

Molecular Classification of Breast Cancer and Its Implications for Contemporary Management: A PRISMA-Guided Narrative Review

Sudhir Kumar Jain^{1*}, Tirlok Chand²

¹Hamdard Institute of Medical Sciences and Research, Jamia Hamdard University, New Delhi, India

²Maulana Azad Medical College, University of Delhi, New Delhi, India

Email: *sudhirkumarjain@jamiahamdard.ac.in

How to cite this paper: Jain, S.K. and Chand, T. (2026) Molecular Classification of Breast Cancer and Its Implications for Contemporary Management: A PRISMA-Guided Narrative Review. *Surgical Science*, 17, 451-463.

<https://doi.org/10.4236/ss.2026.1710042>

Received: September 5, 2026

Accepted: October 19, 2026

Published: October 22, 2026

Copyright © 2026 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

Background: Breast cancer is biologically heterogeneous, and gene-expression studies have demonstrated clinically relevant intrinsic subtypes with differing patterns of prognosis and treatment response. Contemporary management, however, does not rely on intrinsic subtype alone; clinicopathological factors, immunohistochemistry (IHC), *in situ* hybridization, validated genomic assays, germline alterations, and treatment-specific biomarkers are integrated to guide therapy. **Objective:** This paper aims to review the evolution of molecular classification of breast cancer and critically summarize how molecular and biomarker information informs contemporary diagnosis, prognostication, systemic treatment, and precision-oncology strategies. **Methods:** A PRISMA-guided narrative review was conducted using PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, and Google Scholar, with reference-list screening of landmark molecular studies, clinical trials, and major guidelines. Searches covered database inception through June 2025. Titles and abstracts were screened, followed by full-text assessment; two reviewers independently screened and extracted data, with disagreements resolved by discussion and, when necessary, a third reviewer. Evidence was synthesized narratively, with explicit separation of intrinsic molecular subtypes, prognostic assays, predictive biomarkers, and treatment-eligibility biomarkers. **Results:** The reviewed evidence supports a layered model of classification. Intrinsic subtypes are transcriptomic constructs and are not interchangeable with routine IHC-defined clinical categories; in particular, HER2-enriched is not defined by ERBB2 amplification. Validated genomic assays have assay- and population-specific roles in HR-positive/HER2-negative early breast cancer, ranging from recurrence-

risk estimation to chemotherapy-benefit assessment in defined populations. In TNBC, treatment selection is driven primarily by disease setting and validated biomarkers such as germline BRCA1/2 and PD-L1 in specific metastatic contexts, whereas proposed transcriptomic subclasses remain investigational. HER2-low is a treatment-relevant IHC expression category rather than an intrinsic molecular subtype. Overall, molecular information is most useful when integrated with stage, pathology, receptor status, and patient factors. **Conclusion:** Molecular classification has moved breast oncology from morphology-based categorization toward biologically informed treatment selection. Its greatest clinical value arises when molecular information is interpreted in context rather than used as a substitute for stage, histological features, receptor status, patient factors, and validated treatment-specific biomarkers.

Keywords

Breast Cancer, Molecular Classification, Intrinsic Subtypes, HER2-Enriched, Triple-Negative Breast Cancer, HER2-Low, Genomic Assays, Precision Oncology

1. Introduction

Breast cancer is the most frequently diagnosed cancer among women worldwide and remains a major cause of cancer mortality. Its biological heterogeneity is reflected in substantial differences in natural history, endocrine sensitivity, response to chemotherapy, sensitivity to targeted therapies, and patterns of recurrence. Conventional histopathology, tumour grade, stage, and receptor assessment remain essential, but they do not capture the full biological diversity of breast cancer.

Gene-expression profiling provided the foundation for intrinsic molecular classification. Perou and colleagues identified reproducible gene-expression patterns that included luminal, HER2-related, basal-like, and normal-breast-like groups; subsequent work refined these categories and demonstrated associations with clinical outcome [1] [2]. Importantly, intrinsic molecular subtypes and routine clinical biomarkers overlap but are not synonymous. A tumour classified as HER2-enriched by a transcriptomic assay may be HER2-negative by conventional IHC/ISH, while many clinically HER2-positive tumours do not necessarily belong to the HER2-enriched intrinsic subtype.

The therapeutic relevance of molecular information has expanded substantially. Endocrine therapy remains central to hormone-receptor-positive disease, HER2-directed treatment is determined by validated clinical HER2 testing, and genomic assays can refine recurrence-risk estimation and, in selected populations, inform chemotherapy decisions [3]-[8].

This review therefore focuses on the clinically meaningful relationship between molecular classification and treatment while avoiding conflation of prognostic classification, predictive biomarkers, and treatment eligibility.

2. Methods

2.1. Review Design

This systematic narrative review was reported using the PRISMA 2020 framework for transparent identification, screening, eligibility assessment, and reporting of the literature. The review was designed to synthesize landmark molecular studies, contemporary clinical trials, validated genomic assays, and major clinical-practice guidelines rather than to perform a quantitative meta-analysis [9]. Searches were conducted through June 2025 (final search month: June 2025).

2.2. Information Sources and Search Strategy

The information sources were PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, and Google Scholar. Reference lists of key molecular studies, clinical trials, and guideline documents were also screened. The search covered database inception through June 2025. The core concept combined breast cancer with molecular classification/intrinsic subtypes and clinically relevant treatment, biomarker, prognosis, or genomic-assay terms. Database-specific syntax was adapted to each platform; the reproducible search strings used for this revision are provided in Supplementary **Table S1**.

2.3. Eligibility Criteria

Eligible literature comprised peer-reviewed human studies addressing breast-cancer molecular classification, intrinsic subtypes, clinically validated biomarkers, genomic assays, targeted treatment, immunotherapy, antibody-drug conjugates, or precision-oncology approaches. Landmark molecular studies, randomized clinical trials, prospective validation studies, systematic reviews, and major international guidelines were prioritized. Non-human studies, duplicate publications, conference abstracts without adequate full text, and publications without direct relevance to the review question were excluded.

2.4. Screening, Data Extraction, and Reviewer Roles

Titles and abstracts were screened against the predefined eligibility criteria, followed by full-text assessment of potentially relevant reports. Two reviewers independently screened records and extracted data. Disagreements were resolved by discussion and, when required, by a third reviewer. The extraction fields included study design, population, molecular classification or biomarker, clinical setting, treatment decision addressed, principal outcomes, and whether the evidence was prognostic, predictive, or treatment-eligibility defining.

2.5. Full-Text Exclusion

At full-text review, reports were excluded when they did not address the review question or eligible population, used a non-clinical/research-only classification without a relevant management implication, represented a duplicate or overlapping cohort, lacked sufficient clinical information, or did not provide usable full

text. The documented aggregate flow was 176 full-text reports assessed and 82 studies retained; therefore, 94 reports were excluded at full-text stage. The exclusion categories are listed in Supplementary **Table S2**.

2.6. Synthesis

Evidence was synthesized narratively. Particular attention was given to distinguishing intrinsic molecular subtype from IHC-defined clinical subtype, prognostic risk estimation from prediction of treatment benefit, and exploratory molecular associations from validated treatment-selection biomarkers. No quantitative meta-analysis was performed.

3. Results

The evidence synthesis was organized into intrinsic molecular classification, luminal disease, HER2-related disease, TNBC, HER2-low expression, genomic assays, and emerging precision-oncology strategies. The principal finding was that molecular information is most clinically useful when integrated with conventional pathology, anatomical stage, receptor testing, patient characteristics, and the treatment context. The study-selection process is summarized in **Figure 1**.

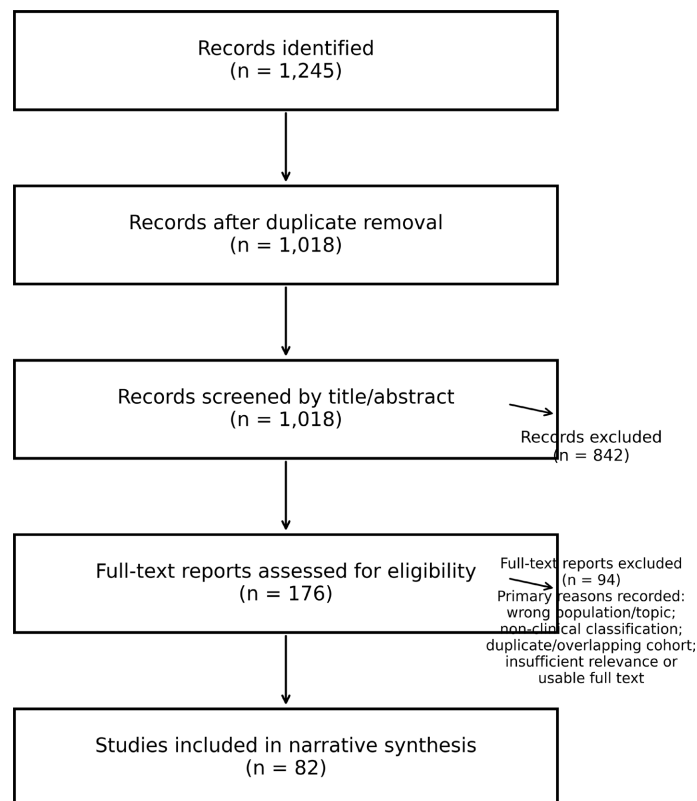


Figure 1. PRISMA 2020 study-selection flow diagram.

3.1. Evolution and Interpretation of Molecular Classification

The original intrinsic taxonomy included Luminal A, Luminal B, HER2-enriched,

basal-like, and normal-like patterns. Gene-expression profiling demonstrated reproducible biological patterns, while subsequent work established the clinical relevance and limitations of these intrinsic categories [1] [2]. Importantly, intrinsic subtypes are transcriptomic constructs and are not interchangeable with routine IHC-defined clinical categories. The relationship between intrinsic molecular patterns and routine clinical testing is summarized in **Table 1** and **Figure 2**. Intrinsic subtypes should not be reconstructed solely from ER, PR, HER2, and Ki-67 values; IHC and ISH remain the standard methods for defining clinical receptor status.

Table 1. Intrinsic molecular patterns and their relationship to routine clinical testing.

Intrinsic pattern	General biological features	Relationship to routine clinical testing	Clinical interpretation
Luminal A	ER-related, relatively low proliferation	Usually HR-positive/HER2-negative, but not identical to an IHC category	Generally endocrine-sensitive; recurrence risk is heterogeneous
Luminal B	Higher proliferation and/or less endocrine-dependent biology than Luminal A	Usually HR-positive; HER2 may be positive or negative	Greater recurrence risk in many cohorts; systemic treatment depends on stage and validated risk assessment
HER2-enriched	High expression of HER2-related and proliferation-associated genes	Not synonymous with HER2 amplification/overexpression	Transcriptomic subtype; anti-HER2 therapy is determined by clinical HER2 status, not the PAM50 label alone
Basal-like	Basal/epithelial and proliferation-associated gene-expression pattern	Frequently overlaps with TNBC, but not completely	Important biological concept; treatment is based on validated clinical biomarkers and disease setting
Normal-like/other	Less consistently reproducible as a clinical category	No direct routine treatment category	Primarily of biological/research interest

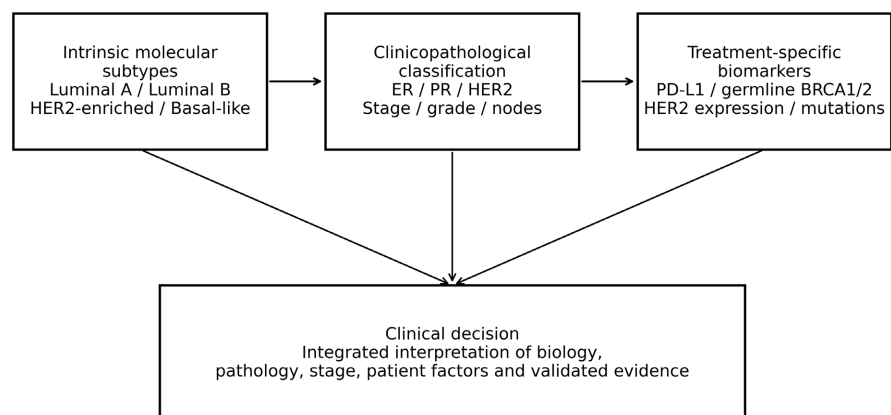


Figure 2. Relationship between intrinsic molecular classification, routine biomarkers, and treatment-specific biomarkers.

3.2. Luminal A and Luminal B Disease

Hormone-receptor-positive, HER2-negative breast cancer constitutes the largest clinical group. Endocrine therapy is the foundation of treatment, but recurrence

risk varies widely. The labels Luminal A and Luminal B are useful biological concepts rather than stand-alone treatment algorithms. Tumour size, nodal status, histological grade, receptor expression, proliferation, patient age/menopausal status, and genomic assay results may all contribute to adjuvant decisions. **Table 1** summarizes the relationship between intrinsic molecular patterns and routine clinical testing.

CDK4/6 inhibitors have expanded adjuvant treatment options for selected higher-risk HR-positive/HER2-negative early breast cancer. In monarchE, abemaciclib plus endocrine therapy improved invasive disease-free survival in a high-risk, node-positive population, with sustained benefit at longer follow-up [10] [11]. NATALEE subsequently demonstrated improved invasive disease-free survival with ribociclib plus a nonsteroidal aromatase inhibitor in a broader stage II/III HR-positive/HER2-negative population [12]. These results should be interpreted within their trial-defined populations rather than assigned generically to all Luminal B tumours.

3.3. HER2-Enriched versus Clinically HER2-Positive Breast Cancer

HER2-enriched is a gene-expression subtype and is not defined by ERBB2 amplification. HER2-enriched tumours may show high expression of HER2-related genes and pathway activation, but transcriptomic HER2-enriched status is not equivalent to HER2 amplification or IHC 3+ status [13]. Therefore, HER2-enriched should not be used as a synonym for clinically HER2-positive disease. For treatment purposes, clinical HER2 status remains based on validated IHC and ISH testing.

For treatment purposes, clinical HER2 status remains based on validated IHC and ISH testing. HER2-positive early breast cancer may receive neoadjuvant and/or adjuvant HER2-directed therapy according to stage and risk, while advanced disease can be treated with HER2-directed agents according to treatment line and clinical context [14] [15].

3.4. Triple-Negative Breast Cancer

TNBC is defined clinically by the absence of ER and PR expression and lack of HER2 overexpression/amplification according to accepted testing criteria. It is biologically heterogeneous, with basal-like, mesenchymal, luminal-androgen-receptor, immune-related, and other proposed transcriptomic groups. These research classifications have not been established as routine treatment-selection biomarkers [16].

In early TNBC, pembrolizumab combined with neoadjuvant chemotherapy and continued after surgery improved event-free outcomes in the KEYNOTE-522 population [17] [18]. PD-L1 expression did not define eligibility for the early-stage KEYNOTE-522 regimen. In metastatic TNBC, however, PD-L1 testing can guide pembrolizumab-containing therapy in appropriate patients, including the KEYNOTE-355 population with PD-L1 combined positive score thresholds spec-

ified by the trial and applicable guidance [19]. Thus, PD-L1 is a treatment-specific biomarker in defined metastatic settings and is not a universal molecular definition of TNBC or a requirement for early-disease pembrolizumab.

Germline BRCA1/2 status is another clinically validated biomarker. In OlympiA, adjuvant olaparib improved invasive and distant disease-free outcomes in patients with high-risk, HER2-negative early breast cancer carrying germline pathogenic or likely pathogenic BRCA1/2 variants after local treatment and chemotherapy [20]. This illustrates the distinction between a molecular alteration that identifies a treatment opportunity and an intrinsic subtype that describes tumour biology.

Sacituzumab govitecan has demonstrated activity in previously treated metastatic TNBC, including in the phase 3 ASCENT trial [21]. Its use should be described according to the disease setting and prior-treatment context rather than as therapy selected solely by an intrinsic TNBC molecular subclass.

3.5. HER2-Low Expression

HER2-low is not an intrinsic molecular subtype. It is a treatment-relevant IHC expression category generally referring to HER2 IHC 1+ or IHC 2+ with negative ISH in the context of clinical-trial eligibility. The ASCO/CAP guideline update retained the established HER2 testing framework while acknowledging the therapeutic relevance of trastuzumab deruxtecan in tumours with IHC 1+ or 2+ without amplification [14] [22]. The biological heterogeneity of HER2-low tumours means that HER2-low should not be presented as a discrete intrinsic molecular class.

DESTINY-Breast04 demonstrated improved progression-free and overall survival with trastuzumab deruxtecan compared with physician's-choice chemotherapy in previously treated HER2-low advanced breast cancer [22]. The clinical implication is treatment-specific: low HER2 expression can provide a target for an antibody-drug conjugate even when the tumour is not HER2-positive by conventional amplification/overexpression criteria.

Emerging evidence has also examined very low HER2 expression, including HER2-ultralow categories. These categories are treatment- and jurisdiction-specific and should not be interpreted as new intrinsic molecular subtypes. Their clinical use should follow the applicable regulatory indication, assay, and guideline.

3.6. Genomic Assays: Prognostic versus Predictive Utility

Multigene assays have an important but specific role in selected HR-positive/HER2-negative early breast cancers. Their clinical roles differ by assay and population. Some assays are primarily prognostic, whereas prospective evidence supports chemotherapy-benefit assessment for specific assays in defined populations [4]-[8]. **Table 2** summarizes the validated clinical context and the distinction between prognostic and predictive utility.

Table 2. Genomic assays: validated populations and prognostic versus predictive roles.

Assay	Principal biological basis	Validated clinical context	Primary role	Key limitation
21-gene Recurrence Score (Oncotype DX)	21-gene expression signature	HR-positive/HER2-negative early breast cancer; evidence includes node-negative disease and selected 1 - 3 node-positive populations	Prognostic risk estimation and, in defined populations, chemotherapy-benefit assessment	Treatment effect varies by age/menopausal status and nodal context
70-gene signature (MammaPrint)	70-gene expression profile	Selected early breast cancer populations with clinical/genomic risk discordance	Risk stratification and chemotherapy decision support	Benefit interpretation depends on clinical-risk group
50-gene PAM50/Prosigna	Intrinsic-subtype and proliferation-related expression	Selected HR-positive/HER2-negative early breast cancer settings	Prognostic risk estimation	Primarily prognostic; not interchangeable with the 21-gene assay
EndoPredict	Gene-expression signature integrating molecular score and clinical features	Selected HR-positive/HER2-negative disease	Prognostic estimation of distant recurrence risk	Not a universal predictor of chemotherapy benefit
Breast Cancer Index	Gene-expression signature	Selected HR-positive early breast cancer after initial endocrine therapy	Late-recurrence risk and assessment of extended endocrine therapy benefit in defined settings	Specific indication; should not be generalized to chemotherapy selection

TAILORx showed that many women with HR-positive/HER2-negative, node-negative disease and intermediate 21-gene recurrence scores can avoid adjuvant chemotherapy without compromising invasive disease-free outcomes, although age and recurrence-score range modify the magnitude of chemotherapy benefit [4] [5]. RxPONDER further demonstrated that menopausal status matters in node-positive disease: postmenopausal women with one to three positive nodes and recurrence scores of 25 or lower did not derive a clinically meaningful chemotherapy benefit, whereas premenopausal women did derive benefit [6]. These findings illustrate why genomic scores should not be interpreted independently of clinical and patient characteristics.

MINDACT provided prospective evidence for use of a 70-gene signature in selected patients with discordant clinical and genomic risk, particularly those with high clinical risk and low genomic risk [7]. Its principal contribution is risk stratification and chemotherapy decision support in its validated population, not a universal prediction of chemotherapy sensitivity.

3.7. Precision Oncology and Actionable Genomic Alterations

Next-generation sequencing can identify alterations with therapeutic implications, particularly in advanced disease. Examples include PIK3CA alterations in HR-positive/HER2-negative breast cancer, ESR1 alterations associated with endocrine resistance, and AKT-pathway alterations. Germline BRCA1/2 status can identify candidates for PARP inhibition in appropriate settings. Molecular testing

should therefore be linked to a specific therapeutic decision; broad genomic profiling does not automatically imply that every detected alteration is clinically actionable.

Precision oncology also increasingly includes circulating tumour DNA, minimal residual disease approaches, transcriptomic signatures, digital pathology, artificial intelligence, and multi-omics integration. These technologies are promising but vary substantially in analytical and clinical validation. Research findings should therefore be distinguished from biomarkers already incorporated into treatment guidance. The clinical questions and corresponding validated uses are summarized in **Table 3**.

3.8. Clinical Integration of Molecular Information

Table 3. Clinical integration of molecular information in contemporary breast-cancer management.

Clinical question	Relevant information	Examples of validated use
What is the tumour's clinical receptor status?	ER, PR, HER2 by validated pathology methods	Defines endocrine and HER2-directed treatment categories
What is the recurrence risk?	Stage, nodes, grade, receptor status, selected genomic assays	Supports adjuvant risk assessment in defined populations
Is chemotherapy likely to add benefit?	Clinical factors plus validated genomic assay where appropriate	21-gene assay in defined HR-positive/HER2-negative populations
Is immunotherapy appropriate?	Disease setting and treatment-specific biomarker requirements	PD-L1 in defined metastatic TNBC settings; not required for KEYNOTE-522 early TNBC
Is a germline-targeted therapy relevant?	BRCA1/2 and other hereditary cancer testing when indicated	Adjuvant olaparib in selected high-risk HER2-negative germline BRCA1/2-associated early breast cancer
Is an antibody-drug conjugate relevant?	HER2 expression, prior therapy, disease setting	Trastuzumab deruxtecan in appropriate HER2-low metastatic disease

4. Discussion

The principal clinical contribution of molecular classification is not the replacement of conventional pathology but its integration with it. Intrinsic subtypes provide a framework for understanding tumour biology, whereas treatment decisions usually depend on receptor status, anatomical stage, histological features, validated biomarkers, patient characteristics, and evidence supporting a particular therapy. The evidence summarized in this review therefore supports a layered rather than a subtype-only model of decision-making.

The distinction between HER2-enriched and clinically HER2-positive disease is important because a transcriptomic label does not establish eligibility for conventional anti-HER2 treatment. Conversely, clinically HER2-positive tumours are defined by validated pathology testing regardless of whether their transcriptomic profile is labelled HER2-enriched [13]–[15].

The role of genomic assays is assay- and population-specific. The 21-gene assay has prospective evidence informing chemotherapy decisions in defined HR-

positive/HER2-negative populations, while other assays have predominantly prognostic roles or different validated indications [4]-[8]. The review therefore avoids the unsupported generalization that all multigene assays predict chemotherapy benefit.

TNBC demonstrates a similar principle. Proposed molecular subtypes have biological and research value, but treatment selection currently relies more heavily on clinical stage, receptor testing, germline BRCA status, PD-L1 in specific metastatic settings, and evidence for particular systemic therapies [16]-[21]. The distinction between early and metastatic disease is particularly important for PD-L1 because the biomarker does not define eligibility for the KEYNOTE-522 early-TNBC regimen [17] [18].

HER2-low further illustrates the difference between taxonomy and therapeutics. HER2-low is best viewed as a treatment-relevant IHC expression category rather than a stable intrinsic molecular subtype [14] [22]. The emergence of antibody-drug conjugates demonstrates that therapeutic classification can evolve faster than biological taxonomy.

Several limitations should be acknowledged. Molecular classifications are influenced by assay platform, tumour heterogeneity, sampling, and temporal evolution. Intrinsic subtype assignment can vary between platforms and may not fully capture changes between primary and metastatic disease or after treatment. Selection of literature in a narrative review can also introduce interpretive bias, and the evidence base for emerging biomarkers evolves rapidly. Access to molecular testing and targeted therapies varies across healthcare systems.

Future research will likely integrate transcriptomic, genomic, epigenomic, proteomic, spatial, radiomic, digital-pathology, and circulating-tumour-DNA data. However, increasingly complex molecular classification will only improve patient care if biomarkers demonstrate analytical validity, clinical validity, clinical utility, and reproducible effects on meaningful patient outcomes.

5. Conclusion

Molecular classification has transformed the understanding and management of breast cancer, but its clinical value lies in integration rather than replacement of clinicopathological assessment. Intrinsic subtypes provide a biologically informative framework; validated receptor testing defines major therapeutic categories; genomic assays refine risk and, in selected populations, chemotherapy decisions; and treatment-specific biomarkers such as germline BRCA1/2 and PD-L1 identify particular therapeutic opportunities. HER2-enriched should be understood as a gene-expression subtype rather than a synonym for ERBB2 amplification, while HER2-low should be regarded as a clinically relevant IHC expression category rather than an intrinsic molecular subtype. Contemporary precision oncology therefore depends on matching each molecular measurement to the specific clinical decision it has been validated to inform.

Declaration of AI Use

The authors declare that AI tools were used to assist with data analysis and figure preparation.

Author Contributions

Both authors contributed equally to the preparation of this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Perou, C.M., Sørlie, T., Eisen, M.B., van de Rijn, M., Jeffrey, S.S., Rees, C.A., *et al.* (2000) Molecular Portraits of Human Breast Tumours. *Nature*, **406**, 747-752. <https://doi.org/10.1038/35021093>
- [2] Sørlie, T., Perou, C.M., Tibshirani, R., Aas, T., Geisler, S., Johnsen, H., *et al.* (2001) Gene Expression Patterns of Breast Carcinomas Distinguish Tumor Subclasses with Clinical Implications. *Proceedings of the National Academy of Sciences*, **98**, 10869-10874. <https://doi.org/10.1073/pnas.191367098>
- [3] Harbeck, N., Penault-Llorca, F., Cortes, J., Gnant, M., Houssami, N., Poortmans, P., *et al.* (2019) Breast Cancer. *Nature Reviews Disease Primers*, **5**, Article No. 66. <https://doi.org/10.1038/s41572-019-0111-2>
- [4] Sparano, J.A., Gray, R.J., Makower, D.F., Pritchard, K.I., Albain, K.S., Hayes, D.F., *et al.* (2018) Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *New England Journal of Medicine*, **379**, 111-121. <https://doi.org/10.1056/nejmoa1804710>
- [5] Sparano, J.A., Gray, R.J., Ravdin, P.M., Makower, D.F., Pritchard, K.I., Albain, K.S., *et al.* (2019) Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer. *New England Journal of Medicine*, **380**, 2395-2405. <https://doi.org/10.1056/nejmoa1904819>
- [6] Kalinsky, K., Barlow, W.E., Gralow, J.R., Meric-Bernstam, F., Albain, K.S., Hayes, D.F., *et al.* (2021) 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. *New England Journal of Medicine*, **385**, 2336-2347. <https://doi.org/10.1056/nejmoa2108873>
- [7] Cardoso, F., van't Veer, L.J., Bogaerts, J., Slaets, L., Viale, G., Delaloge, S., *et al.* (2016) 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. *New England Journal of Medicine*, **375**, 717-729. <https://doi.org/10.1056/nejmoa1602253>
- [8] Andre, F., Ismaila, N., Allison, K.H., Barlow, W.E., Collyar, D.E., Damodaran, S., *et al.* (2022) Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update. *Journal of Clinical Oncology*, **40**, 1816-1837. <https://doi.org/10.1200/jco.22.00069>
- [9] Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., *et al.* (2021) The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ*, **372**, n71. <https://doi.org/10.1136/bmj.n71>
- [10] Johnston, S.R.D., Toi, M., O'Shaughnessy, J., Rastogi, P., Campone, M., Neven, P., *et al.* (2023) Abemaciclib plus Endocrine Therapy for Hormone Receptor-Positive, HER2-Negative, Node-Positive, High-Risk Early Breast Cancer (Monarche): Results

- from a Preplanned Interim Analysis of a Randomised, Open-Label, Phase 3 Trial. *The Lancet Oncology*, **24**, 77-90. [https://doi.org/10.1016/s1470-2045\(22\)00694-5](https://doi.org/10.1016/s1470-2045(22)00694-5)
- [11] Rastogi, P., O'Shaughnessy, J., Martin, M., Boyle, F., Cortes, J., Rugo, H.S., *et al.* (2024) Adjuvant Abemaciclib plus Endocrine Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, High-Risk Early Breast Cancer: Results from a Preplanned Monarche Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. *Journal of Clinical Oncology*, **42**, 987-993. <https://doi.org/10.1200/jco.23.01994>
 - [12] Slamon, D., Lipatov, O., Nowecki, Z., McAndrew, N., Kukiela-Budny, B., Stroyakovskiy, D., *et al.* (2024) Ribociclib plus Endocrine Therapy in Early Breast Cancer. *New England Journal of Medicine*, **390**, 1080-1091. <https://doi.org/10.1056/nejmoa2305488>
 - [13] Prat, A., Pineda, E., Adamo, B., Galván, P., Fernández, A., Gaba, L., *et al.* (2015) Clinical Implications of the Intrinsic Molecular Subtypes of Breast Cancer. *The Breast*, **24**, S26-S35. <https://doi.org/10.1016/j.breast.2015.07.008>
 - [14] Wolff, A.C., Somerfield, M.R., Dowsett, M., Hammond, M.E.H., Hayes, D.F., McShane, L.M., *et al.* (2023) Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO-College of American Pathologists Guideline Update. *Journal of Clinical Oncology*, **41**, 3867-3872. <https://doi.org/10.1200/jco.22.02864>
 - [15] Loibl, S. and Gianni, L. (2017) HER2-Positive Breast Cancer. *The Lancet*, **389**, 2415-2429. [https://doi.org/10.1016/s0140-6736\(16\)32417-5](https://doi.org/10.1016/s0140-6736(16)32417-5)
 - [16] Denkert, C., Liedtke, C., Tutt, A. and von Minckwitz, G. (2017) Molecular Alterations in Triple-Negative Breast Cancer—The Road to New Treatment Strategies. *The Lancet*, **389**, 2430-2442. [https://doi.org/10.1016/s0140-6736\(16\)32454-0](https://doi.org/10.1016/s0140-6736(16)32454-0)
 - [17] Schmid, P., Cortes, J., Puzsai, L., McArthur, H., Kümmel, S., Bergh, J., *et al.* (2020) Pembrolizumab for Early Triple-Negative Breast Cancer. *New England Journal of Medicine*, **382**, 810-821. <https://doi.org/10.1056/nejmoa1910549>
 - [18] Schmid, P., Cortes, J., Dent, R., Puzsai, L., McArthur, H., Kümmel, S., *et al.* (2022) Event-Free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. *New England Journal of Medicine*, **386**, 556-567. <https://doi.org/10.1056/nejmoa2112651>
 - [19] Cortes, J., Rugo, H.S., Cescon, D.W., Im, S., Yusof, M.M., Gallardo, C., *et al.* (2022) Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer. *New England Journal of Medicine*, **387**, 217-226. <https://doi.org/10.1056/nejmoa2202809>
 - [20] Tutt, A.N.J., Garber, J.E., Kaufman, B., Viale, G., Fumagalli, D., Rastogi, P., *et al.* (2021) Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *New England Journal of Medicine*, **384**, 2394-2405. <https://doi.org/10.1056/nejmoa2105215>
 - [21] Bardia, A., Hurvitz, S.A., Tolaney, S.M., Loirat, D., Punie, K., Oliveira, M., *et al.* (2021) Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *New England Journal of Medicine*, **384**, 1529-1541. <https://doi.org/10.1056/nejmoa2028485>
 - [22] Modi, S., Jacot, W., Yamashita, T., Sohn, J., Vidal, M., Tokunaga, E., *et al.* (2022) Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *New England Journal of Medicine*, **387**, 9-20. <https://doi.org/10.1056/nejmoa2203690>

Supplementary Tables

Table S1. Database-specific search strategies used for the literature search (searches through June 2025).

Database	Search strategy
PubMed/MEDLINE	("Breast Neoplasms" [Mesh] OR breast cancer [tiab] OR breast carcinoma [tiab]) AND ("Molecular Classification" [tiab] OR "intrinsic subtype*" [tiab] OR "gene expression" [tiab]) AND (Luminal A [tiab] OR Luminal B [tiab] OR HER2-enriched [tiab] OR triple-negative [tiab] OR basal-like [tiab] OR HER2-low [tiab]) AND (management [tiab] OR treatment [tiab] OR prognosis [tiab] OR biomarker* [tiab] OR "genomic assay*" [tiab])
Scopus	TITLE-ABS-KEY(("breast cancer" OR "breast carcinoma") AND ("molecular classification" OR "intrinsic subtype*" OR "gene expression") AND ("Luminal A" OR "Luminal B" OR "HER2-enriched" OR "triple-negative" OR "basal-like" OR "HER2-low") AND (management OR treatment OR prognosis OR biomarker* OR "genomic assay*"))
Web of Science	TS = (("breast cancer" OR "breast carcinoma") AND ("molecular classification" OR "intrinsic subtype*" OR "gene expression") AND ("Luminal A" OR "Luminal B" OR "HER2-enriched" OR "triple-negative" OR "basal-like" OR "HER2-low") AND (management OR treatment OR prognosis OR biomarker* OR "genomic assay*"))
Cochrane Library	("breast cancer" OR "breast carcinoma") AND ("molecular classification" OR "intrinsic subtype*" OR "gene expression") AND ("Luminal A" OR "Luminal B" OR "HER2-enriched" OR "triple-negative" OR "basal-like" OR "HER2-low") AND (management OR treatment OR prognosis OR biomarker* OR "genomic assay*")
Google Scholar	"breast cancer" "molecular classification" "HER2-enriched" "triple-negative" "genomic assay" management

Table S2. Primary categories used to document reasons for full-text exclusion. The archived draft supplied aggregate counts but not reason-specific frequencies.

Primary full-text exclusion category	Description
Wrong population/topic	Report did not address the review population or molecular-management question.
Non-clinical/research-only classification	Molecular classification without a relevant clinical-management application.
Duplicate/overlapping cohort	Duplicate publication or substantially overlapping cohort without additional relevant information.
Insufficient clinical relevance	No usable information on prognosis, treatment selection, biomarkers, or clinical implications.
No usable full text	Full report could not be assessed adequately for eligibility.