COMED PUSHING THE BOUNDARIES OF COST AND OUTCOME ANALYSIS OF MEDICAL TECHNOLOGIES

UNIVERSITY OF EXETER | MEDICAL SCHOOL

Surrogate Outcomes in Health Technology Assessment: are they as established as they seem?

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Definition of surrogate outcomes*

Disease-centered characteristics ⟷ *Patient-centered characteristics*

Biomarkers
A characteristic that is objectively measured and evaluated as an indicator of normal, pathogenic or pharmacologic responses to a therapeutic intervention.

Surrogate outcomes

A *biomarker* that is intended to substitute and predict for a *final outcome.*

Final outcome
A characteristic that reflects how patients feel, function or survive.

e.g. Carotid intima media thickness → **Cardiovascular Mortality**

e.g. Intraocular pressure → **Loss of vision**

**Biomarkers Definition Working Group, NIH 2001*

WP2 – Use of surrogate outcomes for medical devices

Overall objective and specific tasks

To improve the *decision-making* process concerning new or existing technologies whose evidence base is mainly supported by *surrogate outcomes*

1. To review and map use of surrogate outcomes in economic evaluations in HTA methods guidelines and reports

2. To use various sources of evidence (e.g. RCTs, registries) to validate putative surrogate outcomes

3. To develop a framework for surrogate outcomes-based value determinations and to identify potential levers and barriers to its implementation

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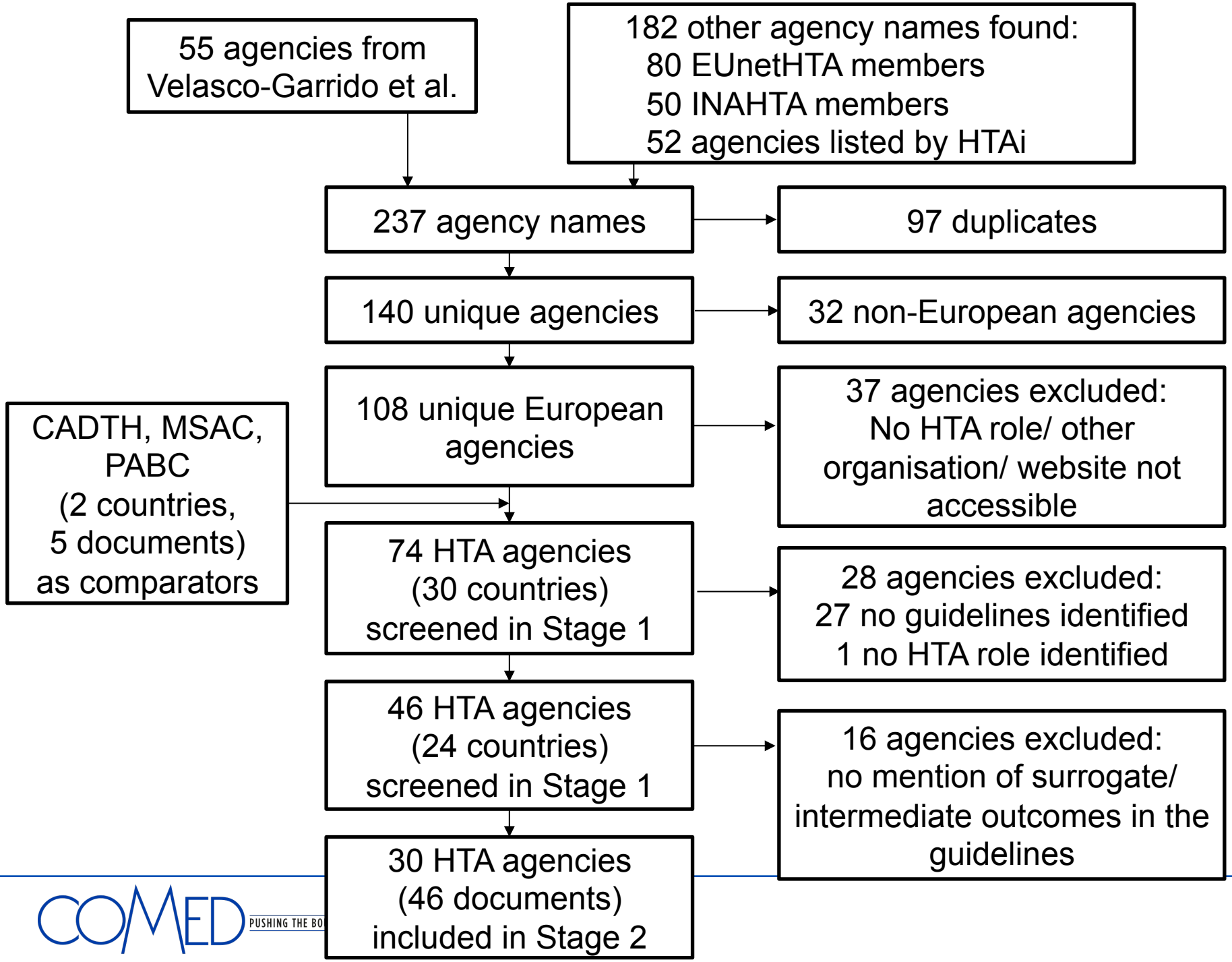
- A. Review of publicly available **methods guidance** from international HTA agencies
- B. Review of **HTA reports** from international agencies that rely on surrogate outcomes

A. Review of methods guidance from international HTA agencies

Summary of data extraction

Definition	Is a definition of surrogate endpoints provided?
Examples	Are example of “reliable” surrogate endpoints provided?
Use	Is use of surrogate endpoints recommended or discouraged in specific situations?
Evidence	What evidence is required for quantifying the the surrogate-final outcome relationship?
Validation methods	Are any validation methods prescribed?
Validation threshold	Are there accepted cut-off values for surrogacy presented?


55 agencies from Velasco-Garrido et al.
182 other agency names found:
80 EUnetHTA members
50 INAHTA members
52 agencies listed by HTAi
237 agency names
97 duplicates
140 unique agencies
32 non-European agencies
108 unique European agencies
37 agencies excluded:
No HTA role/ other organisation/ website not accessible
CADTH, MSAC, PABC
(2 countries, 5 documents)
as comparators
74 HTA agencies
(30 countries)
screened in Stage 1
28 agencies excluded:
27 no guidelines identified
1 no HTA role identified
46 HTA agencies
(24 countries)
screened in Stage 1
16 agencies excluded:
no mention of surrogate/ intermediate outcomes in the guidelines
30 HTA agencies
(46 documents)
included in Stage 2

A. Review of methods guidance from international HTA agencies

Pharmaceuticals vs MDs guidance

	NICE TA guidance	NICE MTEP guidance
Definition	✔	✖
Examples	✔	✖
Use	✔	✔ (refers to intermediate outcomes and acknowledges the limited nature of evidence usually available for medical devices)
Evidence	✔ (evidence must be provided together with an explanation of how the relationship is quantified for use in modelling […] the uncertainty associated […] should be explored and quantified)	✖
Methods	✖	✖
Threshold	✖	✖

A. Review of methods guidance from international HTA agencies

Discussion

- Compared to Velasco-Garrido 2009 (20 documents) we identified 46 documents from 30 agencies
- 15 (33%) referred specifically to pharmaceuticals, 2 (4%) specific for oncology
- The level of consideration varied greatly, from single mention to entirely dedicated documents*
- Guidance regarding evidence, methods and threshold for surrogate validation was limited to a few agencies (IQWIG, G-BA, PBAC, EUnetHTA, INFARMED) and is still unclear in terms of what constitutes a reliable surrogate marker
- In the light of the EU joint HTA proposal, there is an opportunity for further methodological harmonisation on how to handle the uncertainty associated to surrogate outcomes

* Validity of surrogate parameters in oncology (Rapid report), IQWiG-Berichte 80, 2011

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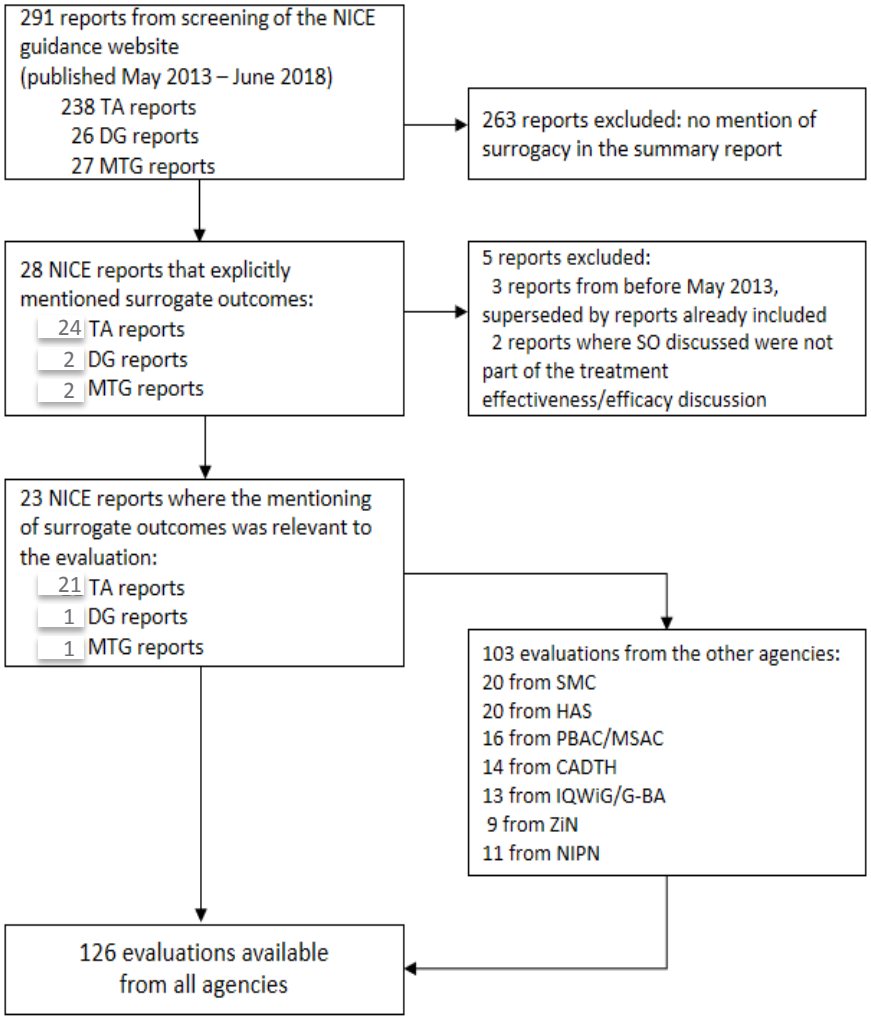
B. Review of HTA reports from international agencies that rely on surrogate outcomes

Objective

① to map the range of methodological approaches adopted *empirically* to the use of surrogate endpoints in HTA reports across international HTA agencies

② to assess how the uncertainty linked to surrogates influence the coverage or reimbursement decisions

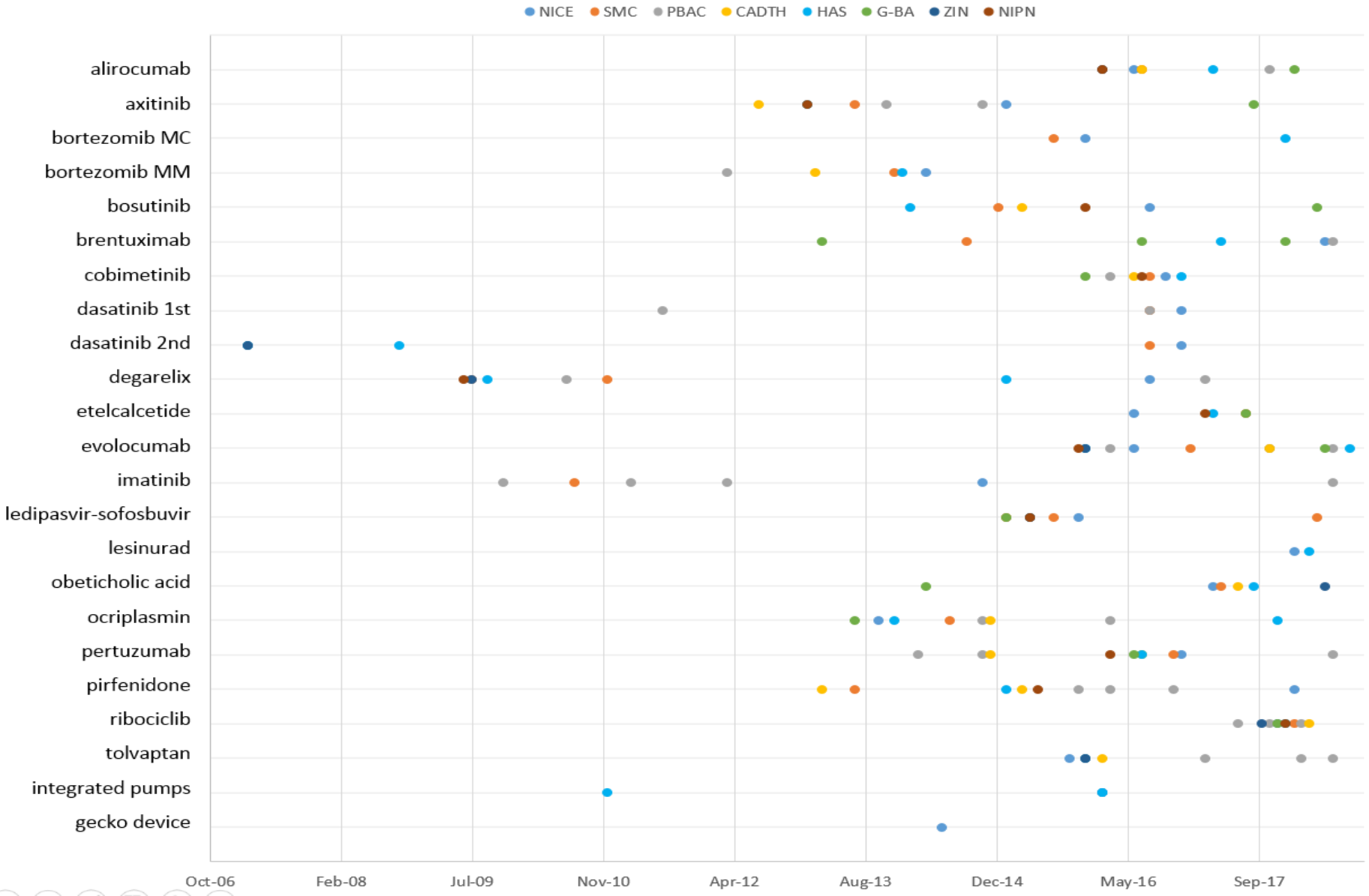


B. Review of HTA reports from international agencies that rely on surrogate outcomes

Agency sampling

Agency (country, acronym)	Guidelines	Mention	Definition	Examples	Use	Evidence	Methods	Threshold
FR HAS	✓	✓			✓	✓		
DE G-BA	✓	✓			✓	✓	✓	
DE iQWIG	✓	✓		✓	✓	✓	✓	✓
HU NIPN	✓	✓			✓			
NL ZIN	✓	✓		✓	✓	✓		
UK HIS	✓	✗						
UK NICE	✓	✓		✓	✓	✓		
EU EUnetHTA	✓	✓	✓	✓	✓	✓	✓	✓
AU MSAC	✓	✓			✓	✓	✓	
AU PBAC	✓	✓	✓	✓	✓	✓	✓	
CA CADTH	✓	✓		✓	✓		✓	

B. Review of HTA reports from international agencies that rely on surrogate outcomes



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Results

Which surrogates considered?

- Progression-free survival: 7 (30%) (i.e. axitinib, bortezomib, brentuximab, cobimetinib, pertuzumab, ribociclib)
- Tumour or hematologic response: 4 (17%) (i.e. bosutinib, dasatinib first and second line, pertuzumab)
- Changes in LDL-C levels: 2 (9%) (i.e. alirocumab, evolocumab)
- Other surrogate endpoints:
  - Biomarkers: parathyroid hormone (PTH), testosterone, prostate specific antigen (PSA), alkaline phosphatase, bilirubin, glycated haemoglobin (HbA1c), sustained virologic response
  - Functional measurements: forced expiratory volume (FEV1), forced vital capacity (FVC), venous blood flow, change in total kidney volume (TKV)
  - Clinical rates (eg. proportion of patients with non-surgical resolution of focal vitreomacular traction)

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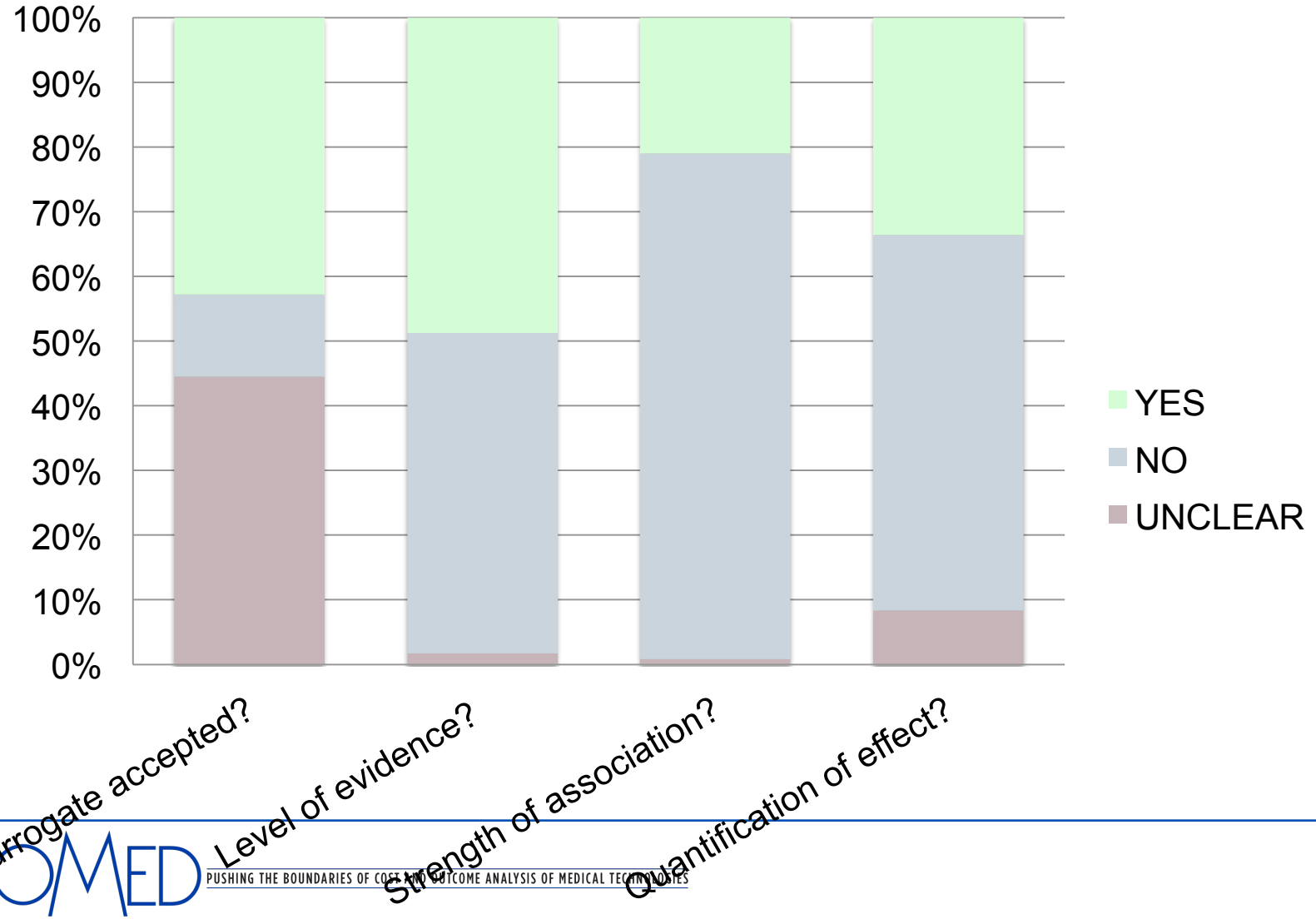
Results



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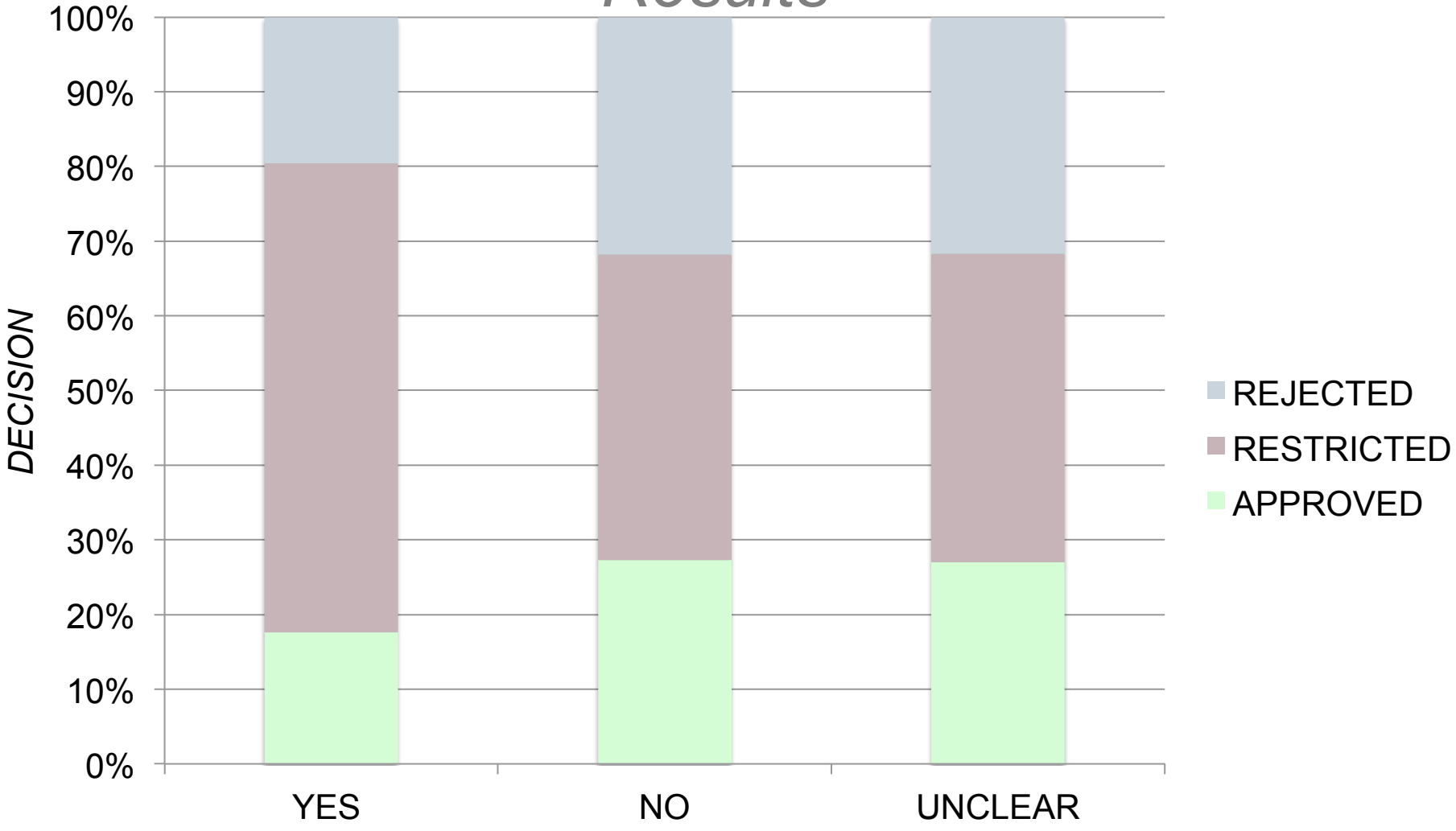

ACCEPTABILITY OF SURROGATE

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Thank you

Q&A

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