

# USE OF SURROGATE ENDPOINTS IN THE HTA SETTING

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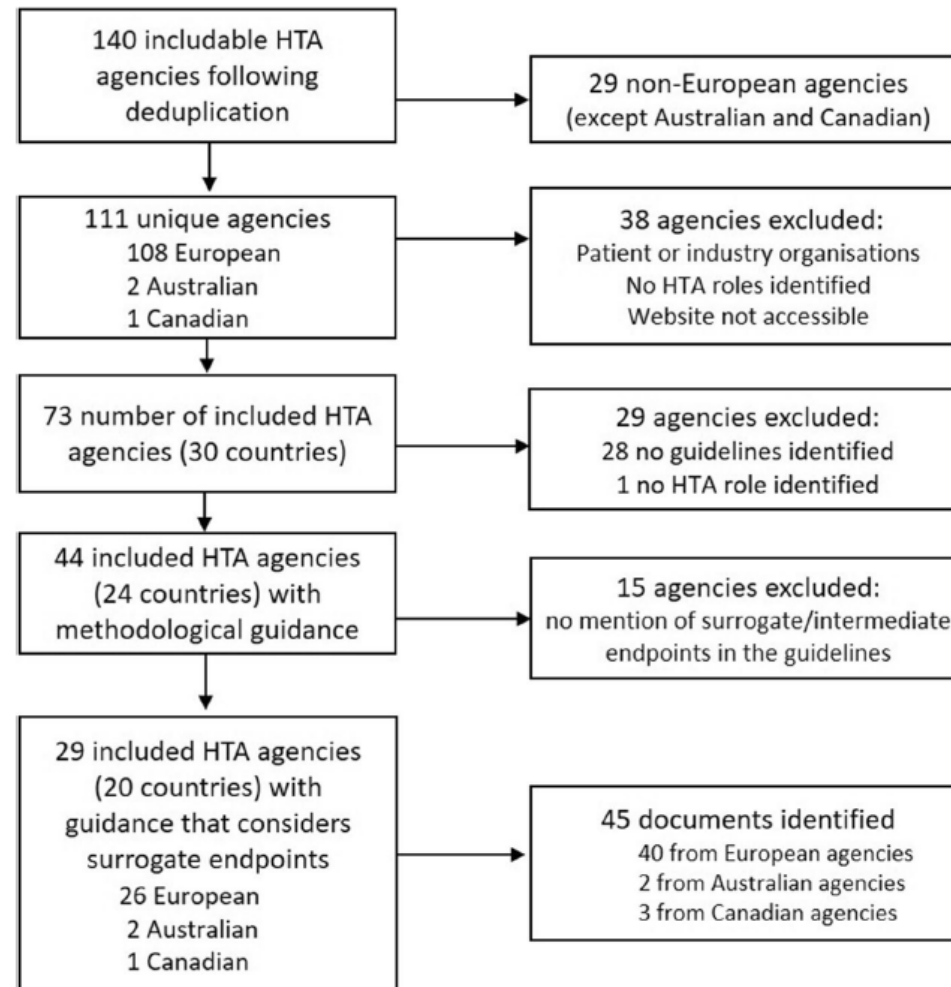
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- ❑ WHAT DO HTA METHODS GUIDELINES CURRENTLY RECOMMEND?
- ❑ HOW IS VALIDATION OF SURROGATE ENDPOINTS EMPIRICALLY ADDRESSED IN HTA REPORTS?
- ❑ WHAT IMPACT DOES USE OF SURROGATE ENDPOINTS HAVE ON THE RECOMMENDATION GIVEN?

# WHAT DO HTA METHODS GUIDELINES CURRENTLY RECOMMEND?

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

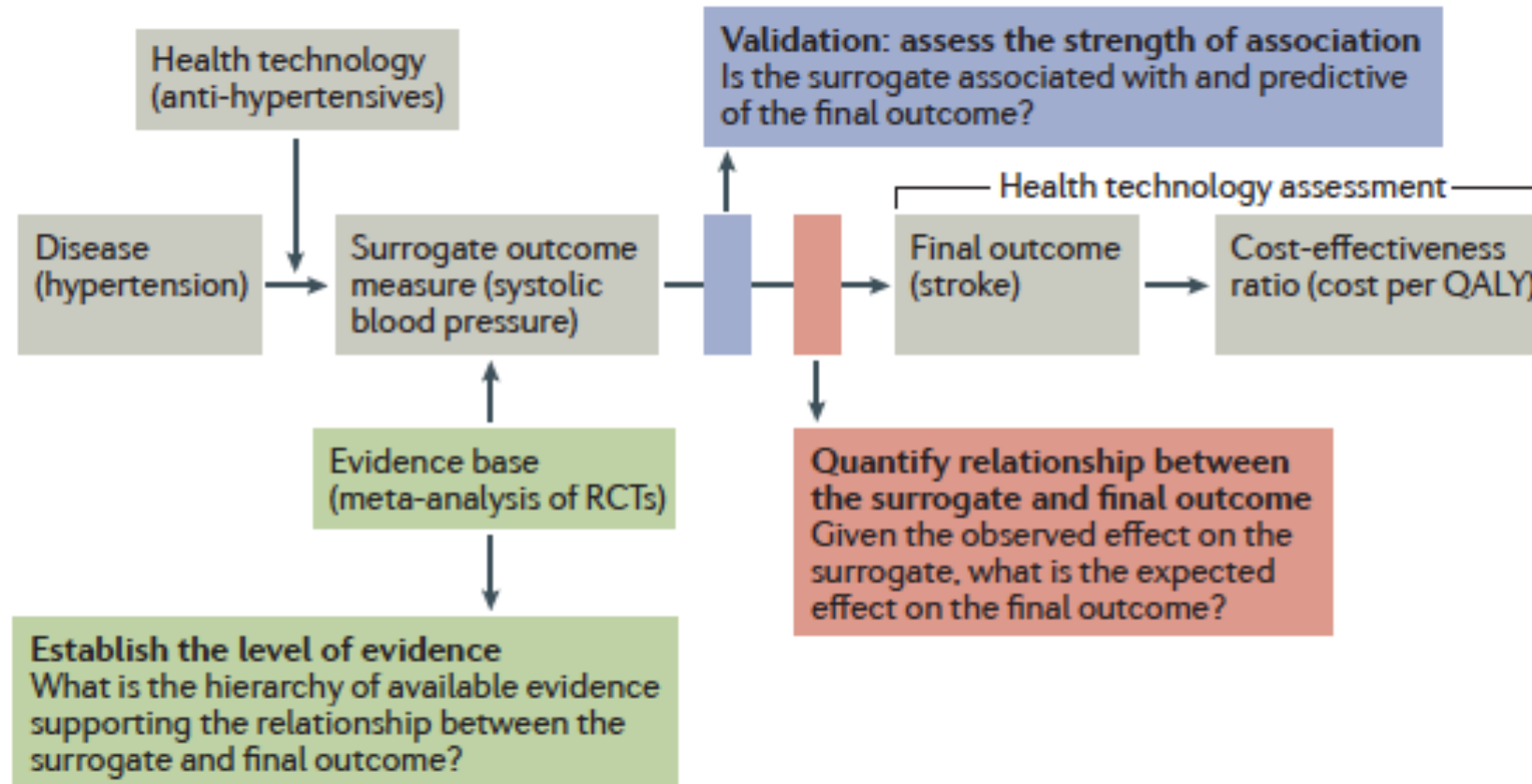


# WHAT DO HTA METHODS GUIDELINES CURRENTLY RECOMMEND?

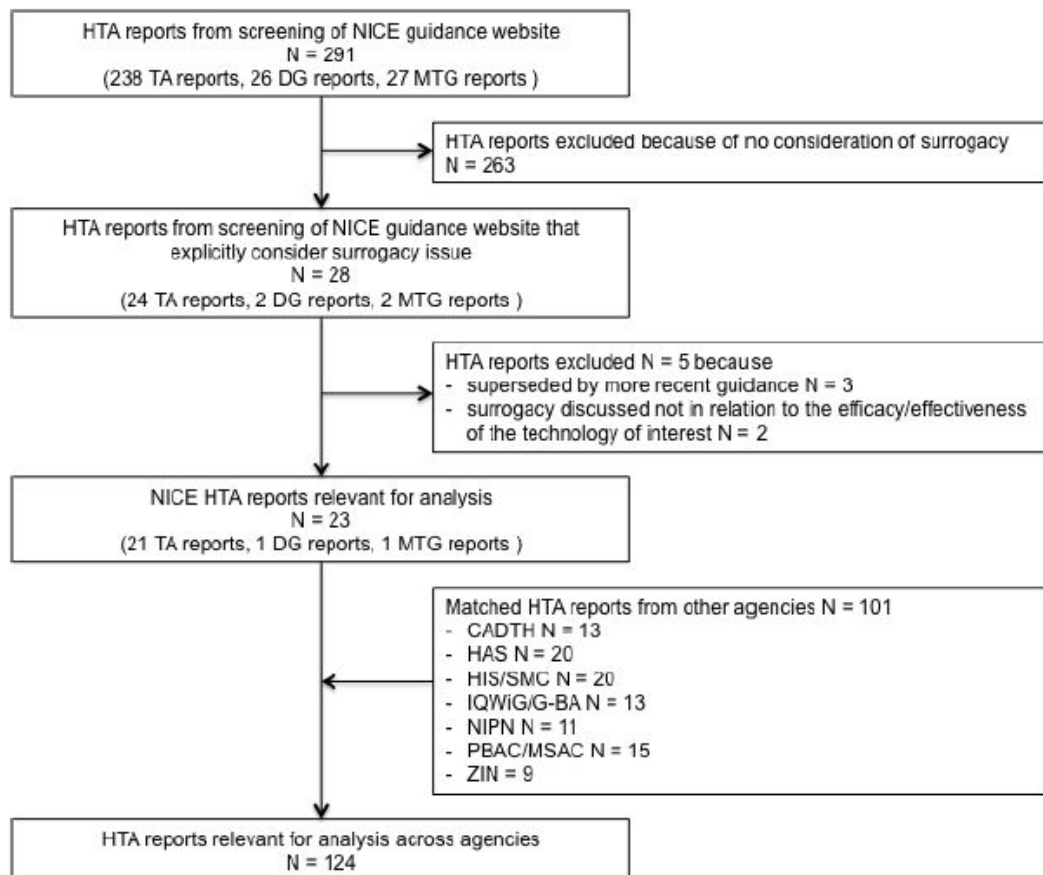
|                     |                                                                             |                                                                                                                                                                                                                                                                                   |
|---------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>44<br/>(98%)</b> | <b>Argument around use of surrogates in the analysis</b>                    | “Surrogate endpoints should be adequately validated: the surrogate–final endpoint relationship must have been demonstrated based on biological plausibility and empirical evidence.”*                                                                                             |
| <b>18<br/>(40%)</b> | <b>Provide specific examples</b>                                            | “Example of surrogate endpoints: biomarkers (e.g. cholesterol level, HbA1c); examples of intermediate endpoints: disease-free survival, angina frequency, exercise tolerance”*                                                                                                    |
| <b>13<br/>(29%)</b> | <b>Give a definition for surrogate endpoint</b>                             | “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”*                                        |
| <b>10<br/>(22%)</b> | <b>Report more detailed methods for the handling of surrogate endpoints</b> | “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”* |
| <b>2 (4%)</b>       | <b>Refer to thresholds for validation</b>                                   | “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”*                                                                                                             |
| <b>3 (7%)</b>       | <b>Specific guidance for disease areas</b>                                  | Oncology, PFS, treatment intent                                                                                                                                                                                                                                                   |
| <b>3 (7%)</b>       | <b>Specific for MDs</b>                                                     | MTEP, MSAC, State Institute for Drug Control                                                                                                                                                                                                                                      |

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

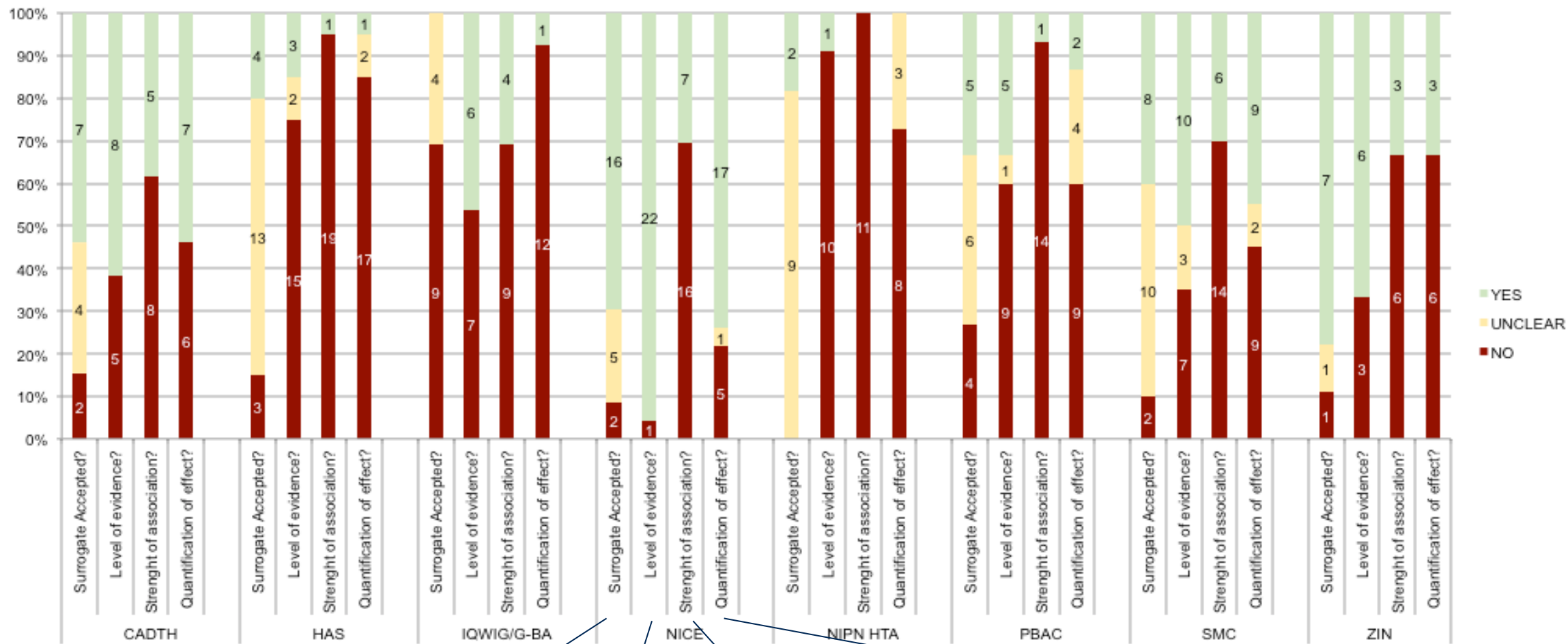
# A PROPOSAL FOR ADOPTION OF A VALIDATION FRAMEWORK



# 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%  |
| <b>HTA Agencies</b>                     |                                       |     |
| 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%  |
| <b>Disease area</b>                     |                                       |     |
| 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%  |
| <b>Surrogate validation</b>             |                                       |     |
| 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% |
| <b>Final recommendation given</b>       |                                       |     |
| Approved                                | 32                                    | 26% |
| Restricted                              | 61                                    | 49% |
| Rejected                                | 20                                    | 16% |
| No recommendation                       | 11                                    | 9%  |

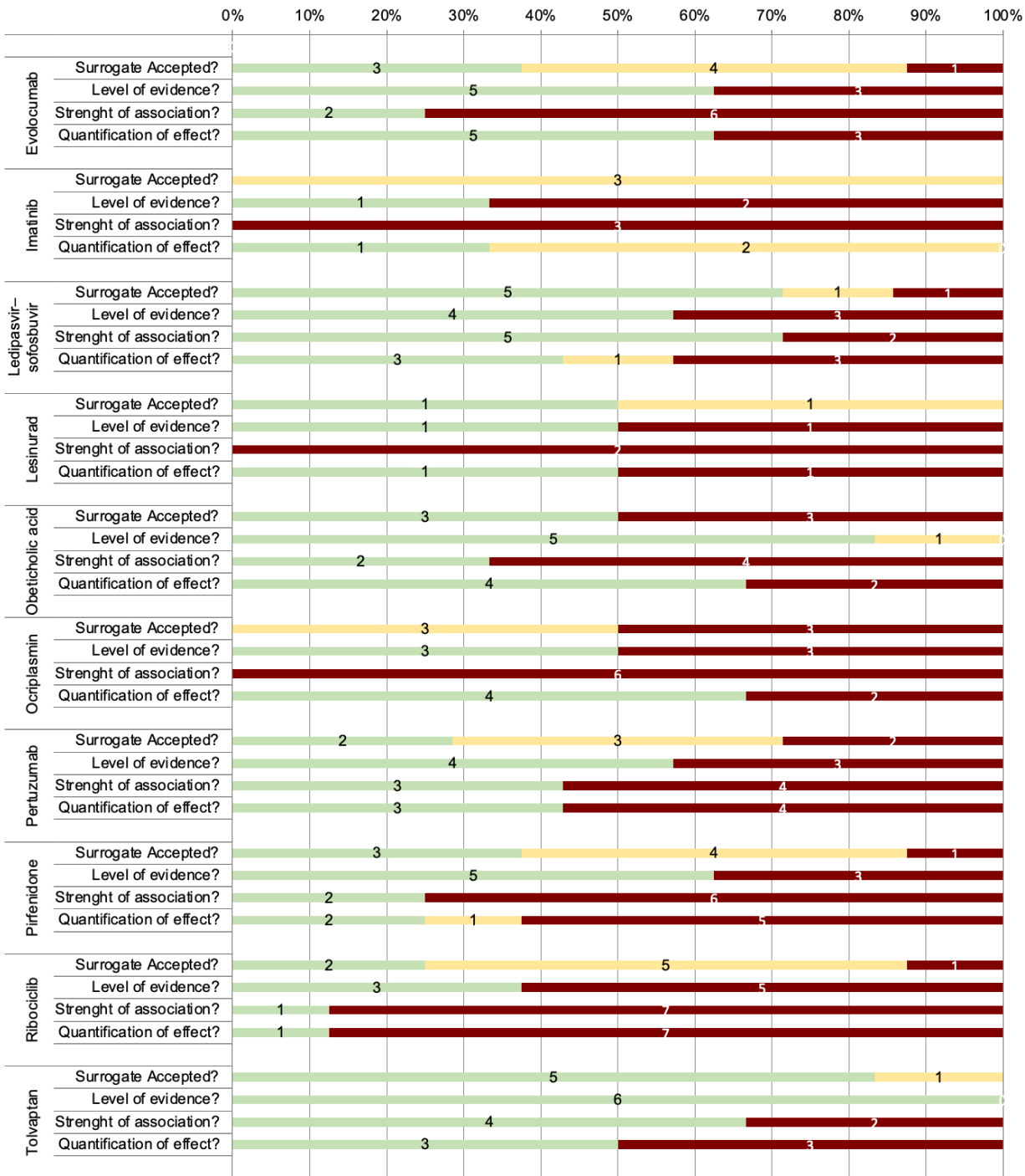


“increase in total kidney volume (TKV) correlates to growth in cyst volume and was considered to be an appropriate surrogate for disease progression”

“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* |
|--------------------------------------------------------------------|-----------------------------------|
| <i>Factors associated with acceptability of surrogate endpoint</i> | 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)<br>[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]                                                                                              | ✓              | ✓              | ✓              | ✓ <sup>1</sup> | ✓     | ✓              | -   | ✓    |
| 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<br>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]                                                                                              | ✓              | ✓              | ✓              | ✓              | -     | ✓ <sup>1</sup> | -   | -    |
| 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<br>Major molecular response [overall survival]                                                              | ✓ <sup>1</sup> | ✓              | -              | ✓ <sup>1</sup> | -     | -              | -   | -    |
| Dasatinib                                     | imatinib-resistant or intolerant chronic myeloid leukaemia (2nd line)                                        | Cancer         | Complete cytogenetic response<br>Major molecular response [overall survival]                                                              | ✓ <sup>1</sup> | ✓              | ✓ <sup>1</sup> | ✓              | -     | -              | ✓   | -    |
| Degarelix                                     | advanced hormone-dependent prostate cancer                                                                   | Cancer         | Prostate specific antigen<br>Testosterone levels [overall]                                                                                | ✓              | ✓ <sup>1</sup> | ✓ <sup>1</sup> | ✓ <sup>1</sup> | -     | -              | ✓   | ✓    |

- 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

Note: <sup>1</sup>multiple evaluations available; <sup>2</sup> reports sought from MSAC; <sup>3</sup> One European Network of HTA (EUnetHTA) report identified <https://www.eunetha.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.

- 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

**THANK YOU**

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