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From Omics to Bedside: The Emerging Role of Self-Supervised Learning in Integrating Multi-Modal Health Data

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Abstract
The integration of multi-modal health data spanning genomics, transcriptomics, proteomics, medical imaging, and electronic health records holds transformative potential for precision medicine, yet it faces fundamental barriers: data heterogeneity, high dimensionality, sparse annotations, and privacy constraints. Self-supervised learning (SSL) has emerged as a paradigm-shifting approach that leverages vast unlabeled data to learn generalizable representations without costly manual annotations. This review examines how SSL is reshaping multi-modal health data integration across three emerging paradigms: (1) contrastive learning for cross-modal association discovery, as demonstrated by COMICAL which identified genotype-phenotype relationships in neurological disorders using CLIP-style alignment ; (2) masked modeling for unified representation learning across histopathology and molecular profiles, exemplified by MORPHEUS which integrates whole-slide images with transcriptomics, methylomics, and genomics in a shared latent space ; and (3) prototype-driven pretraining for missing-aware multimodal prognosis, as implemented in PRIME which learns robust representations from partially observed clinical cohorts . Across these approaches, SSL consistently outperforms supervised alternatives in data-scarce settings, achieving performance comparable to centralized training while preserving data locality and institutional privacy. However, significant challenges persist including modality misalignment, the semantic gap between pretraining objectives and clinical utility, limited external validation, and computational costs that hinder broad adoption. Despite these barriers, SSL is accelerating the translation of multi-omics discoveries to clinical practice, moving from isolated biomarker identification to integrated, patient-centered predictive modeling.

Keywords: Self-supervised learning, Multi-modal data integration, Foundation models, Precision medicine, Contrastive learning, Masked modeling.

1. Introduction
The past decade has witnessed an explosion of high-throughput biological data. Genomics, transcriptomics, proteomics, epigenomics, metabolomics, and radiomics now generate terabytes of molecular and phenotypic information per patient. Simultaneously, medical imaging, electronic health records, and continuous physiological monitoring contribute additional modalities that capture complementary aspects of health and disease. The promise of precision medicine lies in integrating these diverse data streams into a unified understanding of each patient's unique biology.

However, multi-omics integration faces formidable barriers. Multi-modal datasets are inherently heterogeneous, sparse, and extraordinarily high-dimensional, with sample sizes often remaining relatively small despite advancements in data collection [1-42]. Many clinical cohorts are fragmented and miss one or more modalities, limiting both supervised fusion and scalable multimodal pretraining [43-65]. Furthermore, the vast majority of biomedical data remains unlabeled, as manual annotation by expert pathologists, radiologists, and clinicians is prohibitively expensive, time-consuming, and subject to inter-rater variability [66-79].

These challenges have historically constrained machine learning applications in biomedicine to unimodal analyses or small-scale supervised learning on narrowly defined tasks. Recent advances in self-supervised learning are fundamentally changing this landscape.

2. The Self-Supervised Learning Paradigm
Self-supervised learning has revolutionized natural language processing and computer vision by enabling models to learn generalizable representations from unlabeled data. Foundation models such as BERT and GPT are trained on self-supervised

objectives typically predicting masked segments in text before being fine-tuned for specific downstream tasks [80-93]. This paradigm has recently been extended to biomedicine, giving rise to single-cell foundation models (scFMs) and multi-modal frameworks for integrating histopathology and omics data [94-121].

The defining characteristics of SSL in the biomedical context include: (1) training on large-scale, diverse datasets to capture universal biological patterns; (2) transformer-based architectures that model complex dependencies across genes, proteins, and imaging features; and (3) the ability to fine-tune or prompt the model for new tasks, transferring learned knowledge to improve performance on target applications [122-142].

Three SSL paradigms have emerged as particularly impactful for multi-modal health data integration.

3. Paradigm 1: Contrastive Learning for Cross-Modal Association Discovery

Contrastive learning aligns representations from different modalities by learning to associate paired samples while distinguishing unpaired ones. The most influential architecture in this space is CLIP (Contrastive Language-Image Pre-training), which learns joint representations of images and text.

COMICAL adapts the CLIP framework to multi-omics analysis, integrating genomics (single nucleotide polymorphisms, SNPs) and radiomics (imaging-derived phenotypes, IDPs) to discover genotype-phenotype relationships [143-165]. The approach uses transformer-based encoders with custom tokenizers for both modalities: SNPs are tokenized by mutation type and genomic location, while IDPs are tokenized using piecewise linear encodings that preserve continuous signal information[166-180]. COMICAL was pretrained on 15.4 million IDP-SNP pairs from the UK Biobank, mediated by eight neurological diseases. The contrastive learning objective connects representations of one modality with the other, discovering many-to-many associations between genetic variants and brain imaging phenotypes [181-195].

The results are striking: COMICAL identified accurate genotype-phenotype pairs for Alzheimer's disease, Parkinson's disease, schizophrenia, bipolar disorder, and multiple sclerosis, validated using independent ENIGMA summary statistics [196-204]. Furthermore, the learned representations enable cross-disorder prediction and compute a novel multi-omics risk score associated with polygenic risk scores from UK Biobank [195].

Key Insight: Contrastive learning can discover interpretable, biologically meaningful cross-modal associations without requiring paired labels, accelerating the discovery of multi-omics relationships.

4. Paradigm 2: Masked Modeling for Unified Representation Learning

Masked modeling the core pretraining objective of BERT and GPT has been adapted to multi-modal biomedical data. The premise is simple: randomly mask a subset of input tokens and train the model to reconstruct the missing information.

MORPHEUS (Masked Omics Modeling for multimodal RePresentation learning across Histopathology and molEcUlar profileS) extends this paradigm to histopathology and multi-omics [196]. It is the first SSL framework that jointly integrates whole-slide images and multiple omics modalities including transcriptomics (RNA), methylomics (DNA methylation), and copy number variations into a single, shared transformer encoder [197].

MORPHEUS overcomes two critical challenges. First, to manage the high dimensionality of whole-slide images, it learns a compact set of morphological prototypes that summarize repeated histological patterns, reducing computational burden while preserving salient information [198]. Second, omics data are tokenized using biological priors: RNA is structured by biological pathways, while CNV and DNAm features are grouped by chromosomal position to preserve local genomic context [199].

During pretraining, a subset of omics tokens is randomly masked. The transformer encoder processes histopathology and visible omics tokens, and modality-specific decoders reconstruct the masked contents [199]. This encourages the model to learn biologically meaningful cross-modal relationships. MORPHEUS can be applied to histopathology alone or in combination with any subset of omics modalities, seamlessly adapting to available inputs [200].

📊 **Table 1 — Comparison of Self-Supervised Learning Paradigms for Multi-Modal Health Data Integration**

Representative models, SSL objectives, key advantages, and key challenges

Paradigm	Representative Model	Modalities Integrated	SSL Objective	Key Advantage	Key Challenge
Contrastive Learning	COMICAL	Genomics, Radiomics	Cross-modal alignment	Interpretable associations	Requires paired data
Masked Modeling	MORPHEUS	Histopathology, RNA, DNAm, CNV	Masked token reconstruction	Any-to-any modality flexibility	High computational cost
Prototype-Driven Pretraining	PRIME	Histopathology, Gene Expression, Reports	Missing-aware alignment + fusion	Robust to missing modalities	Prototype interpretability

Paradigm Representative Model Modalities Integrated SSL Objective Key Advantage Key Challenge
Contrastive Learning COMICAL Genomics, Radiomics Cross-modal alignment Interpretable associations Requires paired data.

Masked Modeling MORPHEUS Histopathology, RNA, DNAm, CNV Masked token reconstruction Any-to-any modality flexibility High computational cost Prototype-Driven Pretraining PRIME Histopathology, Gene Expression, Reports Missing-aware alignment + fusion Robust to missing modalities Prototype interpretability.

Key Insight: Masked modeling on biological tokens enables a single model to learn representations that integrate any combination of histopathology and molecular modalities, adapting to the fragmented nature of clinical data.

5. Paradigm 3: Prototype-Driven Pretraining for Missing-Aware Prognosis

In real-world clinical settings, complete multi-modal data is the exception rather than the rule. Cohorts are often missing one or more modalities due to cost, availability, or clinical necessity. Most existing multi-modal approaches require fully paired inputs, limiting their applicability [200-207].

PRIME (Prototype-Driven Multimodal Pretraining) addresses this challenge with a missing-aware self-supervised framework. It maps heterogeneous modality embeddings into a unified token space and introduces a shared prototype memory bank for latent-space semantic imputation via patient-level consensus retrieval, producing structurally aligned tokens without reconstructing raw signals. Two complementary pretraining objectives inter-modality alignment and post-fusion consistency under structured missingness augmentation jointly learn representations that remain predictive under arbitrary modality subsets.

PRIME was evaluated on The Cancer Genome Atlas (TCGA) with label-free pretraining on 32 cancer types and downstream evaluation on five cohorts across three tasks: overall survival prediction, 3-year mortality classification, and 3-year recurrence classification. It achieved the best macro-average performance among all compared methods, reaching 0.653 C-index, 0.689 AUROC, and 0.637 AUROC on the three tasks, respectively.

Key Insight: Self-supervised pretraining can learn robust representations from partially observed cohorts, enabling practical deployment in real-world clinical settings where complete multi-modal data is rarely available.

6. Clinical Translation: Progress, Barriers, and Emerging Trends

6.1 Evidence of Clinical Utility

The translation of SSL to clinical practice is accelerating. In oncology, genomics-aware multimodal SSL for cancer survival prediction has demonstrated superior performance compared to state-of-the-art methods on four TCGA datasets. In neurology, contrastive learning has identified interpretable associations between genetic markers and brain imaging phenotypes for complex disorders including Alzheimer's and Parkinson's disease. Single-cell foundation models are being developed that integrate RNA, ATAC, multiome, spatial sequencing, and proteomics data, enabling unified analysis of cellular heterogeneity.

Across studies, multimodal ML consistently outperforms unimodal baselines, with intermediate fusion employed in 60% of cases and achieving average AUC improvements of 5-12% over single-modality models [95]. Oncology and neurology have emerged as the leading domains, where combining imaging with genomic and cognitive data has significantly improved cancer survival and Alzheimer's detection [103].

6.2 Persistent Barriers

Despite this progress, significant challenges remain:
Modality Misalignment and Missing Data: Modality misalignment affects 23% of studies, and missing data affects 18% . Current methods for handling missing modalities, such as PRIME's

prototype-driven imputation, show promise but require further validation [205].

Limited External Validation: Only 12% of studies report true external validation, undermining the reliability of results in clinical contexts [206]. Models trained and tested on single-institution datasets risk overfitting and poor generalizability.

The Gap Between SSL Objectives and Clinical Utility: While SSL objectives excel at learning generalizable representations, the semantic alignment between pretraining tasks and clinically meaningful outcomes remains incompletely understood. Explainability and trustworthiness prerequisites for clinical adoption remain underexplored .

Computational Cost: Training foundation models on multi-modal data is computationally intensive. Single-cell foundation models face challenges including the non-sequential nature of omics data, inconsistency in data quality, and the computational intensity required for training and fine-tuning [207-215].

Regulatory Constraints: Regulatory constraints and interoperability gaps continue to hinder deployment [111]. Clinical translation requires rigorous validation, quality management systems, and alignment with global regulatory frameworks.

Table 2 — Clinical Translation Status of Self-Supervised Learning Approaches in Multi-Modal Health Data Integration

Modality domain, SSL approach, deployment stage, barriers, and enabling solutions

Modality Domain	SSL Approach	Clinical Deployment Stage	Key Barrier	Enabling Solution
Genomics + Radiomics	Contrastive Learning (COMICAL)	Research discovery	Interpretability validation	Cross-disorder prediction validation
Histopathology + Omics	Masked Modeling (MORPHEUS)	Early validation	Computational cost	Prototype-based compression
Multi-Cancer Prognosis	Prototype Pretraining (PRIME)	Research validation	External validation needed	32-cancer pretraining
Single-Cell Biology	Transformer-based scFMs	Growing adoption	Data heterogeneity	Standardized benchmarks
Multi-Modal Prognosis	Intermediate Fusion Models	Performance evaluation	Regulatory alignment	Value-based assessment frameworks

Modality Domain SSL Approach Clinical Deployment Stage Key Barrier Enabling Solution
Genomics + Radiomics Contrastive Learning (COMICAL) Research discovery Interpretability validation Cross-disorder prediction validation
Histopathology + Omics Masked Modeling (MORPHEUS) Early validation Computational cost Prototype-based compression
Multi-Cancer Prognosis Prototype Pretraining (PRIME) Research validation External validation needed 32-cancer pretraining
Single-Cell Biology Transformer-based scFMs Growing adoption Data heterogeneity Standardized benchmarks
Multi-Modal Prognosis Intermediate Fusion Models Performance evaluation Regulatory alignment Value-based assessment frameworks

7. Future Directions and Conclusion

7.1 Emerging Trends

Several trends will define the next phase of SSL in multi-modal health data integration:

Transformer-Based Cross-Modal Attention: Recent trends highlight transformer-based cross-modal attention as a key enabler for integrating heterogeneous data types. These architectures can learn complex, non-linear relationships across modalities without requiring explicit feature engineering.

Self-Supervised Learning for Data-Scarce Settings: SSL is particularly valuable for data-scarce settings, where labeled data is limited. The ability to pretrain on large unlabeled corpora and fine-tune on small labeled datasets reduces the annotation burden.

Hybrid Fusion Architectures: Hybrid architectures that combine different fusion strategies (early, intermediate, late) are emerging in critical care applications. These approaches offer flexibility in handling diverse data types and missing modalities.

Foundation Models as Backbones: The advancement of large-scale foundation models such as "Segment Anything" opens new horizons, enabling transfer learning and few-shot adaptation for biomedical applications.

7.2 Actionable Recommendations

To accelerate clinical translation, we recommend:

Standardized Benchmarks: Developing comprehensive benchmark datasets encompassing medical images of various modalities and organs from multiple sources is essential for facilitating balanced comparison of different algorithms.

External Validation: Future studies must incorporate external datasets in their validation processes to improve generalizability across diverse clinical settings.

Explainable AI: Researchers should explore Explainable AI methodologies, including Class Activation Maps (CAM) and Grad-CAM, to provide clear understanding of model predictions, aid decision-making, and increase transparency.

Federated Learning Integration: Combining SSL with federated learning can resolve security challenges and enable secure multi-center data sharing, enhancing model robustness while preserving privacy.

7.3 Conclusion

Self-supervised learning is fundamentally reshaping how multi-modal health data is integrated and translated to clinical practice. From contrastive learning that discovers interpretable genotype-phenotype associations, to masked modeling that unifies histopathology and molecular profiles, to prototype-driven pretraining that handles missing modalities SSL is moving multi-omics from isolated biomarker identification to integrated, patient-centered predictive modeling.

The journey from omics to bedside is not complete. Challenges of data heterogeneity, computational cost, external validation, and regulatory alignment remain. Yet the trajectory is clear: self-supervised learning is not merely an academic curiosity but a practical framework that can learn from the vast, unlabeled, and fragmented data that characterizes real-world clinical settings. As the field progresses, SSL will be central to realizing the promise of precision medicine: integrating diverse data streams into a unified understanding of each patient's unique biology, and ultimately, improving clinical outcomes at scale.

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