What is the problem from the perspective of health technology assessment (HTA)?

- Accelerated approval more common, beginning to occur more often outside oncology, often with high prices and limited competition
- Determination of comparative clinical effectiveness and fair pricing requires linkage of short-term outcomes to longer-term outcomes that matter to patients: length of life, function/quality of life
- Without pathway for linking surrogate outcomes to the magnitude of benefit for patients, HTA, payers, and others have difficulty assessing the absolute or relative benefits of treatment

The taxonomy is not enough by itself

- Biomarker, surrogate endpoint, reasonably likely surrogate endpoint, validated surrogate endpoint
  - Reasonably likely surrogate endpoint: “supported by **strong mechanistic and/or epidemiologic rationale** such that an effect on the SE is expected to be correlated with …clinical benefit, **but without sufficient clinical data** to show that it is a validated SE.”
  - Validated surrogate endpoint: “supported by a **clear mechanistic rationale and clinical data providing strong evidence**….” “…almost always refers to a biomarker.”

FDA-NIH Biomarker Working Group. Reasonably Likely Surrogate Endpoint. [Text]. 2020; https://www.ncbi.nlm.nih.gov/pubmed/. Accessed 1/21/2021.

Application of key criteria has not been transparent

- Key criteria for assessing candidate surrogate endpoints*
  - Causality (evidence that surrogate on single direct causal pathway…?)
  - Biological Plausibility (is the biology so compelling that it adds….)
  - Specificity(does it appear robust to other factors affecting outcomes)
  - Proportionality (how well does the change in magnitude explain the change in clinical outcome?)
  - Universality (is there evidence across different patient groups….)

**McShane LM. Concepts and Case Study Template for Surrogate Endpoints Workshop. Biomarkers Consortium - Workshop: Defining an Evidentiary Criteria Framework for Surrogate Endpoint Qualification 2018; https://fnih.org/sites/default/files/final/pdf/6-McShaneCase%20Study%20Overview.pdf.*

Inconsistent application of key criteria

- Eteplirsen: FDA documents show that, *a priori*, reviewers considered a 10% increase in dystrophin levels to be a “meaningful” increase.
  - Trials showed a median increase of 0.1% -- drug approved
- Pembrolizumab received approval for advanced cervical cancer with ORR of 14.3% in 77 patients
- FDA has no framework for consistent approach to determining thresholds for meaningful change in surrogate endpoints, or for explaining its final decision

Recommendations*

- Before approving the use of a surrogate endpoint for AA, FDA should publish for public comment a preliminary justification with a “scorecard” against each of the key criteria that FDA has already established.
  - Make a clear *a priori* judgment on threshold for change that would be considered likely to translate into meaningful clinical improvement.
- Benefits of public template/scorecard
  - Fosters internal calibration and public accountability for regulatory decisions
  - Provides support for controversial decisions
  - Strengthen incentives for life science companies to do rigorous science on potential surrogate outcomes prior to FDA submission

*Kaltenboeck A, Mehlman A, Pearson SD. Potential policy reforms to strengthen the accelerated approval pathway. J Comp Eff Res. 2021 Nov;10(16):1177-1186.