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Opportunities in Inflammatory Bowel Diseases: Crohn's Disease and Ulcerative Colitis

PRESENTATION TO THE COMMITTEE FOR THE ASSESSMENT OF NIH RESEARCH ON AUTOIMMUNE DISEASES

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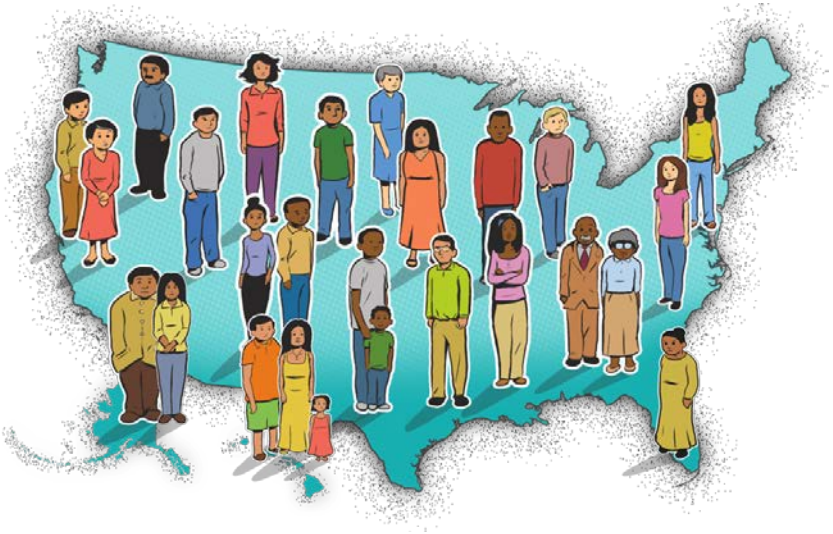
Outline

- Epidemiology
- Recent research advances
- Urgent need for better approaches
- Greatest opportunities for accelerating impact: bedside to bench
  - Environmental triggers
  - Endotypes
  - Standardization
- Conclusion

Epidemiology of IBD

IBD impacts all demographic groups

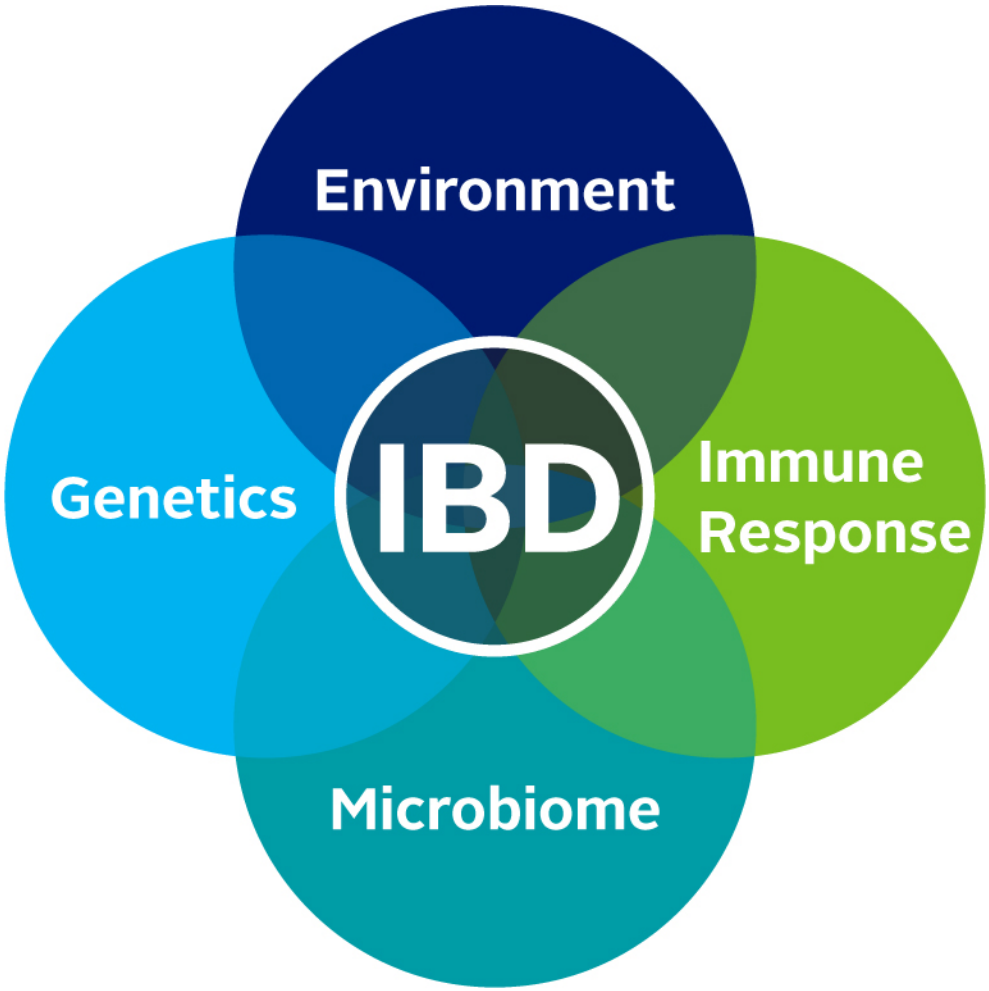
- In, U.S. between 1.6* to 3.1 million**
- Peak occurrence 10- 40 y.o.
- Rising incidence among newly industrialized countries and immigrants from these countries



** Olmstead County data based on medical records*

***Nationwide prevalence data based on patient self-report has been published by CDC*

Complexity of IBD



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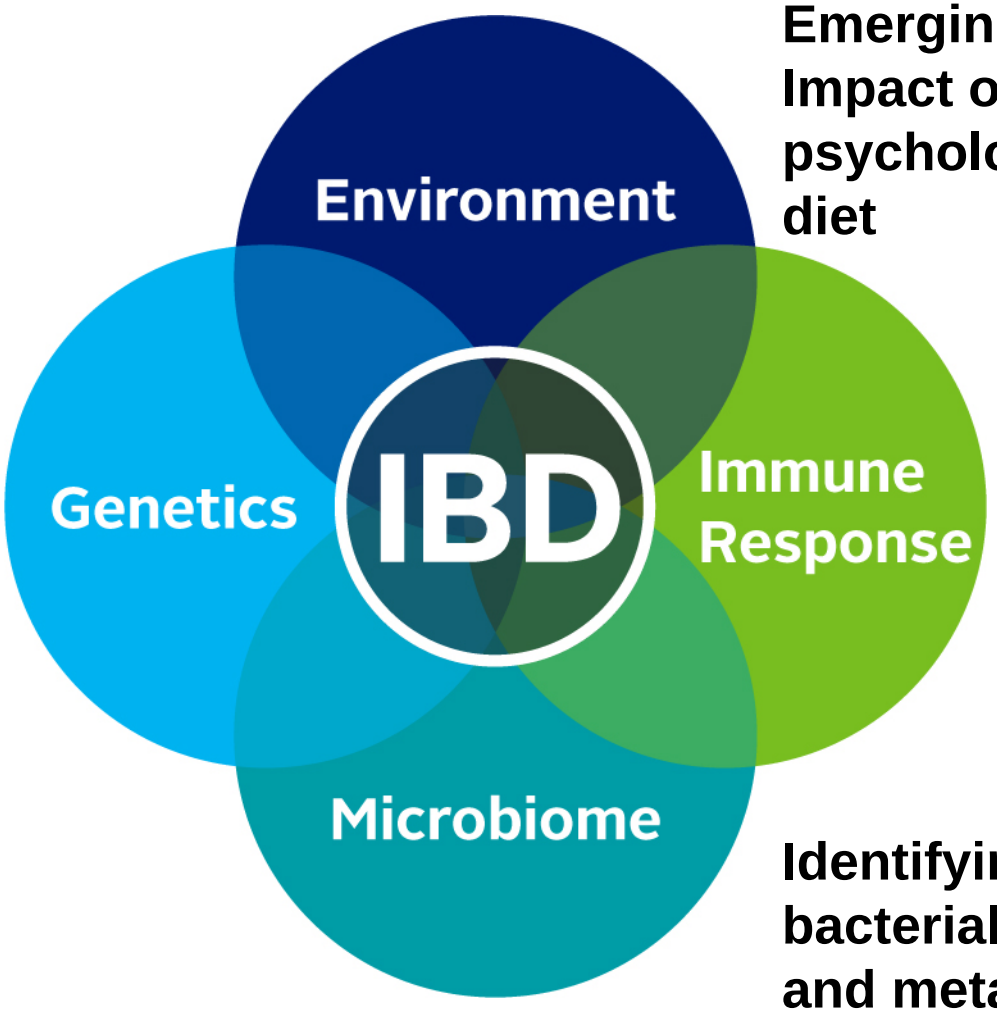
Recent Research Advances

Emerging knowledge: Impact of psychological stress, diet



Identifying specific pathways underlying disease with potential drug targets

Increasing understanding of role of each immune cell type.

Identifying desired bacterial patterns and metabolites

Urgent Need for Better Approaches

No Cure	• Chronic progressive disease without a cure • Increased risk of colorectal cancer
Inadequate Treatment	• <50% patients with long-term response to Rx • No biomarkers predict response to Rx
High Surgery Rates	• About 70% of Crohn's patients • About 30% of ulcerative colitis patients

Greatest Opportunities for Accelerating Impact: Bedside-to-Bench Approach

Environmental Triggers	• Causative role • Susceptibility/onset, progression, relapse
IBD Endotypes	• Underlying mechanistic pathways • A cluster of phenotypes
Standardization	• Enabling comparison of “apples to apples” • Need for common data elements

Environmental Triggers

RESEARCH GAPS

Need to understand the causative role of the environment in IBD susceptibility, progression and relapse

- Define right patient cohorts
- Key environmental factors
- Biological signatures of exposures and relationship to clinical outcomes
- Mechanisms connecting environmental exposures to clinical outcomes

STEPS FORWARD

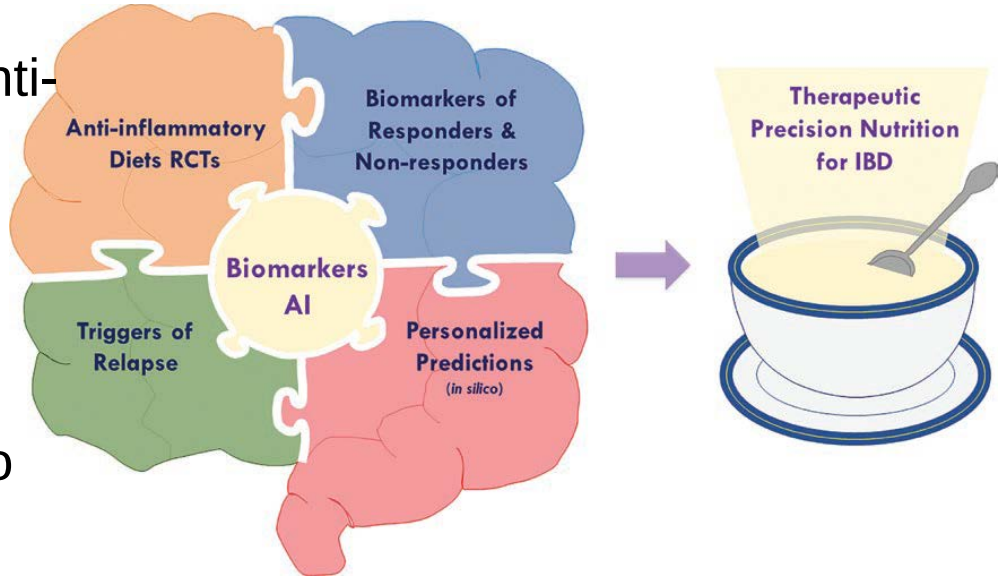
- Epidemiology and exposome
- Focus on priority cohorts (critical unmet needs)
- Systems biology approach
- Hypothesis-driven studies

Inflamm Bowel Dis. 2019 Jun; 25(Suppl 2): S13–S23
doi: 10.1093/ibd/izz076

Example of a bedside-to-bench research approach: Crohn's & Colitis Foundation Precision Nutrition Initiative

Key elements of initiative (4 studies)

- Randomized clinical trials to evaluate **rationally-designed** anti-inflammatory diets
- Identification of proinflammatory "**trigger foods**" that exacerbate symptoms/induce relapse
- Identification of **biomarkers** to predict and measure response to these diets
- Development of ***in silico* predictive tools** required to design evidence-based therapeutic diets to evaluate in trials



Crohn's & Colitis 360 • Volume 2, Number 4, October 2020, doi: 10.1093/crocol/otaa087

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IBD Endotypes: A Bedside-to-Bench Approach

ENDOTYPE VS. PHENOTYPE

Phenotype:
Clinical presentation of the underlying mechanistic pathway

Endotype:
Underlying mechanistic pathway

Patients with a specific endotype present within phenotypic clusters of diseases.

Inflamm Bowel Dis. 2020 Sep 18;26(10):1451-1462. doi: 10.1093/ibd/izaa210. PMID: 32812036; PMCID: PMC7500521.

APPLIED TO ASTHMA

The term asthma is now considered **an umbrella diagnosis** for several diseases **with distinct mechanistic pathways (endotypes)** and **variable clinical presentations (phenotypes)**. The precise definition of these endotypes is central to asthma management due to inherent therapeutic and prognostic implications.*

*Clin Rev Allergy Immunol. 2019 Apr; 56(2): 219–233. doi: 10.1007/s12016-018-8712-1

IBD Endotypes

Unravel heterogeneity*	Underlying mechanisms*	New biomarkers and targets
• Disease presentation • Disease course • Response to treatment • Response to environmental stimuli	• Pro-inflammatory cytokines • Altered immune tolerance • Neuro-inflammation • Triggering by dietary components	• Relevant to subgroup • Diagnostic/ prognostic/ predictive • Targeted therapeutics

* Representational examples only

Standardization: The Need To Define The Bedside

Problem:

Clinical data collection – how patients are classified – varies greatly, complicating efforts to compare results across studies or across collaborations

Example:

Two academic studies evaluated factors associated with response to the same therapy in patients with isolated upper GI disease.

- Used different definitions of isolated upper GI disease
- Both underpowered to generate definitive results
- No definitive conclusions could be drawn. Studies are difficult to replicate, combine, compare due to ambiguous definitions.

Reviewed in: https://academic.oup.com/ibdjournal/article/26/10/1451/5894181

Standardization: Common Data Elements for IBD

Goal:

Create a set of common data elements (CDEs) and associated tools and incentives for standardized data collection in IBD clinical and translational studies

Process:

Follow process that other NIH institutes have implemented, often collaboratively, to develop CDEs

- See details at https://cde.nlm.nih.gov/home; Asthma is a good example. NINDS is working on MS.
- Initial set of CDEs could focus on phenotype definitions
- Need to identify a process to incentivize their use

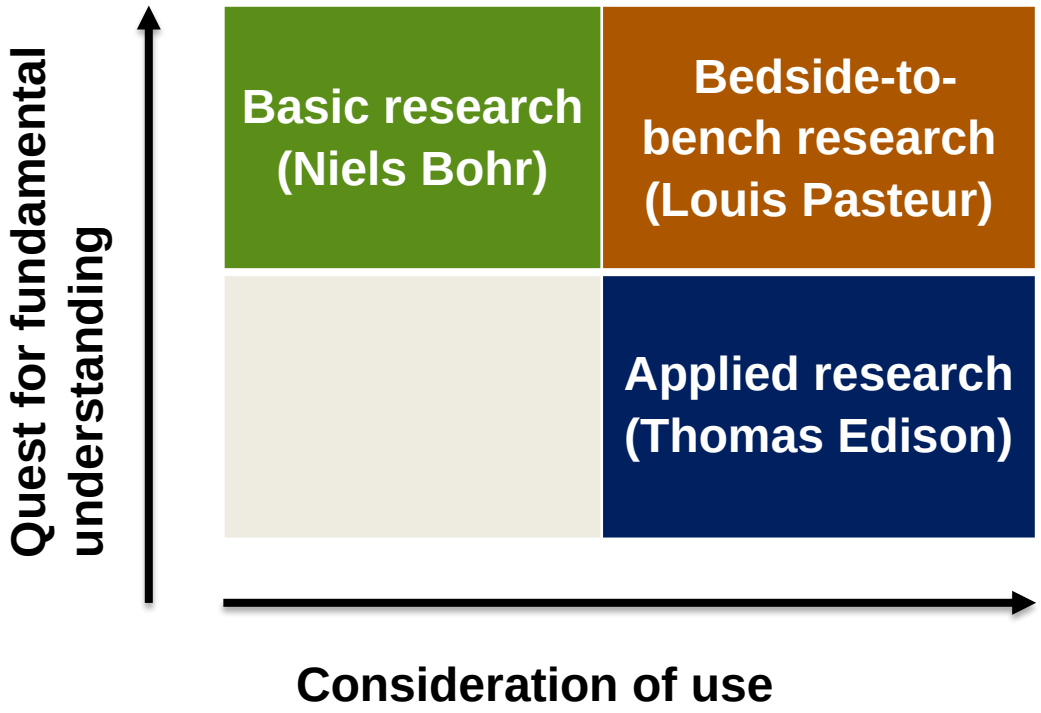
Outcome:

Guidance to yield more efficient research data that can be shared, validated, compared

Conclusion

Innovation is needed to accelerate positive outcomes in IBD

We propose an increased bedside-to-bench emphasis:
Pasteur's quadrant



Environmental Triggers

Endotypes

Standardization

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