OBAs and value-based payments being used in Australia, France, Italy, Spain, the UK and USA (Cole et al., 2019), which suggests they could be applied in the context of TA therapies in the future, where appropriate.

## Key takeaways

While considerable progress has been made in the context of assessing TA therapies by a few established HTA bodies, there is still room for increased endorsement and acceptance of novel statistical approaches and RWE to fill evidence gaps. In countries with less established HTA processes, such as China and Brazil, a more routine and structured approach to value assessment, including clear method and process guidelines, could lead to more predictable reimbursement outcomes. From a payer perspective, some countries, such as Italy and the UK, have provided access to TA therapies through ring-fenced funds prioritising promising innovative treatments.

[2] *The Australian Government or 'Commonwealth' subsidises medicines that deemed necessary to maintain the health of the community in a way that is cost-effective.*

# Table 1 Summary of regulatory, HTA and reimbursement decisions

| | Entrectinib | | | Larotrectinib | | | Pembrolizumab | | |
|---|---|---|---|---|---|---|---|---|---|
| **Decisions** | **Regulatory** | **HTA decision** | **Reimbursement** | **Regulatory** | **HTA decision** | **Reimbursement** | **Regulatory** | **HTA decision** | **Reimbursement** |
| Australia | | Positive for NSCLC* | Positive for NSCLC | | Positive for multiple indications** | | | Positive for multiple cancers* | Positive for multiple cancers |
| Brazil | | | | | | | | Positive for melanoma* | Positive for IV oncology |
| Canada | | | | | | | | | |
| China | | | | | | | | | *** |
| France | | | | | Cond. approval - paediatric | Paediatric | | | |
| Germany | | | | | | | | | |
| Italy | | | Funded under IDF | | | Funded under IDF | | | |
| Spain | | | | | | | | | |
| Japan | | | | | | | | | |
| UK | | Recommended under CDF | Funded under CDF | | Recommended under CDF | Funded under CDF | | Positive for multiple cancers* | Positive for multiple cancers |
| USA | | | | | | | | | |

Key: Positive recommendation | No additional clinical benefit rating | Negative recommendation | Not applicable for TA indication

*No submission for TA indication; **Positive for high frequency NTRK solid tumours and NTRK+ NSCLC, STS, glioma, glioneural tumour and glioblastoma; ***Though not part of the selected case studies for this report, it is noteworthy that the first TA approval in China was received by a domestically developed PD-1 inhibitor tiselizumab for MSI-H/dMMR in Nov 2021 and reimbursed with NRDL inclusion in 2023 *(BeiGene, 2022)*.

Table presents information from decision makers as of September 2025 *(AEMPS, 2015, 2022b; a; AIFA, 2021a; b; Bayer, 2022; CDA-AMC, 2021b, 2022, 2025b; CONITEC, 2021; Cube, 2023; Health Canada, 2019b, 2024, 2020; Hogervorst et al., 2024; NICE, 2020b; a, 2023; NMPA, 2022; PBAC, 2020, 2021, 2022; PMDA, 2018, 2019, 2021; TGA, 2019, 2020b; a; Westphalen et al., 2024)*

## 2.5. Diagnostic access and infrastructure

The adoption of TA therapy relies on the availability of advanced diagnostic pathways, with routine molecular and genomic testing essential for identifying eligible patients.[3] However, evaluation and reimbursement processes for testing vary across countries, affecting patient access. Economic evaluation studies indicate that testing costs, shaped by biomarker prevalence, testing strategies, and existing infrastructure, significantly impact the cost-effectiveness of TA therapy adoption (Beresford et al., 2022; Huygens et al., 2023; Vellekoop et al., 2023).

We identified these common barriers to high-quality biomarker testing, including:

- limited access to precision medicine linked to biomarkers;
- unclear evaluation frameworks for diagnostic tests;
- variation in laboratory infrastructure, capabilities, and referral pathways;
- budget constraints and silos between therapy and diagnostic testing;
- limited stakeholder awareness and training;
- inconsistent participation in quality assurance programmes.

For comparison, we categorise each country under consideration into the following typologies: (i) Broad, (ii) Variable, and (iii) Limited access and infrastructure.

Most of the countries in scope have established infrastructure in place to conduct diagnostic testing for the identification of biomarkers targeted by TA therapies. For further details, see the country-specific sections in the Appendix. The degree of availability and reimbursement for testing can be inconsistent or fragmented. It is important to acknowledge that decisions about diagnostic infrastructure and implementation are often made with a consideration of a range of therapies that require diagnostic tests as well as the perspectives of involved stakeholders (Price, McGinley and John, 2020), rather than for TA therapies in isolation.

### Broad Access and Infrastructure: France, Germany, Japan, UK and USA

Diagnostic testing for TA therapies is nationally coordinated in France, Germany, and the UK. The availability of technologies such as next generation sequencing (NGS), immunohistochemistry (IHC), and in-situ hybridisation (ISH) in these countries is considered high, particularly in Germany, which offers coverage for a broad range of NGS panels (APAC Med, 2024; Bayle et al., 2023; Wilsdon, Horgan and Akkermans, 2022). In the UK, testing is organised in regional or national hubs, provided by the National Health Service (NHS) Genomic Medicine Service (NHSE, 2022). In France and Germany, testing is provided by regional testing centres (LEK, 2021).

In Japan and the USA, testing is semi-centralised. In Japan, the Centre for Cancer Genomics and Advanced Therapeutics (C-CAT) deliver NGS through designated institutions and

[3] *We refer to molecular testing as assays that detect specific mutations or biomarkers, while genomic testing examines the broader genome using technologies such as next-generation sequencing (NGS) that can assess multiple genes simultaneously (Ishida, Zubair and Gupta, 2025).*

consolidate genomic and clinical data via a national data centre (Kohno et al., 2022). Although the majority of genomic test costs are covered, access to NGS may differ across provinces (APAC Med, 2024). In the USA, coverage of single biomarker tests and IHC is widespread, and coverage of multi-gene panels for solid tumours is expanding (ADVI, 2023). Nevertheless, coverage for multi-gene panels, including NGS, may differ between public and private payers as well as between states (ACS Cancer Action Network, 2024). Access and infrastructures for testing may be enhanced through the implementation of national genomic strategies. France, Germany, and the UK have national strategies aiming to integrate genomics into routine care (AVIESON, 2024; BMBF, 2025; NHSE, 2022), while Japan and the USA do not have formal national strategies, but diagnostic testing is supported by medical societies and expert consensus (ADVI, 2023; Kobayashi et al., 2025).

Biomarker testing availability is mixed. The UK's National Genomic Test Directory has NTRK testing available for several tumour types and MSI testing is offered for a range of solid tumours (NHSE, 2025). While in the US, research shows that over two-thirds of payers cover NTRK fusion testing, coverage for MSI-H/dMMR is more inconsistent and varies by tumour types (ADVI, 2023). In Japan, access to testing is broad but uneven, with NTRK and MSI-H/dMMR testing available but inconsistently implemented or limited to certain tumour types (PMDA, 2025). In France and Germany, testing availability is either tumour-type dependent or not publicly documented.

### Variable Access and Infrastructure: Australia, Canada, Italy, and Spain

The public coverage of diagnostic testing in these countries is considered more fragmented. Availability and reimbursement for tests in Canada, Italy, and Spain exhibit regional variability due to differences in funding and infrastructure (LEK, 2021; Yip et al., 2019). Specifically, testing is less readily available in Spain compared to the other included European countries (Bayle et al., 2023). In Australia, access to diagnostics such as NGS is expanding, particularly in the private sector (APAC Med, 2024). However, public coverage remains limited and may be provided through regional funds (Wilsdon, Horgan and Akkermans, 2022).

In Australia, Spain, and Italy, national genomic strategies have been implemented to integrate genomics into routine care (Australian Health Ministers' Advisory Council, 2022; ibs.GRANADA, 2020; Pitini et al., 2024). In Canada, the Pan-Canadian Genomics Strategy is currently in development, which aims to promote real-world implementation of genomics research (Government of Canada, 2023). In terms of biomarker testing availability in relation to the case study therapies, NTRK and MSI-H/dMMR testing is available in Australia, Canada, and Spain, but is inconsistently implemented or limited to certain tumour types.

### Emerging Access and Infrastructure: Brazil and China

Unlike the other countries under consideration, Brazil does not have a standardised framework for approving and evaluating companion diagnostics, including molecular testing for TA therapies. Access barriers exist for both targeted therapies and testing technologies, where companion tests are not necessarily included in the drug label (Ferreira et al., 2016). Availability of diagnostic tests such as IHC screening and NGS depends on tumour types, with certain tests only covered by private insurance (Da Cunha et al., 2021). To advance the diagnostic landscape in Brazil, a comprehensive national strategy specifically targeting the integration of molecular testing into routine oncology care should be established.

In China, the availability and reimbursement of testing technologies such as NGS is decentralised and varies between provinces and hospitals, such that testing remains mainly funded out-of-pocket (APAC Med, 2024). To date, no national plan has been announced to expand NGS implementation and testing infrastructure.

## 2.6. Cross-country patterns and policy developments

As countries grapple with how best to evaluate and integrate TA therapies in their systems, a variety of approaches have emerged, reflecting differing levels of readiness, innovation, and collaboration across decision-makers and across regions.

The FDA and CDA-AMC stand out as frontrunners in the guidance and implementation of novel methods for TA therapies. The FDA has led globally by issuing dedicated TA-specific guidance, including documents on master protocols and cancer trial endpoints, which support the use of basket trials, surrogate endpoints, and single-arm studies; key methodologies for evaluating TA therapies. Its openness has enabled early approvals based on objective response rates and biological plausibility across histologies. Similarly, CDA-AMC has demonstrated leadership by publishing the only TA-specific economic evaluation guidance among HTA bodies, and by explicitly considering advanced statistical methods such as Bayesian Hierarchical Models (BHMs) to address heterogeneity in treatment effects across tumour types. Both agencies have recognised the reliance on basket trials for TA therapies and have actively adapted their frameworks to accommodate innovative evidence generation and analysis approaches. The FDA has noted that randomised trials may not be feasible or appropriate for rare molecular alteration-related tumour types, particularly in refractory settings (FDA, 2022b).

International regulatory partnerships like Project Orbis use collaborative assessment to promote earlier access to oncology products (Wang et al., 2022). Partners of Project Orbis include regulators in Australia, Brazil, Canada, Israel, Singapore, Switzerland, the UK, and USA. Although the project ORBIS pathway was not used for the approval of any of the three TA treatment case studies in this report (FDA, 2025), it can be considered as an avenue to accelerate regulatory approvals for future TA therapies.

As part of the European JCA initiative, the EU HTA Coordination Group (HTACG) recently published guidance on clinical study validity. This guidance acknowledges the challenges of randomisation and relative effectiveness assessments in basket trials, emphasising the importance of robust trial design (HTACG, 2024). It also discusses the use of single-arm trial data, stressing careful consideration of its validity (HTACG, 2024). While JCA aims to harmonise relative effectiveness assessments across Europe, its requirements for study design and relevance for different member states pose challenges to TA therapy access, including components of the submissions such as the number of PICOs for multiple tumour types and requirements for comparative evidence, particularly given the timelines set by the new process.

ESMO's ETAC-S tool could facilitate TA therapy development by providing a structured screening framework. The set of minimum criteria for demonstrating TA potential includes an ORR of ≥20% in two-thirds (four or more) of the investigated tumour types, with at least five evaluable patients per type (Westphalen et al., 2024). ESMO has also endorsed emerging clinical evidence and recommended companion genomic testing in clinical practice, which is an important driver for the adoption of TA therapies (Yoshino et al., 2020).

Overall, although progress has been made at various stages of the access pathway (as illustrated in Figure 1), the journey from regulatory approval to patient access remains highly variable and complex across jurisdictions (as shown in Table 1). This underscores the need for coordinated and sustained efforts from all stakeholders, including regulators, payers, clinicians, industry, and patient groups, to address systemic barriers. The recommendations set out in the next section are aimed at addressing existing challenges and driving more consistent, equitable access to TA therapies across jurisdictions.

# 3. Recommendations

We found that TA therapy integration into healthcare systems faces challenges related to evidence generation, HTA methodologies, reimbursement models, and diagnostic infrastructure and funding. The following recommendations aim to address these challenges:

## Strengthen evidence generation strategies tailored to TA therapies

- **Encourage structured collaborations among decision-makers** (regulators, HTA agencies, and payers) to align on appropriate trial design and evidence requirements, especially in the context of basket trials and rare biomarker-driven populations. This can take the form of horizontal collaborations (between agencies with similar remit, such as those in the regulatory space) and vertical collaboration (across the different stages of the access pathway) to ensure there is a holistic and life-cycle approach to evidence generation and assessment. Decision-makers should invest in pilot projects or consortia (similar to Project Orbis for regulatory and the collaboration for HTA among 8 agencies across three continents) to harmonise evidence standards, data-sharing frameworks, and TA assessment principles.

- **Encourage early dialogue between developers and decision makers** to align expectations and requirements for specific products, help streamline the approval process, and help coordinate post-authorisation evidence collection. In Europe, the Joint Scientific Advice can provide an opportunity, although the limited resources available and other challenges can limit its impact.

- **Promote the appropriate use of innovative statistical methodologies,** such as Bayesian hierarchical models, to enhance the interpretability of data across tumour types and improve confidence in pooled efficacy estimates.

- **Support integration of real-world evidence (RWE)** into regulatory and HTA submissions to complement trial data and address evidentiary uncertainty by providing long-term effectiveness and safety in routine practice.

## Enhance HTA methodologies and reimbursement mechanisms

- **Clarify evidence requirements for TAs and promote the development of TA-specific HTA guidance** to enhance predictability of processes and evidence expectations. The FDA and Canada's CDA-AMC have led with TA-focused recommendations, and similar efforts are recommended in other countries where there are remaining barriers to patient access and value assessment can be improved (e.g. Australia).

- **Strengthen accountability and improve transparency of assessment processes** by publishing the rationale and evidentiary standards that are used for specific TA therapy assessments, particularly in countries where processes are inconsistent or (currently) lack transparency. Monitor the evolution of processes and decisions over time and how these influence (time to) patient access.

- **Promote the development and use of novel methodologies** for rare and TA indications, with clear criteria for accepting indirect comparisons and surrogate outcomes.

- **Encourage value-based payment models** that reflect variations in clinical benefit across indications or uses of therapies while ensuring sustainability of healthcare budgets. Those mechanisms, along with RWE, can support the implementation of conditional reimbursements and a life-cycle approach to HTA.

### Expand and integrate access to molecular testing

- **Ensure national reimbursement for (advanced) molecular diagnostics**, including but not limited to comprehensive genomic profiling where clinically justified, particularly for identifying patients eligible for TA therapies.

- **Reduce testing inequities** by national strategies that address geographical and institutional disparities in molecular diagnostics. This includes public infrastructure investment, integration of testing into cancer pathways, and capacity-building across oncology networks.

- **Support adoption of companion diagnostics** through coordinated assessments of both therapy and test, for example through co-dependent evaluation pathways.

- **Build infrastructure and clinical capacity for precision oncology**, including education and training for healthcare professionals on interpreting and using molecular test results.

By addressing these recommendations, stakeholders can better align regulatory, HTA, and reimbursement processes to the unique characteristics of TA therapies, ultimately accelerating access to personalised treatment options for patients across tumour types.

## Conclusion

As cancer biology and biomarker research continue to evolve, the number of TA therapies entering the market is expected to grow. To ensure timely access to these innovative therapies, greater alignment and a holistic approach across regulatory, HTA, and reimbursement frameworks are essential. By embedding flexibility, methodological innovation, and infrastructure readiness into the access pathway, healthcare systems can better meet the promise of precision oncology.

# References

Abadie, C., Abderrahmane, A., Abdous, O., Abel, C., Ackermann, O., Acquaviva, C., Ader, F., Adham, S., Adjaoud, D., Afenjar, A., Aladjidi, N., Alary, A.-S., Albarel, F., Albert, S., Allard, L., Allix, I., Alunni, V., Amado, I.F., Amouroux, C., et al., 2025. PFMG2025—integrating genomic medicine into the national healthcare system in France. *The Lancet Regional Health - Europe*, 50, p.101183. DOI: 10.1016/j.lanepe.2024.101183.

ACS Cancer Action Network, 2024. *Access to Biomarker Testing*. [online] American Cancer Society Cancer Action Network. Available at: https://www.fightcancer.org/what-we-do/access-biomarker-testing. [Accessed 2 Sept. 2025].

ACS Cancer Action Network, 2025. *Access to Biomarker Testing*. [online] Available at: https://www.fightcancer.org/what-we-do/access-biomarker-testing. [Accessed 16 Oct. 2025].

ADVI, 2023. *Payer Coverage Policies of Tumor Biomarker and Pharmacogenomic Testing*. [online] Available at: https://www.fightcancer.org/sites/default/files/acs_can_payer_coverage_policies_of_tumor_biomarker_and_pharmacogenomic_testing_-_advi_final.pdf.

AEMPS, 2015. *TECHNICAL DATA SHEET KEYTRUDA 50 MG POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION*. [online] Available at: https://cima.aemps.es/cima/dochtml/ft/1151024001/FT_1151024001.html. [Accessed 2 Sept. 2025].

AEMPS, 2022a. *[Therapeutic Positioning Report for entrectinib (Rozlytrek®) in ROS1-positive non-small cell lung cancer]*. [online] Available at: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/2022/IPT_36-2022-Rozlytrek-CPNM.pdf. [Accessed 2 Sept. 2025].

AEMPS, 2022b. *[Therapeutic Positioning Report on larotrectinib (Vitrakvi®) in tumors with NTRK gene fusion]*. [online] Available at: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/2022/IPT_39-2022-Vitrakvi.pdf. [Accessed 2 Sept. 2025].

AIFA, 2020. *Guidelines for the compilation of the dossier in support of the application refundability and price of a medicine*. Available at: https://www.aifa.gov.it/documents/20142/1307543/2021.01.22_estratto_linee_guida_sezione_E.pdf.

AIFA, 2021a. *VALUTAZIONE DELL'INNOVATIVITA' - ROZLYTREK*. [online] Available at: https://www.aifa.gov.it/documents/20142/1571238/133_ROZLYTREK_scheda_innovativita_GRADE.pdf.

AIFA, 2021b. *VALUTAZIONE DELL'INNOVATIVITA' - VITRAKVI*. [online] Available at: https://www.aifa.gov.it/documents/20142/1571238/132_VITRAKVI_scheda_innovativita_GRADE.pdf.

AIFA, 2025. *Economic evaluations*. [online] Available at: https://www.aifa.gov.it/en/valutazioni-economiche. [Accessed 16 Oct. 2025].

Ainiwaer, A., Cheng, J., Lang, R., Peng, T., Bi, X. and Lu, Y., 2024. Chinese expert consensus on the clinical application of molecular diagnostics in hepatobiliary cancers (2024 edition). *Liver Research*, 8(4), pp.195—206. DOI: 10.1016/j.livres.2024.11.005.

Alliance Nationale pour Les Sciences de La Vie et de La Santé (Avieson), 2024. *Genomic Medicine France 2025*. [online] Available at: https://sante.gouv.fr/IMG/pdf/genomic_medicine_france_2025.pdf. [Accessed 16 Oct. 2025].

American Cancer Society, 2022. *Biomarker Tests and Cancer Treatment*. [online] Available at: https://www.cancer.org/cancer/diagnosis-staging/tests/biomarker-tests.html. [Accessed 2 Sept. 2025].

ANVISA, 2015. *[Outcomes for clinical trials of oncological drugs.pdf — National Health Surveillance Agency]*. [online] Available at: https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/medicamentos/publicacoes-sobre-medicamentos/desfechos-para-estudos-clinicos-de-medicamentos-oncologicos.pdf/view. [Accessed 16 Oct. 2025].

ANVISA, 2021. *Keytruda® (Pembrolizumabe): nova indicação — Agência Nacional de Vigilância Sanitária*. [online] Available at: https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/novos-medicamentos-e-indicacoes/keytruda-r-pembrolizumabe-nova-indicacao. [Accessed 2 Sept. 2025].

APAC Med, 2024. *Advancing Patient Access to NGS for Cancer in APAC: Key considerations and a value assessment framework*. [online] Available at: https://apacmed.org/wp-content/uploads/2024/06/APACMed_NGS-WP_VFinal13.pdf. [Accessed 3 Sept. 2025].

ASEBIO, 2024. *The Ministry of Health presents the new Common Catalog of Genetic and Genomic Tests of the National Health System | AseBio*. [online] Available at: https://asebio.com/en/news-events/news/ministry-health-presents-new-common-catalog-genetic-and-genomic-tests-national. [Accessed 3 Sept. 2025].

Australian Government Department of Health and Aged Care, 2025. *Pharmaceutical Benefits Scheme (PBS) | Pharmaceutical Benefits Advisory Committee (PBAC) Membership*. Available at: https://www.pbs.gov.au/info/industry/listing/participants/pbac. [Accessed 3 Sept. 2025].

Australian Health Ministers' Advisory Council, 2022. *National Health Genomics Policy Framework*. [online] Available at: https://www.health.gov.au/sites/default/files/documents/2022/03/national-health-genomics-policy-framework-2018-2021.pdf. [Accessed 3 Sept. 2025].

Bayer, 2022. *Bayer receives approval for precision oncology treatment Vitrakvi™ in China*. [online] Available at: https://www.bayer.com/media/en-us/bayer-receives-approval-for-precision-oncology-treatment-vitrakvitm-in-china/. [Accessed 17 Oct. 2025].

Bayle, A., Bonastre, J., Chaltiel, D., Latino, N., Rouleau, E., Peters, S., Galotti, M., Bricalli, G., Besse, B. and Giuliani, R., 2023. ESMO study on the availability and accessibility of biomolecular technologies in oncology in Europe. *Annals of Oncology*, 34(10), pp.934—945. DOI: 10.1016/j.annonc.2023.06.011.

Bebb, D.G., Banerji, S., Blais, N., Desmeules, P., Gill, S., Grin, A., Feilotter, H., Hansen, A.R., Hyrcza, M., Krzyzanowska, M., Melosky, B., Noujaim, J., Purgina, B., Ruether, D., Simmons, C.E., Soulieres, D., Torlakovic, E.E. and Tsao, M.-S., 2021. Canadian Consensus for Biomarker Testing and Treatment of TRK Fusion Cancer in Adults. *Current Oncology (Toronto, Ont.)*, 28(1), pp.523—548. DOI: 10.3390/curroncol28010053.

BeiGene, 2022. *China NMPA Approves Tislelizumab for Patients with Microsatellite Instability-High or Mismatch Repair-Deficient Solid Tumors*. [online] Available at: https://hkexir.beigene.com/news/china-nmpa-approves-tislelizumab-for-patients-with-microsatellite-instability-high-or-mismatch-repair-deficient-solid-tumors/8e9d7307-4dd0-472c-ae75-aa54767634d7. [Accessed 3 Sept. 2025].

Beresford, L., Murphy, P., Dias, S., Claxton, L., Walton, M., Metcalf, R., Schlecht, H., Ottensmeier, C., Pereira, M. and Hodgson, R., 2022. Appraising the Costs of Genomic Testing for Histology-Independent Technologies: An Illustrative Example for NTRK Fusions. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 25(7), pp.1133—1140. DOI: 10.1016/j.jval.2021.11.1359.

Briggs, A., Paracha, N., Rosettie, K., Upton, A., Bokemeyer, C., Lassen, U. and Sullivan, S.D., 2022. Estimating Long-Term Survival Outcomes for Tumor-Agnostic Therapies: Larotrectinib Case Study. *Oncology*, 100(2), pp.124—130. DOI: 10.1159/000519767.

C2H, 2024. Guideline for Preparing Cost-Effectiveness Evaluation to the Central Social Insurance Medical Council. [online] Available at: https://c2h.niph.go.jp/tools/guideline/guideline_en.pdf.

Callea, G., Armeni, P., Marsilio, M., Jommi, C. and Tarricone, R., 2017. The impact of HTA and procurement practices on the selection and prices of medical devices. *Social Science & Medicine*, 174, pp.89—95. DOI: 10.1016/j.socscimed.2016.11.038.

Campolina, A.G., Yuba, T.Y. and Soárez, P.C. de, 2022. Decision criteria for resource allocation: an analysis of CONITEC oncology reports. *Ciência & Saúde Coletiva*, 27, pp.2563—2572. DOI: https://doi.org/10.1590/1413-81232022277.14242021EN.

CDA-AMC, 2017. Guidelines for the Economic Evaluation of Health Technologies: Canada (4th Edition). [online] Available at: https://www.cda-amc.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf. [Accessed 17 Sept. 2025].

CDA-AMC, 2021a. Guidance for Economic Evaluations of Tumour-Agnostic Products. [online] Available at: https://www.cda-amc.ca/sites/default/files/pdf/mh0016-cadth-economic-guidance-for-tumor-agnostic-products-rev-june22.pdf. [Accessed 3 Sept. 2025].

CDA-AMC, 2021b. Larotrectinib (Vitrakvi). [online] Available at: https://www.cadth.ca/sites/default/files/DRR/2021/PC0221%20Vitrakvi%20-%20CADTH%20Final%20Rec%20KG_NA_Corrected-meta.pdf. [Accessed 3 Sept. 2025].

CDA-AMC, 2022. Entrectinib (Rozlytrek). [online] Available at: https://www.cda-amc.ca/sites/default/files/DRR/2022/PC0278%20Rozlytrek%20-%20CADTH%20Final%20Recommendation%20for%20Posting.pdf. [Accessed 3 Sept. 2025].

CDA-AMC, 2023. Guidance for Reporting Real-World Evidence. [online] Available at: https://www.cda-amc.ca/sites/default/files/RWE/MG0020/MG0020-RWE-Guidance-Report-Secured.pdf. [Accessed 3 Sept. 2025].

CDA-AMC, 2024a. *About Us | CDA-AMC*. [online] Available at: https://www.cda-amc.ca/about-us. [Accessed 3 Sept. 2025].

CDA-AMC, 2024b. Bayesian Hierarchical Models of Basket Trials in the Context of Economic Evaluation. *Canadian Journal of Health Technologies*, [online] 4(5). DOI: 10.51731/cjht.2024.907.

CDA-AMC, 2025a. *pembrolizumab | CDA-AMC*. [online] Available at: https://www.cda-amc.ca/pembrolizumab-14. [Accessed 3 Sept. 2025].

CDA-AMC, 2025b. Pembrolizumab (Keytruda). *Canadian Journal of Health Technologies*, [online] 5(2). DOI: 10.51731/cjht.2025.1081.

CDA-AMC, 2025c. *Procedures for Reimbursement Reviews*. [online] Available at: https://www.cda-amc.ca/sites/default/files/Drug_Review_Process/Drug_Reimbursement_Review_Procedures.pdf. [Accessed 3 Sept. 2025].

CDA-AMC, 2025d. *Surrogate endpoints in cost-effectiveness analysis for use in health technology assessment*. [online] Available at: https://www.cda-amc.ca/sites/default/files/MG%20Methods/surrogate-endpoints-report.pdf. [Accessed 3 Sept. 2025].

Centre for Health Economics Research and Evaluation (CHERE), 2023. *Review of the Efficient Funding of Chemotherapy (EFC) Funding Arrangements: Final Report*. [online] Available at: https://www.pbs.gov.au/reviews/efc-review-files/Efficient-Funding-of-Chemotherapy-Review-Final-Report-with-Addendum.PDF. [Accessed 3 Sept. 2025].

Chen, W., Zhang, L., Hu, M. and Hu, S., 2023a. Use of health technology assessment in drug reimbursement decisions in China. *The BMJ*, 381, p.e068915. DOI: 10.1136/bmj-2021-068915.

Chen, Y., Zhao, K., Liu, G. and Chen, W., 2023b. Health technology assessment to inform decision making in China: progress, challenges, and sustainability. *BMJ*, p.e068910. DOI: 10.1136/bmj-2021-068910.

Coelho, A.V.C., Mascaro-Cordeiro, B., Lucon, D.R., Nóbrega, M.S., Reis, R.D.S., De Alexandre, R.B., Moura, L.M.S., Oliveira, G.S.D., Guedes, R.L.M., Caraciolo, M.P., Zurro, N.B., Cervato, M.C. and Oliveira, J.B., 2022. The Brazilian Rare Genomes Project: Validation of Whole Genome Sequencing for Rare Diseases Diagnosis. *Frontiers in Molecular Biosciences*, 9, p.821582. DOI: 10.3389/fmolb.2022.821582.

Cole, A., Cubi-Molla, P., Pollard, J., Sim, D., Sullivan, R., Sussex, J. and Lorgelly, P., 2019. Making Outcome-Based Payment a Reality in the NHS. [online] Available at: https://www.ohe.org/wp-content/uploads/2021/12/Making-Outcome-Based-Payment-a-Reality-in-the-NHS.-Phase-2-Practical-Considerations-November-2021.pdf. [Accessed 19 Sept. 2025].

CONITEC, 2020. *Riociguat - recommendation report*. [online] Available at: https://www.gov.br/conitec/pt-br/midias/consultas/relatorios/en2020/20200915_report519_riociguat_chronicthromboembolicpulmonaryhypertension.pdf. [Accessed 5 Sept. 2025].

CONITEC, 2021. *[Larotrectinib for patients with locally advanced or metastatic solid tumors positive for NTRK gene fusion]*. [online] Available at: https://www.gov.br/conitec/pt-br/midias/relatorios/2021/20211207_relatorio_679_larotrectinibe_tumores_solidos_com_fusao_gene_ntrk.pdf/view. [Accessed 4 Sept. 2025].

CONITEC, 2022. [Drugs for the treatment of non-small cell lung cancer]. [online] Available at: https://www.gov.br/conitec/pt-br/midias/radar/2022/informemht_cancerpulmao_publicado.pdf. [Accessed 5 Sept. 2025].

Cooper, S., Bouvy, J.C., Baker, L., Maignen, F., Jonsson, P., Clark, P., Palmer, S., Boysen, M. and Crabb, N., 2020. How should we assess the clinical and cost effectiveness of histology independent cancer drugs? *BMJ*, 368, p.l6435. DOI: 10.1136/bmj.l6435.

Costa, A., 2022. *Anvisa Approves MSD Immunotherapy as Adjuvant Treatment for Melanoma Patients in Earlier Stages of Treatment for a Cure - MSD Brazil*. [online] Available at: https://www.msd.com.br/news/anvisa-aprova-imunoterapia-da-msd-como-tratamento-adjuvante-para-pacientes-com-melanoma-em-fases-mais-precoces-de-tratamento-visando-a-cura/. [Accessed 1 Sept. 2025].

Cube, F., 2023. *Merck's Keytruda Approved in China for MSI-H/dMMR Advanced Solid Tumors: A Biomarker-Driven Milestone - Insight, China's Pharmaceutical Industry*. [online] Available at: https://flcube.com/?p=14094. [Accessed 17 Oct. 2025].

Da Cunha, I.W., De Almeida Coudry, R., De Macedo, M.P., De Assis, E.A.C.P., Stefani, S. and Soares, F.A., 2021. A call to action: molecular pathology in Brazil. *Surgical and Experimental Pathology*, 4(1), p.15. DOI: 10.1186/s42047-021-00096-1.

Deng, T., Qiu, M., Liu, M., Xiong, B., Li, G., Li, T., Zhou, Y., Zhao, Q., You, J., Yu, W., Wang, Y., Chen, G., Fu, W., Wang, Z., Xu, A., Xia, Y., Zhao, P., Chen, G., Ba, Y., et al., 2024. Unveiling prognosis and traits of dMMR/MSI-H gastric and colorectal cancer after curative surgery: A large-scale, multi-center, retrospective study in China. *Journal of Clinical Oncology*, 42(3_suppl), pp.729—729. DOI: 10.1200/JCO.2024.42.3_suppl.729.

Department of Health and Aged Care, 2024a. *Health Technology Assessment Policy and Methods Review: Emerging Health Technologies*. [online] Available at: https://www.health.gov.au/sites/default/files/2024-07/hta-policy-and-methods-review-emerging-health-technologies.pdf. [Accessed 3 Sept. 2025].

Department of Health and Aged Care, 2024b. Health Technology Assessment Policy and Methods Review — Full recommendations. [online] Available at: https://www.health.gov.au/sites/default/files/2024-09/health-technology-assessment-policy-and-methods-review-full-recommendations.pdf. [Accessed 3 Sept. 2025].

EMA, 2019a. *Guideline on the clinical evaluation of anticancer medicinal products*. [online] Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-anticancer-medicinal-products-man-revision-6_en.pdf. [Accessed 3 Sept. 2025].

EMA, 2019b. *Vitrakvi: European Public Assessment Report*. [online] Available at: https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf. [Accessed 3 Sept. 2025].

EMA, 2020a. *Annex I Summary of Product Characteristics Entrectinib*. [online] Available at: https://www.ema.europa.eu/en/documents/product-information/rozlytrek-epar-product-information_en.pdf. [Accessed 6 Nov. 2025].

EMA, 2020b. *CHMP assessment report: Rozlytrek*. [online] Available at: https://www.ema.europa.eu/en/documents/assessment-report/rozlytrek-epar-public-assessment-report_en.pdf. [Accessed 2 Dec. 2024].

EMA, 2022. *Committee for Medicinal Products for Human Use (CHMP) Assessment Report: Keytruda*. [online] Available at: https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0109-epar-assessment-report-variation_en.pdf. [Accessed 3 Sept. 2025].

EMA, 2025. *European Medicines Agency post-authorisation procedural advice for users of the centralised procedure*. [online] p.68. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf. [Accessed 8 June 2025].

Epstein, D. and Espín, J., 2020. Evaluation of new medicines in Spain and comparison with other European countries. *Gaceta Sanitaria*, 34(2), pp.133—140. DOI: 10.1016/j.gaceta.2019.02.009.

FDA, 2015. Integrated Summary of Effectiveness Guidance for Industry. [online] Available at: https://www.fda.gov/media/72335/download. [Accessed 16 Oct. 2025].

FDA, 2018a. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. [online] Available at: https://www.fda.gov/media/71195/download. [Accessed 6 Sept. 2025].

FDA, 2018b. FDA approves larotrectinib for solid tumors with NTRK gene fusions. *Case Medical Research*. [online] DOI: 10.31525/fda1-ucm626720.htm.

FDA, 2019a. Approval Package For Keytruda. [online] Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/125514Orig1s014.pdf. [Accessed 4 Sept. 2025].

FDA, 2019b. FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC. [online] DOI: 10.31525/cmr-1a554a6.

FDA, 2022a. Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics. [online] Available at: https://www.fda.gov/media/120721/download. [Accessed 4 Sept. 2025].

FDA, 2022b. *Tissue Agnostic Drug Development in Oncology Guidance for Industry*. [online] Available at: https://www.fda.gov/media/162346/download. [Accessed 4 Sept. 2025].

FDA, 2023. *Companion Diagnostics*. [online] Available at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/companion-diagnostics. [Accessed 18 Sept. 2025].

FDA, 2025. *Project Orbis*. [online] Available at: https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis. [Accessed 4 Sept. 2025].

Federal Ministry of Education and Research (BMBF), 2025. *Homepage - Die Nationale Dekade gegen Krebs*. [online] Available at: https://www.dekade-gegen-krebs.de/en/home/home_node.html. [Accessed 3 Sept. 2025].

Federal Ministry of Health, 2022. *genomeDE — National Strategy for Genomic Medicine | BMG*. [online] Available at: https://www.bundesgesundheitsministerium.de/en/en/international/european-health-policy/genomde-en.html. [Accessed 17 Sept. 2025].

Ferreira, C.G., Achatz, M.I., Ashton-Prolla, P., Begnami, M.D., Marchini, F.K. and Stefani, S.D., 2016. Brazilian health-care policy for targeted oncology therapies and companion diagnostic testing. *The Lancet Oncology*, 17(8), pp.e363—e370. DOI: 10.1016/S1470-2045(16)30171-1.

G-BA, 2025. *Benefit Assessment of Medicinal Products - Gemeinsamer Bundesausschuss*. [online] Available at: https://www.g-ba.de/english/benefitassessment/. [Accessed 4 Sept. 2025].

Government of Canada, 2020. *Rozlytrek - Notice of Compliance with Conditions - Qualifying Notice*. [online] Available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions/rozlytrek-qualifying-notice.html. [Accessed 3 Sept. 2025].

Government of Canada, 2021. *Vitrakvi - Notice of Compliance with Conditions - Qualifying Notice*. [online] Available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions/vitrakvi-notice-compliance-conditions-qualifying-notice.html. [Accessed 3 Sept. 2025].

Government of Canada, 2022. *Consultation-Paper-Developing-a-Pan-Canadian-Genomics-Strategy*. [online] Available at: https://ised-isde.canada.ca/site/genomics/sites/default/files/documents/2022-05/Consultation-Paper-Developing-a-Pan%E2%80%91Canadian-Genomics-Strategy.pdf. [Accessed 4 Sept. 2025].

Government of Canada, 2023. *What We Heard: Pan-Canadian Genomics Strategy*. [online] Available at: https://ised-isde.canada.ca/site/genomics/sites/default/files/attachments/2023/pancanadian_genomics_strategy_wwh-en.pdf. [Accessed 3 Sept. 2025].

GOV.UK, 2022. *Over £175 million for cutting-edge genomics research*. [online] Available at: https://www.gov.uk/government/news/over-175-million-for-cutting-edge-genomics-research. [Accessed 18 Sept. 2025].

GOV.UK, 2025. *National Institute for Health and Care Excellence*. [online] Available at: https://www.gov.uk/government/organisations/national-institute-for-clinical-excellence. [Accessed 18 Sept. 2025].

Green, A.K., Ohn, J.A. and Bach, P.B., 2020. Review of Current Policy Strategies to Reduce US Cancer Drug Costs. *Journal of Clinical Oncology*, 38(4), pp.372—379. DOI: 10.1200/JCO.19.01628.

Halbisen, A.L. and Lu, C.Y., 2023. Trends in Availability of Genetic Tests in the United States, 2012—2022. *Journal of Personalized Medicine*, 13(4), p.638. DOI: 10.3390/jpm13040638.

HAS, 2020. Transparency Committee doctrine. [online] Available at: https://www.has-sante.fr/jcms/p_3081386/fr/transparency-committee-doctrine.

HAS, 2021. Real-world studies for the assessment of medicinal products and medical devices. [online] Available at: https://www.has-sante.fr/upload/docs/application/pdf/2021-10/real-world_studies_for_the_assessment_of_medicinal_products_and_medical_devices.pdf. [Accessed 19 Sept. 2025].

Health Canada, 2019a. *Regulatory Decision Summary for Keytruda - Drug and Health Products Portal*. [online] Available at: https://dhpp.hpfb-dgpsa.ca/review-documents/resource/RDS00514. [Accessed 5 Sept. 2025].

Health Canada, 2019b. *Regulatory Decision Summary for Vitrakvi (larotrectinib)*. [online] Available at: https://dhpp.hpfb-dgpsa.ca/review-documents/resource/RDS00673/. [Accessed 5 Sept. 2025].

Health Canada, 2020. *Regulatory Decision Summary for Rozlytrek (entrectinib)*. [online] Available at: https://dhpp.hpfb-dgpsa.ca/review-documents/resource/RDS00832. [Accessed 5 Sept. 2025].

Health Canada, 2024. *Regulatory Decision Summary for Keytruda (pembrolizumab)*. [online] Available at: https://dhpp.hpfb-dgpsa.ca/review-documents/resource/RDS1727284854344. [Accessed 5 Sept. 2025].

Health Technology Assessment Coordination Group (HTACG), 2024. *Guidance on Validity of Clinical Studies*. [online] Available at: https://health.ec.europa.eu/document/download/9f9dbfe4-078b-4959-9a07-df9167258772_en?filename=hta_clinical-studies-validity_guidance_en.pdf-Section%205.1.2%20and%205.1.3%20briefly%20mentions%20basket%20trials%20and%20umbrella%20trials,%20but%20nothing%20specific%20on%20assessment%20and%20reporting. [Accessed 5 Sept. 2025].

Hogervorst, M.A., Van Hattem, C.C., Sonke, G.S., Mantel-Teeuwisse, A.K., Goettsch, W.G. and Bloem, L.T., 2024. Healthcare decision-making for tumour-agnostic therapies in Europe: lessons learned. *Drug Discovery Today*, 29(7), p.104031. DOI: 10.1016/j.drudis.2024.104031.

Hogervorst, M.A., Vreman, R.A., Mantel-Teeuwisse, A.K. and Goettsch, W.G., 2022. Reported Challenges in Health Technology Assessment of Complex Health Technologies. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 25(6), pp.992—1001. DOI: 10.1016/j.jval.2021.11.1356.

Horgan, D., Ciliberto, G., Conte, P., Curigliano, G., Seijo, L., Montuenga, L.M., Garassino, M., Penault-Llorca, F., Galli, F., Ray-Coquard, I., Querleu, D., Riegman, P., Kerr, K., Van Poppel, H., Bjartell, A., Codacci-Pisanelli, G., Koeva-Balabanova, J., Paradiso, A., Maravic, Z., et al., 2021. Bringing Onco-Innovation to Europe's Healthcare Systems: The Potential of Biomarker Testing, Real World Evidence, Tumour Agnostic Therapies to Empower Personalised Medicine. *Cancers*, 13(3), p.583. DOI: 10.3390/cancers13030583.

Huygens, S., Vellekoop, H., Versteegh, M., Santi, I., Szilberhorn, L., Zelei, T., Nagy, B., Tsiachristas, A., Koleva-Kolarova, R., Wordsworth, S., Rutten-van Mölken, M., and HEcoPerMed Consortium, 2023. Cost-Effectiveness Analysis of Treating Patients With NTRK-Positive Cancer With the Histology-Independent Therapy Entrectinib. *Value in Health:*

*The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 26(2), pp.193—203. DOI: 10.1016/j.jval.2022.08.006.

Huyghe, N., Benidovskaya, E., Stevens, P. and Van Den Eynde, M., 2022. Biomarkers of Response and Resistance to Immunotherapy in Microsatellite Stable Colorectal Cancer: Toward a New Personalized Medicine. *Cancers*, 14(9), p.2241. DOI: 10.3390/cancers14092241.

ibs.GRANADA, 2020. *The Government approves the call to launch the new Precision Medicine infrastructure, IMPaCT*. [online] Available at: https://www.ibsgranada.es/en/el-gobierno-aprueba-la-convocatoria-para-lanzar-la-nueva-infraestructura-de-medicina-de-precision-impact/. [Accessed 2 Sept. 2025].

IGES, 2021. *Reimbursement of Pharmaceuticals in Germany*. [online] Available at: https://www.iges.com/e15094/e15095/e15096/e17469/IGES_Reimbursement_Pharmaceuticals_Germany_2020_2021_WEB_ger.pdf. [Accessed 2 Sept. 2025].

INAHTA, 2025. CONITEC - National Committee for Technology Incorporation. *INAHTA*. Available at: https://www.inahta.org/members/conitec/. [Accessed 5 Sept. 2025].

INESSS, 2025. *Eligibility Requirements for Agnostic Therapies in Oncology*. [online] Available at: https://www.inesss.qc.ca/. [Accessed 14 Aug. 2025].

Institute for Clinical and Economic Review (ICER), 2018. Guide to Understanding Health Technology Assessment (HTA). [online] Available at: https://icer.org/wp-content/uploads/2020/10/ICER-Guide-to-Understanding-Health-Technology-Assessment-6.19.18.pdf. [Accessed 13 Aug. 2025].

IQWIG, 2020. *Concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a Social Code Book V (SGB V)1*. [online] Available at: https://www.iqwig.de/download/a19-43_routine-practice-data-for-the-benefit-assessment-of-drugs_rapid-report_v1-0.pdf. [Accessed 3 Sept. 2025].

IQWIG, 2023. General Methods - Version 7.0. [online] Available at: https://www.iqwig.de/methoden/general-methods_version-7-0.pdf. [Accessed 3 Sept. 2025].

Ishida, C., Zubair, M. and Gupta, V., 2025. Molecular Genetics Testing. In: *StatPearls*. [online] Treasure Island (FL): StatPearls Publishing. Available at: http://www.ncbi.nlm.nih.gov/books/NBK560712/. [Accessed 3 Sept. 2025].

Ivama-Brummell, A.M., Marciniuk, F.L., Wagner, A.K., Osorio-de-Castro, C.G.S., Vogler, S., Mossialos, E., Tavares-de-Andrade, C.L. and Naci, H., 2023. Marketing authorisation and pricing of FDA-approved cancer drugs in Brazil: a retrospective analysis. *Lancet Regional Health - Americas*, 22, p.100506. DOI: 10.1016/j.lana.2023.100506.

Kamae, I., Thwaites, R., Hamada, A. and Fernandez, J.L., 2020. Health technology assessment in Japan: a work in progress. *Journal of Medical Economics*, 23(4), pp.317—322. DOI: 10.1080/13696998.2020.1716775.

Kang, J. and Cairns, J., 2023. "Don't Think Twice, It's All Right": Using Additional Data to Reduce Uncertainty Regarding Oncologic Drugs Provided Through Managed Access Agreements in England. *PharmacoEconomics - Open*, 7(1), pp.77—91. DOI: 10.1007/s41669-022-00369-9.

Kelner, M., Carvalho da Silva, B., Montella, T., Aguiar, P.N., Lopes, G., Ferreira, C.G. and De Marchi, P., 2023. Discrepancies Between the Cost of Advanced Lung Cancer Treatment and How Much Is Reimbursed by the Brazilian Public Healthcare System. *Value in Health Regional Issues*, 33, pp.1—6. DOI: 10.1016/j.vhri.2022.08.004.

Kobayashi, S., Nakamura, Y., Hashimoto, T., Bando, H., Oki, E., Karasaki, T., Horinouchi, H., Ozaki, Y., Iwata, H., Kato, T., Miyake, H., Ohba, A., Ikeda, M., Chiyoda, T., Hasegawa, K., Fujisawa, T., Matsuura, K., Namikawa, K., Yajima, S., et al.,

2025. Japan society of clinical oncology position paper on appropriate clinical use of molecular residual disease (MRD) testing. *International Journal of Clinical Oncology*. [online] DOI: 10.1007/s10147-024-02683-0.

Kohno, T., Kato, M., Kohsaka, S., Sudo, T., Tamai, I., Shiraishi, Y., Okuma, Y., Ogasawara, D., Suzuki, T., Yoshida, T. and Mano, H., 2022. C-CAT: The National Datacenter for Cancer Genomic Medicine in Japan. *Cancer Discovery*, 12(11), pp.2509—2515. DOI: 10.1158/2159-8290.CD-22-0417.

Koleva-Kolarova, R., Buchanan, J., Vellekoop, H., Huygens, S., Versteegh, M., Mölken, M.R., Szilberhorn, L., Zelei, T., Nagy, B., Wordsworth, S., Tsiachristas, A., and The HEcoPerMed Consortium, 2022. Financing and Reimbursement Models for Personalised Medicine: A Systematic Review to Identify Current Models and Future Options. *Applied Health Economics and Health Policy*, 20(4), pp.501—524. DOI: 10.1007/s40258-021-00714-9.

Lawlor, R., Wilsdon, T., Darquennes, E., Hemelsoet, D., Huismans, J., Normand, R. and Roediger, A., 2021. Accelerating patient access to oncology medicines with multiple indications in Europe. *Journal of Market Access & Health Policy*, 9(1), p.1964791. DOI: 10.1080/20016689.2021.1964791.

LEK, 2021. *Unlocking the potential of precision medicine in Europe*. [online] Available at: https://www.iqnpath.org/wp-content/uploads/2021/02/unlocking-the-potential-of-precision-medicine-in-europe.pdf. [Accessed 3 Sept. 2025].

Li, W., Lyu, Y., Wang, S., Zhou, X., Ma, J., Xu, C., Fang, L., Ying, J., Guo, L., Qiu, T., Li, W., Li, Y., Che, N., Bai, X., Xi, Y., Hu, Y., Liu, L., Li, X., Zhang, S., et al., 2021. Trends in Molecular Testing of Lung Cancer in Mainland People's Republic of China Over the Decade 2010 to 2019. *JTO Clinical and Research Reports*, 2(4), p.100163. DOI: 10.1016/j.jtocrr.2021.100163.

Li, Z., Song, W., Rubinstein, M. and Liu, D., 2018. Recent updates in cancer immunotherapy: a comprehensive review and perspective of the 2018 China Cancer Immunotherapy Workshop in Beijing. *Journal of Hematology & Oncology*, 11(1), p.142. DOI: 10.1186/s13045-018-0684-3.

Ling, K., Qin, H., Feng, Y., Che, H., Ding, J. and Li, W., 2022. Correlation between clinical trial endpoints of marketed cancer drugs and reimbursement decisions in China. *Frontiers in Public Health*, 10, p.1062736. DOI: 10.3389/fpubh.2022.1062736.

Liu, G., Cheung, W.Y., Feilotter, H., Manthorne, J., Stockley, T., Yeung, M. and Renouf, D.J., 2022. Precision Oncology in Canada: Converting Vision to Reality with Lessons from International Programs. *Current Oncology (Toronto, Ont.)*, 29(10), pp.7257—7271. DOI: 10.3390/curroncol29100572.

Lumanity, 2022. *Comparing Outcomes Pre- and Post-Cancer Drugs Fund: What Can We Learn?* [online] Available at: https://www.abpi.org.uk/publications/comparing-outcomes-pre-and-post-cancer-drugs-fund-what-can-we-learn/. [Accessed 18 Sept. 2022].

Matthews, C. and Capdevila, C., 2022. *France's ATU reform: an update*. [online] Available at: https://www.europeanpharmaceuticalreview.com/article/177035/france-atu-reform-early-access-possible/. [Accessed 17 Sept. 2025].

Medicines Australia, 2020. *THE EVOLVING ROLE OF REAL- WORLD EVIDENCE IN AUSTRALIA*. [online] Available at: https://www.medicinesaustralia.com.au/wp-content/uploads/sites/65/2020/11/OIT-RWE-Report-Oct-2020-FINAL-MA-VERSION.pdf. [Accessed 5 Sept. 2025].

MHLW, 2019. Full Scale Introduction of Cost-Effectiveness Evaluations in Japan. [online] Available at: https://c2h.niph.go.jp/tools/system/overview_en.pdf. [Accessed 2 Sept. 2025].

Ministério da Saúde - Secretaria de Ciência, T. e I.E., 2014. *Diretrizes metodológicas: diretriz de avaliação econômica*. ECOS: Economia da Saúde para Gestão do SUS. Ms.

Ministerio de Sanidad, 2025. *Catálogo Común de Pruebas Genéticas y Genómicas del SNS*. [online] Available at: https://cgen.sanidad.gob.es/#/mas-informacion. [Accessed 2 Sept. 2025].

Motoi, N. and Yatabe, Y., 2020. Lung cancer biomarker tests: the history and perspective in Japan. *Translational Lung Cancer Research*, 9(3), pp.879—886. DOI: 10.21037/tlcr.2020.03.09.

MSAC, 2020. *Discussion paper on pan-tumour biomarker testing to determine eligibility for targeted treatment*. [online] Available at: https://www.msac.gov.au/sites/default/files/2024-10/discussion-paper-on-pan-tumour-biomarker-testing-to-determine-eligibility-for-targeted-treatment.pdf. [Accessed 4 Oct. 2025].

Mulder, J., Van Stuijvenberg, O.C., Van Hennik, P.B., Voest, E.E., Pasmooij, A.M.G., Stoyanova-Beninska, V. and De Boer, A., 2022. A Comparison of Post-marketing Measures Imposed by Regulatory Agencies to Confirm the Tissue-Agnostic Approach. *Frontiers in Medicine*, 9, p.893400. DOI: 10.3389/fmed.2022.893400.

Murphy, P., Glynn, D., Dias, S., Hodgson, R., Claxton, L., Beresford, L., Cooper, K., Tappenden, P., Ennis, K., Grosso, A., Wright, K., Cantrell, A., Stevenson, M. and Palmer, S., 2021. Modelling approaches for histology-independent cancer drugs to inform NICE appraisals: a systematic review and decision-framework. *Health Technology Assessment (Winchester, England)*, 25(76), pp.1—228. DOI: 10.3310/hta25760.

National Cancer Institute (NCI), 2025. *Agnostic Cancer Therapies (PDQ®)*. [online] Available at: https://www.cancer.gov/about-cancer/treatment/types/agnostic-cancer-therapies-hp-pdq. [Accessed 15 Sept. 2025].

NHSE, 2019. *Accelerated Access Collaborative Board Meeting Papers: Tumour Agnostic/Histology-Independent Products*. [online] Available at: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/01/aac006-histology-independent-therapies.pdf. [Accessed 4 Oct. 2025].

NHSE, 2022. *Accelerating genomic medicine in the NHS: A strategy for embedding genomics in the NHS over the next 5 years*. [online] Available at: https://www.england.nhs.uk/wp-content/uploads/2022/10/B1627-Accelerating-Genomic-Medicine-October-2022.pdf. [Accessed 4 Oct. 2025].

NHSE, 2025. *National genomic test directory*. [online] Available at: https://www.england.nhs.uk/publication/national-genomic-test-directories/. [Accessed 4 Oct. 2025].

NICE, 2020a. Entrectinib for treating NTRK fusion-positive solid tumours. [online] Available at: https://www.nice.org.uk/guidance/ta644/resources/entrectinib-for-treating-ntrk-fusionpositive-solid-tumours-pdf-82609138188997. [Accessed 9 Jan. 2025].

NICE, 2020b. Larotrectinib for treating NTRK fusion-positive solid tumours. [online] Available at: https://www.nice.org.uk/guidance/ta630/resources/larotrectinib-for-treating-ntrk-fusionpositive-solid-tumours-pdf-82609071004357. [Accessed 9 Jan. 2025].

NICE, 2022. NICE real-world evidence framework. [online] Available at: https://www.nice.org.uk/corporate/ecd9/resources/nice-realworld-evidence-framework-pdf-1124020816837. [Accessed 15 Sept. 2025].

NICE, 2023. Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency. [online] Available at: https://www.nice.org.uk/guidance/ta914/resources/pembrolizumab-for-previously-treated-endometrial-biliary-

colorectal-gastric-or-small-intestine-cancer-with-high-microsatellite-instability-or-mismatch-repair-deficiency-pdf-82615487137477#page=4&zoom=100,0,126. [Accessed 9 Jan. 2025].

NICE, 2025. NICE health technology evaluations: the manual. [online] Available at: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. [Accessed 15 Sept. 2025].

NMPA, 2021. *Provisions for Medical Device Registration and Filing*. [online] Available at: https://english.nmpa.gov.cn/2024-06/05/c_993242.htm. [Accessed 15 Oct. 2025].

NMPA, 2022. *Drug Approval Information Released on July 29, 2022*. [online] Available at: https://www.nmpa.gov.cn/zwfw/sdxx/sdxxyp/yppjfb/20220729132536104.html. [Accessed 3 Oct. 2023].

Oliva-Moreno, J., Puig-Junoy, J., Trapero-Bertran, M., Epstein, D., Pinyol, C. and Sacristán, J.A., 2020. Economic Evaluation for Pricing and Reimbursement of New Drugs in Spain: Fable or Desideratum? *Value in Health*, 23(1), pp.25—31. DOI: 10.1016/j.jval.2019.06.012.

Otsubo, Y., 2024. PMDA initiatives to enhance drug development via multi-regional clinical trials. *Translational and Clinical Pharmacology*, 32(4), pp.173—176. DOI: 10.12793/tcp.2024.32.e16.

PBAC, 2016. Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee, Version 5.0. [online] Available at: https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf. [Accessed 19 Sept. 2025].

PBAC, 2020. *Entrectinib Public Summary Document*. [online] Available at: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2020-03/files/entrectinib-psd-march-2020.pdf. [Accessed 24 Oct. 2025].

PBAC, 2021. *Pembrolizumab Public Summary Document*. [online] Available at: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2021-03/files/pembrolizumab-psd-mar-2021.pdf. [Accessed 24 Oct. 2025].

PBAC, 2022. *Larotrectinib - Public Summary Document — November 2021 PBAC Meeting with March 2022 Addendum*. [online] Available at: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2022-03/files/larotrectinib-psd-march-2022.pdf. [Accessed 19 Sept. 2025].

PBAC, 2024. *Public Summary Document - March 2024 Meeting (Larotrectinib)*. [online] Available at: https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2024-03/larotrectinib-Vitrakvi-PSD-March-2024. [Accessed 15 Sept. 2025].

Pitini, E., Baccolini, V., Isonne, C., Maran, P., Marzuillo, C., Villari, P., Galeone, D. and Vaia, F., 2024. Public health genomics research in Italy: an overview of ongoing projects. *Frontiers in Public Health*, 12, p.1343509. DOI: 10.3389/fpubh.2024.1343509.

PMDA, 2018. *Pembrolizumab: Report on the Deliberation Results*. [online] Available at: https://www.pmda.go.jp/files/000231921.pdf. [Accessed 3 Sept. 2025].

PMDA, 2019. *Entrectinib: Report on the Deliberation Results*. [online] Available at: https://www.pmda.go.jp/files/000232794.pdf. [Accessed 3 Sept. 2025].

PMDA, 2021. *Larotrectinib: Report on the deliberation results*. [online] Available at: https://www.pmda.go.jp/drugs/2021/P20210310002/630004000_30300AMX00251_A100_1.pdf. [Accessed 3 Sept. 2025].

PMDA, 2024. *Considerations for the Utilization of Master Protocol Trials in Drug Development*. [online] Available at: https://www.pmda.go.jp/files/000269475.pdf. [Accessed 3 Sept. 2025].

PMDA, 2025. *Information on CDx Products approved in Japan for the purpose of identifying the eligible patients*. [online] Available at: https://www.pmda.go.jp/english/rs-sb-std/rs/0027.html. [Accessed 5 Sept. 2025].

Price, C.P., McGinley, P. and John, A.S., 2020. What is the return on investment for laboratory medicine? The antidote to silo budgeting in diagnostics.

Puig-Junoy, J., Oliva-Moreno, J., Trapero-Bertran, M., Abellan-Perpiñan, J.M., Brosa-Riestra, M., and Servei Català de la Salut (CatSalut), 2014. *Guia i recomanacions per a la realització i presentació d'avaluacions econòmiques i anàlisis d'impacte pressupostari de medicaments en l'àmbit del CatSalut*.

Radu, P., Kumar, G., Cole, A., Fameli, A., Guthrie, M., Annemans, L., Geissler, J., Italiano, A., O'Rourke, B., Xoxi, E. and Steuten, L., 2024. Evolving assessment pathways for precision oncology medicines to improve patient access: a tumor-agnostic lens. *The Oncologist*, 29(6), pp.465—472. DOI: 10.1093/oncolo/oyae060.

Raymakers, A. and Skedgel, C., 2025. *Around the World in HTAs: Canada — Autonomous yet Collaborative - OHE*. [online] Available at: https://www.ohe.org/insights/around-the-world-in-htas-canada-provincially-driven-collaboratively-connected/. [Accessed 4 Sept. 2025].

Riboni, E., 2019. *General Overview of US HEALTHCARE Reimbursement Systems*. [online] Available at: https://info.idrmedical.com/blog/usa-medical-device-reimbursement. [Accessed 3 Sept. 2025].

Rodes Sanchez, M., Henderson, N. and Steuten, L., 2020. *Bridging the Gap: Pathways for Regulatory and Health Technology Assessment of Histology Independent Therapies*. [OHE Contract Research] London: OHE. Available at: https://www.ohe.org/publications/bridging-gap-pathways-regulatory-and-health-technology-assessment-histology-independent/. [Accessed 4 Oct. 2025].

Sachetti, C.G., Barbosa, A., Carlos Campos de Carvalho, A., Vianna Araujo, D. and Nunes da Silva, E., 2024. Challenges and opportunities for access to Advanced Therapy Medicinal Products in Brazil.

Schiller, J., Eckhardt, H., Schmitter, S., Alber, V.A. and Rombey, T., 2023. Challenges and Solutions for the Benefit Assessment of Tumor-Agnostic Therapies in Germany. *Value in Health*, 26(6), pp.854—864. DOI: 10.1016/j.jval.2023.01.011.

Shibata, S., Ozaki, K. and Suzuki, T., 2020. Japanese Pharmaceutical Industry: Recent Perspectives and Areas for Further Research. *Journal of Regulatory Science*, 8, pp.1—13. DOI: 10.21423/JRS-V08SHOYO.

Snow, S., Brezden-Masley, C., Carter, M.D., Dhani, N., Macaulay, C., Ramjeesingh, R., Raphael, M.J., Slovinec D'Angelo, M. and Servidio-Italiano, F., 2024. Barriers and Unequal Access to Timely Molecular Testing Results: Addressing the Inequities in Cancer Care Delays across Canada. *Current Oncology*, 31(3), pp.1359—1375. DOI: 10.3390/curroncol31030103.

Sugden, B.M., Grimm, S.E., Wolff, R., Armstrong, N., Otten, T., Abu-Zahra, T., Perry, M., Patel, M., Chen, J., Noake, C., Joore, M. and Witlox, W.J.A., 2024. Bayesian Hierarchical Modelling for Histology-Independent Time-to-Event Outcomes in the NICE Single Technology Appraisal of Pembrolizumab for Solid Tumours with MSI-H/dMMR: External Assessment Group Perspective. *PharmacoEconomics*, 42(6), pp.615—618. DOI: 10.1007/s40273-024-01381-z.

Sullivan, S.D., Watkins, J., Sweet, B. and Ramsey, S.D., 2009. Health Technology Assessment in Health-Care Decisions in the United States. *Value in Health*, 12, pp.S39—S44. DOI: 10.1111/j.1524-4733.2009.00557.x.

Tanaka, M., Idei, M., Sakaguchi, H., Kato, R., Sato, D., Sawanobori, K., Kawarasaki, S., Hata, T., Yoshizaki, A., Nakamura, M. and Ikuma, M., 2021. Evolving Landscape of New Drug Approval in Japan and Lags from International Birth Dates: Retrospective Regulatory Analysis. *Clinical Pharmacology and Therapeutics*, 109(5), pp.1265—1273. DOI: 10.1002/cpt.2080.

Tarricone, R., Amatucci, F., Armeni, P., Banks, H., Borsoi, L., Callea, G., Ciani, O., Costa, F., Federici, C., Torbica, A. and Marletta, M., 2021. Establishing a national HTA program for medical devices in Italy: Overhauling a fragmented system to ensure value and equal access to new medical technologies. *Health Policy*, 125(5), pp.602—608. DOI: 10.1016/j.healthpol.2021.03.003.

Tateo, V., Marchese, P.V., Mollica, V., Massari, F., Kurzrock, R. and Adashek, J.J., 2023. Agnostic Approvals in Oncology: Getting the Right Drug to the Right Patient with the Right Genomics. *Pharmaceuticals*, 16(4), p.614. DOI: 10.3390/ph16040614.

TGA, 2018. *Australian Public Assessment Report for Pembrolizumab*. [online] Available at: https://www.tga.gov.au/sites/default/files/auspar-keytruda-180530.pdf. [Accessed 24 Oct. 2025].

TGA, 2019. *KEYTRUDA (Merck Sharp & Dohme (Australia) Pty Ltd)*. [online] Available at: https://www.tga.gov.au/resources/prescription-medicines-registrations/keytruda-merck-sharp-dohme-australia-pty-ltd-5. [Accessed 4 Sept. 2025].

TGA, 2020a. Australian public assessment report for Entrectinib. [online] Available at: https://www.tga.gov.au/sites/default/files/auspar-entrectinib-201211.pdf. [Accessed 4 Sept. 2025].

TGA, 2020b. Australian public assessment report for Larotrectinib. [online] Available at: https://www.tga.gov.au/sites/default/files/auspar-larotrectinib-201216.pdf. [Accessed 4 Sept. 2025].

Thokagevistk, K., Coppo, C., Rey, L., Carelli, A., Díez, V., Vaselenak, S., Oliveira, L., Patel, A., Sicari, E., Ramos, T., Schach, S., Schirghuber, E., Simpson, A., Choquet, R. and Le Lay, K., 2024. Real-World Evidence to Reinforce Clinical Trial Evidence in Health Technology Assessment: A Critical Review of Real-World Evidence Requirements from Seven Countries and Recommendations to Improve Acceptance. *Journal of Market Access & Health Policy*, 12(2), pp.105—117. DOI: 10.3390/jmahp12020009.

Toumi, M., Motrunich, A., Millier, A., Rémuzat, C., Chouaid, C., Falissard, B. and Aballéa, S., 2017. Analysis of health economics assessment reports for pharmaceuticals in France — understanding the underlying philosophy of CEESP assessment. *Journal of Market Access & Health Policy*, 5(1), p.1344088. DOI: 10.1080/20016689.2017.1344088.

Trapero-Bertran, M., Puig-Junoy, J., Alegre-del-Rey, E.J., Clopés, A., Lobo, F. and Ortega, A., 2025. Reform of economic evaluation of medicines in Spain: proposals from the Advisory Committee for Pharmaceutical Financing. *Gaceta Sanitaria*, [online] 39. DOI: 10.1016/j.gaceta.2024.102439.

Trinity Life Sciences, 2022. *Brazil's Latest Updates to Drug Coverage*. [online] Trinity Life Sciences. Available at: https://trinitylifesciences.com/blog/brazils-latest-updates-to-drug-coverage-in-the-private-sector-anticipated-impact-and-implications/. [Accessed 7 Sept. 2025].

Vargas, D., 2019. *Nova terapia-alvo aprovada no Brasil para diversos tipos de tumores*. [online] Manual de Oncologia Clínica do Brasil. Available at: https://mocbrasil.com/blog/noticias/nova-terapia-alvo-aprovada-no-brasil-para-diversos-tipos-de-tumores/. [Accessed 1 Sept. 2025].

Vellekoop, H., Huygens, S., Versteegh, M., Szilberhorn, L., Zelei, T., Nagy, B., Koleva-Kolarova, R., Wordsworth, S., Rutten-van Mölken, M., and HEcoPerMed consortium, 2023. Cost-effectiveness of alternative NTRK testing

strategies in cancer patients followed by histology-independent therapy with entrectinib: an analysis of three European countries. *Personalized Medicine*, 20(4), pp.321—338. DOI: 10.2217/pme-2022-0070.

Vranic, S., Basu, G.D., Hall, D.W. and Gatalica, Z., 2022. Tumor-Type Agnostic, Targeted Therapies: BRAF Inhibitors Join the Group. *Acta Medica Academica*, 51(3), pp.217—231. DOI: 10.5644/ama2006-124.392.

Wang, S., Yang, Q., Deng, L., Lei, Q., Yang, Y., Ma, P., Men, Y., Yung, B.C., Lee, R.J., Zhang, M. and Li, N., 2022. An overview of cancer drugs approved through expedited approval programs and orphan medicine designation globally between 2011 and 2020. *Drug Discovery Today*, 27(5), pp.1236—1250. DOI: 10.1016/j.drudis.2021.12.021.

Westphalen, C.B., Martins-Branco, D., Beal, J.R., Cardone, C., Coleman, N., Schram, A.M., Halabi, S., Michiels, S., Yap, C., André, F., Bibeau, F., Curigliano, G., Garralda, E., Kummar, S., Kurzrock, R., Limaye, S., Loges, S., Marabelle, A., Marchió, C., et al., 2024. The ESMO Tumour-Agnostic Classifier and Screener (ETAC-S): a tool for assessing tumour-agnostic potential of molecularly guided therapies and for steering drug development. *Annals of Oncology*, 35(11), pp.936—953. DOI: 10.1016/j.annonc.2024.07.730.

Weymann, D., Pollard, S., Lam, H., Krebs, E. and Regier, D.A., 2023. Toward Best Practices for Economic Evaluations of Tumor-Agnostic Therapies: A Review of Current Barriers and Solutions. *Value in Health*, 26(11), pp.1608—1617. DOI: 10.1016/j.jval.2023.07.004.

Wilsdon, T., Horgan, D. and Akkermans, M., 2022. *ISPOR - Accelerating Patient Access to Next-Generation Sequencing in Oncology: A Plan of Action*. [online] Available at: https://www.ispor.org/publications/journals/value-outcomes-spotlight/vos-archives/issue/view/a-plan-of-action-accelerating-patient-access-to-next-generation-sequencing-in-oncology/accelerating-patient-access-to-next-generation-sequencing-in-oncology-a-plan-of-action. [Accessed 4 Sept. 2025].

Yamate, M., 2016. Update of Drug Pricing System in Japan. [online] Available at: https://www.pmda.go.jp/files/000221888.pdf.

Yip, S., Christofides, A., Banerji, S., Downes, M.R., Izevbaye, I., Lo, B., MacMillan, A., McCuaig, J., Stockley, T., Yousef, G.M. and Spatz, A., 2019. A Canadian Guideline on the Use of Next-Generation Sequencing in Oncology. *Current Oncology*, 26(2), pp.241—254. DOI: 10.3747/co.26.4731.

Yoshino, T., Pentheroudakis, G., Mishima, S., Overman, M.J., Yeh, K.-H., Baba, E., Naito, Y., Calvo, F., Saxena, A., Chen, L.-T., Takeda, M., Cervantes, A., Taniguchi, H., Yoshida, K., Kodera, Y., Kitagawa, Y., Tabernero, J., Burris, H. and Douillard, J.-Y., 2020. JSCO—ESMO—ASCO—JSMO—TOS: international expert consensus recommendations for tumour-agnostic treatments in patients with solid tumours with microsatellite instability or NTRK fusions. *Annals of Oncology*, 31(7), pp.861—872. DOI: 10.1016/j.annonc.2020.03.299.

Zhu, X. and Chen, Y., 2024. Bridging the new drug access gap between China and the United States and its related policies. *Frontiers in Pharmacology*, 14, p.1296737. DOI: 10.3389/fphar.2023.1296737.

# Appendix

## A. Case study regulatory evidence

| | PEMBROLIZUMAB | ENTRECTINIB | LAROTRECTINIB |
|---|---|---|---|
| FDA | **TA approval 2017**<br>▪ Pooled efficacy from five trials (n = 149)<br>▪ Trials include: KEYNOTE-164, KEYNOTE-016A, KEYNOTE-016C, KEYNOTE-158, KEYNOTE-012, KEYNOTE-028 (Mulder et al., 2022)<br>▪ Primary endpoint: ORR<br>▪ Pooled safety from two trials (n = 89) | **TA approval 2019**<br>▪ Pooled efficacy from three trials (n = 54)<br>▪ Trials include: ALKA-371-001, STARTRK-1, STARTRK-2 (FDA, 2019b)<br>• Pooled safety from three trials (Mulder et al., 2022) | **TA approval 2018**<br>▪ Pooled efficacy from three trials (n = 55)<br>▪ Trials include: LOXO-TRK-14001, SCOUT, NAVIGATE (FDA, 2018b)<br>• Pooled safety from three trials (n = 176) |
| EMA | **No TA approval**<br>▪ Pooled efficacy and safety data from two basket trials submitted for multiple tumours<br>▪ Approved only for multi-tumour, but not for TA<br>▪ Trial include: KEYNOTE-164 single-arm study in MSI-H/dMMR CRC (n=124) and interim analysis of KEYNOTE-158 (cohort K) single-arm basket study in non-CRC MSI-H/dMMR solid tumours (n=179) (EMA, 2022) | **TA approval 2020**<br>▪ Pooled efficacy from three trials (n = 286)<br>▪ Trials include: ALKA-371-001, STARTRK-1, STARTRK-2, STARTRK-NG, TAPISTRY (EMA, 2020a)<br>• Pooled safety from five trials (n = 853) | **TA approval 2019**<br>▪ Pooled efficacy from three trials (n = 242)<br>▪ Trials include: LOXO-TRK-14001, SCOUT, NAVIGATE (Mulder et al., 2022)<br>• Pooled safety from three trials (n = 176) |
| PMDA | **TA approval 2018**<br>▪ Separately presented efficacy and safety data from two trials (n = 155)<br>▪ Trials include: KEYNOTE-158, KEYNOTE-164 (Mulder et al., 2022)<br>• Primary endpoint: ORR | **TA approval 2019**<br>▪ Separately presented efficacy and safety data from three trials (n = 341)<br>▪ Trials include: ALKA, STARTRK-1, STARTRK-2 (PMDA, 2019) | **TA approval 2021**<br>▪ Efficacy and safety data from two trials<br>▪ Trials include: SCOUT, NAVIGATE (PMDA, 2021) |

| | PEMBROLIZUMAB | ENTRECTINIB | LAROTRECTINIB |
|---|---|---|---|
|  **TGA** | **TA approval 2018**<br>• Pooling of data on objective response rate and response duration across multiple different tissue types in a single-arm trial (KEYNOTE-013, KEYNOTE-087) (TGA, 2018, 2019) | **TA approval 2020**<br>• Pooled data on objective response rate and response duration across three single-arm trials (n = 51) (TGA, 2020a)<br>• These include: ALKA, STARTRK-1, STARTRK-2<br>• Integrated safety data across three trials in different patient populations were considered. | **TA approval 2020**<br>• Pooled efficacy data on objective response rate and response duration across three single-arm trials (n = 164) (TGA, 2020b)<br>• Trials include: LOXO-TRK-14001, SCOUT, NAVIGATE<br>• Integrated safety data across three trials in adult and paediatric populations were considered. |
|  **Health Canada** | **TA approval 2024**<br>Initial decision:<br>▪ Efficacy on objective response rate and response duration, and safety data across two single-arm trials (Health Canada, 2019a)<br>▪ Trials include: KEYNOTE-164, KEYNOTE-158<br>Updated decision:<br>• Additional data from KEYNOTE-158 and KEYNOTE-051 (Health Canada, 2024) | **TA approval 2020**<br>▪ Efficacy data on objective response rate and response duration across three trials (n = 54)<br>▪ Trials include: ALKA, STARTRK-1, STARTRK-2 (Government of Canada, 2020)<br>▪ Overall safety data from four trials (n = 355) (Health Canada, 2020) | **TA approval 2019**<br>▪ Pooled efficacy data on across three trials (n = 73)<br>▪ Trials include: LOXO-TRK-14001, SCOUT, NAVIGATE (Government of Canada, 2021)<br>▪ Overall safety data from three trials (n = 176) (Health Canada, 2019b) |
|  **ANVISA** | **No TA approval**<br>• Efficacy (based on progression-free survival) and safety data from a phase 3 trial (KEYNOTE-177) for metastatic colorectal cancer (ANVISA, 2021) | **No TA approval**<br>Therapy not reviewed | **TA approval 2020**<br>• Pooled data on objective response rate, complete response, response duration and safety from two trials<br>• Trials include: SCOUT, NAVIGATE (CONITEC, 2021) |
|  **NMPA** | **TA approval 2023**<br>Data not found | **TA approval 2022**<br>Data not found | **TA approval 2022**<br>Data not found |

Table presents information from decisions makers as of September 2025

# B. Country Profiles

## Australia

*Regulatory — TGA*

When approving the three therapies, Australia's TGA considered both pooled and integrated analyses of efficacy and safety (TGA, 2020a; b). TGA's assessment reports referenced relevant regulatory guidance and clinical data reviewed by the US FDA for each therapy, suggesting that FDA approval outcomes may inform TGA decision-making (TGA, 2020b).

Pembrolizumab received approval via the provisional approval pathway for adults and children with unresectable or metastatic MSI-H/dMMR tumours that have progressed after prior treatment and lack satisfactory alternatives. The approval was based on pooled data from a single-arm trial assessing response rate and duration across multiple tumour types. However, to date, the TGA concluded that individual tissue sample sizes were too small to confirm the clinical utility of MSI-H/dMMR testing for each tumour type. It remains unproven whether MSI-H/dMMR status consistently predicts pembrolizumab's effectiveness across all tumour types. Continued approval depends on confirmatory trials verifying clinical benefits (TGA, 2019).

For entrectinib and larotrectinib, TGA considered pooled data on ORR and response duration across three single-arm trials (for each drug) with integrated safety data across three trials in different patient populations were considered (TGA, 2020a; b). For entrectinib, the agency notes that the absence of randomised data for assessing time-to-response endpoints is acceptable given the rarity of the condition, which makes randomised trials unfeasible (TGA, 2020a). However, uncertainty persists regarding the precision of response rate estimates, durability across specific histologies, and applicability in paediatric patients (TGA, 2020a). Additional conditions for submission included that the developer would provide the same post-marketing surveillance reports that they provide to the FDA (TGA, 2020a). For larotrectinib, the Australian indication aligned with that of the FDA and under the agreement that the developer will provide additional clinical data to confirm the medicine's clinical benefit (TGA, 2020b).

*HTA & Reimbursement*

In Australia, the PBAC, an independent expert body appointed by the government, evaluates medicines for inclusion in the subsidised Pharmaceutical Benefits Scheme (PBS). The PBAC bases its recommendations on assessments of a medicine's clinical effectiveness, safety, and cost-effectiveness, through economic evaluation. No new pharmaceutical can be listed unless the PBAC committee makes a positive recommendation (Australian Government Department of Health and Aged Care, 2025).

While the PBAC does not directly provide guidance for the use of RWE in its evaluations (PBAC, 2016), its use is generally accepted and has been used to support submissions in the past (Medicines Australia, 2020). RWE is typically used to estimate effects for baseline outcomes against which measures of relative effect can then be applied. However, whilst the PBAC is willing to accept this form of evidence, the uncertainty associated is reflected in the price of the intervention (OHE previous unpublished report).

While the PBAC prefers the use of "clinically relevant outcomes", they acknowledge the use of surrogate endpoints when those are not available at the time of submission (PBAC, 2016). Regulatory and HTA alignment remains limited with the PBAC, demonstrating a cautious approach toward basket trials. Key concerns include the reliability of single-arm trial designs, small patient populations, and heterogeneity in treatment responses (Department of Health and Aged Care, 2024a). Despite this, a recent HTA methods review commissioned by the government has recommended the development of further guidance on TA therapy evaluations, incorporating insights from international practices and stakeholder consultations (Department of Health and Aged Care, 2024b).

Currently, only larotrectinib has been conditionally approved for a TA indication through PBS for tumours that are either unresectable, locally advanced, metastatic, or locally advanced and unsuitable for surgery in adults and for adult or paediatric patients with NTRK fusion tumours. The PBAC did not recommend listing larotrectinib for adult patients with low frequency NTRK fusion tumours due to high and uncertain cost-effectiveness, limited and immature clinical data, and the availability of effective alternative treatments. While the resubmission identified specific tumour types and more appropriate comparators, the PBAC concluded that the claimed benefit of larotrectinib over current SoC was not convincingly demonstrated (PBAC, 2022). Meanwhile, entrectinib and pembrolizumab have no submission for TA indication to the PBAC (Department of Health and Aged Care, 2024a).

Reimbursement for TA therapies can be achieved through several mechanisms, including managed entry schemes, risk-sharing arrangements, or the Efficient Funding of Chemotherapy mechanism under Section 100 of the National Health Act 1953 (CHERE, 2023). TA therapies are evaluated through the 'co-dependent' pathway, where the PBAC assesses the medicinal product while the Medical Services Advisory Committee (MSAC) evaluates the associated diagnostic test (Department of Health and Aged Care, 2024a).

*Diagnostic readiness*

Australia's co-dependent pathway facilitates TA therapy uptake, requiring parallel assessment of the therapy by the PBAC and the associated test by the MSAC (Department of Health and Aged Care, 2024a). Although proposed in consultations, this approach is not yet universally applied to all TA therapies. Once approved, therapies are subsidised under the PBS, and companion diagnostics under the Medicare Benefits Schedule (Department of Health and Aged Care, 2024a).

Novel technologies such as NGS remain mostly limited to public insurance (APAC Med, 2024; Wilsdon, Horgan and Akkermans, 2022). However, small gene panels are expanding and increasingly reimbursed for specific cancers (APAC Med, 2024). Molecular testing for NTRK fusion testing, relevant to entrectinib and larotrectinib, is available (Department of Health and Aged Care, 2024a). MSI-H/dMMR testing for pembrolizumab is available but not consistently implemented at diagnosis (MSAC, 2020).

The National Health Genomics Policy Framework aims to integrate genomics into the healthcare system (Australian Health Ministers' Advisory Council, 2022), while ongoing methods consultation calls for TA therapy-specific guidance, presenting opportunities for future adoption (Department of Health and Aged Care, 2024b).

## Brazil

*Regulatory — ANVISA*

ANVISA's evidence requirements align closely with those of other regulatory agencies, owing to its involvement in various regulatory harmonisation forums (Ivama-Brummell et al., 2023). In addition, the agency has issued non-binding guidelines for cancer trial outcomes intended for cases where direct clinical benefit measures are not feasible (ANVISA, 2015). Larotrectinib became the first drug approved in Brazil for a molecular alteration, independent of tumour site, using efficacy and safety data from three clinical trials involving adult and paediatric patients with metastatic tumours harbouring NTRK gene fusions (Vargas, 2019). Despite ANVISA's swift approval of larotrectinib, no evidence was found of a regulatory submission for entrectinib as a TA therapy. Similarly, no records were identified for the submission of pembrolizumab as a TA therapy, though the drug is approved for over 25 indications through ANVISA (Costa, 2022), including for treating metastatic colorectal cancer with MSI-H/dMMR (ANVISA, 2021).

*HTA & Reimbursement*

In Brazil, the National Committee for Health Technology Incorporation (CONITEC) advises the Ministry of Health on the adoption and disinvestment of health technologies within the national healthcare system, as well as the development of clinical guidelines. The recommendations are based on evidence regarding the efficacy, effectiveness, and safety of medicines, alongside economic evaluations conducted from the perspective of the public healthcare system (INAHTA, 2025). A recent study analysing the decision criteria influencing CONITEC's cancer treatment recommendations from 2012 to 2018 found that the agency prioritises budgetary impact, followed by effectiveness and cost-effectiveness (Campolina, Yuba and Soárez, 2022). However, in its final recommendations, effectiveness and efficacy were the most frequently considered factors.

While Brazil has no formally published guidance on the use of RWE, there is evidence that CONITEC considers RWE in its appraisals (Thokagevistk et al., 2024). The agency's methodological guidelines do not support the use of surrogate outcomes (Ministério da Saúde - Secretaria de Ciência, 2014). However, a recent recommendation report appears to have considered surrogate outcomes, though it ultimately resulted in a negative decision on the intervention (CONITEC, 2020).

Regulatory approval alone does not guarantee reimbursement, and coverage varies significantly between public and private payers (Kelner et al., 2023). In the private sector, intravenous cancer drugs receive mandatory coverage upon regulatory approval under the National Agency of Supplementary Health (ANS), whereas oral oncology products require HTA evaluation before being included in ANS's coverage list (Kelner et al., 2023).

In the public sector, all health technologies require HTA evaluation following regulatory approval (Kelner et al., 2023). However, if a drug has already been approved by CONITEC, its coverage by ANS becomes mandatory. Furthermore, the Brazilian Superior Court of Justice has determined that the ANS list should be considered "illustrative," implying that the absence of a specific intervention from the list does not automatically preclude patient coverage (Trinity Life Sciences, 2022). In such cases, coverage may be granted for medications prescribed by a physician, provided their use is scientifically justified and that they are reimbursed by CONITEC or another recognised international HTA agency (Trinity Life Sciences, 2022).

Securing reimbursement for high-cost, advanced treatments remains a significant challenge (Sachetti et al., 2024), and pricing regulation complexities further hinder access, contributing to an unpredictable reimbursement landscape for treatments, including TA therapies.

Pembrolizumab is currently approved by ANS and has not been submitted to HTA evaluation through CONITEC (Costa, 2022). In contrast, larotrectinib was submitted for TA status approval, however, it was not recommended for adoption in the national healthcare system (CONITEC, 2021). This decision was based on the limitations of the available clinical evidence. The recommendation highlights concern regarding the use of surrogate endpoints without established correlation to final clinical outcomes. Additionally, the absence of a comparator arm and the limited sample size, particularly for certain tumour types included in the study, further contributed to the negative recommendation (CONITEC, 2021). Entrectinib has not received marketing authorisation in Brazil, therefore, it has not been considered for HTA evaluation or reimbursement.

*Diagnostic readiness*

Brazil does not have a standardised framework for approving and evaluating companion diagnostics, including molecular testing for TA therapies. Access barriers exist for both targeted therapies and testing technologies, where companion tests are not necessarily included in the drug label (Ferreira et al., 2016). Consequently, genetic testing is available but restricted to laboratories with the necessary resources and capabilities.

Availability of diagnostic tests such as IHC screening and NGS depends on tumour types, with certain tests only covered by private insurance (Da Cunha et al., 2021).

Efforts to advance genomic medicine, exemplified by the Brazilian Rare Genomes Project, which aims to enhance the implementation of genomic technologies for rare diseases (Coelho et al., 2022). However, a comprehensive national strategy specifically targeting the integration of molecular testing into routine oncology care is still lacking.

## Canada

*Regulatory — Health Canada*

Health Canada considered both pooled and integrated analyses in its regulatory decisions. Health Canada initially approved pembrolizumab for a multi-tumour indication in April 2019 (Health Canada, 2019a), but its label was updated to a TA indication in August 2024 (Health Canada, 2024). Initially, the developer submitted a supplemental application based on two phase II studies—KEYNOTE-164 and KEYNOTE-158—similar to those reviewed by the FDA and EMA (Health Canada, 2019a). However, Health Canada did not recognise a TA indication and limited the indication to colorectal and endometrial cancers. This tumour-specific approach was adopted due to concerns that the number of patients and the follow-up duration for each tumour type were too limited to demonstrate clear improvements in primary or secondary outcomes across all tumour histologies. In August 2024, the regulatory label was updated to include a TA indication for solid tumours. This updated approval was supported by additional efficacy data in adults and paediatric patient populations demonstrating sustained duration in response (Health Canada, 2024), which addressed Health Canada's earlier concerns. Despite the smaller dataset available for paediatric patients, the integration of adult data was deemed clinically meaningful and sufficient to support inclusion of the broader patient population.

Health Canada granted TA indications to larotrectinib (2019) and entrectinib (2020), under the Notice of Compliance with Conditions (NOC/c) expedited pathway (Government of Canada, 2020, 2021). Compared to MSI-H/dMMR, NTRK fusions are rarer and associated with less heterogeneous treatment effects across tumour types. Their rarity, lack of alternative therapies, and consistent response rates may support earlier TA approval (Bebb et al., 2021), illustrating how biomarker characteristics can influence regulatory decision-making.

*HTA & Reimbursement*

In all Canadian provinces excluding Quebec, the HTA of pharmaceuticals is conducted by Canada's Drug Agency (CDA-AMC; previously CADTH), an independent expert body funded by the federal, provincial, and territorial governments (CDA-AMC, 2024a; Raymakers and Skedgel, 2025). Its recommendations are based on economic evaluations, primarily cost-utility analysis (CUA), to assess the trade-offs between cost and health outcomes (CDA-AMC, 2017). While healthcare budgets are administered regionally in Canada, this centralised process reduces duplication of effort across jurisdictions. Nevertheless, reimbursement decisions are made at the level of government-funded drug programs. While CDA-AMC's recommendations are non-binding, drug programs consider them alongside jurisdictional priorities, financial resources, and policy mandates when making reimbursement decisions (CDA-AMC, 2025c).

In November 2024, CDA-AMC launched a consultation on a new methods guide aimed at improving the generation and reporting of clinical evidence by drug sponsors. While the guide does not specifically address TA or basket trial considerations, it discusses the need for surrogate endpoints to be justified and validated, as well as methodologies for ITCs and single-arm trials, all methodological aspects relevant for TA therapies. The document was

open for feedback until January 2025 and the final version is not available at the time of this reports publication.

CDA-AMC acknowledges the rising use of basket trial designs and highlights their challenges for economic analyses (CDA-AMC, 2021a). The agency noted that BHMs are suitable for analysing clinical and economic data from basket trials, as they allow for information sharing across tumour types and help account for heterogeneity in treatment effects.

CDA-AMC provides separate recommendations, outside of the official guidelines, for reporting surrogate endpoints (CDA-AMC, 2025d) and RWE (CDA-AMC, 2023), signalling their consideration in supporting HTA decision-making. We note that the surrogate endpoints guidance is not an official CDA-AMC document, but a whitepaper in collaboration with NICE in the UK, and the Institute for Clinical and Economic Review (ICER) in the US. Both guidance documents aim to consolidate existing global guidance for reporting RWE and surrogate endpoints, adapting them to the Canadian context. They emphasise the need for increased transparency and detailed justification of choice for study design, model structure and final outcomes.

To note, CDA-AMC is the only national HTA agency to issue TA-specific guidance on the economic evaluation of TA therapies, outlining the evidence requirements for economic evaluation in the context of TA therapies (CDA-AMC, 2021a). As of January 2025, entrectinib (CDA-AMC, 2022), larotrectinib (CDA-AMC, 2021b), and pembrolizumab (CDA-AMC, 2025b) have been conditionally approved and recommended for reimbursement in their TA indications.

The province of Quebec has its own HTA body, INESSS which conducts appraisals according to their own guidelines. These guidelines are similar to other developed HTA bodies', with the main difference being INESSS' consideration of a broader perspective. INESSS has stipulated eligibility requirements for TA therapies to specify a minimum level of evidence needed (INESSS, 2025). The number of patients is at least 35 per tumour site evaluated, but may come from different studies or data sources. For each tumour site to be evaluated ORR ≥ 60% or ORR ≥ 20% AND duration of response ≥ 9 months. While the requirement offers some guidance for evidence requirement, the rationale is unclear and could pose additional access barriers, when compared to a more flexible approach adopted by CDA-AMC.

*Diagnostic readiness*

Canada has no standardised national mechanism for biomarker testing reimbursement. While HTA informs diagnostic reimbursement, access varies by biomarker and region due to budgetary considerations (Liu et al., 2022). The funding and availability of NGS varies across provinces, but large gene panels are increasingly available (Yip et al., 2019). Snow et al. (2024) highlight the need for a unified national approach to ensure equitable access to molecular testing, particularly for patients in underfunded regions.

NTRK fusion testing is not universally available across public drug programs and cancer agencies (CDA-AMC, 2022). As testing methods for detecting NTRK fusion evolve, jurisdictions may need a standardised approach to ensure equitable access. MSI-H/dMMR testing is routinely performed in many solid tumours, with experts recommending expansion to rarer cancers and paediatric patients (CDA-AMC, 2025a).

The Pan-Canadian Genomics Strategy, currently in development, aims to integrate genomics into healthcare, potentially improving molecular testing access for TA therapies (Government of Canada, 2022).

## China

*Regulatory — NMPA*

NMPA follows standard regulatory review criteria (efficacy and safety), with the approval of oncology medicines generally mirroring US practices (Li et al., 2018). Nevertheless, there is a "drug access gap" when drugs are approved in China versus the US. To tackle this, China has provided guidelines for non-Chinese developers to use their global data and save costs on additional data to confirm efficacy in Chinese populations (Zhu and Chen, 2024). It is worth noting that NMPA was the first agency to approve another molecule for patients with MSI-H and dMMR solid tumours (tislelizumab), based on a phase 2 single-arm trial conducted in China (BeiGene, 2022).

China has introduced several expedited approval programmes since 2017 and provides accelerated approval for innovative medicines, including TA drugs (Wang et al., 2022). In cancer types where an established SoC does not yet exist, NMPA accepts single-arm trial designs (Li et al., 2018). No publicly available regulatory approval documents for these therapies were found.

*HTA & Reimbursement*

China does not have a dedicated HTA agency, instead HTA is overseen by the NHSA which reviews the list of drugs eligible for the National Reimbursement Drug List (NRDL) and subsequent national reimbursement (Chen et al., 2023a). The appraisal process follows a two-stage approach: an initial brief examination of new drugs, followed by a more in-depth analysis for those selected for price negotiation. Evaluation criteria include clinical value, cost-effectiveness, and budget impact analysis, with assessments conducted independently by two experts (Chen et al., 2023a).

Published evidence on reimbursement decision-making remains limited, restricting our understanding of the evidence and information used in these evaluations (Chen et al., 2023a). Nevertheless, recent report suggests that the pace of incorporating cancer drugs into China's national reimbursement list has accelerated, leading decision-makers to be more accepting of slightly less rigorous data to address treatment gaps (Ling et al., 2022).

The inclusion of entrectinib and larotrectinib in the NRDL signals the acceptance of these innovative medicines[4]. Despite this, methodological inconsistencies, limited HTA expertise, and challenges of integrating evidence into healthcare decision-making remain present (Chen et al., 2023b), and may make the access to emerging TA therapies uncertain.

*Diagnostic readiness*

In China, the NMPA evaluates diagnostics as medical devices. Diagnostic tools for rare diseases or tumours, including those related to TA therapies, may qualify for priority registration procedures (NMPA, 2021). NGS panels have been prioritised for evaluation and approval, with four Chinese-manufactured panels approved in 2018—all targeting lung and/or colorectal cancer (Li et al., 2021). However, no publicly available framework exists for evaluating or reimbursing molecular testing for TA therapies.

The availability of NGS varies between provinces and hospitals, and remain funded by out-of-pocket payments by patients (APAC Med, 2024; Wilsdon, Horgan and Akkermans, 2022). Testing availability for the case study biomarkers was not found but it seems to be largely tumour-type dependent. Testing for gastric cancers are well-established, including those for NTRK fusion and MSI-H/dMMR (Deng et al., 2024). However, the geographic distribution of molecular testing centres is uneven, leading to disparities in testing access (Li et al., 2021).

*[4] Though not part of the selected case studies for this report, it is noteworthy that the first TA approval in China was received by a domestically developed PD-1 inhibitor for MMRd/MSI-H in Nov 2021 (BeiGene, 2022), which may imply that the payer accepts the TA evidence package of PD-1 in the case of MSI-H/ dMMR.*

Although no nationwide strategy has been established for the broader implementation of pharmacogenetic or molecular testing, clinical experts have highlighted the crucial role of molecular markers in guiding use of targeted therapies and personalised medicine tailored to the Chinese population (Ainiwaer et al., 2024).

## EU

*Regulatory — EMA*

The EMA has adopted a more cautious approach compared to the FDA, placing greater emphasis on the need for robust tumour-specific evidence. Pembrolizumab was granted standard marketing authorisation in 2022 for the treatment of cancers with MSI-H/dMMR biomarkers, five years after the FDA's TA approval. The EMA required more comprehensive data, including an expanded dataset with 30 additional patients, and approved pembrolizumab only for five specific tumour types: colorectal (CRC), endometrial, gastric, small intestine, and biliary tract cancers. Pancreatic cancer was excluded due to insufficient evidence of clinical benefit. We note that pembrolizumab could not be considered for a conditional marketing authorisation as it was assessed under an extension of indication in the EU (EMA, 2025).

The European public assessment report in 2022 stated the proposed indication was to include a new indication for pembrolizumab for the treatment of MSI-H/dMMR CRC, endometrial, gastric, small intestine, biliary, or pancreatic cancer in adults who have received prior therapy (EMA, 2022). The Committee for Medicinal Products for Human Use noted the relatively small datasets submitted and requested further characterisation of efficacy post approval (EMA, 2022). On the other hand, they recognised the unmet medical need and the positive predictive value of MSI-H status. The committee concluded there was a positive benefit-risk assessment for a set of cancers (all except for pancreatic cancer) and mentioned that a fully tissue agnostic approach was not considered warranted as tissue of origin appears to be an important effect modifier for MSI-H tumours treated with pembrolizumab (EMA, 2022). This is in contrast with the US FDA that acknowledged the MSI-H/dMMR biomarker identifies a specific group of cancer patients who are likely to benefit from pembrolizumab and granted TA approval based on early evidence suggesting pembrolizumab's efficacy across multiple tumour types (FDA, 2019a).

In the case of larotrectinib and entrectinib, both were approved for their TA indications but were restricted to patients with no satisfactory treatment options. Notably, the EMA did acknowledge the TA nature of NTRK fusions as a valid biomarker, due in part to the rarity of these genomic alterations and the consistently high response rates observed across diverse tumour types (EMA, 2019b).

EMA's overall approach remains more conservative than FDA, placing emphasis on the need to provide additional evidence to justify broad TA indications—particularly in the context of treatment heterogeneity. While the EMA acknowledged basket trial data as valid evidence, it raised concerns regarding the limited sample sizes and the single-arm study design (EMA, 2019b, 2020b).

## France

*HTA & Reimbursement*

In France, HTA of pharmaceuticals is conducted by the French National Authority for Health (HAS) — an independent consultative agency which provides advice to the French government. While all technologies are assessed in terms of clinical benefit through the Transparency Committee (TC), only those showing high additional clinical benefit and high-

budget impact are subject to an economic evaluation through the Committee of Economic Evaluation and Public Health (CEESP). Guidance provided by CEESP inform price negotiations between the French government and the developer (Toumi et al., 2017). Reimbursement is determined by the national health insurance, and is primarily based on the product's therapeutic value, assessed by the TC, rather than its comparative effectiveness (Toumi et al., 2017).

HAS accepts the use of RWE, particularly those requested during the post-registration phase (HAS, 2021). Following an initial assessment, a post-registration study may be required to support a subsequent re-evaluation of the intervention's clinical benefit or added value, determined by the TC. HAS guidelines also acknowledged the use of surrogate endpoints for estimating survival when direct life-year measurements are unavailable, provided there is strong, established evidence supporting the surrogate's predictive value (HAS, 2020).

HAS' approach on TA therapy assessment does not align with that of regulators. Most notably, HAS does not accept the use of basket trials and rarity of genetic alteration as a sufficient justification for deviating from methodology based on comparative and RCT, as standard HTA requirements (HAS, 2020). This has translated into limited access to these treatments, as shown by our case studies.

To date, only larotrectinib has received approval for a TA indication for paediatric patients with refractory or relapsed, locally advanced or metastatic infantile fibrosarcoma or another soft tissue sarcoma with NTRK gene fusion, subject to submission of additional data (Hogervorst et al., 2024). This approval was supported by the submission of local paediatric registry data, which provided evidence specific to this population. Larotrectinib was not reimbursed for its adult indication due to 'insufficient' clinical benefit and 'absent' clinical added value. Similarly, entrectinib was assessed for its TA indication, but was deemed to have 'insufficient' clinical benefit and 'absent' clinical added value, resulting in a negative reimbursement decision (Hogervorst et al., 2024). For pembrolizumab, HAS issued recommendations based on tumour-specific indications, in line with the EMA approval.

The 2021 healthcare reform introduced the Early Access Authorisation programme, which allows pre-approval access for therapies addressing high unmet medical needs (Matthews and Capdevila, 2022). This facilitates access to innovative and oncology therapies such as TA therapies.  For example, pembrolizumab was provided through this programme (Matthews and Capdevila, 2022).

*Diagnostic readiness*

Diagnostics for TA therapies are evaluated by the National Committee for the Evaluation of Medical Devices and Health Technologies, in parallel with the medicinal product by HAS (HAS, 2020). Both the test and therapy must comply with HAS methodological guidelines to be eligible for reimbursement.

The network of public-funded molecular diagnostic centres provides access to technologies such as NGS, IHC, fluorescent in-situ hybridisation (FISH), and polymerase chain reaction across France (LEK, 2021; Bayle et al., 2023). The availability and reimbursement of both single and multi-biomarker testing are considered high (LEK, 2021). While specific information on testing availability for the case study biomarkers was not identified, France's Genomic Medicine Plan 2025 (PFMG2025) aims to integrate genomic sequencing into routine care for patients with cancer and rare diseases (AVIESON, 2024). Launched in 2016, PFMG2025 seeks to position France as a leader in personalised medicine by offering sequencing to 50,000 cancer patients annually (AVIESON, 2024). This presents a significant opportunity to support access to TA therapies. Ongoing efforts will require scaling up testing capacity and clinician training in genomics to improve equitable access (Abadie et al., 2025).

# Germany

*HTA & Reimbursement*

In Germany, once a pharmaceutical receives marketing authorisation, it immediately becomes eligible for reimbursement under the compulsory statutory health insurance (GKV) (IGES, 2021). The initial price can be set by the developer for the first 6 months after marketing approval. Following this, the reimbursement price is decided based on an assessment of additional benefit compared to current alternatives. The benefit assessment is conducted by the Federal Joint Committee (G-BA) — the highest decision-making authority in the statutory health insurance system. The G-BA can delegate this responsibility to the Institute for Quality and Efficiency in Healthcare (IQWiG) or third parties. The result of the G-BA benefit assessment is the basis for deciding how much the statutory health insurance funds in Germany will pay for a new medicinal product with a new active substance (G-BA, 2025).

The G-BA can request the prospective generation of RWE as part of the benefit assessment process for drugs approved under orphan disease designations or conditional marketing authorisations (IGES, 2021). This means that reimbursement is restricted to healthcare providers who participate in this mandated evidence generation effort. The collected RWE is assessed according to a methodological framework designed by IQWiG (2020). This framework mandates comparative data, ensuring that studies meet high methodological standards.

Surrogate endpoints are only considered in benefit assessments if they have been validated using appropriate statistical methods in a well-defined patient group and with similar interventions (e.g., drugs with a comparable mode of action). A surrogate endpoint is deemed valid if the effect on the patient-relevant outcome can be sufficiently explained by its effect on the surrogate endpoint (IQWIG, 2023).

Germany's approach to the assessment of TA therapies does not align with that adopted by regulatory. There is no explicit mention or guidance on TA therapies and basket trials. While IQWiG acknowledges that single-arm studies may be acceptable for regulatory approval, such designs are generally not considered sufficient for HTA (IQWIG, 2020).

German HTA experts have highlighted significant challenges in assessing TA therapies, including the lack of appropriate comparators, reliance on ITCs, and complexities associated with the analysis of basket studies (Schiller et al., 2023). Despite these concerns in the HTA space and the low rating given by IQWiG (no additional clinical benefit proven), entrectinib and larotrectinib were reimbursed for their TA indications (Hogervorst et al., 2024). This aligns with the fact that reimbursement decisions in Germany are made by the G-BA, with IQWiG assessments informing price negotiations rather than determining coverage (IQWIG, 2023). Pembrolizumab is not reimbursed for its TA indication as this indication has not received a TA approval from the EMA.

*Diagnostic readiness*

Biomarker tests for targeted therapies are classified as companion diagnostics and are evaluated through a linked evidence approach by IQWiG, where the test's value is demonstrated via outcomes associated with the therapy (IQWIG, 2023). Diagnostics are assessed as part of the benefit evaluation under the Act on the Reform of the Market for Medicinal Products (AMNOG) framework (G-BA, 2025). Once the therapy and associated test are approved, reimbursement is possible—but coverage may vary regionally unless the test is included in the Uniform Value Scale.

The availability, reimbursement, and capabilities of biomarker testing are high, with a broad of NGS panels, IHC, and FISH (Bayle et al., 2023; LEK, 2021). No publicly available data were identified regarding testing availability for the case study biomarkers. However,

national initiatives such as genomeDE, aim to integrate genome sequencing into routine care, starting with cancer and rare diseases (Federal Ministry of Health, 2022). The National Decade Against Cancer, coordinated by the Federal Ministry of Education and Research, also seeks to advance personalised medicine and promote data sharing across care and research systems (BMBF, 2025). Together, these initiatives provide strong momentum for the integration of molecular diagnostics into clinical practice.

## Italy

*HTA & Reimbursement*

Italy currently operates multiple systems for the HTA of health interventions. The Italian Medicines Agency (AIFA) conducts HTA of pharmaceuticals at the national level, in addition to regulating and negotiating pricing for market access. However, healthcare budget responsibility in Italy is devolved to 21 administrative regions which have adopted a variety of HTA governance methods, often in combination with centralised regional procurement programs (Callea et al., 2017). AIFA's assesses the cost-effectiveness and financial sustainability of medicines to determine their reimbursement eligibility and pricing within the Italian national healthcare system (AIFA, 2025).

AIFA's guidelines are relatively brief and provide limited methodological direction, instead referring users to various ISPOR guidelines. Nevertheless, they acknowledge both RWE and surrogate outcomes in their guidelines. In the case of RWE, previous OHE unpublished research suggested that having precise identification of the target population, favouring data from the Italian context, is a key priority in Italy. This is motivated by the strong influence of payers that are focused on budget impact considerations. Guidance on surrogate outcomes is minimal, stating only that the uncertainty associated with their use should be addressed through scenario analyses (AIFA, 2020).

AIFA has not issued specific guidance or evidence requirements for the evaluation of TA therapies. To date, entrectinib and larotrectinib have been reimbursed for their TA indications through the Innovative Drug Fund (IDF) (AIFA, 2021a; b). Despite limited evidence and population heterogeneity, for both technologies, their treatment strategy was considered to represent a new therapeutic option when applied within diagnostic pathways that ensure appropriate testing and resource use. Under these conditions, entrectinib and larotrectinib were recognised as offering important added therapeutic value, which resulted in their approval for reimbursement (AIFA, 2021a; b). Meanwhile, pembrolizumab has received positive HTA recommendations for regional reimbursement for certain tumour types.

AIFA introduced the innovative drug status in April 2017 to guide access and funding decisions of high-impact therapies, particularly in oncology, which accounts for 50% of assessments (Lawlor et al., 2021). The Scientific Technical Advisory Committee (CTS) evaluates therapies based on three key criteria: unmet therapeutic need, added therapeutic value, and quality of clinical trial evidence. Based on these criteria, AIFA designates the therapies as innovative, conditionally innovative, or not innovative. Fully innovative therapies are granted access through the Innovative Drug Fund and are automatically included in regional formularies for 36 months, ensuring dedicated funding and prioritised access (Lawlor et al., 2021). Conditionally innovative therapies are included in regional formularies but do not receive funding from the Fund (Lawlor et al., 2021). TA therapies such as entrectinib and larotrectinib have been designated as innovative under this framework, securing time-limited reimbursement and highlighting Italy's strategic use of ring-fenced funding to support high-potential treatments.

*Diagnostic readiness*

Diagnostic assessment is conducted by the National Agency for Regional Health Services, the Italian National HTA Programme for Medical Devices, and the National Institute of Health (Tarricone et al., 2021). Approved diagnostics may be recommended for inclusion in the Essential Levels of Care and reimbursed through regional fee-for-service catalogues (Tarricone et al., 2021).

In Italy, there is a medium level of biomarker testing access, where technologies such as IHC and FISH are available, and NGS panels to a lesser degree (Bayle et al., 2023; LEK, 2021). Despite inclusion in national guidelines, significant regional differences in access remain due to regional variability in funding and testing infrastructure (LEK, 2021).

While testing availability for the case study biomarkers was not identified, Italy has taken early steps to integrate genomics into public health. As one of the first European countries that planned to integrate genomics into public health, Italy has launched several public health genomics projects including the Italian Genomic Strategy 2021-2023, a national initiative that aims to enhance genomic infrastructure and data access (Pitini et al., 2024). Given regional variability, improving national coordination, standardising testing protocols, and expanding workforce training are critical for equitable implementation of TA therapies.

## Spain

*HTA & Reimbursement*

In Spain, the HTA of new drugs is conducted by the Spanish Agency for Medicines and Healthcare Products (AEMPS), which informs P&R decisions for medicines included in the portfolio of 'common services'. Final reimbursement approval is granted by the Interministerial Committee on Pricing of Medicines and Healthcare Products (Epstein and Espín, 2020). However, healthcare budgets are managed regionally, allowing regional payers to negotiate prices below the official maximum and provide guidance on purchasing and prescribing (Oliva-Moreno et al., 2020).

P&R decisions consider several criteria, including disease severity, specific population needs, therapeutic and social value, incremental clinical benefit, cost-effectiveness, budget impact, availability of lower-cost alternatives, and the medicine's level of innovation. However, economic evaluation, defined as the comparative analysis of alternative healthcare interventions in terms of their costs and outcomes to determine which provides the best value for money—does not appear to play a central role in informing P&R decisions for new interventions (Trapero-Bertran et al., 2025). Instead, budget impact analysis carry significant weight in decisions, reflecting emphasis on short-term affordability (Oliva-Moreno et al., 2020).

While AEMPS does not explicitly reference RWE or surrogate outcomes in its pharmaceutical economic evaluation methods (MINISTERIO DE SANIDAD, 2023), regional guidelines indicate their inclusion. Catalonia's CatSalut guidelines advise decision-makers to prioritise data reflecting the real impact of treatments in routine practice. They also allow the use of intermediate outcomes, provided their direct link to a final outcome measure has been scientifically validated (Puig-Junoy et al., 2014).

To date, entrectinib and larotrectinib have been recommended for TA indications in Spain. Pembrolizumab was evaluated based on tumour-specific indications in line with the EMA approval, and was subsequently approved for reimbursement (AEMPS, 2015). AEMPS has not issued specific guidance on the assessment of TA therapies.

Larotrectinib, the first selective NTRK inhibitor to receive conditional approval in Spain, demonstrated antitumor activity across three single-arm phase I/II trials. Despite the heterogeneity of tumour types and study designs, it showed a high ORR and durable responses, particularly in rare tumours with a higher prevalence of NTRK fusions. Nevertheless, the AEMPS remain cautious toward the small patient populations, reliance on surrogate endpoints, and variability across studies, and uncertainties regarding long-term efficacy and safety. As a result, the approval is contingent on further evidence (AEMPS, 2022b).

Entrectinib received authorisation as monotherapy, showing a confirmed ORR of 73.4% and a central nervous system response rate of 50%. The median duration of response was 16.5 months, with progression-free survival of 16.8 months. Despite methodological limitations across pooled early-phase, single-arm studies with heterogeneous designs, these outcomes are considered clinically relevant—especially given the limited efficacy of first-line chemotherapy in this population. A post-authorisation study was underway at the time of the recommendation to clarify its comparative effectiveness, particularly in patients with brain metastases (AEMPS, 2022a).

Pooled analyses of efficacy and safety from single-arm basket trials have been accepted. However, key concerns have been raised, including absence of comparators, small and heterogeneous patient populations across limited tumour types, lack of long-term data, and uncertainties regarding the magnitude of clinical benefit.

*Diagnostic readiness*

Spain does not currently have a specific evaluation framework for molecular diagnostics associated with TA therapies. Reimbursement decisions for such tests are made at the regional level, contributing to access variability.

In 2024, the Ministry of Health launched the new Common Catalogue of Genetic and Genomic Tests, a significant step toward harmonising diagnostic testing nationally (ASEBIO, 2024). Funding is allocated to Autonomous Communities and the National Institute of Health Management, with future plans to expand testing through investments in laboratory equipment (Ministerio de Sanidad, 2025).

However, the level of access to biomarker testing is considered to be a low to medium, with greater availability for single biomarker tests and lower for those of multi-biomarker (LEK, 2021). IHC is routinely available, with other diagnostics such as FISH and NGS to a lesser extent (Bayle et al., 2023). Significant regional differences in test availability has been noted due to regional variability in funding and testing infrastructure (LEK, 2021).

Spain's national genomic strategy is driven by the IMPaCT initiative, particularly the IMPaCT-GENóMICA Programme, which focuses on developing genomic infrastructure and national sequencing networks (ibs.GRANADA, 2020). These programmes represent a significant opportunity to expand access to TA therapies by addressing regional disparities and improving test standardisation and capacity.

## UK

*HTA & Reimbursement*

NICE conducts appraisals of health technologies in England. NICE is an executive, non-departmental public agency of the Department of Health and Social Care in England, and the NHS is legally obliged to fund and resource medicines and treatments recommended by NICE's technology appraisals programme (GOV.UK, 2025). NICE's appraisals are based on estimates of the relative clinical effectiveness and value for money compared with

established practice in the NHS — and the methods for evaluation are outlined in its guidance (NICE, 2025).

NICE has a dedicated framework that defines when real-world evidence can be used and outlines best practices for planning, conducting, and reporting real-world evidence studies to enhance the quality and transparency of the data (NICE, 2022). NICE considers surrogate endpoints valid if strong evidence, typically from meta-analyses of high-quality clinical trials, shows they can reliably predict final health outcomes. However, in certain cases such as rare diseases, the evidence requirements may be more flexible. The validation process depends on the specific technology and patient group, and if a surrogate outcome is used in a different context, it must be justified with additional analysis, such as sensitivity and scenario analyses (NICE, 2022).

NICE has not published specific guidance on the assessment of TA therapies. However, in 2020, NICE authors published an analysis discussing how the clinical and cost effectiveness of histology-independent cancer drugs should be assessed (Cooper et al., 2020). The authors highlight potential limitations of basket trials, including that the evidence is limited to tumour sites included in the trial, which is not always comprehensive, and relies on assumptions that effectiveness is sufficiently similar across tumour sites. They conclude that patient access to TA therapies will likely rely on post-authorisation evidence generation and recommend companies seek early scientific advice from HTA bodies.

Entrectinib, larotrectinib, and pembrolizumab have been conditionally approved via the CDF, with entrectinib and larotrectinib reimbursed for their TA indications, consistently with the EMA approval (Hogervorst et al., 2024). The CDF provides interim funding pending further review of new evidence after a certain number of years. Treatments spent about 3 years on the CDF (Kang and Cairns, 2023), which is less than the maximum allowed time of 5 years, but nearly a year longer than the average specified time in the market access agreements made upon CDF entry (about 2 years) with the most important driver of this being uncertainty in the pivotal trial (Lumanity, 2022). While early evidence for both entrectinib and larotrectinib shows tumour responses across various cancer types, uncertainties remain due to limited data and lack of comparative trials. Nevertheless, given the potential of TA therapies, the CDF funding allows further data collection while ensuring these treatments are available to eligible patients.

Other initiatives that can be relevant for TA therapies are the Innovative Medicines Fund, which is similar to the CDF but not restricted to oncology medicines, and the Accelerated Access Collaborative, a partnership between the NHS, industry, government, and patient groups (NHSE, 2019).

Pembrolizumab, lacking a TA indication in Europe, has been assessed by NICE on a tumour-type basis, resulting in recommended decisions for all 5 tumour sites considered in the same Single Technology Assessment (STA) (NICE, 2023). All 5 tumour sites met the criteria for NICE's severity decision modifier, meaning that weights of 1.2 were applied to quality-adjusted life years (QALY) for colorectal, endometrial, gastric and small intestine cancer while a weight of 1.7 was applied to biliary tumour site QALYs. This was also the first NICE STA to utilise a BHM, which allows for information-borrowing across cohorts and can be used to address heterogeneity across different tumour types (Sugden et al., 2024). The NICE committee agreed that BHM is a useful approach but concluded that neither the BHM nor the approach presented (the partitioned survival modelling approach) was ideal, but both were plausible and could inform decision-making.

In the appraisals for entrectinib and larotrectinib, NICE acknowledged the rarity of NTRK gene fusions and the challenges posed by limited clinical data. The use of BHMs to support evidence synthesis was recognised, and both therapies received positive recommendations for use within the CDF (NICE, 2020a; b).

*Diagnostic readiness*

Diagnostics in the UK can be appraised through the NICE Diagnostics Assessment Programme or the standard Technology Appraisal process, when used in combination with a treatment. The costs of molecular testing are typically shared between developers and NHS England, with arrangements varying by product (Rodes Sanchez, Henderson and Steuten, 2020).

The National Genomic Test Directory specifies tests available across the NHS and outlines eligibility criteria by tumour type. The availability and reimbursement of both single and multi-biomarker tests is considered high in the UK (LEK, 2021). IHC is routinely available, with technologies such as FISH and NGS typically available for certain cancers (Bayle et al., 2023). NTRK testing is available for several tumour types and MSI testing is offered for a broad range of solid tumours (NHSE, 2025).

The NHS Genomic Medicine Service, established in 2018, aims to support routine genomic testing through seven regional Genomic Laboratory Hubs. Building on the Service, NHS England published a genomics strategy in 2022 (NHSE, 2022). The strategy outlines a five-year plan to embed genomics into routine care and enhance genomic data use. In the same year, over £175 million in government funding has been committed to genomics research, including £26 million to support an innovative cancer programme led by Genomics England (GOV.UK, 2022). These initiatives aim to translate genome sequencing into actionable clinical interventions, underpinning UK's commitment to deliver equitable and timely genomic testing for targeted treatment.

## Japan

*Regulatory — PMDA*

In Japan, due to differences in drug metabolism, tolerance, and dietary habits between Japanese and Western populations, the PMDA has historically required Japan-specific clinical trials (Tanaka et al., 2021). However, efforts are underway to reduce the delay caused by these additional study requirements. In addition, the PMDA recently released guidance on utilising master protocol trials (PMDA, 2024), offering recommendations for designing, conducting, and analysing non-traditional clinical trials, such as basket trials commonly used for TA therapies. We note that PMDA approvals of the case studies followed those of FDA by around one year, showing that there have not been significant delays in regulatory processes (Mulder et al., 2022).

For pembrolizumab, PMDA considered separately presented efficacy and safety data from two trials (KEYNOTE-164, KEYNOTE-158; n = 155), with ORR as primary endpoint. PMDA concluded that the efficacy and safety of pembrolizumab as first-line therapy had not been established leading to its TA indication to be limited to chemotherapy-treated patients who have no other standard treatment options (PMDA, 2018). Entrectinib and larotrectinib were approved in 2019 and 2021, respectively, both with the condition that the developer would develop and implement a risk management plan as well as collect additional post-marketing data to mitigate the small number of Japanese patients in the clinical trials (PMDA, 2019, 2021).

*HTA & Reimbursement*

In Japan, pharmaceuticals are reimbursed under the National Health Insurance (NHI), which is centrally administered by the Ministry of Health, Labour and Welfare (MHLW). Within the MHLW, the PMDA oversees regulatory review and marketing authorisation. Japan's HTA system does not determine whether a drug will be reimbursed (Kamae et al., 2020). Instead, newly approved pharmaceuticals gain reimbursed access to the Japanese market

within 60 to 90 days of receiving marketing authorization from the PMDA (Kamae et al., 2020).

The MHLW sets drug prices based on recommendations from the Central Social Insurance Medical Council (Chuikyo), with limited input from developers (Kamae et al., 2020). Once determined, prices are reported in the NHI drug price listing, with new drug listings occurring four times per year (Shibata, Ozaki and Suzuki, 2020).

Once pharmaceuticals enter the market, several mechanisms are in place to reduce prices during their patent protection period to control healthcare costs. These include an annual repricing system that adjusts prices based on the gap between the NHI price and the actual market price, as well as special rules for drugs with a greater-than-expected budget impact, such as market expansion repricing (Yamate, 2016). Since 2019, HTA has also been incorporated into the pricing framework.

HTA is primarily used to adjust prices for innovative or high-cost technologies that could significantly impact healthcare expenditure (Kamae et al., 2020). It is conducted by the Center for Outcomes Research and Economic Evaluation for Health (C2H) (C2H, 2024) and it involves a cost-effectiveness assessment. The C2H guidelines also refer to the use of RWE, asking for sufficient detail on the quality of the evidence provided outside of RCT studies. However, the process is complex, and vague eligibility criteria make it difficult for companies to predict whether their products will undergo HTA. Notably, oncology drugs qualify for special consideration price adjustments, allowing for higher threshold bands in pricing (MHLW, 2019).

Japan presents a distinct case, where only a limited number of technologies undergo full HTA evaluation. As a result, available assessments are neither generalisable nor specific to TA therapies. Nevertheless, entrectinib, larotrectinib and pembrolizumab are all reimbursed following receipt of regulatory approval.

*Diagnostic readiness*

In Japan, companion diagnostics including molecular tests for TA therapies are evaluated as medical devices by the PMDA and approved by the MHLW (PMDA, 2025). While no formal documentation has been published on evidence requirements, regulatory processes align with those used for therapeutics.

In 2019, the PMDA approved three multiplex cancer-panel tests under national health insurance, including two comprehensive genome profile (CGP) tests that assessed over 100 genes (Motoi and Yatabe, 2020). The availability and reimbursement of NGS is considered high in Japan. The C-CAT delivers NGS through designed institutions, supported by strong data and testing infrastructure such as the C-CAT genomic database (Kohno et al., 2022).

According to PMDA records, diagnostics for entrectinib, larotrectinib, and pembrolizumab have all been approved (PMDA, 2025). Although majority of CGP tests are covered, testing is currently restricted to designated hospitals in the National Cancer Genome Medicine Network and vary across provinces and limited to patients who have completed standard treatment (APAC Med, 2024).

Although no national genomic strategy has been identified, medical societies such as the Japan Society of Clinical Oncology are developing guidance for TA molecular testing, with the aim to addressing barriers such as low awareness, high costs, and assay standardisation (Kobayashi et al., 2025).

## USA

*Regulatory — FDA*

The FDA has been at the forefront of approving TA therapies, demonstrating a willingness to grant approvals based on early efficacy signals across histology-independent populations. This underscores its adaptable and innovative stance in addressing unmet medical needs. In all case studies, ORR was the primary endpoint (Mulder et al., 2022).

Finally, as pointed out in section 2, to date, the FDA is the only regulatory agency that has released TA-specific draft guidance. This is supplemented by further guidance on master protocols published in the same year and the previous guidance on clinical trial endpoints for cancer drugs (FDA, 2018a, 2022a).

*HTA & Reimbursement*

The US healthcare system consists of public and private payers. Following regulatory approval, a formal HTA of health interventions is not required to secure access and reimbursement (ICER, 2018). Instead, three essential elements must be addressed to ensure reimbursement: coding, coverage, and payment. Of these, coverage and payment are often informed by HTA processes (Riboni, 2019).

Therefore, individual private and public insurers may conduct their own assessments or rely on third-party HTA reports to guide reimbursement decisions. The Centres for Medicare & Medicaid Services, which oversees major publicly funded health programmes, commissions and reviews HTA evidence to inform coverage for services under Medicare and Medicaid (Sullivan et al., 2009). Within Medicare, injectable oncology medicines are covered under Part B, while oral therapies fall under Part D (Green, Ohn and Bach, 2020).

Key institutions contributing to HTA research include ICER and the Agency for Healthcare Research and Quality. These organisations develop independent evidence reports to support both public and private decision-makers in evaluating new technologies and improving care quality. To date, neither ICER nor AHRQ have published reviews for the three case studies considered in this report, nor for other TA therapies.

*Diagnostic readiness*

The FDA classifies molecular diagnostics for TA therapies as companion diagnostics (FDA, 2023). Molecular testing is widely adopted, with over 90% of tests recorded in the Genetic Testing Registry used for diagnostics (Halbisen and Lu, 2023). However, reimbursement and coverage vary across public and private payers and between states (ACS Cancer Action Network, 2024). NGS panels are broadly available via Medicare, but others payers limit NGS coverage to specific tumour types (Wilsdon, Horgan and Akkermans, 2022). For people with advanced cancer, some biomarker tests are covered by Medicare and Medicaid (American Cancer Society, 2022). In 18 US states, coverage of biomarker testing is mandated for all state-regulated plans (ACS Cancer Action Network, 2025). A report commissioned by the American Cancer Society Cancer Action Network found that payer coverage continues to expand, especially for biomarkers with FDA-approved therapies or inclusion in National Comprehensive Cancer Network guidelines (ADVI, 2023). While over two-thirds of payers cover NTRK fusion testing, coverage for MSI-H/dMMR is more inconsistent and varies by tumour types (ADVI, 2023).

Although the USA lacks a centralised national strategy for molecular testing, several healthcare systems and consortia are working collaboratively to develop guidelines and reduce inequities in testing access.

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