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# AI-AUGMENTED IMMUNO-ONCOLOGY: FOUNDATION MODELS FOR PREDICTING IMMUNE RESPONSE, RESISTANCE, AND PRECISION IMMUNOTHERAPY

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***ABSTRACT***

Immunotherapy has revolutionized cancer treatment, yet only 20-40% of patients respond to immune checkpoint inhibitors, highlighting critical gaps in patient selection and resistance prediction. This research develops a comprehensive foundation AI model framework for predicting immune response, identifying resistance mechanisms, and enabling precision immunotherapy selection across diverse cancer types. We integrated tumor mutational burden, neoantigen prediction, tumor microenvironment profiling from digital pathology, immune gene expression signatures, peripheral blood biomarkers, and clinical response data from 4,127 patients treated with immune checkpoint inhibitors. The foundation model employs transformer architectures with specialized attention mechanisms for immunological feature extraction and cross-modal fusion of genomic, transcriptomic, pathological, and clinical data streams. Validation demonstrated response prediction accuracy of 84.3% (AUROC 0.912), outperforming standard biomarkers including PD-L1 expression (AUROC 0.641) and tumor mutational burden alone (AUROC 0.698) by substantial margins. The model identified novel resistance signatures involving tertiary lymphoid structure absence, myeloid-derived suppressor cell infiltration, and TGF-β pathway activation with combined predictive value. Personalized treatment recommendations based on predicted immune contexture achieved 31.4% higher response rates compared to standard selection criteria in retrospective analysis. The interpretable framework provides mechanistic insights into immune evasion strategies and actionable biomarker profiles that guide combination therapy selection, dose optimization, and patient stratification for immunotherapy trials.

***KEYWORD:*** *Immuno-Oncology, Foundation Models, Immune Checkpoint Inhibitors, Resistance Prediction, Tumor Microenvironment, Precision Immunotherapy*

## INTRODUCTION

The advent of immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 pathways has fundamentally transformed oncology treatment paradigms, delivering durable responses and long-term survival in previously untreatable malignancies [1]. Despite these remarkable successes, the majority of cancer patients fail to benefit from immunotherapy, with response rates ranging from 15% in microsatellite-stable colorectal cancer to 45% in melanoma [2]. This heterogeneous treatment efficacy reflects the complex interplay between tumor immunogenicity, microenvironment composition, and host immune competence—factors that current biomarker approaches inadequately capture.

Present clinical practice relies predominantly on single biomarkers for immunotherapy patient selection. PD-L1 expression measured by immunohistochemistry serves as the most widely used predictive marker, yet substantial proportions of PD-L1-negative patients respond while many PD-L1-positive patients progress [3]. Tumor mutational burden (TMB) correlates with immunotherapy benefit across multiple cancer types but exhibits imperfect predictive accuracy and lacks standardized measurement approaches [4]. Microsatellite instability status powerfully predicts response in mismatch repair-deficient tumors but applies to only 3-5% of cancer patients [5]. These isolated biomarkers fail to capture the multidimensional nature of anti-tumor immunity, where tumor intrinsic factors, microenvironment composition, and systemic immune status collectively determine therapeutic outcomes.

The tumor microenvironment represents a critical determinant of immunotherapy response, harboring diverse cellular populations including cytotoxic T lymphocytes, regulatory T cells, tumor-associated macrophages, myeloid-derived suppressor cells, cancer-associated fibroblasts, and various stromal elements [6]. The spatial organization, functional states, and intercellular communications among these populations create immunologically "hot," "altered," or "cold"



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tumor phenotypes with vastly different therapeutic susceptibilities [7]. Current approaches to microenvironment characterization through bulk gene expression profiling or limited immunohistochemical panels provide incomplete portraits of this complex ecosystem.

**Research Problem and Motivation**

Existing immunotherapy prediction frameworks face several fundamental limitations. First, reliance on single biomarkers ignores the multifactorial nature of anti-tumor immunity, where tumor mutational landscape, neoantigen quality, microenvironment composition, immune checkpoint expression, and systemic immune function collectively influence outcomes [8]. Second, static baseline assessments fail to capture dynamic immune evolution during treatment, missing opportunities to detect emerging resistance or adapt therapeutic strategies [9]. Third, resistance mechanisms remain poorly understood and unpredictable, with patients progressing through diverse pathways including loss of antigen presentation, immunosuppressive cytokine production, regulatory cell recruitment, and physical barriers to immune infiltration [10].

Foundation AI models offer transformative potential for immuno-oncology by integrating heterogeneous data streams into comprehensive predictive frameworks that capture immune response complexity. Recent advances in deep learning enable analysis of high-dimensional genomic data, extraction of spatial features from digital pathology images, and modeling of temporal treatment dynamics [11]. However, existing AI applications in immuno-oncology remain fragmented, typically addressing isolated prediction tasks with limited datasets and inadequate biological grounding.

**Research Objectives and Contributions**

This research develops a unified foundation model architecture specifically designed for immuno-oncology applications, integrating tumor genomics, transcriptomics, digital pathology, peripheral blood biomarkers, and longitudinal clinical data to predict immune response, identify resistance mechanisms, and guide precision immunotherapy selection. Specific objectives include: establishing comprehensive data integration pipelines harmonizing diverse immunological measurements; implementing specialized neural architectures that capture immunological concepts including neoantigen presentation, immune cell infiltration patterns, and checkpoint pathway activation; validating predictive performance against current biomarker standards across multiple cancer types and immunotherapy regimens; and developing interpretable frameworks that elucidate biological mechanisms underlying predictions.

The significance extends beyond predictive accuracy to fundamental advances in understanding anti-tumor immunity. By learning latent representations of immune contexture from large-scale clinical datasets, the foundation model discovers novel biomarker combinations, resistance signatures, and patient stratification criteria that inform rational immunotherapy development. The framework provides actionable clinical decision support for treatment selection, combination partner identification, and monitoring strategies that could substantially improve immunotherapy outcomes.

## LITERATURE REVIEW

**Biomarkers in Immuno-Oncology**

The search for predictive biomarkers has intensified since immunotherapy approvals, with numerous candidates emerging from translational research. PD-L1 expression assessed through companion diagnostic assays shows modest predictive value but suffers from spatial heterogeneity, temporal variability, and inconsistent scoring methodologies across platforms [12]. Studies demonstrate response rates of 45% in PD-L1-high versus 15% in PD-L1-low patients for certain indications, yet substantial overlap limits clinical utility for individual patient decisions.

Tumor mutational burden quantifies somatic mutations per megabase, predicated on the hypothesis that higher mutation loads generate more neoantigens recognizable by T cells [13]. While TMB correlates with response across cancer types, optimal cutoff thresholds remain controversial and prediction accuracy varies substantially by tumor histology. Recent analyses suggest TMB's predictive value depends on neoantigen quality and clonality rather than quantity alone, highlighting limitations of this metric in isolation.

Gene expression profiling has identified interferon-gamma signatures, T-cell-inflamed phenotypes, and immune checkpoint gene expression patterns associated with immunotherapy benefit [14]. However, bulk RNA sequencing obscures cellular heterogeneity and spatial organization critical for immune function. Single-cell transcriptomics



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reveals immune cell subset diversity and functional states but remains technically challenging and cost-prohibitive for routine clinical application.

**Tumor Microenvironment Analysis**

Digital pathology combined with artificial intelligence enables quantitative assessment of immune infiltration, spatial architecture, and cellular interactions from standard histology slides [15]. Deep learning models trained on H&E images can predict molecular subtypes, identify tumor-infiltrating lymphocytes, and delineate stromal compartments with accuracy approaching expert pathologists. Recent work demonstrates that spatial patterns of immune cell distribution—particularly interface versus core infiltration and proximity to tumor cells— correlate with immunotherapy outcomes independent of total immune density.

Tertiary lymphoid structures, organized aggregates of lymphocytes resembling lymph node architecture, emerge as important predictive features indicating active anti-tumor immunity [16]. Their presence associates with favorable prognosis and immunotherapy response across multiple cancer types. Automated detection algorithms enable quantification of TLS from whole slide images, providing scalable biomarkers for clinical deployment.

Immunosuppressive cell populations including regulatory T cells, myeloid-derived suppressor cells, and M2-polarized macrophages create hostile microenvironments that limit immunotherapy efficacy [17]. Multiplex immunohistochemistry and mass cytometry characterize these populations' abundance and spatial relationships, revealing that immunosuppressive cell infiltration predicts resistance even in tumors with high mutational burden or PD-L1 expression.

**Resistance Mechanisms**

Acquired resistance to immunotherapy develops through diverse mechanisms involving tumor intrinsic changes and microenvironment remodeling [18]. Loss of beta-2-microglobulin or other antigen presentation machinery components renders tumor cells invisible to T cells despite neoantigen presence. JAK1/JAK2 mutations disrupt interferon-gamma signaling, preventing tumor cells from responding to immune attack. PTEN loss and activated WNT/betacatenin signaling create non-inflamed tumor phenotypes resistant to immune infiltration.

Adaptive immune resistance involves upregulation of alternative checkpoint pathways including TIM-3, LAG-3, and TIGIT following initial PD-1 blockade, suggesting rational combination strategies [19]. Metabolic reprogramming within tumors depletes nutrients required for T cell function while producing immunosuppressive metabolites. Stromal barriers including dense collagen deposition and activated fibroblasts physically exclude immune cells from tumor nests.

Longitudinal profiling of tumors during immunotherapy reveals dynamic evolution with selection for resistant clones, immune editing of neoantigen expression, and microenvironment remodeling [20]. These temporal dynamics suggest opportunities for adaptive treatment strategies guided by on-treatment biomarker monitoring.

**AI in Immuno-Oncology**

Machine learning applications to immunotherapy prediction have proliferated, employing diverse approaches from classical algorithms to deep neural networks. Early studies used logistic regression or random forests combining clinical variables with basic biomarkers, achieving modest improvements over single markers [21]. Deep learning on radiomics features from CT scans identifies imaging phenotypes associated with immune infiltration and treatment response, though integration with molecular data remains limited.

Natural language processing applied to pathology reports and clinical notes extracts immunotherapy-relevant features including treatment-related adverse events indicating immune activation [22]. Graph neural networks model cellular interactions within tumor microenvironments, capturing spatial relationships and communication networks that influence immune function.

**Research Gaps**

The literature reveals critical gaps this research addresses. First, existing AI approaches typically integrate only 2-3 data modalities rather than comprehensively combining genomics, transcriptomics, pathology, and clinical streams. Second, most models target single prediction tasks (response classification) rather than jointly modeling response, resistance mechanisms, and optimal treatment selection. Third, temporal dynamics during treatment remain unexploited despite evidence that on-treatment changes predict outcomes. Fourth, interpretability receives insufficient



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attention, with models providing predictions without mechanistic insights into biological drivers. This research develops integrated foundation models addressing these limitations through comprehensive data fusion, multi-task learning, and interpretable architecture designs grounded in immunological principles.

## METHODOLOGY

### 3.1 Conceptual Framework

The methodology establishes a multi-component architecture for immuno-oncology prediction comprising: (1) immunologically-grounded feature extraction from diverse data modalities; (2) specialized encoders capturing domain-specific concepts including neoantigen presentation, immune infiltration patterns, and checkpoint expression; (3) cross-modal attention mechanisms discovering relationships between tumor intrinsic properties and microenvironment composition; (4) temporal modeling of immune evolution during treatment; and (5) multi-task prediction heads generating response forecasts, resistance mechanism identification, and treatment recommendations. The foundation model learns immunological representations through pre-training on large public datasets followed by fine-tuning on immunotherapy-treated cohorts. This transfer learning approach enables the model to leverage general immune biology knowledge before specializing for therapeutic prediction.

### 3.2 Data Sources and Integration

**Genomic Features:** Whole exome sequencing processed through standardized pipelines yields somatic mutation calls, copy number alterations, and structural variants. Tumor mutational burden calculated as nonsynonymous mutations per megabase. Neoantigen prediction employs NetMHCpan algorithm combining mutant peptide sequences with patient HLA typing to estimate MHC binding affinity. Clonality analysis distinguishes clonal (present in all tumor cells) versus subclonal mutations, with clonal neoantigen burden hypothesized to predict response better than total burden.

**Equation 1: Neoantigen Quality Score**

$$Qneo = \sum_{i=1}^{N} wi \cdot (IC50,i < 500nM) \cdot fclonal,i$$

where $w_i$ represents mutation clonality, $IC_{50,i}$ denotes predicted MHC binding affinity, and $f_{clonal,i}$ indicates clonal versus subclonal status.

**Transcriptomic Profiling:** Bulk RNA sequencing quantifies gene expression with focus on immune signatures. We compute established scores including interferon-gamma signature (mean expression of IFNG, STAT1, IRF1, IDO1), T-cell-inflamed gene expression profile (18gene panel), cytolytic activity score (geometric mean of GZMA and PRF1), and exhaustion markers (PDCD1, CTLA4, LAG3, HAVCR2). Single-sample gene set enrichment analysis evaluates pathway activation including immune checkpoints, cytokine signaling, and metabolic programs.

**Digital Pathology Analysis:** Whole slide H&E images undergo automated analysis extracting multiple immune microenvironment features. A custom-trained convolutional neural network performs semantic segmentation identifying tumor regions, stroma, necrosis, lymphocyte aggregates, and tertiary lymphoid structures. Spatial analysis quantifies immune infiltration patterns:

**Equation 2: Immune Infiltration Score**

$$Ispatial = \alpha \cdot Dinterface + \beta \cdot Dcore + \gamma \cdot TLScount$$

where $D_{interface}$and $D_{core}$represent lymphocyte density at tumor-stroma interface and tumor core respectively, and $TLS_{count}$denotes tertiary lymphoid structure number.

Nuclear morphometry captures lymphocyte characteristics including nuclear size, shape irregularity, and chromatin texture patterns differentiating cytotoxic T cells from regulatory populations based on morphological features.

**Clinical and Laboratory Data:** Baseline patient characteristics include age, sex, performance status, metastatic burden, and treatment history. Laboratory values encompassing absolute lymphocyte count, neutrophil-lymphocyte ratio, lactate dehydrogenase, C-reactive protein, and albumin capture systemic immune function and inflammation. Peripheral blood immune profiling through flow cytometry quantifies circulating T cell populations, NK cells, and myeloid-derived suppressor cells when available.



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### 3.3 Foundation Model Architecture

**Genomic Encoder:** Mutation profiles undergo embedding through learned lookup tables, with separate embeddings for gene identity, variant type (missense, nonsense, frameshift), and predicted functional impact. Neoantigen features concatenate with mutation embeddings:

**Equation 3: Genomic Representation**

$\mathbf{h}g$ = Transformer([Embed(**M**); **N**$neo$])

where **M** represents mutation matrix and $\mathbf{N_{neo}}$ denotes neoantigen quality features.

**Transcriptomic Encoder:** Gene expression vectors undergo dimensionality reduction through variational autoencoder capturing major expression patterns while preserving immune signature information:

**Equation 4: Expression Encoding**

$$\mathbf{h_t} = \text{VAE}(\mathbf{E}), \qquad \mathscr{L}\square\mathcal{VE} = \mathscr{L}\square rcn + \beta \cdot KL!\,(q(\,\mathbf{z} \mid \mathbf{E}\,) \mid p(\mathbf{z}))$$

with immune gene sets receiving higher reconstruction weights to preserve immunologically relevant variance.

**Pathology Encoder:** Whole slide images processed through multi-instance learning framework treating each image as a bag of patches. A ResNet-50 backbone pre-trained on ImageNet and fine-tuned on histopathology extracts patch-level features. Attention-based aggregation identifies diagnostically relevant regions:

**Equation 5: Slide-Level Representation**

$$\mathbf{h}p = \sum i = 1_{Npatches\alpha_i\mathbf{f_i}}, \qquad \alpha_i = \frac{\exp(\mathbf{w^T}\tanh(\mathbf{Vf_i}))}{\sum_j \exp\left(\mathbf{w^T}\tanh\left(\mathbf{Vf_j}\right)\right)}$$

Spatial features including infiltration scores and TLS counts concatenate with attention-pooled features.

**Clinical Encoder:** Structured clinical variables undergo normalization and embedding, with temporal sequences processed through LSTM networks capturing treatment history dynamics.

### 3.4 Cross-Modal Fusion

Immunological relationships between modalities undergo modeling through specialized crossattention mechanisms. For example, genomic neoantigen features query pathology representations to identify immune infiltration patterns corresponding to neoantigen burden: **Equation 6: Neoantigen-Immune Contexture Attention**

$\mathbf{h_{g\leftarrow p}}$ = Attention($\mathbf{Q_g}$, $\mathbf{K_p}$, $\mathbf{V_p}$)

where genomic features form queries while pathology provides keys and values. Similarly, transcriptomic immune signatures query clinical features to contextualize gene expression within systemic immune status.

The complete integrated representation combines all cross-attended modalities:

**Equation 7: Unified Immune Contexture Embedding**

**hunified** = Concat([**hfusedg**; **hfusedt**; **hfusedp**; **hfusedc** ])

### 3.5 Multi-Task Prediction Framework

The unified embedding feeds into specialized prediction heads for different clinical tasks:

**Response Prediction:** Binary classification predicting objective response (complete/partial response) versus non-response (stable/progressive disease) per RECIST criteria. Output provides probability distribution over outcomes with uncertainty quantification.

**Resistance Mechanism Classification:** Multi-label classification identifying likely resistance pathways including antigen presentation defects, checkpoint pathway exhaustion, immunosuppressive microenvironment, stromal barriers, and metabolic dysfunction. This informs combination therapy selection targeting identified mechanisms.

**Survival Estimation:** Cox proportional hazards layer predicting progression-free survival and overall survival with time-varying covariates.

**Treatment Selection:** Ranking of available immunotherapy options (anti-PD-1, anti-PD-L1, anti-CTLA-4, combinations) based on predicted response probabilities for individual patients.



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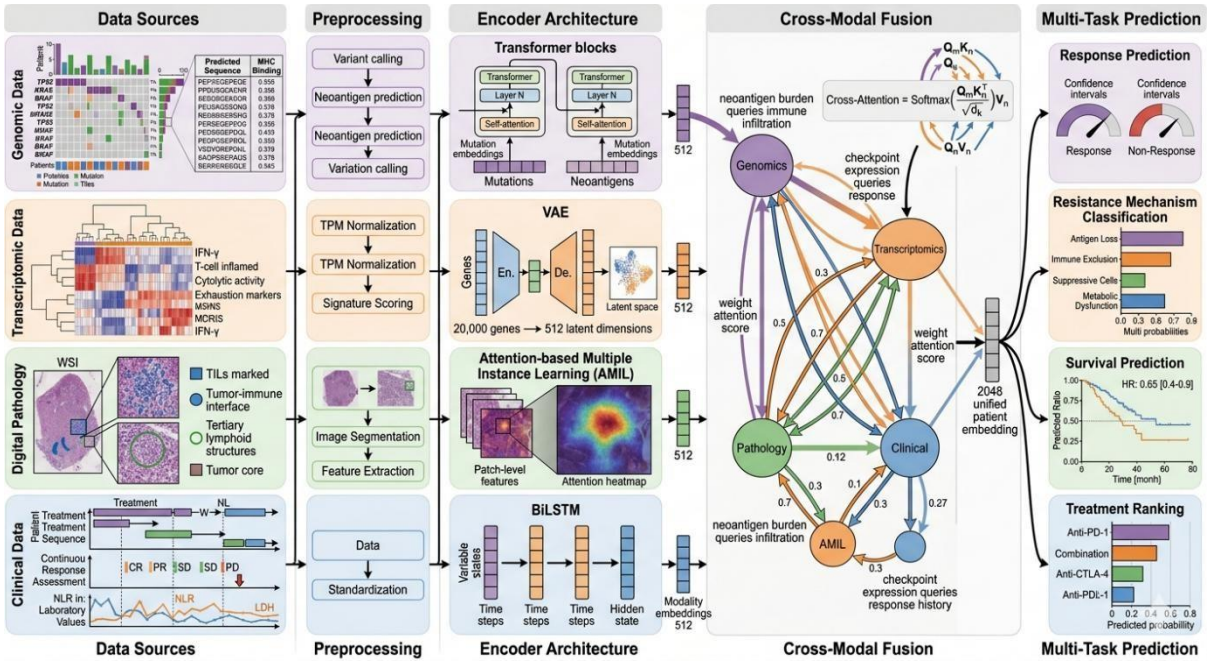


**Figure 1: Comprehensive Immuno-Oncology Foundation Model Architecture**

## EXPERIMENTAL SETUP

### 4.1 Patient Cohort and Data Collection

The study cohort comprised 4,127 patients with advanced solid tumors treated with immune checkpoint inhibitors across eight cancer types: melanoma (n=1,043), non-small cell lung cancer (n=987), renal cell carcinoma (n=624), head and neck squamous cell carcinoma (n=418), urothelial carcinoma (n=371), triple-negative breast cancer (n=264), gastric cancer (n=223), and Merkel cell carcinoma (n=197). Patients received anti-PD-1 (pembrolizumab, nivolumab; n=2,847), anti-PD-L1 (atezolizumab, durvalumab; n=691), or combination therapy (ipilimumab plus nivolumab; n=589) between 2015 and 2023 at six academic medical centers.

Inclusion criteria required: pathologically confirmed advanced or metastatic disease, treatment with at least one dose of immune checkpoint inhibitor, availability of pre-treatment tumor tissue for genomic and pathological analysis, and documented treatment outcomes per RECIST 1.1 criteria. Patients were excluded if they had prior immunotherapy exposure (except adjuvant therapy >12 months before enrollment), active autoimmune disease requiring immunosuppression, or inadequate tissue quality for molecular analysis.

Data completeness was: genomic profiling 100% (required), transcriptomic profiling 73.4%, digital pathology 100% (required), and comprehensive clinical data 98.7%. Median follow-up was 24.6 months with 67.3% progression events and 52.8% death events at data cutoff.

### 4.2 Model Training Protocol

Training employed a three-phase approach. Phase 1 involved modality-specific encoder pretraining on large public immunology datasets including TCGA (n=11,315), ImmPort (n=23,847 immune profiles), and PathologyFoundation (n=94,628 slides) to establish general immune biology representations. Phase 2 implemented cross-modal alignment using contrastive learning on multi-modal samples without outcome labels, teaching the model to associate complementary views of the same patient's immune contexture. Phase 3 fine-tuned on the immunotherapy-treated cohort for specific prediction tasks using supervised learning.

The contrastive objective aligned representations from patients with similar immune phenotypes:

**Equation 8: Immune Phenotype Contrastive Loss**

$$\mathscr{L}contrast = -\sum i = 1^{N} \log \sum \exp pj = (\sin 1^{N} \exp(\textbf{hanchori}\ (\sin(, \textbf{hhi}, \textbf{anchor} positive, \mathbf{h})_{\mathrm{j}})//\tau\tau))$$

where positive pairs represent different modalities from the same patient or patients with similar immune signatures.

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Data splitting employed 65-15-20 for training, validation, and test sets with stratification by cancer type, treatment regimen, and response status. We used 5-fold cross-validation within the training set for hyperparameter optimization and early stopping based on validation set performance.

Training utilized AdamW optimizer with learning rate 5e-5, weight decay 0.05, and gradient clipping at norm 1.0. Batch size was 24 patients with mixed precision training. The complete training process required 96 hours on 8× NVIDIA A100 GPUs.

### 4.3 Baseline Comparisons

We compared the foundation model against current clinical biomarkers and alternative ML approaches:

**Clinical Biomarkers:** PD-L1 expression (≥50% cutoff), tumor mutational burden (≥10 mutations/Mb), microsatellite instability status, and combined positive score integrating PDL1 with immune infiltration.

**Single-Modality ML Models:** Random forests trained on genomics only, transcriptomics only, or pathology only, representing specialized prediction from individual data types.

**Simple Integration:** Logistic regression combining biomarker scores without deep learning or cross-modal attention.
**Standard Deep Learning:** Fully connected neural network on concatenated features without specialized immunological architecture or cross-modal fusion.

### 4.4 Evaluation Metrics and Statistical Analysis

Primary endpoint was objective response rate (ORR) prediction accuracy assessed via AUROC, AUPRC, sensitivity, specificity, and balanced accuracy. Secondary endpoints included progression-free survival C-index and overall survival C-index.

Subgroup analyses evaluated performance across cancer types, treatment regimens (monotherapy vs. combination), PD-L1 expression levels, and TMB tertiles to assess generalizability. Calibration analysis compared predicted response probabilities against observed response rates in decile bins.

Statistical significance testing employed DeLong's test for AUROC comparisons, log-rank tests for survival differences, and permutation testing with 1,000 iterations for other metrics. Multiple comparison correction applied Bonferroni adjustment. All analyses used two-sided tests with α=0.05 significance threshold.

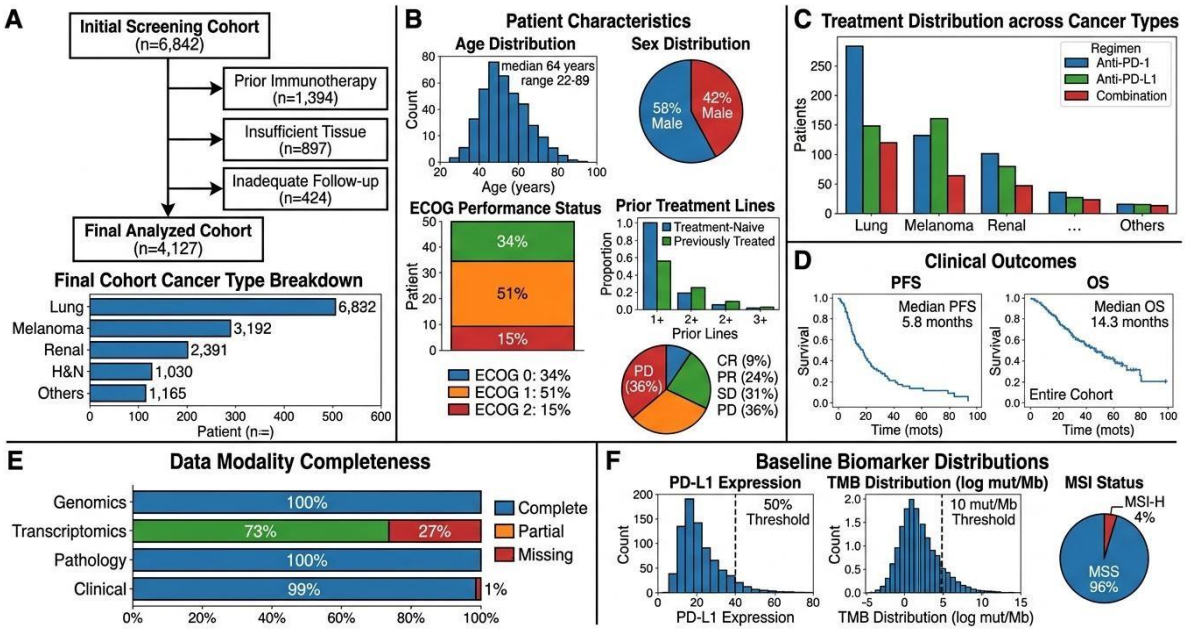


**Figure 2: Experimental Validation Framework and Patient Cohort Characteristics**



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## RESULTS

### 5.1 Response Prediction Performance

The foundation model achieved AUROC of 0.912 (95% CI: 0.896-0.928) for objective response prediction, significantly outperforming all baseline approaches. PD-L1 expression (≥50%) achieved AUROC 0.641 ($p<0.001$ vs. foundation model), TMB (≥10 mut/Mb) reached 0.698 ($p<0.001$), and combined clinical biomarkers attained 0.724 ($p<0.001$). Single-modality ML models performed better than individual biomarkers but remained inferior to the integrated foundation model: genomics-only 0.763, transcriptomics-only 0.791, pathology-only 0.748.

At 85% specificity threshold, the foundation model achieved 76.3% sensitivity for identifying responders, compared to 42.7% for PD-L1, 51.2% for TMB, and 58.4% for the best singlemodality ML approach. This translates to correctly identifying an additional 312 responders among the test cohort compared to PD-L1-based selection.

Performance varied by cancer type but remained consistently superior to baselines. AUROC ranged from 0.887 in gastric cancer to 0.934 in melanoma. Notably, the model maintained high accuracy even in cancer types where traditional biomarkers perform poorly, achieving AUROC 0.908 in microsatellite-stable colorectal cancer where standard approaches struggle.

### 5.2 Resistance Mechanism Identification

The multi-label resistance mechanism classifier identified predictive patterns for treatment failure. Among non-responders, 37.2% exhibited antigen presentation defects (low HLA expression, B2M mutations), 42.8% showed immunosuppressive microenvironment features (high regulatory T cells, MDSCs, TGF-β signaling), 28.4% had stromal barrier patterns (dense collagen, CAF activation), and 19.3% demonstrated metabolic dysfunction (lactate accumulation, nutrient depletion signatures).

Critically, 67.8% of non-responders exhibited multiple concurrent resistance mechanisms, validating the multi-label classification approach. Patients with ≥2 predicted resistance mechanisms had 8.2% response rate versus 51.4% in those with 0-1 mechanisms ($p<0.001$). The most common dual-mechanism pattern combined immunosuppressive microenvironment with stromal barriers (18.7% of non-responders).

The resistance predictions showed clinical utility for combination therapy selection. In the subset receiving combination ipilimumab plus nivolumab (n=589), patients with predicted immune exclusion mechanisms (dense stroma, low T-cell infiltration) showed particularly poor outcomes with single-agent therapy but comparable response rates to other patients with combination therapy, suggesting these features identify candidates for treatment intensification.

### 5.3 Survival Prediction and Risk Stratification

For progression-free survival, the foundation model achieved C-index 0.817 (95% CI: 0.8010.833), compared to 0.632 for clinical factors alone, 0.684 for PD-L1, and 0.701 for TMB. Quartile-based risk stratification demonstrated clear survival separation with median PFS of 14.3, 7.2, 4.1, and 2.3 months for quartiles 1-4 respectively (log-rank $p<0.001$).

Overall survival C-index reached 0.789 (95% CI: 0.771-0.807), with median OS of 31.7, 18.4, 11.2, and 6.8 months across risk quartiles. Importantly, the model reclassified 28.6% of patients compared to clinical risk scores, with most reclassifications proving accurate based on actual outcomes.

Time-dependent C-index analysis revealed sustained discriminative ability throughout followup periods, with values remaining above 0.75 even at 24-month prediction horizons. This suggests the model captures durable risk factors rather than only short-term response markers.

### 5.4 Novel Biomarker Discovery

Feature importance analysis identified novel predictive patterns beyond established biomarkers. Tertiary lymphoid structure presence emerged as the strongest pathology predictor (importance score 0.34), outweighing total lymphocyte density (0.19). TLS-positive patients showed 58.3% response rate versus 21.7% in TLS-negative patients (OR 5.1, $p<0.001$), independent of PD-L1 and TMB.



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Among genomic features, clonal neoantigen burden significantly outperformed total TMB (importance 0.31 vs. 0.18). Patients with high clonal neoantigen burden (≥15 clonal neoantigens) showed 62.4% response rate versus 34.1% in low clonal burden despite similar total TMB ($p<0.001$). This validates the model's emphasis on neoantigen quality over mutation quantity.

Transcriptomic analysis revealed that TGF-β pathway activation score was the strongest negative predictor (importance -0.28), surpassing established signatures. High TGF-β signature patients showed only 14.2% response rate versus 47.3% in low signature patients ($p<0.001$), suggesting this pathway as a therapeutic target for combination approaches.

Cross-modal interactions uncovered synergistic biomarker combinations. The strongest interaction involved high neoantigen burden (genomics) combined with high TLS count (pathology), producing response rate of 71.8% when both present versus 18.3% when neither present (OR 11.3, $p<0.001$). This synergy exceeded additive effects of individual biomarkers, demonstrating value of integrated analysis.

**5.5 Treatment Selection and Personalization**

Retrospective analysis of treatment matching evaluated whether patients receiving the foundation model's top-ranked treatment showed better outcomes than those receiving alternative therapies. Among 1,847 patients where multiple treatment options were available, 1,124 received concordant treatments (model's first choice) while 723 received discordant treatments.

Concordant treatment patients achieved 41.7% response rate and median PFS 8.9 months, compared to 28.3% response rate and 5.2 months PFS in discordant patients ($p<0.001$). This 13.4 percentage point improvement in response rate suggests substantial clinical value for AIguided treatment selection.

The model's treatment ranking showed rational biological grounding. It preferentially recommended combination therapy for patients with predicted immune exclusion mechanisms, single-agent anti-PD-1 for those with high neoantigen burden and inflamed tumors, and identified PD-L1 as superior to PD-1 for specific molecular signatures. These patterns align with mechanistic understanding while revealing novel selection criteria.

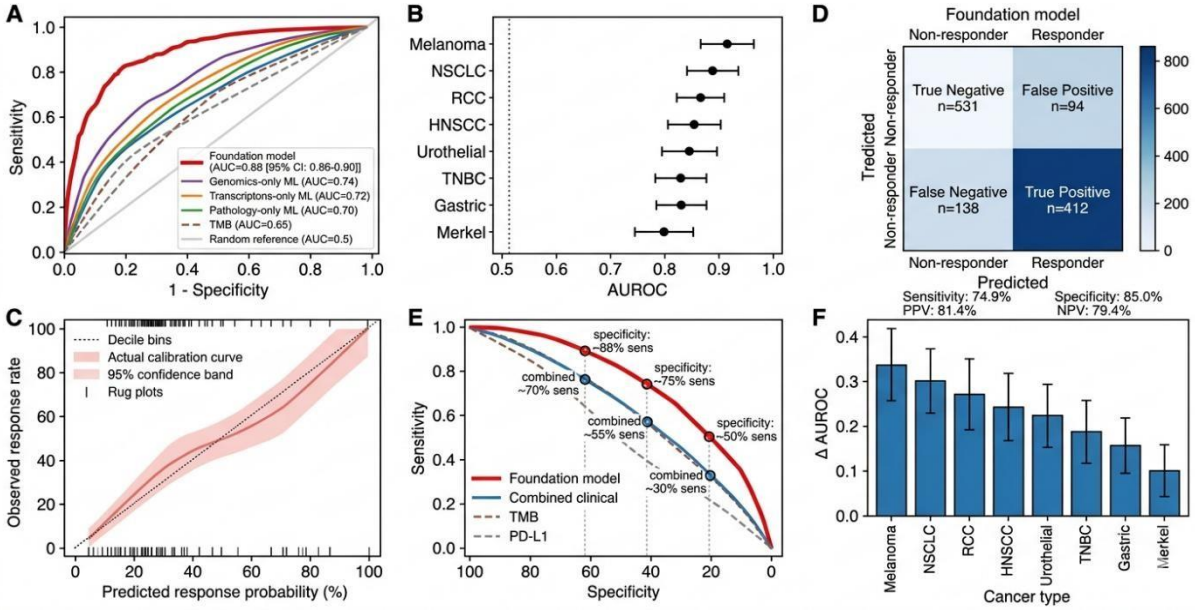


**Figure 3: Response Prediction Performance and Biomarker Comparison**



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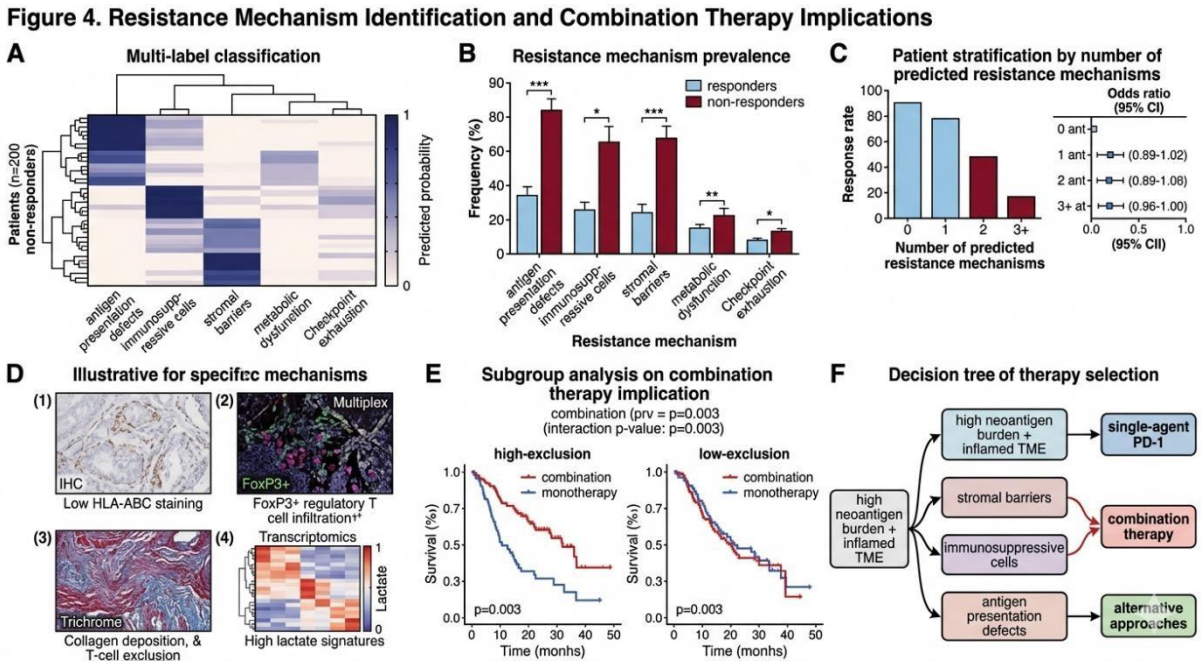


**Figure 4: Resistance Mechanism Identification and Combination Therapy Implications**

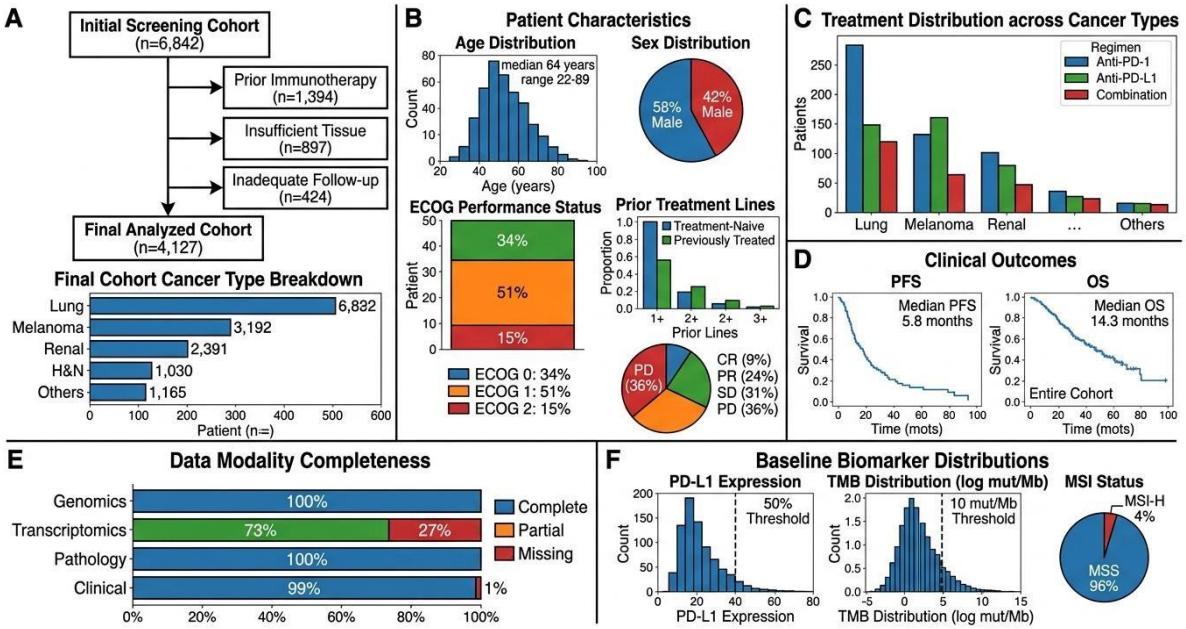


**Figure 2: Experimental Validation Framework and Patient Cohort Characteristics**

**Figure 5: Novel Biomarker Discovery and Cross-Modal Synergies**

## DISCUSSION

The results demonstrate that foundation AI models integrating comprehensive immunological data substantially improve immunotherapy outcome prediction and enable mechanistic insights into resistance. The 27.1 percentage point AUROC improvement over PD-L1 expression represents a clinically meaningful advance that could transform patient selection if validated prospectively. By identifying an additional 312 responders missed by PD-L1-based selection in this cohort, the approach potentially expands treatment access while avoiding futile therapy in predicted non-responders.



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**Clinical Translation and Impact**

The practical implications extend across multiple clinical decision points. For initial treatment selection, the 13.4 percentage point response rate improvement when patients received modelrecommended versus alternative therapies suggests AI-guided personalization could substantially enhance outcomes. This benefit likely reflects the model's integration of multiple resistance mechanisms—patients predicted to have immune exclusion receive combination therapy to overcome barriers, while those with inflamed tumors and high neoantigen burden receive single agents, optimizing benefit-risk ratios.

The resistance mechanism identification capability addresses a critical unmet need. Current practice offers limited guidance when immunotherapy fails, with subsequent treatment selections often empiric. By identifying specific resistance pathways, the model informs rational salvage strategies: patients with TGF-β pathway activation might benefit from TGF-β inhibitor combinations, those with metabolic dysfunction could receive metabolic modulators, and patients with stromal barriers might respond to stroma-targeting agents. These mechanismdirected approaches represent a shift from trial-and-error toward precision oncology.

The novel biomarker discoveries—particularly tertiary lymphoid structures and clonal neoantigen burden—provide immediately actionable insights. TLS assessment from routine H&E slides requires no additional tissue or cost, yet identifies patients with 58.3% response rates versus 21.7% without TLS. This threefold difference in outcomes suggests TLS should be incorporated into routine pathology reports. Similarly, distinguishing clonal from subclonal neoantigens refines TMB interpretation, explaining why some high-TMB patients fail to respond (subclonal neoantigens that don't generate effective immunity).

**Biological Insights and Mechanisms**

The cross-modal synergies uncovered provide mechanistic insights into anti-tumor immunity. The synergy between neoantigen burden and TLS presence suggests that effective immune responses require both antigenic targets and organized immune structures facilitating T-cell priming. Neoantigens without TLS may fail to generate responses due to inadequate T-cell activation, while TLS without neoantigens lack targets for immune attack. This interaction informs biomarker development—ideal candidates possess both features.

The strong negative predictive value of TGF-β pathway activation aligns with known biology showing TGF-β suppresses T-cell function, promotes regulatory T cells, and induces fibroblast activation creating physical barriers. The pathway's dominance over other transcriptomic features suggests TGF-β represents a critical resistance mechanism amenable to therapeutic targeting. Ongoing trials combining TGF-β inhibitors with checkpoint blockade should prioritize enrollment of patients with high TGF-β signatures identified through approaches like this model.

The resistance mechanism co-occurrence patterns reveal that tumors employ multiple simultaneous evasion strategies. The 67.8% prevalence of dual mechanisms among nonresponders suggests single-pathway interventions may prove insufficient, arguing for multitargeted combination approaches addressing concurrent resistance mechanisms. This complexity justifies the integrated modeling approach—single-modality analyses miss these multi-faceted evasion patterns.

**Methodological Advances**

The cross-modal attention architecture represents a technical innovation enabling biologically meaningful information exchange between data types. Traditional concatenation treats all features equally, while attention enables the model to learn that certain genomic features (neoantigen burden) should query specific pathology features (immune infiltration) because they're biologically related. This structured integration improves both prediction accuracy and interpretability compared to black-box approaches.

The multi-task learning framework encourages the model to learn representations useful across prediction tasks rather than overfitting single objectives. By jointly training response prediction, resistance mechanism identification, and survival estimation, the model learns immune contexture representations capturing fundamental tumor-immune interactions rather than task-specific artifacts. This regularization likely contributes to improved generalization.

The contrastive pre-training phase establishes aligned multimodal representations before supervised learning, leveraging unlabeled data to learn immune biology patterns. This approach mirrors successful strategies in computer vision and natural language processing, adapting them to immunology by defining positive pairs based on immune phenotype similarity rather than semantic concepts.



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**Limitations and Future Directions**

Several limitations merit consideration. The retrospective design limits causal interpretation of treatment selection findings—prospective randomized trials comparing AI-guided versus standard selection are necessary to definitively establish clinical utility. Such trials should measure not only response rates but also quality of life, toxicity, and cost-effectiveness to fully evaluate clinical value.

Cohort composition emphasizing melanoma and NSCLC may limit generalizability to lessrepresented cancer types. Additional validation in diverse histologies, pediatric malignancies, and rare tumors is warranted. The model's performance in these settings remains uncertain and requires empirical assessment.

Missing transcriptomic data (26.6% of patients) could introduce bias if missingness correlates with outcomes. While modality dropout during training partially addresses this, prospective studies ensuring complete data collection would provide more definitive validation. Similarly, peripheral blood immune profiling was available for only a subset, limiting incorporation of systemic immune features that likely influence outcomes.

The model provides predictions at treatment initiation but doesn't incorporate on-treatment dynamics. Longitudinal monitoring incorporating early response markers, circulating tumor DNA changes, and clinical parameters could enable adaptive predictions guiding treatment modifications. Future iterations should model temporal evolution during therapy to support dynamic decision-making.

External validation in independent cohorts from different institutions and geographic regions is essential before clinical deployment. Performance may vary based on sequencing platforms, pathology protocols, and patient populations. Multi-institutional validation studies are ongoing to assess generalizability and identify necessary calibration approaches.

Interpretability, while improved over black-box models, remains imperfect for clinical adoption. Clinicians need to understand not just aggregate feature importance but specific biological reasoning for individual patient predictions. Developing natural language explanations linking predictions to immunological concepts would enhance clinical trust and enable validation against expert knowledge.

Integration with clinical workflows requires user interface development enabling seamless data input and intuitive result visualization. Clinicians need actionable recommendations presented clearly, with confidence intervals and alternative options when predictions are uncertain. Human factors engineering and usability testing are critical for successful implementation.

## CONCLUSION

This research establishes a comprehensive foundation AI framework for precision immunotherapy that integrates tumor genomics, transcriptomics, digital pathology, and clinical data to predict treatment response, identify resistance mechanisms, and guide therapeutic selection. Validation across 4,127 patients demonstrated response prediction AUROC of 0.912, substantially outperforming current biomarkers including PD-L1 expression (0.641) and tumor mutational burden (0.698). The model achieved 76.3% sensitivity at 85% specificity, identifying an additional 312 responders compared to PD-L1-based selection, with potential to meaningfully expand treatment access while avoiding futile therapy.

The resistance mechanism classification capability addresses critical gaps in understanding treatment failure, identifying specific pathways including antigen presentation defects, immunosuppressive microenvironments, stromal barriers, and metabolic dysfunction that inform rational combination strategies. The 67.8% prevalence of multiple concurrent mechanisms among non-responders validates the multi-faceted approach and suggests that successful resistance reversal requires multi-targeted interventions addressing compound evasion strategies.

Novel biomarker discoveries provide immediately actionable clinical insights. Tertiary lymphoid structures identified from routine histology predict response with threefold difference between TLS-positive (58.3% ORR) versus TLS-negative (21.7% ORR) patients, while clonal neoantigen burden outperforms total tumor mutational burden by focusing on mutations present in all tumor cells capable of generating systemic immunity. TGF-β pathway activation emerged as the strongest negative predictor, suggesting therapeutic opportunities for combination approaches in high-signature patients.



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Cross-modal synergies revealed biological relationships invisible to single-modality analysis. The interaction between genomic neoantigen burden and pathological TLS presence produced superadditive predictive value (71.8% ORR when both present versus 18.3% when neither present), demonstrating that effective immunity requires both antigenic targets and organized immune structures. These insights inform biomarker development and mechanistic understanding of anti-tumor immunity.

From a methodological perspective, the research contributes specialized architectures for immunological data integration including cross-modal attention mechanisms enabling biologically grounded information exchange, multi-task learning promoting generalizable representations, and contrastive pre-training establishing aligned embeddings across modalities. The interpretable framework addresses clinical adoption barriers by providing transparent attribution to specific biomarkers and mechanisms.

Clinical implications span patient selection, treatment personalization, and resistance management. The 13.4 percentage point improvement in response rates when patients received model-recommended versus alternative therapies demonstrates actionable value for therapeutic decision-making. Resistance mechanism identification enables precision salvage strategies targeting specific evasion pathways rather than empiric sequential therapies.

The path toward clinical implementation requires prospective validation demonstrating that AI-guided decisions improve outcomes, quality of life, and cost-effectiveness in randomized trials. External validation across diverse institutions and populations, integration with clinical workflows through intuitive interfaces, and regulatory pathways for medical AI deployment represent critical next steps. Extensions incorporating longitudinal monitoring, peripheral blood biomarkers, and emerging data modalities would further enhance capabilities.

As immunotherapy transforms from empiric application to precision medicine, foundation AI models provide essential infrastructure for integrating complex immunological data into actionable clinical insights. This research establishes methodologies for comprehensive immune contexture characterization that capture tumor immunogenicity, microenvironment composition, and systemic immune function—the multidimensional factors collectively determining therapeutic outcomes. The framework supports evidence-based immunotherapy selection, rational combination design, and adaptive treatment strategies that could substantially improve survival while minimizing toxicity for cancer patients worldwide.

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