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Review Article

Host Immune Response Signatures for Early Breast Cancer Detection: Biological Rationale, Current Evidence, and Clinical Translation

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Abstract

Early breast cancer may induce a systemic immune response before abundant tumor-derived material reaches the circulation, creating a potential source of amplified liquid-biopsy biomarkers. However, the extent to which host-response signatures can support early detection or population screening before diagnosis remains uncertain. This structured narrative review examines the biological basis, analytical platforms, evidence, clinical roles, and translational requirements of circulating autoantibodies, leukocyte transcriptomic and epigenetic profiles, immune-cell phenotypes, adaptive immune-receptor repertoires, soluble mediators, extracellular vesicles, and integrated multi-omics. PubMed/MEDLINE and citation networks were searched through August 31, 2026 using a predefined diagnostic review framework. Evidence was organized by intended use, sample timing, comparator spectrum, and validation maturity, with appraisal informed by established diagnostic-accuracy and prediction-model standards. Proof-of-concept estimates include a mean area under the curve of 0.96 for a machine-learning T-cell receptor model in 98 women, 80.8% sensitivity and 61.6% specificity for a 28-autoantibody panel, and an external-validation area under the curve of 0.951 for a 20-analyte proteome-metabolome model involving 662 participants. These estimates are not directly comparable: most derive from retrospective case-control or diagnostic cohorts with established cancer, healthy or benign comparators, post-diagnosis sampling, data-driven thresholds, and limited independent validation. Consequently, discrimination between known cases and controls must not be equated with detection of occult disease or population screening utility. Breast-specific prediagnostic evidence and screening validation remain sparse. Host-response signatures are therefore best considered investigational, complementary biological sensors rather than replacements for mammography. Their most plausible future roles include triage after equivocal imaging, enrichment for supplemental imaging, and longitudinal surveillance in high-risk populations. Translation requires prospective prediagnostic cohorts, representative benign and inflammatory controls, locked algorithms, high-specificity performance, calibration at screening prevalence, external validation, subgroup fairness, reproducibility, and evidence that testing improves cancer yield or stage distribution without unacceptable false-positive procedures, overdiagnosis, cost, or inequity.

Keywords: Breast cancer; Early detection; Biomarkers; Liquid biopsy; T-cell receptor; Autoantibodies; Transcriptome; Population screening.
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Introduction

Breast cancer screening has reduced mortality, yet anatomical imaging remains constrained by breast density, tumor phenotype, access, false-positive recalls, overdiagnosis, and imperfect sensitivity for biologically aggressive interval cancers.[1] These limitations have intensified interest in blood-based detection. Most

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Table 1. PICO/PIRD framework

P – Population	I – Index test	C – Comparator/reference	O – Outcomes
Asymptomatic women in screening cohorts; women with imaging-detected or clinically suspected breast lesions.	Blood-based host-response signatures: autoantibodies; leukocyte transcriptomic or epigenetic profiles; immune-cell phenotypes; TCR/BCR repertoires; cytokine, complement, immune-enriched proteomic, extracellular-vesicle, or integrated systemic multi-omic models	Cancer-free participants, benign breast disease, negative imaging, or standard screening/diagnostic pathways. Histopathology was the preferred reference standard; longitudinal follow-up was accepted to verify absence of cancer	Primary: stage-specific sensitivity and specificity. Secondary: AUC, positive and negative predictive values, likelihood ratios, calibration, incremental value beyond imaging/risk models, lead time, false-positive burden, and external-validation performance

Selected non-breast studies were considered only as contextual evidence of biological lead time or technical feasibility. AUC, area under the curve; BCR, B-cell receptor; PICO, Population-Intervention-Comparator-Outcome; PIRD, Population-Index test-Reference standard-Diagnosis; TCR, T-cell receptor.

liquid-biopsy programs seek tumor-derived signals—circulating tumor DNA, methylation, fragmentomics, extracellular vesicles, or proteins. Early lesions, however, may shed very little material.[2] A complementary strategy is to measure the host response: the coordinated perturbation of innate and adaptive immunity induced by tumor antigens, tissue remodeling, stromal signaling, and nascent immune escape.

The immune system may act as a biological amplifier. A small antigenic stimulus can expand lymphocyte clones, induce durable autoantibodies, reprogram circulating leukocytes, and alter soluble inflammatory networks. These effects may be detectable when the tumor itself remains radiologically occult or contributes DNA below analytical limits. Yet amplification has a cost: host-response signals are not inherently cancer-specific and are modified by aging, menopause, adiposity, infection, vaccination, autoimmune disease, smoking, medication, and social determinants.

This narrative review examines the biological basis, analytical platforms, current evidence, clinical roles, and translational requirements for host immune response signatures in early breast cancer detection. It also connects detection with immune characterization across the disease continuum. Our prior work on residual human epidermal growth factor receptor 2 (HER2)-positive disease emphasized that immune contexture carries prognostic information after neoadjuvant therapy.[3] The present review moves upstream, asking whether systemic immune sensing can identify malignancy before or alongside conventional diagnosis.

Throughout this review, three distinct evidentiary claims are separated. Diagnostic discrimination denotes classification of participants with already established cancer versus controls. Prediagnostic detection requires a signal in specimens collected before clinical or radiologic diagnosis. Population screening additionally requires performance in asymptomatic, representative populations at low disease prevalence, with prespecified thresholds and demonstrated clinical utility. Evidence for the first claim cannot be extrapolated automatically to the second or third.

Literature search and evidence appraisal

We conducted a structured narrative review because the evidence spans heterogeneous biomarker platforms, intended uses, populations, specimen timing, comparators, and performance measures that do not support valid quantitative pooling. The review is narrative rather than systematic or scoping: it uses an explicit diagnostic Population-Intervention-Comparator-Outcome (PICO)/Population-Index test-Reference standard-Diagnosis (PIRD) framework and structured critical appraisal to make study selection and interpretation transparent, but does not claim exhaustive database coverage, duplicate independent screening of every retrieved record, or Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-compliant study accounting. The review question was: among asymptomatic women undergoing breast cancer screening or women evaluated for a suspected breast lesion, how accurately do blood-based host immune-response signatures identify preclinical or early-stage breast cancer compared with cancer-free or benign-disease controls, using histopathology and/or longitudinal clinical follow-up as the reference standard?

Because this is a diagnostic-accuracy review, the conventional PICO framework was adapted so that the intervention corresponds to the index test. This formulation is also compatible with the PIRD framework. The review framework is summarized in Table 1.

PubMed/MEDLINE was searched from database inception through August 31, 2026, supplemented by backward and forward citation tracking. The complete search was: (("Breast Neoplasms"[Mesh] OR "breast cancer"[tiab] OR "breast neoplasm*"[tiab]) AND ("Early Detection of Cancer"[Mesh] OR "early detection"[tiab] OR screen*[tiab] OR prediagnos*[tiab]) AND ("immune response"[tiab] OR autoantibod*[tiab] OR leukocyte*[tiab] OR "peripheral blood mononuclear cell*"[tiab] OR PBMC[tiab] OR transcriptom*[tiab] OR methylat*[tiab] OR epigen*[tiab] OR immunophenotyp*[tiab] OR cytokine*[tiab] OR complement[tiab] OR "T-cell receptor"[tiab] OR TCR[tiab] OR "B-cell receptor"[tiab] OR BCR[tiab] OR proteom*[tiab] OR "extracellular vesicle*"[tiab] OR exosome*[tiab] OR multiomic*[tiab] OR "multi-omic*"[tiab])). The search was restricted to human studies and English-language publications; the publication-date limit ended August 31, 2026. Because this was a structured narrative review with iterative citation chaining rather than a PRISMA systematic review, a deduplicated record-flow count was not generated.

We included peer-reviewed human studies evaluating a measurable circulating host-response signature for cancer

detection, with priority given to breast-specific cohorts, early-stage disease, screening populations, prediagnostic samples, independent validation, and clinically interpretable diagnostic-performance estimates. Systematic reviews, diagnostic-accuracy studies, prospective or retrospective cohorts, and rigorously described case-control studies were eligible. Selected multicancer or non-breast studies were included only when they provided direct evidence of biological lead time or technical feasibility relevant to immune-based detection. We excluded animal-only studies, purely tissue-based assays without a circulating component, prognostic-only studies with no detection relevance, single case reports, conference abstracts without sufficient methods, non-peer-reviewed claims, and studies lacking an appropriate comparator or verifiable outcome.

Potentially relevant records were screened by title and abstract and then assessed in full text against the predefined eligibility criteria. Initial screening and extraction were performed by one reviewer; included studies and all numerical performance estimates used in the text or tables were independently checked by a second reviewer, with disagreements resolved by consensus and consultation with a third author when required. Data items included population and setting, sample size, disease stage, comparator spectrum, sample timing relative to diagnosis or treatment, biospecimen, analytical platform, index-test definition, threshold derivation, reference standard, validation design, sensitivity, specificity, area under the curve (AUC), predictive values, and major risks of bias. Results were synthesized by biomarker class and evidence maturity. Estimates were not pooled because intended use, population spectrum, assays, thresholds, reference standards, and validation designs differed substantially.

Diagnostic studies were appraised using domains derived from Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2): patient selection, conduct and interpretation of the index test, appropriateness of the reference standard, and participant flow and timing.[4] Prediction-model studies were additionally assessed against Prediction model Risk Of Bias ASsessment Tool (PROBAST) principles, including overfitting, feature-selection leakage, calibration, external validation, and applicability.[5] Reporting completeness was considered in relation to Standards for Reporting Diagnostic Accuracy Studies (STARD) and Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD).[6,7] Given the narrative design, appraisal informed the weight assigned to each result rather than generating a numerical quality score.

Comparator groups were treated as clinically non-equivalent. Healthy volunteers provide proof-of-concept contrast but can exaggerate discrimination; benign breast disease and abnormal-imaging controls better approximate diagnostic practice; inflammatory, infectious, autoimmune, and comorbidity controls test immune specificity; and screening-negative participants with longitudinal follow-up are required to estimate performance in the intended screening population.

Evidence was interpreted using a six-level maturity hierarchy: (1) biological plausibility; (2) retrospective diagnostic discrimination; (3) independent external validation; (4) breast-specific prediagnostic validation; (5) prospective screening validation with locked thresholds; and (6) clinical-utility or outcome evidence. No reviewed host-response assay has yet reached levels 5 or 6 for routine breast cancer screening. Accordingly, this review evaluates the biological basis, current evidence, and translational requirements of host immune-response signatures for early breast cancer detection. Prediagnostic studies in non-breast cancers were treated as contextual evidence of temporal feasibility and were not assigned level 4. Representative studies and their maturity assignments are summarized in Table 2.[8-14]

Why the host response may precede a tumor-derived signal

Tumor initiation can generate altered proteins, aberrant post-translational modifications, cell death products, and inflammatory danger signals. Antigen-presenting cells process these cues and activate T- and B-cell responses. Even when immune surveillance does not eliminate the lesion, clonal expansion and antibody production can leave a systemic footprint. Concurrently, tumor-secreted factors alter myelopoiesis, monocyte differentiation, neutrophil activation, platelet behavior, and interferon-related transcription. The resulting signature is distributed across cells and plasma rather than confined to a single analyte.

This model reframes early detection as a signal-integration problem. Tumor-derived biomarkers may offer tissue specificity, whereas host-derived biomarkers provide amplification. Their errors may be partly nonoverlapping, making combined models biologically attractive. Longitudinal sampling adds a further dimension: deviation from an individual's immune baseline may be more informative than a single population threshold. The proposed tumor-host pathway and its validation safeguards are summarized in Figure 1.

Major classes of host immune signatures

Autoantibodies and tumor-associated antigen recognition

Autoantibodies are stable, abundant, and experimentally accessible. They may arise against overexpressed, mutated, misfolded, or aberrantly modified tumor-associated antigens, including p53, MUC1, HER2, HSP60/HSP70, NY-ESO-1, and endophilin A2. Individual autoantibodies usually have high specificity but low sensitivity because immune recognition is heterogeneous. Panels often outperform single targets.

In a discovery-validation study, a 28-autoantibody panel achieved 80.8% sensitivity, 61.6% specificity, and AUC 0.756 for early breast cancer.[8] A four-antibody panel against BMI-1, HSP70, NY-ESO-1, and p53 yielded AUC 0.819, 63.4% sensitivity, and 90.2% specificity overall; for early-stage disease, AUC was 0.805 with 59.6% sensitivity at 90.2% specificity.[9] A systematic review found individual-marker pooled sensitivities of approximately 10%–56%, whereas panels reported 60%–87% sensitivity, albeit with substantial heterogeneity.[15] These data support multiplexing but also illustrate the central screening trade-off: modest specificity becomes problematic when disease prevalence is low.

Specificity estimates for autoantibody panels are conditional on the comparator spectrum. Performance against exceptionally healthy controls may decline when benign breast disease, chronic inflammatory disorders, autoimmune disease, infection, or other cancers are represented; these groups should be included prospectively before screening claims are made.

Table 2. Representative studies and maturity of host-response evidence

Study/platform	Population/stage	Comparator	Timing/design	Validation	Performance	Evidence maturity
Autoantibody panel; Anderson *et al.*[8]	Early-stage invasive breast cancer; cohorts 1–3 included 53, 51, and 51 cases, respectively	Cohort 1 screening controls; Cohorts 2–3 benign breast disease controls	Cohort 1 sampled at routine mammography before diagnosis; Cohorts 2–3 collected before therapy; retrospective case-control selection	Independent blinded Cohort 3 for biomarker validation; classifier assessed by leave-one-out cross-validation	Se 80.8%; Sp 61.6%; AUC 0.756	2: retrospective discrimination
Four-autoantibody panel; Hong *et al.*[9]	123 breast cancer cases (94 early stage); 123 age-matched controls	Age-matched normal controls	Samples collected at diagnosis before treatment; case-control	No independent validation; model developed and evaluated in the same cohort	AUC 0.819; Se 63.4%; Sp 90.2%	2: retrospective discrimination
PBMC immunophenotype; Foulds *et al.*[10]	67 cases; 23 matched controls; multiple stages	Matched cancer-free controls	Post-diagnosis; observational case-control	No independent external validation	Cancer-associated Treg and myeloid shifts	2: retrospective discrimination
PLR; Zhang *et al.*[11]	NHANES; 19,734 participants	Population participants without breast cancer	Cross-sectional; diagnosis history/prevalence	Internal analysis	OR 1.35; AUC 0.59	2: association; weak discrimination
TCR machine learning; Zuckerbrot-Schuldenfrei *et al.*[12]	98 women; established breast cancer vs healthy status	Healthy controls	Post-diagnosis; case-control; high-dimensional ML	Cross-validation; no independent external cohort	Mean AUC 0.96	2: retrospective discrimination
Prediagnostic TCR; Yu *et al.*[13]	466 women; ovarian cancer and controls	Cancer-free controls	Prediagnostic samples up to 4 years; non-breast evidence	Temporal validation	Stage I and prediagnostic repertoire changes	Supporting prediagnostic evidence (non-breast); not assigned a breast-specific maturity level
Integrated systemic host-response model (ProMeta-BC); Zhang *et al.*[14]	662 participants; malignant and benign breast findings	Benign breast disease	Diagnostic sampling; prospective multicenter study	Independent external validation	AUC 0.973 training; 0.951 external; 8/9 imaging-negative cancers	3: external diagnostic validation

Evidence maturity: 2, retrospective diagnostic discrimination; 3, independent external validation. AUC, area under the curve; ML, machine learning; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PBMC, peripheral blood mononuclear cell; PLR, platelet-to-lymphocyte ratio; Se, sensitivity; Sp, specificity; TCR, T-cell receptor; Treg, regulatory T cell.

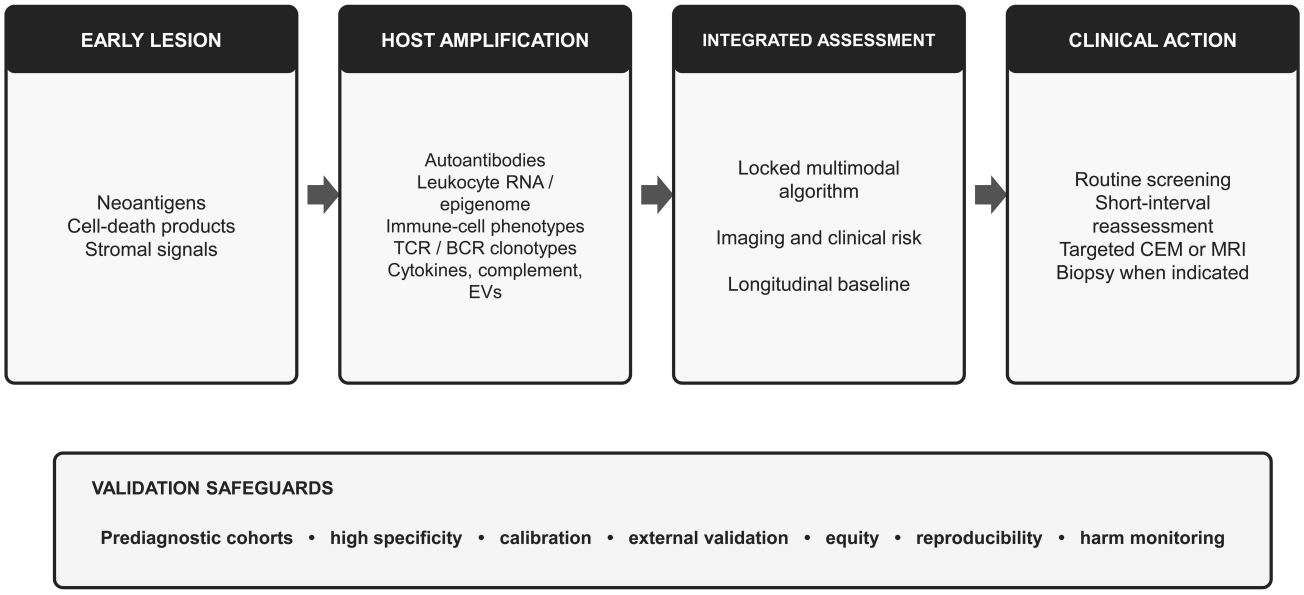


Fig. 1. From early tumor–host interaction to a clinically actionable immune–imaging pathway. An early lesion can generate antigens, cell-death products, and stromal signals that are amplified through circulating host responses. A locked algorithm can integrate these orthogonal immune features with imaging, clinical risk, and longitudinal baselines to support calibrated clinical actions. Prediagnostic sampling, high specificity, calibration, external validation, equity, reproducibility, and harm monitoring are essential safeguards. All depicted pathways and clinical applications are investigational and require prospective validation. BCR, B-cell receptor; CEM, contrast-enhanced mammography; EVs, extracellular vesicles; MRI, magnetic resonance imaging; TCR, T-cell receptor.

Peripheral-blood transcriptomic and epigenetic signatures

Circulating leukocytes integrate cytokine exposure, antigen presentation, metabolic stress, and shifts in cell composition. Whole-blood or peripheral-blood mononuclear-cell RNA profiles can therefore distinguish patients with breast cancer from controls and identify immune subgroups.[16,17] A 2024 isoform-level peripheral blood mononuclear cell (PBMC) analysis identified a disease-associated *RASGEF1A* isoform, illustrating how transcript resolution may add information beyond gene-level abundance.[17] Early microarray studies demonstrated the feasibility of gene-expression detection in asymptomatic patients.[18] More recent work emphasizes deconvolution of cell composition and use of single-cell methods to separate true state changes from altered proportions.

Epigenetic remodeling of leukocytes may provide a more stable record of exposure. Peripheral-blood methylation profiling identified thousands of CpG sites associated with breast cancer progression, with top signals enriched for immune functions.[19] However, age and immune-cell composition strongly influence methylation, requiring cell-aware normalization and prospective validation. A classifier trained on samples collected after diagnosis may learn consequences of symptoms, biopsy, or stress rather than preclinical cancer biology.

Most breast transcriptomic and epigenetic studies used samples collected after diagnosis. Such signatures may reflect symptoms, diagnostic procedures, biopsy-associated inflammation, treatment exposure, psychological stress, or altered general health. Prediagnostic specimens collected before any diagnostic intervention constitute a distinct and substantially stronger level of evidence.

Immune-cell composition, activation, and systemic inflammation

Flow and mass cytometry can quantify regulatory T cells, activated T cells, natural killer cells, monocyte subsets, and myeloid-derived suppressor cells. In one study of 67 patients and 23 matched controls, breast cancer was associated with more activated/suppressive regulatory T cells, intermediate monocytes, and granulocytic myeloid-derived suppressor cells.[10] Such changes are mechanistically plausible but platform-intensive and vulnerable to sample-processing delay.

Routine inflammatory measures—including neutrophil-to-lymphocyte, platelet-to-lymphocyte, and systemic immune-inflammation indices—are inexpensive but nonspecific. In a 2026 National Health and Nutrition Examination Survey analysis of 19,734 participants, the platelet-to-lymphocyte ratio was associated with breast cancer prevalence (odds ratio 1.35, 95% confidence interval 1.09–1.67), yet discrimination was weak (AUC 0.59).[11] These markers may contribute contextual features to multivariable models.

Accordingly, platelet-to-lymphocyte and related indices should be treated as contextual covariates or low-cost components of multivariable models, not as stand-alone screening tests.

Adaptive immune receptor repertoires

T-cell receptor (TCR) and B-cell receptor (BCR) repertoires encode antigen exposure through clonal frequency, diversity, V(D)J use, and sequence motifs. Machine learning can recognize distributed cancer-associated patterns without prespecifying the

antigen. In 98 women, peripheral-blood T-cell receptor profiling distinguished patients with breast cancer from healthy controls with a mean AUC of 0.96.[12] A separate 2025 study reported improved early detection across multiple cancer types using a peripheral-blood TCR predictor.[20] These estimates are encouraging but require large external validations across age, ancestry, breast subtype, infection history, and sequencing laboratories.

For high-dimensional repertoire models, internal cross-validation estimates model stability within the same source population but do not constitute external validation. Transportability requires locked preprocessing and thresholds, geographically and ancestrally distinct cohorts, harmonized sequencing platforms, explicit sample-size-to-feature justification, control of class imbalance, nested hyperparameter optimization, leakage prevention, calibration assessment, and interpretable analyses of influential clonotypes or features.

The strongest conceptual evidence for temporality comes from other tumor types. In a study involving 466 women with ovarian cancer and controls, reproducible T-cell receptor changes were strongest in stage I disease and detectable in prediagnostic samples up to four years before conventional diagnosis.[13] The deep-learning iCanTCR framework similarly demonstrated pan-cancer classification from TCRβ sequences.[21] These studies suggest immune memory can carry a prediagnostic signal, but breast-specific lead-time and clinical utility remain unproven.

Soluble immune mediators, complement, and immune-enriched proteomics

Cytokines, chemokines, complement fragments, acute-phase proteins, and immunoglobulin features reflect a coordinated host response. Single mediators are rarely sufficiently specific; multiplexed proteomics can capture network behavior. In 2026, a prospective multicenter study of 662 participants profiled 5,549 proteins and 630 metabolites and developed ProMeta-BC, a 15-protein/5-metabolite model. It achieved an AUC of 0.973 in training and 0.951 in external validation for benign-versus-malignant discrimination and detected 8 of 9 imaging-negative cancers.[14] Although not purely immune-derived, the model illustrates the performance gains possible when systemic biology is integrated across molecular layers.

Because ProMeta-BC combines proteins and metabolites from multiple physiological pathways, it is described here as an integrated systemic host-response model rather than a specifically immune-derived assay.

Extracellular vesicles also carry proteins and RNAs shaped by tumor–host communication. Microfluidic immunofluorescence platforms are advancing rapidly.[22] Their future value will depend on analytical reproducibility, scalable preanalytics, and demonstration that measured signals reflect early disease rather than specimen handling.

Integration with imaging and risk models

The most defensible near-term role is adjunctive, not substitutive. Mammography provides localization and captures ductal carcinoma *in situ* and calcification-dominant disease; an immune assay provides orthogonal biology. A positive immune signature could trigger targeted imaging, contrast-enhanced mammography, magnetic resonance imaging (MRI), or shortened follow-up, whereas a negative result might refine—but should not automatically override—imaging findings.[23]

Four use cases merit prospective evaluation: (1) supplemental triage in women with dense breasts; (2) adjudication of low-suspicion or discordant imaging findings; (3) risk enrichment before expensive MRI; and (4) longitudinal surveillance in genetically or clinically high-risk individuals. The BRAID randomized trial has reinforced the value of supplemental imaging in dense breasts while also documenting recall and biopsy rates.[23] An immune test would need to demonstrate incremental benefit beyond age, family history, polygenic risk, density, and imaging—not merely a significant association.[24] These four investigational contexts are depicted in Figure 2.

The operating threshold must match the clinical role. Population screening demands very high specificity because even a test with 95% specificity produces approximately 50 false-positive results per 1,000 cancer-free individuals. At a 0.5% cancer prevalence, 70% sensitivity and 95% specificity yield a positive predictive value of only about 6.6%. By contrast, in a selected diagnostic population with 10% prevalence, the same assay yields a positive predictive value near 61%. Reporting AUC alone therefore obscures clinical consequences.[25]

Table 3 illustrates how a fixed assay with 70% sensitivity and 95% specificity behaves across plausible prevalence settings. The calculation is illustrative rather than a performance claim for any specific assay.

Methodological barriers and standards for translation

Biological confounding and specificity

Immune biomarkers respond to physiological and inflammatory states that may be more prevalent than cancer in screening populations. Age, menopause, ancestry, human leukocyte antigen genotype, adiposity, smoking, recent infection or vaccination, autoimmune disease, chronic inflammatory illness, immunomodulatory medication, prior cancer, and treatment exposure can change cell composition, transcription, methylation, clonality, cytokines, and antibodies. Development datasets should measure these variables prospectively; include benign, inflammatory, autoimmune, and infectious controls; prespecify exclusion windows for transient perturbations; use stratification or causal adjustment where justified; and report subgroup calibration rather than relying only on adjusted associations.[26]

Machine-learning validation and transportability

Computational immune signatures require an analysis plan that matches model complexity to effective sample size. Feature selection, preprocessing, imputation, and hyperparameter tuning must occur entirely within resampling loops to prevent leakage. Class imbalance should be handled without contaminating validation folds. Apparent performance should be accompanied by optimism-corrected estimates, calibration intercept and slope, clinically relevant operating points, and decision-curve analysis. Final models should be locked before independent external testing across sites, ancestry groups, sequencing batches, and prevalence settings. Interpretability analyses should identify whether predictions depend on biologically plausible immune features or

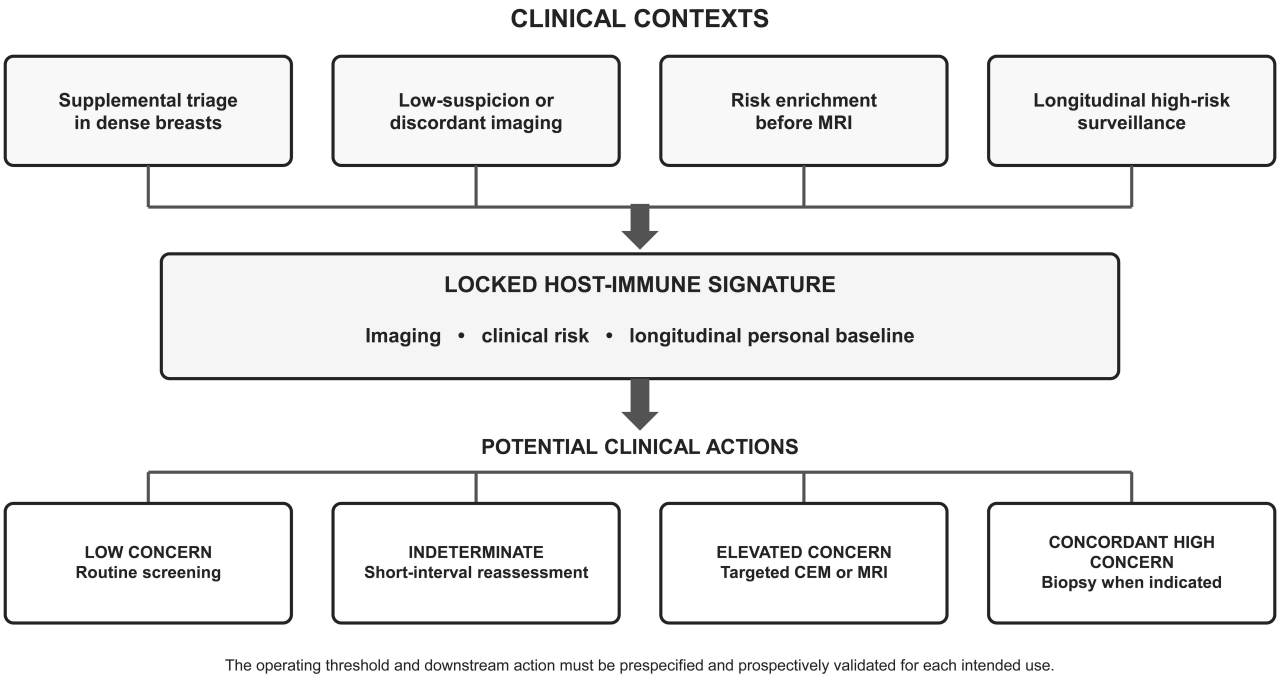


Fig. 2. Proposed clinical positioning of host immune signatures across four investigational adjunctive contexts: supplemental triage in women with dense breasts, adjudication of low-suspicion or discordant imaging, risk enrichment before magnetic resonance imaging, and longitudinal surveillance in high-risk individuals. The same assay may require different thresholds and downstream actions according to the intended-use population. Host-response testing should complement, rather than replace, imaging and validated clinical risk assessment. All depicted pathways and clinical applications are investigational and require prospective validation. CEM, contrast-enhanced mammography; MRI, magnetic resonance imaging.

Table 3. Performance of a fixed assay with 70% sensitivity and 95% specificity across plausible prevalence settings

Prevalence	Expected cancers/1,000	True positives	False positives	PPV	NPV
0.5%	5	3.5	49.8	6.6%	99.8%
1.0%	10	7.0	49.5	12.4%	99.7%
2.0%	20	14.0	49.0	22.2%	99.4%
5.0%	50	35.0	47.5	42.4%	98.4%
10.0%	100	70.0	45.0	60.9%	96.6%

NPV, negative predictive value; PPV, positive predictive value.

technical artifacts.[27-29]

Additional translational requirements

Prediagnostic sampling and spectrum bias: Discovery studies involving symptomatic cases and exceptionally healthy controls inflate performance. Nested case-control studies within screening cohorts and prospective specimen collection before diagnosis are essential.[30]

Stage- and subtype-specific sensitivity: Performance must be reported separately for ductal carcinoma *in situ*, stage I disease, node-negative tumors, interval cancers, and hormone receptor-positive/HER2-negative, HER2-positive, and triple-negative subtypes.

Analytical reproducibility: Collection tube type, fasting status, time to processing, storage, freeze-thaw cycles, sequencing depth, reagent lot, and laboratory site require harmonization and external quality assurance.[31]

Clinically meaningful endpoints: Required outcomes include cancer yield, stage distribution, interval-cancer rate, positive predictive value, false-positive procedures, time to resolution, overdiagnosis, quality of life, cost-effectiveness, and ultimately advanced-stage incidence or mortality.

Reporting: Investigators should follow STARD for diagnostic accuracy, TRIPOD/PROBAST principles for prediction models, and report the complete intended-use pathway and reference standard.[5-7,27,28,32]

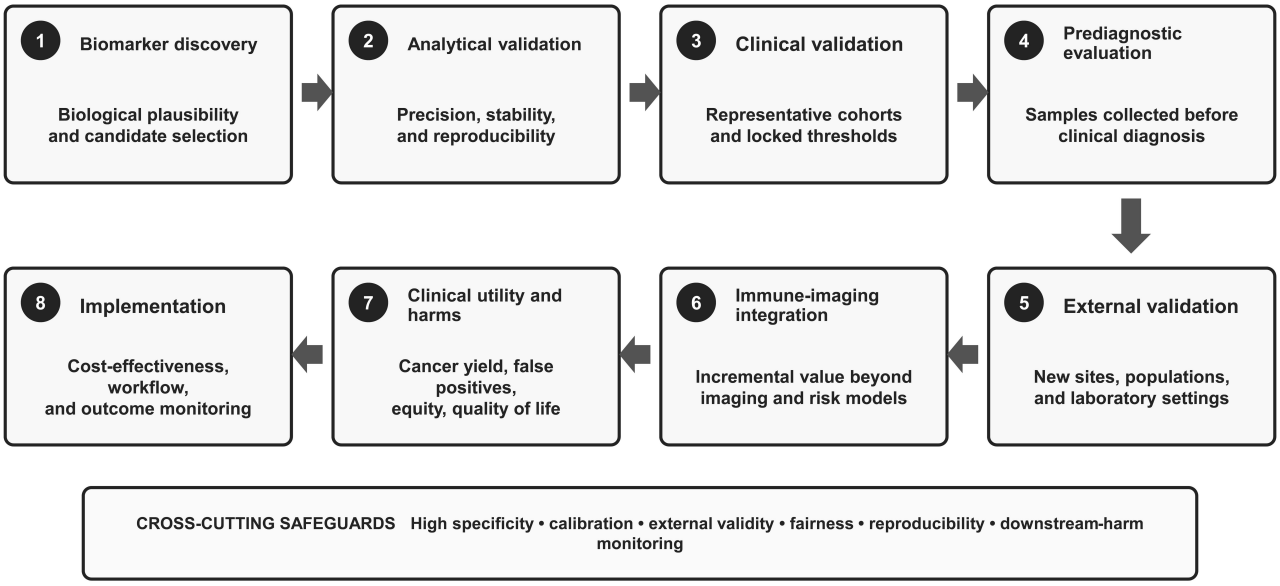


Fig. 3. Evidence-to-implementation roadmap for host immune response biomarkers. Translation requires sequential analytical, clinical, prediagnostic, and external validation before immune-imaging integration and prospective assessment of clinical utility. Cross-cutting safeguards should be prespecified throughout development and continue after implementation. All depicted pathways and clinical applications are investigational and require prospective validation.

From residual-disease immunology to an early-detection continuum

Immune profiling is often divided into diagnosis, prognosis, and treatment prediction, but these represent points along a continuum. In HER2-positive breast cancer, immune-related gene-expression signatures and tumor-infiltrating lymphocytes have prognostic and predictive relevance in neoadjuvant trials.[3,33,34] Residual disease after therapy represents a selected ecosystem shaped by tumor biology and treatment. The same conceptual framework—joint interpretation of tumor burden and immune state—can be moved earlier, provided one avoids assuming that a prognostic marker is automatically a detection marker.

A future assay might combine a tumor-proximal component (cell-free DNA methylation or fragmentomics), a host-amplified component (TCR/BCR or autoantibody pattern), and an anatomic component (imaging). Discordant signals would not be treated as technical failure but as information: a host-positive/tumor-negative result might indicate a very small lesion or nonmalignant inflammation; a tumor-positive/host-negative result might identify immunologically silent disease. Longitudinal trajectories could help resolve these states.[12,14,22]

Currently validated versus investigational applications

No circulating host immune-response assay is currently validated for routine breast cancer population screening, replacement of mammography, or autonomous biopsy referral. All clinical roles proposed in this review—including dense-breast triage, adjudication of equivocal imaging, MRI enrichment, and longitudinal high-risk surveillance—remain investigational. Their evaluation should proceed through prospective studies with prespecified thresholds and management algorithms, followed by comparative clinical-utility trials assessing cancer yield, stage distribution, interval cancers, false-positive procedures, time to resolution, overdiagnosis, quality of life, cost-effectiveness, equity, and ultimately advanced-stage incidence or mortality. The staged evidence-to-implementation pathway is summarized in Figure 3.[12-15,20-22]

Future research agenda

• Establish large prospective biobanks embedded in organized screening, with serial samples and linkage to interval cancers.

• Benchmark immune signatures against, and in combination with, state-of-the-art imaging, clinical risk models, and tumor-derived liquid-biopsy assays.

• Prioritize locked, parsimonious panels that can be transferred across laboratories rather than continually expanding discovery signatures.

• Use longitudinal personalized baselines and explicitly model transient immune perturbations.

• Ensure geographic, ancestral, socioeconomic, and comorbidity diversity, including populations in low- and middle-income countries.

• Evaluate implementation outcomes and downstream harms before claiming screening readiness.

Limitations

This review has several limitations. The search was structured but not systematic or exhaustive, was limited to PubMed/MEDLINE

and English-language publications, and did not include PRISMA-compliant study accounting. Initial screening and data extraction were performed by one reviewer, quantitative pooling was not undertaken because of substantial methodological heterogeneity, and narrative evidence weighting necessarily involved reviewer judgment. In addition, the cited literature is dominated by retrospective or diagnostic case-control designs, selected comparator groups, limited external validation, pre-analytical heterogeneity, and incomplete control of biological confounding. These factors limit the generalizability of current performance estimates to population screening.

Conclusions

Host immune response signatures offer a biologically credible means of amplifying faint tumor-associated signals, but current breast evidence supports proof-of-concept diagnostic discrimination rather than population-screening readiness. Most estimates arise from retrospective or diagnostic cohorts with established disease, post-diagnosis sampling, selected comparators, and limited independent validation. No host-response assay is clinically validated to replace standard breast screening or to direct biopsy autonomously. The field should progress through breast-specific prediagnostic cohorts, prospective screening validation with locked thresholds, and clinical-utility studies that demonstrate benefit beyond imaging and risk models while controlling false-positive cascades, overdiagnosis, cost, and inequity. A calibrated immune-imaging strategy remains a promising investigational destination, not a current standard of care.

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Conflict of interest

The authors declare no conflicts of interest related to this work.

Author contributions

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