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USE OF SURROGATE ENDPOINTS IN THE HTA SETTING

Oriana Ciani, PhD

Associate Professor of Practice
Government, Health & Not-for Profit Division
CERGAS (Center for Research on Health and Social Care Management)
SDA Bocconi

CONFLICTS AND DISCLOSURES

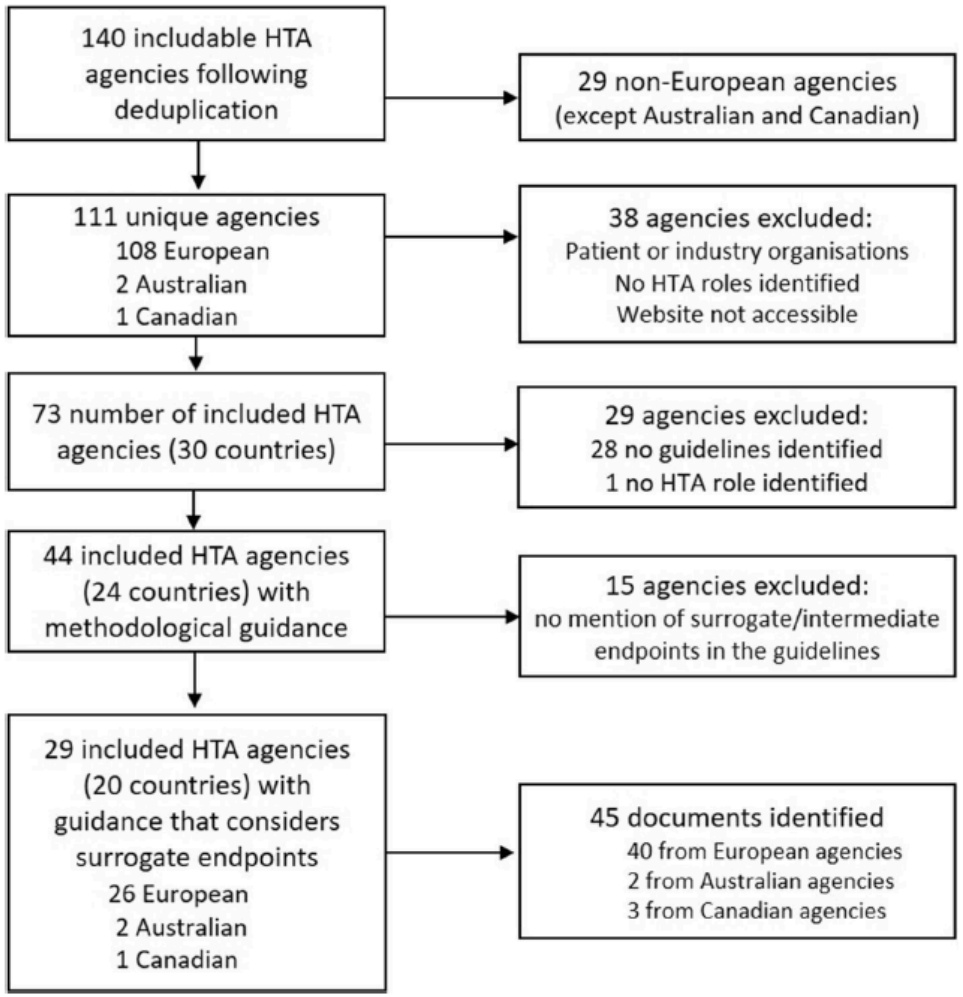
- I have served as a paid consultant for Janssen&Cilag
- I have received research funding from the European Union's Horizon 2020 programme
- I have no financial or any other conflicts relating to specific products mentioned in this presentation

OUTLINE

- WHAT DO HTA METHODS GUIDELINES CURRENTLY RECOMMEND?
- HOW IS VALIDATION OF SURROGATE ENDPOINTS EMPIRICALLY ADDRESSED IN HTA REPORTS?
- WHAT IMPACT DOES USE OF SURROGATE ENDPOINTS HAVE ON THE RECOMMENDATION GIVEN?

WHAT DO HTA METHODS GUIDELINES CURRENTLY RECOMMEND?

Fig. 1 Summary of agencies and documents selection. *HTA* health technology assessment



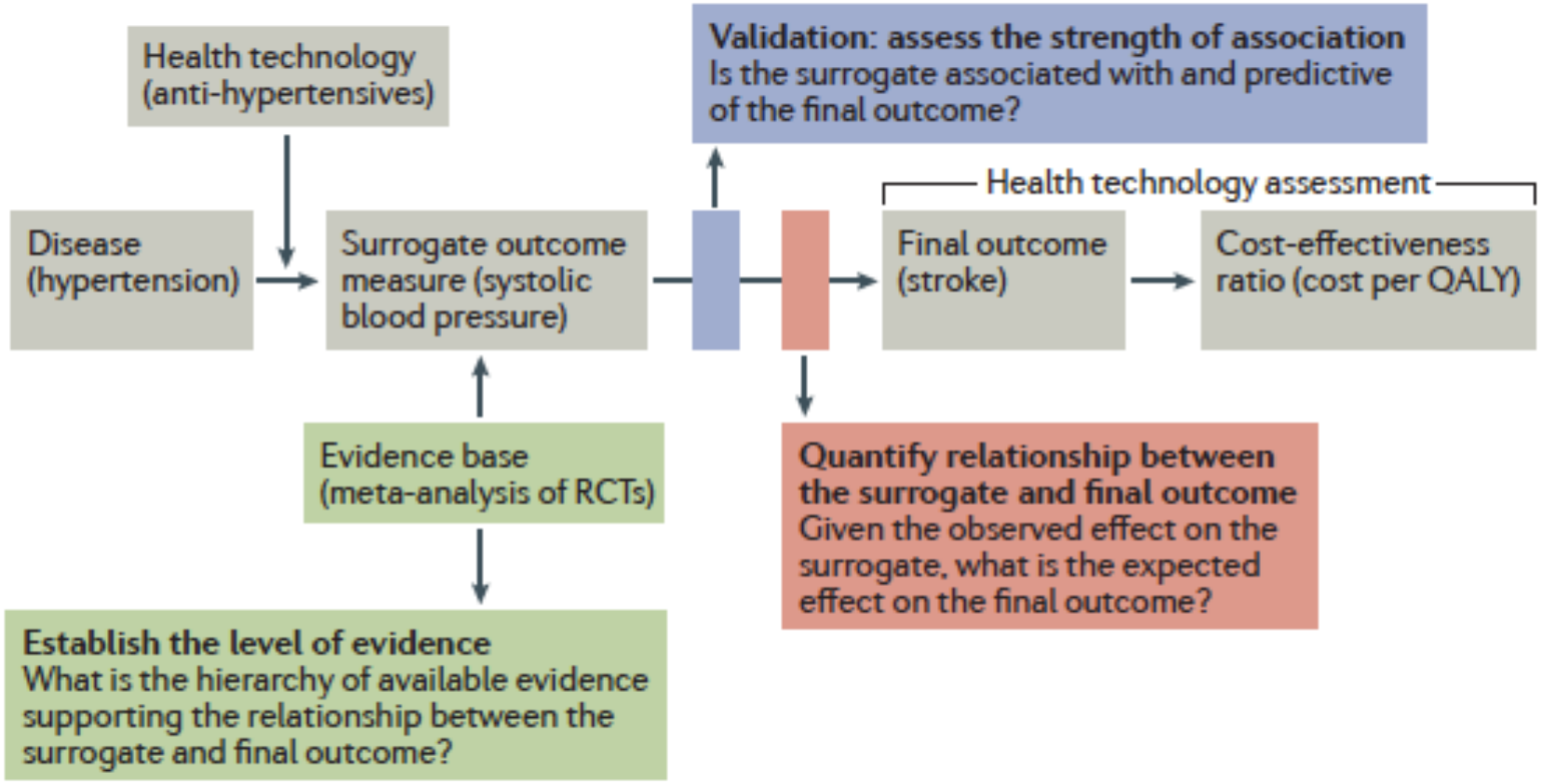
Grigore B, Ciani O, Dams F, Federici C, de Groot S, Möllenkamp M, Rabbe S, Shatrov K, Zemplenyi A, Taylor RS. Surrogate Endpoints in Health Technology Assessment: An International Review of Methodological Guidelines. Pharmacoeconomics. 2020 Oct;38(10):1055-1070.

WHAT DO HTA METHODS GUIDELINES CURRENTLY RECOMMEND?

44 (98%)	**Argument around use of surrogates in the analysis**	"Surrogate endpoints should be adequately validated: the surrogate–final endpoint relationship must have been demonstrated based on biological plausibility and empirical evidence."*
18 (40%)	**Provide specific examples**	"Example of surrogate endpoints: biomarkers (e.g. cholesterol level, HbA1c); examples of intermediate endpoints: disease-free survival, angina frequency, exercise tolerance"*
13 (29%)	**Give a definition for surrogate endpoint**	"A biomarker can be defined as a characteristic that is objectively (reliably and accurately) measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention"*
10 (22%)	**Report more detailed methods for the handling of surrogate endpoints**	"currently, there is no systematic, transparent and widely agreed-upon process of biomarker validation…correlation of the effects on the surrogate and the effects on the clinical endpoint based on meta-analyses of several RCTs, as well as the surrogate threshold effect"*
2 (4%)	**Refer to thresholds for validation**	"There is no clear consensus of which correlation values are sufficient to assume adequate surrogacy, but values of between about 0.85 and 0.95 are often discussed"*
3 (7%)	**Specific guidance for disease areas**	Oncology, PFS, treatment intent
3 (7%)	**Specific for MDs**	MTEP, MSAC, State Institute for Drug Control

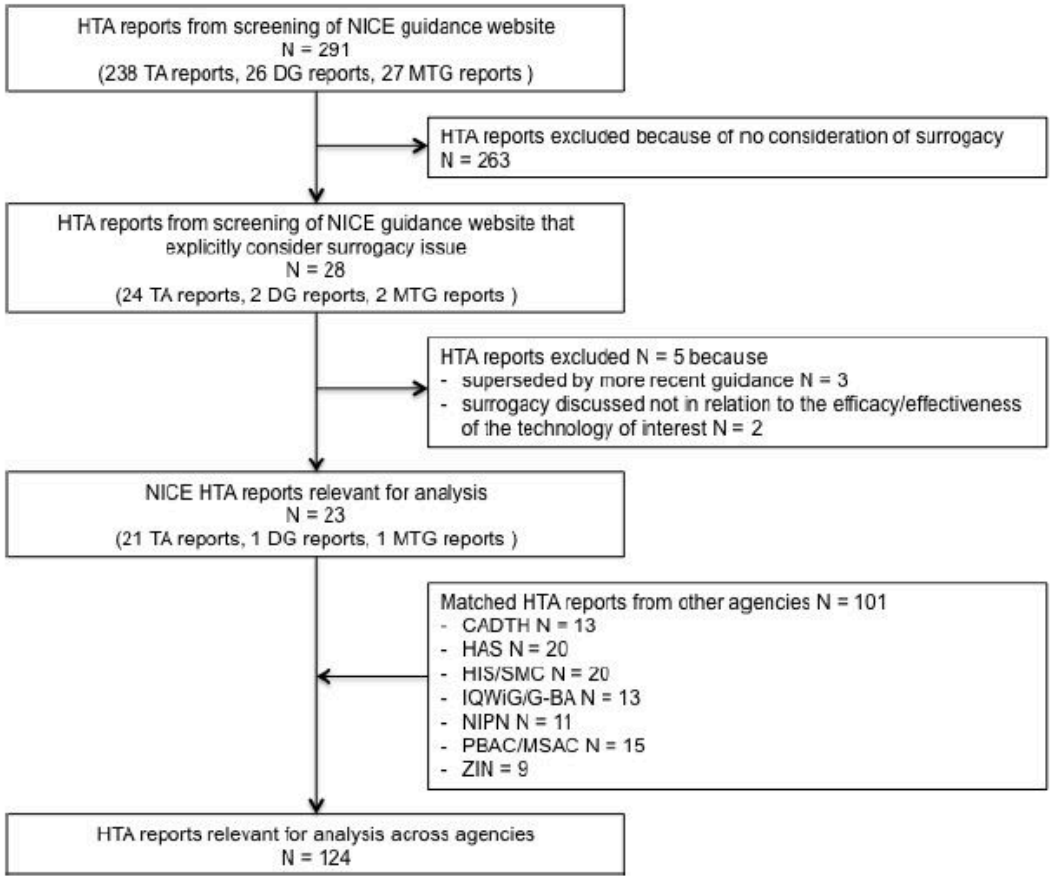
*Endpoints used in relative effectiveness assessment of pharmaceuticals Surrogate Endpoints, EUnetHTA 2015

A PROPOSAL FOR ADOPTION OF A VALIDATION FRAMEWORK



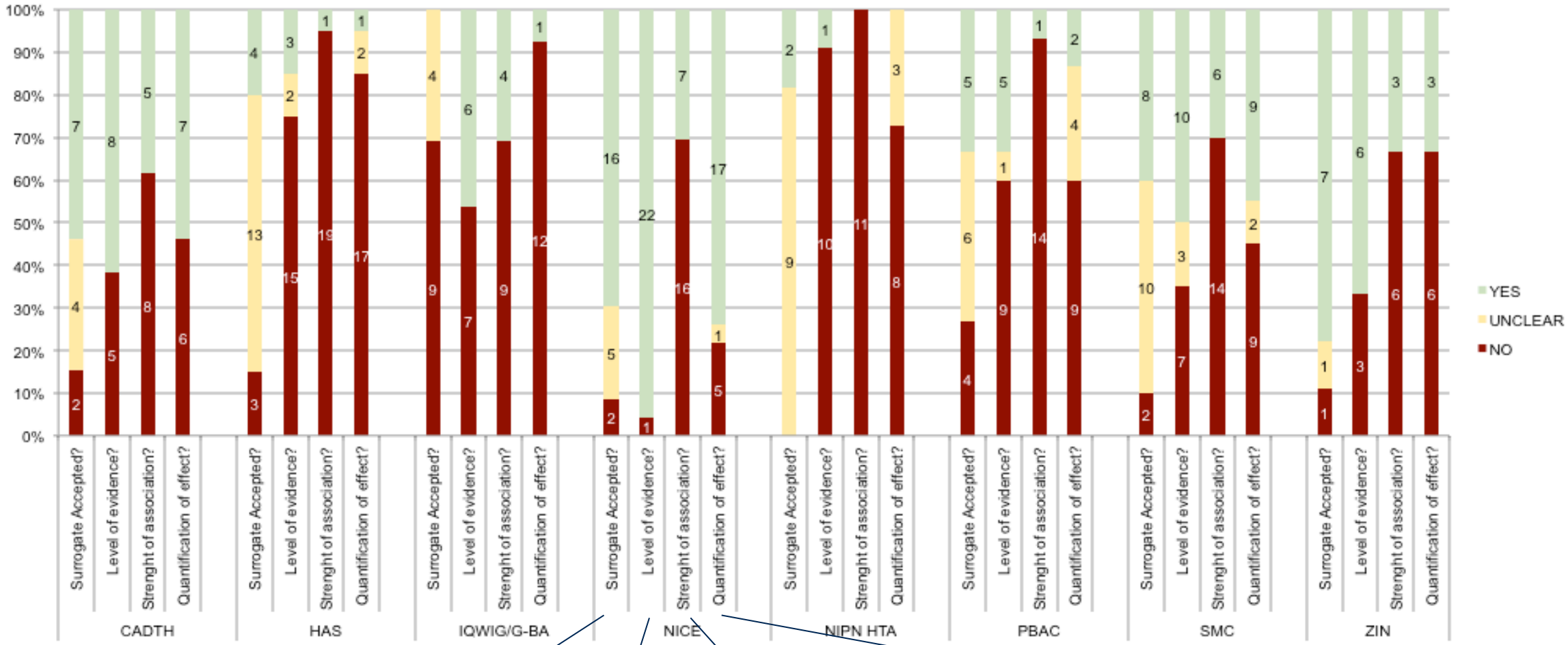
Ciani O, Buyse M, Drummond M, Rasi G, Saad ED, Taylor RS. Use of surrogate end points in healthcare policy: a proposal for adoption of a validation framework. Nat Rev Drug Discov. 2016 Jul;15(7):516.

HOW IS VALIDATION OF SURROGATE ENDPOINTS EMPIRICALLY ADDRESSED IN HTA REPORTS?



Characteristics	Total number of HTA reports (N = 124)	
Drugs	122	98%
Medical device	2	2%
HTA Agencies		
NICE	23	19%
HIS/ SMC	20	16%
HAS	20	16%
PBAC/ MSAC	15	12%
CADTH	13	10%
IQWiG / G-BA	13	10%
ZiN	9	7%
NIPN	11	9%
Disease area		
Cancer	65	52%
Cardiovascular	17	14%
Pulmonology	8	6%
Nephrology	8	6%
Endocrinology	7	6%
Infectious Disease	7	6%
Ophthalmology	6	5%
Gastroenterology	6	5%
Orphan status	8	6%
Surrogate validation		
Surrogate accepted (YES)	49	40%
Level of evidence assessed (YES)	61	49%
Strength of association provided (YES)	27	22%
Quantification of effect provided (YES)	40	32%
Final recommendation given		
Approved	32	26%
Restricted	61	49%
Rejected	20	16%
No recommendation	11	9%

Ciani O et al. Validity of Surrogate Endpoints and their Impact on HTA Recommendations: A Retrospective Analysis across International Agencies. *Under review*

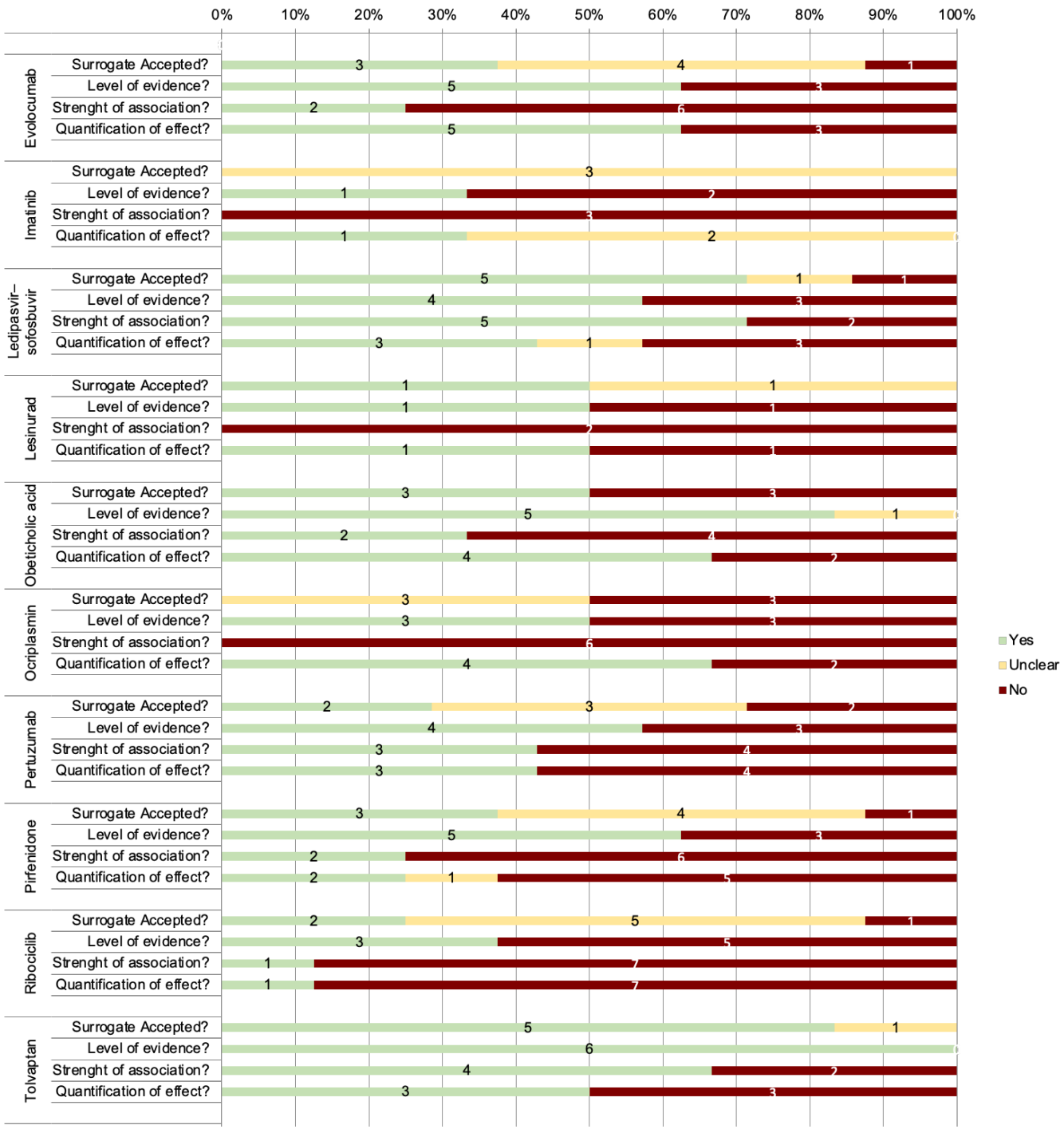


"increase in total kidney volume (TKV) correlates to growth in cyst volume and was considered to be an appropriate surrogate for disease progression"

"IPD meta-analysis of RCTs for the evaluation of pathological complete response of pertuzumab in HER2+ breast cancer"

"changes in %FVC correlate with changes in a disease specific HRQoL measure (i.e. Spearman's correlation coefficient of -0.32)"

"the risk reduction for cardiovascular mortality was 0.64 per 1.0 mmol/l reduction in LDLC rate (95% CI 0.40 to 1.04) and 0.64 for myocardial infarction (95% CI 0.43 to 0.96)"



- The different level of scrutiny applied translates into different declared level of acceptability for the same surrogate endpoint, in mostly the same indication, and based on what is theoretically the same evidence available to each appraisal committee.
- Overall, the level of agreement across the eight agencies was 0.10 (p = 0.04)

	Multivariate regression analysis*
Factors associated with acceptability of surrogate endpoint	Odds ratios (95%CI) [p value]
Level of evidence assessed	4.60 (1.60 -13.18) [p = 0.005]
Strength of association provided	1.23 (0.40 - 3.74) [p = 0.72]
Quantification of effect provided	1.17 (0.38 - 3.61) [p = 0.78]
Orphan status	0.52 (0.81 – 3.39) [p = 0.50]

*from mixed-effect logistic regression with clustering at the level of the health technology. OR>1 indicates higher odds of the surrogate deemed acceptable

WHAT IMPACT DOES USE OF SURROGATE ENDPOINTS HAVE ON THE RECOMMENDATION GIVEN?

Technology	Indication	Clinical area	Main surrogate endpoint(s) [Patient-centered endpoint substituted for]	NICE	HIS/ SMC	HAS	PBAC/ MSAC	CADTH	IQWiG / G-BA	ZiN	NIPN
Alirocumab	primary hypercholesterolaemia and mixed dyslipidaemia	Cardiovascular	Low-density lipoprotein cholesterol, Total cholesterol to high-density lipoprotein cholesterol ratio [incidence of cardiovascular events]	✓	✓	✓	✓	✓	✓	✓	✓
Axitinib	advanced renal cell carcinoma after failure of prior systemic treatment	Cancer	Progression-free survival [overall survival]	✓	✓	✓	✓[1]	✓	✓	-	✓
Bortezomib	previously untreated mantle cell lymphoma	Cancer	Progression-free survival [overall survival]	✓	✓	✓	-	-	-	-	-
Bortezomib	induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation	Cancer	Response rate Progression-free survival [overall survival]	✓	✓	✓	✓	✓	-	-	-
Bosutinib	previously treated chronic myeloid leukaemia	Cancer	Major cytogenetic response [overall survival]	✓	✓	✓	-	✓	✓	-	✓
Brentuximab vedotin	CD30-positive Hodgkin lymphoma	Cancer	Progression-free survival [overall survival]	✓	✓	✓	✓	-	✓[1]	-	-
Cobimetinib (in combination with vemurafenib)	unresectable or metastatic BRAF V600 mutation-positive melanoma	Cancer	Progression-free survival [overall survival]	✓	✓	✓	✓	✓	✓	-	✓
Dasatinib	untreated chronic myeloid leukaemia (1st line)	Cancer	Complete cytogenetic response Major molecular response [overall survival]	✓[1]	✓	-	✓[1]	-	-	-	-
Dasatinib	imatinib-resistant or intolerant chronic myeloid leukaemia (2nd line)	Cancer	Complete cytogenetic response Major molecular response [overall survival]	✓[1]	✓	✓[1]	✓	-	-	✓	-
Degarelix	advanced hormone-dependent prostate cancer	Cancer	Prostate specific antigen Testosterone levels [overall	✓	✓[1]	✓[1]	✓[1]	-	-	✓	✓

Note: [1]multiple evaluations available; [2] reports sought from MSAC; [3] One European Network of HTA (EUnetHTA) report identified https://www.eunethta.eu/the-joint-assessment-on-continuous-glucose-monitoring-cgm-real-time-and-flash-glucose-monitoring-fgm-as-personal-standalone-systems-in-patients-with-diabetes-mellitus-treated-with-insuli/ ■ = approved for reimbursement; ■ = restricted reimbursement (either restricted prescription or subject to a price change); ■ = rejected.

- 32 (26%) full, 61 (49%) restricted (e.g. PAS, risk-sharing), 20 (16%) rejected approval
- Overall, the level of agreement across the eight agencies is 0.18 (p = 0.004)

Factors associated with positive recommendation	Multivariate regression analysis*
Acceptability of surrogate endpoint	0.71 (0.23 - 2.20) [p = 0.55]
Level of evidence assessed	0.32 (0.07 - 1.37) [p = 0.12]
Strength of association provided	2.30 (0.51 - 10.45) [p = 0.28]
Quantification of effect provided	1.12 (0.27 - 4.74) [p = 0.87]
Orphan status	8.61 (1.03 - 72.94) [p = 0.047]

*from mixed-effect logistic regression with clustering at the level of the health technology. OR>1 indicates higher odds of technology receiving positive recommendation

DISCUSSION

- Infrequent application of formal validation processes in HTA reports
  - acceptance of proposed surrogates often relies on suboptimal level of evidence (e.g. expert opinion)
  - use in regulatory assessments is often cited as a proof of surrogate validity
- When CEA are performed, surrogates are key model parameter
  - used as prognostic marker influencing transition probabilities
  - used as predictors of utility value or resource consumption/ costs (usually not backed by high quality evidence)
  - however, most commonly models are developed around immature survival data that extrapolated secondary endpoints over the lifetime horizon of the model, without taking into account any element of the validation of the primary surrogate endpoint
- The main approaches to handling decision uncertainty driven by surrogates are
  - restricted approval, price discount, risk-sharing agreement (e.g. PAS)
  - resort to more permissive pathway (e.g. rare disease, CDF)

- ➢ Call for application of sound surrogate validation methods in HTA reports
- ➢ Need to promote trial data sharing to perform indication-specific surrogate validation studies
- ➢ More standardized consideration of the issue of surrogacy across HTA agencies, across jurisdictions and between regulatory and reimbursement decision-making bodies

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

THANK YOU

oriana.ciani@unibocconi.it
o.ciani@exeter.ac.uk
@OrianaCiani