

Prognostic and Predictive Factors

Invasive breast carcinoma

Disease extent • tumor biology • therapeutic vulnerability

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Distinguish prognostic from treatment-predictive information.
- Interpret anatomic extent, grade, subtype, and biomarker findings.
- Relate treatment response and actionable alterations to clinical decisions.
- Integrate these variables without treating any single factor as destiny.

Outcome depends on two complementary dimensions

Disease extent

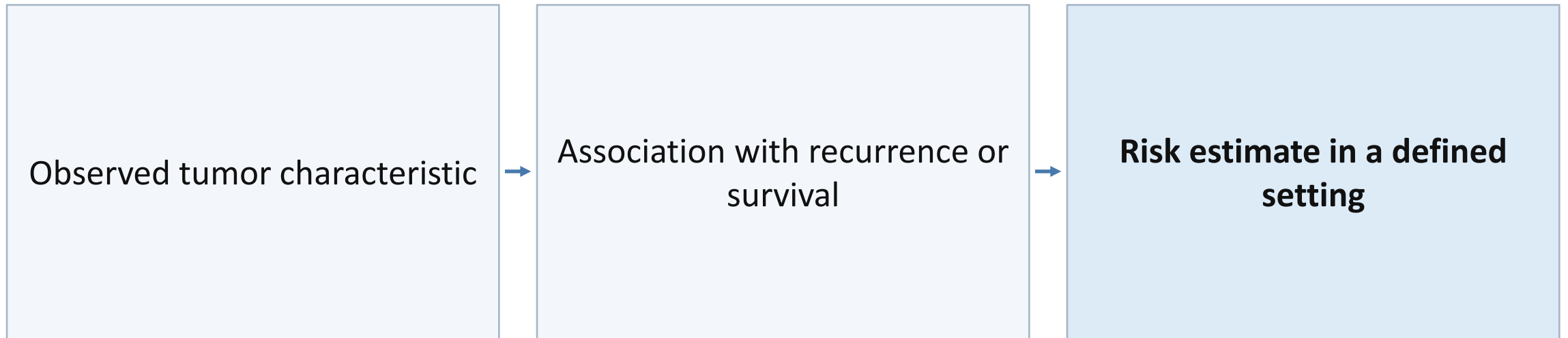
Distant metastasis, regional nodal involvement, primary tumor size, and local invasion.

Tumor biology

Grade, histologic subtype, ER/PR/HER2, proliferation, gene expression, and treatment sensitivity.

What makes a factor prognostic?

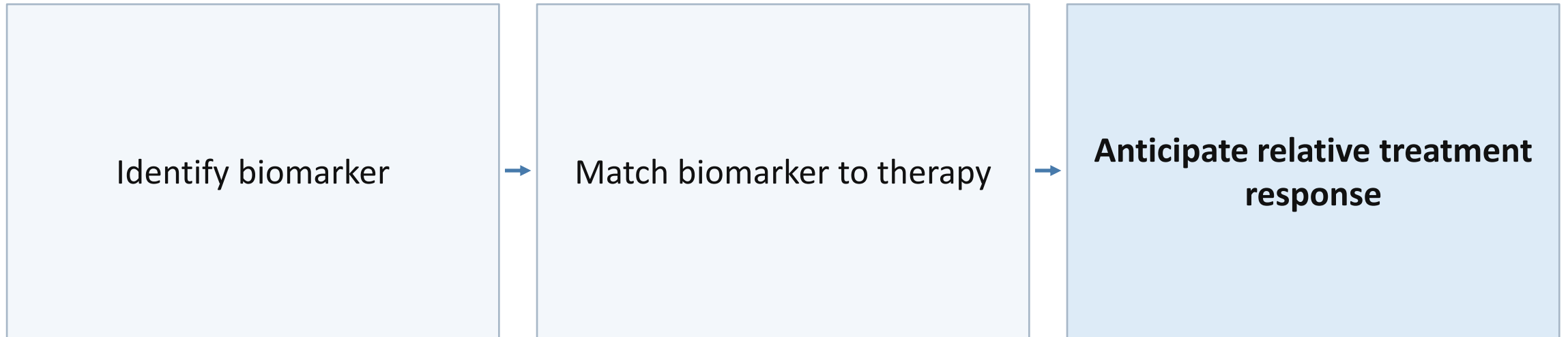
Prognosis estimates the likely course of disease



Prognostic information may matter even when no specific treatment is being selected.

What makes a factor predictive?

Prediction concerns benefit from a particular intervention



A predictive association is specific to a therapy and does not guarantee response.

Diagnostic, prognostic, and predictive are not synonyms

Biomarker role	Clinical question
Diagnostic	What tumor or molecular phenotype is present?
Prognostic	How is this cancer likely to behave?
Predictive	Does this finding imply benefit or resistance for a defined therapy?

Anatomic findings and biology answer different questions

Primarily prognostic	Often prognostic and predictive
Tumor size and local extension	ER expression and endocrine responsiveness
Regional lymph node metastasis	HER2 status and HER2-directed treatment
Distant metastatic spread	Proliferation and chemotherapy sensitivity

Major factor groups in the breast cancer report

Extent

M category
Nodal disease
Tumor size/local spread

Morphology

Nottingham grade
Special histologic type
Lymphovascular invasion

Biology

ER / PR / HER2
Gene profiles
Treatment response

Categories interact; They are not independent substitutes for complete staging.

Why prognostic markers matter

Patient counseling

Clarify anticipated disease course and the uncertainty around individual estimates.

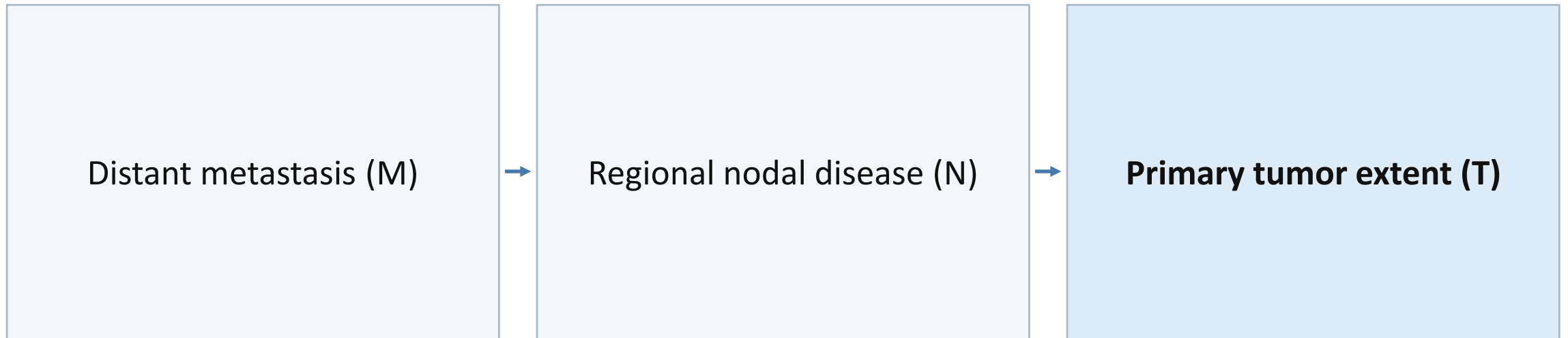
Treatment selection

Balance recurrence risk against potential benefit and treatment toxicity.

Research

Stratify risk groups and interpret therapeutic trial results.

Extent of disease: Descending prognostic hierarchy



Among extent-related factors, metastatic spread is paramount.

Distant metastasis is the dominant adverse factor

- Metastasis beyond regional lymph nodes carries the greatest prognostic weight.
- When distant metastases are present, cure is generally unlikely.
- Meaningful long-term remission or palliation remains possible, especially in selected ER-positive or HER2-positive cancers.

Metastatic disease: Prognosis is not a therapeutic absolute

Anatomic implication

Distant disease defines systemic spread and supersedes primary-tumor size as the major prognostic signal.

Biologic qualification

ER and HER2 expression may identify effective systemic treatment options despite metastatic presentation.

Axillary nodes: Most informative when M0

- In the absence of distant metastasis, axillary nodal status is the leading anatomic prognostic factor.
- Extent of nodal involvement matters: The number of positive nodes refines risk.
- A clinical examination cannot reliably replace histologic assessment.

Clinical nodal assessment has both error directions

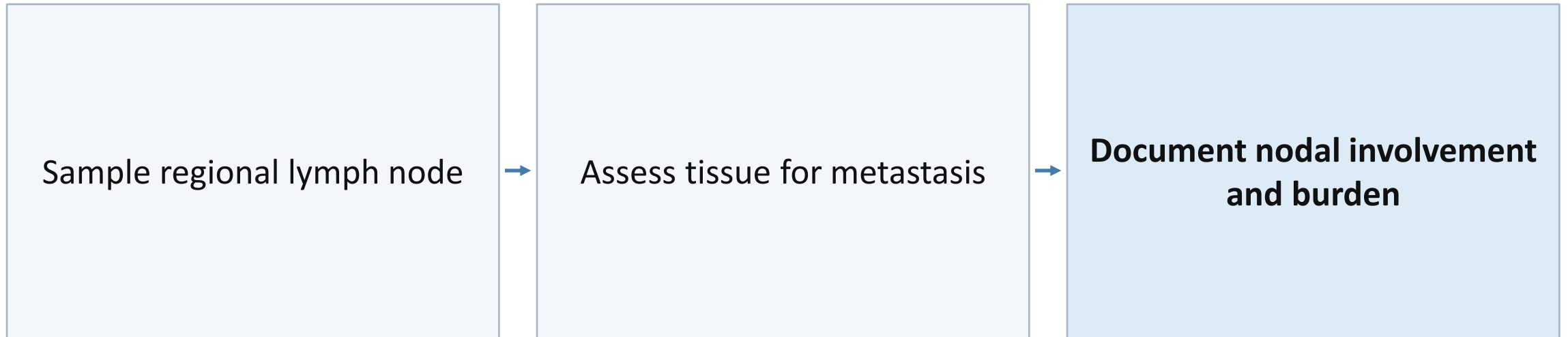
False positive

Palpable lymph nodes may be reactive rather than metastatic.

False negative

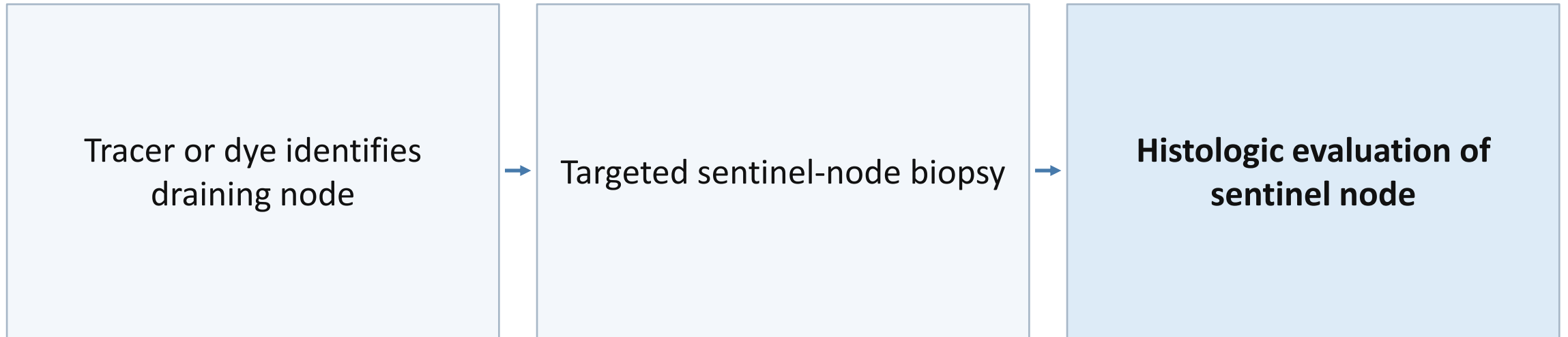
Small metastatic deposits may exist in clinically unremarkable nodes.

Histology determines the pathologic nodal finding



Histopathology improves nodal assessment compared with palpation alone.

Sentinel nodes are the first drainage station



Negative sentinel nodes make more distant axillary involvement less likely.

Node burden and long-term disease-free survival

10-year disease-free survival; Approximate ranges (%)

No involved axillary nodes



70–80%

1–3 involved nodes



35–40%

>10 involved nodes



10–15%

Historical textbook group-level estimates; Not contemporary individualized forecasts.

Node-negative status does not eliminate systemic risk

What it supports

Absence of histologically detected axillary metastasis predicts a more favorable outcome.

What it does not exclude

About 10–20% of axillary node-negative patients develop distant recurrence estimates.

Breast cancer may disseminate through several routes

Primary invasive breast carcinoma

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graph TD; A[Primary invasive breast carcinoma] --> B[Axillary lymphatic drainage]; A --> C[Internal mammary lymphatic routes]; A --> D[Hematogenous dissemination];
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The diagram is a flowchart illustrating the dissemination routes of primary invasive breast carcinoma. At the top, a light blue box contains the text 'Primary invasive breast carcinoma'. Three arrows originate from the bottom center of this box and point downwards to three separate boxes below. The left box is light blue and contains 'Axillary lymphatic drainage'. The middle box is light gray and contains 'Internal mammary lymphatic routes'. The right box is light blue and contains 'Hematogenous dissemination'.

Axillary lymphatic drainage

Internal mammary lymphatic
routes

Hematogenous dissemination

Primary-tumor diameter also stratifies outcome

10-year survival in node-negative breast carcinoma (textbook estimates)

Primary tumor <1 cm



>90%

Primary tumor >2 cm



77%

The >90% group is represented by a 90% lower-bound bar; Values are not risk-adjusted contemporary predictions.

Size matters, but is not the entire T category

Dimension

Maximum invasive tumor size contributes to the T category.

Skin

Ulceration or dermal involvement may alter local-stage assessment.

Chest wall

Deep local invasion confers a more advanced pattern of disease.

Locally advanced extension complicates control

- Invasion of skin or chest-wall structures represents aggressive local spread.
- Large infiltrative tumors can be harder to control through local therapy.
- Local extension is clinically important even before distant metastasis is established.

Inflammatory carcinoma is a clinical presentation

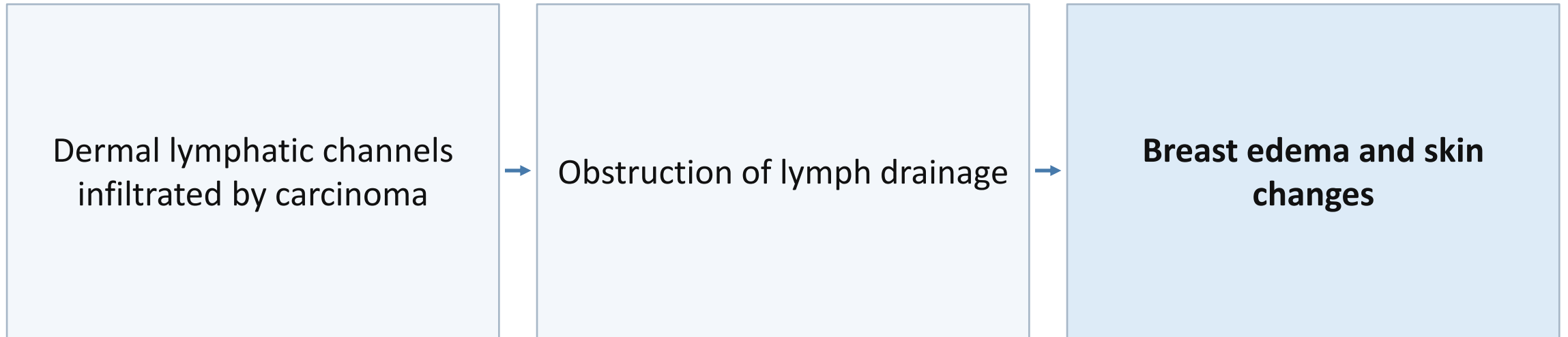
Pathologic driver

Extensive tumor emboli plug dermal lymphovascular channels.

Clinical phenotype

Diffuse erythema, edema, skin thickening, and often peau d'orange; Usually no discrete palpable mass.

Why skin becomes red and edematous



“Inflammatory” does not necessarily imply inflammatory-cell infiltration.

Do not confuse inflammatory carcinoma with infection

Observation	Interpretation
Erythema and edema	Can reflect lymphovascular tumor emboli rather than infection.
Peau d'orange	Edematous skin tethered by Cooper ligaments.
Diagnostic consequence	Clinical mimicry may delay recognition of carcinoma.

Histologic grade adds information within stage

- Nottingham grading assesses degree of differentiation in invasive carcinoma.
- High-grade tumors have worse outcomes than low-grade tumors within comparable stage groups.
- Grade contributes to the AJCC 8th-edition prognostic staging framework.

Three components of Nottingham grade

Tubule formation

How strongly do malignant cells retain gland-forming differentiation?

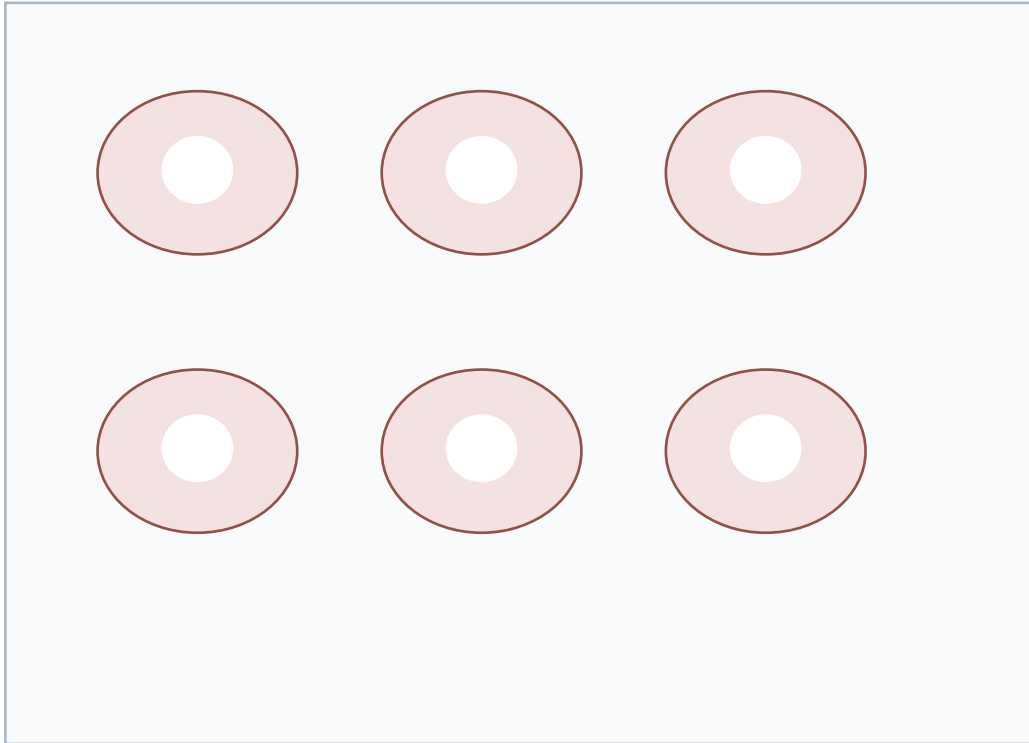
Nuclear pleomorphism

How variable and atypical are tumor-cell nuclei?

Mitotic activity

How frequent is cell division on microscopy?

Grade 1: Well-differentiated morphology



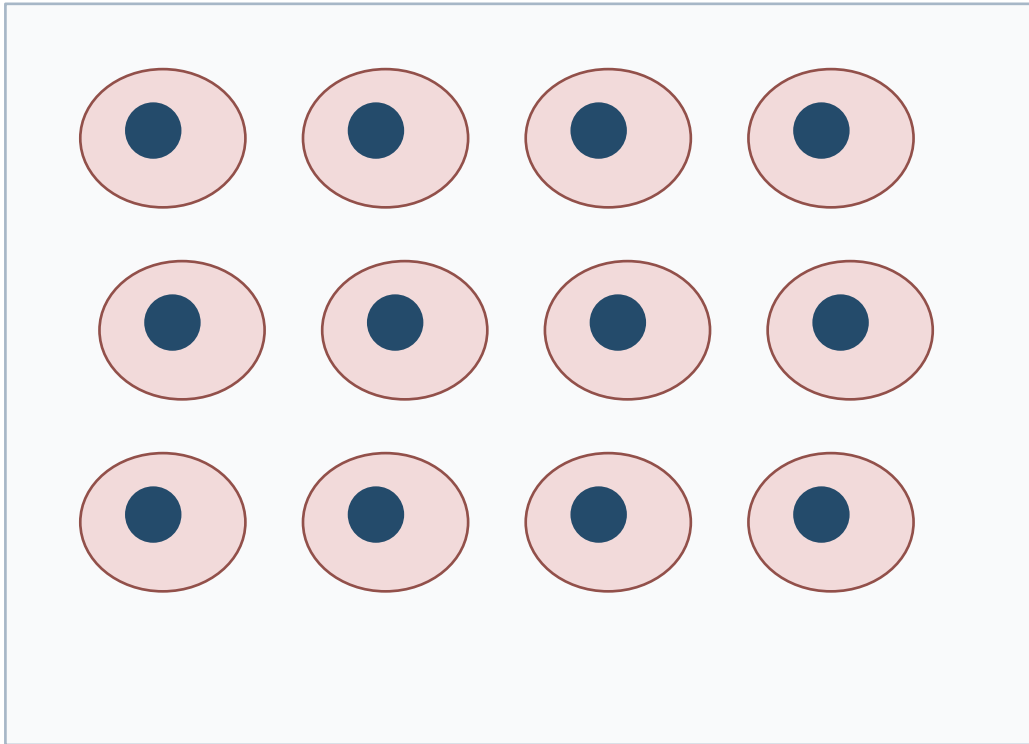
Simplified morphology schematic — not a histologic specimen

Tubular or cribriform architecture

Small relatively uniform nuclei

Low proliferative activity

Grade 2: Intermediate differentiation



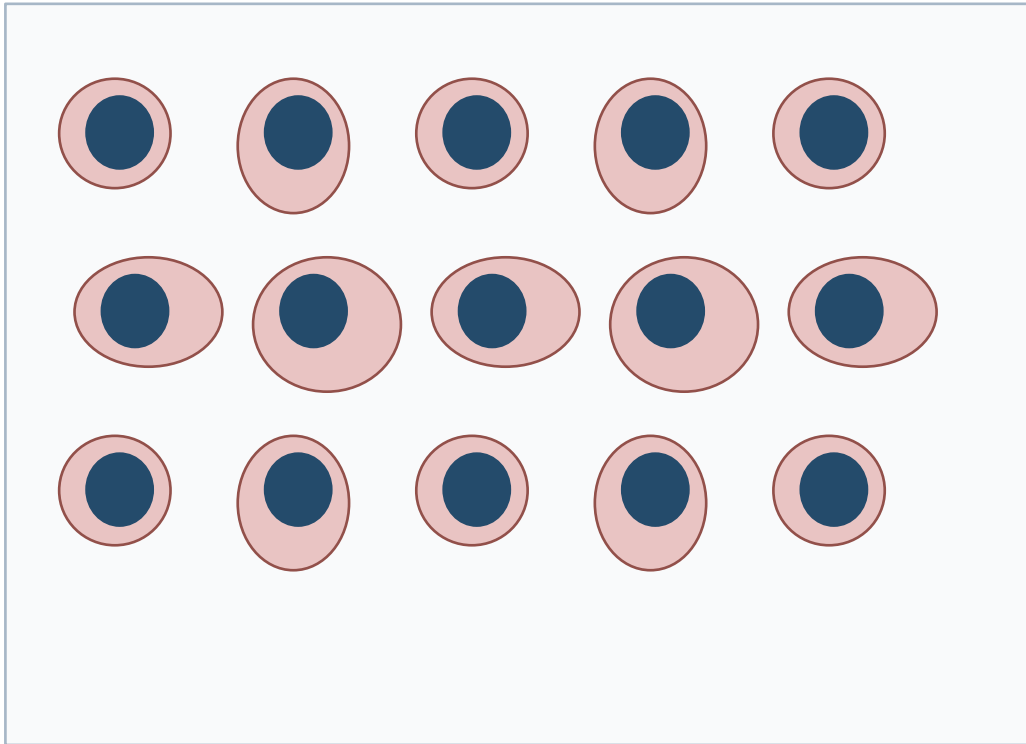
Simplified morphology schematic — not a histologic specimen

Mixture of glandular and solid growth

Greater nuclear variation

Intermediate mitotic activity

Grade 3: Poorly differentiated morphology



Simplified morphology schematic — not a histologic specimen

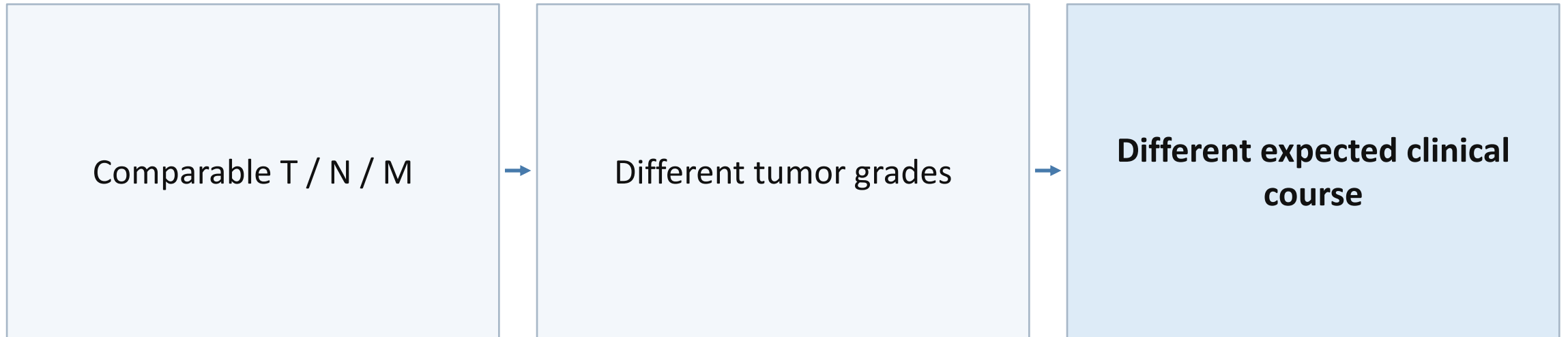
Ragged nests or solid sheets

Enlarged pleomorphic nuclei

Frequent mitoses; Necrosis may occur

Grade is prognostic beyond tumor dimensions

Patients with similar anatomic extent can differ biologically



The relative direction is supported; No grade-specific survival percentage is inferred.

Special histologic types are clinically informative

- Invasive carcinoma of no special type is morphologically heterogeneous.
- Some special types are closely linked to favorable clinical behavior.
- Other types show substantial prognostic variation within the category.

Favorable special types: Why morphology matters

Histologic type	Source-supported implication
Tubular carcinoma	Well-formed infiltrating tubules; Consistently favorable prognosis.
Cribriform carcinoma	Invasive cribriform nests; Consistently favorable prognosis.
Adenoid cystic carcinoma	Rare salivary gland-like TNBC subtype with relatively favorable outcome.
Secretory carcinoma	Rare salivary gland-like subtype; May harbor actionable NTRK fusion.

Metaplastic carcinoma is not prognostically uniform

Typical pattern

Many metaplastic carcinomas are triple-negative and associated with unfavorable clinical outcomes.

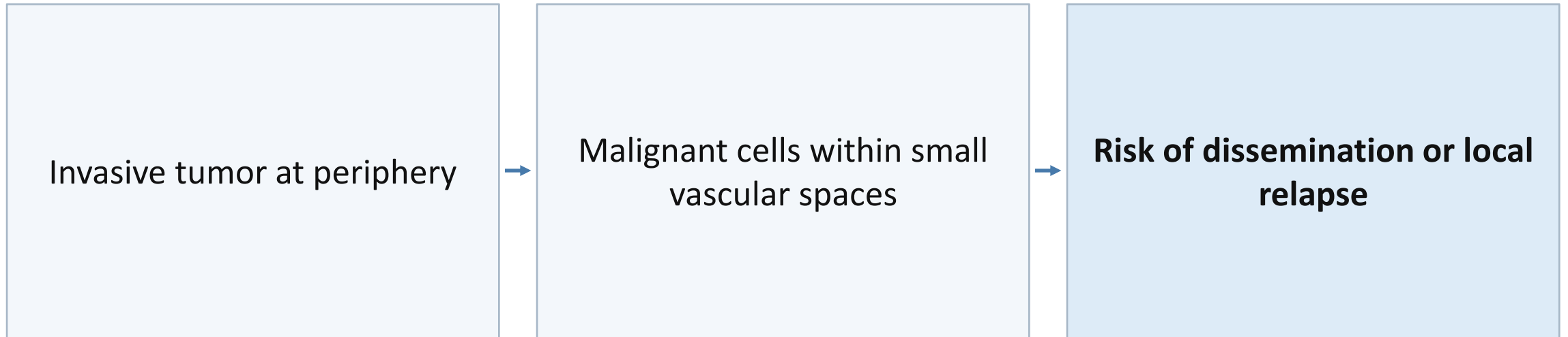
Important exceptions

Low-grade adenosquamous and fibromatosis-like metaplastic variants may be indolent.

Histologic type can influence chemotherapy response

Pattern	Neoadjuvant response
Invasive carcinoma of no special type	Reference pattern for response comparison.
Invasive lobular carcinoma	Less responsive to neoadjuvant chemotherapy.
Metaplastic carcinoma	Less responsive to neoadjuvant chemotherapy.

Lymphovascular invasion is a vascular-space finding



Simplified causal schematic; Identification requires histologic assessment.

Lymphovascular invasion adds risk when nodes are negative

Overall survival

Associated with adverse prognosis, particularly in patients without nodal metastasis.

Local control

Associated with a higher probability of local recurrence.

Different anatomic contexts of tumor emboli

Lymphovascular finding	Clinical significance
Peritumoral lymphovascular invasion	Additional adverse prognostic information.
Extensive dermal lymphatic tumor emboli	Can underlie inflammatory breast carcinoma presentation.

Tumor biology is captured through multiple assays

Immunohistochemistry

ER and PR nuclear staining;
HER2 membrane staining;
Proliferation markers.

Molecular analysis

HER2 amplification and tumor
DNA alterations.

Expression signatures

Quantitative tumor mRNA
panels enriched for
proliferation-related genes.

Major clinical biomarker phenotypes

Luminal

Typically ER-positive and HER2-negative; Variable grade and proliferation.

HER2-positive

HER2-driven cancers may be ER-positive or ER-negative.

Triple-negative

ER-negative, PR-negative, HER2-negative; Biologically heterogeneous.

Estrogen receptor: Prognostic and predictive

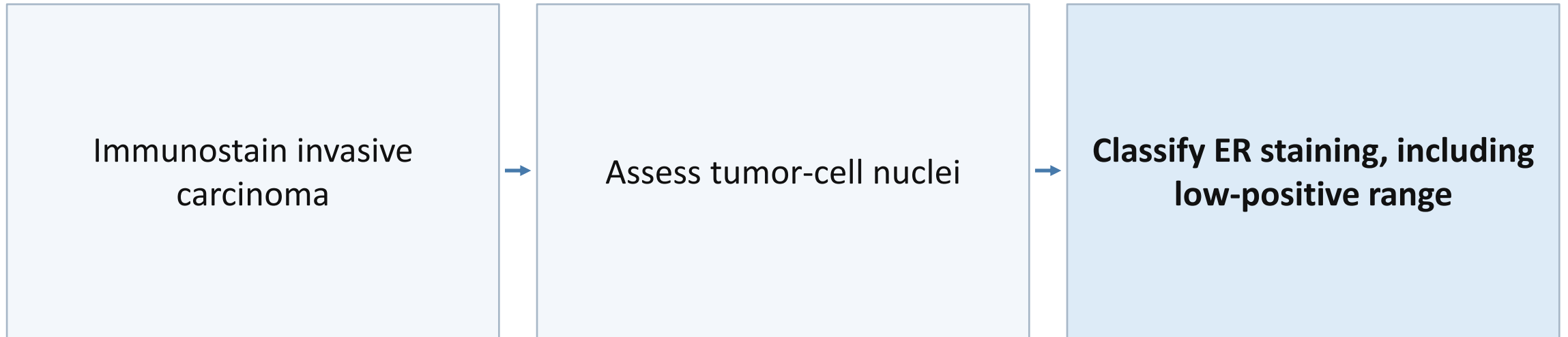
Prognostic dimension

Higher ER expression usually corresponds to a more favorable tumor phenotype.

Predictive dimension

ER expression identifies cancers likely to benefit from endocrine therapy.

ER status is based on nuclear immunoreactivity

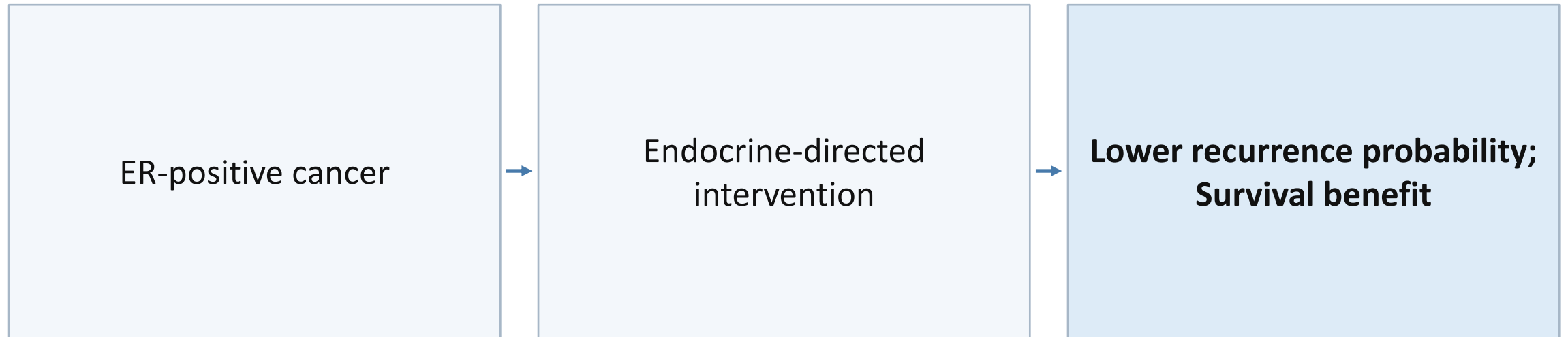


Robbins 11th ed. Uses $\geq 1\%$ nuclear staining to define ER positivity.

ER-low positive tumors need a distinct interpretation

ER expression	Source-supported implication
<1% tumor-cell nuclei	Below the textbook positivity threshold.
1–10% positive nuclei	Low-positive group; Worse prognosis than ER-high cancers.
High ER expression	Often more endocrine responsive, but extent and grade remain relevant.

ER expression connects marker to therapy



Predictive implication applies to endocrine treatment, not every therapy.

Progesterone receptor adds biologic resolution

- ER-positive carcinomas commonly coexpress PR.
- PR positivity is defined by $\geq 1\%$ nuclear staining.
- Low PR in an ER-positive tumor is associated with worse outcomes than high ER/high PR expression.

Joint ER and PR patterns modify prognostic thinking

ER-high / PR-high

Relatively favorable receptor-expression combination.

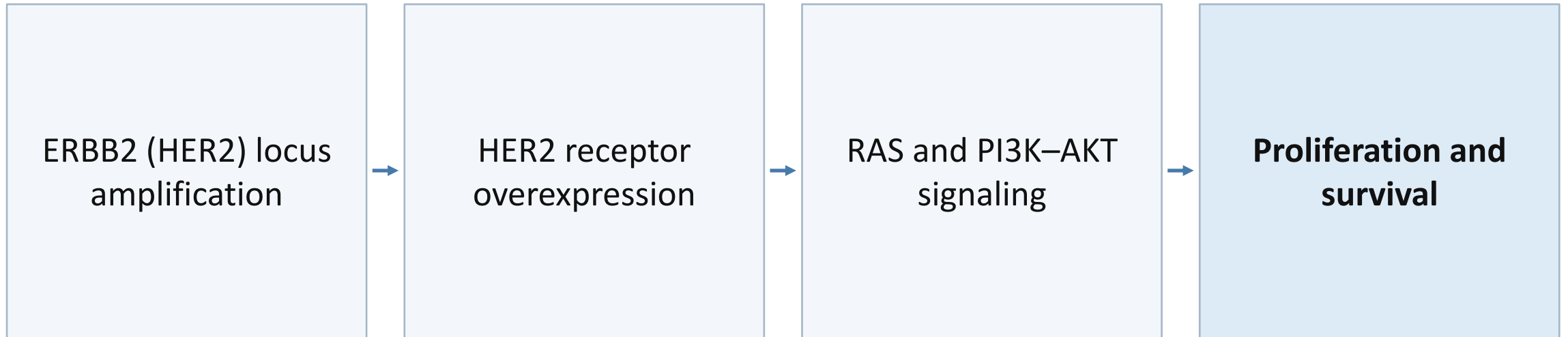
ER-positive / PR-low

Clinical outcomes are less favorable than high expression of both receptors.

ER-/PR-/HER2-

Triple-negative phenotype lacks endocrine and HER2 treatment targets.

HER2 biology: Amplified growth signaling



Schematic shows source-described growth/survival signaling, not a complete molecular pathway.

HER2 is evaluated at protein and gene levels

Immunohistochemistry

Assesses HER2 protein expression at the tumor-cell membrane.

In situ hybridization

Assesses HER2 gene amplification; Source figure describes comparison with a chromosome 17 probe.

HER2 has adverse biology and therapeutic value

Untreated tumor biology

HER2 positivity is associated with aggressive clinical behavior.

Therapy prediction

HER2 positivity can identify cancers responsive to HER2-targeted treatment.

Triple-negative does not mean one uniform disease

- The triple-negative definition is absence of ER, PR, and HER2 expression.
- Most TNBCs are high-grade and show marked proliferation and genomic instability.
- Rare special histologic types of TNBC have much more favorable behavior.

Molecular grouping should not override histology

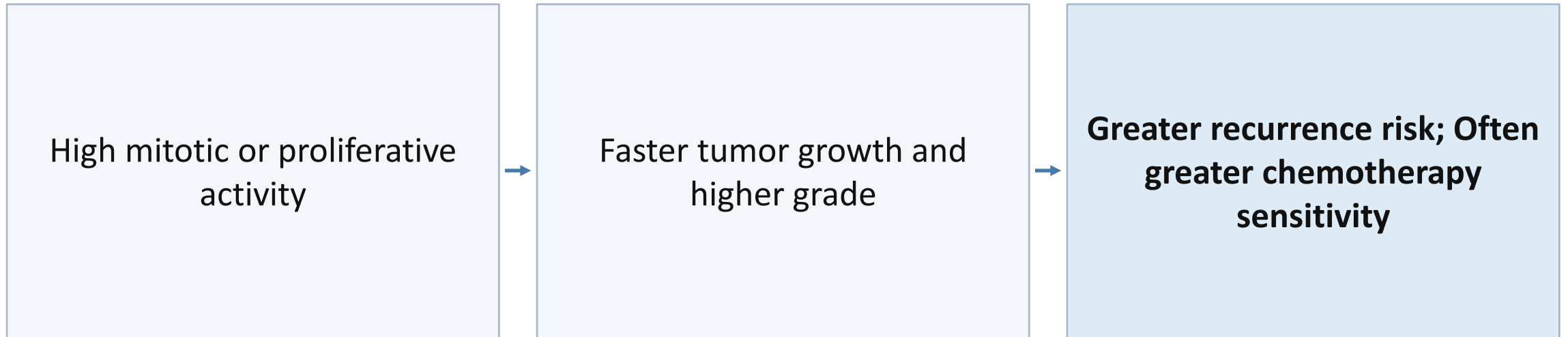
Typical TNBC

High-grade tumor, often TP53 altered, with greater genomic instability.

Important subtype exception

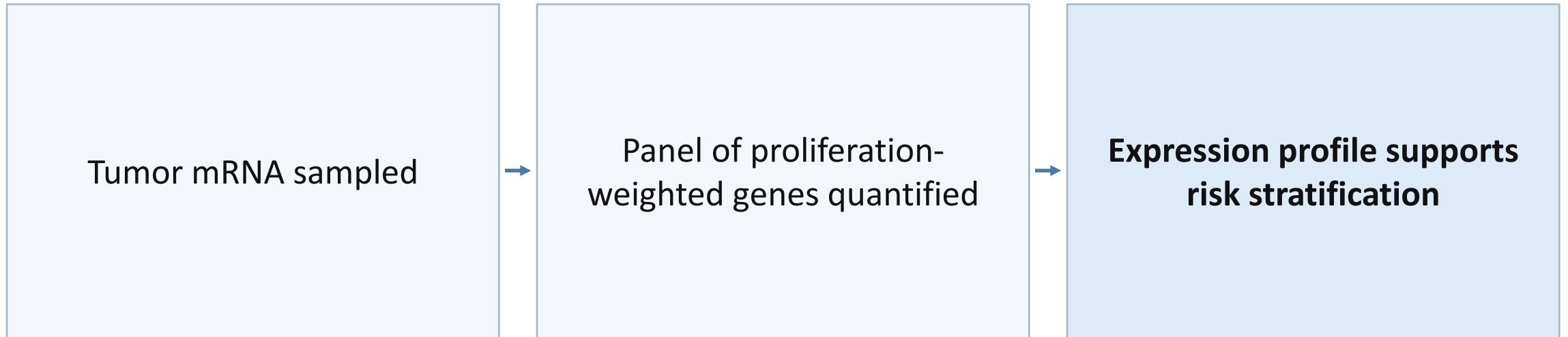
Adenoid cystic, secretory, and some low-grade metaplastic tumors behave differently.

Proliferation links biology to outcome



The last association is subtype-dependent; Molecular assays often enrich for proliferation genes.

What multigene expression tests measure



No proprietary score thresholds are asserted because the source excerpt does not provide them.

Principal clinical role of gene expression profiling

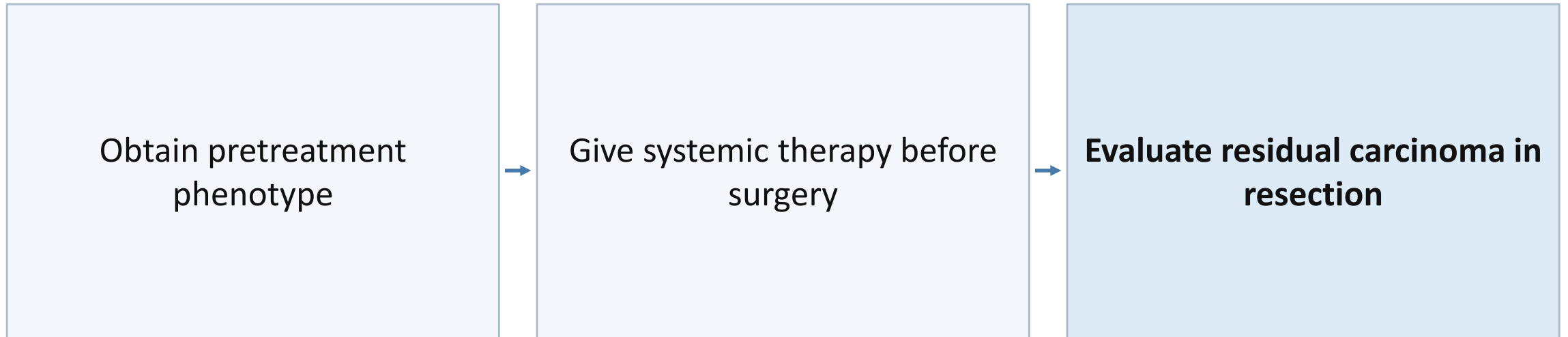
Population most relevant

Selected slowly proliferating, ER-positive breast cancers.

Decision supported

Identify patients unlikely to derive sufficient chemotherapy benefit to justify its toxicity.

Neoadjuvant treatment provides a response readout



The observed response is new biologic information beyond the initial biopsy.

Pathologic complete response is an observed endpoint

Complete regression

No residual invasive carcinoma in the post-treatment specimen (conceptual description; Definitions may differ by protocol).

Residual disease

Persistent carcinoma after treatment indicates an incomplete pathologic response.

Response predicts prognosis differently by subtype

Tumor group	Prognostic importance of response
Triple-negative breast carcinoma	A strong response is associated with better prognosis.
HER2-positive carcinoma	A strong response is associated with better prognosis.
Most luminal carcinomas	Pathologic response is less powerful as a prognostic indicator.

Tumor-infiltrating lymphocytes: What is measured?

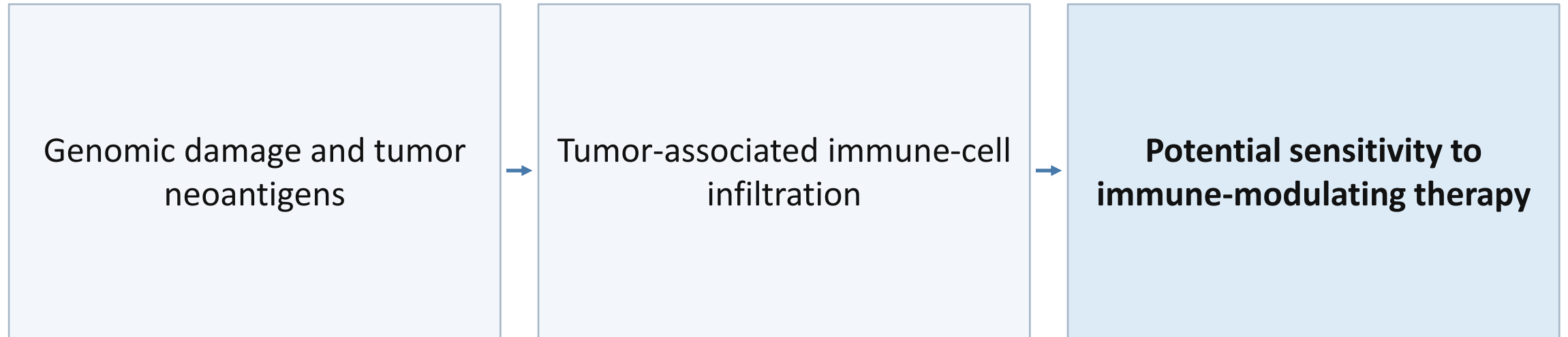
Cellular constituents

Lymphocytes and plasma cells within tumor tissue and stroma.

Clinical association

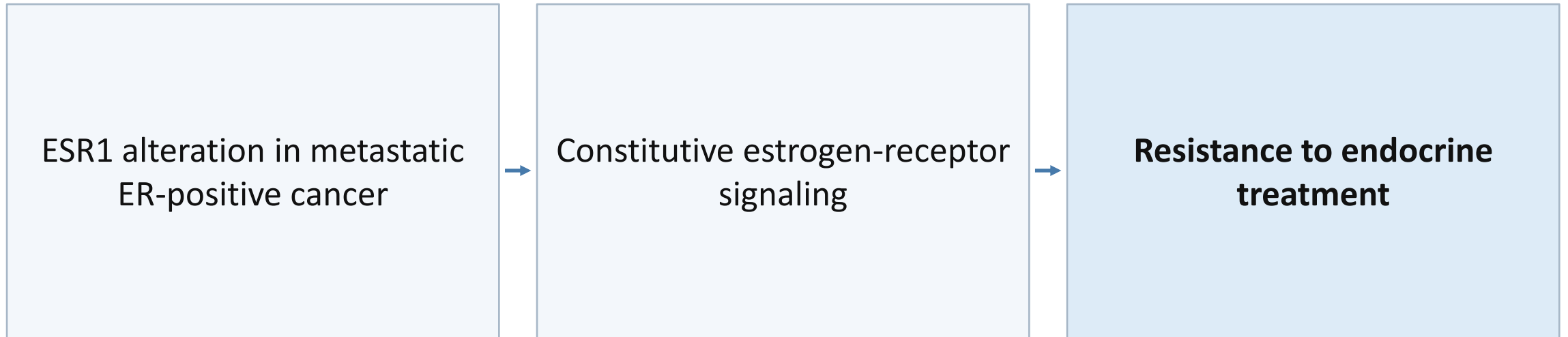
Prominent TILs correlate with improved prognosis and greater neoadjuvant responsiveness in HER2 cancers and TNBC.

Why immune context is biologically relevant



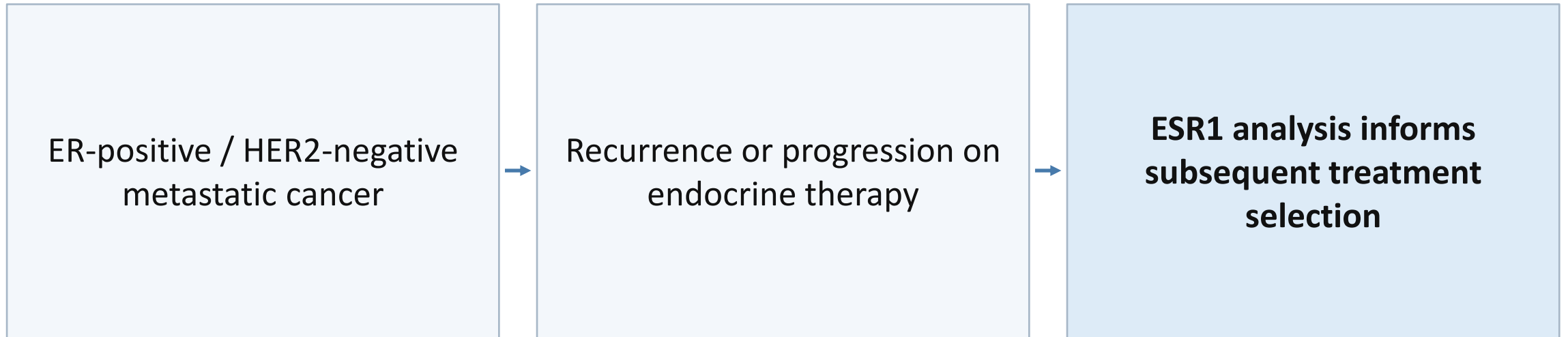
Conceptual context from adjacent TNBC section; No direct deterministic causal claim.

ESR1 mutation is an endocrine-resistance mechanism



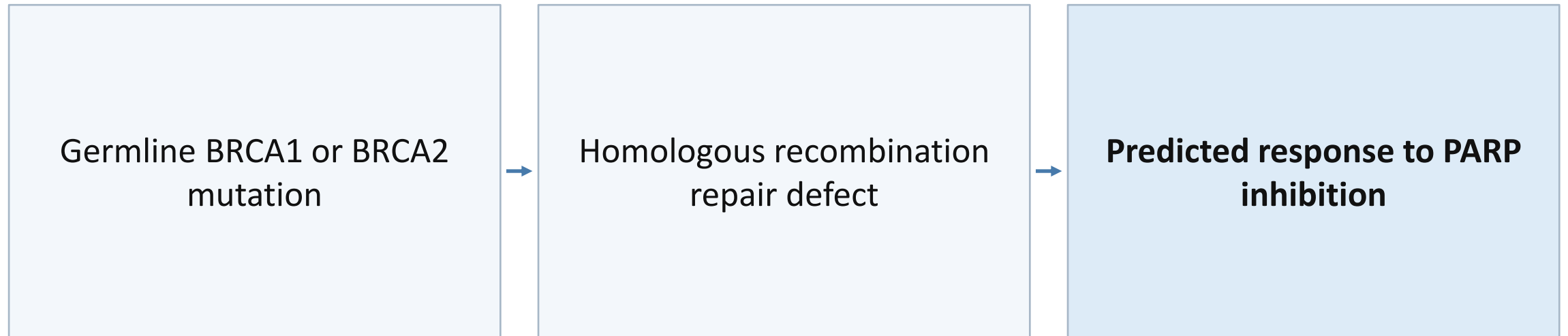
Source describes acquired resistance and adverse clinical behavior.

When ESR1 testing becomes informative



Timing/setting follows the Robbins 11th-edition discussion; Not a complete clinical guideline.

Germline BRCA1/BRCA2 predicts PARP targeting



Specific patient selection and treatment eligibility require current clinical protocols.

PIK3CA identifies a PI3K-pathway vulnerability



Actionability depends on indication, treatment line, and regimen; No drug-specific eligibility rules shown.

NTRK fusion is important in secretory carcinoma



Rare histologic subtype supplies a strong prompt to assess an actionable alteration.

Immune checkpoint biomarkers are context-specific

PD-L1

Expression assessed in tumor cells and/or immune cells.

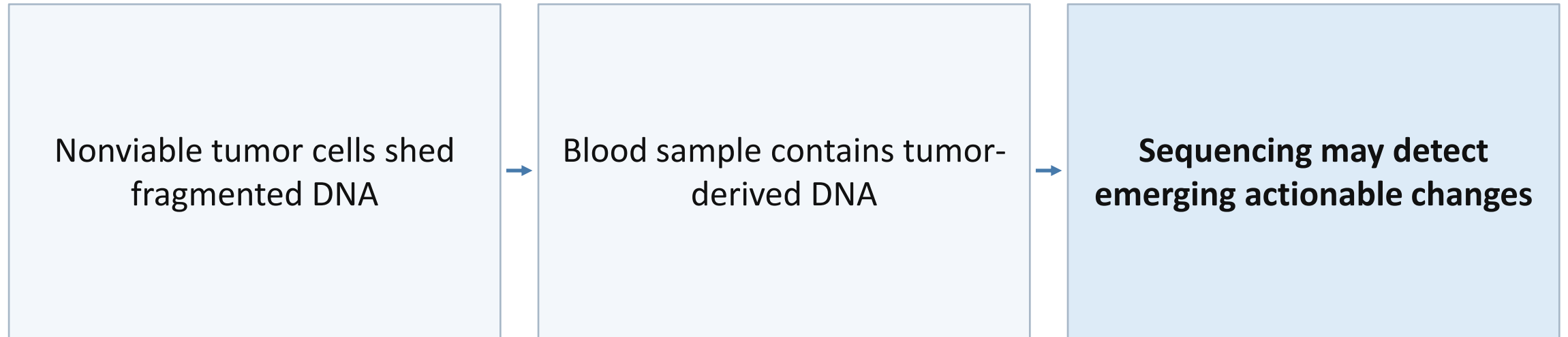
Tumor mutational burden

Sequencing-based estimate of somatic mutational load.

Mismatch repair deficiency

Potential immunotherapy-associated feature; Rare in breast cancer.

Circulating tumor DNA samples evolving mutations

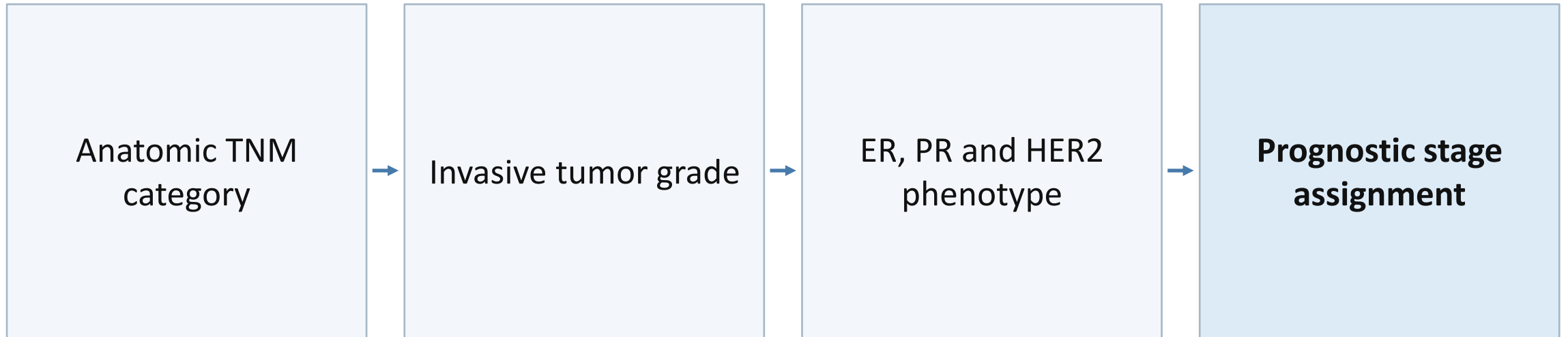


Textbook example: PIK3CA; Negative ctDNA does not logically exclude a tumor alteration.

Biomarker-to-therapy map

Biologic feature	Therapeutic implication
ER expression	Endocrine-directed treatment
HER2 positivity	HER2-targeting agents
Germline BRCA1 / BRCA2	PARP inhibitor sensitivity
PIK3CA mutation	PI3K-pathway targeting
NTRK fusion	TRK-directed kinase therapy

AJCC 8th-edition staging: Anatomic plus biology



Edition explicitly corresponds to the Robbins source, not a claim about all subsequent stage versions.

Anatomic stage and prognostic stage are not identical

Anatomic framework

T: Primary tumor
N: Regional nodes
M: Distant metastasis

AJCC 8th prognostic framework

Uses anatomic extent plus grade and biomarker profile; Selected multigene results may contribute.

Core elements of a prognosis-oriented pathology report

Size and locally advanced features of invasive carcinoma

Axillary or sentinel-node metastatic status and burden

Nottingham histologic grade and histologic subtype

Lymphovascular invasion, ER, PR, and HER2 findings

Relevant molecular test results and post-neoadjuvant response

Application case: ER-low carcinoma

Clinical vignette

A patient has surgically excised invasive breast carcinoma with ER nuclear staining in 5% of tumor cells, low PR expression, and no known distant metastasis.

Why should “ER-positive” not be the entire prognostic summary?

Case interpretation: Low ER is not equivalent to ER-high

Receptor positivity and expected biologic behavior must be separated.

- ER staining of 5% falls in the low-positive range (1–10%).
- Low ER expression is associated with less favorable behavior than high ER expression.
- Stage, grade, PR, HER2, and nodal findings are still needed.

Application case: Residual TNBC after chemotherapy

Clinical vignette

Pretreatment biopsy shows triple-negative invasive carcinoma. After neoadjuvant chemotherapy, viable residual invasive tumor remains in the operative specimen.

Which newly observed feature modifies the prognosis?

Case interpretation: Treatment response is biologic information

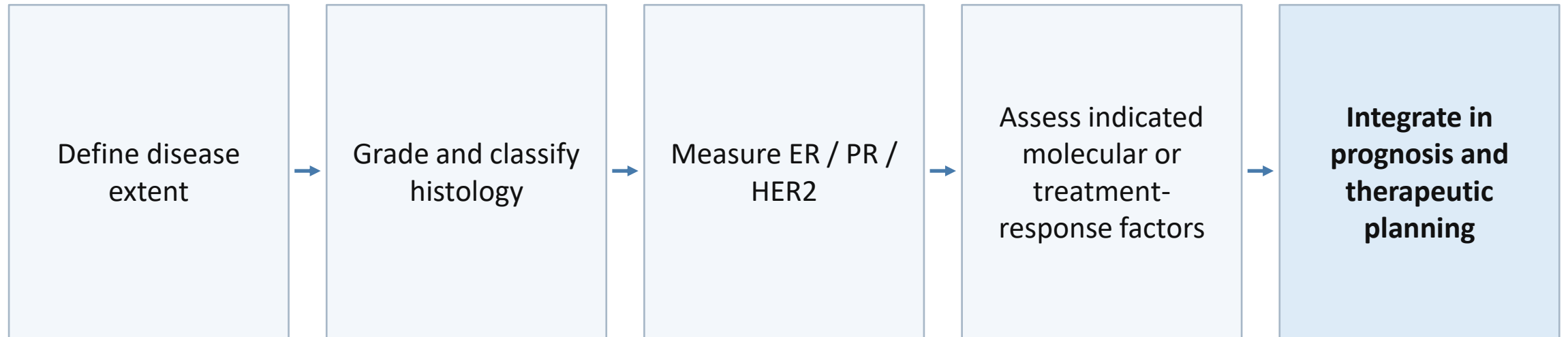
Residual disease after neoadjuvant treatment is a prognostically relevant observation in TNBC.

- Neoadjuvant therapy permits direct assessment of in vivo response.
- For TNBC and HER2-positive cancers, response correlates strongly with prognosis.
- Residual tumor implies a less favorable response than pathologic complete regression.

Interpretation pitfalls

Pitfall	More defensible interpretation
One factor predicts an individual outcome	Use stage plus grade, subtype, biomarkers, and context.
Prognostic equals predictive	A poor prognosis does not itself specify a drug target.
ER-low is identical to ER-high	Low ER expression is a biologically distinct risk signal.
All TNBC has identical prognosis	Recognize rare favorable special histologic subtypes.

Integrated clinical reasoning



Management is multidisciplinary; No single pathology parameter replaces clinical assessment.

Final synthesis

Extent

M status dominates; Nodal burden and local tumor extent sharpen baseline risk.

Biology

Grade, histologic type, ER/PR/HER2, proliferation, and immune infiltrates refine prognosis.

Prediction

Receptors, actionable alterations, and neoadjuvant response inform treatment-specific decisions.

Principal reference

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).

Chapter 23, The Breast: “Prognostic and Predictive Factors,” pp. 964–965; adjacent sections on carcinoma subtypes and AJCC breast cancer staging (pp. 959–966).

Key source tables: 23.4 (molecular subtypes), 23.5 (prognostic factors), 23.6 (AJCC 8th-edition anatomic stage).