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Ascending to new heights for novel therapeutics for eosinophilic esophagitis

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Title: Ascending to new heights for novel therapeutics for eosinophilic esophagitis

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Abbreviations: **EoE** – eosinophilic esophagitis; **eos/hpf** – eosinophils per high-powered field; **PEC** – Peak eosinophil count; **I-SEE** – Index of Severity of EoE; **PPI** – proton pump inhibitor; **EREFS** – EoE Endoscopic Reference Score; **EoE-HSS** – EoE Histology Scoring System; **DSQ** – Dysphagia Symptom Questionnaire; **PRO** – Patient Reported Outcome; **EEsAI** – EoE Activity Index; **FDA** – Food and Drug Administration; **EMA** – European Medicines Agency; **BOS** – Budesonide Oral Suspension; **BOT** – Budesonide Orodispersible Tablet; **PEESSv2** - Pediatric EoE Symptoms Score; **DD** - Dysphagia days, **DFD -** Dysphagia free days; **IBD** – Inflammatory Bowel Disease; **NRS** – Numerical Rating Scale; **PGIS** – Patient Global Impression of Severity; **DST** – Dysphagia Stress Test; **EDP** – EoE Diagnostic Panel

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Introduction:

Since the initial descriptions of eosinophilic esophagitis (EoE) in the early 1990's, great progress has been made including refinement of diagnostic criteria and clinical trial design, development of novel therapeutics, identification of therapeutic targets, engagement with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) regarding regulatory pathways for drug approval, dissemination of educational and guidance documents supported by professional academic allergy/immunology and gastroenterology societies, development and validation of clinical outcomes, investigative efforts including a National Institutes of Health multicenter grant (Consortium of Eosinophilic Gastrointestinal Disease Researchers), and close collaboration with patient advocacy groups.[1-8] These efforts resulted in approvals of a budesonide tablet formulation by the EMA in 2018 and a monoclonal antibody for IL-4Rα (dupilumab) in 2022-2023 by both the FDA and EMA.[9, 10]

The Assessment of Clinical endpoints in Eosinophilic esophagitis for Novel Therapeutics (ASCENT) meeting was convened on May 5, 2023, to critically re-evaluate efficacy endpoints informed by results of clinical trials in EoE.[11] The impetus for ASCENT included identification of difficulties in demonstrating symptom response in clinical trials, recognition of substantial dissociation between symptom and histologic response in trials of eosinophil-targeted biologics, and advances in newer outcomes for disease activity in EoE. Prior to the meeting, an international group of multidisciplinary clinicians and researchers with expertise in epidemiology, pediatric and adult gastroenterology, allergy/immunology, and pathology focused on EoE, reviewed the literature, and conducted teleconferences. During the in-person meeting, presentations summarized the topics followed by group discussions to identify gaps in knowledge, unmet needs, and potential paths forward with the goal of updating and improving the assessment of efficacy of therapeutics in EoE. This commentary summarizes the major points of discussion.

Ascending the Mountain: Progress and pitfalls in clinical trials

Development of new therapeutics has progressed tremendously, with more than 40 clinical trials published since the first trial reported in 2006. The 2020 release of the FDA guidance for drug development in EoE set a regulatory framework for the field, including a requirement for co-primary endpoints (histologic response defined as peak eosinophil count (PEC) ≤6 eos/hpf and symptom improvement measured by a validated patient-reported outcome (PRO).[1] Additionally, the PRO had to demonstrate both a significant and clinically meaningful improvement compared to placebo. Previous discussions with the FDA, and the formalization of this guidance, stimulated the development of multiple validated outcome metrics. However, limitations of the guidance were also noted including the requirement for co-primary endpoints independently showing benefit in two domains, the focus on eosinophil count as the sole histologic outcome, and lack of consideration of other potential endpoints including those related to novel drug mechanisms. This background set the stage for the discussion about strengths and limitations of previously conducted clinical trials and the outcome metrics used.

Patient reported outcomes

Patient reported outcomes (PROs) are critical to drug approval in EoE as per FDA guidance.[1] Early EoE clinical trials using non-validated metrics did not show a symptom benefit, leading to development of a number of validated PROs, including the Dysphagia Symptom Questionnaire (DSQ), the EoE Symptom Activity Index (EEsAI), and the Pediatric EoE Symptoms Score (PEESSv2) (Table 1).[11] Given FDA requirements for daily capture of a metric with a 24-hour recall, the DSQ was commonly used in phase 3 studies, although a Numerical Rating Scale (NRS) rating dysphagia with a simple 0-10 Likert scale was accepted by EMA for the budesonide orodispersible tablet (BOT) program.[10] The DSQ is responsive to treatment, showing significant improvement in dysphagia symptoms

compared to placebo, in parallel to improvements in biologic outcomes such as histologic and endoscopic severity, in the budesonide oral suspension (BOS) and dupilumab programs.[9, 12] Additionally, DSQ did not show benefit compared to placebo in a study of an eosinophil depleting agent that also did not lead to endoscopic improvements or improvement in non-eosinophil histologic activity.[13] However, because dysphagia symptoms are dissociated from histology in EoE, due in part to persistent fibrostenosis, prior esophageal dilation, or dietary behavioral modifications, a pure symptom benefit is very difficult to demonstrate.[14] Additionally, FDA guidance requires that improvement in symptoms must also reflect a “meaningful” clinical benefit, a threshold that is vague, difficult to quantify, and thus a bar that is hard to attain for anti-inflammatory therapies in EoE that have minimal impact on symptom-inducing fibrostenotic changes. Therefore, in addition to continuing to improve PROs, flexibility in implementing and interpreting PROs is needed in EoE.

Peak esophageal eosinophil count (PEC)

Eosinophils remain a readily assessed and reliable biomarker for EoE diagnosis. Concerns exist about the reliance on the PEC to determine the efficacy of therapeutic interventions, as the PEC only reflects one cell type in the myriad of inflammatory cells present in EoE that include lymphocytes (ILC2, Th2), antigen presenting cells, basophils, mast cells, and fibroblasts. The limitation of the PEC as the primary endpoint was suggested in the well-described dissociation between symptoms measured using validated PRO instruments and the PEC.[14, 15] More recently, two phase 3, placebo-controlled randomized clinical trials failed to demonstrate significant improvement in symptoms and endoscopic activity over placebo despite near complete elimination of esophageal mucosal eosinophils.[13, 16] Such data have highlighted a major drawback to the interpretation of PEC in clinical trials of novel therapeutics in EoE. Although PEC may be a reasonable endpoint for broadly acting therapeutic categories such as diet therapy and topical corticosteroids, it fails to adequately assess disease activity for

therapies specifically targeting the eosinophil.[9, 12] Additional structural abnormalities (i.e. basal zone hyperplasia, dilation of intercellular spaces) as well as remodeling consequences (subepithelial inflammation and fibrosis) are not captured by PEC but are captured with the eosinophilic esophagitis histology scoring system (EoE-HSS).[17]

Eosinophilic esophagitis Histology Scoring System (EoE-HSS)

To establish a more comprehensive assessment of the inflammation and tissue injury that affects the esophageal mucosa, Collins et al developed a systematic platform, the EoE-HSS.(Table 1)[17] Recognizing that PEC fails to capture important aspects of EoE related pathology, the investigators created an assessment of the distribution and severity of eosinophilia and epithelial abnormalities that includes basal zone hyperplasia, surface epithelial alteration, lamina propria fibrosis, dilated intercellular spaces and dyskeratotic epithelial cells. The EoE-HSS has been validated in 2 independent studies and is responsive to therapy in placebo-controlled, randomized clinical trials.[9, 12] The overall EoE-HSS showed a modest but significant improvement with benralizumab compared to placebo, attributed to the eosinophil-related features (PEC, eosinophil abscess and eosinophil surface layering).[13] Structural, non-eosinophil-dependent components of EoE-HSS did not improve with benralizumab suggesting that these abnormalities may more accurately identify treatment benefits (or lack thereof) for eosinophil-depleting, targeted therapeutics.

Eosinophilic esophagitis endoscopic reference Score (EREFS)

The EoE endoscopic reference score (EREFS) is a validated instrument for the assessment of endoscopically identified inflammatory and remodeling aspects of EoE activity (Table 1).[18, 19] Unlike PEC, EREFS provides a “global,” macroscopic view of EoE activity that is not dependent on a specific inflammatory cell type. Furthermore, endoscopic activity includes remodeling consequences of subepithelial inflammation and fibrostenosis (i.e., rings, strictures). The accuracy of EREFS has been established in both children

and adult EoE patients, with over 95% of adults demonstrating endoscopic activity in prospective studies.[9, 12, 20] While the correlation of EREFS with validated PROs has been poor, retrospective studies have demonstrated an association between severity of EREFS and clinically relevant disease complications such as food impaction and use of esophageal dilation.[21] Endoscopic assessment is a primary determinant of overall disease activity based on physician global assessment and significant improvement in endoscopic activity is evident in multiple, placebo-controlled trials in association with both symptom and histologic efficacy.[9, 12, 22] In the benralizumab trial, neither EREFS nor symptoms improved compared to placebo despite the marked reduction in PEC.[13] Natural history studies identifying a progressive risk of esophageal strictures with EoE are based on the endoscopic demonstration of strictures, emphasizing the relevance of endoscopic assessment.[23] Moreover, endoscopic assessment of mucosal healing has been used as primary or co-primary endpoints for clinical trials of chronic, gastrointestinal inflammatory diseases including reflux esophagitis, peptic ulcer disease, ulcerative colitis and Crohn's disease.

Clinical Trial Design

Clinical trial design and inclusion/exclusion criteria influence the outcomes selected. To date, clinical trials in EoE have had traditional designs. These primarily have been "induction" studies where patients with active symptoms and elevated eosinophil counts, who are off therapy, are randomized to either placebo or active treatment, with outcomes assessed at a single time point (end of the blinded phase). However, this design, when coupled with the limitations of PROs in EoE, has led to enrolling a highly selected patient population and very high screen fail rates. [12] For example, the most severely fibrostenotic patients, those who require frequent dilation, those who are on other treatments, and those who cannot come off treatments are excluded from trials. In order to mimic clinical care, potential study designs could allow for combination or add-on treatments (as is done in asthma trials) or allow for esophageal dilation both by stratifying on dilation status at randomization and as an

intercurrent event during the trial. Time-to-event designs or designs consistent with an estimand framework could assess for clinically meaningful multicomponent/composite outcomes, such as stricture occurrence/recurrence, need for dilation, food impactions, and “disease flares”, or assess for steroid-free remission, and, in so doing, ensure proper handling of the intercurrent events. Another design could allow induction with a short-term steroid course, with subsequent randomization to long-term maintenance medication or placebo.

Reaching the summit: Lessons learned from clinical trial endpoints in allergic disease and inflammatory bowel disease

Lessons can be learned from other diseases such as inflammatory bowel disease or atopic disorders. In asthma, another atopic disease, asthma exacerbations and asthma control, severity, and lung function are accepted outcomes. An often-used outcome measure in atopic dermatitis is the investigator global assessment of skin activity, while more recent trials use the Eczema Area Severity Index which is based on the percentage of skin surface area involved and severity of disease. These types of outcomes based on visual inspection are analogous to measuring improvement in endoscopic activity with EREFS in EoE. In eosinophilic granulomatosis and polyangiitis, mepolizumab was approved with an endpoint that had a clinician-reported outcome in addition to reduction in corticosteroid use, and the same medication was approved for hypereosinophilic syndrome with a multi-component outcome of “disease flare”. These FDA-allowed outcomes show that there can be regulatory flexibility, which could potentially be applied to EoE. Additional analogies exist, potentially suitable as endpoints in therapeutic trials. Lung function is measured with FEV1 in asthma whereas in EoE esophageal narrowing and distensibility as a result of remodeling can be assessed with measures of diameter and compliance using impedance planimetry. Acute food impactions can be regarded as analogous to asthma exacerbations and a reduction in frequency or increased time to impaction might be considered as an endpoint in trials. In inflammatory bowel disease, while the use of patient reported outcomes continues to be relevant, endoscopic outcomes have emerged as clinically

meaningful endpoints.[24] Furthermore, histologic remission is being examined as a potential treatment goal.[24] Thus, for both allergic diseases as well as for IBD, there is a fundamental shift in primary endpoints in trials that highlight the relevance of epithelial or mucosal healing to patient outcomes.

Discovering New Heights: Novel outcome metrics and biomarkers of EoE disease activity

Despite the fact that eosinophils provide an attractive biomarker in the tissue, a number of previously underappreciated factors create the need to consider increasing the scope of what is assessed. EoE inflammation and remodeling extends deeper than the epithelium, thus being inadequately assessed with routine esophageal mucosal biopsies.[21] During the last several years, new approaches have been developed as potential endpoints in clinical trials and are summarized in Table 2S. Impedance planimetry has gained momentum for quantification of remodeling effects in both pediatric and adult EoE, providing more precise determination of esophageal biomechanics than endoscopy.[25] Simplified measures of dysphagia frequency are currently being applied as alternatives to the DSQ as a co-primary PRO. Furthermore, performance-related outcomes are a novel approach to quantify dysphagia with less confounding by adaptive eating behaviors. The dysphagia stress test using water, bread and a pill, as well as a “sandwich test” have assessed swallowing difficulties in the setting of an observed food challenge.[26] These metrics could provide support for use as complementary endpoints or potentially replacing symptoms and histology as co-primary endpoints (Figure).

Defining New Footholds: A proposal for modified endpoints and future directions for clinical trials in eosinophilic esophagitis

Despite the marked increase in the prevalence and understanding of EoE over the previous three decades, there is only one FDA approved treatment for this disease in the United States as of 2023 and two EMA approved treatments. The field has been both surprised and concerned in the last year by the results of two distinct therapies in rigorous Phase 3 trials achieving the most robust reductions in esophageal eosinophilia in the absence of symptom benefit.[13, 16] A third Phase 3 trial of a swallowed topical steroid optimized for esophageal delivery failed to achieve FDA approval despite meeting prespecified co-primary endpoints.[12] In light of these developments and with several novel compounds under study, an updated appraisal of the approach to EoE clinical trial design is both timely and appropriate.[1] In particular, major limitations to the continued reliance on enumeration of eosinophils alone, and definitions of success utilizing currently validated PROs are evident.

To move the field forward, we propose that endpoints based on EREFS and EoE-HSS should replace the PEC as they are both validated and responsive in placebo-controlled, clinical trials and, more importantly, provide a more global and comprehensive assessment of disease activity. A number of other novel outcome metrics (Table 2) may supplant these metrics over the next decade (Figure). At the same time, flexibility in clinical and biologic outcomes, considering drug mechanism of action and expected clinical effect will be important aspects of future trials. Finally, consideration should be given to a multicomponent outcome of "clinicopathologic" response, where both symptom-based and biologic outcomes (EREFS, EoE-HSS) are improved in the same patient, in contrast to the co-primary outcome concept. Indeed, "clinicopathologic" response was the primary outcome in the budesonide orodispersible tablet program approved by the EMA, and is what we strive for in clinical practice.

In conclusion, it is increasingly clear that the definition of treatment success in EoE is more nuanced than simple reliance on eosinophil density and a continued focus on only symptom-based PRO metrics. To advance the field and ultimately benefit patients with new therapeutics, there is an urgent need for a new framework for clinical trials using available, validated and objective measures of disease activity. In the near future, novel outcome metrics that provide a readout on measures of disease severity and improved patient-reported outcomes are becoming available. Ongoing dialogue among all stakeholders including investigators, industry, regulatory authorities (FDA, EMA), and patient advocacy groups is vital if we are to continue to improve the lives of our patients.

Table 1. Assessment of Clinical Outcome Metrics in Current Trials in Eosinophilic Esophagitis

Clinical Outcome Metric	Advantage	Limitation	Proposed modifications
Dysphagia Symptom Questionnaire (DSQ)	1. Validated 2. Responsive to therapy in placebo-controlled trials 3. Daily instrument	1. Clinical interpretation of scores difficult due to summation of frequency and intensity scores 2. Clinically meaningful threshold does not account for contribution from fibrostenotic stricture 3. High placebo response 4. Does not address food modification and avoidance behaviors 5. Not validated for use in children under 11 years old	1. Use of only frequency score (Dysphagia days (DD), dysphagia free days(DFD)) 2. Use to determine complete symptom response (an outcome that does not require a meaningful change analysis, since being completely asymptomatic is by definition meaningful)
Eosinophilic esophagitis Activity Index (EEsAI)[11]	1. Validated 2. Includes food avoidance and modification behaviors 3. Responsive to therapy in placebo-controlled trials	1. 7-day scoring not recommended by FDA due to concerns for recall bias 2. Not designed for daily use in the current format 3. Not validated in children	1. Validate a score with 1 day recall
Numerical rating score (NRS)	1. Responsive to budesonide in European placebo-controlled trial[10] 2. Daily instrument	1. Not validated 2. Metric is a global rating system rather than direct assessment of dysphagia frequency and/or intensity 3. FDA acceptance uncertain	1. Continued qualitative and validation work
Peak eosinophil count (PEC)	1. Outcome matches diagnostic criteria 2. Objective marker of histologic inflammation 3. Responsive to therapy in placebo-controlled trials 4. Reproducible	1. Limited correlation with symptom activity 2. Recent trials with near complete PEC depletion failed to demonstrate symptom or endoscopic improvement[13, 16]	1. Incorporation of additional aspects of pathology (see EoE-HSS)

	5. Generalizable to clinical practice	3. Oversimplification of global esophageal inflammation to one feature and one cell type of histopathology in a single high-power field	
EoE Histology Scoring System (EoE-HSS)[17]	1. Objective marker of histologic inflammation and tissue injury 2. Validated 3. Captures both severity and extent of pathology in multiple locations 4. Responsive to therapy 5. Quantifies both eosinophilic inflammation as well as non-eosinophil dependent aspects of mucosal inflammation	1. Recent trials demonstrated significant improvement despite lack of symptom or endoscopic response[13] 2. Current scoring includes eosinophil-dependent aspects of histopathology 3. Complexity for routine clinical practice	1. Modified score to separate eosinophil dependent metrics from structural abnormalities
EoE Endoscopic Reference Score (EREFS)[18]	1. Objective marker of esophageal inflammation and remodeling 2. Validated 3. Captures global rather than focal pathology 4. Responsive to therapy in placebo-controlled trials 5. Simplicity 6. Assessment is independent of specific inflammatory cell 7. Generalizable to clinical practice 8. Severity associated with clinically relevant outcomes (food impaction, esophageal dilation)	1. Weak correlation with validated dysphagia-patient reported outcomes, especially if a mixture of dilated and non-dilated patients is examined 2. Sensitivity lower in pediatric cohorts 3. Association with disease complications based on retrospective data 4. Metrics for defining response and remission proposed but require additional validation 5. Variability in scoring methods across trials 6. Limited accuracy for detection and quantification of stricture diameter 7. Limited quantification of affected surface area	1. Further comparison of global worst score vs more granular assessment of the longitudinal extent of endoscopic activity 2. Integration of stricture severity assessment 3. Validation of thresholds for response and remission

Table 2S. Novel disease activity outcomes for eosinophilic esophagitis

Clinical Outcome Metric	Advantages	Limitations	Comments
Dysphagia days (DD), Dysphagia free days, Frequency of dysphagia episodes, Complete resolution of dysphagia	Metric is more straightforward and readily interpretable than DSQ; Responsiveness demonstrated in randomized controlled trials; Complete resolution does not need to be anchored (clinical meaningfulness of being symptom free is by definition)	Does not account for severity of dysphagia episodes that are relevant to patient perspective based on patient focus group and concept elicitation; Few patients may achieve complete symptom relief	Metrics already being used in some Phase 3 clinical trials instead of DSQ
Multi-component outcome of symptom with histologic response (Defines responder group that combines both symptom and histologic response threshold)	Mirrors the goal of therapy in clinical practice; Accepted as primary outcome in the BOT phase 3 trial[10]	Concept requires FDA acceptance in EoE	FDA guidance on this type of multi-component outcome development is available (https://www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf)
Pediatric EoE Scoring System (PEESSv2)	Validation; Assesses frequency and severity across pediatric age groups; Proxy (i.e., parent) version available; Available in multiple languages; Potential association with biomarkers	One month recall period; Responsiveness has not been fully demonstrated; Multiple symptom domains might lead to no change in the overall score if there is improvement in one domain and worsening in another	Large unmet need for PROs for the pediatric EoE population
Esophagram	Objective marker of remodeling.	Poor sensitivity for mucosal inflammation; Likely underestimates stricture diameter due to inability to control for intraluminal distension pressure; Not validated as outcome for EoE; Radiation exposure	Addition of barium tablet might improve test performance
Dysphagia stress test (DST) (Performance-related outcome)[26]	Conceptual appeal; Aligns with FDA's "functions" requirement for a clinical outcome metric; Reduces problems of food avoidance behavior; Clinically relevant metric	Further validation needed to support use; Some subjectivity in interpretation of patient difficulty; Possible concern of food impaction during the test; Needs observer to administer; May be difficult to standardize with patient dietary preferences/requirements	Need regulatory alignment on the path to acceptance for an observer-reported outcome

Index Severity for Eosinophilic Esophagitis (I-SEE)[8]	Multidimensional instrument that assesses clinical severity of EoE in children and adults; Responsiveness to therapy shown in adult and pediatric studies	Complexity in interpretation due to multidimensional aspects of total score; was not developed or validated as a regulatory endpoint	May be more appropriate as an instrument for clinical practice or screening severity for clinical trials
Impedance planimetry	Objective biomarker of esophageal remodeling consequences; Distensibility plateau associated with food impaction; Responsiveness to therapy demonstrated in small studies	Analyses paradigms are being refined; Cost is a concern for widespread application; Current metrics restricted to measurement of distal esophagus; Contribution of muscle contractions at the lower esophageal sphincter can be a confounder for strictures of the esophagogastric junction; Operator variability	Regulatory alignment needed to understand how clinical meaningfulness of impedance planimetry could be demonstrated
Eosinophilic esophagitis diagnostic panel (EDP) – mRNA transcriptome	Objective biomarker of multiple aspects of disease activity; Correlation (weak) with symptom outcomes; Requires minimal tissue sampling	Correlation with symptom outcomes is limited; Complexity in interpretation for multidimensional aspects of disease pathogenesis; Needs additional validation	Provides information on disease pathogenesis that may facilitate precision medicine
Mucosal impedance	Objective surrogate biomarker of mucosal inflammation; Provides global rather than focal view of mucosal integrity	Mucosal impedance measures impaired barrier function which is only one aspect of the pathology of EoE; Cost is a concern for widespread application; Further validation needed; Studies needed to demonstrate association with clinical outcomes and/or disease complications	
Physician global assessment (Clinician-reported outcomes)	Provides a composite physician interpretation of symptoms, endoscopic and possibly histologic outcomes	Needs validation as endpoint; Complexity in interpretation as evaluates multiple aspects of disease activity	
Patient global impression of severity (PGIS)	Anchor required by FDA to show meaningful change in a PRO, so potentially more “direct” and efficient outcome metric; Change from one category to another well understood for patient impact; Simple to use; Applicable across multiple symptoms	Acceptance by FDA as endpoint uncertain; Does not directly quantify primary symptom of dysphagia;	

Disease worsening/relapse or complications (e.g., esophageal dilation, stricture development, food impaction, Emergency Department visits, and growth and nutrition, or escalation of therapy such as add on therapies or esophageal dilation)	Objective outcomes that are clinically meaningful to patients and providers	Low frequency of events and prolonged length of time to identify events may be prohibitive (i.e., large sample size, prolonged study duration)	
Duration of steroid-free remission	Conceptually aligns with steroid-free remission in asthma and eosinophilic granulomatosis and polyangiitis	Disease relapse criteria need to be defined; If relapse is based on symptoms and objective biomarker of active disease activity, need to consider limitation of PEC for targeted therapeutics	

Figure legend

Evolution of Clinical Trial Endpoints in Eosinophilic Esophagitis. Abbreviations: PEC Peak eosinophil count; DSQ Dysphagia Symptom Questionnaire, EREFS EoE endoscopic Reference Score, EoE-HSS EoE Histology Scoring System; DD Dysphagia Days, DST Dysphagia Stress Test, PGIS Patient Global Impression of Severity; EDP Eosinophilic esophagitis diagnostic panel; EEsAI EoE Activity Index; PRO Patient reported Outcome

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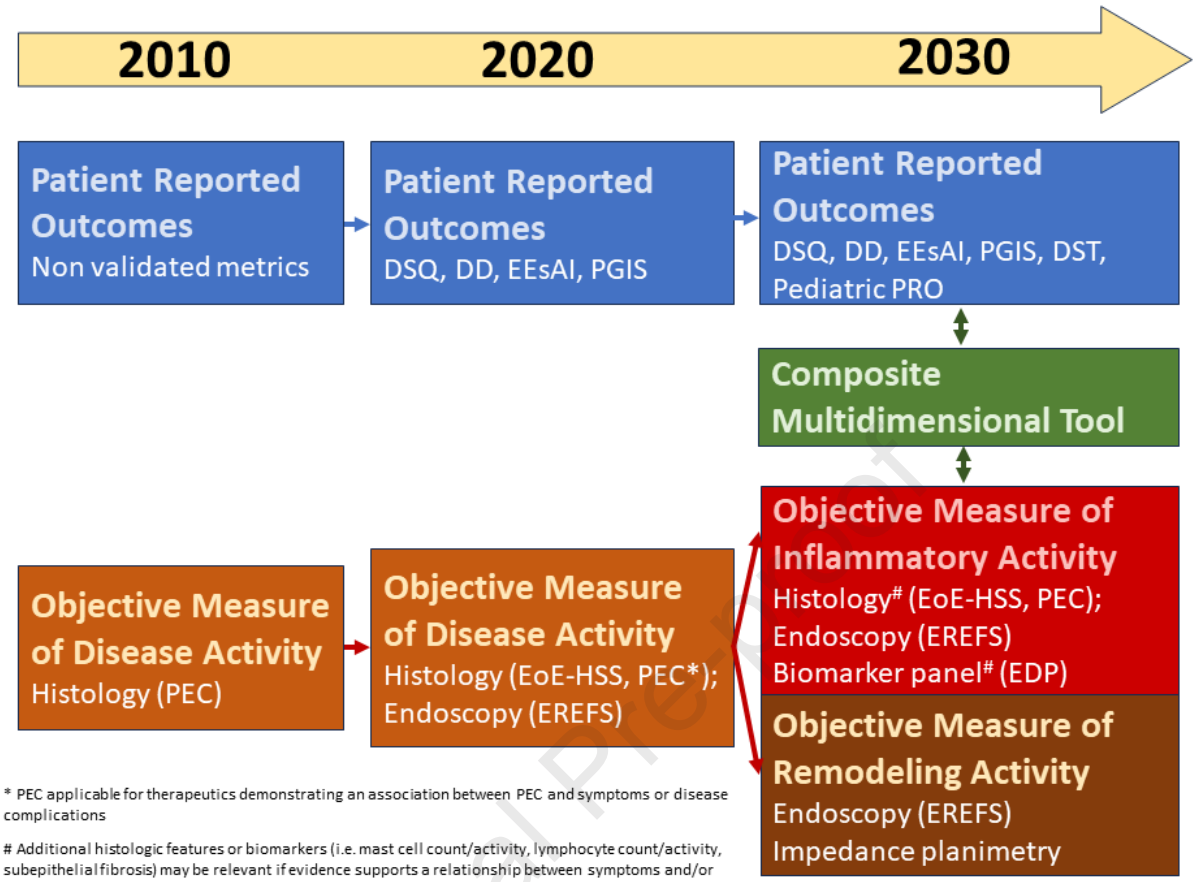

* PEC applicable for therapeutics demonstrating an association between PEC and symptoms or disease complications

Additional histologic features or biomarkers (i.e. mast cell count/activity, lymphocyte count/activity, subepithelial fibrosis) may be relevant if evidence supports a relationship between symptoms and/or disease complications with that measure