Disease Monitoring: Implementing the STRIDE II Recommendations

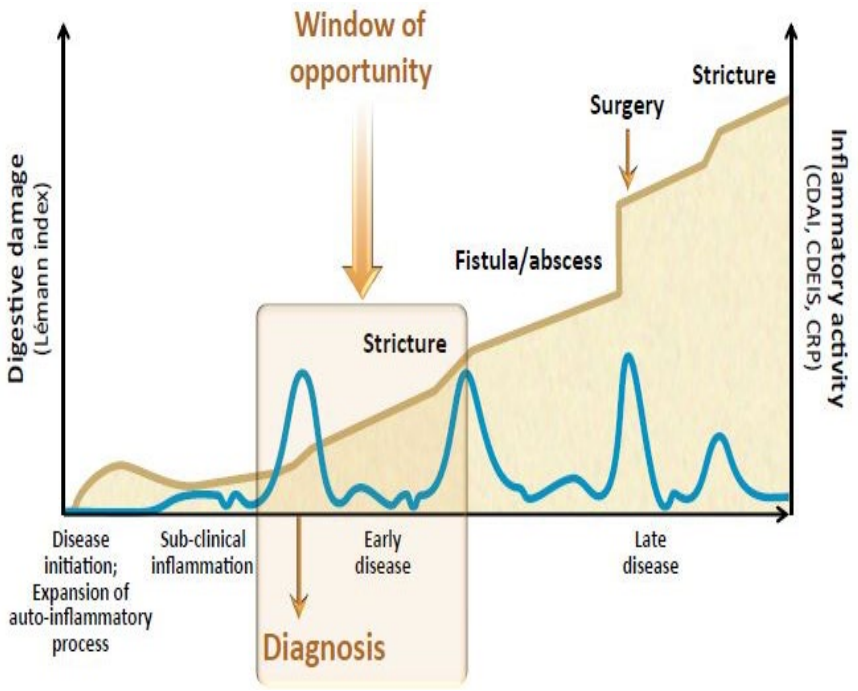
Jennifer Seminerio, MD
Director of Inflammatory Bowel Disease USF Health

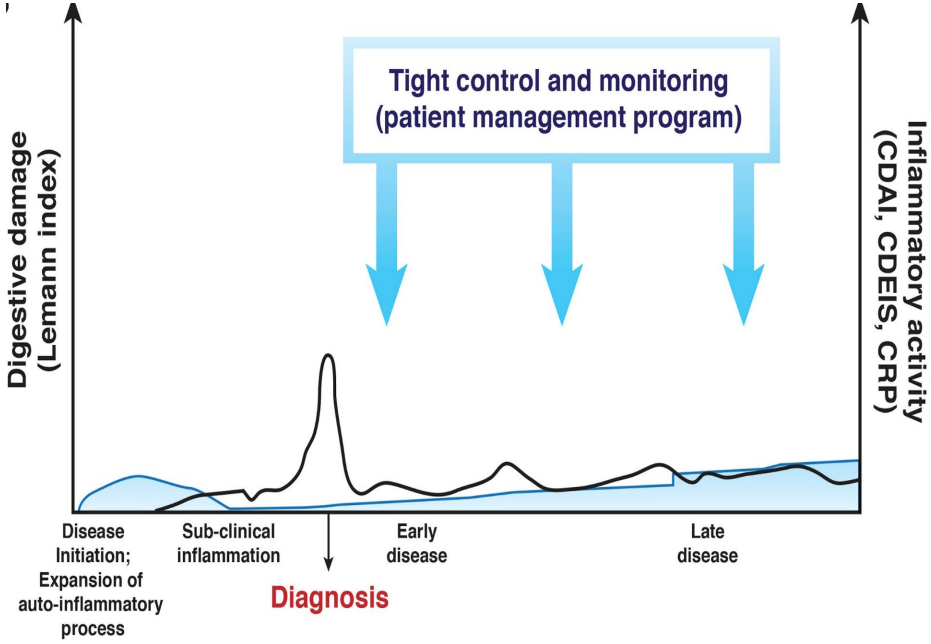
UNIVERSITY OF Cincinnati

DISCLOSURES

- **Advisory Boards:** BMS, AbbVie, Janssen, Pfizer, Takeda, Prometheus

- **Consulting:** BMS, AbbVie, Janssen, Pfizer, Takeda





- Early intervention
  Treat to Target
  Optimization of medical therapy
  Therapeutic Drug Monitoring
  Personalization

Jones et al. Clin Gastroenterol Hepatol 2008
Colombel et al. Gastroenterology 2017

UNIVERSITY OF Cincinnati

Background

- The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative
  - Began in 2013
    - Evidence based expert consensus process
  - Proposed targets/Position statement in 2015
- Advanced diagnostic tools and advent of new medical modalities
  - New complexity to the algorithm
  - Discussions:
    - Which treatment
    - Treatment Goals
    - Treatment Targets

Gastroenterology 2021;160:1570–1583

STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International

Update the position statement from the previous STRIDE guidance based on new evidence, review endpoints in an escalating algorithm focused in the clinical adult and pediatric setting

Iris Dotan,[16] Maria T. Abreu,[3] and Axel Dignass,[17] on behalf of the International Organization for the Study of IBD

[1] Shaare Zedek Medical Center, the Hebrew University of Jerusalem, Jerusalem, Israel; [2]Hospital for Sick Children, Toronto, Canada; [3]Division of Gastroenterology, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida; [4] Humanitas Clinical and Research Center – IRCCS, Rozzano and Humanitas University, Department of Biomedical Sciences, Pieve Emanuele, Milan, Italy; [5]Cincinnati Children's Hospital, University of Cincinnati, Cincinnati, Ohio; [6]Department of Medicine B for Gastroenterology and Hepatology, University Hospital Münster, Münster, Germany; [7]Division of Gastroenterology, University of California San Diego, La Jolla, California; [8]Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York; [9]Medical University of Vienna, Department of Internal Medicine III, Division Gastroenterology and Hepatology, Vienna, Austria; [10](Private Practice), Hofheim, Germany; [11]Department of Surgery, Amsterdam UMC, University of Amsterdam, Locatie AMC, The Netherlands; [12]Inserm UMR1153 CRESS, équipe ECSTRRA, Université de Paris, Paris, France; [13]Section of Gastroenterology, Hepatology and Nutrition, University of Chicago Medicine, Chicago, Illinois; [14]Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York; [15]Department of Gastroenterology and Inserm NGERE U1256, University Hospital of Nancy, University of Lorraine, Vandoeuvre-lès-Nancy, France; [16] Division of Gastroenterology, Rabin Medical Center, Petah Tikva, Israel and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; and [17]Department of Medicine I, Agaplesion Markus Hospital, Goethe University, Frankfurt/Main, Germany

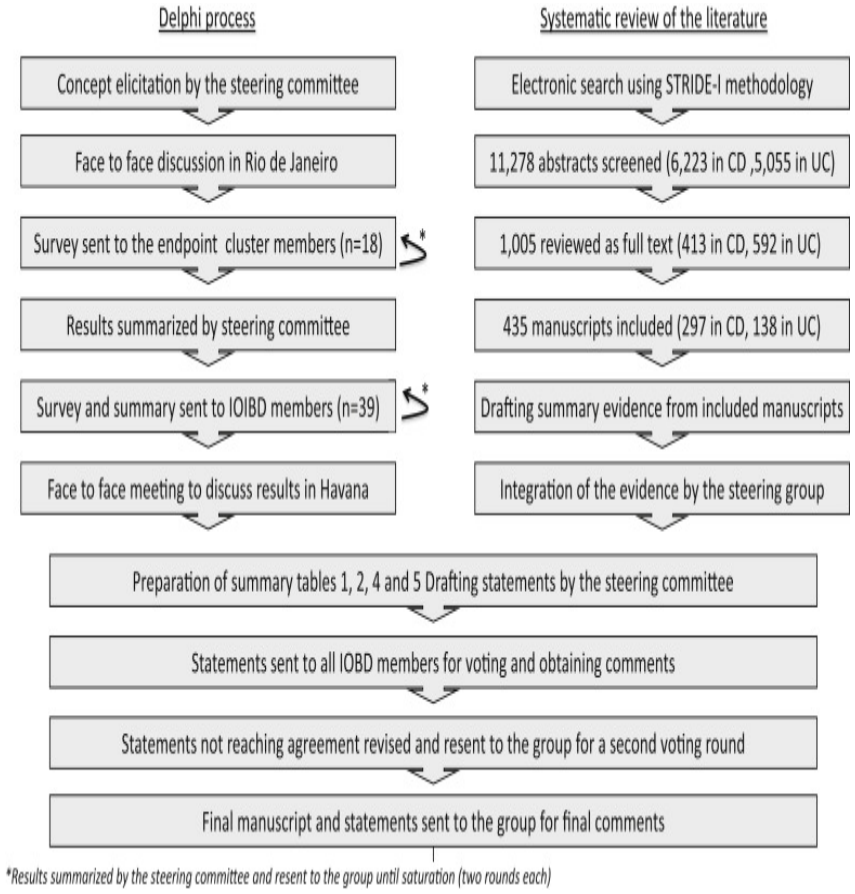
See Covering the Cover synopsis on page 1435.

BACKGROUND: The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) has proposed treatment targets in 2015 for adult patients with inflammatory bowel disease (IBD). We aimed to encompasses evidence- and consensus-based recommendations for treat-to-target strategies in adults and children with IBD. This frameworkshould be adapted to individual patients and local resources to improve outcomes.

Keywords: Treat-to-Target; Endoscopic Healing; Biologics; Patient-Reported Outcomes; Biomarkers.

UNIVERSITY OF Cincinnati

Methods



- Steering committee of 10 IOIBD members
- Separate targets for UC, CD
  - Clinical, endoscopic, histologic, imaging, biomarkers and PROs
- Survey to all IOIBD members asking about targets
  - Stepwise recalculation
  - In person meetings
  - Final Voting
    - 75% participants scored statements 7-10

UNIVERSITY OF Cincinnati

Table 2. Recommendations for Treating to Target in CD and UC by the IOIBD (70 Participated of 89 Invited)

Recommendations	Voting results: Strength of recommendation[c]	Voting results: % votes 7–10
Clinical		
1. **Clinical response is an immediate treatment target.** Consider changing treatment if this target has not been achieved.[a]	9.0	94
2. Clinical response should be defined as: a) CD: decrease of at least 50% in PRO2 (abdominal pain and stool frequency), and in children decrease in PCDAI of at least 12.5 points and in wPCDAI at least 17.5 points b) UC: decrease of at least 50% in PRO2 (rectal bleeding and stool frequency), and in children decrease in PUCAI of at least 20 points	8.3	84
3. **Clinical remission is an intermediate (ie, medium-term) treatment target.** Consider changing treatment if this target has not been achieved.[a]	8.7	94
4. Clinical remission should be defined as: a) CD: PRO2 (abdominal pain ≤1 and stool frequency ≤3) or HBI <5; in children by PCDAI (<10 points or <7.5 excluding the height item) or wPCDAI (<12.5 points) b) UC: PRO2 (rectal bleeding=0 and stool frequency=0) or partial Mayo (≤3 and no score >1), and in children PUCAI <10 points	8.5	81
5. Clinical response or remission are insufficient to be used as long term treatment targets	8.3	80
6. **In children, restoration of normal growth is a long-term treatment** target. Consider changing treatment if this target has not been achieved.	9.3	98
Endoscopic and transmural assessment		
7. **Endoscopic healing is a long-term target.** Consider changing treatment if this target has not been achieved.	8.7	87
8. Assessment of endoscopic healing can be achieved by sigmoidoscopy or colonoscopy. When not feasible, alternatives in CD can be capsule endoscopy or balloon enteroscopy.	8.3	86
9. Endoscopic healing should be measured by: a) CD: SES-CD <3 points or absence of ulcerations (e.g. SES-CD ulceration subscores = 0) b) UC: Mayo endoscopic subscore = 0 points, or UCEIS ≤1 points	8.5	85
10. Histologic remission is not a treatment-target in either CD or UC. Nonetheless, in UC it could be used as an adjunct to endoscopic remission to represent a deeper level of healing.	7.7	80
11. Transmural healing (assessed by CTE, MRE, or bowel ultrasound) is not a treatment-target in either CD or UC. Nonetheless, in CD it should be used as an adjunct to endoscopic remission to represent a deeper level of healing.	7.5	77
Biomarkers		
12. **Normalization of CRP (to values under the upper limit of normal) and fecal calprotectin (to 100–250 μg/g)[b] is an intermediate treatment target in UC and CD.** Consider changing treatment if this target has not been achieved.	8.2	80
Quality of life and disability		
13. **Absence of disability and normalized health-related quality of life are long-term treatment targets.** Consider changing treatment if this target has not been achieved.	7.7	75

[a]Time to achieving the target vary based on therapy and mechanism of action (Table 3).
[b]The cutoff value of fecal calprotectin is dependent on the desired outcome. Lower thresholds (eg, <100 μg/g) have been proposed for reflecting deep healing (both endoscopic and transmural healing) or histological healing, whereas higher values (eg, <250 μg/g) reflect less stringent outcomes (eg, MES of 0 or 1 in UC).
[c]Calculated as the mean score of all responders (on a scale of 1–10 where "10" demotes complete agreement and "1" complete disagreement).
NOTE. The following 2 statements were removed after the second voting given low endorsement: "Absence of health-related fatigue is a long-term treatment target" (47% agreement) and "Absence of health-related anxiety and depression is a long-term treatment target" (37% agreement).
CTE, computerized tomography enterography; MRE, magnetic resonance enterography; PRO, patient reported outcome; PUCAI, pediatric UC activity index; SES-CD, simple endoscopic score in CD; UCEIS, endoscopic index of severity; wPCDAI, weight pediatric CD activity index.

Table 1. Ranking of Importance of Short-Term Treatment Goals in IBD (1, Most Important; 5, Least Important) (Mean Values)

Crohn's disease (n = 39)		Ulcerative colitis (n = 36)	
Goals (order of importance)	Score	Goals (order of importance)	Score
Clinical remission	1.8	Clinical remission	2.3
Endoscopic response	2.1	Clinical response	2.4
Clinical response	2.2	Endoscopic response	2.4
Normalization of CRP/ESR	2.2	Normalization of CRP/ESR	2.7
Normalization of calprotectin	2.6	Normalization of calprotectin	2.7
Transmural healing	3.1	Histological healing	2.7
Histological healing	3.4	Transmural healing	4.2

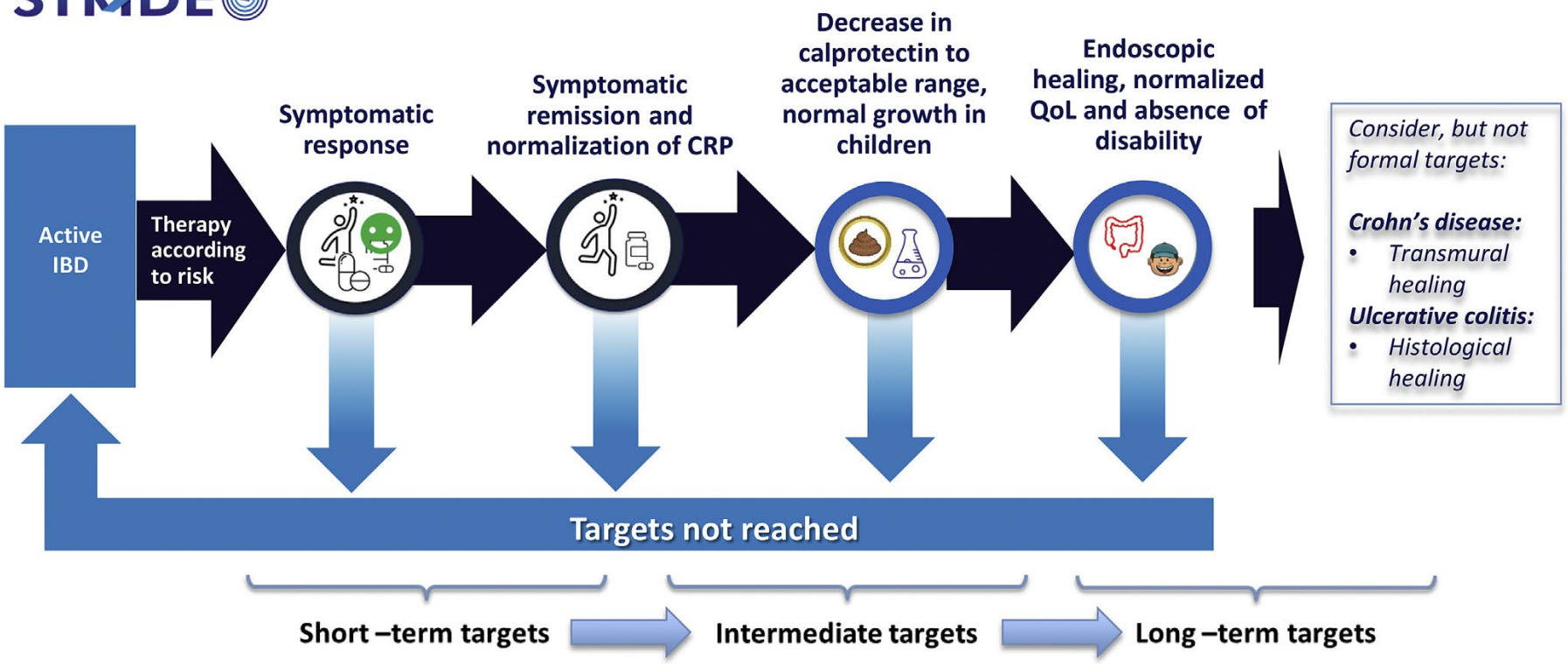
UNIVERSITY OF Cincinnati

STRIDE-II

Table 3. What Is New in STRIDE-II?

- The STRIDE group, under the auspices of the IOIBD, has updated the 2015 first reported STRIDE recommendations and has developed 13 updated and new recommendations for treating to target in CD and UC (STRIDE-II recommendations).
- Time to expected response, remission, and endoscopic healing with the different treatments have been introduced for incorporating the treatment targets.
- STRIDE-II added clinical response and remission as well as normalization of CRP as immediate and short-term targets.
- Reduction of FC to an acceptable range has been added as a formal intermediate treatment target.
- Pediatric targets, reflected by different measuring scales and the addition of restoration of normal growth as a formal treatment target have been added.
- Restoration of QoL and absence of disability have been added to EH as long-term targets.
- Transmural healing in CD and histological healing in UC have been newly recognized as important adjunctive measures but were not endorsed as formal new treatment targets.

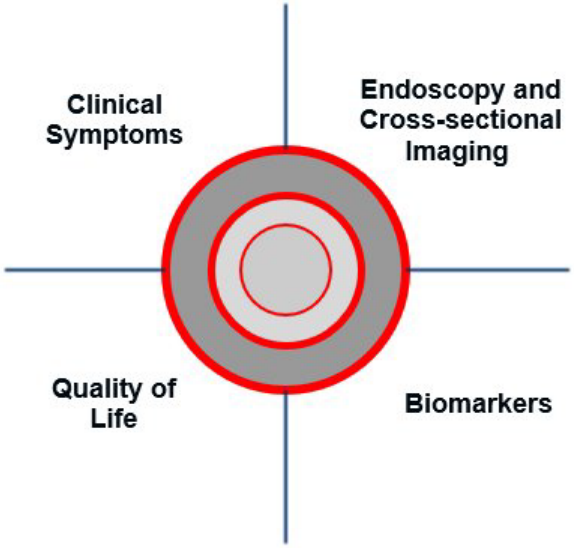
The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) - **consensus among international IBD experts on treatment targets** for adult and pediatric IBD patients after careful review of existing evidence



Turner et al. Gastroenterology 2021

UNIVERSITY OF Cincinnati

TREAT TO TARGET strategy combines *clinical symptoms* and *normalization of quality of life/disability* with objective measures of intestinal inflammation/damage



Preventing Structural Damage and Improve Patient Outcomes

UNIVERSITY OF Cincinnati

Crohn's Disease

Targets

- Clinical response and remission
- Normalization of biomarkers (Fecal calprotectin and CRP)
- Endoscopic response
- Quality of life and disability
- Transmural healing
- Histological healing

Clinical Response and Remission

Immediate

- 50% improvement of abdominal pain and bowel habits

Resolution of symptoms alone is not a sufficient target

- Resolution of abdominal pain and normalization of bowel habits

Jones et al. Clin Gastroenterol Hepatol 2008
Peyrin-Biroulet et al. Gut 2014

UNIVERSITY OF Cincinnati

Clinical Targets- in children

Long-term

- Restoration of normal growth

Jones et al. Clin Gastroenterol Hepatol 2008
Peyrin-Biroulet et al. Gut 2014

UNIVERSITY OF Cincinnati

Serum and Fecal Biomarker Targets

- CRP and fecal calprotectin
  - Fecal calprotectin demonstrates the highest sensitivity (82%), specificity (72%), PPV, NPV
  - Fecal calprotectin has a higher correlation with disease activity in the colon vs the ileum
    - Threshold target: most prognostic significance
      - Cutoff of 150 ug/g = gray zone
      - <600 ug/g = possible inflammation
  - CRP: high specificity, lower sensitivity
  - Combination CRP and fecal calprotectin most accurately predicts relapse
- If failure of biomarker normalization should consider endoscopic evaluation, irrespective of symptoms

Gisbert et al. Inflamm Bowel Dis 2009
DeVos et al. Inflamm Bowel Dis 2013

- Cross Sectional Imaging
  - Adjunct Assessment:
    - Not a formal treatment target
  - Ultrasound
    - Bedside
    - Assess degree of inflammation
    - Can evaluate the entire GI tract (transmural)
    - Can be repeated
    - Limitations: cost, expertise, access
  - MRE and CTE
    - Transmural inflammation
    - Evaluation of small bowel
    - Assess for strictures, fistulas, abscesses
    - Limitations: cost, radiation (CT), may miss lesions

- **Endoscopic Targets**
- Endoscopy: Mucosal healing
  - Sustained clinical remission
  - Decrease in hospitalization
  - Decrease in need for surgery
  - Increase in health-related quality of life
- Limitations:
  - Costly
  - Ability to rapidly repeat
  - Disease location

Baert et al. Gastroenterology 2010
Peyrin-Biroulet et al. Am J Gastroenterol 2015
Rutgeerts et al. Gastroenterology 2012
Hebuterne et al. Gut 2013

- **Histological healing**
  - Assumption: Deeper remission=better outcomes
  - Rated low: remission not a target
    - Lack of validated measuring tool
    - Insuffienent data
    - Overall therapeutic ability to reach target

Magro et al. J Crohns Colitis 2013

UNIVERSITY OF Cincinnati

- **Quality of Life and Disability**
  - Patient's report about how they function or feel in relation to a health condition and/or its therapy
  - Formal Long term targets
    - Restoration of QoL
      - Food-related QoL, fatigue, depression, anxiety, sexual dysfunction, and body image
    - Reduction in disability
  - Assess Independently of markers
  - Correlation with markers of disease is low
  - Important to other aspect of disease.. Patient Centric

- **Composite End-Points**
  - Combining several targets vs looking at them individually
  - Strategy to improve patient outcomes
  - Multiple studies have shown benefits in a multiple targets approach to treatment

Ulcerative Colitis

Targets

- Clinical response and remission
- Normalization of biomarkers (Fecal calprotectin and CRP)
- Endoscopic response
- Quality of life and disability
- Histological healing
- Transmural healing

Clinical Response and Remission

Immediate

- 50% improvement of rectal bleeding and stool frequency

Intermediate

- Resolution of rectal bleeding and stool frequency

Resolution of symptoms alone is not a sufficient target
But unlike CD endoscopic inflammation correlates well with symptoms

Jones et al. Clin Gastroenterol Hepatol 2008
Peyrin-Biroulet et al. Gut 2014

UNIVERSITY OF Cincinnati

Clinical Targets- in children

Long-term

- Restoration of normal growth

Jones et al. Clin Gastroenterol Hepatol 2008
Peyrin-Biroulet et al. Gut 2014

UNIVERSITY OF Cincinnati

- **Biomarker Targets**
- CRP and fecal calprotectin
  - Low cost, noninvasive, ?easy
  - Fecal calprotectin: 83% sensitivity 74% specificity (cutoff ≤168 ug/g)
    - Sensitive
    - Correlates with disease acitivy, endoscopic acitivy and histologic indices
    - Unclear
      - Predictive value for relapse and while in remission
  - ESR/CRP
    - Modestly correlate with diseae activity
- If failure of biomarker normalization should consider endoscopic evaluation, irrespective of symptoms

Yoon et al. Dig Dis Sci 2014
Molander et al. Inflamm Bowel Dis 2012

- Cross Sectional Imaging
  - Transmural healing
- Imaging is not a target in UC
- Increasing use of bedside ultrasound:
  - May become valuable long term
  - Tool to assess inflammation

- **Endoscopic Healing**
- Preferred long term goal in STRIDE-1
- Mucosal healing:
  - MES subscore of 0 (normal mucosa): superior disease outcome
  - MES subscore of 1 (erythema, decrease vascular pattern, mild friability): minimum target
  - Associated with sustained clinical remission, steroid-free remission, and decrease in colectomy

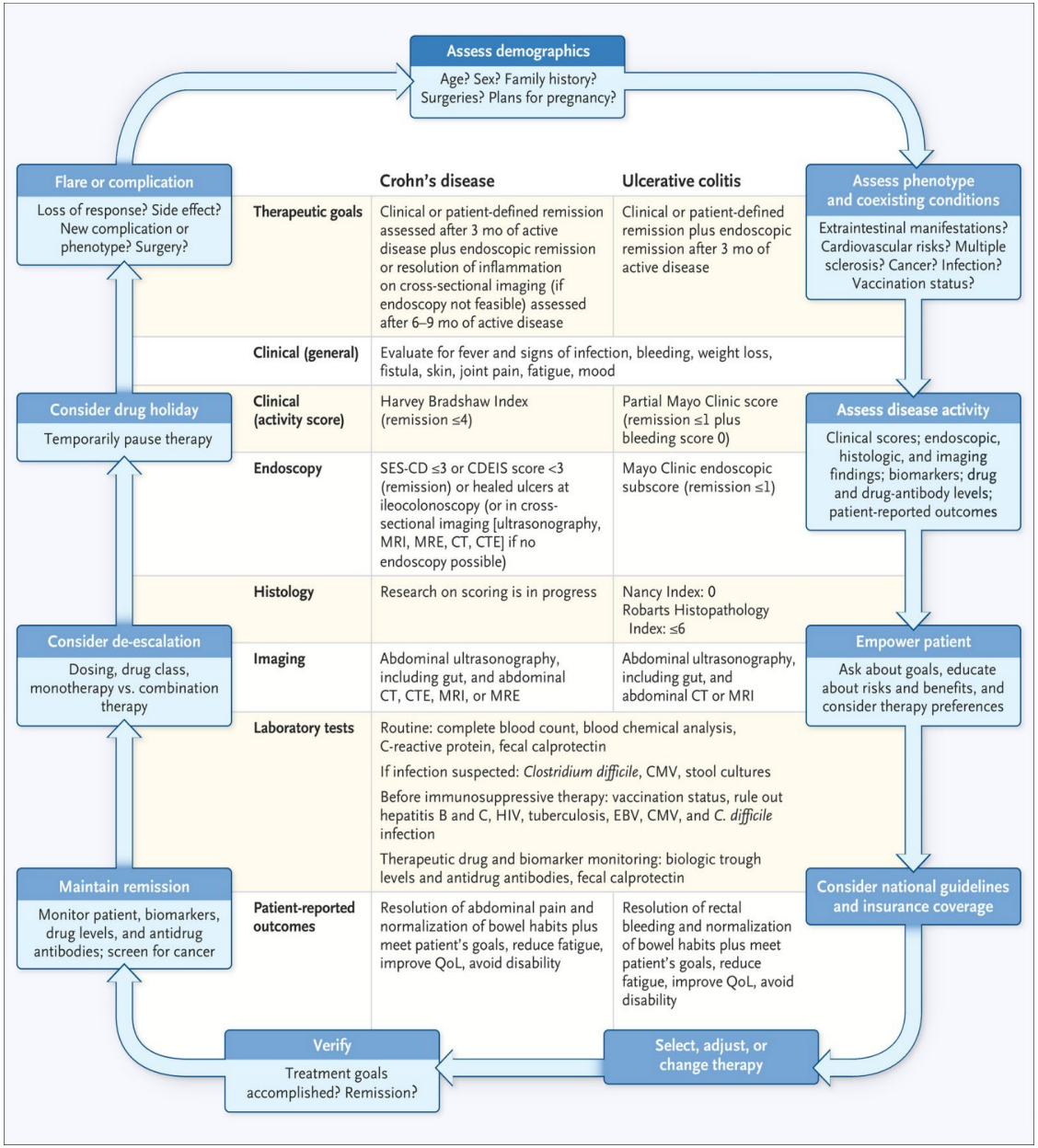
Colombel et al. Gastroenterology 2011
Kim et al. Scan J Gastroenterol 2016

UNIVERSITY OF Cincinnati

- **Histologic Healing**
  - Not a formal target
  - Advent of therapeutic goal to prevent malignancy and lead to long term remission
  - Absence of inflammation and structural changes
    - More likely to be symptom-free
    - Reduce risk for relapse
    - Decrease need for surgery
    - Decrease need for hospitalization
    - Reduction in colorectal cancer risk
  - Balanced over cost, risks of therapy
  - May only be beneficial in extreme cases

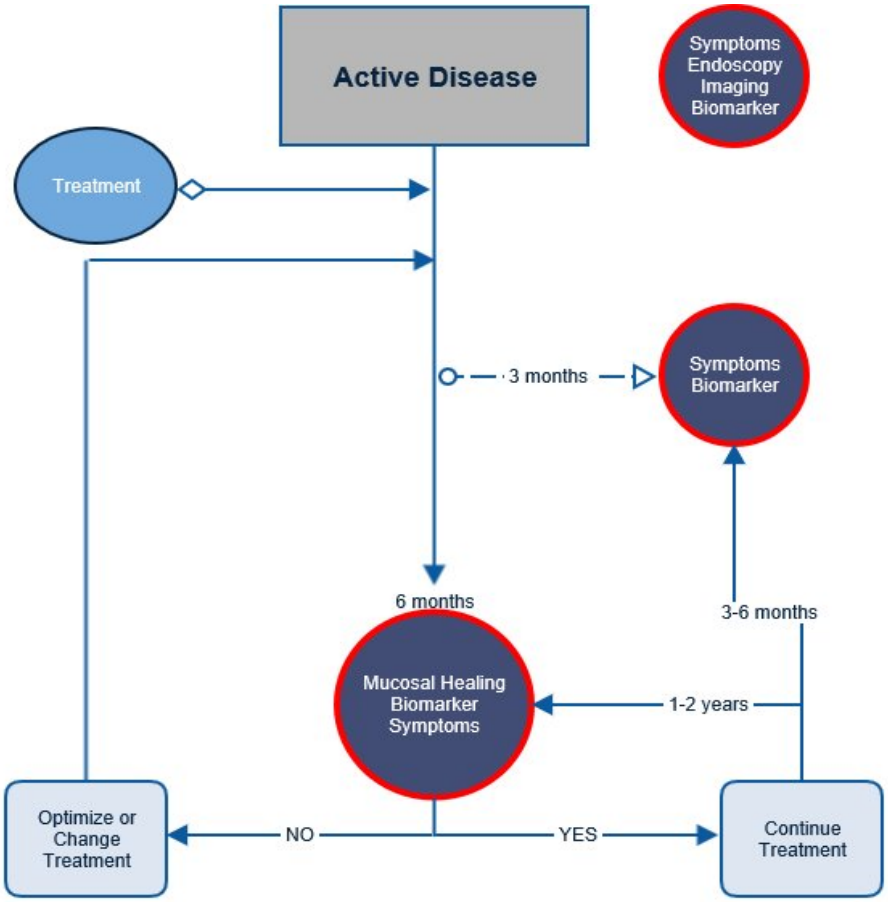
Bitton et al. Gastroenterology 2001
Rutter et al. Gastroenterology 2004
Gupta et al. Gastroenterology 2007
Azad et al. Saudi J Gastroenterol 2011

Medical Management Cycle for Inflammatory Bowel Disease. Therapeutic goals are adapted from the STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) initiative.[5]
CDEIS denotes Crohn's Disease Endoscopic Index of Severity SES-CD Simple Endoscopic Score for Crohn's Disease.



Baumgart, D. C., and C. Le Berre. 2021. 'Newer Biologic and Small-Molecule Therapies for Inflammatory Bowel Disease', *N Engl J Med, 385: 1302-15.*

UNIVERSITY OF Cincinnati



Bouguen et al. Clin Gastroenterol Hepatol. 2015

UNIVERSITY OF Cincinnati

Table 4. Time (Mean Number of Weeks) Required for Achieving the Goal After Starting Treatment for CD (n = 39) and UC (n = 36), Based on the Delphi-like Process and the Systematic Review of the Evidence

	Clinical response	Clinical remission	Norm of CRP/ESR	Decrease of FC[a]	EH
Crohn's disease					
Oral steroids/EEN	2	4	5	8	13
Budesonide	3	6	8	10	15
Thiopurines	11	15	15	17	24
Methotrexate	9	14	14	15	24
Anti-TNF	2–4	4–6	9	11	17
Vedolizumab	11	17	15	17	24
Ustekinumab	7	13	11	14	19
Ulcerative colitis					
Oral 5-ASA	4	8	8	10	13
Oral Steroids	2	2	5	8	11
Locally active steroids[b]	3	8	8	9	13
Thiopurines	11	15	15	15	20
Adalimumab	6	11	10	12	14
Infliximab	5	10	9	11	13
Vedolizumab	9	14	14	15	18
Tofacitinib	6	11	9	11	14

Turner et al. Gastroenterology 2021

Table 5. Gaps in Knowledge and Areas for Future Research

- PROs
  - o Gap: PRO2 for both CD and UC have been formulated from existing measures as a temporary measure to meet the regulatory agencies' requirement in clinical trials. They were not a product of stringent psychometric development and evaluation.
  - o Future research: PROs should be developed aiming at use in clinical practice, with high reliability, face validity, construct validity, responsiveness, and feasibility.
- HRQOL
  - o Gap: Current measuring tools were developed as research tools and are too cumbersome for using in routine clinical practice.
  - o Future research: Development and validation of a shorter measuring tool for everyday use.
- Histology and transmural healing
  - o Gap: It is still unclear whether these are significant enough to justify the increased utilization of medical treatment to achieve these extended endpoints. This is the reason why they were not selected as formal treatment target for STRIDE-II.
  - o Future research: More prospective studies, preferably randomized-controlled, are needed to explore the number-needed-to treat to these targets for achieving superior clinical outcomes.
- Endoscopic healing
  - o Gap: The thresholds to define remission or response remain un-validated.
  - o Future research: More studies are needed to link the optimal thresholds with specific outcomes

HRQOL, health related quality of life.

STRIDE-II Conclusions

- Important-Immediate
  - Symptom Relief (rated highest via patients)
- Intermediate
  - Serum and Clinical biomarkers
- Long-Term-Achievable Targets
  - 1. Clinical Remission
  - 2. EH
  - 3. Restoration of QoL
  - 4. Absence of Disability

STRIDE-II Conclusions

- Ultimate Target: Complete deep healing
  - Clinical remission + complete endoscopic and histological healing + transmural healing
  - Need more research
    - Is the gain worth the risks of treatment
    - Is this achievable with currently available treatments
    - Transmural healing indices
  - Things Change: An algorithm can't always be followed

Take-home Points

TREAT TO TARGET strategy aims at

- Clinical remission
- Endoscopic healing
- Restoration of normal growth in children, Normalization of quality of life
- Absence of disability

Thank you

QUESTIONS???