

**Prognostic Markers Beyond TNM:  
They Are Here to Stay**  
(What are they and how do they affect staging?)

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**Disclosures**

- Nothing to Disclose

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**The Strengths of Anatomic Staging**



- Common language of patient classification across the global cancer community
  - Patient care
  - Research
- Basis of historical cancer data comparisons
  - Relates contemporary patients to like patients in past 70 years, allowing tracking of changing management approaches and outcomes
- Common denominator of classification of cancer cases, achievable for nearly all patients
  - Sole source of patient classification in low- and middle-income countries
- Utility as cornerstone of evaluation and treatment decisions
- Anatomic stage codified by TNM remains the strongest prognostic factor for solid tumors.

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### Persistent Challenges to TNM Staging

### CHALLENGE



TNM does not meet needs of clinicians and patients

- Individualized prognosis
- Predict value of therapy
- TNM risks marginalization

TNM is largely limited to anatomic information

- Lacks biological data
- Lacks impact of response

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### Vision for AJCC Version 9 Staging System

TNM stage groupings that define valid and meaningful classification of patients, critical for current clinical practice

Prognostic stage groupings included when justified by validated data for non-anatomical factors

Evidence-based prognostication for individualization of treatment



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### Commitment to Rigor in Evaluation of New Elements

#### Levels of Evidence - Abbreviated

- I: The available evidence includes consistent results from multiple appropriate studies
- II: The available evidence is obtained from at least one appropriate study with external validation
- III: The available evidence is problematic
- IV: The available evidence is nonexistent



- Data sources
- NCDIB
  - SEER
  - Multi-institutional databases
  - International databases
  - Publications

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**The Bin Model of TNM**

Stage Groupings Are “Bins” of All the Possible Combinations of T, N, and M

**Bin Model: Each value designation of a new factor must be**

TNM Stage	Primary Tumour	Lymph Metastasis	Distant Metastasis
0	TIS	N0	M0
I	T1	N0	M0
	T2	N0	M0
II	T3	N0	M0
	T4	N0	M0
IIIA	T1,2	N1	M0
IIIB	T3,4	N1	M0
IIIC	Any T	N2	M0
IV	Any T	Any N	M1

**Bin model is inflexible: a calculator becomes a necessity**

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**Classifier vs. Calculator: Roles in Precision Medicine**

- For the 8<sup>th</sup> Edition, the Personalized Medicine Core of the AJCC offered an additional perspective: individualized prognosis and computational approaches.
- Classifiers group patients into ordered risk strata with probability-estimate cut-points.
  - TNM = a classifier with ordered strata (I, II, III, IV) of increasingly poor prognosis.
  - Classifiers are constrained by the number of categories that are manageable.
  - Classifiers are limited by the variability of prognosis of patients within a given risk class.
- Risk calculators are prognostication tools with individualized probability estimates.
  - Algorithm: designed for more precise estimate of outcome for an individual patient through computational integration of a variety of patient-specific data elements.
  - AI may be deployed for this task.

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**Analysis of Prognostication Tools: State of the Science**

PMC undertook an intensive search to locate all existing prognostication tools.

Initial observations: wide variation in quality, consistency, outcome assessed, inclusion of validation (internal or external)

PMC developed and published guidelines for prognostication tool quality.

Kattan et al. CA Can J Clin 2016; 66:370-4.

PMC evaluated all identified tools according to published quality guidelines.

Results published in 8<sup>th</sup> Edition chapters, as appropriate.

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**AJCC Endorsed Prognostication Tools**

- 30 prognostication models/tools were identified and critically reviewed.
- At that time, only two were found to have met all predefined AJCC inclusion and none of the exclusion criteria, and both have been externally validated.
  - Adjuvant! Online (currently unavailable)
  - PREDICT-Plus
- Adjuvant! Online: developed to assist decision-making about adjuvant therapy in *early-stage* disease
  - Probability estimates made according to a proprietary system
- PREDICT-Plus developed to predict outcome in women treated for *early-stage* breast cancer in the United Kingdom
  - Open system

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**Going Forward**

- AJCC encourages the development of calculators that are backed up by the AJCC content management system as the single source of truth and quality control.
- AJCC encourages the development of high-quality prognostication tools by the community using the AJCC published quality criteria will serve as a guideline.
  - Kattan MW, et. American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. CA Can J Clin 2016; 66:370-4.

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**Key Takeaways**

- The TNM staging system continues to be the single most robust prognosticator for solid malignancies.
- The TNM staging system based on anatomical factors remains fundamental to patient classification for clinical management and for research worldwide.
- The AJCC is committed to evidence-based inclusion of validated non-anatomical prognostic factors of clinical relevance to refine prognosis and support current clinical practice.
- The AJCC is committed to maintaining a framework that permits worldwide application of TNM when analysis of non-anatomical factors may not be possible.

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**Thank you**

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