MAYO CLINIC

Using Worldwide Data for the Next AJCC Version

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Disclosures

- Consulting/advisory role (to myself): Yiviva Inc, Regeneron, Hoosier Cancer Research Network, Kronos Bio, Mirati Therapeutics Inc. Genmab US, Inc., HopeAI, Inc., BMS, and AbbVie
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Background – Colon Cancer (CC)

- Recent analyses highlight nonhierarchical outcomes using the 7th/8th Edition AJCC staging system for CC.
  - For instance, the 5-year survival rate for stages I and IIIa patients (pts) closely align.
- Additionally, tumor deposits (TDs) have been established as significant prognostic indicators.
- The AJCC Colon Cancer Expert Pannel commissioned this study to develop an updated pathological staging system for CC.

Objectives

- **Primary objective**
  - To develop and propose updated pathological staging system for colon cancer patients by performing risk classification analyses based on individual patient data (IPD) from National Cancer Database (NCDB)
  - To evaluate its validity based on IPD from large randomized clinical trials and real-world cohort data
- **Recal cancer staging system**
  - A separate analysis is currently ongoing

International Collaboration

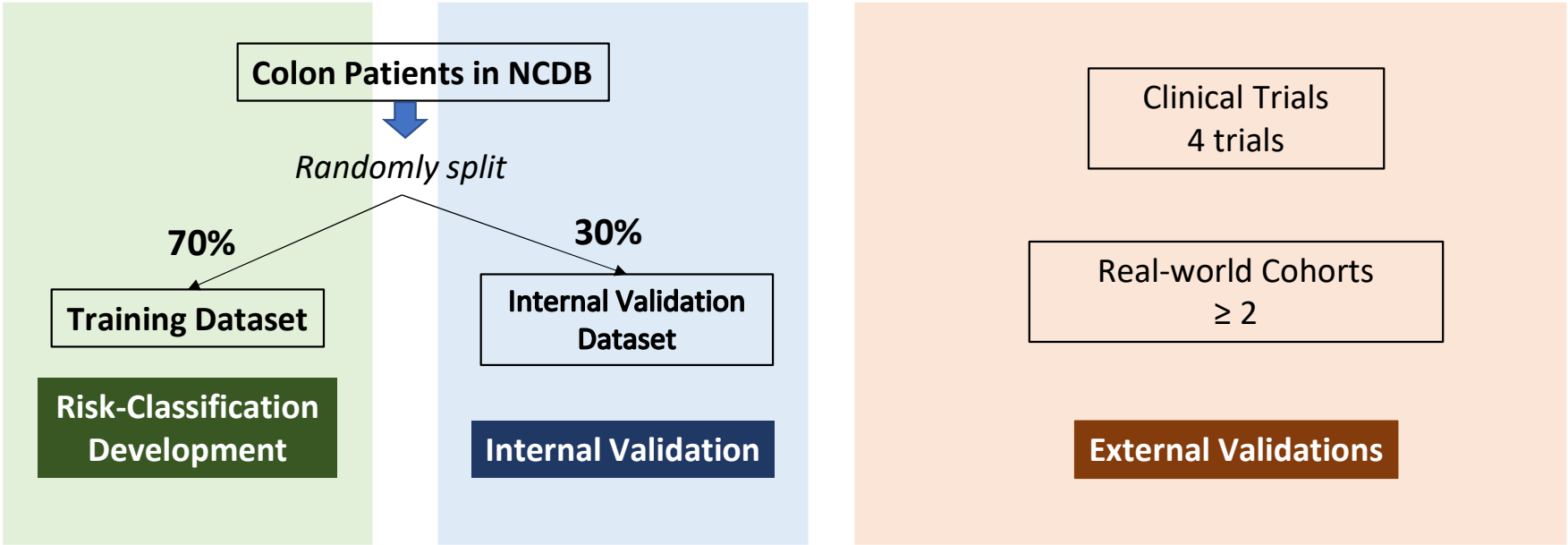
Statistical Experts

- *MAYO CLINIC STATISTICIANS:*
  - Qian Shi, PhD, Levi Pederson, MS, Jesse Dixon, MS
- *INDEPENDENT STATISTICIANS*:
  - Greg Yothers, PhD, Karla Ballman, PhD
- *NCDB STATISTICIAN:* Bryan Palis, PhD

Clinical Experts

- *AJCC COLORECTAL PANEL*:
  - Richard Goldberg, MD, Qian Shi, PhD, Scott Steele, MD, George Chang, MD, Elliot Asare, MD, Key Washington, MD, Chanjuan Shi, MD
- *MAYO CLINIC INVESTIGATORS*:
  - Qian Shi, PhD, Steve Alberts, MD, Zhaohui Jin, MD, Mark Ma, MD
- *ACCENT/IDEA INVESTIGATORS*:
  - Qian Shi, PhD, Jeff Meyerhardt, MD, Thierry Andre, MD, Julien Taieb, MD, Romain Cohen, MD, Jeanne Tie, MD, Steve Alberts, MD, Takayuki Yoshino, MD

Risk Classification – Development Strategies



Overall stage: I, II, III, and IV

Substaging within overall stage categories

Risk Classification – General Considerations

General Requirements

- Overall and sub staging levels:
  - 4-level overall staging classification (Stage I, II, III, and IV)
  - No more than 3 sub-levels within each overall staging level.
- The survival probabilities of all sub-staging levels are required to be hierarchical from high to low in a consecutive order

Statistical Method: Log rank test to compare individual consecutive pair-wise overall/sub-staging levels

Stringent Statistical Criteria

Analyses	Significance Level for All Consecutive Pair-Wise Comparisons		KM Curves Complete Separation: No overlaps/crossover
	Overall levels	Sub-levels	
Training	< 0.001	< 0.005	After 12m, all pairs of sub-levels
Internal Validation	< 0.025	< 0.05	After 12m, 80% pairs of sub-levels
External Validation	Totality of the results across various external validation datasets will be evaluated		

Training and Internal Validation Datasets: NCDB

Inclusion Criteria

- Diagnosed in 2010 to 2017 (prior to AJCC 8th edition release date of Jan 1, 2018)
- Cancer identification for primary site (ICD-O 3rd edition): C180, C182-189, C199
- Diagnosis age: 18 years old and older
- Histology (ICD-O 3rd edition):
  - Histologic terms: 8000, 8010, 8013, 8020, 8041, 8070, 8140, 8265, 8480, 8481, 8490, 8510, 8560
  - Behavior codes: Carcinoma in situ, Invasive
- First and only cancer diagnosis: Sequence number "00"
- Analytic cases, excluding cases where initial diagnosis at reporting facility and all treatment/decision (to treat or not to treat) done elsewhere: Class of case in 10, 11, 12, 13, 14, 20, 21, 22

Data Requirements

- Follow-up time is > 0 and not missing
- Maximum data availabilities on "raw" data:
  - T categories
  - Number of positive regional lymph nodes (as opposed to N categories)
  - Number of tumor deposits (as opposed to present vs. absent)
  - Use number of distant mets at diagnosis to verify M0 vs. M1 categories

External Validation Datasets – Clinical Trials

Trials (Group)	Enrolling region	Accrual time	N
N0147 (Alliance)	USA, Canada	2004 – 2009	798
IDEA France (PRODIGE/GERCOR)	France	2009 – 2014	1936
C80702 (Alliance)	USA, Canada	2010 – 2015	2009
DYNAMIC (WEHI)	Australia	2015 – 2019	441

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Current Status

- Updated pathologic staging system for colon cancers was developed and successfully validated based on internal validation dataset and external clinical trials dataset.
- An abstract based on current results was submitted to ASCO 2025 meeting.
- Continuous efforts were undertaken to obtain real-world cohorts to serve as additional external validation datasets.

Why Additional External Validations?

- Patients enrolled in clinical trials are highly selected, and treatment management within trials may not fully represent real-world clinical practice.
- Importance of full scope of the external validations
  - To assess the generalizability and robustness of the updated staging system – whether it maintain predictive accuracy across different demographic, clinic and genetic backgrounds.
  - To strengthen confidence in updated staging system for its reliability and its utility and adoption into clinical practice worldwide, benefiting patient risk stratification and treatment decisions.

External Validation Datasets – Real-world Cohorts

Cohort	Region	Diagnoses Time	Status	Estimated N
Japanese Cohort	Japan	2014 – 2019	Data abstraction	> 2000
Belgian Cancer Registry	Belgium	Up to 2017	Agreed to participate	~5600
National Disease Registration Service	UK	TBD	Negotiation	TBD
Netherlands Cancer Registry	Netherlands	TBD	Negotiation	TBD

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Key Takeaways & Final Thoughts

- A well-structured and rigorous pre-planned risk classification strategy is fundamental for staging system development and refinements.
- Full scope of validation is essential. It ensures generalizability, robustness, and clinical adoption of the next AJCC stating system.
- Rigorous validation, especially external validations based on different sources of data, should be prioritized to enhance risk classification credibility.
- Collaboration across institutions, research groups, and countries is crucial for broader validation efforts.
- ***Validated staging systems are not just numbers – they impact real patients worldwide. Let's ensure we build risk classification models that truly benefit patients in cancer care.***

QUESTIONS & ANSWERS