



Bridging the gap:  
Pathways for regulatory  
and health technology  
assessment of histology  
independent therapies

Marina Rodes Sanchez  
Nadine Henderson  
Lotte Steuten

[ohe.org](https://ohe.org)

CONSULTING | REPORT  
AUGUST 2020



**AUGUST 2020**

# Bridging the gap: pathways for regulatory and health technology assessment of histology independent therapies

**Marina Rodes-Sanchez**

Office of Health Economics, London

**Nadine Henderson**

Office of Health Economics, London

**Lotte Steuten**

Office of Health Economics, London

---

**Please cite this report as:**

Rodes Sanchez M., Henderson N., Steuten L., 2020. Bridging the Gap: Pathways for Regulatory and Health Technology Assessment of Histology Independent Medicines. OHE Consulting Report, London: Office of Health Economics. Available at: <https://www.ohe.org/publications/bridging-gap-pathways-regulatory-and-health-technology-assessment-histology-independent>

**Corresponding Author:**

Lotte Steuten  
[lsteuten@ohe.org](mailto:lsteuten@ohe.org)

For further information please contact:

**Lotte Steuten, PhD**

Vice-President and Head of Consulting, OHE  
Honorary Visiting Professor at City, University of London

**Tel** +44 (0)207 747 1441

**Email** [lsteuten@ohe.org](mailto:lsteuten@ohe.org)



## About OHE Consulting Reports

Many of the studies OHE Consulting performs are proprietary and the results are not released publicly. Studies of interest to a wide audience, however, may be made available, in whole or in part, with the client's permission. They may be published by OHE alone, jointly with the client, or externally in scholarly publications. Publication is at the client's discretion.

Studies published by OHE as OHE Consulting Reports are subject to internal quality assurance and undergo a rapid external review, usually by a member of OHE's Editorial Panel. Any views expressed are those of the authors and do not necessarily reflect the views or approval of the OHE's Editorial Panel or Research and Policy Committee, or its sponsors.

### Funding and Acknowledgements

This consultation briefing study was commissioned and funded by F. Hoffmann-La Roche Ltd.

# Table of Contents

---

<b>Executive Summary</b> .....	<b>iv</b>
<b>1 Introduction</b> .....	<b>1</b>
<b>2 Methods</b> .....	<b>2</b>
2.1 Literature review.....	2
2.2 External and internal interviews.....	2
2.3 Case studies.....	2
<hr/>	
<b>3 Results</b> .....	<b>3</b>
3.1 Regulatory assessment and reimbursement decisions of histology independent drugs over time.....	3
3.2 Evidence requirements for regulatory assessment and HTA of histology independent drugs.....	5
3.3 Bridging the gap between regulatory and HTA.....	6
3.4 Case studies.....	12
3.4.1 United Kingdom.....	12
3.4.2 France.....	13
3.4.3 Canada.....	15
<hr/>	
<b>4 Conclusion</b> .....	<b>17</b>
<b>References</b> .....	<b>20</b>
<b>Appendix: HTA Assessment details</b> .....	<b>22</b>

# Executive Summary

Histology independent therapies constitute a paradigm shift in how oncology patients are diagnosed and treated because they target cancer based on specific genomic or molecular alterations of cancer cells rather than tissue of origin. While potential game-changers, satisfying an unmet need of patients across the world, these types of therapies face significant challenges in evidence development, adoption, and reimbursement in many parts of the world. This is in part due to the way in which these new technologies are assessed for regulatory purposes and reimbursement recommendations, and in part to the genomic testing infrastructure required to ensure that the patients most likely to respond to these treatments are identified and can gain timely access.

Against this background, reconsideration of the pathways for evidence development to inform regulatory approval and Health Technology Assessments (HTAs) is necessary to ensure appropriate patient access to drugs for licenced indications.

This OHE Consulting Report provides an in-depth analysis of adaptive pathways for regulatory and health technology assessment of histology independent therapies in Canada, France, Germany, Italy, Spain, and the UK. The results are based on a combination of comprehensive literature review, country-level expert interviews and case studies for the UK, France, and Canada.

## **Aligning assessments: flexibility before uniformity**

Increasing awareness among decision makers about histology independent therapies, including the benefits and challenges they pose to health systems, is a critical first step. Yet, considering the different purposes of regulatory and health technology assessments, and the differences between national HTA-bodies, the 'door-opener' will vary across countries. Rather than aiming for a uniform HTA approach, flexibility from all stakeholders is the key.

## **Evidence generation pre-HTA: changing the picture**

Histology independent therapies are faced with multiple challenges to 'fit the picture' of evidence requirements for HTA. Generating comparative data is considered to be the main, though not the only, hurdle. Changing the picture requires novel and more advanced trial designs and analytic methods to reduce the uncertainty in HTA. Further research on how to improve (basket) trial-designs, use indirect comparison methods, leverage real-world evidence, and advance analytic techniques is in progress. This requires manufacturers, clinical triallists and methodologists to engage in early dialogues to agree on how to adapt the study designs, and decision-makers to then accept these types of evidence.

## **Managing uncertainty post-HTA: conditions matter**

Conditional reimbursement schemes have been instrumental in facilitating patient access to histology independent therapies to date and in stimulating further research. Whereas such schemes are not universally existent and may be limited in the number of therapies they can accommodate, outcomes-based payment schemes could be viewed as a viable alternative or a complement. These arrangements would allow (continued) risk sharing and data collection to manage real-world uncertainty and provide more flexibility regarding the commercial arrangement to be agreed between manufacturers and payers directly. While the pharmaceutical industry takes on a significant part of the data collection burden, there is an expectation of shared responsibility and shared access to data from HTA and other stakeholders.



### **Genomic testing: scale to precision**

A mature genomic testing landscape, with routine availability and reimbursement of advanced genomic tests, is critical to unlocking the potential of histology independent therapies to contribute to the delivery of high-value patient care. As healthcare systems begin to embrace precision medicine, and genomic testing will be scaled up, this will facilitate the approval of histology independent therapies as well as other therapies and contribute to evidence development. While Next-Generation Sequencing (NGS) becomes more mainstream and affordable, flexibility is required to appropriately apportion the costs of such genomic testing in single technology HTAs. Real-world evidence collected as part of conditional reimbursement or outcome-based payment schemes will shed further light on how genomic testing can best inform histology independent treatment decisions.

# 1 Introduction

Histology independent therapies – also known as tissue independent or tumour agnostic therapies – are an important subcategory of personalised healthcare and represent a new era in patient care and drug development. These therapies are distinct from conventional anti-cancer treatments, in that they target cancer based on specific genomic or molecular alterations of cancer cells rather than the tissue of origin. As such, the same drug has potential to be used to treat various unique types of cancer as long as the common biomarker targeted by the drug is present. These therapies constitute a paradigm shift in how oncology patients are diagnosed and treated, moving towards precision medicine, rather than the “one size fits all” approach based on a single anatomical location, regardless of the type of therapy.

While potential game-changers, satisfying an unmet need of patients across the world, these types of therapies face significant challenges in evidence development, adoption, and reimbursement in many parts of the world. This is in part due to the way in which these new technologies are assessed for value and reimbursed, and in part to the diagnostic infrastructure required to ensure that the patients most likely to respond to these treatments are identified and can gain timely access. In particular, the two sequential yet separate processes of regulatory and reimbursement decision making creates challenges and uncertainty for manufacturers, HTA-bodies and payers. Most importantly, however, a discordance between regulatory approval and HTA-recommendations can lead to false hope of rapid reimbursement and inequitable patient access (Wang, 2018).

While the above is true for most new medicines, the disconnect may be particularly challenging for histology independent therapies, for a number of (interrelated) reasons. Trial designs to study the effectiveness of histology independent therapies differ from the histology-anatomy driven anti-cancer trials, especially where the genomic alteration targeted has a very low prevalence and in effect targets an (ultra)rare population. Such low total patient numbers may not only prevent randomisation at the population level but also mean that statistical proof of effect and estimation of between-tumour heterogeneity is problematic. Also, given the heterogeneity of the target population, it is particularly difficult to identify a clear standard of care (SoC) to serve as an appropriate comparator. This limits the possibility of generating comparative evidence. The need to rely on surrogate endpoints and the dependence on diagnostic testing infrastructure are challenges that further complicate the evidence development and assessment of histology independent therapies.

In recognition of these methodological challenges but also the ‘unmet clinical need’ that exists in patients with rare or ultra-rare diseases, regulatory bodies have implemented flexible approaches to regulatory approval, providing options to accelerate the regulatory review process. These approaches are known as adaptive pathways and their application has also been considered for histology independent therapies in some contexts. As a result, however, HTA-bodies are increasingly confronted with large uncertainty in the evidence base available to inform coverage and reimbursement decisions (Kanavos and Ferrario, 2017).

As regulatory agencies, HTA-bodies, payers as well as manufacturers have been developing their thinking, if not approaches, regarding the assessment of histology independent therapies in the last few years, we performed an in-depth analysis of pathways for regulatory and health technology assessment of Histology independent therapies in various countries. Based on a combination of literature review, expert interviews, and case studies, we report the challenges and identify opportunities to overcome those.

## 2 Methods

### 2.1 Literature review

We performed a focused review of the published literature to gather information about the regulatory and HTA processes, evidence requirements and any recent developments herein, as well as on regulatory approval of and reimbursement recommendations for histology independent therapies in Canada, France, Germany, Italy, Spain, and the UK.

We included peer-reviewed articles and grey literature, such as white papers, to inform the current state of affairs, challenges identified and ongoing developments. To this end, we also reviewed published materials (e.g. slide decks) of presentation sessions and roundtables on Histology independent therapies as provided by authoritative organisations like EUnetHTA, EFPIA, and others.

To obtain a more in-depth understanding of specific requirements and/or country-specific information, we explored websites of regulatory and HTA agencies, including EMA (EU), FDA (US), CanHealth (CA), NICE (UK), and HAS (FR).

### 2.2 External and internal interviews

We performed eleven individual interviews; seven were with HTA experts, not (currently) affiliated with an HTA-body, that were selected to cover a range of perspectives and countries; four were with industry representatives to provide the manufacturer perspective on access and evidence requirements for Histology independent therapies.

All interviews were conducted via telephone by two members of the OHE team. A semi-structured interview format was used; interviewees were sent the interview guide in advance of the interview, together with a pre-read and a short questionnaire. The interview materials were developed by the OHE Consulting team and reviewed by the funder for compliance purposes. Interviews were audio recorded and key themes and results were extracted by two members of the OHE team.

The views and opinions expressed through answering the questionnaire and during the interviews were those of the individual country expert alone and may not necessarily be generalisable to a 'country-perspective'. The responses to the questionnaire, where experts were asked to use a 10-point Likert-scale to rate the extent to which they agreed with various statements, were recoded into low (rating 0-3), medium (rating 4-6) and high (rating 7-10) agreement brackets and reported graphically.

### 2.3 Case studies

For a selection of countries whose HTA agencies have previously appraised histology independent therapies – the UK, France, and Canada – we have performed in-depth case studies, collecting, analysing, and triangulating data on:



- Country-specific adaptive pathways and HTA processes, specifically the extent to which special provisions exist relevant to histology independent therapies, such as the acceptability of data from single arm trials, the existence of coverage with evidence schemes, etc;
- Key aspects of value dossiers and recommendations as provided by HTA agencies (e.g. from NICE website) including but not limited to information on trial design, identification of active comparator(s), types of data used (including RWE), analytic methods applied, choice of endpoints, and the way NGS was accounted for;
- Clinical treatment guidelines for specific patient groups, including role (and reimbursement situation) of genomic testing;
- Awareness and perspectives of leading clinicians, patient groups, regulators and HTA agencies or payers regarding Histology independent therapies, the challenges in their assessment and potential solutions;
- Other relevant contextual factors, e.g. health system, policy and regulatory factors.

We analysed relevant aspects of published value dossiers and recommendations provided by HTA agencies regarding trial design, identification of active comparator(s), types of data used (including RWE), analytic methods applied, choice of endpoints, and the way genomic testing was accounted for.

The perspectives of each country level expert were incorporated to provide more detailed insights to complement the published information. All experts interviewed have extensive experience and understanding of histology independent therapies, however, their views may not be representative of the regulatory or HTA agencies in their respective countries.

## 3 Results

### 3.1 Regulatory assessment and reimbursement decisions of histology independent drugs over time

The regulatory approvals of the anti-PD-1 antibody pembrolizumab and the NTRK inhibitors larotrectinib and entrectinib have heralded a paradigm shift in cancer treatment approaches.

Pembrolizumab was approved in May 2017 by the US FDA for the treatment of adult and paediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or dMMR solid tumours, and became the first drug to receive a histology independent approval in the US (FDA, 2017).

Larotrectinib received priority review, breakthrough therapy designation and orphan product designation before becoming the second drug to receive histology independent FDA approval for the treatment of adult and paediatric patients with solid tumours with NTRK gene fusions, in November 2018. In 2019 it became the first histology independent cancer treatment to receive conditional approval in the European Union. Larotrectinib has also received regulatory approval in Brazil and Canada (Brennan, 2019).

Entrectinib was granted breakthrough therapy and orphan drug designation by the US FDA in 2017. In Europe, entrectinib was first designated PRIME status in October 2017 (Brennan, 2019). In Japan,

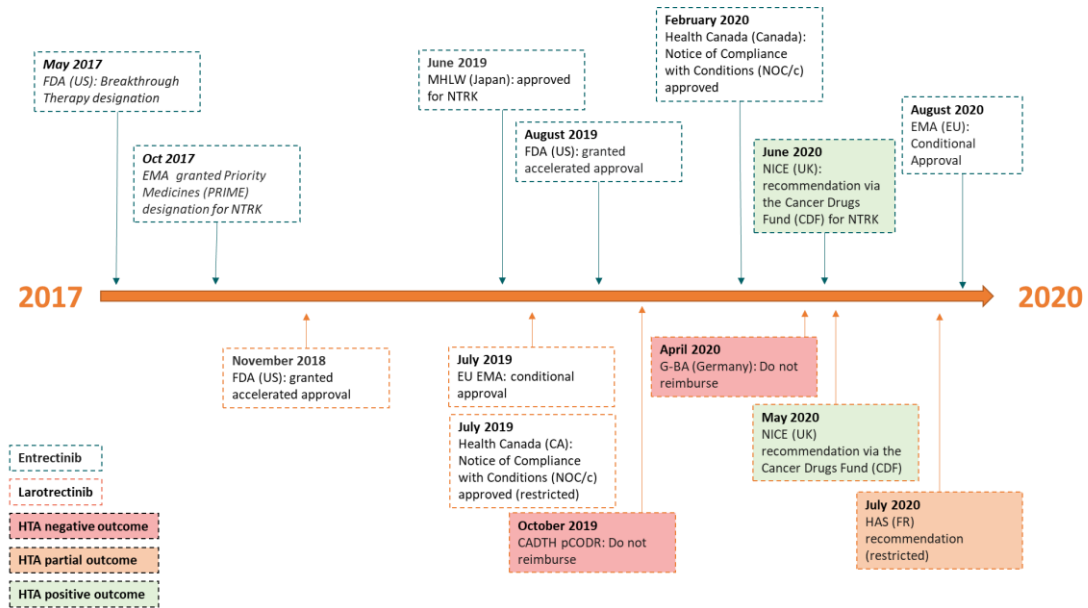
entrectinib received Sakigake Designation in March 2018, followed by approval from the Ministry of Health, Labour and Welfare granted in 2019 (Roche, 2019). Subsequently, the FDA approved entrectinib in Aug 2019. In May 2020, EMA's CHMP recommended EU approval under conditional marketing authorisation for people with NTRK fusion-positive solid tumours and for people with ROS1-positive, advanced non-small cell lung cancer (NSCLC) (EMA, 2020). The drug has also received approval from health authorities in Australia, Canada, Hong Kong, Israel and South Korea (GlobeNewswire, 2020).

Regulatory advancements, however, have yet to translate into positive HTA recommendations in most countries. While pembrolizumab has been on the market for years and positive HTA recommendations have gradually covered new indications as more evidence became available, the approval route has been different for NTRK inhibitors, as detailed in Figure 1.

For larotrectinib a conditional reimbursement decision was issued in England via the Cancer Drug Fund, in May 2020 (NICE, 2020a). In France, a partial favourable reimbursement decision was issued in July 2020: only approved for the treatment of paediatric patients with NTRK fusion positive refractory or relapsing childhood fibrosarcoma or other soft tissue sarcoma, and not for other paediatric indications in the marketing authorisation or adults with a NTRK positive solid tumour (HAS, 2020). A similarly restricted recommendation had initially been suggested by Health Canada in July 2019, who issued a Notice of Compliance with Conditions (Government of Canada, 2019). The Canadian committee concluded that in all other solid tumour with an NTRK gene fusion, the reimbursement of larotrectinib would not be recommended, as they were not convinced of its net clinical benefit based on the available evidence (CADTH, 2019). The CADTH pan-Canadian Oncology Drug Review (pCODR) expert review committee subsequently overturned their initial recommendation, issuing a final 'Do not reimburse' recommendation.

For entrectinib, obtaining reimbursement has been challenging as well. In Europe, UK's NICE announced in June 2020 that the drug will be made available for use in England via the Cancer Drug Fund, hence under a coverage with evidence development scheme that will be reviewed in about two years (NICE, 2020b). Health Canada approved entrectinib under the Notice of Compliance with Conditions (NOC/c) in February 2020 (Government of Canada, 2020), after which the manufacturer requested a voluntary withdrawal of the submission (CADTH, 2020). In the US, Japan, and Israel, entrectinib is reimbursed according to label. To date, other HTA-bodies or health authorities have not yet provided recommendations for either a histology-independent or a restricted indication of entrectinib.

The timeline of regulatory approval and reimbursement recommendations for these two histology independent therapies is shown in Figure 1.



**FIGURE 1: TIMELINE OF REGULATORY AND HTA APPROVALS**

### 3.2 Evidence requirements for regulatory assessment and HTA of histology independent drugs

HTA and regulatory bodies have fundamentally different evidence requirements, which are in part reflective of their different objectives. Whereas costs are beyond the scope of regulatory assessment, they are relevant to most HTAs. In addition, although both bodies assess the clinical data, they demand different levels and types of evidence.

Regulatory approval can be granted when there is enough evidence that the drug is efficacious and safe to use, but HTA bodies also need to be satisfied the drug is clinically effective and offers good value for money compared with the next best treatment option. As a result, regulators will often accept evidence coming from single-arm, basket, or umbrella trials, that generally have a primary endpoint of objective response rate across all patients with the genomic aberration. Most HTA bodies, however, require comparative evidence regarding progression-free and/or overall survival, as well as insight into between-tumour heterogeneity.

Key-challenges in the evidence development for histology independent therapies that contribute to the gap between regulatory approval and HTA reimbursement decisions include:

**Evidence versus an active comparator:** HTA agencies tend to request the new treatment to be compared to the active comparator(s) that are most relevant to their country (for example, the SoC). Histology independent therapies will cover multiple standards of care and comparators, and in some cases, it is considered not clinically feasible or economically effective to collect robust comparative clinical data. In addition, for a new biomarker, the natural history of disease is often not well enough understood to compare the new treatment against. This complicates the definition of a representative consistent value for a payer across all the applications of the therapy.

**Biomarker-based or surrogate endpoints:** a divergence remains between the approaches taken by regulatory authorities and HTA bodies. Ambiguity regarding the link of biomarker-based or other

surrogate endpoints to overall survival may lower the level of evidence, as perceived by an HTA panel.

**Small sample size:** given that the prevalence of the genomic aberration targeted by the drug is often low, the clinical evidence to inform reimbursement decisions will likely need to be based on studies with small sample sizes. Furthermore, the understanding of novel trial designs, such as basket or umbrella trials, as well as (statistical) methods required for robust assessment of (relative) effectiveness is limited in this setting.

**Heterogeneity:** HTA agencies are concerned that patient outcomes may be different between tumour types, and that the key clinical evidence might not be generalisable to clinical practice because of the distribution of tumour types, including potentially unrepresented tumour types, and the unknown effect of patient characteristics (NICE, 2020c).

**Next-generation sequencing (NGS):** HTA bodies may require the full cost of NGS to be included in the cost-effectiveness analysis of a specific histology independent therapy, making the demonstration of value even more challenging since the healthcare system benefits of NGS are broader than those that can be directly attributed to the therapy under assessment in question, yet its benefit can also not be accrued without it. Furthermore, different countries have different access levels to NGS, and this may vary even between institutions (academic vs local general hospitals), which will also have an impact on patients' access to histology independent therapies.

While not every challenge mentioned above may be unique to the assessment of histology independent drugs, they coalesce in this novel class of therapies and solutions that are acceptable to all stakeholders have yet to be found.

### 3.3 Bridging the gap between regulatory and HTA

When NTRK inhibitors first obtained breakthrough therapy designation by the FDA, Priority Review and even in some instances PRIME designation by the EMA and Sakigake designation (innovative pharmaceutical product) in Japan, it did so leveraging processes that are specifically designed to:

- i) expedite the development and assessment of drugs that are intended to treat a serious condition in areas of high unmet need, and
- ii) allow for the use of preliminary clinical evidence that demonstrates substantial improvement over available therapy on a clinically significant endpoint.

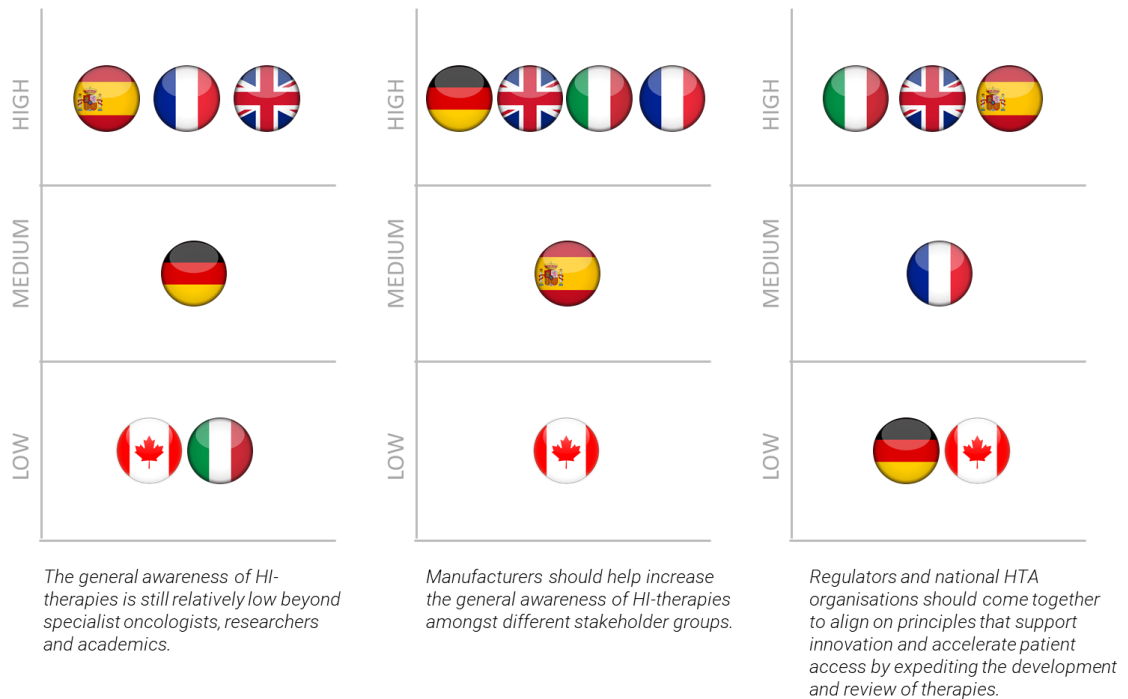
HTA bodies, however, are still in early phases of figuring out (if and) how to adapt to the challenges posed by histology independent drugs. As such, the gap between regulatory and HTA has, in effect, widened. While moving towards increasingly more precision medicine, of which histology independent therapies are a clear example, it is important for all stakeholders to collaborate to ensure that efficiencies gained in the regulatory pathway are not lost in the divide between regulatory and HTA.

#### Increasing awareness is the first step

Bridging the gap between regulatory and HTA first of all requires an awareness of what histology independent therapies entail; how these change the way patient populations and treatments against cancer are characterised, and the specific challenges they face when assessed for value.

The HTA-experts interviewed were largely in agreement with the statement that “The general awareness of histology independent (HI) - therapies is still relatively low beyond specialist oncologists, researchers and academics”. There is also a fair amount of concurrence between individual’s responses that “Manufacturers should help increase the general awareness of HI-therapies amongst different stakeholder groups” (Figure 2).

Interviewees’ opinions varied, however, on whether “Regulators and national HTA organisations should come together to align on principles that support innovation and accelerate patient access by expediting the development and review of therapies”. Experts from Italy, Spain and the UK reported high levels of agreement this statement, whereas those from France, Germany and Canada were less or not convinced. (Figure 2)

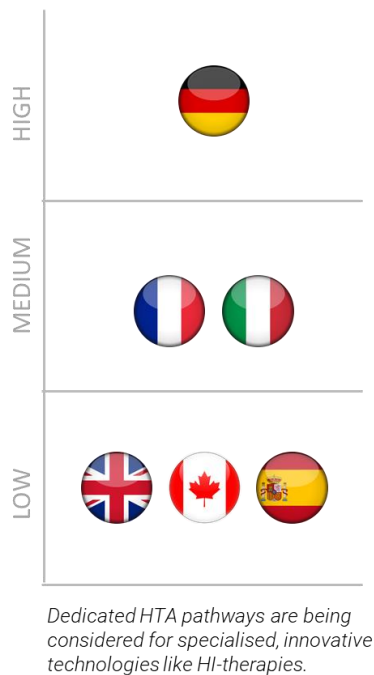


**FIGURE 2: AWARENESS AND PERCEIVED NEED TO ALIGN REGULATORY AND HTA PATHWAYS**

When considering how alignment may look like, it is relevant to note that in Europe, regulatory approval is done at the European level, whereas reimbursement decisions are for individual countries to decide. Some interviewees suggest that the European network for HTA (EUnetHTA) may contribute to harmonising HTA across countries. Others point out that different countries in Europe have such fundamental different views on what evidence is needed for HTA, including the acceptability of surrogate endpoints, that this would be near impossible to achieve in the short to medium term. For example, while NICE in the UK places much emphasis on health economics, notably including quality of life and patient reported outcomes; HTA-bodies in Spain, Germany and France largely stay away from this, considering disease progression and survival data as the main types of evidence to inform reimbursement decisions. Industry representatives interviewed acknowledge that there will not be a unified approach by HTA bodies soon, and therefore the ‘door-opener’, in terms of evidence requirements, will vary across countries. Rather than a uniform HTA approach, they consider some degree of flexibility as the key to improve the status quo.

### Evidence generation pre-HTA: changing the picture

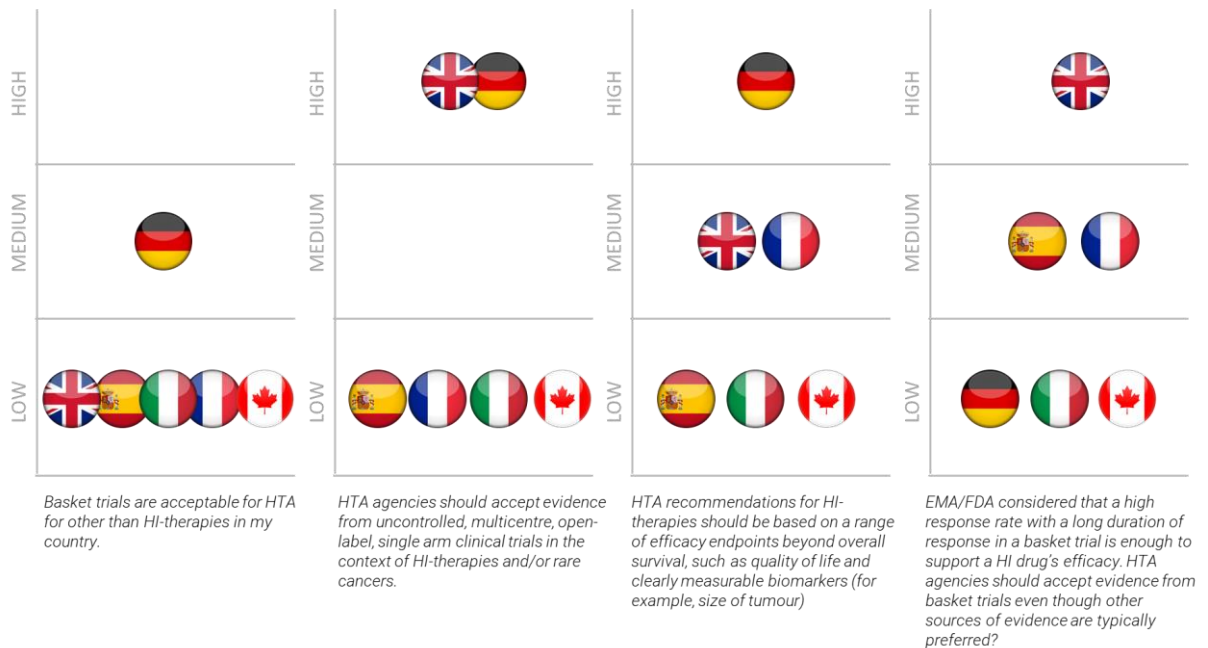
Among the various evidentiary challenges mentioned, generating comparative data is perceived as the main hurdle. Where some HTA-experts acknowledge that this is particularly complicated given the nature of histology independent drugs, clinical experts emphasise this is precisely their key value. So far, HTA has focused on generating evidence for histology independent therapies that ‘fits the picture’ rather than considering adaptive HTA-pathways for such therapies, as reflected by experts’ opinion on whether *“Dedicated HTA pathways are being considered for specialised, innovative technologies like HI-therapies”* (Figure 3). Clinical opinion, however, points out the need to ‘change the picture’ to reflect the paradigm shift brought about by these treatments.



**FIGURE 3: ACCEPTANCE OF DEDICATED HTA PATHWAYS FOR HISTOLOGY INDEPENDENT THERAPIES**

Novel types of trial designs, such as basket trials, to study the effect of one drug on a single genomic alteration in a variety of tumour types at the same time, are one way to reflect the unique nature of histology independent drugs. HTA experts so far have been reluctant to accept these (Figure 4) and point to the challenge of designing these basket trials a priori. At present, there is no consensus of how to set up exploratory and confirmatory basket trials. Yet for HTA-bodies this is critically important to also allow for a better understanding of heterogeneity between tumour types.

Some experts point to using indirect comparisons that may allow to compare data from single arm trials to other sources of data. In some countries indeed, evidence from single arm studies might be acceptable when the natural history of the disease is well understood and documented, and when this shows a high unmet need (Figure 4). Some HTA-experts interviewed also commented that low patient numbers per tumour site would not necessarily be a core problem when there is good knowledge of disease-prognosis of a tumour with this mutation. Particularly for new biomarkers however such data is not readily available. Work needs to be done to establish these baseline data and the endpoints considered in such studies should move beyond response rates and include disease progression, survival and quality of life to be accepted by HTA-bodies (Figure 4).



**FIGURE 4: ACCEPTANCE OF (NOVEL) TRIAL TYPES AND ENDPOINTS**

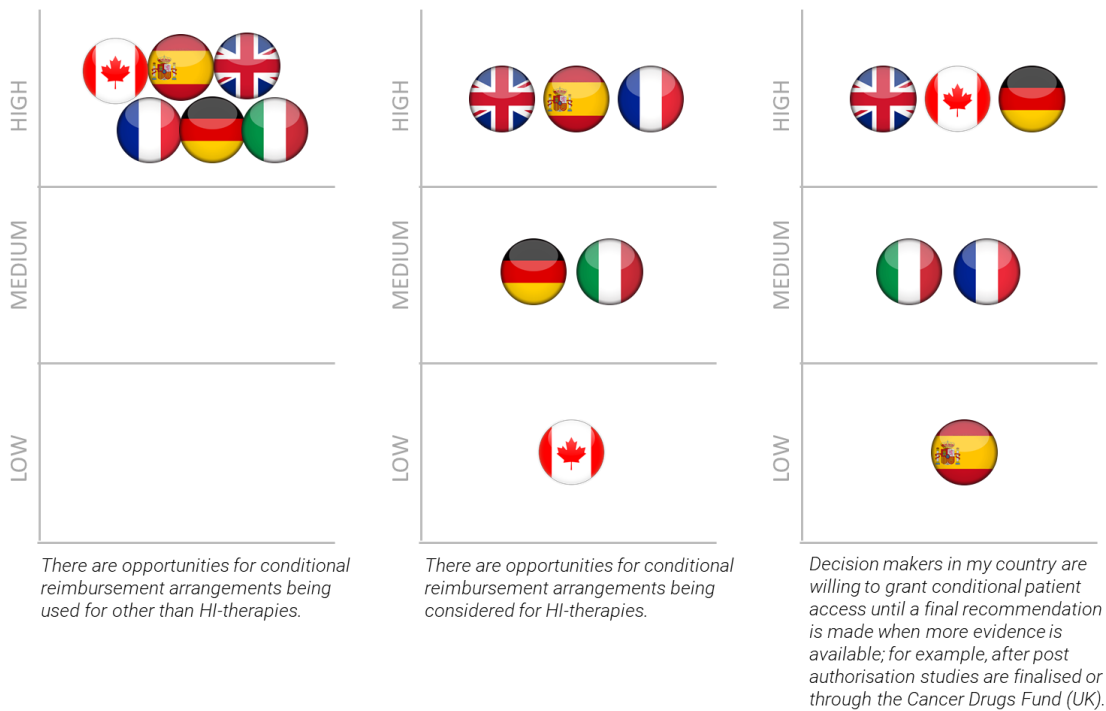
The above indicates that ‘changing the picture’ requires novel and more advanced trial designs and analytic methods to reduce the uncertainty in HTA. This requires manufacturers, clinical triallists and HTA methodologists to engage in early dialogues to agree on how to adapt the study designs, as is increasingly common for example in the UK. It is then on HTA-bodies to accept these types of evidence. In the meantime, however, decision uncertainty regarding the incremental (cost-) effectiveness of histology independent therapies will remain; even a changed picture may be blurry for a while.

### Managing uncertainty post-HTA

Managed entry agreements, including conditional reimbursement, outcome-based payment, and other risk-sharing schemes, can facilitate patient access whilst sharing financial risk and incentivising further data collection. In the short term, this requires less change from HTA-bodies regarding evidence requirements, and various countries, e.g. France, Germany, Italy, and the UK already have such schemes in place.

HTA-experts interviewed however noted that having conditional reimbursement schemes in place, does not necessarily mean that these are an option for histology independent drugs (Figure 5). In France, for example, a minimum level of data is expected to be provided to have a ‘reasonable expectation’ of incremental effectiveness of the drug, before it can enter such an arrangement. In Canada, a conditional access pathway is possible, but its use is discouraged because there are no clear processes and protocols for executing such a scheme. HTA-experts from France, Spain, Germany and Canada also commented that any positive recommendation, either before or after conditional reimbursement and re-assessment, would most likely be limited to specific tumour types, where data is most convincing; instead of granting a true histology independent approval as would be the case in the UK.





**FIGURE 5: AVAILABILITY OF CONDITIONAL REIMBURSEMENT SCHEMES**

Industry-affiliates interviewed support conditional reimbursement or outcome-based payment schemes, which would be mutually beneficial for all stakeholders involved, particularly in the short to medium term. They are concerned, however, that conditional reimbursement schemes are only a temporary solution. While effective for a limited number of drugs, more structural adaptations of HTA are required when increasingly more novel therapies are expected to come to market in the future.

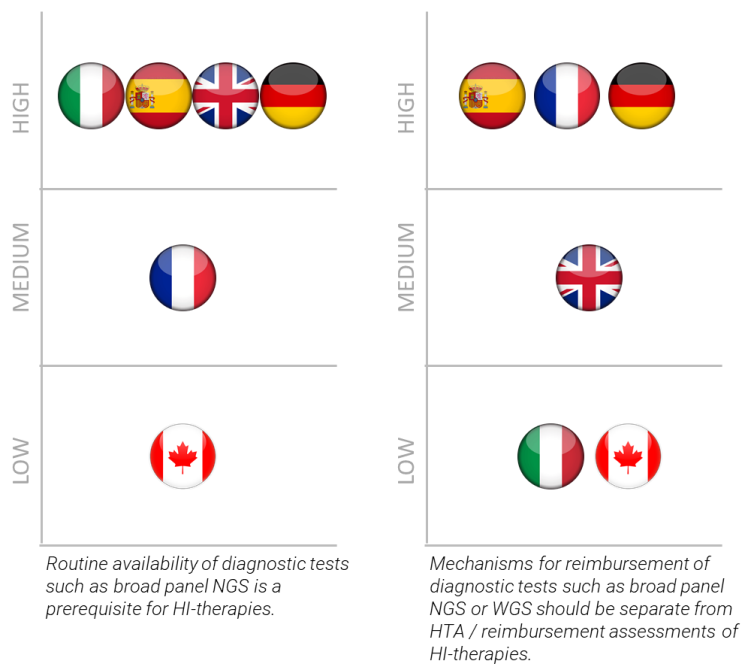
The above indicates that gaining multiple stakeholder input and designing fit-for-purpose arrangements is needed to ensure these are truly beneficial to all stakeholders involved, irrespective of which tumour type the therapy is used in. Notably, outcomes-based payment schemes could be viewed both as a viable alternative to conditional reimbursement schemes (in countries where these is not established), or a complement (in countries where they are, like the UK). These arrangements would allow (continued) risk sharing and data collection to manage real-world uncertainty and provide more flexibility regarding the commercial arrangement to be agreed between manufacturers and payers directly. They could also allow for collection of safety and other data, including biomarker data and relevant patient-reported outcomes that are not typically collected in trials and are not available at scale in routine healthcare databases. Investments in data infrastructure are required to do this. While pharmaceutical industry takes on a significant part of the data collection burden, there is an expectation of shared responsibility and shared access to data from payers and other stakeholders.

### Navigating genomic testing

The genomic testing landscape has a strong impact on the uptake of histology independent therapies. Quoting from a NICE co-authored paper: “unless all patients with cancer receive routine genomic testing, it will be difficult to predict which patients can effectively be treated with a histology independent drug” (Cooper et al., 2020).



Some countries included in this study, such as the UK, Germany, France and to some extent Canada are scaling up the usage of NGS. France, for example, per its Genomic Medicine Plan 2025, aims to become one of the leading countries in personalised and precision medicine by integrating genomic medicine into the care pathway and providing access for all patients with cancer and rare diseases by 2025 (Aviesan, 2016). Whereas the majority of HTA-experts responded that broad panel next-genome-sequencing (NGS) is required for histology independent therapies, there's divergence of opinion as to whether the mechanism for reimbursement of NGS should be considered separate from a reimbursement decision of the therapy (Figure 6). Industry representatives consider the absence of routine availability and reimbursement NGS a critical hurdle for obtaining reimbursement, particularly for the first companies bringing a histology independent drug to market.



**FIGURE 6: DIAGNOSTIC AVAILABILITY AND REIMBURSEMENT REQUIREMENTS**

From an HTA perspective, however, the true problem underlying this is not so much whether or not to consider costs of diagnostics in the economic evaluation of a histology independent treatment; rather, the challenge is how to apportion the costs of NGS platforms to one specific treatment.

In countries that are scaling up the usage of NGS for multiple purposes, the cost of performing such a test to identify candidate patients for a histology independent treatment would be relatively low. In such a case, the cost of genomic testing is less likely to be a major cost driver in the economic evaluation of the drug. In countries where high-quality genomic testing would basically need to be implemented from scratch, those costs may be prohibitive to the payer for one specific treatment; and it would be unreasonable to expect these costs could be fully offset by the treatment's incremental net benefit in a small patient population. In such countries, however, existing lower cost tests, such as an immunohistochemistry (IHC) test can be used as a screening tool to reduce the NGS cost burden.

The first step towards a solution may be to acknowledge that the need for and usage of broad genomic testing will only increase in the future, to inform a multitude of treatment pathways. This will reduce the apportionable cost of testing per treatment, yet methods need to be developed to accurately include genomic testing for histology independent therapies in economic evaluations. In

addition to the apportioning problem, HTA may need to consider that, in clinical practice, genomic testing may be done earlier or later in the treatment pathway, than tested in the basket trial. This may change the relevant comparator, which differs by treatment line and tumour type, further complicating the economic evaluation.

While these problems are challenging, they are also temporary. When NGS becomes more mainstream and affordable, and the effect of histology independent drugs will start to be observed in clinical practice, these uncertainties will gradually decrease. In the meantime, scenario analyses as part of economic evaluations can inform different plausible scenarios for (future) NGS usage and costs. Real-world evidence collected as part of conditional reimbursement or outcome-based payment schemes will shed light on how genomic testing can best inform histology independent treatment decisions.

## 3.4 Case studies

### 3.4.1 United Kingdom

#### **HTA landscape**

In the UK, NICE is responsible for conducting HTAs and providing reimbursement recommendations to NHS England. There are no specific guidelines regarding the evaluation of histology independent therapies at present, but NICE commissioned methods research to address whether the existing technology appraisal approaches could be applied and whether any changes are required. The pre-publication report (Murphy, 2020) provides recommendations from researchers at the University of York and the University of Sheffield and is being considered as part of NICE's ongoing review of its evaluation methods.

NICE has an established conditional reimbursement with evidence development pathway, called the Cancer Drugs Fund (CDF), which was designed to provide access to promising new oncology treatments via managed entry arrangements (MEAs), demanding ongoing evidence collection to address clinical uncertainty. Currently, this fund is limited to £340 million per year, and focuses on funding cancer treatments that are awaiting full NICE assessment (NHS England, 2016).

While NICE generally prefers data from randomised controlled trials, it has demonstrated a willingness to accept innovative trial designs through their assessment of medicines based on single-arm basket trials. Prior to the evaluation of histology independent therapies, NICE had approved indications for pembrolizumab and atezolizumab based on biomarker tests, also signalling an openness to recommend innovative new therapies.

#### **Diagnostic testing landscape**

NHS England have committed to introducing NGS for solid tumours at the point of diagnosis of local advanced or metastatic disease for around 100,000 patients a year. It is expected that all seven planned Genomic Hubs around England will be ready for testing and that pathways will become embedded in clinical practice by 2021. It may take a further 12 months for molecular testing to become fully embedded in practice (NGS England, 2018).

This presents the potential for identifying NTRK gene fusions through the addition of targeted DNA gene panels. Currently, testing for NTRK gene fusions is only available through the NHS for mammary analogue secretory cancer (MASC) and secretory breast carcinoma.

### HTA recommendations to date

In May 2020, NICE issued its first fully histology independent recommendation, when larotrectinib was recommended for use in the Cancer Drugs Fund, following the overturning of an initial negative recommendation. Their final appraisal document for entrectinib was issued in June 2020, also positively recommending entrectinib through the Cancer Drugs Fund; full publication is expected in Aug 2020 (NICE, 2020). While details on these HTA assessments are provided in the Appendix, the key motivating factors for these include:

- End-of-life criteria: given that both therapies satisfied the end-of-life criteria, the threshold was adjusted up to £50,000 per QALY, further enabling NICE's positive recommendations.
- Cancer Drugs Fund: given the plausible yet uncertain cost-effectiveness of the therapies, this conditional reimbursement pathway was critical to receive a positive recommendation and the opportunity to collect further data in clinical practice.
- Diagnostic testing infrastructure: in its appraisal documents on entrectinib, NICE note that their methods guide was not designed to address a system-wide overhaul in diagnostic techniques. The cost of testing will depend on the testing strategy implemented by NHS England. In addition, the manufacturer agreed to bear a percentage of the cost of NGS testing, with NHSE covering the remainder of those costs NICE also recognised that entrectinib is innovative and its use in clinical practice would help accelerate NHS England's developments in genomic testing.

Despite these two positive, albeit conditional, reimbursement recommendations, the UK HTA-expert commented that the Cancer Drugs Fund is great for its purposes but that there is general reluctance in the UK to think about more creative ways of managing uncertainty, especially given difficulties during the set-up phase. An example of those are innovative payment mechanisms, such as outcome-based payment schemes, that go beyond simple discounts, and may also be leveraged for drugs coming out of the CDF. They also argued that there is a lack of awareness in the HTA community about basket trials and how they should be designed well. Their view was that, at present, there are exploratory studies that show promise but ultimately do not provide the necessary level of clarity. Registry data and real-world evidence are the only way forward, from their viewpoint.

The challenges faced by histology independent therapies and the steps that need to be taken to address these challenges are not unique to histology independent treatments only. Rather, the issues are broader and some stretch to phase II data. There are questions on how surrogate endpoints, as used for regulatory approval, can be validated and meaningfully integrated into a cost-effectiveness analysis. Further challenges relate to interpreting progression-free survival and overall survival from such outcomes in phase II studies, as well as issues around quantifying heterogeneity in a way that is useful to HTA – for example, by examining whether, based on objective response rate, it is possible to see any differences by tumour type across the whole range of trials of different histology independent drugs conducted to date. While not unique to histology independent therapies, the various methodological and data challenges coalesce in their assessment. The UK case study, however, shows that ways can be found that are consistent with the principles of HTA yet flexible to accommodate paradigm-shifting therapies.

Details of both assessments are provided in the Appendix.

### 3.4.2 France

#### HTA landscape

In France, the Haute Autorité de Santé (HAS) evaluates the clinical benefit of drugs, medical devices, procedures, and other health technologies, assessing added benefit over existing therapeutic strategies. When innovation is claimed and potentially associated with a significant impact on health spending, health products and technologies are required to undergo a health economic evaluation. Prior to being assessed by the HAS, the local regulatory agency (Agence Nationale de Sécurité du Médicament et des produits de santé/ANSM), may require a reassessment of the evidence provided to the EMA for marketing authorisation. Pertaining in particular to medicines where single-arm or basket trials are concerned, this signals that the data accepted by the EMA are not necessarily considered sufficient for national decision-making in France.

Interviews indeed confirmed that single-arm trials are only likely to be accepted by HAS when the natural history of the disease is well-established. In addition, the need to rely on surrogate endpoints and a dearth of comparative data are complicating the assessment. When presented with more than one of these challenges, as is often the case for histology independent therapies, the chances of obtaining a positive reimbursement are low.

To provide patient access to products that do not yet have marketing authorisation but are developed for conditions with high unmet needs, France has a well-established early access scheme that allows temporary use authorisation (ATU). This pathway can be leveraged by any product for the diagnosis, prevention or treatment of severe or rare conditions if there is currently no other intervention available and when its efficacy and safety known to date, justify the use in patients. The pathway can be used for groups of patients (cohort ATU) or at the individual patient level (named patient ATU). In addition, a Recommendation for Temporary Use (RTU) would allow monitoring off-label prescribed medicines, provided that there is an unmet need, and that the benefit/risk ratio of the medicinal product is presumed favourable, based on published data on effectiveness and safety.

### **Diagnostic testing landscape**

As per its Genomic Medicine Plan 2025, France aims to become one of the leading countries in personalised and precision medicine by integrating genomic medicine into the care pathway and providing access for all patients with cancer and rare disease by 2025. The French government has committed to implementing next generation sequencing, with the Ministry of Health providing funding for all diagnostic tests capped at about €380 million and around 12 per cent of addressable cancer patients receiving NGS testing (Aviesan, 2016).

### **HTA recommendations to date**

In July 2020, HAS issued a favourable opinion on larotrectinib for the treatment of paediatric patients with NTRK fusion positive refractory or relapsing childhood fibrosarcoma or other soft tissue sarcoma (HAS, 2020). The clinical benefit was declared moderate in these subgroups but considered insufficient in all other authorised indications. Thus, HAS issued a 'no reimbursement' opinion for all other paediatric indications in the marketing authorisation and also in all adults with a NTRK positive solid tumour. Key motivating factors for this recommendation include:

1. Lack of comparative data: HAS was reluctant to issue a favourable opinion in the absence of comparative data. It argued that a well-designed basket study does not can include comparators and suggest that a resubmission is made once comparative data is available.
2. Reluctance to issue a full histology independent recommendation: The Transparency Committee was not convinced of the clinical effectiveness of larotrectinib in all NTRK positive tumours and thus limited their positive recommendation of larotrectinib to a small subgroup of paediatric patients. The committee stated that, upon receipt of further evidence to fully establish the clinical benefit, they may reconsider their initial recommendation.

Details of the larotrectinib assessment are provided in the Appendix. There is no evidence to indicate that entrectinib has been considered by the Transparency Committee at present.

### 3.4.3 Canada

#### HTA landscape

There are two HTA bodies in Canada, the primary one being the Canadian Agency for Drugs and Technologies in Health (CADTH) which operates in all except one province. Quebec has its own HTA body, Institut national d'excellence en santé et services sociaux (INESSS). CADTH conducts evaluations of clinical, economic, and patient evidence on cancer drugs through the pan-Oncology Drug Review (pCODR) process.

Regarding regulatory and HTA alignment, Canada has several pre-submission processes which can open lines of communication between manufacturers, regulators and HTA. To decrease the time between regulatory review to reimbursement, Health Canada and relevant HTA organisations began to collaborate in 2018 in an aligned review process for all biological and pharmaceutical new drug submissions where the manufacturer intends to seek HTA process on a pre-NOC (Notice of Compliance) basis (Siu et al., 2019).

As part of the alignment process between Health Canada and the HTA organisations, a manufacturer has the opportunity, but not the obligation, to submit to the CADTH Common Drug Review up to six months (or 180 days) before the anticipated date of regulatory approval. The CADTH pan-Canadian Oncology Drug Review (pCODR) has allowed a 6-month pre-NOC submission since its inception, reflecting the urgency of the therapeutic area and the generally unmet need of improving survival of cancer patients. The alignment of Health Canada review and HTA process was expected to reduce duplication and reduce time lags between regulatory approval and reimbursement recommendation. It is important to note that this process, in essence, only lengthens the pre-NOC submission threshold to HTA organisations: the duration of review by Health Canada and HTA organizations do not change and manufacturers must still remain compliant with all submission requirements.

Furthermore, the Early Parallel Scientific Advice initiative enables Health Canada and CADTH to collaborate and share perspectives while each formulating independent advice regarding a sponsor's specific drug development plan (CADTH, 2019b). The program aims to be particularly beneficial for drugs for rare diseases; new therapeutic areas; complex, adaptive, or unusual trial designs; or development plans that may include the use of real-world evidence. CADTH states that Early Parallel Scientific Advice could be sought on topics such as target population, choice of comparator, trial design and duration, end points and statistical issues (i.e. stratification, subgroups). This project was initially expected to launch in Spring 2020, however, it has been put on hold and a decision is expected to be made in October 2020.

The Canadian country level expert pointed out that while there is no explicit conditional approval pathway in Canada, recommendations have previously been made based on conditional approval, for example in the case of venetoclax (CADTH, 2018a). The practical implications of this are unclear, as there is no payer mechanism in place to support this. Further to this, clinician feedback on the larotrectinib pCODR initial recommendation included a group of clinical oncologists that "strongly disagreed with limiting the recommendation" arguing that the recommendation should be tumour-site agnostic, and alluded to the lack of a conditional reimbursement pathway (CADTH, 2019c).

CADTH's 2018-2021 strategic plan (CADTH, 2018b) outlines three high level goals that signal progress towards more aligned and dynamic assessment pathways, namely: i) to close the gap between evidence, policy and practice; ii) to adopt a life-cycle approach to HTA; iii) to anticipate health system and technology trends, and iv) to develop agile management strategies. Three specific

activities that are meant to help achieve these goals are particularly pertinent to history independent therapies:

1. Align drug and medical device review processes with federal, provincial, and territorial priorities throughout all phases of the technology life cycle.
2. Implement programs for reassessment and disinvestment.
3. Advance initiatives across the health technology life cycle that will improve access, appropriate use, and affordability.

The strategic plan acknowledges the need for better alignment between CADTH and Canada's regulatory agency Health Canada, as corroborated by the findings of our literature review and interviews. The two key adjustments proposed by CADTH to facilitate alignment, are co-developing an approach to system-wide prioritisation and advancing scientific methodology for regulatory review and HTA across the entire life cycle of technologies. CADTH's plan to implement programs for reassessment is done in recognition that, increasingly, decisions with considerable uncertainty at product launch are unavoidable. Therefore, it aims to establish guidelines for the reassessment of drugs already in use which will rely in part on the use of observational and other real-world data.

CADTH's annual business plan (2020-2021) reiterates its commitment to incorporating real-world evidence, citing that they will continue their work to go beyond traditional assessments of new drugs and technologies. They aim to further integrate the collection and analysis of real-world evidence into CADTH reviews; intending to conduct at least two reviews that incorporate real-world evidence (CADTH 2020b).

### **Diagnostic testing landscape**

Regulation of diagnostic services in Canada takes place at the provincial level. This can lead to different regulatory frameworks and approaches. In addition, the process to gain access to diagnostic tests and labs can vary substantially between provinces. Access to genomic tests, e.g. companion diagnostics, is thus scattered. Next-generation sequencing is available through academic medical centres in the more populated areas of British Columbia, Ontario, and Quebec, but reimbursed only in British Columbia for a limited hotspot panel for certain tumour types.

HTA is used to inform diagnostic reimbursement recommendations. In addition to an assessment by CADTH, the HTA may come from a variety of sources including provincial HTA agencies (e.g. INESSS), provincial ministries of health, and hospitals. Once a positive recommendation has been issued, funding may come from different sources, including hospitals, provincial cancer agencies, pharmaceutical companies, and private payers.

Regardless of the current reimbursement of genomic testing in Canada, HTA requires the cost of testing to be included in cost effectiveness analysis of treatment when required to identify eligible patients.

### **HTA recommendations to date**

For larotrectinib the initial recommendation published by the pCODR expert review committee was "Reimburse with clinical criteria and/or conditions". This recommendation was restricted to adult and paediatric patients with salivary gland or soft tissue sarcoma, and paediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma. For these subgroups, further conditions

to reimbursement included that the cost-effectiveness should be improved to an acceptable level; and budget impact and access to testing also needed to be addressed by the manufacturer. The committee concluded that in all other solid tumour with an NTRK gene fusion, the reimbursement of larotrectinib would not be recommended, as they were not convinced of its net clinical benefit based on the available evidence (CADTH, 2019).

The manufacturer and various patient groups disagreed with the decision to not allow access to all eligible patients with NTRK fusion cancer, arguing amongst others that this decision would lead to “inequitable access for NTRK fusion cancer patients and significant ethical concerns”. They requested to expand larotrectinib access to all eligible patients, particularly to patients with thyroid, lung, colorectal, gastrointestinal stromal or central nervous system cancer. The pCODR expert review committee subsequently overturned their initial recommendation, issuing a final ‘Do not reimburse’ recommendation. Larotrectinib was also considered by Quebec’s HTA body (INESSS), who issued a “refusal of registration” recommendation (INESSS, 2019).

Entrectinib was approved for adult patients with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, that have a NTRK gene fusion without a known acquired resistance mutation, and with no satisfactory treatment options, by Health Canada in February 2020, under the Notice of Compliance with Conditions (NOC/c). The pCODR process was initiated following the submission in July 2019, however, the manufacturer subsequently requested a voluntary withdrawal of the submission (CADTH, 2020).

The main motivating factor behind these HTA decisions pertains to uncertainty and heterogeneity between tumour types. While the HTA committee recommended reimbursing larotrectinib for certain tumour types where clinical benefit had been proven, they considered that due to this heterogeneity the decision uncertainty in other tumour types was too high to recommend unconditional reimbursement.

Details of the assessment are provided in the Appendix.

## 4 Conclusion

Histology independent therapies, targeting specific genomic alterations in a tumour regardless of its anatomical location or histology, have created a paradigm-shift in the understanding and treatment of cancer. Yet, by ‘changing the picture’ of cancer treatment, these novel therapies are faced with multiple challenges to ‘fitting the picture’ of evidence that is typically required by decision-makers.

To promote patient access to such novel therapies, addressing an area of high medical need where it is difficult to collect data via traditional routes and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine, regulatory bodies have implemented adaptive pathways. HTA bodies, however, are still in early phases of determining (if and) how to adapt their assessment of histology independent drugs. As such, the gap between regulatory and health technology assessment has, in effect, widened. Whereas many of these therapies may represent the last hope for patients with cancer, this gap may unduly delay their access.

To bridge it, policymakers, regulators, payers, industry and the medical society will need to undertake multiple activities that collectively ensure access to safe, effective and high-value new therapies, leading the way towards precision medicine for all.

### **Aligning assessments: flexibility before uniformity**



Whereas increasing awareness among decision makers about histology independent therapies, including the benefits and challenges they pose to health systems, is a critical first step; more alignment between regulatory and (the various) HTA processes may not be achievable or necessarily desirable. Considering the different purposes of regulatory and health technology assessments, and the differences between national HTA-bodies, the 'door-opener' will vary across countries. Rather than aiming for a uniform regulatory and HTA approach, the results of this study indicate that flexibility from all stakeholders is the key.

### **Evidence generation pre-HTA: changing the picture**

Among the various evidentiary challenges mentioned, generating comparative data is considered the main hurdle. Where some HTA-experts acknowledge that this is particularly complicated given the nature of histology independent drugs, clinical experts emphasise this is precisely their key value.

Changing the picture requires novel and more advanced trial designs and analytic methods to reduce the uncertainty in HTA. Further research on how to improve (basket) trial-designs, use indirect comparison methods, leverage real-world evidence, and advance analytic techniques is in progress. This requires manufacturers, clinical triallists and methodologists to engage in early dialogues to agree on how to adapt the study designs, and decision-makers to then accept these types of evidence. In the meantime, however, the changed picture may be blurry while more data on the real-world value of histology independent therapies accumulates.

### **Managing uncertainty post-HTA: conditions matter**

Managed entry agreements are increasingly used to deal with decision uncertainty post HTA. Conditional reimbursement with evidence development agreements has been instrumental in facilitating patient access to histology independent therapies particularly in countries that have transparent processes and supporting payer mechanism for this in place like the UK. While an effective solution for a limited number of drugs, and a temporary one, they may inadvertently cause more structural solutions to be postponed. The latter is concerning particularly when more histology independent therapies come to market in the future.

Outcomes-based payment schemes could be viewed both as a viable alternative to conditional reimbursement schemes (in countries where these are not established), or a complement (in countries where they are, like the UK). These arrangements would allow (continued) risk sharing and data collection to manage real-world uncertainty and provide more flexibility regarding the commercial arrangement to be agreed between manufacturers and payers directly.

Multiple stakeholder input and designing fit-for-purpose arrangements are needed to ensure conditional reimbursement or outcomes-based payment schemes achieve their dual purpose of facilitating patient access while stimulating further research, irrespective of tumour type. While the pharmaceutical industry takes on a significant part of the data collection burden, there is an expectation of shared responsibility and shared access to data from HTA and other stakeholders.

### **Genomic testing: scale to precision**

Advances in genomic medicine are at the core of many novel anti-cancer medicines. As such, the absence of routine availability and reimbursement of advanced genomic tests is considered a critical





hurdle for obtaining reimbursement, particularly for the first companies bringing a histology independent drug to market in countries where genomic testing availability is limited.

However, the need for and usage of genomic testing will only increase in the future, informing a multitude of treatment decisions. As healthcare systems begin to embrace precision medicine, and genomic testing will be scaled up, they will facilitate the approval of histology independent therapies. While NGS becomes more mainstream and affordable, flexibility is required to appropriately consider the costs of genomic testing in HTA, e.g. using scenario analyses for (future) NGS usage and costs. Real-world evidence collected as part of conditional reimbursement or outcome-based payment schemes will shed further light on how genomic testing can best inform histology independent treatment decisions.

## References

Aviesan. Genomic medicine France 2025. Published February 2016. Available at: <https://solidarites-sante.gouv.fr> [Accessed 5 June 2020]

Brennan Z. EMA Recommends Conditional Approval for First Tissue-Agnostic Cancer Treatment. Regulatory Affairs Professionals Society. Regulatory Affairs Professional Society. Published July 2019. Available at: <https://www.raps.org> [Accessed 9 July 2020]

CADTH. Venetoclax (Venclexta) CLL – pERC Final Recommendation. Published 2018a. Available at: <https://www.cadth.ca> [Accessed 3 July 2020]

CADTH. 2018-2021 Strategic Plan. Published 2018b. Available at: <https://www.cadth.ca> [Accessed 2 July 2020]

CADTH. Larotrectinib for Neurotrophic Tyrosine Receptor Kinase (NTRK) Locally Advanced or Metastatic Solid Tumours. Published 2019a. Available at: <https://www.cadth.ca> [Accessed 30 June 2020]

CADTH. Notice to Industry: Health Canada and CADTH launch new initiative to provide early parallel scientific advice. Published 2019b. Available at: <https://www.cadth.ca> [Accessed 10 August 2020]

CADTH. Pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Larotrectinib). Published 2019c. Available at: <https://www.cadth.ca> [Accessed 10 August 2020]

CADTH. Entrectinib (TBD) for Neurotrophic Tyrosine Receptor Kinase (NTRK) Fusion-Positive Solid Tumours. Published 2020a. Available at: <https://www.cadth.ca> [Accessed 30 June 2020]

CADTH. 2020-2021 Business Plan. Published 2020b. Available at: <https://www.cadth.ca> [Accessed 2 July 2020]

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

ClinicalTrials.gov. A Study to Test the Safety and Efficacy of the Drug Larotrectinib for the Treatment of Tumors With NTRK-fusion in Children (SCOUT). Published 2015. Available at: <https://clinicaltrials.gov> [Accessed 30 June 2020]

ClinicalTrials.gov. A Study to Test the Effect of the Drug Larotrectinib in Adults and Children With NTRK-fusion Positive Solid Tumors (NAVIGATE). Published 2015. Available at: <https://clinicaltrials.gov> [Accessed 30 June 2020]

European Medicines Agency. Rozlytrek. Published May 2020. Available at: <https://www.ema.europa.eu> [Accessed 10 May 2020]

U.S Food and Drug Administration. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. Published May 2017. Available at: <https://www.fda.gov> [Accessed 5 August 2020]

GlobeNewswire CHMP recommends EU approval of Roche's Rozlytrek for people with NTRK fusion-positive solid tumours and for people with ROS1-positive, advanced non-small cell lung cancer. Published May 2020. Available at: <https://www.globenewswire.com> [Accessed 24 June 2020]

Government of Canada. Notice of Compliance with conditions (NOC/c). Published: February 2020. Available at: <https://www.canada.ca> [Accessed 17 July 2020]

Government of Canada. Vitrakvi - Notice of Compliance with Conditions - Qualifying Notice. Published 2019. Available at: <https://www.canada.ca> [Accessed 17 July 2020]

HAS Sante. Vitrakvi. Published July 2020. Available at: <https://www.has-sante.fr> [Accessed 30 June 2020]

INESSS. VITRAKVI<sup>MC</sup> – Tumeurs solides porteuses d’une fusion d’un gène NTRK. Published 2019. Available at: <https://www.inesss.qc.ca/> [Accessed 30 June 2020]

Kanavos P, Ferrario A, 2017. Managing Risk and Uncertainty in Health Technology Introduction: The Role of Managed Entry Agreements. *Global Policy*, 8(2). doi:10.1111/1758-5899.12386

Murphy et al. Modelling approaches for histology-independent cancer drugs to inform NICE appraisals. Published 2020. Available at: <https://www.nice.org.uk> [Accessed 29 June 2020]

National Institute for Health and Care Excellence. Cancer patients to benefit from new histology independent treatment. Published June 2020 (b). Available at: <https://www.nice.org.uk> [Accessed 18 June 2020]

National Institute for Health and Care Excellence. Larotrectinib for treating NTRK fusion-positive solid tumours Technology appraisal guidance [TA630]. Published May 2020 (a). Available at: <https://www.nice.org.uk> [Accessed 30 June 2020]

National Institute for Health and Care Excellence. Larotrectinib for treating NTRK fusion-positive solid tumours. Published June 2020 (c). Available at: <https://www.nice.org.uk> [Accessed 18 June 2020]

NHS England. Cancer drugs fund. Published 2016. Available at: <https://www.england.nhs.uk/cancer/cdf/> [Accessed 19 June 2020]

NHS England. Genomic laboratory hubs. Published 2018. Available at: <https://www.england.nhs.uk/genomics/genomic-laboratory-hubs/> [Accessed 20 June 2020]

Roche. Japan becomes the first country to approve Roche’s personalised medicine Rozlytrek. Published June 2019. Available at: <https://www.roche.com> [Accessed 5 June 2020]

Siu E, Tomalin A, West K, Anderson S, Wyatt, 2019. An ever-evolving landscape: an update on the rapidly changing regulation and reimbursement of biosimilars in Canada. *GaBI Journal*, 8(3):107-118. doi:10.5639/gabij.2019.0803.014

Wang T, McAuslane N, Liberti L, Leufkens H, Hövels A, 2018. Building Synergy between Regulatory and HTA Agencies beyond Processes and Procedures-Can We Effectively Align the Evidentiary Requirements? A Survey of Stakeholder Perceptions. *Value Health*, 21(6):707-714. doi:10.1016/j.jval.2017.11.003

# Appendix: HTA Assessment details

## **United Kingdom**

### **Larotrectinib**

Larotrectinib (Vitrakvi, Bayer) was evaluated via NICE's standard pathway for HTA, known as Single Technology Appraisal (STA). This process commenced in July 2018, prior to CHMP positive opinion being granted, when the draft scope of the evaluation was agreed upon by the relevant NICE committee. Questions for consultation put forward in the draft included considerations towards the appropriateness of appraising larotrectinib through the STA process. During consultation, the manufacturer noted that larotrectinib does not fit to the current STA process and argued that the existing HTA processes would need to be adapted to accommodate the complexity and uncertainty associated with the innovative treatment. NICE dismissed these concerns, stating that that it had been agreed by scoping workshop attendees that an STA would be appropriate and that close working between the NICE technical team, ERG and company could help resolve any issues.

The final scope, published in March 2019, stipulated that the economic modelling should include the costs associated with diagnostic testing for NTRK fusion in people with advanced solid tumours who would not otherwise have been tested (NICE, 2019).

NICE's Appraisal Consultation Document (draft guidance document) regarding larotrectinib for treating advanced neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours, in adults and children who have no satisfactory treatment options was published in January 2020. The initial decision from NICE stated that it "can't be recommended for use in the NHS because at its current price, it doesn't have the potential to be cost-effective". The reasons for this decision included the lack of comparators in the trial data, little evidence about effectiveness for every type of NTRK fusion-positive tumour. Additionally, the document stated that the cost-effectiveness estimates for larotrectinib were very uncertain because of limitations in the data, such as the substantial uncertainty about how long people would live after their disease gets worse (NICE, 2020).

The company's base-case model gave a deterministic incremental cost-effectiveness ratio (ICER) of £35,309. Whilst above NICE's threshold range of £20,000 - £30,000, it is not uncommon for treatments to be recommended at similar ICERs by NICE, particularly for innovative therapy areas. Following the committee meeting, the ERG provided a revised ICER of £46,822 per QALY, which included updated assumptions according to the committee's preferences. It was further noted that the analysis had not included the diagnostic costs, which would further increase the ICER. In addition, further scenarios regarding major uncertainties were addressed by the ERG. The primary concern was the implausible post-progression survival, which after adjusting for saw an increase in the ICER to between £84,469 and £101,897 per QALY. This led the committee to conclude that the ICER range was above what it would normally consider cost-effective even if larotrectinib was considered to meet the end-of-life criteria, which allows ICERs up to £50,000 per QALY. The committee thus initially concluded that larotrectinib did not meet the criteria for inclusion in the Cancer Drugs Fund. This decision was driven by the belief that even with additional data collection, at the proposed price, larotrectinib did not have plausible potential to be cost effective. The committee also noted that some key uncertainties were unlikely to be resolved, including evidence for a comparator treatment and further characterisation of NTRK gene fusions.

Following the publication of the ACD, the manufacturer and patient groups have an opportunity to respond to comments and consult with the committee on key issues. During the consultation, the manufacturer did provide an updated patient access scheme discount. The revised ICER estimates

following the discounted price were calculated by the ERG and include the estimated diagnostic testing costs; the updated ICER was estimated at £30,888 per QALY and a further estimate including post-progression survival equivalent for larotrectinib and comparator was £48,161 per QALY. The consultation also led to the reconsideration of the appropriateness of larotrectinib for inclusion in the Cancer Drugs Fund.

The final appraisal document states that the data from larotrectinib trials were promising, because tumour response rates were good, and it showed that larotrectinib was likely to improve overall and progression free survival. It recommends larotrectinib for use within the Cancer Drugs Fund as an option for treating advanced NTRK fusion-positive solid tumours if the disease is locally advanced or metastatic, or when surgery could cause severe health problems and patients have no other satisfactory treatment options. This indication is in line with the EMA conditional marketing authorisation for the drug. The committee noted that the updated ICER range, after the price discount, fell within what is usually considered a cost-effective use of NHS resources for drugs that meet the end-of-life criteria.

Recommendation through the Cancer Drugs Fund means that the decision is conditional on further evidence gathering. The NICE committee cites the following reasons for the conditional recommendation: "The cost-effectiveness estimates for larotrectinib are very uncertain because: they are based on data from a population that is different to that seen in NHS clinical practice and there is substantial uncertainty about how long people would live after their disease gets worse. Collecting more data would help to address some of the uncertainties in the clinical evidence. Larotrectinib has the potential to be a cost-effective use of NHS resources at its current price so it is recommended through the Cancer Drugs Fund while these data are collected."

The data collection agreement is published by NICE as part of the Managed Access Agreement. It details the clinical trials which will supply the additional data and expected dates for reporting to NICE for CDF guidance review. The planned interim analysis will be submitted to NICE in the second quarter of 2023 and the final analysis is expected in September 2024. Following the submission of the additional data, NICE will review the findings and may update its guidance accordingly.

### **Entrectinib**

Entrectinib was also evaluated via NICE's standard, single technology assessment, pathway for HTA. This process commenced in November 2018. The draft scope of the evaluation was agreed upon by the relevant NICE committee. As with the larotrectinib process, questions for consultation were put forward regarding the appropriateness of the STA process and NHS testing capabilities.

During the consultation process, the manufacturer submitted further clinical trials that had not been included in the draft scoping by NICE, including three further single-arm basket trials. The data from these trials had also informed the EMA regulatory approval. The manufacturer also put forward the argument that the economic evaluation base case should assume that patients have previously been identified as eligible for treatment because of the rarity of NTRK fusions, genomic screening will not be conducted solely for the purpose of identifying an entrectinib eligible patient. NICE advised that the costs of the diagnostic testing should be incorporated, though a sensitivity analysis should be provided without the testing costs.

Unlike the larotrectinib's evaluation pathway, NICE evaluation of entrectinib did not include an Appraisal Consultation Document. Instead, the guidance did not undergo this step and the final appraisal document was published without public consultation. The guidance recommended entrectinib for use within the Cancer Drugs Fund as an option for treating NTRK positive tumours in line with the marketing authorisation.

The company's revised base case after the technical engagement stage estimated the ICER associated with entrectinib to be £49,358 per QALY gained. However, this did not include several assumptions preferred by the committee. The final ICER range considered incorporated the preferred assumptions, a new commercial arrangement from the company and genomic testing at the point of diagnosis of a locally advanced or metastatic cancer costing per patient with an NTRK fusion-positive tumour. The committee concluded that entrectinib had plausible potential for cost-effectiveness if it met the end-of-life criteria. Yet, given the high level of uncertainty in the evidence provided, further data would be required before entrectinib could be included in NHS routine commissioning. Additionally, the committee recognised that entrectinib is innovative and its use in clinical practice would help accelerate NHS England's developments in genomic testing. These reasons led the committee to determine that entrectinib meets the criteria to be included in the Cancer Drugs Fund.

The data collection agreement is published by NICE as part of the Managed Access Agreement. It details the clinical trials which will supply the additional data and expected dates for reporting to NICE for CDF guidance review. The additional data sets expected include an ongoing entrectinib trial, Public Health England routine cancer data sets and real-world data (clinical outcomes and tumour genomic profiling) from the US. The planned interim analysis will be submitted to NICE in December 2023 and the final analysis is expected in September 2027. Following the submission of the additional data, NICE will review the findings and may update its guidance accordingly.

## **France**

### **Larotrectinib**

HAS issued a favourable opinion for the treatment of paediatric patients with NTRK fusion positive refractory or relapsing childhood fibrosarcoma or other soft tissue sarcoma, in July 2020. The clinical benefit was declared moderate in these specific subgroups; for all other authorised indications the clinical benefit was insufficient. Thus, HAS issued an unfavourable opinion for all other paediatric indications in the marketing authorisation and in all adults with a NTRK positive solid tumour.

Prior to the publication of HAS's opinion on larotrectinib, the country-level expert suggested that given the uncertainty around the relevance of clinical results, the French transparency committee are likely to give preference to reimbursing histology independent therapies only in subtypes of tumours where the data are more consistent. HAS indeed only recommended larotrectinib for specific tumour types.

The committee noted that the favourable opinion was made despite the low level of evidence and pending new efficacy and tolerance data. Therefore, the decision is subject to the submission of comparative data of larotrectinib to the best supportive care for these patients within 12 months and establishment of an exhaustive register listing all children treated by larotrectinib in France.

The committee stated that in the context where no comparative data are available to increase the certainty of the conclusion on the effect of treatment with larotrectinib, the introduction of this medicinal product into the therapeutic strategy will be accompanied by the caveat "greater risk-taking than for drugs whose effectiveness is based on a comparison made with a risk control of wrongly concluding that the treatment is effective".

Furthermore, the committee argued that a basket-study does not, in principle, oppose the integration of control groups for specific tumour types. To illustrate the feasibility of a comparative study without considering tumour location, the committee cited, by way of example, that in the phase II SHIVA study, carried out from the year 2012 onward, patients were randomized between various targeted therapies chosen according to the molecular profile of the tumour and the investigator's

choice of treatment in patients with solid tumours refractory to standard treatment. The committee also asserted that the absence of a direct comparison was even less justified as around a quarter of patients included had not been previously treated with systemic cancer drugs.

The use of larotrectinib for the favourable indications within the therapeutic strategy will first require guidance on the initiation and discontinuation of treatment. Given the complexity of the management of these exceptional paediatric tumours, the transparency committee recommend that this decision is made within the framework of the proposal for a multidisciplinary consultation meeting (réunion de concertation pluridisciplinaire/RCP) to regulate the use of larotrectinib.

Despite the initial unfavourable opinion and concerns with the data submitted the Committee considered that the clinical development of larotrectinib should be continued, via the SCOUT and NAVIGATE studies (ClinicalTrials.gov, 2015). They reiterate the importance of having good quality data and suggest that a randomised, comparative study with overall survival as a primary endpoint with sufficient power in each patient cohort could be adequate to recommend larotrectinib in the future.

### **Entrectinib**

There is no evidence to indicate that entrectinib has been considered by the Transparency Committee at present.

### **Canada**

#### **Larotrectinib**

The initial recommendation published by the pCODR expert review committee was “Reimburse with clinical criteria and/or conditions”. This recommendation was restricted to specific tumour types, limiting reimbursement to adult and paediatric patients with salivary gland or soft tissue sarcoma, and paediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma. Further conditions included the cost-effectiveness being improved to an acceptable level and feasibility of adoption, addressing issues with budget impact and access to testing). The committee concluded that in all other solid tumours with an NTRK gene fusion, reimbursement of larotrectinib is not recommended, as they were not satisfied that the evidence showed a clear net clinical benefit.

The manufacturer disagreed with the decision to not extend access to all eligible patients with NTRK fusion cancer, suggesting that this would cause inequity for NTRK fusion cancer patients and significant ethical concerns. They requested to expand larotrectinib access to all eligible patients, particularly for patients with thyroid, lung, colorectal, or gastrointestinal stromal tumours and for cancer of the central nervous system.

Following this request, the committee reconsidered and subsequently overturned their initial recommendation, issuing a final recommendation of ‘Do not reimburse’. This may be the only example of the pCODR revoking an initial positive recommendation and replacing it with a negative recommendation. They recognised that whilst the provided data may be sufficient for a regulator to provide access to a promising new treatment in tumours with high unmet need, the high degree of uncertainty around the net clinical benefit of larotrectinib compared to available treatment options was too high to support public reimbursement. Also, the committee did not draw any definitive conclusions regarding the cost-effectiveness of larotrectinib, primarily due to the heterogeneity of the patients in the pooled analysis. Considering the ongoing clinical trials expected to be completed in 2022 and 2023, they noted, however, the potential for resubmission and encouraged the provision of updated or additional evidence from these trials, along with real-world evidence.

Larotrectinib was also considered by Quebec’s HTA body (INESSS), who issued a “refusal of registration” recommendation. INESSS cites that whilst the results suggest that larotrectinib has a significant clinical benefit, the extent of its effect differs depending on the tumour type. Moreover, larotrectinib had not been compared to standard treatment. Considering these concerns as well as several other methodological limitations, the INESSS was unable to recognise the therapeutic value of larotrectinib. This lack of recognised therapeutic value meant that other aspects including cost-effectiveness and budget impact were not assessed.

### ***Entrectinib***

In February 2020, Health Canada, under the Notice of Compliance with Conditions (NOC/c), approved entrectinib for adult patients with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, and with no satisfactory treatment options.

The pCODR process was initiated following the submission in July 2019, however Roche subsequently requested a voluntary withdrawal of the submission.





### **About us**

Founded in 1962 by the Association of the British Pharmaceutical Society, the Office of Health Economics (OHE) is not only the world's oldest health economics research group, but also one of the most prestigious and influential.

OHE provides market-leading insights and in-depth analyses into health economics & health policy. Our pioneering work informs health care and pharmaceutical decision-making across the globe, enabling clients to think differently and to find alternative solutions to the industry's most complex problems.

Our mission is to guide and inform the healthcare industry through today's era of unprecedented change and evolution. We are dedicated to helping policy makers and the pharmaceutical industry make better decisions that ultimately benefit patients, the industry and society as a whole.

*OHE. For better healthcare decisions.*

### **Areas of expertise**

- Evaluation of health care policy
- The economics of health care systems
- Health technology assessment (HTA) methodology and approaches
- HTA's impact on decision making, health care spending and the delivery of care
- Pricing and reimbursement for biologics and pharmaceuticals, including value-based pricing, risk sharing and biosimilars market competition
- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics

[ohe.org](https://www.ohe.org)