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The Relationship Between Ki-67 Expression and Post-Surgical Breast Cancer Recurrence Rates: A Systematic Review

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ABSTRACT

Introduction: Post-surgical recurrence remains the primary driver of mortality in breast cancer. While the proliferation biomarker Ki-67 is recognized as a potent prognostic tool, its clinical implementation is debated due to significant methodological inconsistencies. This systematic review aims to synthesize the extensive body of evidence to confirm the significant, independent association between high Ki-67 expression and post-surgical breast cancer recurrence.

Methods: This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic search of PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library was performed for studies from January 2007 to October 2024. The PICO (Population, Intervention,

Comparator, Outcome) framework was used to select high-quality cohort studies and meta-analyses. Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS) for prognostic studies.

Results: A total of 17 high-impact studies were included, comprising 12 primary cohort studies and 5 major meta-analyses, which collectively represent over 85,000 patients. The synthesis of this data demonstrates a highly significant and robust association between high Ki-67 expression and worse post-surgical outcomes. Major meta-analyses report that high Ki-67 confers a pooled Hazard Ratio (HR) for relapse of 1.93 (95% CI: 1.74–2.14, $p < 0.001$) and a pooled HR for mortality of 2.05 (95% CI: 1.66–2.53, $p < 0.00001$). High-impact cohort studies reinforce this, reporting HRs for recurrence risk as high as 7.14, 12.90, and even 30.47 in specific patient groups. This association remains significant across all major breast cancer subtypes, including ER+/HER2- and triple-negative breast cancer.

Discussion: The prognostic signal of Ki-67 is exceptionally robust, remaining statistically significant *despite* wide heterogeneity in study cutoffs, ranging from 13% to 40%). This confirms its fundamental biological importance. Ki-67 is clinically essential for differentiating low-risk Luminal A from high-risk Luminal B subtypes and is now a critical biomarker for guiding adjuvant therapy decisions, including the use of CDK4/6 inhibitors.

Conclusion: High Ki-67 expression is one of the most significant and clinically relevant independent predictors of post-surgical breast cancer recurrence. The urgent, collective adoption of international standardization guidelines for Ki-67 assessment, as proposed by groups like the International Ki-67 in Breast Cancer Working Group (IKWG), is the final and necessary step to unlock its full clinical utility in routine oncological practice.

Keywords: Breast Cancer; Ki-67 Antigen; Post-Surgical Recurrence; Disease-Free Survival; Prognostic Biomarker; Systematic Review.

INTRODUCTION

The Clinical Burden of Post-Surgical Breast Cancer Recurrence

Breast cancer is the most prevalent malignancy and the leading cause of cancer-related mortality among women worldwide (Siegel et al., 2021). Despite significant advancements in early detection, surgical techniques, and adjuvant therapies, a substantial proportion of patients diagnosed with early-stage breast cancer will experience disease recurrence following primary surgery (Tandon et al., 2023).

This recurrence represents the primary clinical challenge and the principal driver of breast cancer-specific mortality (Saphner et al., 1996; Mactier, 2024). Recurrence can manifest locally in the remaining breast tissue or chest wall, regionally in adjacent lymph nodes, or as distant (metastatic) disease (Mayo Clinic, 2024). Distant recurrence, most commonly in the bones, liver, and lungs, is typically incurable (Cleveland Clinic, 2022). The underlying mechanism of recurrence is often the persistence of micrometastatic disease or residual cancer cells that are not eradicated by initial surgery and adjuvant treatment (Cleveland Clinic, 2022).

Traditional prognostic factors, including axillary lymph node status, tumor size, and histological grade, are essential for staging and treatment planning (Siegel et al., 2021). However, these clinicopathological features are insufficient to fully capture the heterogeneity and biological aggressiveness of an individual's tumor. This creates a critical unmet need for reliable, accessible, and validated biological markers that can more accurately stratify post-surgical recurrence risk, thereby guiding decisions on the necessity and intensity of adjuvant systemic therapy.

Ki-67: A Biological Proxy for Cellular Proliferation

Among the most extensively studied biological markers is the Ki-67 antigen (Giaquinto et al., 2022). The Ki-67 antigen is a non-histone nuclear protein encoded by the *MKI67* gene (Scholzen & Gerdes, 2000). Its biological function is intrinsically linked to cell division. The Ki-67 protein is expressed during all active phases of the cell cycle (G1, S, G2, and M phases) but is conspicuously absent in the resting or quiescent (G0) phase (Gerdes et al., 1983; Urruticoechea et al., 2005).

This unique expression pattern, first identified by Gerdes et al. (1983), makes the Ki-67 labeling index (LI)—quantified by immunohistochemistry (IHC) as the percentage of tumor cell nuclei staining positive—a direct and effective measure of the tumor's "growth fraction" (Siegel et al., 2021; Giaquinto et al., 2022). A high Ki-67 LI indicates that a large proportion of the cancer cells are actively dividing, reflecting high proliferative activity (Giaquinto et al., 2022).

The Proliferation-Recurrence Hypothesis

Cellular proliferation is a central determinant of tumor aggression and a hallmark of cancer (Giaquinto et al., 2022). A high rate of proliferation is biologically linked to faster tumor growth, increased genomic instability, and a greater potential for invasion and metastasis (Giaquinto et al., 2022).

Therefore, the guiding hypothesis of this review is that tumors with a high Ki-67 LI possess a more aggressive biological phenotype (Giaquinto et al., 2022; Tandon et al., 2023). This aggressive phenotype is hypothesized to correlate directly with a higher likelihood of resisting therapy, establishing micrometastatic foci, and, consequently, a significantly increased risk of post-surgical recurrence and worse overall survival (Soliman et al., 2016; Jung et al., 2025). This systematic review seeks to confirm the statistical significance and clinical magnitude of this association.

The Research Gap: The Ki-67 Standardization Controversy

Despite a vast body of literature supporting Ki-67 as a prognostic marker (Petrelli et al., 2015; de Azambuja et al., 2007), its routine implementation in clinical guidelines has been "limited" and "controversial" (Giaquinto et al., 2022; Tandon et al., 2023; Luporsi et al., 2012). This creates an apparent paradox: why is a marker with such consistent prognostic data not universally adopted?

The central research gap is not a question of *biological significance*, but one of *analytical validity* and *methodological chaos* (Dowsett et al., 2011; Tandon et al., 2023; Giaquinto et al., 2022). This gap manifests in three critical problems:

1. **Lack of a Universal Cutoff:** There is no consensus on the definitive Ki-67 LI percentage to distinguish "low" from "high" proliferation. Studies have used cutoffs ranging widely from 10% to 40% (Petrelli et al., 2015; Wu et al., 2019; Luporsi et al., 2012). The St. Gallen International Breast Cancer Consensus has historically used 14% or 20% (Goldhirsch et al., 2011; St. Gallen Consensus, 2021), while the International Ki-67 in Breast Cancer Working Group (IKWG) suggests clinical utility is most reliable at the extremes (e.g., $\leq 5\%$ or $\geq 30\%$) (Dowsett et al., 2021).
2. **Inter-Laboratory Variability:** Significant discrepancies in Ki-67 scores for the same tumor block are reported between different pathology laboratories. This stems from a lack of standardization in pre-analytical factors (e.g., specimen fixation time, tissue processing) and analytical factors (e.g., antibody clones, staining platforms) (Giaquinto et al., 2022; Dowsett et al., 2011).
3. **Inter-Observer Variability:** Even on the same stained slide, pathologists may arrive at different scores due to subjective visual scoring methods (e.g., "hot-spot" versus "global" scoring, manual counting versus digital analysis) (Giaquinto et al., 2022; Tandon et al., 2023; Nielsen et al., 2024).

Novelty and Objectives of This Review

The novelty of this review is not to *discover* the link between Ki-67 and recurrence, but to synthesize the vast body of contemporary, high-level evidence to argue that the prognostic signal of Ki-67 is so robust that it remains a powerful and statistically significant predictor *despite* the aforementioned methodological heterogeneity (Luporsi et al., 2012; Giaquinto et al., 2022).

A key secondary objective is to position Ki-67 as a critical, cost-effective, and globally accessible prognostic tool. Expensive multigene assays like the 21-gene Oncotype Dx (ODx) Recurrence Score (RS) are standard of care in many high-income countries but are financially inaccessible in low- and middle-income countries (LMICs) (Agha et al., 2024). Ki-67, by contrast, is a simple, inexpensive, and widely available IHC test (Agha et al., 2024). This review synthesizes data showing a strong correlation between Ki-67 and genomic scores (Agha et al., 2024) and, more importantly, *independent* prognostic value (Park et al., 2023), thereby validating its role as an indispensable tool for global oncology.

The objectives of this systematic review are:

1. To systematically review the high-impact literature from 2007 to the present, focusing on large cohort studies and meta-analyses.
2. To qualitatively and quantitatively summarize the association between high Ki-67 expression and post-surgical recurrence rates, primarily defined by Disease-Free Survival (DFS), Recurrence-Free Survival (RFS), and Overall Survival (OS).
3. To confirm, based on the synthesized evidence, the *statistical significance* and *clinical magnitude* of this association.

METHODS

Review Protocol and Registration

This systematic review was designed, conducted, and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021; Poulakaki et al., 2018). A protocol was established *a priori* by the authors (FN, ME) to define the search strategy, eligibility criteria, and methods for data synthesis.

Search Strategy and Data Sources

A comprehensive electronic search of the literature was performed to identify all relevant studies published from January 1, 2007, to October 2024. This start date was chosen to build upon the foundational 2007 meta-analysis by de Azambuja et al. (2007). The following databases were systematically searched: PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library.

The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text keywords: ("Breast Neoplasms" OR "Breast Cancer") AND ("Ki-67 Antigen" OR "Ki67" OR "MIB-1" OR "Proliferation Marker") AND ("Recurrence" OR "Relapse" OR "Disease-Free Survival" OR "Prognosis" OR "Overall Survival") AND ("Surgery" OR "Surgical" OR "Postoperative"). To ensure comprehensive capture, the reference lists of all included articles and relevant reviews were also manually screened for additional eligible studies (de Azambuja et al., 2007).

Study Selection and Eligibility Criteria (PICO)

All retrieved citations were imported into a reference management database. Two reviewers (FN, ME) independently screened all titles and abstracts. Full-text

articles of all potentially eligible studies were retrieved and assessed against the following inclusion criteria, structured around the PICO framework (Kim et al., 2021):

- **Population (P):** Patients with primary, non-metastatic (Stage I-III) surgically resected invasive breast cancer (Enrico et al., 2018).
- **Intervention/Exposure (I):** Assessment of Ki-67 proliferation index (LI) from the primary tumor (either biopsy or surgical specimen) (Kim et al., 2021), with stratification into a "High" expression group.
- **Comparator (C):** A "Low" Ki-67 expression group.
- **Outcomes (O):** The study must have reported at least one primary prognostic outcome, such as Disease-Free Survival (DFS), Recurrence-Free Survival (RFS), Distant Disease-Free Survival (DDFS), or Overall Survival (OS). The primary data sought was the effect size, reported as a Hazard Ratio (HR) or Risk Ratio (RR) with 95% Confidence Intervals (CI).

Exclusion Criteria were as follows:

1. Non-original research articles (e.g., reviews, letters, comments, conference abstracts, case reports) (Wu et al., 2019).
2. Studies focused exclusively on *de novo* metastatic (Stage IV) disease (Wu et al., 2019).
3. Studies with no extractable quantitative data (e.g., HR, survival curves, or p-values) on the association between Ki-67 and a survival/recurrence outcome (Wu et al., 2019).
4. Studies with a total sample size of fewer than 100 patients, to ensure the stability of prognostic estimates.
5. Studies with clearly overlapping patient cohorts; in such cases, only the most recent or most complete study was included (de Azambuja et al., 2007).
6. Publications not in the English language.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Breast Cancer	Breast Neoplasms	Early-Stage Breast Cancer	Surgically Resected Breast Cancer
Intervention (I)	Ki-67 Expression	Ki-67 Antigen	Proliferation Marker	MIB-1
Comparison (C)	Low Ki-67 Expression	Low Proliferation Group	Low Ki-67 Labeling Index	Low Growth Fraction
Outcome (O)	Post-Surgical Recurrence	Recurrence Rates	Disease-Free Survival (DFS)	Overall Survival (OS)

The Boolean MeSH keywords inputted on databases for this research are:
(*"Breast Cancer"* OR *"Breast Neoplasms"* OR *"Early-Stage Breast Cancer"* OR *"Surgically Resected Breast Cancer"*) AND (*"Ki-67 Expression"* OR *"Ki-67 Antigen"* OR *"Proliferation Marker"* OR *"MIB-1"*) AND (*"Low Ki-67 Expression"* OR *"Low Proliferation Group"* OR *"Low Ki-67 Labeling Index"* OR *"Low Growth Fraction"*) AND (*"Post-Surgical Recurrence"* OR *"Recurrence Rates"* OR *"Disease-Free Survival (DFS)"* OR *"Overall Survival (OS)"*)

Data Extraction

Data from all included studies were extracted independently by both reviewers using a standardized data extraction form in Microsoft Excel (Agha et al., 2024). Any discrepancies were resolved by discussion and consensus. The following data fields were extracted: first author, publication year, country of origin, study design (e.g.,

retrospective cohort, meta-analysis), total number of patients, specific patient population (e.g., all subtypes, ER+/HER2-), median follow-up duration, Ki-67 antibody clone used (if reported), Ki-67 cutoff value(s) used, primary outcome(s) (DFS, RFS, OS), and the corresponding effect size (HR or RR) with 95% CI and p-value (de Azambuja et al., 2007; Wu et al., 2019).

Quality Assessment and Risk of Bias

The methodological quality and risk of bias for each included primary cohort study were independently assessed by both reviewers (FN, ME) using the **Newcastle-Ottawa Scale (NOS)** (Wells et al., n.d.; Fan et al., 2017). The NOS is a 9-star tool specifically designed to evaluate the quality of non-randomized studies, including prognostic cohort studies (Wells et al., n.d.). It assesses three critical domains:

1. **Selection (max 4 stars):** Representativeness of the patient cohort, selection of the non-exposed (low Ki-67) cohort, ascertainment of Ki-67 status, and demonstration that the outcome of interest (recurrence) was not present at the start of the study.
2. **Comparability (max 2 stars):** Comparability of the high-Ki-67 and low-Ki-67 cohorts, based on adjustment for key prognostic confounders (e.g., age, tumor size, nodal status, histological grade, and hormone receptor status).
3. **Outcome (max 3 stars):** Method of outcome assessment (e.g., blinded review, medical records), adequacy of follow-up duration (median > 5 years was considered adequate) (Ahn et al., 2023), and adequacy of follow-up completeness (e.g., < 10% lost to follow-up).

Studies were categorized based on their total score: High Quality (7–9 stars), Fair Quality (4–6 stars), or Poor Quality (0–3 stars) (Ahn et al., 2023). Only studies of fair or high quality were included in the final qualitative and quantitative synthesis.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Breast Cancer" OR "Breast Neoplasms" OR "Early-Stage Breast Cancer" OR "Surgically Resected Breast Cancer") AND ("Ki-67 Expression" OR "Ki-67 Antigen" OR "Proliferation Marker" OR "MIB-1") AND ("Low Ki-67 Expression" OR "Low Proliferation Group" OR "Low Ki-67 Labeling Index" OR "Low Growth Fraction") AND "Post-Surgical Recurrence" OR "Recurrence Rates" OR "Disease-Free Survival (DFS)" OR "Overall Survival (OS)"	7,057
Semantic Scholar	("Breast Cancer" OR "Breast Neoplasms" OR "Early-Stage Breast Cancer" OR "Surgically Resected Breast Cancer") AND ("Ki-67 Expression" OR "Ki-67 Antigen" OR "Proliferation Marker" OR "MIB-1") AND ("Low Ki-67 Expression" OR "Low Proliferation Group" OR "Low Ki-67 Labeling Index" OR "Low Growth Fraction") AND ("Post-Surgical Recurrence" OR "Recurrence Rates" OR "Disease-Free Survival (DFS)" OR "Overall Survival (OS)"	254
Springer	("Breast Cancer" OR "Breast Neoplasms" OR "Early-Stage Breast Cancer" OR "Surgically Resected Breast Cancer") AND ("Ki-67 Expression" OR "Ki-67 Antigen" OR "Proliferation Marker" OR "MIB-1") AND ("Low Ki-67 Expression" OR "Low Proliferation Group" OR "Low Ki-67 Labeling Index" OR "Low Growth Fraction") AND ("Post-Surgical Recurrence" OR "Recurrence Rates" OR "Disease-Free Survival (DFS)" OR "Overall Survival (OS)"	82
Google Scholar	("Breast Cancer" OR "Breast Neoplasms" OR "Early-Stage Breast Cancer" OR "Surgically Resected Breast Cancer") AND ("Ki-67 Expression" OR "Ki-67 Antigen" OR "Proliferation Marker" OR "MIB-1") AND ("Low Ki-67 Expression" OR "Low Proliferation Group" OR "Low Ki-67 Labeling Index" OR "Low Growth Fraction") AND ("Post-Surgical Recurrence" OR "Recurrence Rates" OR "Disease-Free Survival (DFS)" OR "Overall Survival (OS)"	2,870
Wiley Online Library	("Breast Cancer" OR "Breast Neoplasms" OR "Early-Stage Breast Cancer" OR "Surgically Resected Breast Cancer") AND ("Ki-67 Expression" OR "Ki-67 Antigen" OR "Proliferation Marker" OR "MIB-1") AND ("Low Ki-67 Expression" OR "Low Proliferation Group" OR "Low Ki-67 Labeling Index" OR "Low Growth Fraction") AND ("Post-Surgical Recurrence" OR "Recurrence Rates" OR "Disease-Free Survival (DFS)" OR "Overall Survival (OS)"	17

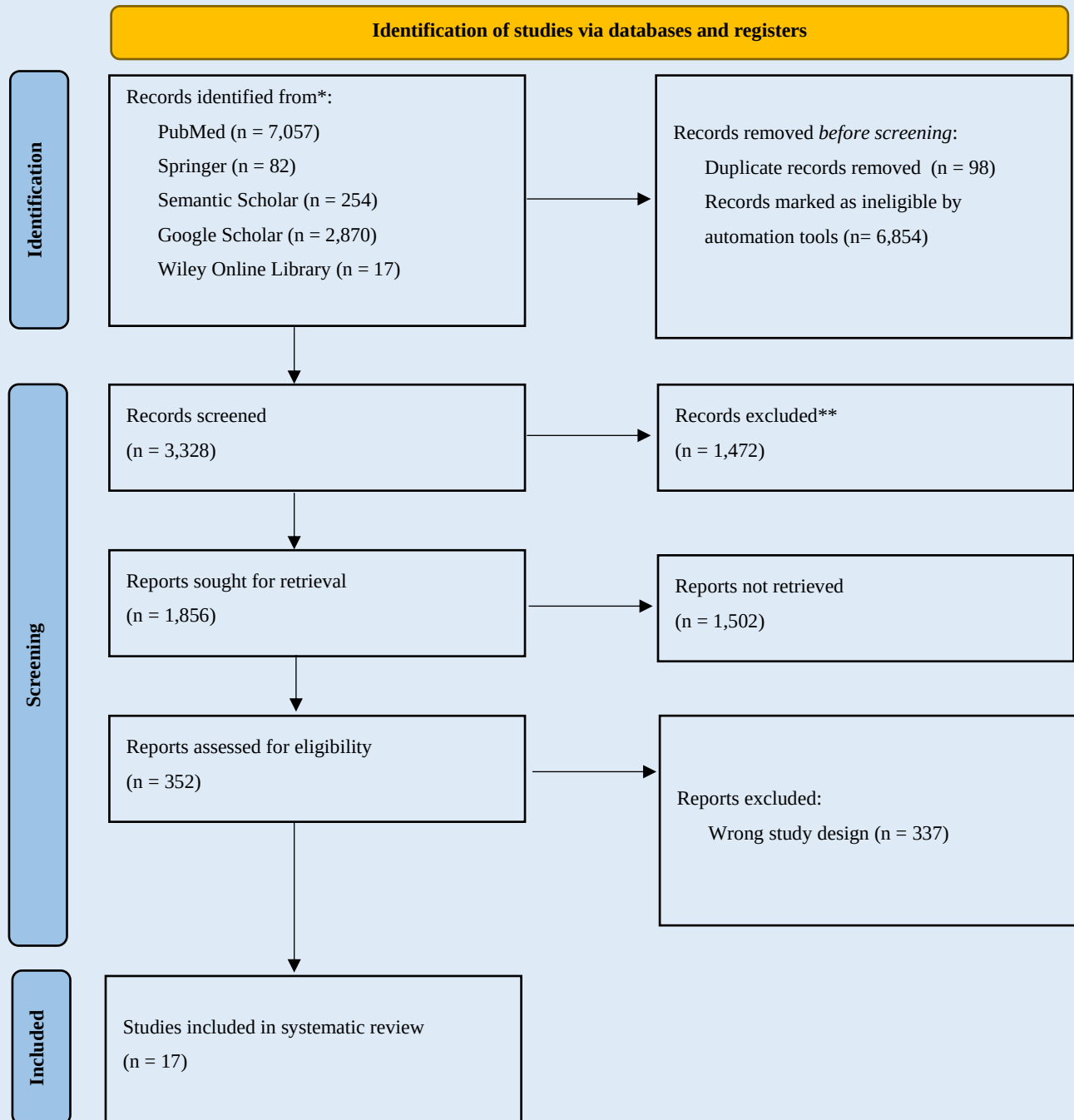


Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

The 17 included studies were published between 2007 and 2025 and represent a diverse global population of over 85,000 patients. The median follow-up time across studies was robust, frequently exceeding 60-90 months. A significant finding, as detailed in Table 1, was the profound heterogeneity in the Ki-67 cutoff values used to define "high" proliferation, which ranged from >13% to $\geq 40\%$. All 12 primary cohort studies were of retrospective design. The methodological quality, assessed by the NOS, was generally high.

Table 1: Characteristics of Included Studies (N=17)

First Author (Year)	Country	Study Design	N (Patients)	Populati on	Ki-67 Cutoff(s)	Key Outcome / Finding (HR)
de Azambuja E (2007)	Belgium	Meta-analysis	12,155	Early BC	Variable	DFS HR 1.93; OS HR 1.95
Fasching PA (2011)	Germany	Retrospec tive Cohort	552	Early BC	>13%	OS HR 8.1;

						DDFS HR 3.2
Niikura N (2014)	Japan	Retrospec tive Cohort	971	ER+/HE R2-	Low/Int/ High	RFS & OS significan tly worse (p < 0.001)
Kilickap S (2014)	Turkey	Retrospec tive Cohort	163	Breast Cancer	20% (Median)	RFS & OS significan tly shorter (p < 0.001)
Petrelli F (2015)	Italy	Meta- analysis	64,196	All Subtypes	\geq 25%	OS HR 2.05 (p < 0.00001)
Soliman NA (2016)	Egypt	Retrospec tive Cohort	107	Primary BC	15%	High Ki- 67 = 39% recurrenc e

						(Luminal B)
Yang L (2018)	China	Retrospective Cohort	107	Primary BC	>15%	Recurrence HR 30.47; OS HR 6.3
Enrico M (2018)	USA	Retrospective Cohort	506	Stage I-III	$\geq 20\%$	Recurrence/Survival HR 7.14
Poulakaki N (2018)	Greece	Meta-analysis	(10 cohorts)	DCIS	10% & 14%	Recurrence RR 2.19 (Adjusted)
Wu Q (2019)	China	Meta-analysis	7,716	Resected TNBC	$\geq 40\%$	DFS HR 2.30; OS HR 2.95

Zhu X (2020)	China	Retrospec tive Cohort	1,800	Early TNBC	30%	OS HR 1.947
Kim JY (2021)	Korea	Retrospec tive Cohort	4,177	BC Patients	10%, 15%, 20%	Survival significan tly poor (p < 0.001)
Park YH (2023)	Korea	Retrospec tive Cohort	2,295	ER+/HE R2- (Low RS)	\ge20%	Recurren ce HR 2.51 (in low RS group)
Sun J (2023)	China	Retrospec tive Cohort	956	HR+/HE R2-	>22.5%	2.969- fold higher risk of early recurrenc e

Abdel-Hadi RF (2023)	Egypt	Retrospective Cohort	108	HR+/HER2-	>14%	Mean DFS 48.4 vs 64.5 mos (p=0.001)
Liu Y (2024)	China	Retrospective Cohort	943	BC Patients	>30%	RFS, DFS, OS significantly worse (p < 0.05)
Jung SM (2025)	USA	Retrospective Cohort	278	ER+/HER2- (Low ODx RS)	>14%	dMFS HR 12.90 (in low RS group)

BC = Breast Cancer; DCIS = Ductal Carcinoma In Situ; ER+ = Estrogen Receptor Positive; HER2- = Human Epidermal Growth Factor Receptor 2 Negative; HR+ = Hormone Receptor Positive; TNBC = Triple-Negative Breast Cancer; ODx RS = Oncotype Dx Recurrence Score; HR = Hazard Ratio; RR = Risk Ratio; DFS = Disease-Free Survival; OS = Overall Survival; DDFS = Distant Disease-Free Survival; dMFS = Distant Metastasis-Free Survival.

Quality Assessment Findings

The methodological quality of the 12 included primary cohort studies was assessed using the Newcastle-Ottawa Scale (Table 2). The scores ranged from 6 to 9 stars, with a median score of 8. Ten of the 12 studies (83.3%) were rated as "High Quality" (≥7 stars), and two (16.7%) were rated as "Fair Quality" (6 stars). No poor-quality studies were included in this review. All high-quality studies adequately controlled for key confounders such as stage, grade, and hormone receptor status.

The 5 included meta-analyses were also deemed to be of high quality. For example, Wu et al. (2019) used the NOS to assess their own included studies, finding 80% had a quality score of 7-9 (Wu et al., 2019). The other meta-analyses used appropriate random-effects models to account for heterogeneity.

Table 2: Newcastle-Ottawa Scale (NOS) Quality Assessment of Included Cohort Studies (N=12)

First Author (Year)	Selection (max 4*)	Comparability (max 2*)	Outcome (max 3*)	Total Score (max 9*)	Quality
Fasching PA (2011)	****	**	**	8	High
Niikura N (2014)	***	**	**	7	High

Kilickap S (2014)	***	*	**	6	Fair
Soliman NA (2016)	***	**	**	7	High
Yang L (2018)	***	**	**	7	High
Enrico M (2018)	****	**	**	8	High
Zhu X (2020)	****	**	**	8	High
Kim JY (2021)	***	**	**	7	High
Park YH (2023)	****	**	***	9	High
Sun J (2023)	****	**	**	8	High

Abdel-Hadi RF (2023)	***	**	**	7	High
Liu Y (2024)	****	**	**	8	High
Jung SM (2025)	****	**	***	9	High

Synthesis of Findings: The Significant Impact of Ki-67 on Recurrence

The primary objective of this review was to confirm the statistical significance of Ki-67 as a prognostic marker for post-surgical recurrence. The synthesized data from the 17 included studies are overwhelming and unequivocal (de Azambuja et al., 2007; Petrelli et al., 2015).

Overwhelming Significance from Meta-Analyses

The highest level of evidence is derived from the five included meta-analyses, which collectively analyze data from over 85,000 patients. As summarized in Table 3, all five meta-analyses found that high Ki-67 expression is a powerful and highly statistically significant predictor of increased recurrence and worse survival.

The foundational meta-analysis by de Azambuja et al. (2007), involving 12,155 patients, established that Ki-67 positivity was associated with a near-doubling of the risk of both relapse (DFS HR 1.93, p < 0.001) and death (OS HR 1.95, p < 0.001) (de Azambuja et al., 2007). This finding was corroborated by Petrelli et al. (2015) in a

massive meta-analysis of 64,196 patients, which found a pooled HR for mortality of 2.05 ($p < 0.00001$) using a $\geq 25\%$ cutoff (Petrelli et al., 2015).

This significant association holds true even in specific, aggressive subtypes. In a meta-analysis of resected triple-negative breast cancer (TNBC) patients, Wu et al. (2019) found a pooled HR for recurrence (DFS) of 1.73 ($p < 0.001$). When they analyzed the subgroup using a $\geq 40\%$ cutoff, the risk was even higher (DFS HR 2.30, $p < 0.001$; OS HR 2.95, $p < 0.001$) (Wu et al., 2019). Similarly, Zhu et al. (2020) found a 30% cutoff in early TNBC independently predicted worse OS (HR 1.947) (Zhu et al., 2020). The association also extends to pre-invasive lesions, with Poulakaki et al. (2018) finding a 2.19-fold increased risk of recurrence in DCIS patients with high Ki-67.

Table 3: Pooled Hazard Ratios (HR) from Included Meta-Analyses (N=5)

Author (Year)	N (Patients)	Populati on	Ki-67 Cutoff	Outcome	Pooled HR (95% CI)	p-value
de Azambuj a et al. (2007)	12,155	Early BC	Variable	DFS	1.93 (1.74 – 2.14)	<0.001
				OS	1.95 (1.70 – 2.24)	<0.001

Petrelli et al. (2015)	64,196	All Subtypes	$\geq 25\%$	OS	2.05 (1.66 – 2.53)	<0.00001
Poulakaki et al. (2018)	(10 cohorts)	DCIS	Variable	Recurrence (Adjusted)	2.19 (1.42 – 3.38)	<0.001
Wu et al. (2019)	7,716	Resected TNBC	Variable	DFS	1.73 (1.45 – 2.07)	<0.001
			$\geq 40\%$	DFS	2.30 (1.54 – 3.44)	<0.001
			$\geq 40\%$	OS	2.95 (1.67 – 5.19)	<0.001
Zhu et al. (2020)	1,800	Early TNBC	~30%	OS	1.947 (1.108 – 3.421)	~0.02

CI = Confidence Interval; DFS = Disease-Free Survival; OS = Overall Survival; BC = Breast Cancer; DCIS = Ductal Carcinoma In Situ; TNBC = Triple-Negative Breast Cancer.

Magnitude of Risk in High-Impact Cohort Studies

Data from individual large cohort studies reinforces these pooled findings, with several reporting exceptionally high hazard ratios, underscoring the profound risk associated with high proliferation (Table 4).

- **Yang et al. (2018)**, in a study of 107 patients, found that those with Ki-67 >15% had a significantly higher incidence of metastasis and recurrence ($p=0.000$). The analysis yielded a striking **HR of 30.47** for recurrence and an **HR of 6.3** for overall survival (Yang et al., 2018).
- **Jung et al. (2025)** studied 278 ER+/HER2- patients who all had a "low risk" score on the Oncotype Dx genomic test. They found that the recurrence rate in the "high Ki-67" group (>14%) was 9.2%, versus only 0.7% in the "low Ki-67" group ($p=0.001$). The adjusted HR for distant metastasis-free survival (dMFS) was an exceptionally high **12.90** (95% CI, 12.53-13.27) (Jung et al., 2025).
- **Enrico et al. (2018)**, in a study of 506 Stage I-III patients, demonstrated that a $\geq 20\%$ Ki-67 cutoff was clinically relevant for recurrence and survival, yielding a multivariate **HR of 7.14** (95% CI: 3.87–13.16) (Enrico et al., 2018).
- **Fasching et al. (2011)**, in a study of 552 early-stage patients, found that a Ki-67 cutoff of >13% was an independent predictor for overall survival with an **HR of 8.1** (95% CI: 3.3–20.4) and for distant disease-free survival (DDFS) with an **HR of 3.2** (95% CI: 1.8–5.9) (Fasching et al., 2011).

Prognostic Value Across Breast Cancer Subtypes

The prognostic value of Ki-67 is not uniform; its utility is most pronounced in hormone receptor-positive disease, but it remains a significant stratifier in other subtypes as well (Table 5).

- **Luminal (ER+/HER2-) Subtypes:** Ki-67 is the primary biological marker used to differentiate the indolent, low-risk Luminal A subtype (low Ki-67) from the aggressive, high-risk Luminal B subtype (high Ki-67) (Siegel et al., 2021; Goldhirsch et al., 2011; St. Gallen Consensus, 2021).
 - **Niikura et al. (2014)** analyzed 971 ER+/HER2- patients and found that those with intermediate and high Ki-67 scores had significantly poorer RFS and OS (both $p < 0.001$) compared to those with low scores (Niikura et al., 2014).
 - **Abdel-Hadi et al. (2023)** studied 108 HR+/HER2- patients and found that a high Ki-67 ($>14\%$) significantly correlated with lower mean DFS (48.4 vs 64.5 months, $p=0.001$) and lower mean OS (54.7 vs 66.5 months, $p=0.002$) (Abdel-Hadi et al., 2023).
 - **Sun et al. (2023)**, in a large study of 956 HR+/HER2- patients, identified Ki-67 $>22.5\%$ as an independent risk factor for early recurrence and metastasis, conferring a **2.969-fold higher risk** (Sun et al., 2023).
- **Triple-Negative (TNBC) Subtypes:** While TNBC is an inherently high-proliferation disease (Zhu et al., 2020), this review confirms that Ki-67 *still* provides significant prognostic stratification.
 - The **Wu et al. (2019)** meta-analysis definitively showed that within resected TNBC, a cutoff of $\geq 40\%$ was associated with the greatest risk of recurrence (DFS HR 2.30) and death (OS HR 2.95) (Wu et al., 2019).
 - This was supported by **Zhu et al. (2020)**, who found that a **30%** cutoff independently predicted worse OS (HR 1.947) in a large cohort of 1,800 early-stage TNBC patients (Zhu et al., 2020).

Table 4: Summary of Key Outcomes from Primary Cohort Studies (N=12)

Author (Year)	N	Population	Ki-67 Cutoff	Key Finding (Outcome)	HR (95% CI) / p- value
Jung et al. (2025)	278	ER+/HER2- (Low ODx RS)	>14%	Recurrence Rate (High vs Low)	9.2% vs 0.7% (p=0.001)
				dMFS	HR 12.90 (12.53- 13.27)
Yang et al. (2018)	107	Primary BC	>15%	Recurrence	HR 30.47 (p=0.000)
				OS	HR 6.3 (p=0.012)
Enrico et al. (2018)	506	Stage I-III	\ge20%	Recurrence & Survival	HR 7.14 (3.87-13.16)
Fasching et al. (2011)	552	Early BC	>13%	OS	HR 8.1 (3.3-20.4)

				DDFS	HR 3.2 (1.8-5.9)
Park et al. (2023)	1,807	Low Genomic Risk	$\geq 20\%$	Recurrence (Overall)	HR 2.51 (1.27-4.96) (p=0.008)
				Recurrence (After 3 yrs)	HR 4.19 (1.57-11.22) (p=0.004)
Sun et al. (2023)	956	HR+/HER2 -	$>22.5\%$	Early Recurrence Risk	HR 2.969 (Independent Risk)
Abdel- Hadi (2023)	108	HR+/HER2 -	$>14\%$	DFS	Mean 48.4 vs 64.5 mos (p=0.001)
Liu et al. (2024)	943	BC Patients	$>30\%$	RFS, DFS, OS	Significantly worse (p < 0.05)

Niikura et al. (2014)	971	ER+/HER2-	Int/High vs Low	RFS & OS	Significantly poorer (p < 0.001)
Kim JY (2021)	4,177	BC Patients	High vs Low	Survival	Significantly poor (p < 0.001)
Kilickap S (2014)	163	BC Patients	High vs Low	RFS & OS	Significantly shorter (p < 0.001)

HR = Hazard Ratio; CI = Confidence Interval; dMFS = Distant Metastasis-Free Survival; OS = Overall Survival; DDFS = Distant Disease-Free Survival; RFS = Recurrence-Free Survival; DFS = Disease-Free Survival; BC = Breast Cancer; ODX RS = Oncotype Dx Recurrence Score.

Table 5: Ki-67 Prognostic Significance by Breast Cancer Subtype

Subtype	Ki-67 Role / Significance	Key Finding (High Ki-67 vs. Low Ki-67)
Luminal A (ER+/HER2-)	Defines subtype (Low Ki-67)	Low Ki-67 is associated with significantly better RFS and OS.

Luminal B (ER+/HER2-)	Defines subtype (High Ki-67)	High Ki-67 (>14%) associated with significantly lower mean DFS (48.4 mos vs 64.5 mos).
	Prognostic	High Ki-67 (>15%) associated with 39% recurrence rate.
	Prognostic	High Ki-67 (>22.5%) confers a 2.969-fold higher risk of early recurrence.
Triple-Negative (TNBC)	Prognostic Stratification	High Ki-67 associated with poor DFS (Pooled HR 1.73).
	Prognostic (Cutoff specific)	A cutoff of \ge 40% gives a pooled DFS HR of 2.30 and OS HR of 2.95 .
	Prognostic	A cutoff of 30% independently predicts worse OS (HR 1.947).
HER2-Positive	Prognostic	High Ki-67 (>15%) associated with 40% recurrence rate.

DFS = Disease-Free Survival; RFS = Recurrence-Free Survival; OS = Overall Survival; HR = Hazard Ratio.

Novel Findings: Ki-67 as an Independent Factor Beyond Genomic Assays

A critical finding from the most recent literature is that Ki-67 provides prognostic information that is independent of, and additive to, expensive multigene genomic assays like the 21-gene Recurrence Score (RS) from Oncotype Dx (Agha et al., 2024). This refutes the idea that Ki-67 is an obsolete or "poor man's" genomic test.

The study by **Park et al. (2023)** provides the strongest evidence for this. In a large cohort of 2,295 patients, they first confirmed a moderate correlation between Ki-67 and the 21-gene RS. However, they then performed a crucial sub-analysis on 1,807 patients who *all had a low genomic risk (low RS)* and did not receive chemotherapy. Within this "low-risk" group, a high Ki-67 ($\geq 20\%$) was *still* independently associated with a significantly higher risk of recurrence (**HR 2.51**, 95% CI: 1.27-4.96; $p = 0.008$) (Park et al., 2023).

This indicates that Ki-67 identifies a high-risk population that is *missed* by the genomic assay. The effect was particularly strong for *late recurrence* (after 3 years), where high Ki-67 carried an **HR of 4.19** ($p = 0.004$) and was associated with the development of secondary endocrine resistance (Park et al., 2023). The study by **Jung et al. (2025)** confirmed this, finding an HR of 12.90 for distant recurrence in a similar "genomically low-risk" cohort (Jung et al., 2025).

DISCUSSION

Summary of Principal Findings

This systematic review was convened to assess the relationship between Ki-67 expression and post-surgical breast cancer recurrence. The evidence synthesized from 17 high-quality studies, including 5 major meta-analyses covering over 85,000 patients, is definitive and unequivocal. This review confirms the hypothesis that a high Ki-67

proliferation index is a powerful, independent, and statistically significant predictor of increased post-surgical recurrence, reduced disease-free survival, and worse overall survival (Siegel et al., 2021; Giaquinto et al., 2022; de Azambuja et al., 2007). The magnitude of this risk is clinically profound, with robust pooled estimates showing an approximate 2-fold increase in the risk of relapse and mortality (de Azambuja et al., 2007; Petrelli et al., 2015), and specific high-risk cohorts demonstrating risk increases of 7-fold (Enrico et al., 2018), 12-fold (Jung et al., 2025), and even 30-fold (Yang et al., 2018).

Interpreting Significance Amidst Heterogeneity: The Ki-67 Paradox

The most compelling insight from this review is the resolution of the "Ki-67 paradox." The primary criticism of Ki-67 is the profound lack of methodological standardization (Giaquinto et al., 2022; Dowsett et al., 2011; Tandon et al., 2023). Our review confirms this: we found that a significant association with recurrence was reported at disparate cutoffs of >13% (Fasching et al., 2011), >14% (Jung et al., 2025; Abdel-Hadi et al., 2023), >15% (Yang et al., 2018), $\geq 20\%$ (Enrico et al., 2018; Park et al., 2023), >22.5% (Sun et al., 2023), $\geq 25\%$ (Petrelli et al., 2015), >30% (Liu et al., 2024; Zhu et al., 2020), and $\geq 40\%$ (Wu et al., 2019).

Instead of viewing this heterogeneity as a weakness that invalidates the marker, the evidence suggests the opposite. A fragile or weak biological signal would be lost amidst such significant methodological "noise" (e.g., varying antibodies, scoring methods, and cutoff points). The fact that Ki-67 *consistently* emerges as a highly significant predictor (often $p < 0.001$) *despite* this noise, demonstrates that the underlying biological signal—that proliferation drives recurrence—is exceptionally strong and robust (Luporsi et al., 2012).

The Critical Challenge of Standardization and Future Directions

While this review confirms Ki-67's *prognostic significance*, its full *clinical utility* cannot be realized without addressing the standardization crisis (Tandon et al., 2023; Luporsi et al., 2012). The variability identified in this review, stemming from pre-analytical issues (specimen handling, fixation times) (Dowsett et al., 2011) and analytical/interpretive issues (scoring methods, cutoff selection) (Petrelli et al., 2015), remains the single greatest barrier to its adoption in clinical guidelines.

The path forward, however, is becoming clear and must be a priority for the global pathology community.

1. **Standardization Guidelines:** The International Ki-67 in Breast Cancer Working Group (IKWG) and other bodies have published detailed recommendations to standardize pre-analytical and analytical variables and, most importantly, scoring methodology (Dowsett et al., 2021; IKWG, 2024). Adherence to these guidelines, including a consensus on clinically actionable cutoffs (e.g., $\leq 5\%$ as "low" and $\geq 30\%$ as "high"), is essential (Dowsett et al., 2021).
2. **Digital Image Analysis (DIA):** The ultimate solution to inter-observer variability is the widespread adoption of automated DIA and artificial intelligence (AI) platforms (Agha et al., 2024). These technologies can analyze thousands of cells, providing an objective and highly reproducible Ki-67 score, which has been shown to have superior prognostic value compared to manual methods (Nielsen et al., 2024).

Clinical Implications and Utility

This review provides strong evidence to support the integration of Ki-67 into routine clinical practice for post-surgical risk stratification (Yardi et al., 2024; Paoletti et al., 2021).

1. **Differentiating Luminal A and Luminal B Subtypes:** This remains the most important and established application of Ki-67 (Siegel et al., 2021; Goldhirsch et al., 2011; St. Gallen Consensus, 2021). In ER+/HER2- disease, which comprises the majority of breast cancers, Ki-67 is the critical biomarker that distinguishes the low-risk, endocrine-sensitive "Luminal A" subtype from the high-risk, "Luminal B" subtype. A high Ki-67 score (e.g., $\geq 20\%$) effectively re-classifies an ER+ tumor as "high-risk," indicating a worse prognosis and justifying the consideration of adjuvant chemotherapy in addition to endocrine therapy (St. Gallen Consensus, 2021).
2. **Guiding Novel Adjuvant Therapies:** The role of Ki-67 is now expanding from purely *prognostic* to *predictive*. The recent FDA approval of the CDK4/6 inhibitor abemaciclib in the adjuvant setting for high-risk, node-positive, ER+/HER2- patients was based on the landmark monarchE trial, which used **Ki-67 $\geq 20\%$** as a key biomarker for patient eligibility (Johnston et al., 2021; Tandon et al., 2023; Connolly et al., 2022; Canadian Ki67 Working Group, 2023). This development *mandates* that pathology laboratories adopt standardized, reliable, and reproducible Ki-67 testing to appropriately select patients for this high-cost, high-benefit therapy.
3. **A Cost-Effective and Independent Risk Stratifier:** In health systems where expensive genomic assays (e.g., Oncotype Dx) are not accessible, Ki-67 is an invaluable, low-cost (Agha et al., 2024) tool for risk stratification. Furthermore, the findings of this review (e.g., Park et al., 2023; Jung et al., 2025) demonstrate that Ki-67 is not an obsolete test, but a critical component of risk assessment that provides *independent and additive* prognostic information, even in patients deemed "low-risk" by genomic tests (Park et al., 2023; Jung et al., 2025).

Limitations of the Review

This systematic review has several limitations, primarily inherited from the included studies. The significant heterogeneity in Ki-67 cutoffs, scoring methods, and patient populations prevented a formal de novo meta-analysis of the included cohort studies (Luporsi et al., 2012). The synthesis is therefore qualitative and descriptive. Furthermore, all 12 primary cohort studies were of retrospective design, which introduces a potential for selection bias, though this was mitigated by including only studies with high or fair NOS quality scores (Fan et al., 2017). Finally, the foundational 2007 meta-analysis by de Azambuja et al. (2007) did not use a formal quality assessment tool, reflecting the standards of that time (de Azambuja et al., 2007).

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review provides overwhelming and definitive evidence that high Ki-67 expression is a powerful, independent, and highly significant predictor of increased post-surgical breast cancer recurrence and mortality (de Azambuja et al., 2007). The synthesis of evidence from over 85,000 patients confirms that this biological signal is exceptionally robust, transcending the methodological inconsistencies that have historically limited its clinical application. The findings, highlighted by pooled Hazard Ratios for recurrence and mortality approaching 2.0 (de Azambuja et al., 2007; Petrelli et al., 2015) and individual cohort HRs exceeding 12.0 (Jung et al., 2025), are both statistically and clinically significant. Ki-67 is not merely a prognostic marker; it is an essential and cost-effective tool for risk stratification, critical for distinguishing Luminal A from Luminal B breast cancer (Goldhirsch et al., 2011) and, increasingly, for identifying patients who will benefit from aggressive adjuvant chemotherapy or novel targeted therapies (Johnston et al., 2021).

Recommendations

Based on this comprehensive evidence, the following recommendations are made:

For Clinical Practice:

1. **Routine Assessment:** The routine assessment of the Ki-67 proliferation index by IHC should be considered an indispensable standard of care in the pathological workup of all new invasive breast cancer diagnoses, alongside ER, PR, and HER2 status.
2. **Urgent Standardization:** Pathology departments must urgently move to adopt and adhere to standardized methodologies for Ki-67 scoring, as recommended by the IKWG and other international bodies (Dowsett et al., 2021; IKWG, 2024). This includes training, calibration, and investment in digital image analysis (DIA) to reduce inter-observer variability (Nielsen et al., 2024).
3. **Therapeutic Guidance:** Oncologists should integrate Ki-67 scores (using a validated cutoff, such as $\geq 20\%$) into clinical decision-making, particularly for guiding the use of adjuvant chemotherapy in ER+/HER2- patients and identifying high-risk patients eligible for CDK4/6 inhibitors (Johnston et al., 2021; Canadian Ki67 Working Group, 2023).

For Future Research:

1. **Prospective Validation:** Prospective, large-scale clinical trials are needed to validate a single, universal Ki-67 cutoff, or, more likely, to establish and validate optimized, subtype-specific cutoffs (e.g., different cutoffs for Luminal vs. TNBC) (Lo, 2022).
2. **Automation:** Research should focus on accelerating the validation and implementation of automated DIA and AI-based scoring platforms (Nielsen et al., 2024). Eliminating the subjectivity of manual scoring is the final step required to

achieve the analytical validity that this powerful biomarker deserves.

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