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Potential Areas of Focus for the Future EU HTA Methodology: Discrepancies Between EUnetHTA and National Evaluations

Podium Session: Key Trends in HTA Policy - Present and Future

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Background Situation in Europe

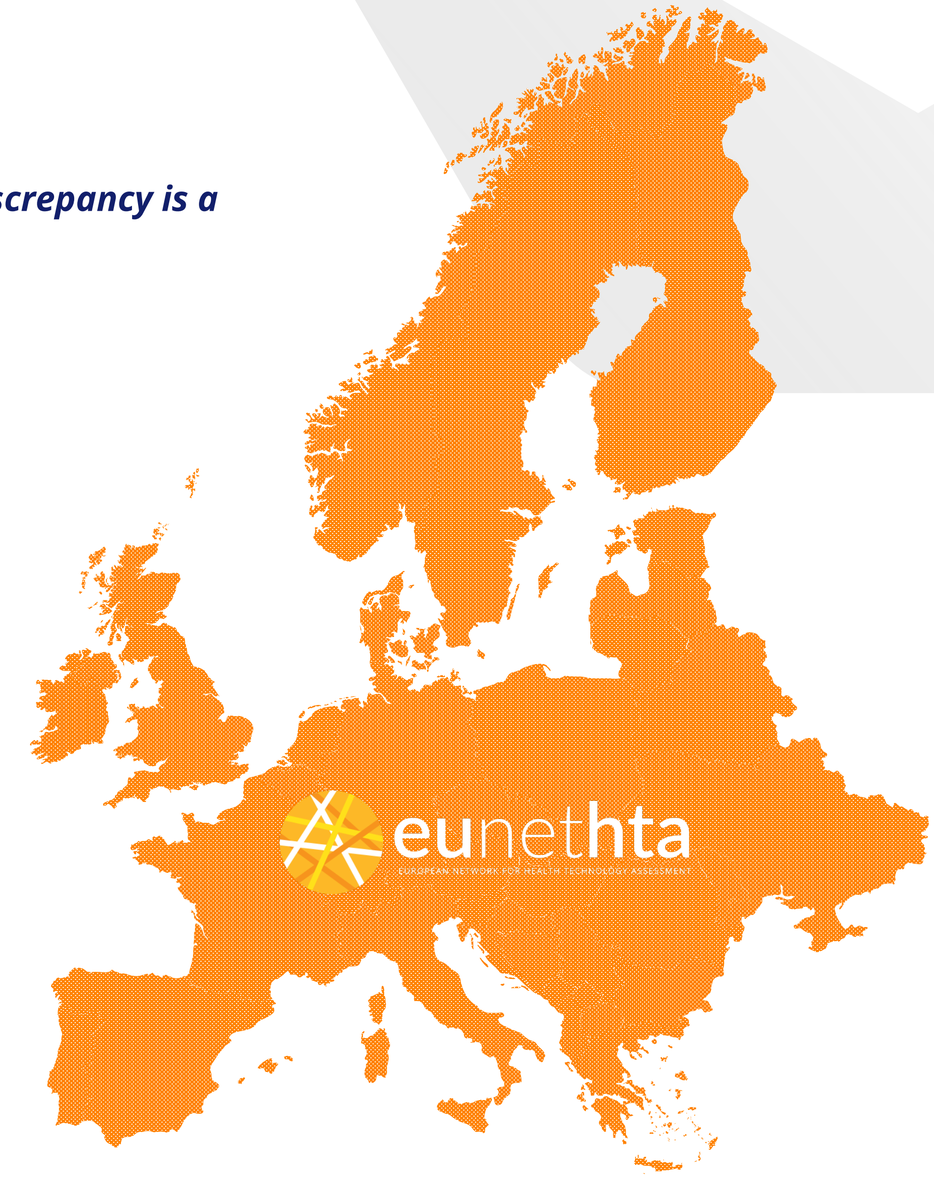
Learnings from previous assessment models suggest that aligning on points of discrepancy is a paramount goal for a successful future EU HTA collaboration.

- The EUnetHTA Working Package 7 Final Report *(2020)* described the following:

  > *"Most of the agencies surveyed, still reported factors that prevented or limited the extent to which JCAs were used nationally"*

- Among those factors, the misalignments with regards to **reliability, scientific rigor, assessment methodology and the quality of evidence** were highlighted

- The EUnetHTA 21 joint consortium is aiming to support the future EU HTA system under the EU HTA Regulation through **building on the achievements and lessons learned from previous EUnetHTA Joint Actions**



EU: European Union; EUnetHTA: European Network for Health Technology Assessment; HTA: Health Technology Assessment; JCA: Joint Clinical Assessment

Objectives of the Study

Research question: what are the areas of discrepancy between the assessments at the national vs EUnetHTA level and how do they impact the national HTA outcomes?

The aim of this research is to:

- Identify the **areas where discrepancies between EUnetHTA and national evaluations existed**, and
- Understand whether these areas have **impacted the national HTA outcomes**

EUnetHTA: European Network for Health Technology Assessment; HTA: Health Technology Assessment

Research Framework

ASSESSMENT SELECTION CRITERIA

Pharmaceuticals with **JA3 (2016-2021) EUnetHTA Relative Effectiveness Assessments (REAs)** and **published national HTA reports/results** in at least **three out of the four countries** in scope were selected for this analysis

SELECTED ASSESSMENTS

Siponimod ***Midostauren*** ***Alectinib*** ***Brolucizumab*** ***Polatuzumab*** ***Crizanlizumab*** ***Regorafenib***

ANALYSIS METHODOLOGY

P	**Population** considered		**Subgroups** considered	**Slicing** of the **population**	
	Comparators considered			**O**utcomes considered	
S	Evaluation of the **internal validity** of the pivotal study **(study level)**	Evaluation of the **internal validity** of the pivotal study **(outcome level)**	Evaluation of the **external validity** of the pivotal study	Evaluation of the **study design** and **outcome analysis**	Consideration of the **ITC evidence**

Ten assessment elements relevant to the **PICOS framework** were chosen as the basis for the comparison

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EUnetHTA: European Network for Health Technology Assessment; HTA: Health Technology Assessment; JA: Joint Assessment; ITC: Indirect Treatment Comparison; PICOS: Population, Intervention, Comparators, Outcomes, Study Design Framework

EUnetHTA Assessment

The EUnetHTA methodology varied corresponding to the author and co-author countries. Generally, the EUnetHTA assessed the transferability and the quality and robustness of the evidence more rigorously than the included outcomes and type of evidence.

Included Assessments	Therapeutic Area	Date of EUnetHTA Assessment	*Assessment population*	*Subgroups considered*	*Slicing of the population*	*Comparators considered*	*Outcomes considered*	*Internal Validity (Study Level)*	*Internal Validity (outcome level)*	*External validity of the study*	*Study design and outcome analysis*	*Consideration of the ITC evidence*
Regorafenib[1]	Oncology	10/2017			X							X
Midostauren[2]	Oncology	11/2017			X							
Alectinib[3]	Oncology	02/2018			X							
Polatuzumab[4]	Oncology	02/2020								X		
Brolucizumab[5]	Eye disorders	03/2020			X							
Siponimod[6]	Neurologic disorders	03/2020	X	X	X							
Crizanlizumab[7]	Haematology	11/2020			X							X

Legend:

- Major limitation
- Identified limitation, but not a main reason for a negative conclusion
- X — Not-commented on or evidence not submitted
- Positive or no negative comments
- Evidence strength point

Note: [1]Regorafenib (Oct 2017); [2]Midostauren (Nov 2017); [3]Alectinib (Feb 2018); [4]Polatuzumab (Feb 2020); [5]Brolucizumab (Mar 2020); [6]Siponimod (Mar 2020); [7]Crizanlizumab (Nov 2020) |
EUnetHTA: European Network for Health Technology Assessment; ITC: Indirect Treatment Comparison; PICOS: Population, Intervention, Comparators, Outcomes, Study Design Framework
Source: EUnetHTA; Alira Health analysis

German Assessment

Evidence robustness, outcome relevance, and transferability to the German clinical setting are the focal points of misalignment.

Included Assessments / Assessment Items	*Assessment population*	*Subgroups considered*	*Slicing of the population*	*Comparators considered*	*Outcomes considered*	*Internal Validity (Study Level)*	*Internal Validity (outcome level)*	*External validity of study*	*Study design and outcome analysis*	*Consideration of the ITC evidence*
Midostauren[1]	NO	YES	NA	YES	NO	YES	NO	NO	NO	NA
Alectinib[2]	YES	NO	NA	NO	NO	YES	NO	NO	NO	NA
Polatuzumab[3]	YES	NO	NO	YES	NO	YES	NO	NA	NO	NA
Brolucizumab[4]	NA	NA	NA	NO	NA	NA	NA	NA	NO	NA
Siponimod[5]	YES	YES	NO	NO	NO	NO	NO	NA	NO	NA
Crizanlizumab[6]	YES	NO	NA	YES	NO	YES	YES	YES	YES	NA

Relevance and validity of the outcomes

The **selection and operationalization of endpoints** were the **most frequent points of misalignment** between the EUnetHTA and the German assessments

Study design issues

Limitations in study design were the **most frequent drivers for negative impact on benefit ratings**

Slicing of the population

The G-BA considers the population defined in the EMA-approved indication but **slices the population** per comparative therapy **according to the German setting**, when applicable

The comparison against one comparator and the ODD status eased the assessment challenge

A **proven added benefit** is **automatically** determined for drugs with an **ODD status**. With and without an ODD status, evidence on comparative effectiveness against **one of the assigned ACTs** would be sufficient (per population slice).

Legend:

- YES — No misalignment existed
- NO — Discrepant national assessment of the item from EUnetHTA's assessment
- NA — Misalignment is unclear, analysis is not mentioned or conducted

- National HTA misaligned with the EUnetHTA. Assessment item with high impact on the overall rating of the added benefit
- National HTA misaligned with the EUnetHTA. Limitations identified by the national HTA body
- Misalignment existed. Assessment Item with a positive impact on the overall rating of the added benefit
- Misalignment existed, with no or unclear impact on the overall rating of the added benefit

Note: [1]Midostauren (Jan 2018); [2]Alectinib (Mar 2018); [3]Polatuzumab (May 2020); [4]Brolucizumab (Jul 2020); [5]Siponimod (May 2020); [6]Crizanlizumab (Mar 2021)| ACT: Appropriate comparative therapy; EMA: European Medicine Agency; EUnetHTA: European Network for Health Technology Assessment; G-BA: The Federal Joint Committee (*Gemeinsamer Bundesausschuss*); HTA: Health Technology Assessment; ITC: Indirect Treatment Comparison; ODD: Orphan Drug Designation | Source: EUnetHTA; G-BA; Alira Health analysis

French Assessment

Overall, the design and external validity of the pivotal study were main points of focus in the French HTA assessments.

Included Assessments / Assessment Items	*Assessment population*	*Subgroups considered*	*Slicing of the population*	*Comparators considered*	*Outcomes considered*	*Internal Validity (Study Level)*	*Internal Validity (outcome level)*	*External validity of study*	*Study design and outcome analysis*	*Consideration of the ITC evidence*
Regorafenib[1]	YES	YES	YES	YES	YES	NA	NA	YES	YES	NA
Midostauren[2]	YES	NA	NA	NO	NO	YES	NA	NO	NO	NA
Alectinib[3]	YES	NA	NA	YES	YES	NA	NA	NA	NO	NA
Polatuzumab[4]	YES	NO	NO	NO	NO	YES	YES	NO	YES	NA
Brolucizumab[5]	YES	YES	NA	YES	NA	NA	NA	YES	NO	NA
Siponimod[6]	YES	YES	YES	YES	YES	NO	YES	NA	NO	NA
Crizanlizumab[7]	YES	NO	NA	YES	YES	NA	NA	NO	NO	NA

Study design and outcome analysis

Limitations with regards to **study design were the most common drivers for negative impact on benefit ratings** by the HAS

Transferability of the evidence

Limitations relevant to **insufficient reflection of the French routine clinical setting** and **patient demographics** were the **second** most identified **misalignments and drivers for negative impact on benefit rating**

Indirect treatment comparisons

In none of the analyzed assessments **did the HAS accept the ITC evidence**, due to **methodological limitations**

Limitations hindering robust comparisons

In addition to the quality of evidence and magnitude of effect, the **HAS appraisals are influenced by factors that are external to the evidence**, such as **therapeutic need**

Legend:

- YES — No misalignment existed
- NO — Discrepant national assessment of the item from EUnetHTA's assessment
- NA — Misalignment is unclear, analysis is not mentioned or conducted

- National HTA misaligned with the EUnetHTA. Assessment item with high impact on the overall rating of the added benefit
- National HTA misaligned with the EUnetHTA. Limitations identified by the national HTA body
- Misalignment existed. Assessment Item with a positive impact on the overall rating of the added benefit
- Misalignment existed, with no or unclear impact on the overall rating of the added benefit

Note: [1]Regorafenib (November 2017); [2] Midostauren (June 2018) ; [3]Alectinib (May 2018) ; [4]Polatuzumab (Jun 2020); [5]Brolucizumab (December 2020); [6]Siponimod (July 2020); [7]Crizanlizumab (May 2021) | EUnetHTA: European Network for Health Technology Assessment; HAS: French National Authority for Health (*Haute Autorité de Santé*); HTA: Health Technology Assessment; ITC: Indirect Treatment Comparison | Source: EUnetHTA; HAS; Alira Health analysis

Italian Assessment

Overall, the misalignment between the AIFA's and EUnetHTA's evaluations was minimal. The robustness of the scientific evidence and issues relevant to subgroup analyses were the main discrepancy areas but had no impact on the evaluation outcomes.

Included Assessments / Assessment Items	Assessment population	Subgroups considered	Slicing of the population	Comparators considered	Outcomes considered	Internal Validity (Study Level)	Internal Validity (outcome level)	External validity of study	Study design and outcome analysis	Consideration of the ITC evidence
Regorafenib[1]	YES	NO	YES	YES	YES	NO	NO	YES	YES	NA
Midostauren[2]	YES	NO	NA	YES	YES	NO	NA	NA	NA	NA
Alectinib[3]	YES	NA	NA	YES	YES	NO	YES	NA	NA	NA
Brolucizumab[4]	YES	NO	NA	YES	YES	NA	NA	NO	NA	NA
Siponimod[5]	YES	YES	YES	NO	YES	NA	NA	NA	NA	NA
Crizanlizumab[6]	YES	NO	NA	NO	NO	YES	YES	NO	NA	NA

The transferability of evidence to the Italian setting

Although not consistently discussed in their HTA reports, the **generalizability of trial outcomes** seems to be a **critical assessment point for the AIFA**

A possibly different approach for assessing the quality of evidence

The **description of the methodology** used for assessing the **quality of evidence** was **not discussed** in all AIFA reports. The quality of the evidence was **globally rated as low, medium, or high**

Limitations hindering robust comparisons

In addition to the assessment of the quality of the evidence, the outcome of the AIFA appraisal is usually **influenced by factors external to the evidence**, such as **therapeutic need**

Research limitations

Due to the **lack of publicly available clinical assessment reports,** only a **limited understanding** of the assessment criteria could be obtained. The **regional assessment reports** were consulted for the assessments for which **no publicly available AIFA HTA report could be identified**

Legend:

- YES — No misalignment existed
- NO — Discrepant national assessment of the item from EUnetHTA's assessment
- NA — Misalignment is unclear, analysis is not mentioned or conducted

- National HTA misaligned with the EUnetHTA. Assessment item with high impact on the overall rating of the added benefit
- National HTA misaligned with the EUnetHTA. Limitations identified by the national HTA body
- Misalignment existed. Assessment Item with a positive impact on the overall rating of the added benefit
- Misalignment existed, with no or unclear impact on the overall rating of the added benefit

Note: [1]Regorafenib (Feb 2018); [2]Midostauren (Dec 2017) ; [3]Alectinib (Jan 2018); [4]Brolucizumab (Jan 2021); [5]Siponimod (Apr 2020) & Siponimod (Mar 2018); [6]Crizanlizumab (Jan 2021) |
AIFA: Italian Medicines Agency (*Agenzia italiana del farmaco*); EUnetHTA: European Network for Health Technology Assessment;
HTA: Health Technology Assessment; ITC: Indirect Treatment Comparison | Source: EUnetHTA; AIFA; Alira Health analysis

Spanish Assessment

Overall, the misalignment between the AEMPS' and EUnetHTA's evaluations was minimal. The transferability of evidence to the Spanish context is a main area of misalignment.

Included Assessments / Assessment Items	*Assessment population*	*Subgroups considered*	*Slicing of the population*	*Comparators considered*	*Outcomes considered*	*Internal Validity (Study Level)*	*Internal Validity (outcome level)*	*External validity of study*	*Study design and outcome analysis*	*Consideration of the ITC evidence*
Regorafenib[1]	YES	NO	YES	YES	YES	NA	NA	NO	YES	NA
Midostauren[2]	YES	YES	NA	YES	YES	NA	NA	NA	NO	NA
Alectinib[3]	YES	YES	NA	YES	YES	NA	NA	NA	NA	NA
Polatuzumab[4]	YES	NO	NO	NO	YES	YES	YES	NO	YES	NA
Brolucizumab[5]	YES	NA	NA	YES	YES	NA	NA	YES	NA	NA
Siponimod[6]	YES	YES	YES	NO	YES	NA	YES	NA	NA	NA

Choice of comparator

The **transferability of evidence to the Spanish context** depends highly on choosing the locally approved comparator. **Failing to include the appropriate comparator led to a negative benefit rating**

Relevance of the population in the pivotal study

The **transferability of evidence to the Spanish context** depends on studying the innovation in a **population that reflects the Spanish patient population**

The AEMPS cited the EUnetHTA reports in 50% of cases

The AEMPS HTA reports are designed to **support funding decisions**, therefore, they **perform complementary analyses to the EUnetHTA's**

Limitations hindering robust comparisons

In addition to the assessment of the quality of evidence, the outcome of the AEMPS appraisals is usually **influenced by factors external to the evidence**, such as **therapeutic need** and **incremental benefit** compared with existing alternatives

Legend:

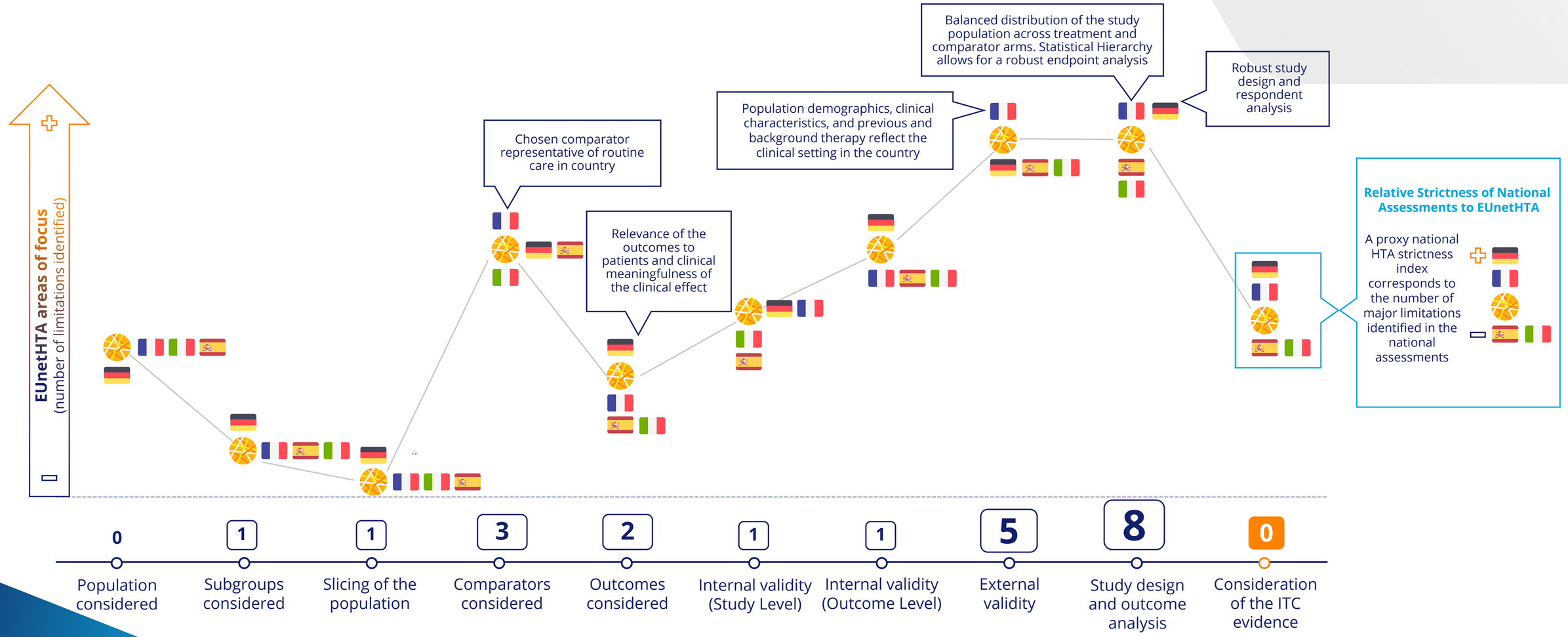
- YES — No misalignment existed
- NO — Discrepant national assessment of the item from EUnetHTA's assessment
- NA — Misalignment is unclear, analysis is not mentioned or conducted

- National HTA misaligned with the EUnetHTA. Assessment item with high impact on the overall rating of the added benefit
- National HTA misaligned with the EUnetHTA. Limitations identified by the national HTA body
- Misalignment existed. Assessment Item with a positive impact on the overall rating of the added benefit
- Misalignment existed, with no or unclear impact on the overall rating of the added benefit

Note: [1]Regorafenib (Mar 2015); [2] Midostaurina (Mar 2019); [3] Alectinib (Aug 2018); [5] Polatuzumab (Nov 2021); [4] Brolucizumab (Jul 2022); [6]Siponimod (Apr 2021) |
AEMPS: Spanish Medicine and Health Products Agency (*Agencia Española de Medicamentos y Productos Sanitarios*); EUnetHTA: European Network for Health Technology Assessment; HTA: Health Technology Assessment; ITC: Indirect Treatment Comparison | Source: EUnetHTA; AEMPS; Alira Health analysis

Cross-Country Analysis

The transferability of the evidence and the design of the pivotal study are among the key points of focus for EUnetHTA. Nevertheless, the most frequent misalignments with national HTAs occurred in these two areas. Afterward, came the choice of comparators and outcomes.



X Frequency of misalignments associated with negative impact on the national benefit rating

0 In none of the assessments was the ITC evidence considered (or not submitted by the applicant) at the national level

Comparison With Previous Literature

In line with the literature, our work has identified a methodological heterogeneity in the clinical appraisals across the EUnetHTA and countries in scope. Additionally, our analysis employed a larger set of assessment criteria and examined whether those misalignments occurred in areas considered of high relevance to the country's HTA.

	Chassagnol 2020[1]	Giuliani 2018[2]	Kisser 2021[3]	EUnetHTA 2017[4]
Title	**REAs from Joint Actions (JA1–3) were reviewed and compared versus HTA in France, Germany, UK, Italy**	**Leveraging EUnetHTA's conceptual framework to compare HTA decision drivers in France, Italy, and Germany from a manufacturer's point of view**	**Towards compatibility of EUnetHTA JCA methodology and German HTA: a systematic comparison and recommendations from an industry perspective**	**An analysis of HTA and reimbursement procedures in EUnetHTA partner countries: final report**
Objective	Analyses of both the EUnetHTA assessment and the national appraisals' key process and content characteristics for 12 REAs	Outcomes, decision drivers, commonalities and differences of HTA appraisals by the HAS, AIFA, and G-BA	Comparison of all pharmaceutical compounds that had undergone both EU JCA (during EUnetHTA JA3) and German assessments between January 2016 and June 2020	Analysis of reimbursement procedures within 31 EUnetHTA partner countries
Criteria	> Choice of evidence (use of evidence beyond RCTs e.g., usage of single-arm trials and indirect evidence) > Choice of comparative treatments > Choice of endpoints > Choice of subgroups	Nine domains of the EUnetHTA core model: CUR; TEC; SAF; EFF; ECO; ETH; ORG; SOC; LEG	> Choice of population > Study Intervention > Comparator > Endpoints > Subgroup Analysis	> Engagement in HTA cooperation > Use of jointly produced HTA information > Re-use of national, regional and local HTA information from other jurisdictions
Results	High heterogeneity of HTA appraisals across the four countries, only three assessments received positive recommendations in all four countries	HTA drivers: 1. Subgroups and orphan designation in Germany 2. Unmet need in Italy 3. Safety considerations (all three countries)	EU JCA had a more inclusive approach with regards to indirect comparisons, single-arm trials and surrogate endpoints. Conversely, subgroup and sensitivity analyses were requested more often and/or included in German assessments	The study identifies differences in working practices for the assessment of health technologies and a frequent use of HTA from other jurisdictions

Search databases: PubMed and the ISPOR Website. Date of literature search: Sep 27th, 2022 / Note: [1] Chassagnol (2020) ; [2] Giuliani (2018) ; [3] Kisser (2021) ; [4] EUnetHTA
CUR: health problem and current use of technology; TEC: description and technical characteristics of technology; SAF: safety ; EFF: clinical effectiveness; ECO: cost and economic evaluation; ETH: ethical analysis; ORG: organizational aspects; SOC: patient and social aspects; LEG: legal aspects

Study Limitations

- The **difference in nature** between the **EUnetHTA's clinical assessments** and the **national agency HTA appraisals** hindered the ability to understand the impact on the national benefit rating per assessment item
- **Small number** of assessments analyzed
- The degree to which the **EUnetHTA assessment methodology** is followed is usually **influenced by the author and co-author countries**
- This analysis **lacked the comparison** based on the **type of clinical trials included and the SLR sources and methodology**

EUnetHTA: European Network for Health Technology Assessment; HTA: Health Technology Assessment; SLR: Systematic literature search

Key Conclusions of the Study

Reaching a consensus on methods with regards to the choice of outcomes, the assessment of robustness of the evidence, and the ITC methodology would be key in the discussions focusing on the development of the future EU HTA.

- The **least frequent misalignment** between the EUnetHTA and national assessments was seen on the points for which the EUnetHTA adopted a **comprehensive approach** or followed a **widely accepted assessment methodology**
- The **most frequent misalignment** occurred in items corresponding to **relevance to the local context** and **methodologies with suboptimal consensus** across the member states. A **negative impact on national benefit ratings usually originated from those areas**
- There is a **need** for the development of **broadly accepted criteria** that defines **preferrable and potentially acceptable evidence types for HTA purposes, for the direct and indirect comparisons**
- Within the future EU HTA model, **joint consultations could focus on suggesting clear recommendations and scenario implications** for the applicant with regards to **population characteristics** and **choice of the comparators and outcomes**

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EUnetHTA: European Network for Health Technology Assessment; HTA: Health Technology Assessment; SLR: Systematic literature search

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Thank You

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