Changes to the AJCC 8th Ed and the Future of Cancer Staging

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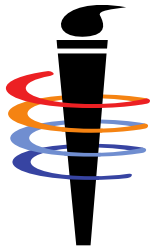


AJCC
American Joint Committee on Cancer
Validating science. Improving patient care.

Disclosures

- I have no financial disclosures relevant to this presentation
- Member of the AJCC 8th Ed Cancer Staging Manual editorial board
- Chair, AJCC

Overview of Today's Talk

- Why have a cancer staging system?
- What are the features/components of cancer staging?
- When is stage assigned?
- Who stages the cancer patient?
- Changes in the AJCC 8th Ed Cancer Staging Manual breast chapter
- Challenges in staging after neoadjuvant therapy
- Future of cancer staging
- Free AJCC resources available

Why: Staging – The Foundation of Cancer Care

- Understanding the extent of cancer, its prognosis, and impact of therapy are central to personalized care; and to improving cancer impact on society
- Staging is the common language of cancer care
  - Clinical care
    - Define extent and prognosis of cancer
    - Guide appropriate treatment
    - Basis for Guidelines
      - NCCN Guidelines all use cancer stage as a foundation for recommendation
    - Statification of patients for clinical trials

Cancer Surveillance

- Longitudinal cancer surveillance statistics (Center for Disease Control and SEER-NCI)
- measure early detection efforts - impact screening could have on the stage distribution of disease at the time of diagnosis (American Cancer Society)

New Cancer Diagnosis

Delivering the news

Delivering Bad News

Delivering Bad News

New Cancer Diagnosis – Questions Patients Ask*

- What do I have?
- How serious is it? Could I die from it?
- What are my treatment options?
- What comes next?

* If they don't ask, it is still what they are thinking

New Cancer Diagnosis – Question Patient is Told to Ask

What is my stage?

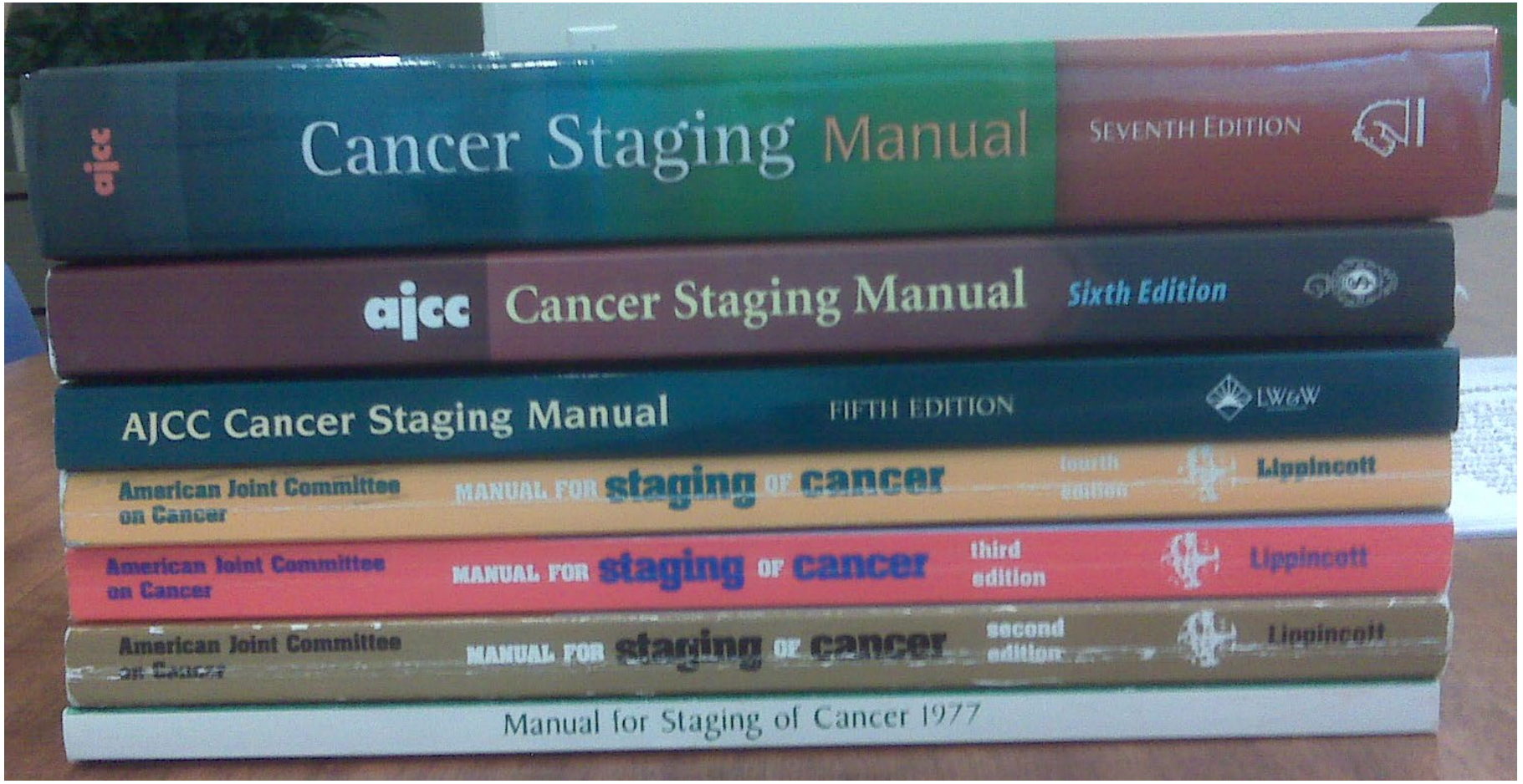
What?: Foundation of Cancer Classification

- **3 Historical axes of tumor description:**
  - Topographic site
  - Histologic type
  - Anatomic extent of disease

TNM Classification of Cancer

- **T** = primary **T**umor
- **N** = **N**odal spread
- **M** = Distant **M**etastasis

AJCC 1st through 7th Editions 1977 - 2010



Key Elements and Terminology of Staging

- STAGE: The aggregate information resulting from T, N, M
  - Anatomic groups – Anatomy only
  - Prognostic stage groups – Anatomy PLUS key non-anatomic factors

- Categories: The individual information on
  - T
  - N
  - M
  - There is no such thing as “T-Stage” or “N-Stage” – they are categories

T, N, M categories: Breast Cancer Example

Category	Description
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (DCIS)
T1mi	Tumor ≤ 0.1 cm
T1a	Tumor >0.1 – 0.5 cm
T1b	Tumor >0.5 – 1.0 cm
T1c	Tumor >1.0 – 2.0 cm
T2	Tumor >2.0 – 5.0 cm
T3	Tumor >5.0 cm
T4	Tumor invades chest wall or skin

Category	Description
Category	Description
NX	Regional nodes cannot be assessed
N0	No regional node spread
N1mi	Regional node spread; ≤0.2mm
N1	1 – 3 positive regional nodes
N2	4 – 9 positive regional nodes
N3	≥10 positive regional node Infraclavicular nodes Supraclavicular nodes Positive axillary and internal mammary nodes

Category	Description
M0	No distant metastases
M1	Distant metastases present
(There is no MX category in any TNM staging	

Stage: Groups Based on T, N, M

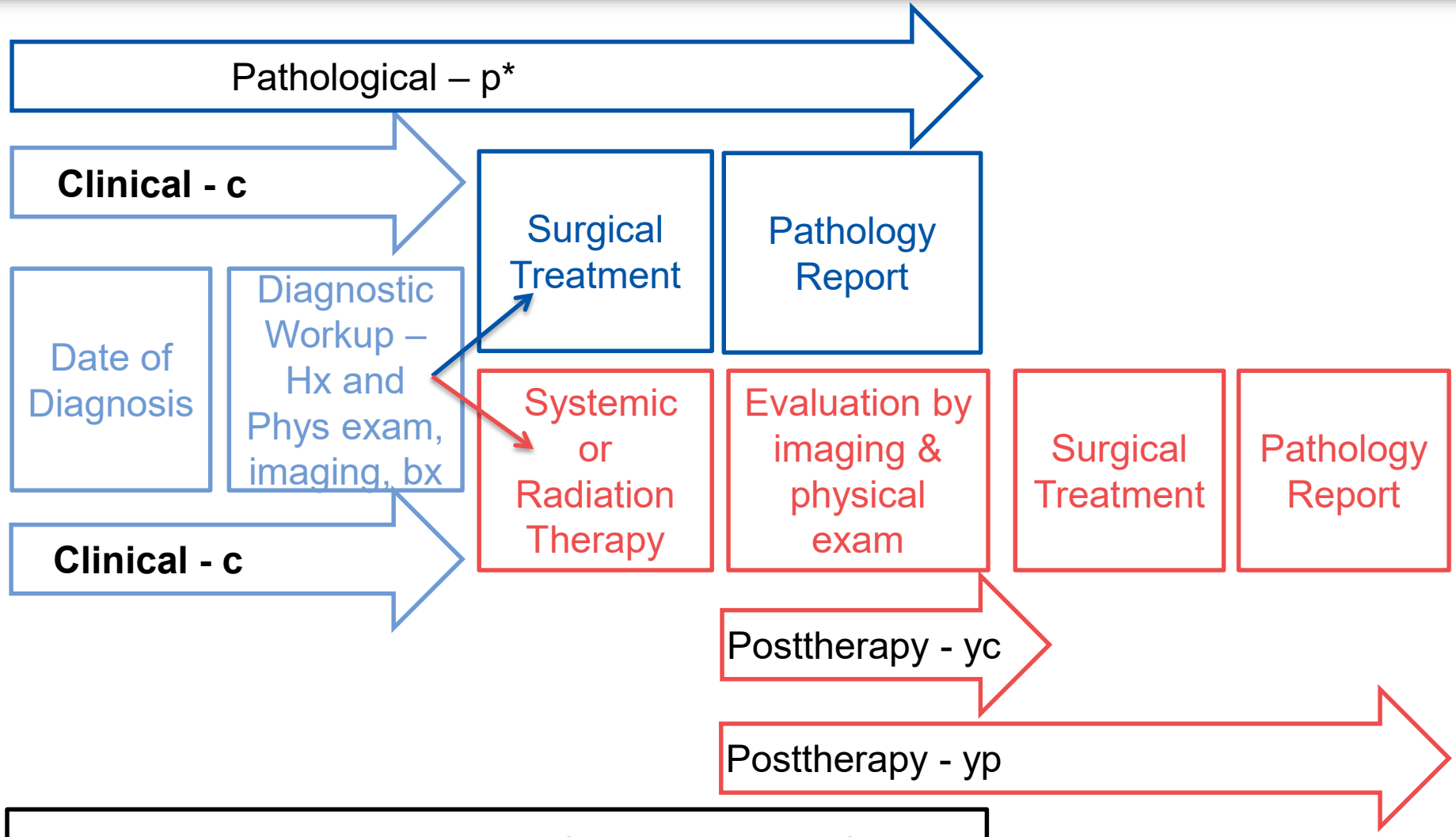
- Stage Groups defined by combinations of T, N and M for patients with generally similar prognosis
- Prognostic Stage Groups defined by similar groups of T, N, M + selected non-anatomic factors
- **In general:**

– Stage 0	non-invasive cancer
– Stage I	Small cancers; node negative
– Stage II	Larger/more extensive plus/minus positive nodes
– Stage III	Larger/extensive; increasing extent of positive nodes
– Stage IV	Cancers with distant metastases

When?: Staging Classifications – Time Points of Staging

- **Clinical**
  - Before initiation of treatment: prefix ”c” – cT, cN
  - All information from history, physical examination and imaging
  - Whatever is available – advanced imaging NOT required
- **Pathological**
  - Clinical information
  - PLUS results of surgery (if surgery initial treatment): prefix pT, pN
- **Post-therapy (post-neoadjuvant)**
  - Clinical or pathologic information after completion of systemic or radiation therapy if this treatment precedes / replaces surgery: prefix ycT; ycN, prefix ypT; ypN if surgery then performed
- Less Commonly Used:
  - Recurrent – Extent of disease at recurrence: prefix rT, rN
  - Autopsy – For cancer identified only at autopsy

Understanding Stage Classifications



•Includes post-surgery imaging if within 4 months of Dx;
in the absence of disease progression or systemic Rx or RT

Who?: Where does cancer data come from?

- Hospital Tumor Registries – abstracted chart data
  - Prior to 1992 only 38 states had state cancer registries and only 39 states reported 100% of their cancers.
- National Program of Cancer Registries (NPCR)
  - 1992 - Cancer Registries Amendment Act, Public Law 102-515 – demo, site, stage, incidence, treatment
  - 1998 - Congressional mandate Public Law (1998 Code): CDC authorized to provide funding for: set standards, provide training, develop computerized reporting systems

Who Assigns the Stage?

- Cancer providers – surgeons, medical and radiation oncologists
  - Site and clinical stage at diagnosis – cTNM
  - Treatment – surgery, chemotherapy, etc
- Pathologists – pathological stage: pTN(M, only if M1)
- Ultimately, only the managing physician has access to all the data and should assign the pTNM

Who Reports the Data?

- Cancer Registrars – NAACCR, NCRA
  - Report to:
    - National Cancer Database (NCDB)
    - State Registry
    - SEER – collects from NCI-designated centers

National Cancer Database

- National cancer outcomes database
- Begun in 1989
- Captures 70% all newly diagnosed invasive cancers in U.S.
- From registrars in 1500 CoC-approved hospitals
- Data on 26 million cancer cases

Current Dilemma of Staging Relevance

- 42F w/ 1 cm breast mass, clinically node negative
- 75F w/ 1 cm breast mass, clinically node negative

Both patients – T1b N0 M0 clinical stage IA

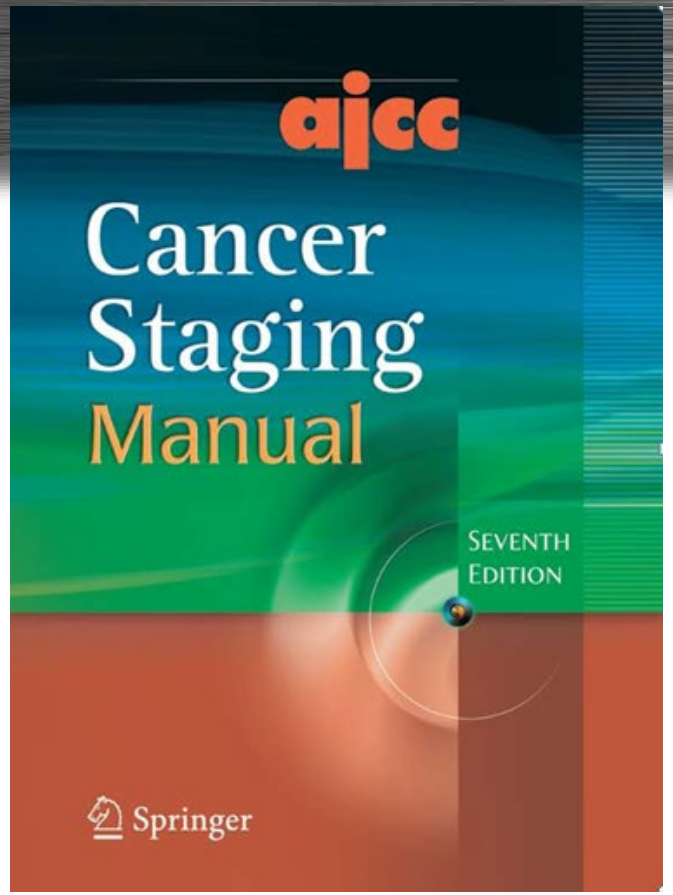
Current Dilemma of Staging Relevance

- 42F w/ 1cm breast mass, clinically node negative.
  - Core needle biopsy = Grade III IDC, ER-, PR-, Her2-
- 75F w/ 1 cm breast mass, clinically node negative
  - Core needle biopsy = Grade I tubular IDC, ER+ PR+, Her2-

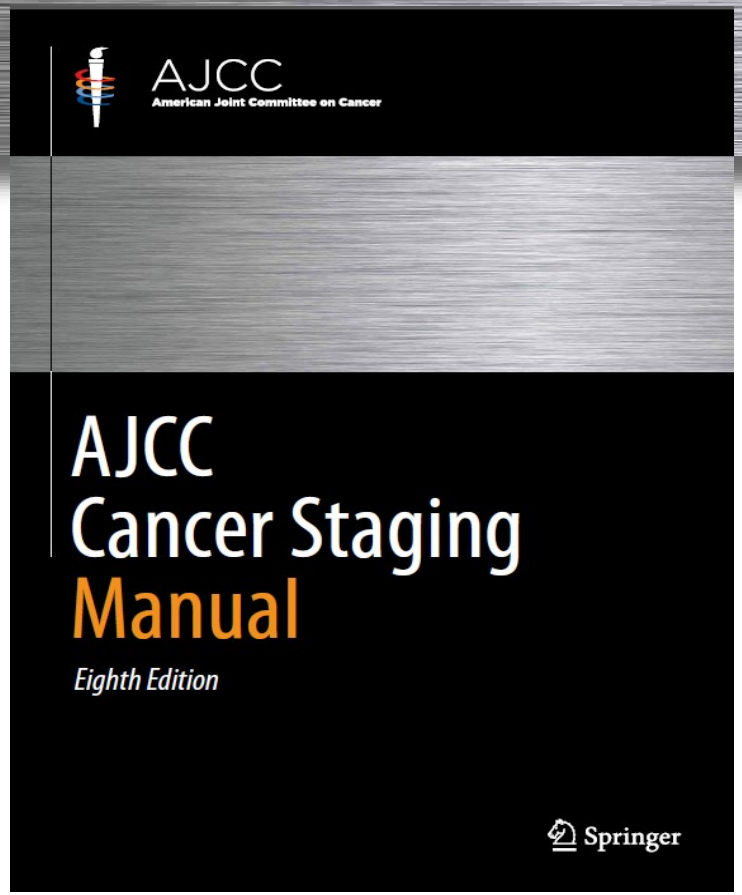
Both patients – T1b N0 M0 clinical stage IA

Most Fundamental Problem

- An individual patient is not a survival curve
- Individual cancer treatment outcome is binomial:
  - Cancer recurs
  - Cancer never recurs

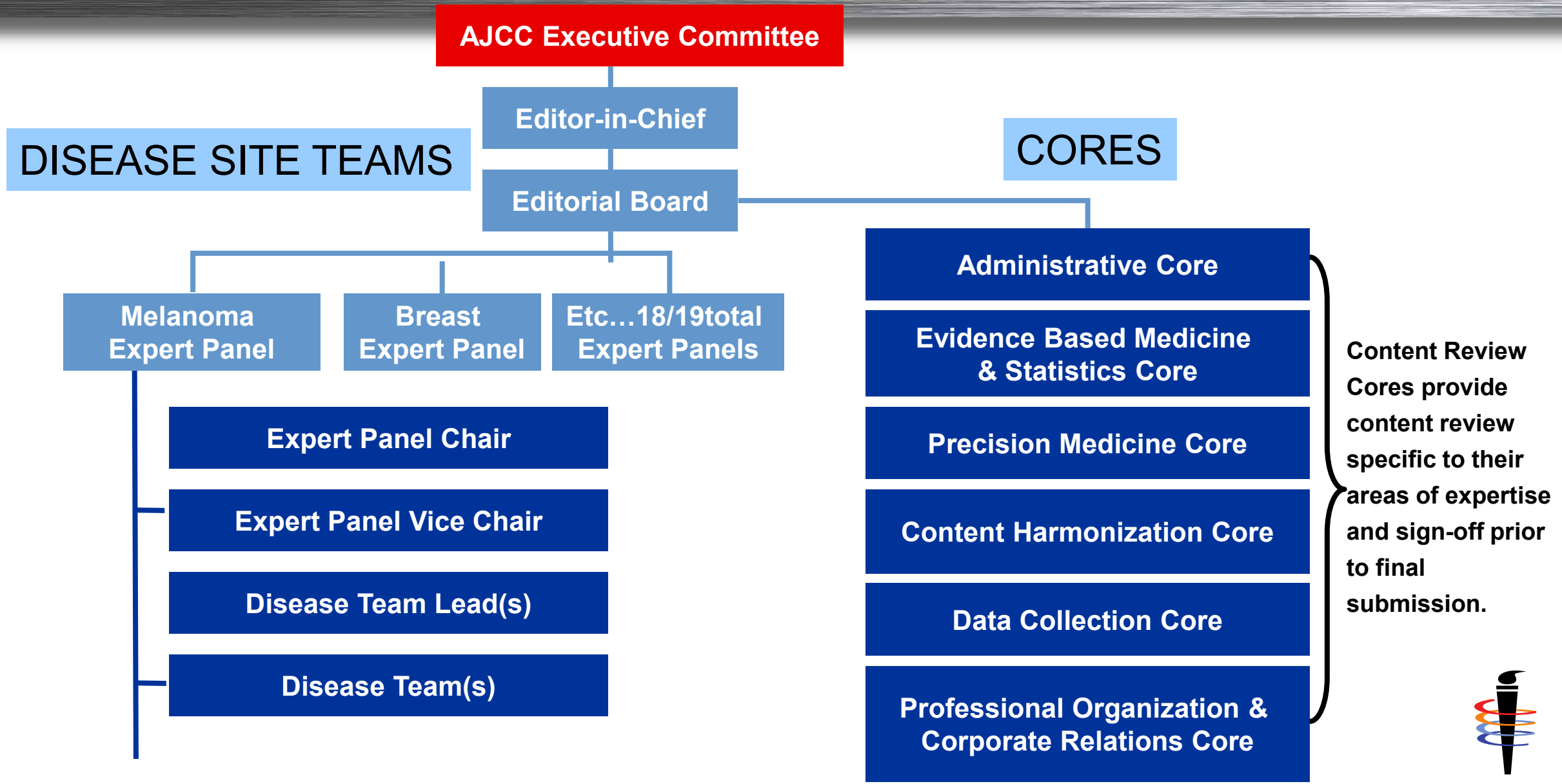


- 3-Year Project
- 57 Chapters
- 16 Task Forces
- 266 individuals from
  - 5 continents
  - 11 countries



- 3-Year Project
- 83 Chapters
- 18 Expert Panels + 7 Cores
- 430 individuals from
  - 6 continents
  - 22 countries
  - 184 institutions

8th Edition Editorial Organization & Structure



Chapter 1 - Staging Rules

- Team of 15 physicians and 1 registrar reviewed Chapter 1, line by line over 2 years
- Harmonization Summit September 2015
  - Full day for vetting staging rules
  - Approximately 60 physicians in attendance
  - Registrars also participated
- Final chapter considerably expanded, reviewed/edited by 8 physicians

- 7th Edition chapter: 11 pages

- 8th Edition chapter: 28 pages

8th Ed New Features

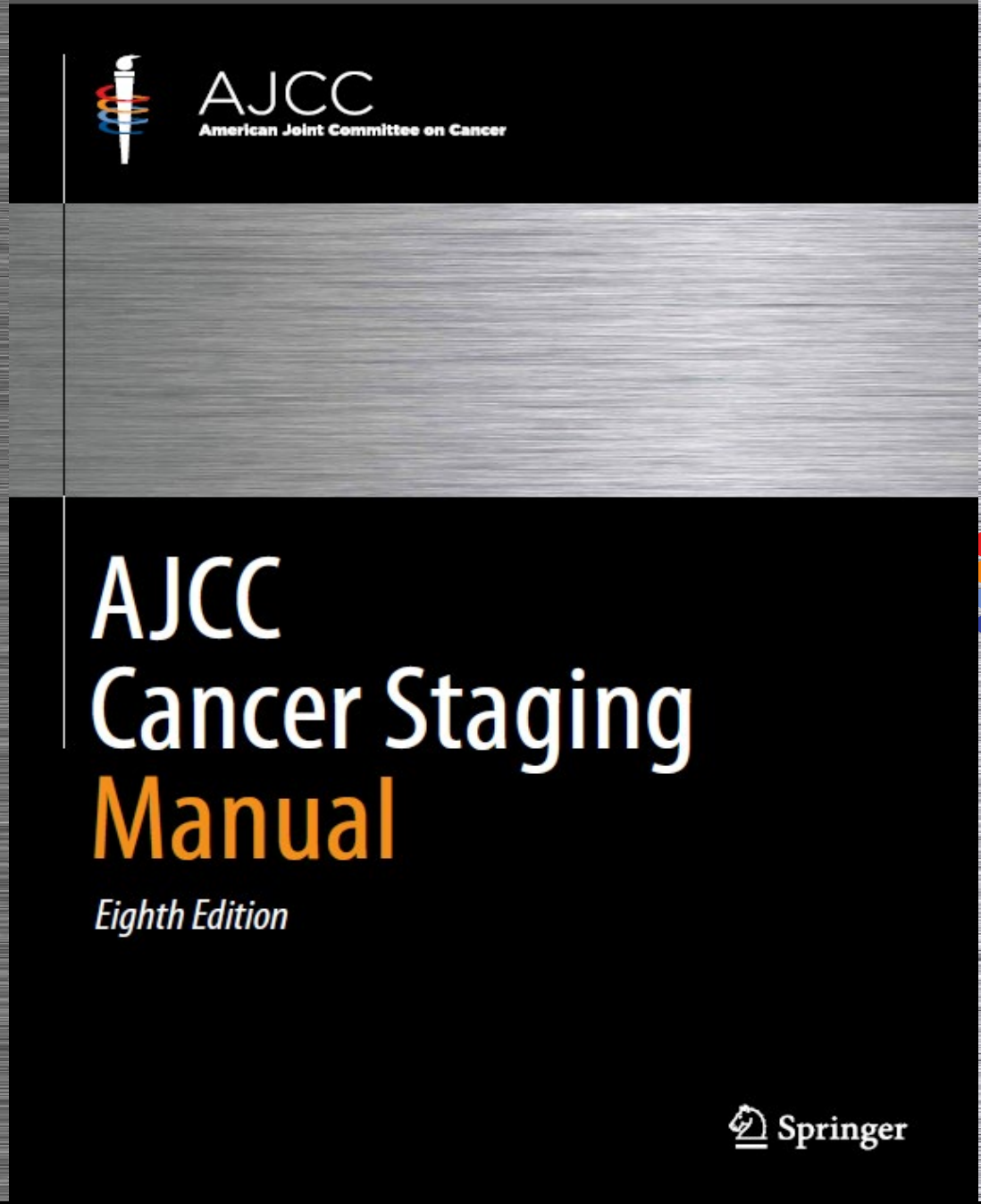
- Levels of Evidence (LOE) provided when revisions to staging systems are made
- Imaging section
- Risk Assessment Models for select cancer sites
- Recommendations for Clinical Trial Stratification (web only)
- Prognostic factors
  - Required for prognostic stage grouping
  - Recommended for clinical care
  - Emerging factors (web only)

The 8th Edition

Published Late 2016

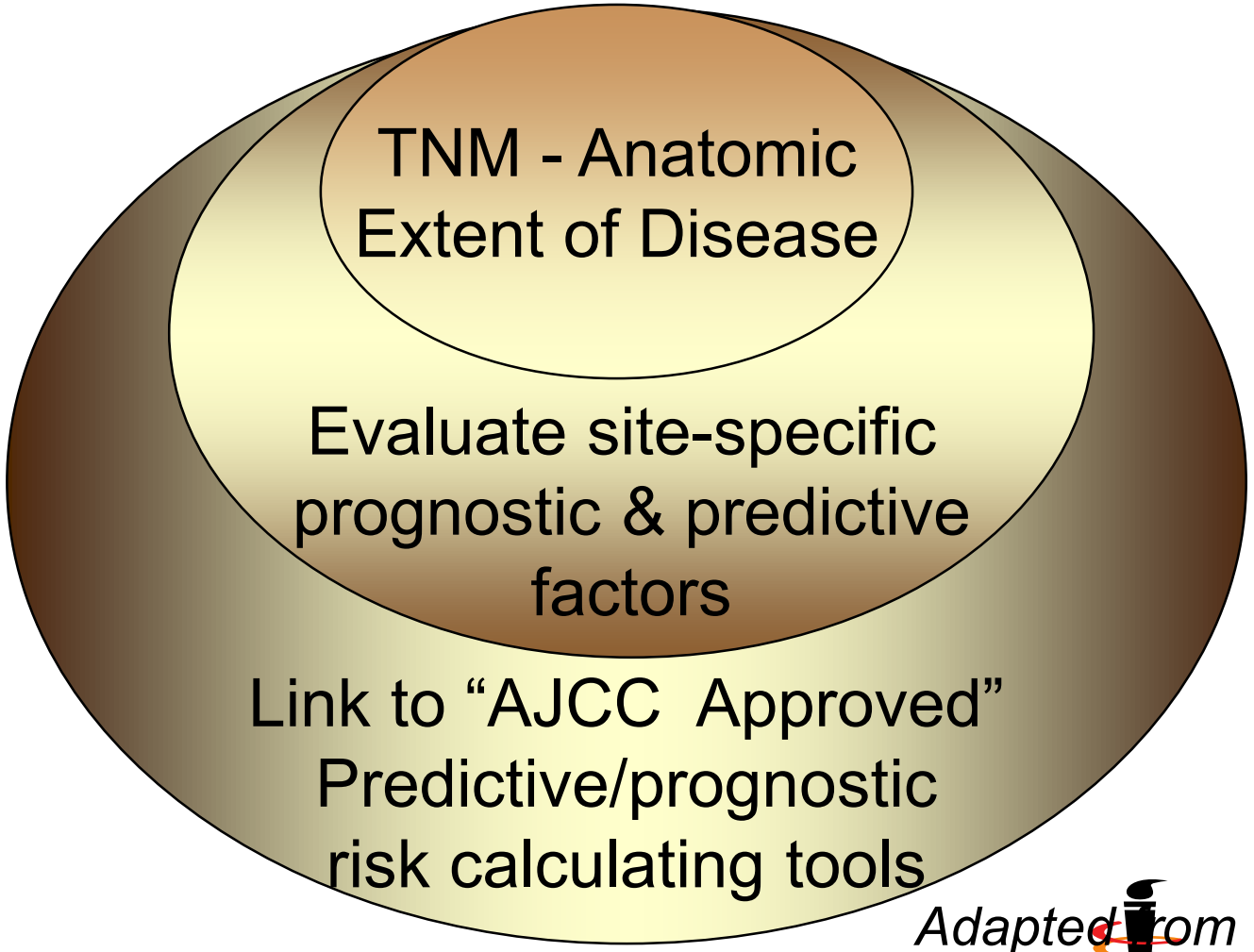
Breast Updated
November 2017

Effective for Cases
Dx'd 1/1/2018



American Joint Committee on Cancer (AJCC) 8th ed. Editorial Board Strategy

- Maintain anatomic extent of disease - TNM foundation
- Incorporate evidence-based non-anatomic factors, including molecular markers
- Era of precision medicine → evolution from a "population based" to a "more personalized" approach
- "One size fits all" model does not exist



Adapted from Mahul Amin

AJCC Cancer Staging Manual. 8th Ed. New York: Springer; 2017

Limitations of Anatomic Staging

- Anatomic stage alone does not meet the needs of patients

- Rapid evolution in understanding cancer biology has made other factors beyond anatomy as or MORE important in defining prognosis; and in defining optimal therapy

Staging Needs to Be Relevant to Practice

- Anatomic staging valuable but not always sufficient
  - Many cancer types do not have validated non-anatomic factors to modify anatomic state
  - Advanced cancer characterization and biomarker determination not available in many parts of the world
- Providers use other information
  - Biomarkers / subtypes
  - Genomic profiling
  - Specific molecular targets
- “Staging” must incorporate new information beyond anatomy to remain relevant and useful

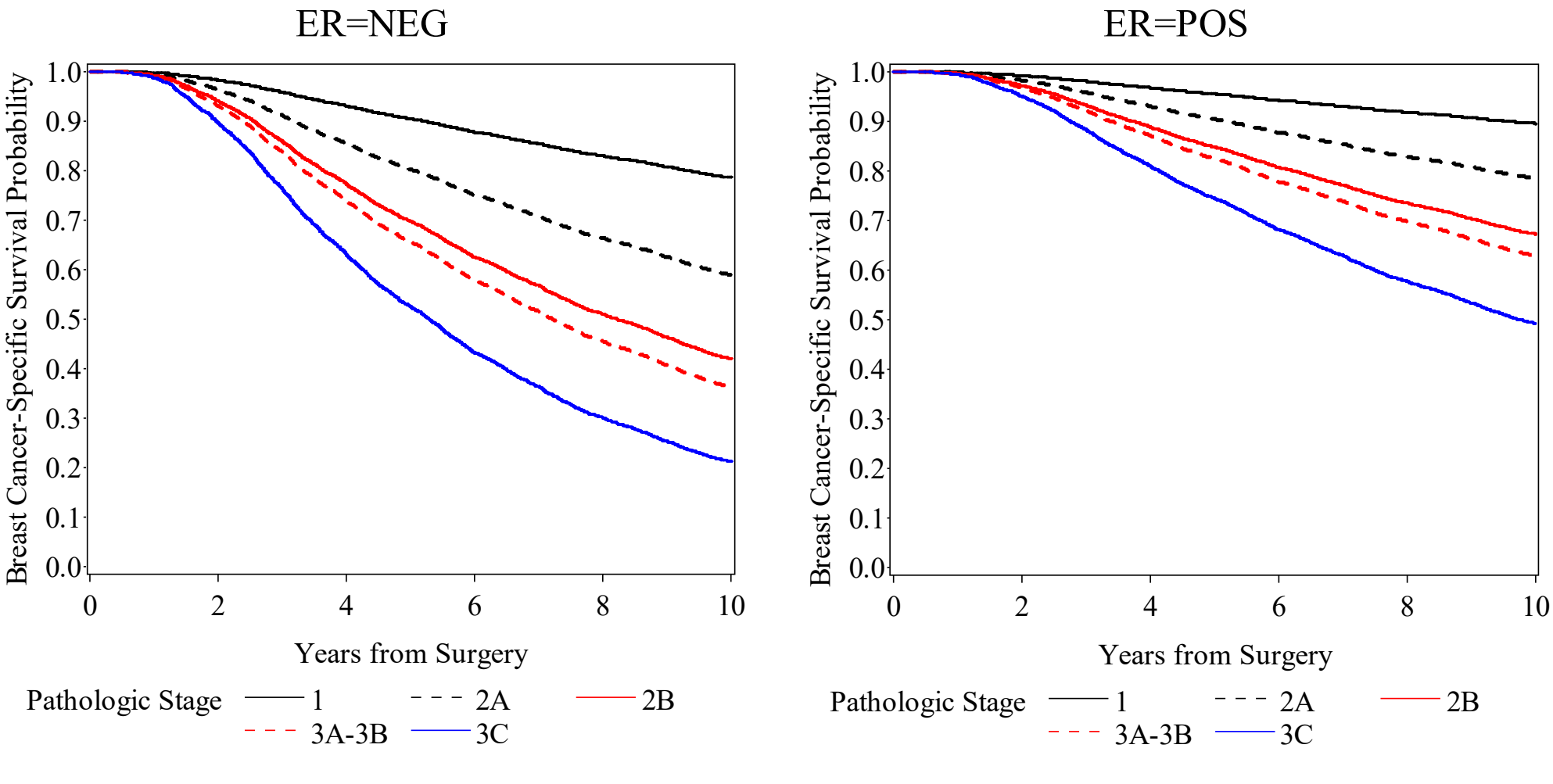
Evolution of Anatomic to AJCC "Prognostic" Staging

- Non-anatomic factors in AJCC TNM since inception
  - Soft tissue sarcoma – grade included in 1st Edition AJCC Manual
  - Bone – grade including in 2nd Edition AJCC Manual
  - Thyroid – Age and histologic type included in 2nd Edition Manual
- Beginning in the 6th and 7th Editions of AJCC Staging, marked increase in use of non-anatomic factors incorporated to defining Stage Groups
- Non-anatomic factors used primarily to modify anatomic stage
- Maintain ability to derive pure anatomic stage
  - Comparisons over time
  - Allow use of stage around the world as the common language of cancer – even where it is not possible to obtain non-anatomic information

Changes in 8th Ed Breast Cancer Staging

- Biology trumps anatomical extent
- Both are important!

Cox regression 10-year breast cancer specific survival estimates by pathologic stage and ER status

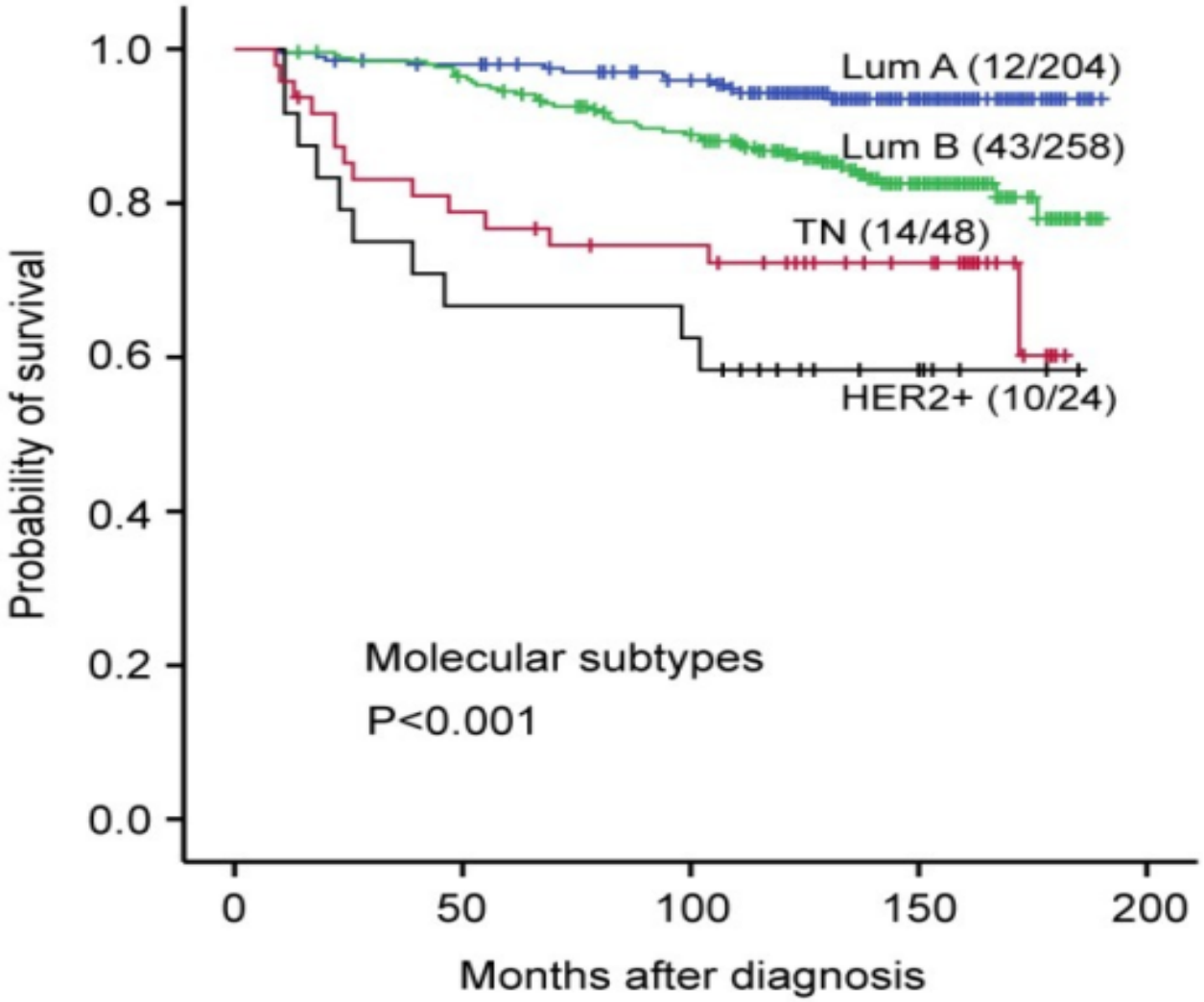


Breast Cancer Molecular Subtypes are Central to Prognosis and Treatment:

Current usage based primarily on ER, PR, HER2 expression

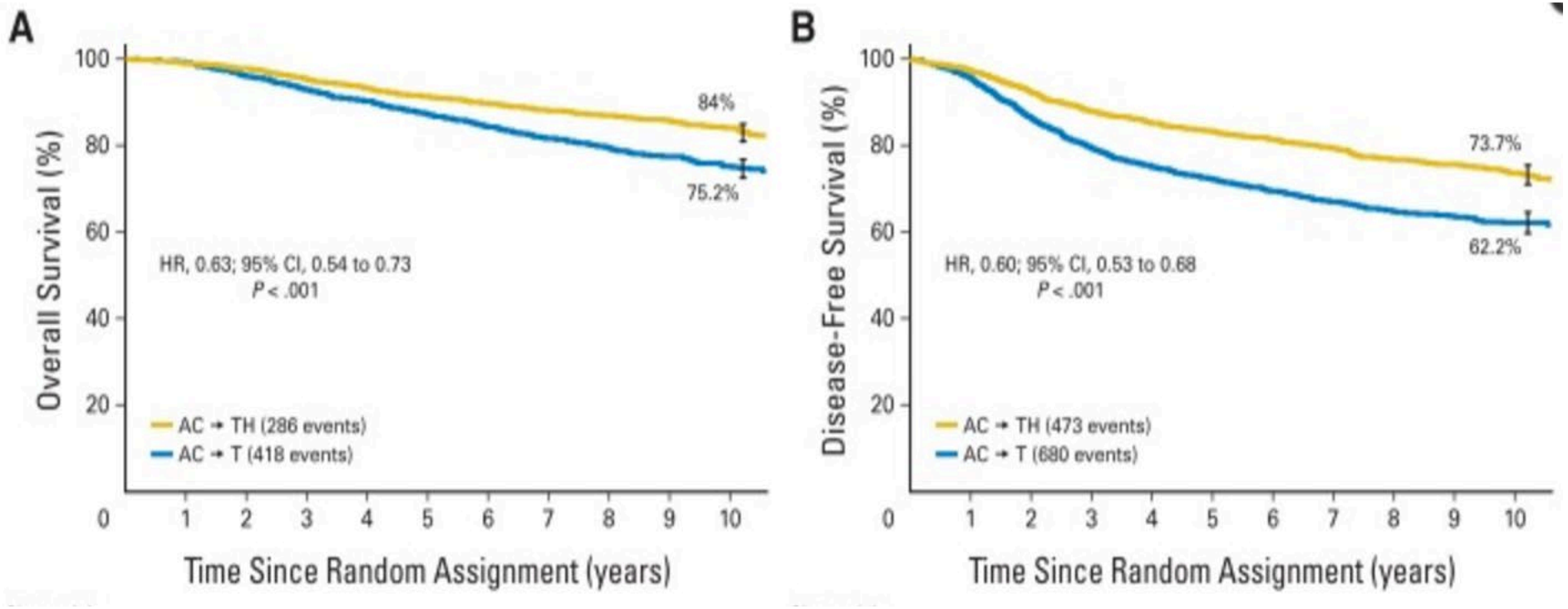
Subtype	Characteristics
Luminal A	ER(+) &/or PR(+); HER2 (-)
Luminal B	ER(+) &/or PR(+); HER2 (+)
HER2	ER(-), PR(-); HER2(+)
Basal-Like	ER(-); PR(-); HER2 (-)

Breast Cancer Survival by Subtype



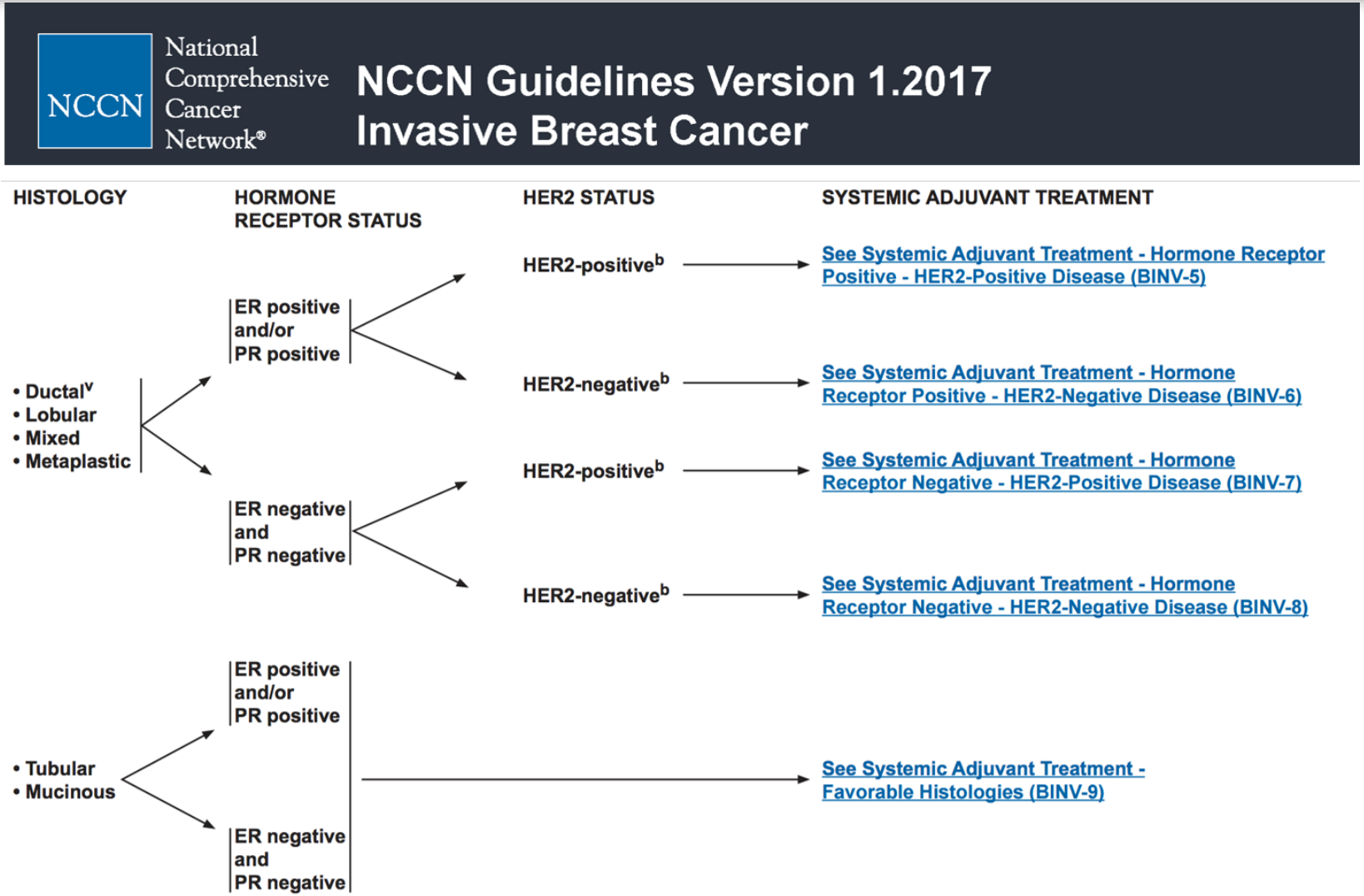
Knutsvik G, Stefansson IM, Aziz S, Arnes J, Eide J, Collett K, Akslen LA - PLoS ONE (2014)

Treatment Also Defined by Biomarkers: Impact of Trastuzumab in HER2(+) Breast Cancer



Perez EA et al. J Clin Oncol 2014;32(33):3744

Anatomic Stage Insufficient for Treatment Decisions



Major Changes in Breast Cancer Staging with 8th Edition

- Lobular carcinoma in situ (LCIS) no longer included in AJCC Staging
  - LCIS is a “benign” entity and not cancer
  - Should not be in a cancer staging system
  - Issue with “pleomorphic” LCIS – but insufficient data available
- Prognostic Staging – Incorporation of Grade, HER2, ER, PR
- Incorporation of genomic profiling to assign pathological prognostic stage group

Evolution to Prognostic Staging: Breast Cancer

- The AJCC 8th Edition Breast Staging incorporates key prognostic factors into the primary staging
  - Anatomic stage groups still maintained
    - Clinical Stage
    - When biomarkers not available.
- "Prognostic Stage" will the the primary stage recorded in cancer registries in the United States
- Requires:
  - T; N; M
  - Grade; HER2; Estrogen Receptor; Progesterone Receptor
  - Genomic profiles (OncotypeDx™) as appropriate

Evolution to Prognostic Staging: Breast Cancer

- The AJCC 8th Edition Breast Staging incorporates key prognostic factors into the primary staging
  - Anatomic stage groups still maintained for use in areas of world where biomarkers are not available.
- "Prognostic Stage" will the the primary stage recorded in cancer registries in the United States
  - Decision made on 2 separate studies
    - E Mittendorf – Using MDACC dat
    - DJ Winchester – Using NCDB
  - Final changes based on NCDB analysis
- Requires:
  - T; N; M
  - Grade; HER2; Estrogen Receptor; Progesterone Receptor

NCDB Analysis: Survival Range for Assignment to Prognostic Stage Group

- NCDB Analysis of cases Dx 2010-2012
- Complete biomarker data
- Survival ranges defined for each stage group
- Group assigned based on survival; not anatomy

	Clinical Stage		Pathologic stage		
AJCC 7th Edition Stage	N	3-Year Overall Survival	N	3-Year Overall Survival	Designated Survival Range for New Schema
IA	195,045	95.1%	170,876	96.2%	94-100%
IB	2,648	94.7%	9,107	95.8%	92-<94%
IIA	79,783	90.3%	69,679	93.3%	88-<92%
IIB	29,473	87.0%	29,273	90.8%	85-<88%
IIIA	14,142	83.1%	17,206	87.9%	80-<85%
IIIB	8,865	69.8%	2,166	68.6%	70-<80%
IIIC	4,299	72.3%	7,023	78.7%	<70%

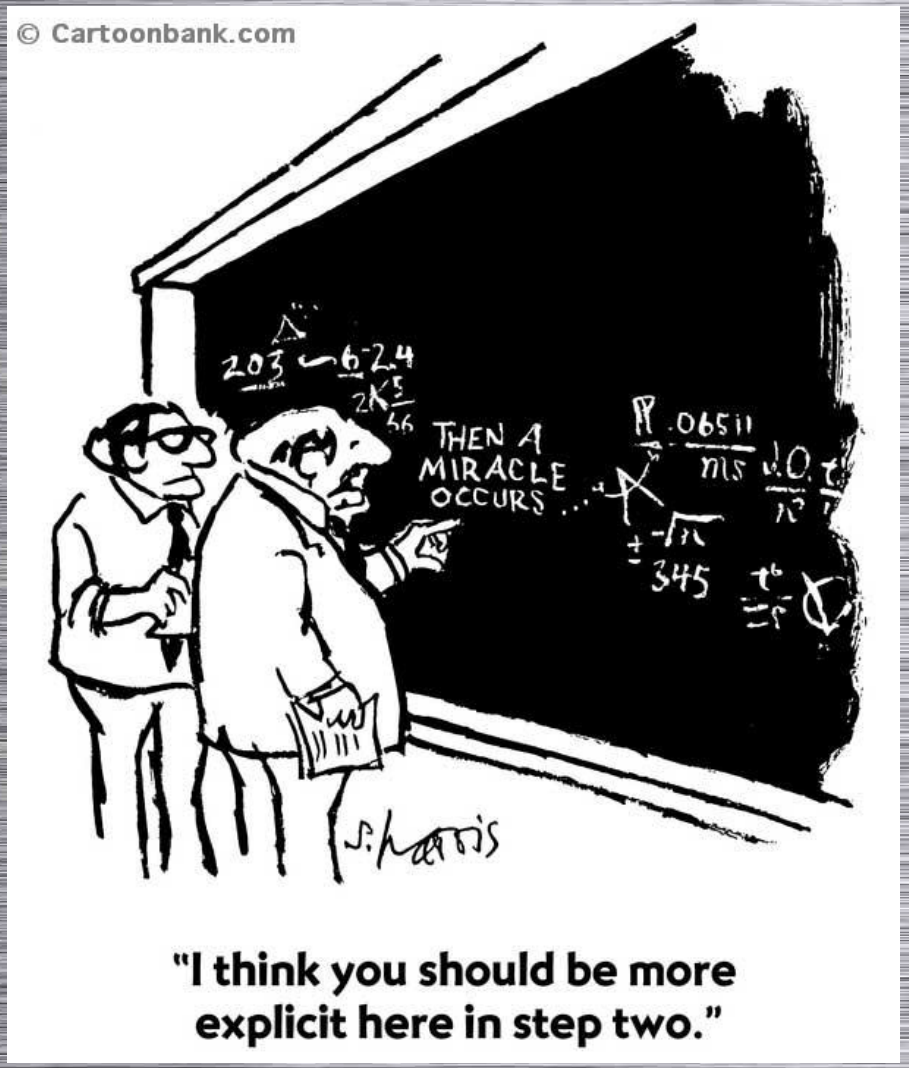
Example: Prognostic Staging Groupings

- Separate tables for clinical and pathological prognostic staging
- Complex, cumbersome
- Clinically relevant
- Calculator needed and available

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Clinical Prognostic Stage Group is…
T2 N1 MO T3 N0 M0	1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIB
	3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB

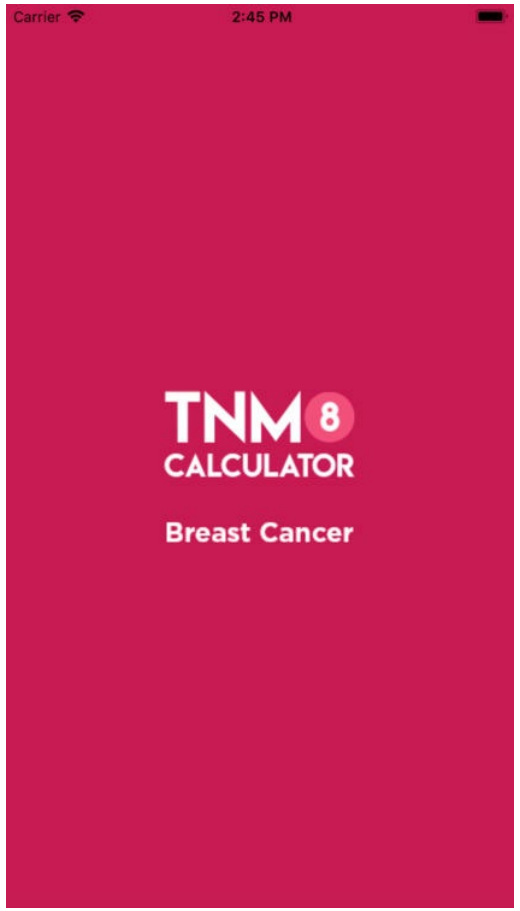
Implementing Prognostic Stage in Practice

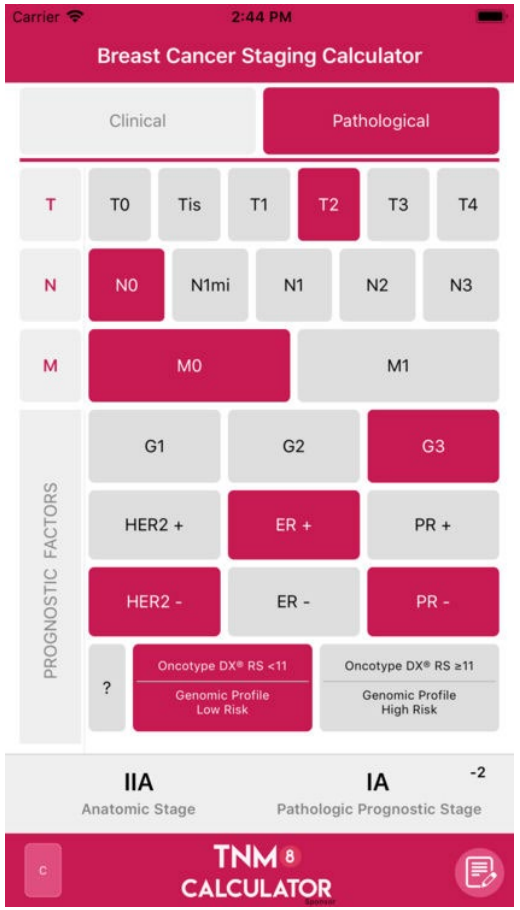
Cannot memorize tables!!



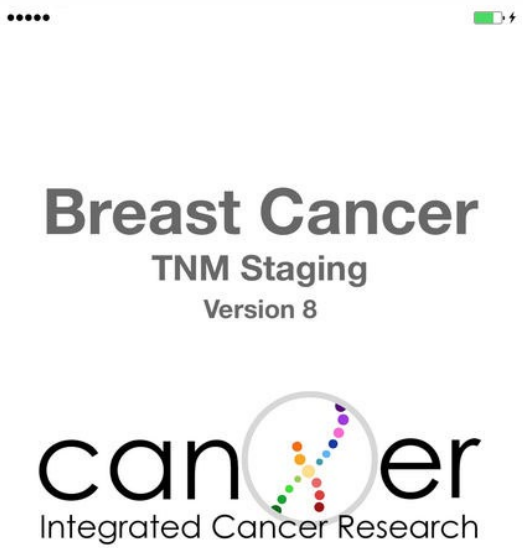
Two Staging Calculators – Available at App Store

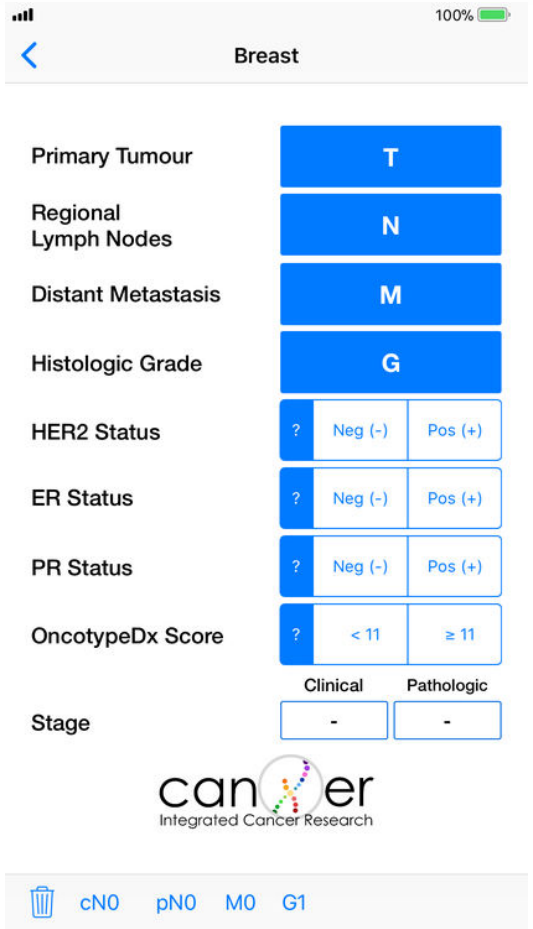
*** I am not endorsing nor have any interest in any software tool**





TNM8 Breast Cancer Calculator





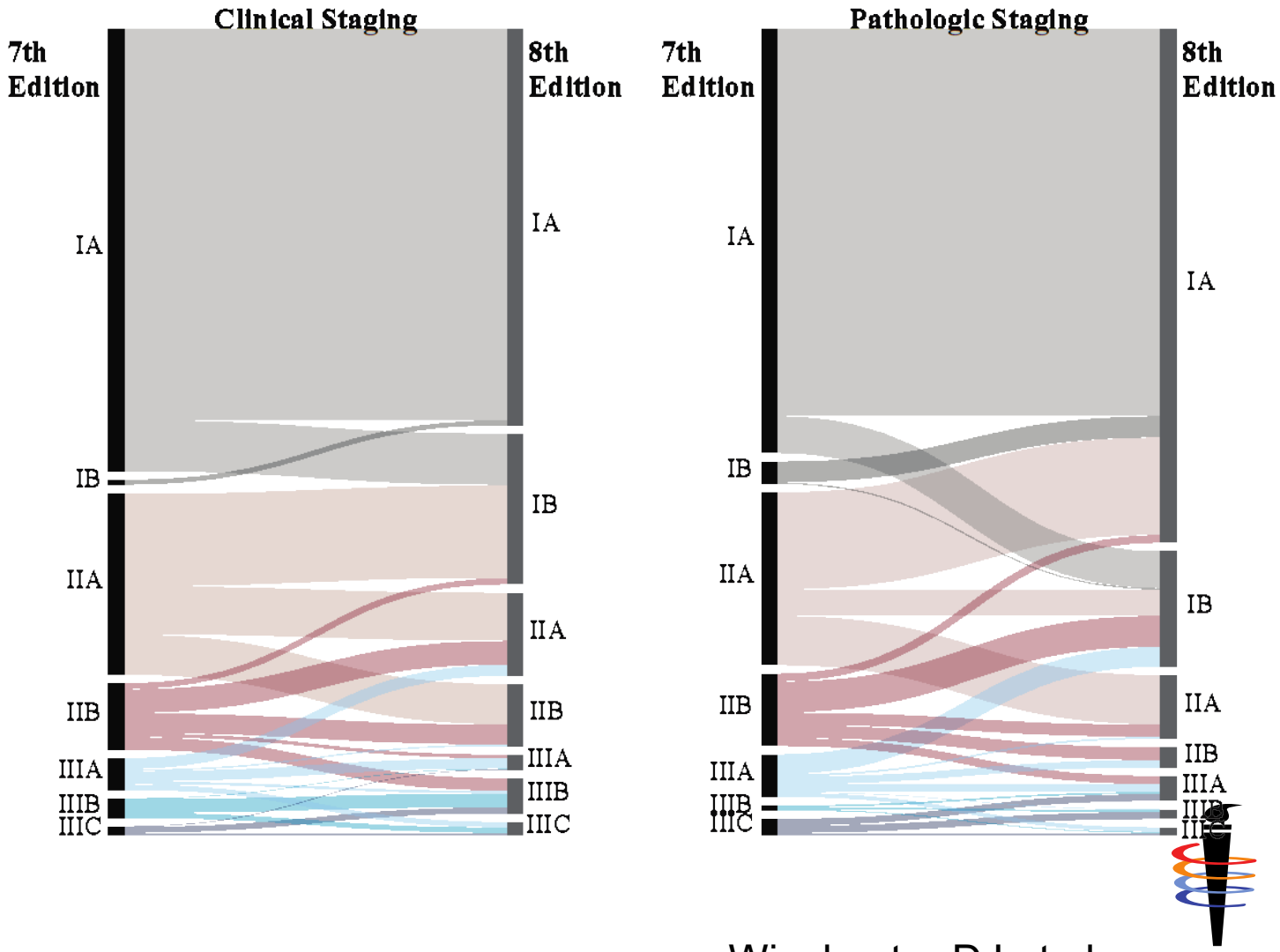
Breast cancer Staging TNM8 Integrated Cancer Research Ltd

Stage Reassignments with Prognostic Staging

- Addition of key biomarkers changes stage groups compared to anatomic staging.

- Clinical: 36% reassigned
  - 20% downstaged
  - 16% upstaged

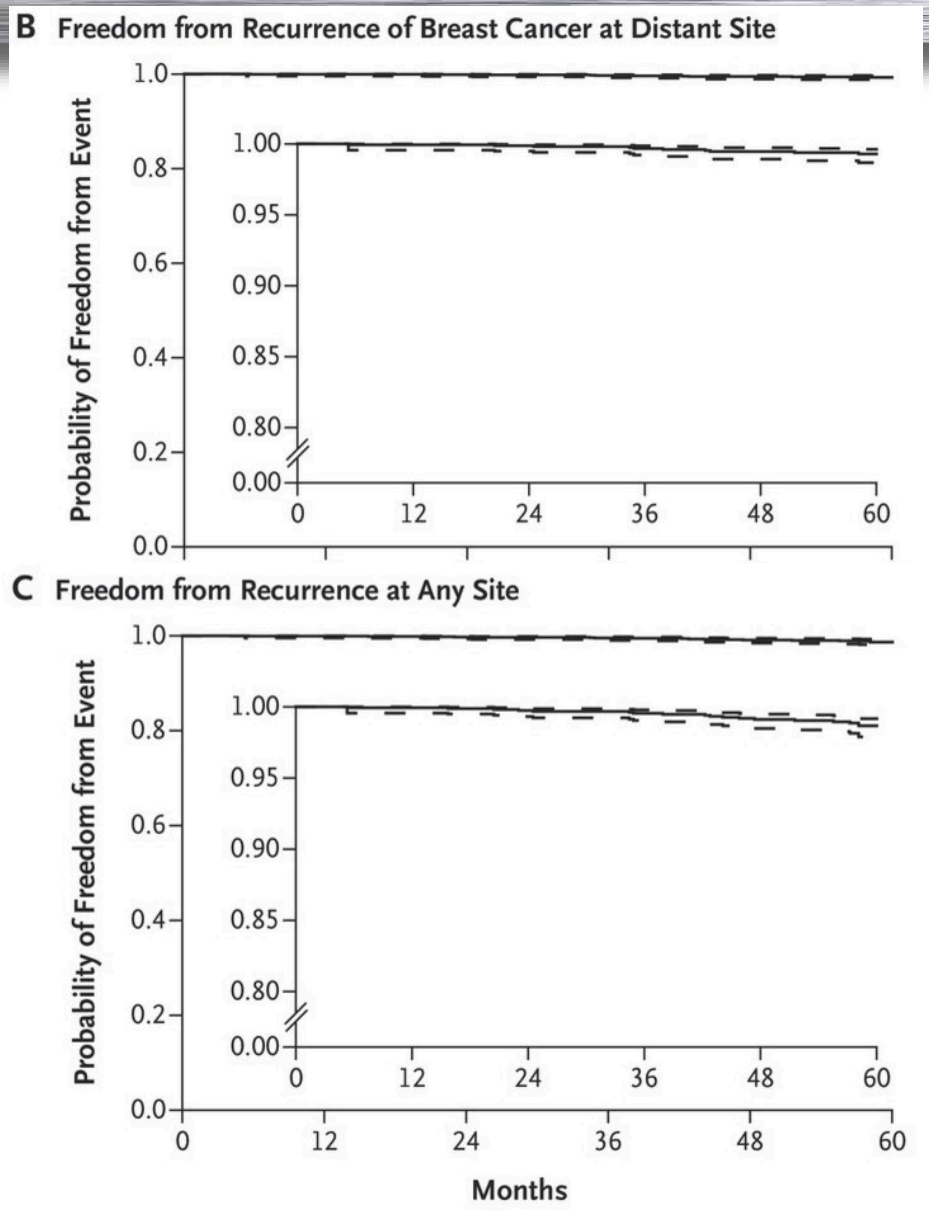
- Pathological – 39% reassigned



Winchester DJ et al

Genomic Profiles: Inclusion Based on Level I Evidence

- Breast panel included low risk findings on genomic profiles with Level I Evidence
  - Classify appropriate cases as Stage IA
- As of time of printing (early August 2016) only 21 Gene Recurrence Score (OncotypeDx™) had Level I Evidence supporting: T1-T2 N0 M0 ER(+) HER2(-); RS <11 – Stage Group IA
- Debate on including other profiles
  - Mammaprint – Based on MINDACT data published late August 2016
  - Others



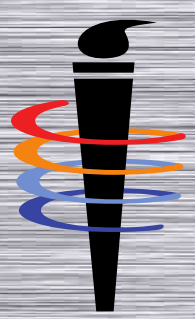
Sparano JA et al. NEJM 2015;373:2005

Selection of Genomic Profiles for Use in Clinical Care

The AJCC determined to include OncotypeDx in assigned Stage IA to T1-2 N0 ER+ HER2- RS<11; but recognizes that other profiles may be useful in clinical management.

The AJCC Manual is NOT a practice guideline and the Expert Panel is NOT a guideline developer. Physicians are to use the best information available at the time to plan treatment, including the determination to use (one or several) genomic panels, and which genomic panel to select.

Post Neoadjuvant Therapy Classification



AJCC 8th Edition Staging: 1-Page Guide

POST NEOADJUVANT THERAPY STAGING CLASSIFICATION RULES

- yc Clinical
  - Includes physical exam and imaging assessment
  - *After* neoadjuvant systemic/radiation therapy

- yp Pathological
  - Includes all information from yc staging,
  - Surgeon's operative findings and
  - Pathology report from resected specimen

Post Neoadjuvant Therapy Staging

- Assigned after neoadjuvant therapy and surgical resection

- ypT category
  - Largest focus of residual tumor
  - Treatment-related fibrosis near invasive tumor NOT used
  - Multiple foci of residual tumor, use (m)

- ypN category
  - Largest focus of residual tumor in nodes
  - Treatment-related fibrosis near nodal tumor deposits NOT used

- M category
  - If M1 prior to therapy, remains M1 following neoadjuvant therapy
  - Regardless of observed response to therapy

- Assign degree of response to therapy

Stage Group Exceptions

Breast

- Clinical stage group table
- Pathological stage group table
- NO stage group assignment for posttherapy (yp)
  - Must record ypT ypN cM Grade

Neoadjuvant Response

- cT2 cN1 cM0 invasive ductal breast cancer. Neoadjuvant chemo 6 cycles followed by MRM w/axillary dissection. Pathology report is no residual tumor, nodes negative.
- Neoadjuvant therapy destroyed all tumor, complete pathological response
- ypT0 ypN0 cM0 stage 99
- Entered into new data item for posttherapy staging
- Reminder - must meet criteria for neoadjuvant

Posttherapy Classification Assignment

- Posttherapy classification assigned **regardless** of response

- Always assign ypT ypN cM
  - Does **NOT** depend on response to treatment
  - Even if pt responds completely, no evidence of tumor
  - Even if pt has partial response, tumor or nodes shrink
  - Even if pt did not respond, tumor/nodes stayed the same
  - Even if pt did not respond, tumor/nodes grew while on treatment
    - Not considered progression that stops staging
    - Not considered progression that makes surgery subsequent treatment

Colorectal Staging Tables – 8th Ed

AJCC PROGNOSTIC STAGE GROUPS

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1–T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3–T4a	N1/N1c	M0	IIIB
T2–T3	N2a	M0	IIIB
T1–T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3–T4a	N2b	M0	IIIC
T4b	N1–N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

AJCC Cancer Staging Manual. 8th Ed. New York: Springer; 2017

Esophagus – Adenocarcinoma 8th Ed Staging Tables

Clinical (cTNM) (Fig. 16.9)

When cT is…	And cN is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T1	N1	M0	IIA
T2	N0	M0	IIB
T2	N1	M0	III
T3	N0–1	M0	III
T4a	N0–1	M0	III
T1–4a	N2	M0	IVA
T4b	N0–2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Pathological (pTNM) (Fig. 16.10)

When pT is…	And pN is…	And M is…	And G is…	Then the stage group is…
Tis	N0	M0	N/A	0
T1a	N0	M0	G1	IA
T1a	N0	M0	GX	IA
T1a	N0	M0	G2	IB
T1b	N0	M0	G1–2	IB
T1b	N0	M0	GX	IB
T1	N0	M0	G3	IC
T2	N0	M0	G1–2	IC
T2	N0	M0	G3	IIA
T2	N0	M0	GX	IIA
T1	N1	M0	Any	IIB
T3	N0	M0	Any	IIB
T1	N2	M0	Any	IIIA
T2	N1	M0	Any	IIIA
T2	N2	M0	Any	IIIB
T3	N1–2	M0	Any	IIIB
T4a	N0–1	M0	Any	IIIB
T4a	N2	M0	Any	IVA
T4b	N0–2	M0	Any	IVA
Any T	N3	M0	Any	IVA
Any T	Any N	M1	Any	IVB

Postneoadjuvant Therapy (ypTNM) (Fig. 16.11)

When yp T is…	And yp N is…	And M is…	Then the stage group is…
T0–2	N0	M0	I
T3	N0	M0	II
T0–2	N1	M0	IIIA
T3	N1	M0	IIIB
T0–3	N2	M0	IIIB
T4a	N0	M0	IIIB
T4a	N1–2	M0	IVA
T4a	NX	M0	IVA
T4b	N0–2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

AJCC Cancer Staging Manual. 8th Ed. New York: Springer; 2017

8th Edition API

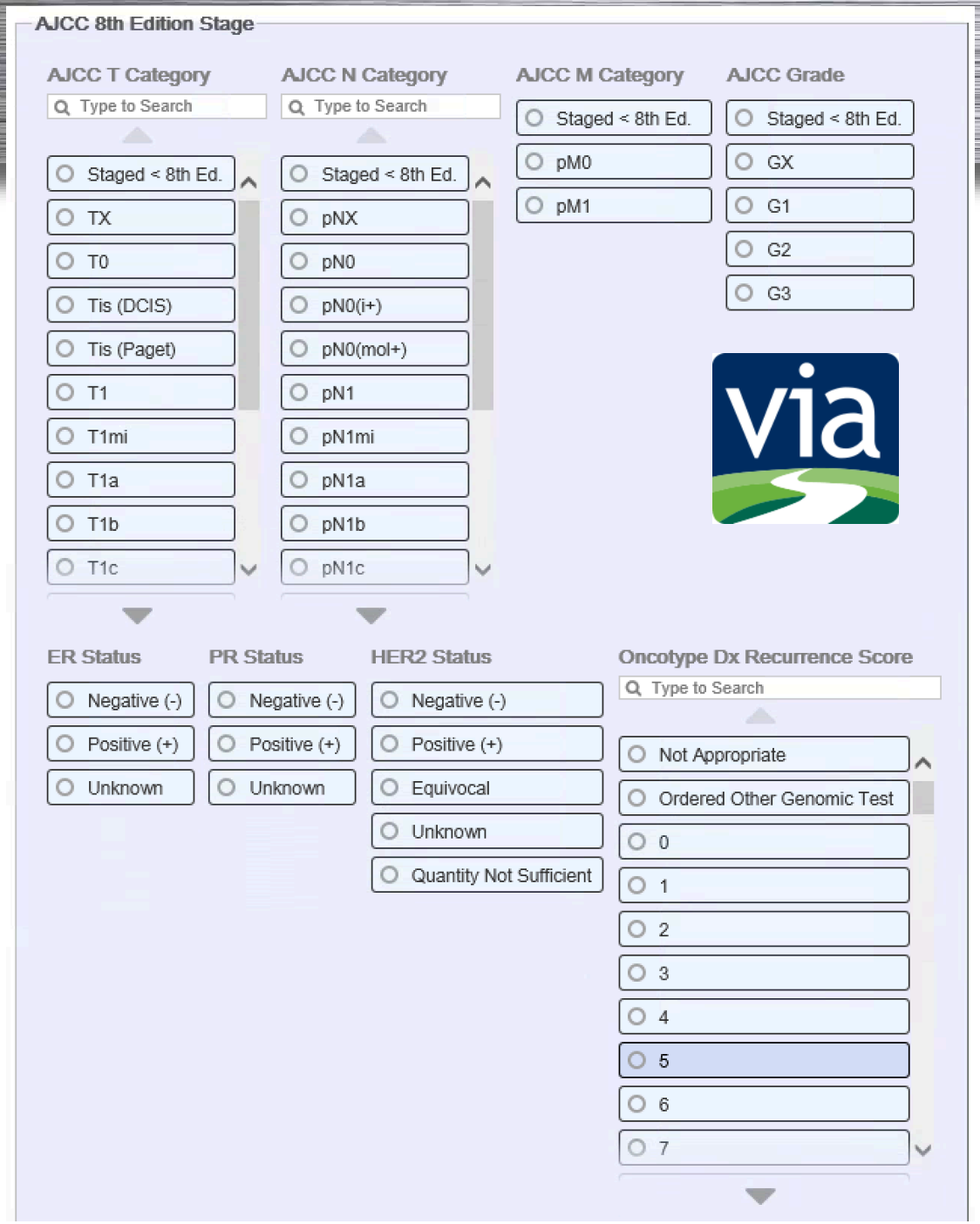
- License and deliver content professional organizations that need to update their products based on AJCC content
  - UICC: TNM + Stage groups for TNM manual
  - CAP: cancer protocols
  - NCCN: clinical practice guidelines
  - ASCO: CancerLinQ
  - American Cancer Society: patient education
  - Standard setters and registry software developers
- Content being made available to vendors through API (currently being validated by registry vendors)

Incorporation into Daily Work Flow

- Staging must be incorporated into EHR's
- Electronic data capture of key elements to present to managing physician to define final stage assignment
- Integrate with oncology care pathways to define therapy
- Include biologic / genomic data for individual cases
- Incorporate into tools to assist patients with understanding and assisting with treatment decisions

Staging Calculators in Medical Records Systems

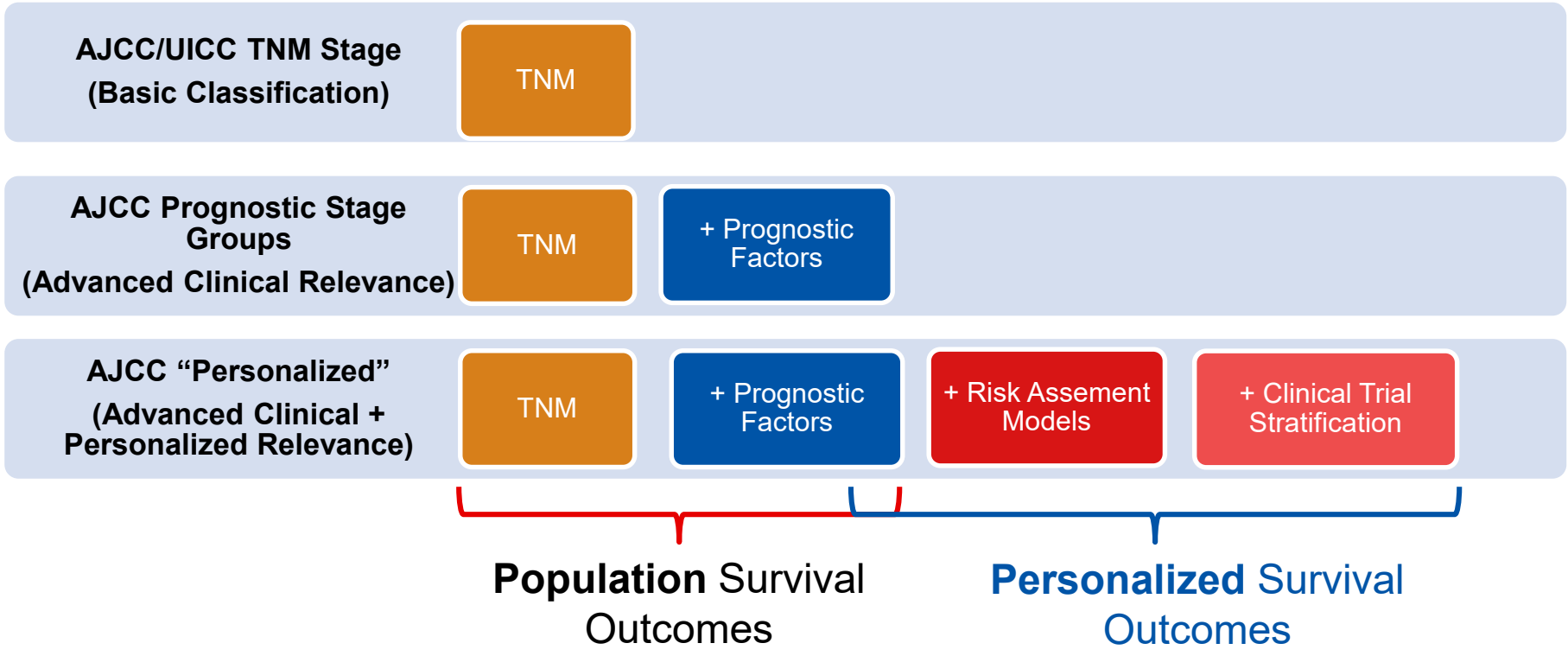
- AJCC licensing its Application Program Interface to EHR and pathway systems
- Direct entry by provider
  - Records and documentation
  - Decision support
- Example: Pathological staging screen from VIA Oncology Pathways



AJCC Vision – Evolution to Prognostic Staging

The Transition from Population Based to a more "Personalized" Approach

Cancer Stage → **Comprehensive Cancer Profile**



E-Book AJCC 8th Ed Cancer Staging Manual – available as Kindle version on Amazon

AJCC Free Resources – www.cancerstaging.org

- Cancer Staging forms
- Chapter 1 – rules of cancer staging (under Cancer Staging Resources tab)
- Entire new breast chapter – revised in 2017
- Breast staging webinar – Dr. Gabriel Hortobagyi
- Physician webinars on colorectal, melanoma, gynecological, lung, prostate, breast, head & neck, changes to the 8th Ed (education tab, click physician)
- registrar webinars
- Staging moments – beginning of 2019