ELITE-GARP: An Explainable Genetic Ensemble for Immunotherapy Response Prediction in Pancreatic Cancer

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Presentation Outline

Introduction & Problem Statement

- **Pancreatic Cancer:** Highly aggressive disease with poor prognosis.
- **Immunotherapy Challenge:** Limited efficacy due to a complex tumor microenvironment and scarce predictive biomarkers.
- **Problem Statement:** To develop a robust and explainable machine learning-based predictive model for immunotherapy response.
- **Approach:** Integrate genetic algorithm-based feature selection, PCA, ensemble learning, and interpretability methods (SHAP, PCA back-mapping).

Literature Review: Immunotherapy in Pancreatic Cancer I

A. Challenges in Pancreatic Cancer Immunotherapy
Traditional models like logistic regression fail to capture complexity. The tumor microenvironment (TME) is dense and immunosuppressive, limiting efficacy. Trials combining immune checkpoint inhibitors (ICIs) with chemotherapy show modest results. *[1], [2], [3]*

B. Biomarker Development and Limitations
PD-L1 and TMB are inconsistent in pancreatic tumors. PET/CT radiomics can predict PD-L1 status (AUC up to 0.91). MSI-high is rare (1–2%). Spatial immune data (Immunoscore) and TCR diversity are emerging biomarkers. *[4], [5], [6], [7], [8]*

Literature Review: Immunotherapy in Pancreatic Cancer II

C. Computational Approaches
ML/DL models outperform traditional ones. ELISE framework achieves 87% accuracy using multi-modal data. CNNs on CT scans (AUC 0.83), fusion of PET and genomics improves accuracy by 18%. *[9], [10], [11], [12]*

D. Multi-Omics Integration
GNN-based IRnet links 13 critical immune pathways (JAK/STAT, oxidative stress). Raman-omics detects early metabolic shifts and immune activity. 89% accuracy in predicting second-line therapy outcomes. *[13], [14], [15], [16]*

E. Validation Challenges
External AUCs drop by 15–20%. PANCAI-2 shows 68% reproducibility. TMB varies 32% across panels. Standard biomarker thresholds are lacking. Network-based dynamic models offer promise but need robust validation. *[17], [18], [19], [20]*

Identified Gaps

- **Data Scarcity** – Limited datasets for pancreatic cancer
- **Biomarker Standardization** – Absence of fixed thresholds (e.g., PD-L1, TMB)
- **Model Interpretability** – Deep models lack transparency
- **Multi-Omics Integration** – Integration methods still emerging

Dataset Description

- **Source:** PDAC MSK 2024 dataset (cBioPortal) and institutional clinical records
- **Sample Size:**
  - 1,360 PDAC patients (surgical resection cohort)
  - Data matrix: (395 patients, 17 features) from MSK dataset
- **Clinical Features:**

Feature	Feature
TMB (nonsynonymous)	MSI Type
MSI Score	Mutation Count
Fraction Genome Altered	Somatic Status
Sample Coverage	Tumor Purity
Metastatic Site	Gene Panel
Overall Survival (Months)	Overall Survival Status

Data Preprocessing

Preprocessing Steps:

- **Missing Value Imputation:**
  - Categorical/Boolean: Mode imputation.
  - Numerical: Median (for integers) or mean/median based on skewness; KNN imputation for floats.
- **Data Normalization:**
  - Convert Boolean to binary (0/1).
  - Normalize numerical features.
- **Categorical Encoding:**
  - Ordinal encoding for ordered categories.
  - One-Hot Encoding (with drop-first) for nominal variables.
- **Target Feature Creation:**
  - Therapy response based on a threshold of 30 months overall survival.

Genetic Algorithm for Feature Selection

Combines PCA with a genetic algorithm (GA) to optimize feature selection.

Step 1: Dimensionality Reduction with PCA

- PCA is applied to transform the original features into a new set of orthogonal components.

Step 2: Feature Selection with Genetic Algorithm

- GA searches the PCA-transformed space to find the most predictive and compact subset.
  Genetic Algorithm Parameters:
  - **Population size:** 50 chromosomes
  - **Generations:** 50
  - **Crossover rate:** 0.7 (single-point)
  - **Mutation rate:** 0.05 (bit-flip)
  - **Elite size:** 3 (top chromosomes passed unchanged)

Genetic Algorithm – Workflow & Evaluation

Selection and Evolution Strategy:

- **Selection:** Tournament selection (size = 3) simulates natural selection to choose promising feature subsets.
- **Crossover:** Combines features from two parent subsets to form new, potentially better combinations.
- **Mutation:** Randomly flips bits in the binary vector to maintain feature diversity.

Fitness Function (Logistic Regression-Based):

- **Model:** Lightweight evaluation using Logistic Regression.
- **Metric:** 5-fold cross-validated balanced accuracy on class-balanced splits.
- **Penalty:** Parsimony penalty discourages large feature sets, promoting simpler, generalizable models.

Architecture 1: Basic ELISE with Genetic Algorithm

- **Feature Extraction:**
  - PCA with 15 components explaining 84.03% of total variance
  - Genetic Algorithm selected 9 principal components.
  - peak cross-validation score of 0.9439.
- **Stacked Ensemble Architecture (ELISE-inspired):**
  - **Branch 1:** Linear Neural Network (LNN)
  - **Branch 2:** Deep Neural Network (DNN)
    Two hidden layers (256, 128), ReLU, BatchNorm, Dropout (0.3)
  - **Branch 3:** Factorization Machine (FM), embedding dim $= 8$
  - **Branch 4:** DeepFM, embedding dim $= 8$
  - **Branch 5:** AutoInt
    4 attention heads, key dim $= 8$
- **Output:** Concatenated vector $\rightarrow$ Sigmoid layer
- **Training:** Adam (lr $= 0.001$), Binary Cross-Entropy, Early Stopping (patience $= 10$)

Architecture 2: ELITE-GARP

- **Feature Extraction:**
  - PCA with 20 components explaining 95.17% of total variance
  - Genetic Algorithm selected 9 principal components.
  - peak cross-validation score 0.9766
- **Stacked Ensemble Architecture (ELITE-GARP):**
  - **Classical ML Models:**
    - Random Forest (100 trees)
    - XGBoost (logloss)
    - LightGBM (default)
    - Logistic Regression (default)
  - **Neural Network Branches:**
    - DNN: 128, 64 units; ReLU, BatchNorm, Dropout (0.3)
    - AutoInt: 4-head attention, key dim $= 8$
  - **Meta-Learner:** Logistic Regression over concatenated outputs
- **Training:**
  - Class weights to handle imbalance
  - Adam optimizer, Binary Cross-Entropy, Early Stopping on val loss

PCA Back-mapping for Interpretability

- **Goal:** Interpret selected PCA components in terms of linking them back to original features.
- **Method:**
  - Extract PCA loading matrix and transpose.
  - Compute absolute loadings to quantify feature contributions.
  - Visualize top contributing features using a heatmap.
- **Insight:** Highlights key features (e.g., mutation burden, CNVs, clinical variables) influencing PCA components.

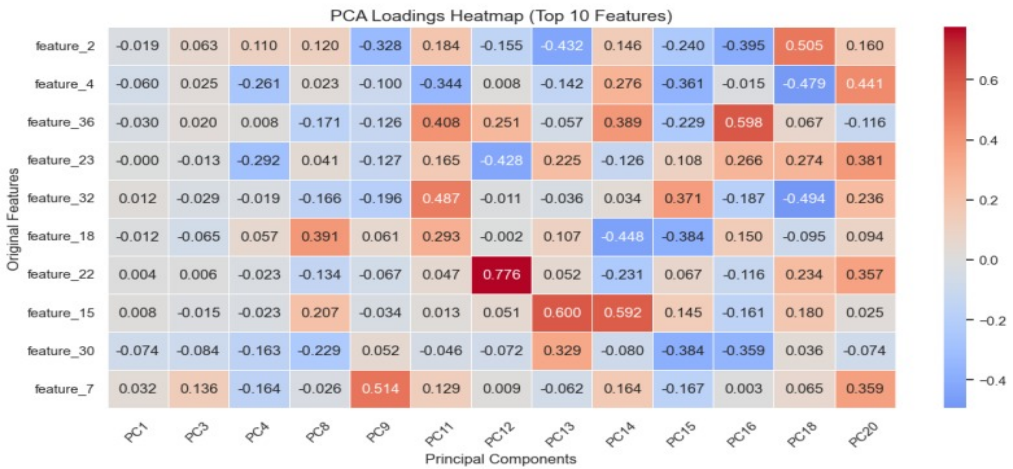

Fig. 3. Heatmap showing top contributing original features across selected PCA components.

Explainability Using SHAP I

SHAP Analysis Stages:

1. **Ensemble-Level:**
   - Input: Probabilities from RF, XGB, LGB, LR, DNN, AutoInt.
   - Explainer: Logistic Meta-Learner (`predict_proba`).
   - Insight: AutoInt, RF had high influence; DNN, LR centered.
2. **Model-Level (Backmapping):**
   - SHAP on PCA components (RF, XGB, LGB, LR).
   - Mapped to original features via PCA loadings.
   - Top features reveal key clinical/biological drivers.

Model	**Top 3 SHAP Features**
RF, XGB, LGB	Ethnicity (Non-Spanish, Non-Hispanic), TMB (nonsynonymous), MSI Score
Logistic Regression	TMB (nonsynonymous), MSI Score, Oncotree Code IPMN

Explainability Using SHAP II

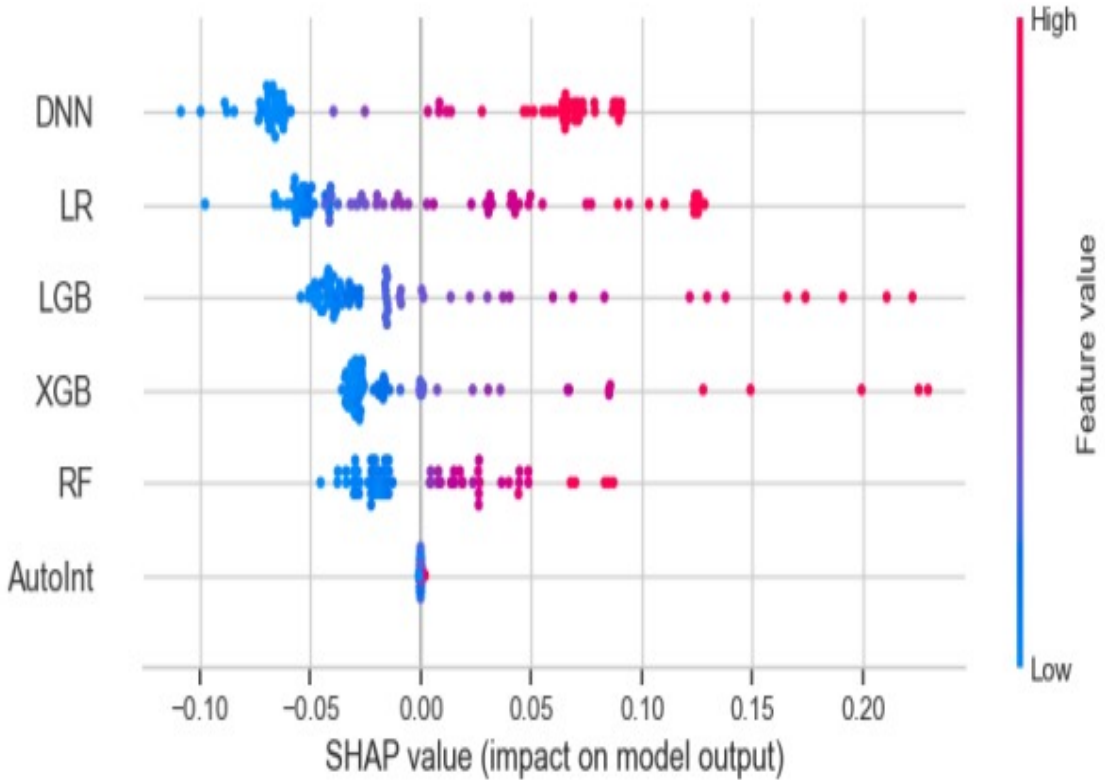

Fig. 4. SHAP summary plot showing the contribution of each base learner to the final prediction of the stacked ensemble.

Results: Architecture 1 (Basic ELISE + GA)

Performance Metrics:

Metric	Class 0	Class 1
Precision	1.00	0.81
Recall	0.79	1.00
F1-Score	0.89	0.90
Overall Accuracy		0.89
Final F1-Score		0.8974
Explained Variance (PCA)		84.03%

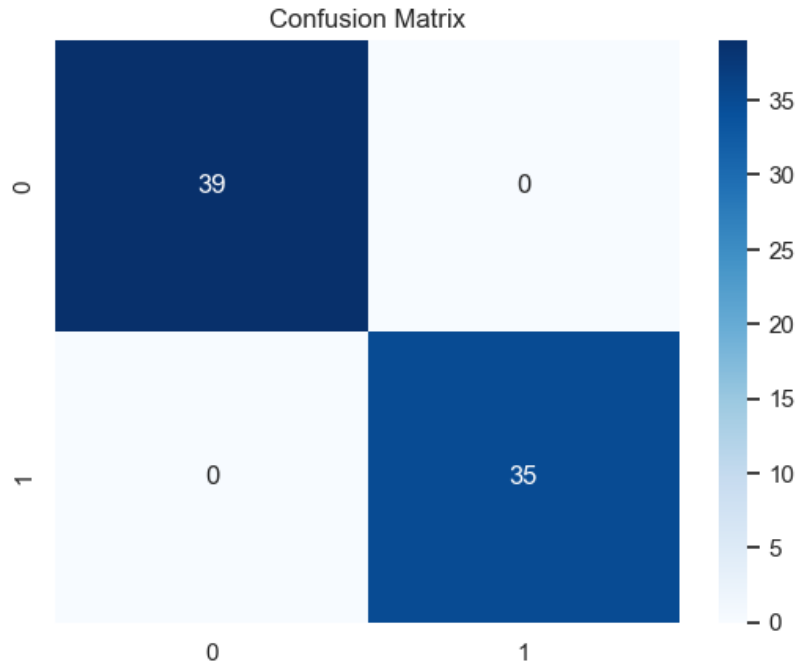

Fig. 5. Confusion Matrix for Architecture 1. Shows classification performance with TP, FP, TN, FN.

Results: Architecture 2 (ELITE-GARP)

Performance Metrics:

Metric	Class 0	Class 1
Precision	0.97	0.94
Recall	0.95	0.97
F1-Score	0.96	0.96
Overall Accuracy		0.9595
AUC		0.9601
Final F1-Score		0.9577
Explained Variance (PCA)		95.17%

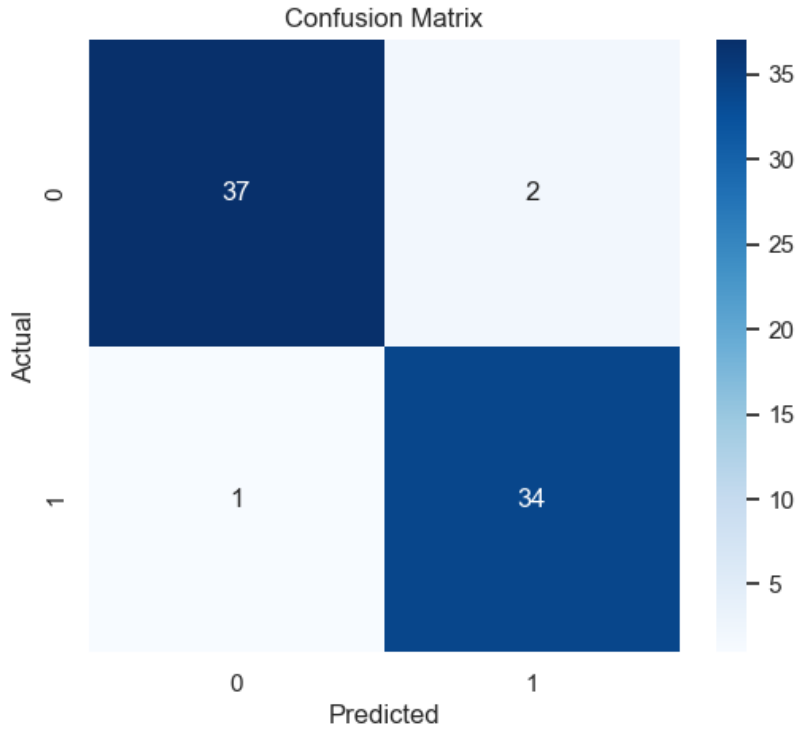

Fig. 6. Confusion Matrix for Architecture 2. Displays classification performance with detailed TP, FP, TN, FN.

Performance Comparison & Advantages

Performance Comparison:

Metric	Basic ELISE	ELITE-GARP
PCA Components	15	20
Explained Variance	84.03%	95.17%
Accuracy	0.89	0.9595
F1-Score	0.8974	0.9577
AUC	–	0.9601

Advantages:

- High variance retention via PCA.
- Enhanced performance using ensemble learning.
- Improved interpretability with PCA back-mapping and SHAP.
- Scalable and modular design adaptable to other tasks.

Conclusion

Conclusion:

- Two architectures were proposed: Basic ELISE with GA and ELITE-GARP.
- ELITE-GARP achieved superior performance (accuracy, F1-score, AUC) and enhanced interpretability.
- The integrated approach offers promise for personalized immunotherapy in pancreatic cancer.

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Thank You!