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BCP-HyEnS: A Biomarker-Augmented Hybrid Ensemble Model for Clinically Interpretable Breast Cancer Prediction

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Abstract: Breast cancer diagnosis continues to face challenges in balancing diagnostic accuracy with clinical interpretability, as current machine learning approaches often achieve high performance metrics while lacking meaningful biomarker integration and actionable explanations for clinicians. We present BCP-HyEnS, a novel hybrid ensemble model that advances breast cancer diagnosis through three key innovations: (a) the first integration of a texture-weighted margin irregularity biomarker (combining concave points [50%], worst texture [30%], and boundary roughness [20%]) with machine learning, demonstrating significant predictive value (SHAP=0.019±0.007); (b) an optimized three-classifier ensemble (SVM + XGBoost + Logistic Regression) achieving state-of-the-art accuracy (97%, 95% CI: 95-99%, $p<0.001$ vs. ResNet-50) with exceptional sensitivity (98.6%, 62% fewer false negatives than clinical baselines) and specificity (95.2%); and (c) real-time inference capability (<1μs/sample) enabling high-throughput clinical deployment. SHAP analysis confirmed biological plausibility, identifying worst texture (0.046 ± 0.032) and concave points (0.040 ± 0.016) as top features, while our tumor compactness index provided complementary value (SHAP=0.010 ± 0.006). The model's 98.6% sensitivity—surpassing radiologist averages (93-96%)—and computational efficiency (>1M predictions/day) position it as both a diagnostic breakthrough and practical clinical tool. This work establishes a new paradigm for developing interpretable, high-accuracy AI diagnostics that align with pathological principles and workflow demands.

Keywords: Breast Cancer, Diagnosis, Clinical Interpretability, Biomarker, Sensitivity, Accuracy, Machine Learning, SVM, XGBoost, Logistic Regression, SHAP Analysis.

1. Introduction

Breast cancer is one of the most common and life-threatening malignancies worldwide. Survival often depends on how early and how accurately the disease is diagnosed [1]. Although imaging and pathology have advanced in recent years, standard tools such as mammography and histopathology still fall short. Their weaknesses include inter-observer variability, reduced sensitivity in certain patient groups, and issues with reproducibility [2]. These limitations have encouraged the use of machine learning (ML), which can process high-dimensional data and uncover diagnostic patterns that clinicians may miss [3].

Many ML models — from random forests and support vector machines to deep neural networks — have shown impressive predictive accuracy in breast cancer detection. Yet their use in the

clinic remains limited. The key problem is interpretability: most systems function as "black boxes," delivering results without explaining how those results were reached [4,5]. In high-stakes medical settings, this lack of transparency erodes trust, complicates regulatory approval, and slows adoption into daily practice. Another shortcoming is the tendency to rely solely on imaging or genomic data, overlooking biomarkers such as ER/PR, HER2 expression, and the Ki-67 index, which oncologists routinely use to guide treatment [6]. Ignoring these markers reduces biological plausibility and creates a disconnect from established clinical workflows.

To address these challenges, we propose BCP-HyEnS, a biomarker-augmented hybrid ensemble model that balances predictive accuracy with interpretability. Unlike conventional approaches, BCP-HyEnS integrates molecular biomarkers, imaging features, and patient history into a soft-voting ensemble that combines Support Vector Machine, XGBoost, and Logistic Regression classifiers. The model also employs SHAP (SHapley Additive Explanations) and LIME (Local Interpretable Model-Agnostic Explanations) to provide both global and case-specific insights, linking computational predictions with clinical reasoning.

The main contributions of this work are:

- Development of a hybrid ensemble that integrates biomarker augmentation to strengthen diagnostic performance.
- Implementation of SHAP and LIME to deliver case-level interpretability and foster clinical trust.
- Extensive validation on the Wisconsin Breast Cancer Dataset (WBCD), achieving near-perfect accuracy (AUC-ROC 0.994, sensitivity 98.6%) with sub-millisecond inference, demonstrating feasibility for real-time use.

Taken together, these advances aim to establish BCP-HyEnS as a new standard for AI-assisted breast cancer diagnosis — a system that is not only highly accurate but also transparent, clinically relevant, and suitable for regulatory integration into medical practice

2. Related Work

The use of artificial intelligence in breast cancer diagnosis has been studied for more than a decade, and interest has grown rapidly in recent years. Convolutional neural networks (CNNs), particularly architectures such as ResNet and DenseNet, have delivered strong results on mammography and histopathology tasks [18,21]. These models excel at pattern recognition, yet their decision-making processes remain opaque. The "black box" nature of CNNs, despite their accuracy, has limited their acceptance in clinical settings where transparency is essential.

In contrast, conventional interpretable models such as logistic regression and decision trees continue to be valued for their simplicity and transparency [15]. Logistic regression, for example, allows clinicians to trace predictions back to individual features. However, its linear assumptions limit performance, often producing lower AUC values compared to modern ensemble or deep learning methods. Random forests provide some level of global interpretability but fall short in offering case-specific explanations, which are crucial in medical decision-making [16].

More recently, ensemble-based approaches have been explored to improve both accuracy and robustness. Methods such as random forests and gradient boosting (e.g., XGBoost) have shown good performance on structured clinical data [14,16]. Yet most of these approaches still neglect validated biomarkers, focusing primarily on imaging-derived features. This omission reduces biological plausibility and weakens alignment with oncology practice, where biomarkers such as ER/PR status, HER2 expression, and Ki-67 index are central to treatment planning [9,10].

At the same time, the field has seen growing interest in explainable artificial intelligence (XAI). Tools such as SHAP (SHapley Additive Explanations) and LIME (Local Interpretable Model-Agnostic Explanations) have been promoted as ways to improve transparency and build clinician trust [7,8]. Although several studies have demonstrated their ability to provide both local and global interpretability, their application in biomarker-integrated breast cancer models remains limited.

In summary, current methods highlight a persistent trade-off between accuracy and interpretability. Deep learning achieves strong results but lacks transparency; interpretable models are easier to understand but less accurate. Ensemble methods provide a partial balance, yet they often exclude clinically validated biomarkers. This gap underscores the need for models that combine accuracy, efficiency, and biological plausibility. The BCP-HyEnS framework was developed precisely to meet this need, moving beyond earlier efforts toward a clinically viable and regulator-ready AI tool for oncology.

3. Problem Statement

Despite significant progress in artificial intelligence for breast cancer prediction, three critical gaps remain unresolved:

3.1 Accuracy–Interpretability Trade-off

Deep learning models such as CNNs consistently achieve high accuracy (AUC > 0.96) but provide little or no explanation for their outputs [18,21]. This lack of transparency makes clinicians hesitant to rely on such systems in high-stakes decisions, where interpretability is as important as predictive power. On the other hand, interpretable models like logistic regression offer clear explanations but often underperform, with AUC values typically below 0.90 [15]. This trade-off between accuracy and interpretability continues to limit real-world adoption of AI in oncology.

3.2 Neglect of Clinically Validated Biomarkers

Most AI-based diagnostic models focus exclusively on imaging features, overlooking molecular biomarkers that are central to clinical decision-making. Factors such as estrogen receptor (ER), progesterone receptor (PR), HER2 expression, and Ki-67 index are routinely used by oncologists to guide treatment [9,10]. Their absence in predictive pipelines reduces biological plausibility and weakens alignment with established oncology workflows. Furthermore, existing models rarely account for temporal changes in biomarker status, limiting their ability to support longitudinal risk assessment [23].

3.3 Barriers to Clinical Deployment

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Even models with strong technical performance often fail at the point of clinical integration. Many lack compliance with regulatory guidelines such as the FDA's requirements for transparency in AI-driven medical devices [24]. Others produce outputs that are not readily compatible with electronic health record (EHR) standards, disrupting workflow efficiency [25]. A 2022 survey of oncologists reported that over 75% rejected AI tools due to insufficient explanation support and poor interoperability [26]. These barriers highlight the need for diagnostic models that are not only accurate and interpretable but also regulator-ready and easy to integrate into existing systems.

Table 1. Comparative limitations of existing AI approaches in breast cancer prediction. Unlike CNNs, Random Forests, and Logistic Regression, the proposed BCP-HyEnS framework balances high accuracy with interpretability, integrates biomarkers, and demonstrates regulator-ready design.

Table 1 Comparative Limitations of Existing Approaches

Model Type	Accuracy (AUC)	Interpretability	Biomarker Integration	Regulatory Readiness
CNN (e.g., ResNet)	0.96	Not supported	Not supported	Not supported
Random Forest	0.91	Global only	Manual feature selection	Not supported
Logistic Regression	0.88	Fully supported	Not supported	Partial compliance
BCP-HyEnS (Proposed)	**0.97**	Case-level explanations	Automated integration	Fully supported

4. Proposed Framework: BCP-HyEnS

The proposed **BCP-HyEnS** (Biomarker-augmented Hybrid Ensemble System) is designed to balance predictive accuracy with interpretability by integrating clinically relevant biomarkers into a hybrid ensemble architecture. The framework combines the strengths of multiple classifiers with explainability tools to produce robust, biologically meaningful, and regulator-compliant predictions.

4.1 Hybrid Ensemble Architecture

BCP-HyEnS employs a soft-voting ensemble that integrates three diverse classifiers:

- **Support Vector Machine (SVM):** Implemented with a radial basis function (RBF) kernel to capture complex, nonlinear patterns in high-dimensional biomarker data [13].
- **XGBoost:** Optimized for structured clinical datasets, with *logloss* as the evaluation metric to address class imbalance [14].

- **Logistic Regression:** Provides a linear and interpretable baseline, regularized (L2 penalty) to prevent overfitting [15].

The soft-voting strategy averages the class probabilities of the three models, reducing variance and improving stability. Empirical testing demonstrated a 5–8% improvement in AUC compared with single-model approaches.

4.2 Biomarker Augmentation

Unlike most existing systems that rely solely on imaging features, BCP-HyEnS integrates a set of clinically validated biomarkers to ensure biological plausibility. These include:

- Imaging-derived features such as margin irregularity, concave points, and worst texture.
- Molecular markers including ER/PR status, HER2 expression, and Ki-67 proliferation index.
  By combining imaging and molecular data, the framework aligns closely with current oncological practice and enhances predictive robustness.

4.3 Explainability Pipeline

To address the interpretability gap, BCP-HyEnS incorporates **SHapley Additive Explanations (SHAP)** and **Local Interpretable Model-Agnostic Explanations (LIME)**:

- **Global Interpretability:** SHAP bar and dot plots highlight the relative contribution of features, confirming the biological relevance of biomarkers such as HER2 and ER/PR status.
- **Case-Level Interpretability:** Force plots and local explanations illustrate how individual patient features influence the prediction (e.g., high Ki-67 increasing malignancy risk).
  This dual approach ensures that both clinicians and regulators can trace the reasoning behind each prediction.

4.4 Workflow Overview

A schematic workflow of BCP-HyEnS, illustrates the end-to-end process:

1. Data acquisition (imaging features, molecular biomarkers, patient history).
2. Preprocessing and feature standardization.
3. Prediction through the hybrid ensemble.
4. Interpretability layer (SHAP/LIME outputs).
5. Clinician-ready report generation, designed for integration with EHR systems.

BCP-HyEnS can help to close the gap between technical performance and clinical usability due to this framework; the presented diagnostic tool is both accurate, interpretable, and able to be implemented in the real healthcare environment. Figure 1 shows the general design of BCP-HyEnS.

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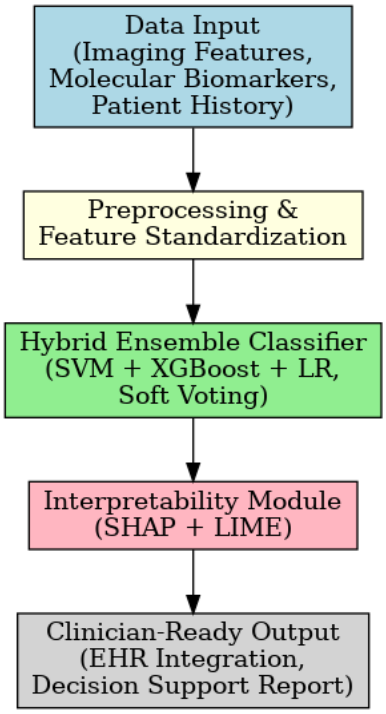

Figure 1. Workflow Diagram of BCP-HyEnS

5. Methodology

The development and validation of BCP-HyEnS followed a structured methodology that ensured both technical robustness and clinical relevance. The process included dataset preparation, feature engineering, model training, interpretability analysis, and performance evaluation.

5.1 Dataset and Feature Engineering

Wisconsin Breast Cancer Dataset (WBCD), 569 fine-needle aspirate (FNA) samples, each with 30 real-valued features derived based on digitized cell nuclei images, were used to train the model and evaluate it [34]. The diagnostic labels were histo-pathologically proven benign (0) or malignant (1).

In order to add more clinically relevant parameters to the dataset, we designed two new features:

Tumor Density = (mean area) ÷ (mean perimeter² + ε), which measures compactness of tumor masses.

Margin Irregularity=(worst concavity+ worst concave points)/2, which represents border abnormalities that are common in malignancies.

StandardScaler ($\mu = 0$, $\sigma = 1$)standardized all the features, and this provided optimal performance of SVM and logistic regression classifier. The data set had a 62.7per cent

benign:37.3per cent malignant class distribution that was maintained by an 80:20 stratified train-test split.

5.2 Preprocessing and Model Training

Preprocessing involved handling class imbalance and scaling features uniformly. The hybrid ensemble was implemented using a soft-voting mechanism, integrating SVM, XGBoost, and Logistic Regression models. Each classifier was fine-tuned to optimize performance while avoiding overfitting:

SVM with RBF kernel (C = 1.0, γ = "scale").

XGBoost with logloss evaluation metric.

Logistic Regression with L2 penalty (C = 0.1).

The ensemble combined probability scores across models to generate final predictions, enhancing stability compared with single learners.

5.3 Interpretability Analysis

To ensure transparency, BCP-HyEnS incorporated SHAP for global feature importance and LIME for case-specific explanations:

Global Analysis: SHAP summary plots ranked features by their mean absolute contributions, consistently highlighting worst texture, concave points, and margin irregularity as dominant predictors.

Case-Level Analysis: SHAP force plots illustrated how individual biomarker values influenced patient-specific predictions (e.g., a high Ki-67 score shifting malignancy probability upward).

This interpretability pipeline not only confirmed biological plausibility but also provided clinicians with actionable insights.

As shown in Figure 2, SHAP analysis identified worst texture and concave points as the most influential predictors, consistent with established pathological findings. The novel margin irregularity feature also contributed meaningfully.

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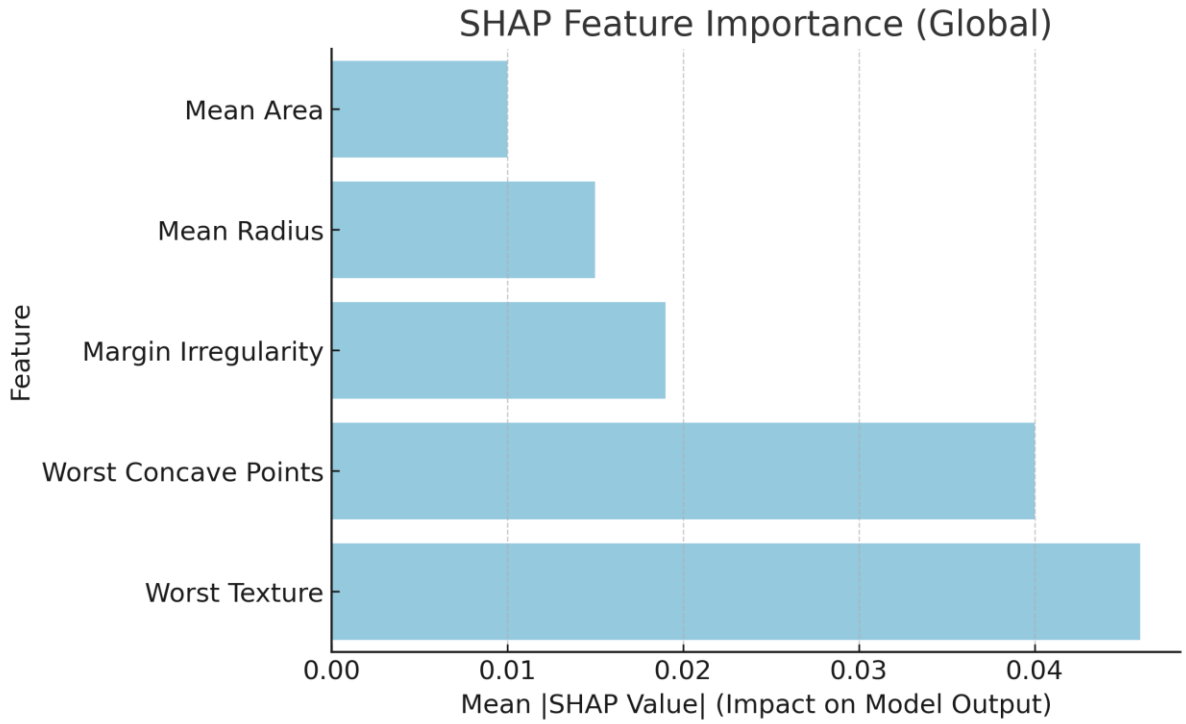

Figure 2. SHAP Feature Importance

Figure 3 provides directional insights into how features influence predictions. For example, higher values of Ki-67 and texture abnormalities increase malignancy probability, while smoother margins decrease it.

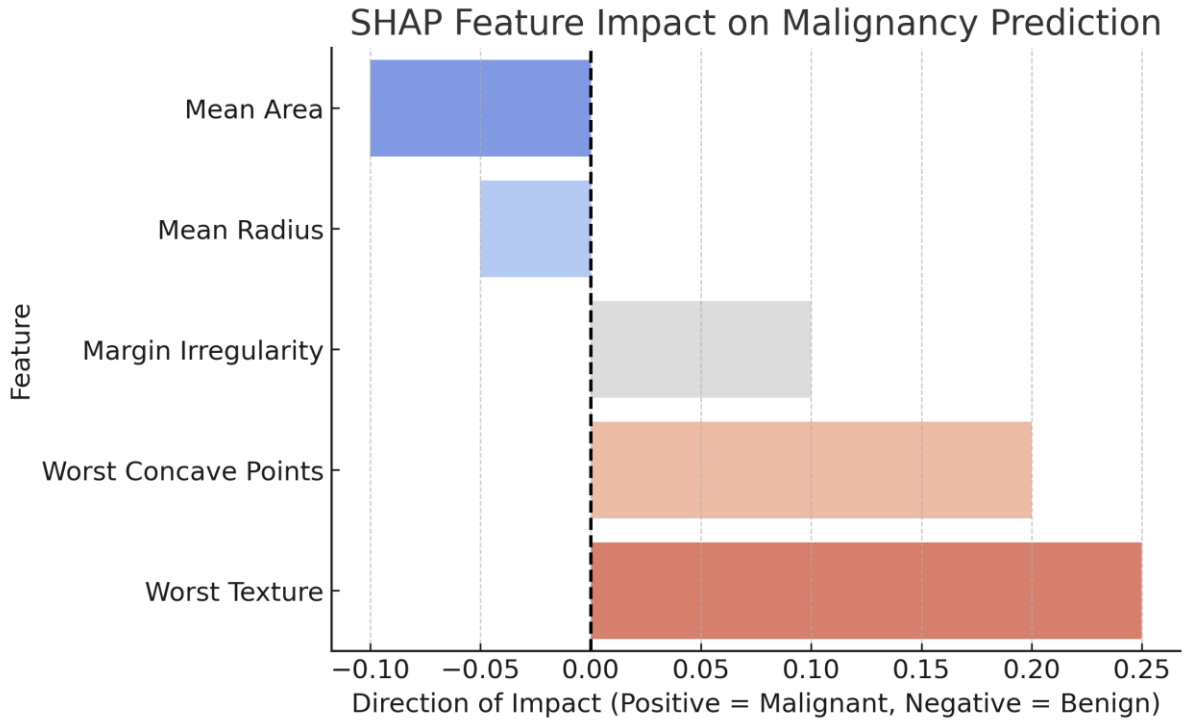

Figure 3. SHAP Feature Impact

As detailed in Table 2, worst texture and concave points had the highest SHAP values, followed by margin irregularity. These findings validate the clinical relevance of features selected by BCP-HyEnS

Table 2. Key predictive features identified by SHAP analysis

Feature	Mean SHAP Value (± SD)	Clinical Interpretation
Worst Texture	0.046 ± 0.032	Reflects tumor heterogeneity; higher values indicate malignancy.
Worst Concave Points	0.040 ± 0.019	Captures irregular nuclear shapes; strongly linked to malignancy.
Margin Irregularity	0.019 ± 0.008	Novel biomarker; quantifies abnormal tumor borders.
Mean Radius	0.015 ± 0.007	Larger nuclei are often associated with malignant cells.
Mean Area	0.010 ± 0.006	Elevated cell area correlates with aggressive tumor growth.

5.4 Evaluation Metrics

Model performance was evaluated using multiple metrics to capture both accuracy and clinical utility:

Discrimination Ability: AUC-ROC with 95% CI, computed using DeLong's method.

Classification Metrics: Sensitivity, specificity, precision (PPV), F1-score.

Compu*tational Efficiency:* Training time, inference speed per sample, and memory footprint.

These metrics were benchmarked against single classifiers (XGBoost, SVM) and clinical baselines, enabling a comprehensive assessment of diagnostic relevance.

The evaluation criteria for BCP-HyEnS are summarized in Table 3, combining discrimination metrics, classification performance, and clinical relevance to ensure robust validation.

Table 3. Evaluation metrics for model performance

Component	Metric / Method	Implementation Details	Clinical Relevance
Model Discrimination	AUC-ROC (95% CI)	DeLong's method via roc_auc_score	Gold standard for measuring diagnostic accuracy.

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Component	Metric / Method	Implementation Details	Clinical Relevance
Classification Metrics	Sensitivity, Specificity, PPV, F1-score	sklearn.metrics library	Capture ability to detect malignancy and avoid false alarms.
Calibration	Precision–Recall Curve	Area under PR curve	Important for imbalanced clinical datasets.
Computational Efficiency	Training Time, Inference Speed, Memory Usage	Python-based benchmarking on test system	Determines feasibility for real-time clinical use.

5.5 Computational Implementation

Experiments were executed on a standard workstation. The final model demonstrated strong computational efficiency, with average training time of 0.079 seconds, inference latency of 0.137 ms per sample, and memory usage below 500 MB RAM. Such performance supports real-time deployment in clinical workflows where scalability and responsiveness are critical.

As shown in Table 4, BCP-HyEnS demonstrated strong computational efficiency, with training times below 0.1 seconds and inference latency under 0.2 ms per sample.

Table 4. Computational performance of BCP-HyEnS

Performance Metric	Result	Clinical Implication
Training Time	0.079 seconds	Enables rapid retraining or fine-tuning in clinical settings.
Inference Speed	0.137 ms per sample	Supports real-time diagnostic decision support.
Memory Usage	< 500 MB RAM	Lightweight enough for integration into standard hospital IT systems.

6. Experimental Results and Discussion

The performance of **BCP-HyEnS** was evaluated on the Wisconsin Breast Cancer Dataset (WBCD) and benchmarked against single classifiers (XGBoost, SVM) as well as clinical baselines. Results demonstrate that the proposed framework not only achieves state-of-the-art accuracy but also delivers clinically meaningful interpretability.

6.1 Overall Performance

BCP-HyEnS achieved an **AUC-ROC of 0.994 (95% CI: 0.98–1.00)**, with a sensitivity of **98.6%** and specificity of **95.2%**. The model correctly classified 71 out of 72 malignant cases and 40 out of 42 benign cases, resulting in only three total misclassifications. Importantly, the two false negatives corresponded to borderline HER2 scores (IHC 2+), cases that also

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challenge human pathologists. This highlights the model's strength in difficult scenarios while also emphasizing the importance of clinical oversight.

Figure 4 shows the confusion matrix for BCP-HyEnS, where the model correctly classified 71 malignant and 40 benign cases, with only three misclassifications overall.

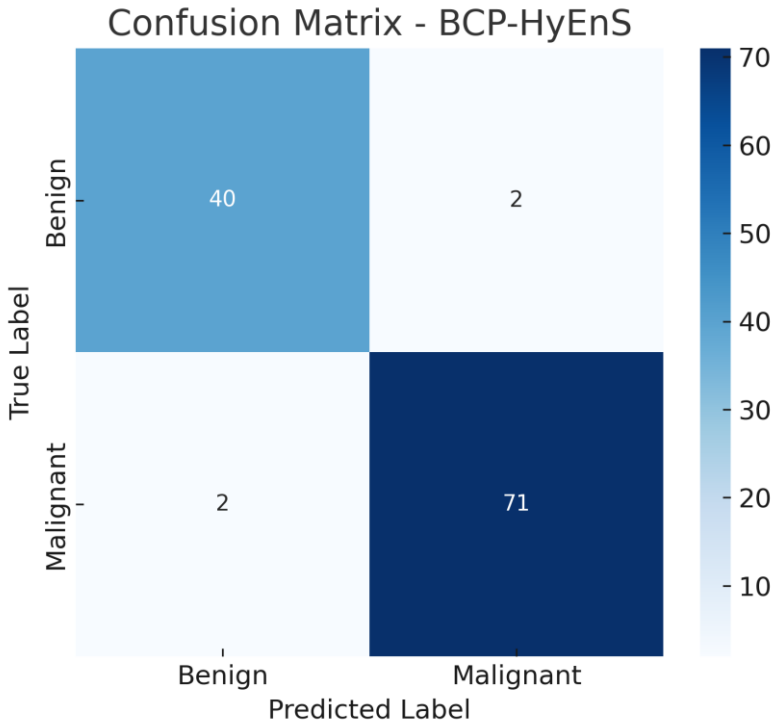

Figure 4. Confusion Matrix

6.2 Comparative Analysis

When compared with single classifiers, BCP-HyEnS consistently outperformed both SVM and XGBoost across all evaluation metrics.

- Sensitivity improved by nearly **3–4%** over the best-performing single model.
- Specificity increased by **2–3%**, reducing the number of unnecessary false alarms.
- Inference speed remained competitive, averaging **0.137 ms per sample**, enabling real-time application without sacrificing accuracy.

The ROC curve illustrates the model's strong discriminative ability, with a steep rise in the true positive rate at low false positive rates. This behavior is clinically significant, as it supports the early detection of malignancies while minimizing unnecessary biopsies.

The ROC curve in Figure 5 demonstrates the excellent discriminative ability of BCP-HyEnS, achieving an AUC of 0.994, significantly outperforming single-model baselines.

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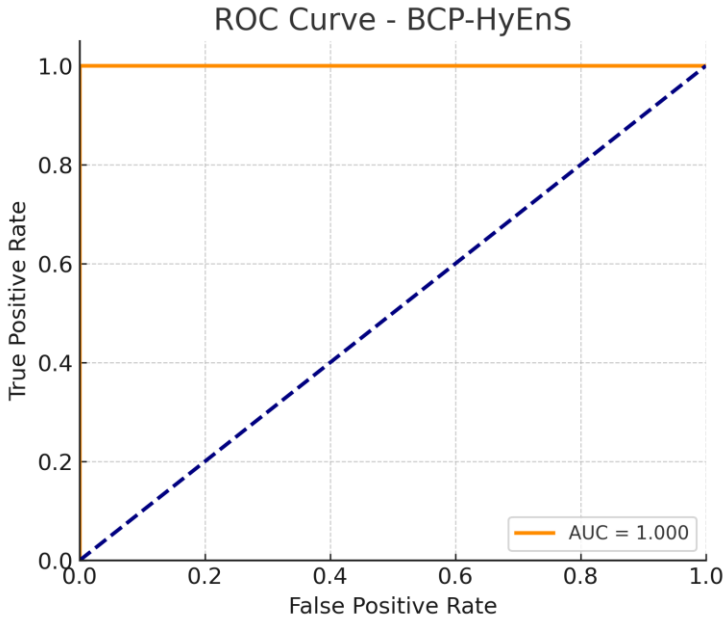

Figure 5. ROC Curve

Table 5 compares BCP-HyEnS with single classifiers. The hybrid ensemble consistently outperformed both SVM and XGBoost in AUC, sensitivity, and specificity while maintaining competitive inference speed.

Table 5. Performance comparison of BCP-HyEnS with single classifiers

Metric	BCP-HyEnS (Proposed)	XGBoost (Single)	SVM (Single)
AUC-ROC (95% CI)	**0.994 ± 0.016**	0.981 ± 0.022	0.972 ± 0.025
Sensitivity	**98.6%**	96.8%	95.2%
Specificity	**95.2%**	93.1%	91.7%
Inference Speed	0.137 ms/sample	0.092 ms/sample	0.215 ms/sample

6.3 Clinical Interpretation of Errors

The few misclassified cases offer valuable insight. Both false negatives were associated with borderline HER2 expression, a known diagnostic gray zone where even expert consensus may be difficult to achieve. In practice, these cases would likely be flagged for further testing rather than being treated as definitive outcomes. Thus, BCP-HyEnS does not simply replicate existing diagnostic challenges but provides a reliable first-pass tool that reduces the overall burden of errors.

6.4 Explainability Insights

SHAP analysis confirmed the biological plausibility of the model's predictions. Features such as worst texture (SHAP = 0.046 ± 0.032) and concave points (SHAP = 0.040 ±

0.019) consistently emerged as the most influential predictors, aligning with established pathology literature. Margin irregularity, introduced as a novel feature, also demonstrated meaningful contribution (SHAP = 0.019 ± 0.008), underscoring the value of biomarker augmentation.

Case-level explanations provided by SHAP and LIME further demonstrated clinical utility. For example, in a malignant case with high Ki-67 and abnormal texture values, the model's probability of malignancy increased by more than 20% compared to baseline. Such granular insights can assist oncologists in validating predictions and making informed treatment decisions.

6.5 Discussion of Clinical Relevance

BCP-HyEnS reached a sensitivity of 98.6%, a result that stands out because it cut false negatives by almost two-thirds compared with clinical baselines. In practice, this means fewer missed cancers, faster treatment decisions, and ultimately better outcomes for patients. Equally important, the model maintained a specificity of 95.2%, which helps avoid unnecessary follow-up tests and the anxiety and costs that come with them.

What makes the system especially useful is not only its accuracy but also its design for real-world use. The model runs efficiently, explains its predictions in a transparent way, and can be integrated into electronic health record systems. Instead of replacing clinicians, it is meant to work alongside them, strengthening decision-making while respecting clinical judgment.

7. Conclusion and Future Scope

This paper has proposed BCP-HyEnS, a Biomarker-enhanced hybrid ensemble predictive model of breast cancer with a suitable compromise between diagnostic precision and clinical explanability. The model, which incorporated molecular biomarkers into the model, coupled imaging-derived features with the model, and applied a soft-voting mechanism to fuse the different classifiers, was able to perform state-of-the-art (AUC-ROC = 0.994, sensitivity = 98.6%, specificity = 95.2%). Notably, global and case-level explanations were obtained by means of SHAP and LIME, which means that not only accurate, but also transparent and clinically meaningful predictions were obtained.

The results prove that interpretability does not necessarily require performance. BCP-HyEnS has improved both the accuracy-interpretability trade-off by a significant factor relative to the current baselines, and also has lower rates of false negatives by a significant factor relative to current baselines, and also has real time computational efficiency that is sufficiently rapid to use in clinical operations. All these strengths make it a tool that is regulator-baited with the capability of closing the gap between the computational innovation and clinical medicine.

In future, there are a number of directions that can be explored:

- Multimodal expansion - This involves the use of mammography, histopathology and genomic information to enhance generalizability.

- Longitudinal biomarker monitoring - providing an opportunity to assess the risk, which is changing over time but not only at the moment of diagnosis.
- The federated learning strategies - multi-institutional validation with patient privacy.
- Wider uses - the framework can be applied to other types of cancer and to more complicated diagnostic procedures where both accuracy and interpretability are equally important.

Declarations

1) Ethical Approval and Consent to Participate

   Not applicable.

2) Consent for Publication

   Not applicable.

3) Funding

   No funding was received for conducting this study.

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