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Graph Artificial Intelligence in Medicine

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Abstract

In clinical artificial intelligence (AI), graph representation learning, mainly through graph neural networks and graph transformer architectures, stands out for its capability to capture intricate relationships and structures within clinical datasets. With diverse data—from patient records to imaging—graph AI models process data holistically by viewing modalities and entities within them as nodes interconnected by their relationships. Graph AI facilitates model transfer across clinical tasks, enabling models to generalize across patient populations without additional parameters and with minimal to no retraining. However, the importance of human-centered design and model interpretability in clinical decision-making cannot be overstated. Since graph AI models capture information through localized neural transformations defined on relational datasets, they offer both an opportunity and a challenge in elucidating model rationale. Knowledge graphs can enhance interpretability by aligning model-driven insights with medical knowledge. Emerging graph AI models integrate diverse data

modalities through pretraining, facilitate interactive feedback loops, and foster human–AI collaboration, paving the way toward clinically meaningful predictions.

INTRODUCTION

With simultaneous advances in clinical information and omics-based technologies, the medical landscape has dramatically shifted toward a data-centric approach (1). Precision medicine aims to provide a more precise approach to disease diagnosis, treatment, and prevention based on individuals' unique medical histories and biological profiles (2). Clinical data, encompassing patients' medical histories; patient-collected samples with genetic, genomic, and molecular information extracted from these samples; and data recorded during patients' interactions with the health care system are poised to inform the development of powerful prediction models (3).

However, health care systems optimize data collection and curation for patient care and health care administration instead of data-driven research. Most electronic health records (EHRs) come in structured, semistructured, and unstructured data, including structured data tables, images, waveforms, and clinical notes. These datasets describe a multitude of complex and interconnected concepts, resulting in data that are both high-dimensional and heterogeneous in nature (4). However, EHRs often suffer from suboptimal data quality (due to the fast-paced environment and lack of manual curation) and high levels of sparsity (due to patterns of nonrandom missingness associated with health care practices) (5, 6). Given these challenges related to the secondary use of EHRs for precision medicine applications, transforming this information into a representation that algorithms can readily utilize is nontrivial and currently an active area of study (7, 8).

Representation learning aims to automatically extract a computer-readable representation of the data, optimized in such a way that it captures valuable information for some downstream or target task (e.g., disease prediction) (9). Most computational models assume that input data are formatted in a gridlike structure such as a vector or matrix. For example, an image is a matrix with values representing the color at each pixel, and text can be tokenized into vectors. However, given the implicit connectivity of the human body, information regarding the relational structure underlying human biology should be fundamental when performing representation learning for clinical tasks. Enforcing a gridlike data format is also prohibitive for modeling multiple data modalities, since inputs will not have a uniform shape across data types (e.g., image, text, audio). However, given that decision-making performed by clinicians inherently relies on weighing multiple types of information—ranging from histopathology images to vital signs—limiting prediction algorithms to a single data modality likely would severely limit a model's performance and utility (10).

Graphs provide a principled way of explicitly modeling relational structure in data representations. These nonlinear data structures present a formal framework for encoding complex relationships between objects or entities without imposing a strict ordering or shape. This highly versatile approach has been adopted in multiple biomedical applications, showing success in various clinical tasks (**Table 1**). Graphs also balance flexibility and structure when representing data, allowing the natural integration of multiple data modalities and providing a strategy to leverage interdependencies across modalities. Graphs can be defined solely by the connections between elements within a patient's medical record. Additionally, they can include links to external resources, such as medical knowledge bases, imaging databases, and genetic biobanks, providing a unified representation of the patient across medical modalities (11, 12). Not only are graphs naturally more interpretable to users, but also algorithms operating on graphs have inherent algorithmic mechanisms for incorporating explainability, such as attention-based feature importance (13).

Table 1 Examples of clinical tasks, descriptions, and how graph representation techniques can benefit

Medical task	Description	Relational data	Transfer learning	Multimodality	Explainability	References[a]
Drug repurposing and off-label prescription	The practice of identifying new therapeutic uses for existing drugs. Key challenges involve modeling the complex interactions between genes, pathways, targets, and drugs and the resulting exponential search space.	Yes	Yes	Yes	Yes	25–28
Medical safety and pharmacovigilance	Adverse drug reactions are the undesirable (potentially harmful) side effects associated with drug use. Key challenges include modeling complex interactions between biological and chemical processes and the effects of polypharmacy.	Yes	Yes	Yes	Yes	19, 29
Imaging for neurological disease diagnosis	Techniques for the visualization and assessment of brain function. A key challenge is incorporating various image modalities, including MRI, CT, PET, and EEG.	Yes	No	Yes	No	30–32
Genetics for rare-disease diagnosis	The characterization of medical conditions caused by extremely uncommon genetic mutations. The key challenge is the small size or complete lack of labeled cases.	No	Yes	Yes	Yes	33–36
Interpretable prognostic biomarkers	The microscopic examination of tissues or cells to identify diseases or abnormalities in tissue samples. Whole-slide images are often divided into smaller images or patches. A challenge is maintaining topological properties across subimages.	Yes	No	No	Yes	37, 38
Disease–gene association for complex diseases	Inferring a relationship between specific genes or mutations and the susceptibility or development of a particular complex disease. Key challenges include modeling complex biological processes and the associated omics data.	Yes	Yes	Yes	Yes	39–41
Early disease detection	Predicting the risk of an individual developing a disease based on their medical history as recorded in the EHR. Key challenges include the data quality and incompleteness associated with the secondary use of EHRs.	No	Yes	Yes	Yes	12, 42, 43

[a]The list of references for each task is not exhaustive.

Abbreviations: CT, computed tomography; EEG, electroencephalography; EHR, electronic health record; MRI, magnetic resonance imaging; PET, positron emission tomography.

In this article, we review graphs and graph representation learning in clinical artificial intelligence (AI). Although there are many innovative biomedical applications of graph representation in genomics (14–16), proteomics (17, 18), and therapeutics (19–21), we focus on applications utilizing clinical data collected in the health care setting. Many concepts and ideas described here apply across multiple application domains. We begin with an overview of graph representational learning to highlight the key concepts relevant to this review but refer readers to other publications for a more in-depth review of graph representation learning theory (22–24). We then discuss

how graph representation techniques specifically address many of the current challenges in clinical AI algorithm development. Each of the following sections discusses the utility of graphs in transfer learning, multimodal learning, and explainability. We underscore the potential of graphs in clinical AI, emphasizing the convergence of multimodal learning, transfer learning across patient populations and clinical tasks, and the imperative of human-centered AI.

ALGORITHMS FOR LEARNING GRAPH REPRESENTATIONS AND EMBEDDINGS

Graphs can encode rich relational structure in biomedical data, providing useful frameworks for representing EHR relational databases (44, 45), medical ontologies (46), and connections between different therapeutics (47). Formally, a graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ is defined by the sets of nodes (vertices) $\mathcal{V}$ and edges $\mathcal{E}$ with optional node features $\mathbf{X}^V$ and edge features $\mathbf{X}^E$. Traditional graphs are typically homogeneous, where nodes and edges are of a single type. We can also represent a graph in which nodes and edges belong to multiple types, forming a heterogeneous graph. For example, type 1 diabetes mellitus and insulin can be represented as a disease and a drug node in a graph where a shared edge between the two nodes denotes the disease as an indication for a specific drug.

We can use the relational structure encoded by graphs in various prediction tasks. First, node prediction refers to the task of learning a function (f) to predict either properties or labels (y) associated with a set of nodes (v_i) in a graph: $f(v_i) = y$. Edge prediction, also known as link prediction, aims to learn a function f such that for any two nodes v_i and v_j, f predicts whether or not an edge exists between the nodes: $f(v_i, v_j) = y \in \{0, 1\}$. Graph prediction seeks to learn a function f that predicts a property y describing an entire graph $\mathcal{G}_i$: $f(\mathcal{G}_i) = y$. Many more learning tasks can be performed on graphs, such as graph generation and node and graph clustering. For a comprehensive survey on graph learning tasks, refer to Waikhom & Patgiri (48).

Representation Learning Basics

Representation learning refers to learning an embedding space, namely a space of vectors, that represents a given set of input data. We define a representation space or embedding space $z_1, \ldots, z_n \in \mathcal{Z}$, where each z_i vector can represent nodes, edges, or entire graphs. Usually, z_i represents an embedding for node v_i and a concatenation of z_i and z_j is used to represent an edge e_{ij}. A graph can be represented by an aggregation of node embeddings where a given function, such as sum or average, is applied across the set of nodes in a graph.

Embedding methods are broadly grouped into those that produce shallow and deep representations. Methods that estimate shallow embeddings characterize nodes on the basis of some predefined notion of distance within the graph, such as node cooccurrence encountered in random walks (49), local connectivity defined by graph traversal (50), or relations defined within a knowledge graph (51, 52). The embedding space is then optimized to reflect this notion of distance. However, shallow embedding methods are inherently transductive, such that the learned embeddings do not generalize to nodes not observed in training. In contrast, deep embedding methods use neural network–based inference to learn a function that captures more complex relationships between nodes (53). The resulting optimized graph neural network (GNN) allows for inductive learning, where embeddings can be generated for nodes not present in the original training graph.

Embedding representations enable the mathematical description of various prediction tasks. For example, consider the task of finding patients with similar clinical profiles. Although one could use a straightforward database query, formally quantifying similarity among patients would be difficult to explicitly define. An embedding space naturally formulates this objective as a

nearest-neighbor search. Given the embedding z_i for a patient and some predefined distance function D (e.g., Euclidean distance), identifying similar patients involves finding the m patients $z_{j_1}, \ldots, z_{j_m} \in \mathcal{Z}$ that have the shortest distance to z_i. This distance function offers a natural way to define patient similarity, avoiding costly expert-curated rules to determine a similarity metric.

Graph Neural Networks

GNNs are a class of neural network models designed for learning on graph-structured data. GNNs can learn representations of nodes, edges, and even entire graphs. The graph representation learning field has developed many different network architectures that all aim to capture different types of complex relationships within graph-structured data. For node-, edge-, and graph-level prediction tasks, message-passing and transformer-based architectures are among the most common.

Message-passing neural networks (MPNNs) are GNNs that consist of several layers that propagate information within the graph (**Figure 1*a***). For a node u at layer l, the MPNN gathers information from the nodes around v (called messages), aggregates these messages into a message feature $\mathbf{m}_u^{(l)}$, and then performs an update to the embedding $\mathbf{h}_u^{(l)}$ corresponding to node u. Mathematically, we can write this update as follows: $\mathbf{h}_u^{(l)} = \text{UPD}[\mathbf{m}_u^{(l)}, \mathbf{h}_u^{(l-1)}]$, where UPD$(\cdot)$ refers to a function that integrates messages with the current node embedding. Typically, $\mathbf{h}_v^{(0)}$ is initialized with X_u^V, that is, the node feature vector for node u. After propagating messages across several layers, the resulting function is able to capture complex dependencies present within the graph. Variants of MPNNs modify the message-passing and update procedures (53–56). For example, the popular graph attention network (GAT) uses an attention mechanism to learn along which edges to propagate information (57).

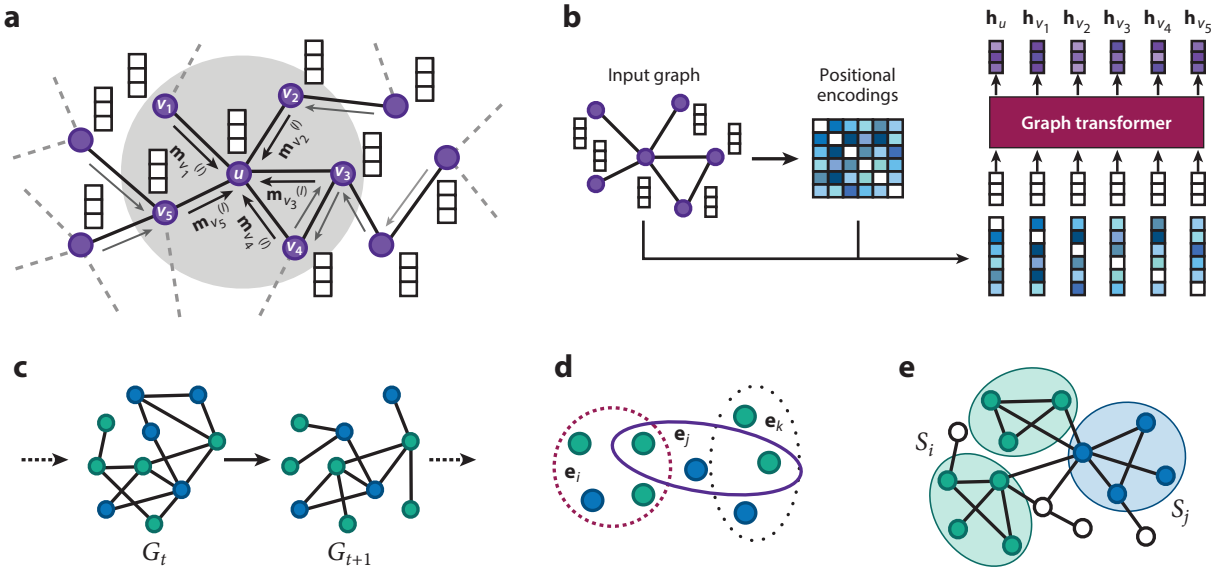

Figure 1

Variants of neural networks for graphs, including temporal graphs, hypergraphs, and subgraphs. (*a*) A message-passing scheme by which messages are propagated along edges for each node. (*b*) An example of a graph transformer, where the graph is expanded into a sequence with positional encodings. (*c*) Temporal graphs sampled over times t and $t + 1$; these methods often use variants of the networks shown in panels *a* and *b* to learn representations at each step. (*d*) A hypergraph, where hyperedges (rounded shapes) can encompass more than two nodes. (*e*) A subgraph neural network, which learns representations for S_i and S_j even when these subgraphs are disconnected.

Graph transformers are neural networks that directly feed node embeddings into a transformer architecture, omitting the use of message passing. These models represent nodes as sequences, and then positional encodings are appended to the input, which incorporates relational information defined by the graph (58, 59) (**Figure 1*b***). Graph transformers generally offer greater expressivity than MPNNs (60), and recent research has sought to combine MPNNs and graph transformers to increase model expressivity (61, 62).

Learning on More Complex Graphs

Graphs in health care may be dynamic over time or contain more complex relations between entities. In this section, we highlight a few variants of GNNs that operate in challenging data regimes.

Temporal GNNs learn on dynamic graphs, that is, graphs where nodes and edges change over time. A dynamic graph $\mathcal{G}^D$ is defined as a sequence of graphs and associated time steps $1, \ldots, T$: $\mathcal{G}^D = \{\mathcal{G}_1, \ldots, \mathcal{G}_T\}$. Temporal GNNs learn representations for nodes at each time step, providing a formal mechanism for temporal predictions (63–65). These models can handle time-varying factors such as patient states throughout their stay in the intensive care unit (66).

Hypergraph GNNs learn on hypergraphs, which are generalizations of graphs that enable n-level connections between nodes through hyperedges. Message passing is then performed along hyperedges instead of standard binary edges (67). Hypergraph GNNs have been used to learn drug–disease relationships (68) and EHR data (69–71).

Subgraph GNNs learn representations for subgraphs, subsets of nodes, and edges in a larger graph. A subgraph is formally defined as $S = (V', E')$, where $V' \subseteq \mathcal{V}$ and $E' \subseteq \mathcal{E}$ for some graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$. A message-passing network operating on subgraphs learns a representation for S_i: $f(S_i) = z_i$ (35, 72). Subgraph GNNs help classify diseases, which can be represented as subgraphs of many phenotype nodes and edges (36).

INDUCTIVE BIASES AND TRANSFER LEARNING ON KNOWLEDGE GRAPHS

We proceed with a discussion of how medical knowledge can be integrated into neural network design to implement more reliable health care AI models. We highlight how medical knowledge, such as biological pathways and medical ontologies, can inform neural network structure through the use of relationships defined in biomedical knowledge bases. Not only can the incorporation of this domain-specific knowledge promote model interpretability, but also it can help avoid overparameterizing deep learning models.

Designing Neural Architectures That Incorporate Medical Knowledge

The underlying structure of heterogeneous graphs mirrors the connections that humans formulate when making decisions. For example, a biological pathway captures the series of interactions that must occur between molecules in a cell to create a gene product (73). In a biologically and medically constrained neural network, the propagation of neural messages mirrors the logical transitions between ideas or concepts. As such, domain-specific graphs have been used to design the architectures of GNNs (**Figure 2*a***).

Biological pathways provide a natural relational structure to inform neural network architectures. The recently developed P-NET uses hierarchical biological knowledge to integrate both coarse- and fine-grained biological processes into the model architecture. Propagating messages along the path of a biological pathway forces the model to use this existing knowledge to generate accurate and interpretable predictions (73, 74). Specifically, the input layer reads in the patient's

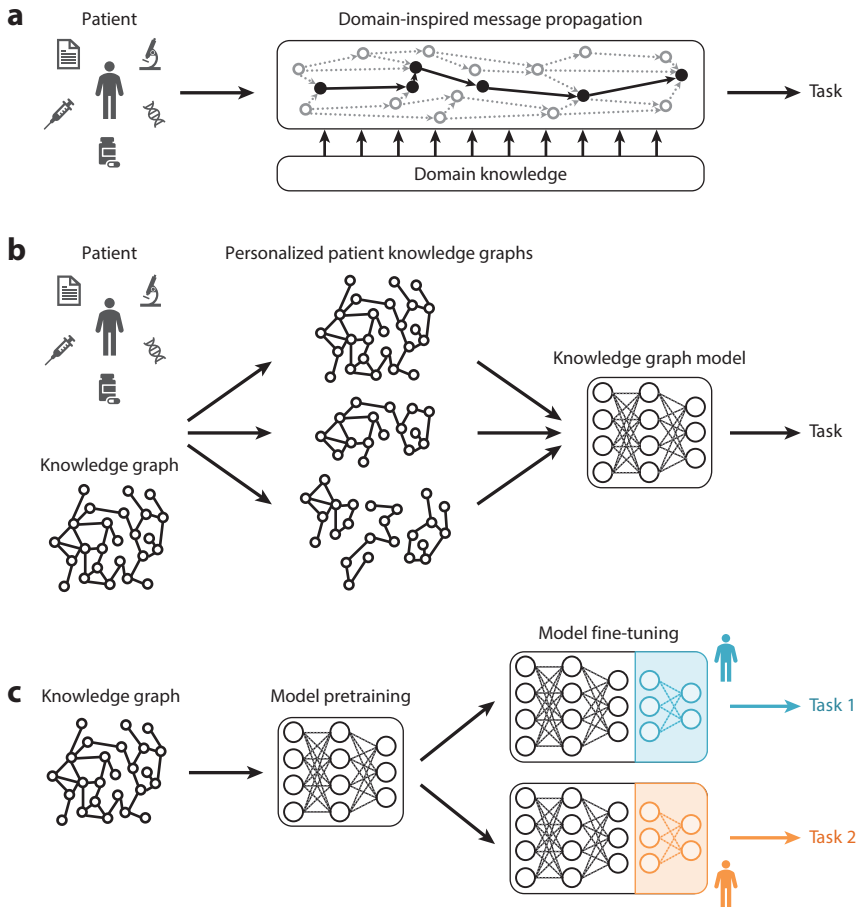

Figure 2

Strategies for incorporating inductive biases and enabling transfer learning on knowledge graphs. (*a*) Biologically informed neural network architectures. (*b*) Supplementing patient data with biomedical ontologies. (*c*) Fine-tuning large pretrained models across a broad range of clinical tasks.

profile, followed by three hidden layers of genes, pathways, and biological processes. The connections among P-NET's hidden layers are determined by known parent–child relationships between genes, pathways, and biological processes (74). A recent study (73) proposed using biologically informed neural networks (BINNs). The BINN architecture is formulated such that the input layer consists of proteins, the hidden layers are composed of biological pathways, and the output layer contains the biological process. Training a BINN with protein quantities as input enables biomarker identification and pathway analysis (73). By defining the network's layers and connections through biological relationships, biologically informed models avoid overparameterization, provide enhanced interpretability, and incorporate external knowledge to improve predictions.

For clinical data and the associated medical concepts (e.g., diagnostic codes, lab tests, and medications), relational structure is often embedded through standardized medical ontologies (75). A medical ontology is a structured representation (often hierarchical) of knowledge about medical concepts and their interrelationships (75). These ontologies can provide a formal basis for incorporating clinical domain knowledge in prediction models. For example, hierarchical

attention propagation learns embeddings of medical concepts by hierarchically propagating attention weights across the entire medical ontology, outperforming prior approaches that learn only attention weights over ancestors (76). Other approaches use the hyperbolic space to effectively capture hierarchical structure (77, 78). Accurate capturing of the granularity of medical concepts across hierarchical levels through embeddings has been used to inform patient representations (79, 80), which can be described as sets of embeddings corresponding to the medical concepts listed in the patients' EHRs.

Rather than aggregating embeddings of each node's direct neighbors, models may define a node's neighborhood on the basis of the specific domain and task. For example, repurposing a drug entails identifying other diseases associated with the drug's biological target. So, finding these new candidate indications for the drug requires looking at nodes two hops away: a disease associated with the drug's target. This guilt-by-association principle has been incorporated directly into the model: For each drug or disease node, generate sequences of drug, protein, and disease nodes (using random walks) to learn semantic similarities between the nodes (81). As a result, the embeddings of drugs (or diseases) are near those of the proteins associated with the drugs (or diseases). New drug–disease relationships are inferred using embedding distance. Neighborhood aggregation strategies have also been designed to address a fundamental limitation in biology or medicine. Performing drug repurposing for poorly characterized diseases can be challenging because of a limited understanding of the affected genes and biological pathways. These query diseases' embeddings have been augmented by identifying similar diseases (using a domain-specific similarity metric) and aggregating them with the query diseases (28). A similarity metric can be the number of shared pathways, for example. Augmenting the embeddings of these poorly characterized diseases has enabled zero-shot prediction (i.e., prediction with no training examples) of a drug's indications and contraindications (28).

Contextualizing Patient Data Using Medical Knowledge

Patients are not treated in isolation, independently of any prior knowledge. They must be considered within the context of their medical history, existing knowledge about each disease or drug, and results of biological experiments. Such information can be encoded in a heterogeneous network. For example, patient–doctor encounters, including longitudinal hospital visits, may be modeled as a heterogeneous graph (82, 83). A knowledge graph, a particular type of heterogeneous graph, consists of interactions between drugs and proteins; associations among drugs, diseases, and proteins derived from clinical trials and population-level analyses; involvement of proteins in biological pathways; and more (47, 81, 84). Medical ontologies and biomedical knowledge may also be combined into a single unified network (47, 85). There are many ways to consider patient information in specific contexts, such as overlaying patient features directly onto a reference graph, constructing patient-specific networks or subnetworks, and creating patient similarity networks via domain-specific similarity metrics (**Figure 2*b***).

Overlaying patient data on a global reference graph effectively uses the data's underlying topology to enrich predictions, allowing interpretation of patient-level information by bridging health care process data and medical knowledge. Augmenting patient representations generated from medical records with representations learned from existing biomedical knowledge (e.g., by concatenating the embeddings generated for the two data modalities) is one way to integrate prior knowledge about diseases and drugs for diagnosing and treating patients in a more data-driven manner (86). Instead of integrating the independently generated representations, the model can consider the patient-specific data alongside the input graph. Multiomic features of patients or diseases are directly incorporated into the network as node features (87). By predicting these node

features during training, the model learns an integrated view of the diseases, thereby improving the identification of biomarkers, detection of disease modules, prediction of drug efficacy in patients, and interpretability of predictions (87). For more information on multimodal learning, where modality-specific models are used to integrate multimodal data, refer to the section titled Multimodal Learning on Clinical Datasets, below.

Patient data have also been used to alter the underlying graph or to construct patient graphs or subgraphs. This strategy further distinguishes the learned patient representations, as their topologies differ depending on the included nodes and edges (i.e., based on their patient-specific data). The underlying graph is modified by adding nodes representing individual patients and connecting them to other nodes (e.g., phenotype, disease, or medication nodes) that appear in the patient's medical record (88–90). Features are also added to these edges based on the relevance of each node in the graph to the patient, such as high or low measurement relative to the distribution of values observed in the patient population (90). Alternatively, edges can be contracted to specify the topology tailored to a given disease in the underlying graph (91). The graph representation learning model is trained on the new graph with patient nodes or disease-specific contracted edges. Rather than inserting nodes or edges, one can extract subgraphs of patients' data from the underlying graph to train a subgraph-level representation (36). This type of approach optimizes the representations of the underlying graph and of the patient subgraphs.

In contrast, personalized patient graphs are extracted and treated as independent graphs (85). In this case, the underlying graph is no longer involved during training. For example, a stage-aware hierarchical attention relational network considers both a medical ontology and a knowledge graph, extracts personalized patient graphs from the knowledge graph, and jointly models the hierarchical structure of the ontology and patient graphs for each patient (85). Patient similarity is learned across these approaches that train on modified underlying networks or extracted patient graphs. In order to explicitly indicate that patients share similar patterns, patients can form a network where nodes are patients and edges indicate their similarity based on domain-specific criteria. Patient data and external biomedical knowledge have been used to construct patient similarity networks. Similarity between patients is commonly based on the overlap between diagnostic codes [e.g., *International Classification of Diseases* (ICD)] and basic patient features (e.g., age, sex) (92). For rare-disease diagnosis, accounting for the frequency of the causal genes (i.e., genes harboring the mutations causing the disease) and diseases in the similarity metric injects domain knowledge into and improves the predictive ability of the model (92). GNNs can be used directly on patient similarity graphs or in combination with sequence models, such as recurrent neural networks, to predict future medical events.

Model Pretraining on Patient Populations and Fine-Tuning Across Clinical Tasks

Annotated clinical datasets are often limited in size. However, traditional deep learning requires large annotated databases with millions of data points. As such, novel clinical AI algorithms must maximize the utility of the available data. The modern paradigm to do so involves pretraining on a large-scale dataset without labels (i.e., unsupervised or self-supervised learning) and fine-tuning on a small labeled dataset for a specific task. Intuitively, the model learns implicit signals from a large-scale unlabeled dataset during pretraining and then transfers the knowledge to a specialized task while refining model parameters using a few labeled examples (**Figure 2*c***).

The pretraining and fine-tuning paradigm for transfer learning has demonstrated broad success in clinical applications. Pretraining can be performed self-supervised on a general dataset unrelated to the medical domain (93–95). To enable downstream medical question and answer (Q&A),

models first learn patterns in language. Med-PaLM (93) and Med-PaLM 2 (94) are pretrained on the general text and fine-tuned on medical Q&A, which can be long form or multiple choice. They demonstrate the benefit of instruction tuning, a data-, parameter-, and compute-efficient strategy to fine-tune the model for diverse clinical tasks. For clinical tasks on imaging, models are usually pretrained on general images in a self-supervised manner. SAIS, a surgical AI system, uses a visual transformer pretrained on ImageNet via contrastive learning on augmented images to fine-tune for identifying intraoperative surgical activities (95). Pretraining has also been performed on large medical datasets. Med-BERT (96) and NYUTron (97) are pretrained on EHRs: Med-BERT pretrains on 28,490,650 patients via masked language modeling and prediction of prolonged hospital stays. NYUTron pretrains on 387,144 patients with 4.1 billion words through masked language modeling. In addition, different data modalities have been combined for clinical applications. PLIP (98) pretrains on pathology images and captions by aligning their representations in a self-supervised manner and freezes the image decoder to fine-tune on text generation for specific clinical tasks.

Graph-based approaches have also adopted the pretraining and fine-tuning paradigm for clinical applications. TxGNN pretrains on a knowledge graph via link prediction and fine-tunes on predicting indication–contraindication relationships (28). SHEPHERD also pretrains on a rare-disease knowledge graph via link prediction but fine-tunes on a dataset of simulated rare-disease patients (36). Evaluated on rare-disease patients in a zero-shot manner, SHEPHERD outperforms state-of-the-art approaches (36). GODE pretrains joint representation of drugs via contrastive learning based on their molecular graphs and knowledge subgraphs (99). The resulting representations are fine-tuned using a multilayer perceptron for a downstream task (99). More recently, MolCAP (100) pretrains a graph transformer on four self-supervised tasks regarding molecular reactivity: predicting the formal charge, hydrogen content, chirality, and bond order between atom pairs that occur after a chemical reaction. Manual and automatically generated prompts are used to fine-tune the model for downstream tasks, such as drug toxicity and absorption (100). G-BERT combines GNNs and text transformers to enable medication recommendation using structured EHRs (101). G-BERT uses a GAT to generate diagnostic and medication code representations based on their neighborhood in the ICD-9 and ATC (Anatomical Therapeutic Chemical Classification System) ontologies. During pretraining, G-BERT performs two tasks: predicting the masked medical code in a single visit and predicting the unknown drugs that treat a given disease or unknown diseases that are treated by a given drug. These approaches demonstrate the success of pretraining and fine-tuning on graphs, including molecular and knowledge graphs. However, other clinical data modalities complement networked data well.

Many approaches extract medical entities from clinical notes and map them to nodes in a knowledge graph. Using knowledge graphs to augment text can improve prediction stability, reliability, and interpretability while minimizing hallucination (102). One approach involves aligning the medical concepts' representations generated from a knowledge graph (i.e., based on each concept's local neighborhood) and text (i.e., based on each concept's definition) (103). For a graph-based medical question (by doctor) and answer (by patient) system, the models either use pretrained language models (on general or biomedical text) for continued pretraining on a publicly available medical Q&A dataset (e.g., MedDialog-EN) (104, 105) or perform contrastive learning to differentiate among medical entities during pretraining (106). In these approaches, knowledge graphs are used to generate complementary graph-based representations that are passed through the decoder alongside the language-based representations (105), modify the masked ground truth token for token classification after the encoder layer (and the same hidden features are input to the decoder) (104), and narrow down the range of symptoms to inquire about for identifying a

disease (106). For details about multimodal integration, refer to the section titled Multimodal Learning on Clinical Datasets.

Looking forward, there are many opportunities to innovate. The utility of pretraining varies with domains and data modalities (107); no one strategy is universally effective and beneficial across tasks (108). Pretraining may not even be necessary (109). Furthermore, prompting and instruction tuning are still not well defined for graphs in general. However, prompting of molecular graphs shows that prompts can improve the downstream performance of GNNs (100).

MULTIMODAL LEARNING ON CLINICAL DATASETS

In clinical datasets, structured and unstructured features often describe patients across various modalities (110). For example, EHRs may encompass free clinical text, family history, imaging and laboratory studies, medications, and billing codes. Additionally, biobanked patients may have matched omics profiling (e.g., whole-exome sequencing). External biodata available from wearable biosensors and other external data sources can provide measurements of environmental exposures that may affect patient health. Integration of these complementary modalities promises to offer a unified view of patient health, enabling computational models to make precise and personalized clinical predictions. Fusion of multimodal clinical data can occur at different stages in the modeling process, allowing information learned from each data channel to inform other modalities. These fusion strategies can be delineated into three broad categories: early, intermediate, and late integration (111, 112) (**Figure 3**).

Early Integration

In early integration, fusion occurs at the data level. Diverse data sources are transformed into the same feature space and passed as input to a unimodal architecture. The interactions between biomedical entities can be explicitly modeled in a graph-structured format such as a heterogeneous knowledge graph, where knowledge-informed descriptions and relationships are encoded into graphs upon which a GNN can learn (47, 113). For example, in LIGHTED, multimodal clinical features from patient encounters are extracted via manually defined feature engineering steps to form patient feature–encounter graphs (114). A heterogeneous relational GNN embeds these multimodal graphs; raw feature vectors and encounter node embeddings are provided to a long short-term memory network to learn patient trajectories for opioid overdose prediction.

Other examples of early integration include genomic data integration, where genomic datasets, like gene expression profiles, DNA methylation, and single-nucleotide polymorphisms, are integrated at the data level. These diverse datasets can be represented as multilayer graphs, where each layer corresponds to a specific genomic data type. GNNs or graph transformers can be trained on these integrated graph structures to predict phenotypic outcomes or disease susceptibilities. In another example, brain imaging data from different modalities, such as functional magnetic resonance imaging (fMRI), MRI, and diffusion tensor imaging (DTI), can be integrated early on. After integration, these data can be represented as brain connectivity graphs, where nodes represent brain regions and edges represent connections or activations. GNNs are then applied to these graphs for tasks like disease classification or cognitive-state prediction. However, by lacking modality-specific encoders that can learn the idiosyncrasies of each modality, early integration strategies may not fully exploit cross-modal interactions.

Intermediate Integration

In intermediate integration, fusion occurs at the encoder level. Unlike in early integration, modality-specific encoders are combined in the model to create unified representations; unlike

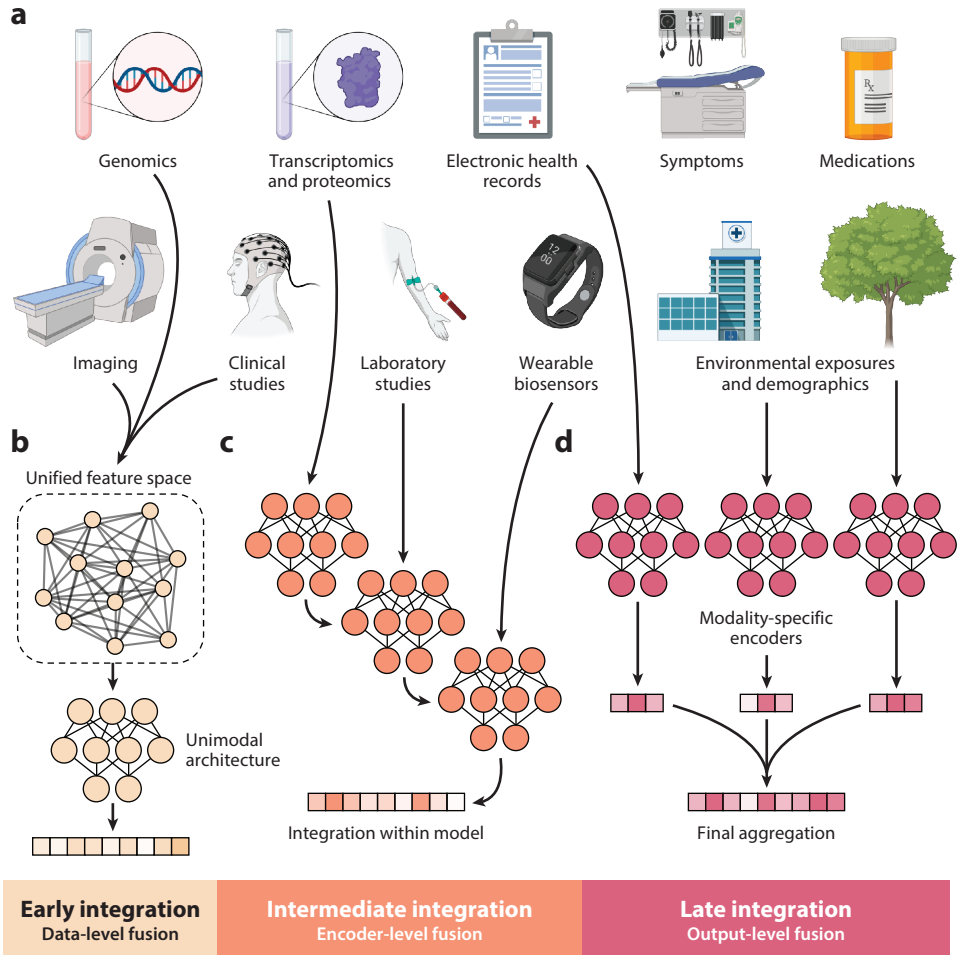

Figure 3

Deep learning on (*a*) multimodal clinical datasets including omics data, medical imaging, electronic health records, and more. Data modalities can be fused through (*b*) early, (*c*) intermediate, and (*d*) late integration strategies. Figure adapted from images created with BioRender.com.

in late integration, information from different modalities is combined during convolution rather than after. Loss from the objective function propagates back to modality-specific channels whose outputs are often successively aggregated to create unified embeddings. Various clinical features, events, and outcomes have been successfully predicted using intermediate integration approaches on graphs, including patient survival in cancer (115); adverse drug events (116); freezing of gait from footstep pressure maps and video recordings in Parkinson's disease (117); and steatosis, ballooning, and fibrosis in histological stains of nonalcoholic steatohepatitis (118).

Intermediate integration offers the most flexibility to design integration strategies informed by prior knowledge of how different patient-level datasets depend on one another. For example, the knowledge-enhanced autodiagnosis (KAD) model uses three tiers of integrated learning to combine a medical knowledge graph with radiology images and correlated textual descriptions for the automated diagnosis of chest X-ray images (119). During training, radiology images are passed to an image encoder (e.g., ResNet-50 or ViT-16) while the matched textual descriptions

are passed to a language encoder; the outputs of each encoder are then jointly passed through a transformer architecture to provide a final prediction.

Graphs can also enable domain knowledge–informed modality integration. For example, in studies of the human brain, graph-based integration of MRI and DTI modalities has been informed by expert-created brain anatomical atlases, such as the Automated Anatomical Labeling (AAL) atlas, with AAL regions of interest as nodes (120, 121). In a recent study (121), modality-specific convolutional autoencoders learned representations of structural MRI and DTI scans. An AAL-informed brain network fuses the autoencoder outputs; a graph transformer then learns this network to estimate brain age as a biomarker for Alzheimer's disease. Together with KAD, these examples demonstrate how graph-guided learning can integrate structural and functional connectomics data at the representation learning and integration levels to provide multidimensional phenotypic characterization.

Late Integration

Finally, in late integration, fusion occurs at the output level. Different unimodal architectures are trained individually or jointly to learn modality-specific representations, which can then be aggregated for downstream prediction. Graph-based late integration strategies have allowed the prediction of 30-day all-cause hospital readmission (122), survival analysis in cancer (123, 124), and diagnosis of mild cognitive impairment (125), among other applications. In these architectures, GNN can play either role: the feature extractor or the feature aggregator. For example, in MOGONET, weighted sample similarity networks are constructed from mRNA expression data, DNA methylation data, and microRNA expression data; these networks are then used to train omics-specific GNNs, whose predictions are combined in a fully connected final network for patient classification (126). Both the unimodal encoders and the final view correlation discovery network are jointly trained. In MOGONET, the GNN acts as the unimodal encoder but can also act as the feature integrator. For example, in DeepNote-GNN, a pretrained BERT language model is used to generate embeddings from clinical admission notes; a GNN then learns on the similarity graph from these representations for prediction of 30-day hospital readmission (127).

Within the medical realm, integration techniques—encompassing early, intermediate, and late stages—have established a critical foundation for harnessing information from various sources and modalities. Despite its innovative utilization of graph-based configurations, early integration encounters limitations, stemming primarily from the lack of encoders tailored to individual modalities. By contrast, intermediate integration offers a sophisticated equilibrium. Late integration adopts a more phased approach, permitting comprehensive learning specific to each modality before fusion. Moving forward, these integration paradigms highlight the need to develop methods based on data characteristics and clinical use cases, including consideration of end users and the existing workflows within which the methods are implemented.

EXPLAINABILITY WITH GRAPH NEURAL NETWORKS

Although the accuracy of clinical AI algorithms has achieved remarkable prediction performance, usability requires building trust within the clinical community. Providing model transparency and explainability will be crucial for obtaining domain experts' trust and confidence in these models for high-stakes decision-making (128, 129). Model explainability broadly describes the degree to which a model and its predictions can be communicated through clear, logical descriptions. These descriptions can be based on visualizations, text, statistics, or counterfactuals but do not necessarily assume that the user knows the exact model construction details (130).

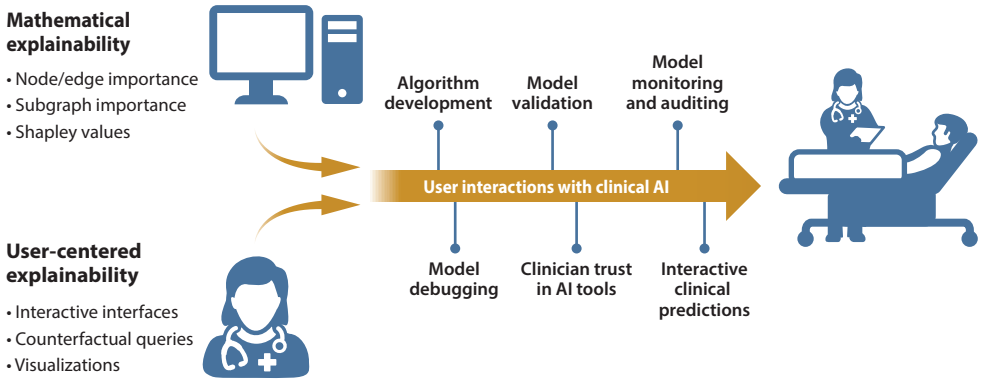

Figure 4

Mathematical and user-centered explainability for clinical artificial intelligence (AI) tools affect various stakeholders, including data scientists, researchers, clinicians, patients, and administrators. Images were obtained under an Adobe Stock Education License: © ink drop/Adobe Stock and santima.studio (02) (*top left*), © ssstocker/Adobe Stock (*bottom left*), © Feodora/Adobe Stock (*right*).

In practice, the processes and methodologies used to achieve each concept depend on the relevant stakeholders and the context of the model's downstream use. A stakeholder is defined as anyone who interacts with or is affected by the decisions based on the model's output (131). Providing model explanations for clinical AI models is unique because the resulting decisions propagate to diverse users with various needs and backgrounds, including clinicians, nurses, technicians, patients, and policy makers (132). Meeting the needs of the full spectrum of stakeholders requires solutions that leverage different explanation modalities (**Figure 4**). The flexibility of graph representation learning algorithms provides a unique basis for constructing model explanations that can be tailored to different stakeholder audiences. Most explainability techniques for deep graph representations are local (sample-level) explainability (133).

Mathematical Explainability

Traditional methods rooted in the field of explainable AI machine learning typically rely on mathematical modalities of explanation (134). These techniques tend to be more statistically or data oriented and focus on the model's internal mathematical mechanisms. Often, these forms of explanation require a degree of a priori understanding or knowledge of the prediction model and problem setup. Explanation techniques vary according to where they are incorporated into the modeling process. Ante hoc techniques involve incorporating mechanisms for explainability directly within the model from its initial construction. The parameters describing the predictor's explanation are learned during the training process (135, 136). For example, the attention mechanisms used in GATs are learnable weights indicating the amount of contribution from a given neighbor node. In contrast, post hoc explainability techniques are applied only after the regular training process is completed and therefore do not alter the original prediction model. One of the most widely used post hoc explanation methods is SHAP (137), which uses concepts from game theory to estimate feature contribution scores. SHAP has been adapted for GNNs where nodes and their features are assigned contribution scores (138).

Explanations can be presented in various forms or modalities. The first mathematical modality is based on attribution maps, which assign importance scores to the features in a graph; most often, these scores are provided over graph nodes (139), edges (140), or both (141). Attribution scores can also be presented as discrete values, such as {0, 1}, thereby selecting discrete entities in a graph,

such as a subgraph or a set of nodes (140, 142), rather than providing continuous scores over every candidate node in the graph (139). In the literature, attribution maps are the most-explored modality for method development. Another modality of explanations in graphs is that of counterfactual explanations. These explainers present information in terms of counterfactuals, that is, assessments of alternative scenarios, such as predicting another label for a given node. The critical insight obtained by counterfactual explainers is that interpreting multiple counterfactuals for one sample, as opposed to one explanation via an attribution map, increases human interpretability. Counterfactual explainers for graphs often focus on creating perturbations in graph structure that might cause a change in prediction (143, 144). Such explanations may be necessary for health care, where assessing alternative outcomes for predictions, such as from diagnostic systems, dramatically increases the transparency for downstream users such as clinicians.

Human-Centered Explainability and Interactions

There is often a divide between what constitutes an optimal explanation for clinicians and for data scientists or machine learning researchers. For example, developers use explainable AI tools to debug, probe, and audit models, whereas researchers utilize these tools to discover novel patterns in data (129). Clinicians use explainable AI as a single tool in their overall assessment of a patient, including their current patient observations and knowledge from clinical practice (145). Unlike in pure discovery, results must fit within the current clinical context and known medical literature—thus, an explainability tool in this setting would need to demonstrate that it satisfies these criteria for it to be trustworthy for clinicians (146).

Given the natural logic structure imposed by graphs, graph representation models offer inherent opportunities for user-focused explainability. Studies have constructed interactive user interfaces for counterfactual queries regarding a graph's edges and nodes (147). Additionally, a formal user study for drug repurposing prediction allowed path-based explanations to be analyzed and compared (148). This user study reported overall positive feedback from medical professionals, demonstrating that graph-based user explanations are as a promising technique for biomedical explanations.

CHALLENGES AND FUTURE DIRECTIONS

While graph AI holds tremendous promise for advancing biomedical research and health care, numerous challenges and practical considerations still need to be addressed to fully utilize these techniques' potential. A key benefit of graph models is their ability to naturally incorporate multimodal datasets such as genetic sequences, biomarker measurements, and imaging data through heterogeneous graph models. As these datasets become more complex, fusing this information into a cohesive graph representation will require advanced data harmonization, feature engineering, and graph construction techniques. An inherent challenge of modeling multiple modalities is the issue of missing modalities, which is akin to missing data, except the missingness is by modality type (149). Accurately modeling these patterns is especially relevant in the health care setting, where we cannot assume that all types of measurements will be uniformly collected over individuals (150) and where much of the missingness in clinical data is nonrandom and may even be informative for certain problems (151).

Moreover, clinical data modalities inherently have very intricate relational dependencies. For example, a clinical marker may be reflected in a laboratory test, clinical note, or radiology report. Still, depending on the exact modality, the record may have varying contexts and interpretations for diagnosis. Such complex relations between modalities can lead to modality collapse. In modality collapse, the model, during learning, focuses solely on a subset of the provided modalities (149).

This issue can arise when some modalities are beneficial during the training process and others are ignored. However, those modalities may be informative when the model is asked to make new predictions during inference. The study of modality collapse in general and specific techniques for addressing this phenomenon when modeling biomedical data represent an active area of ongoing research.

The scalability of GNNs remains a practical concern, mainly when dealing with large-scale, high-dimensional biomedical datasets. Scaling computations involves exploring distributed computing, parallel processing, and hardware acceleration techniques to handle the computational demands of training complex graph models on extensive biomedical datasets. For example, modeling long-range connections in a large graph would require numerous layers (a k-layer GNN considers neighbors at most k hops away), but most GNNs are only a few layers deep because of computational constraints. However, increased scalability does not depend solely on increased hardware capabilities. Even methods that attempt to scale past $k = 3$ layers run into issues of oversmoothing. Here, node representations of different classes are indistinguishable, which is hypothesized to be a result of the message-passing scheme.

Although minibatching is a common technique for modeling datasets too large to fit on a single GPU, creating random graph partitions does not always ensure effective training. This straightforward approach can lead to batches with highly imbalanced node and edge types when modeling heterogeneous graphs, prompting a new heterogeneous minibatch sampling algorithm to address these concerns. Thus, developing algorithmic techniques that can efficiently learn representations from massive graphs will also be essential for applying graph-based methods to high-dimensional medical datasets.

Additionally, ensuring the interpretability and reliability of graph-based models is crucial in biomedical applications to ensure that clinical AI algorithms are fair and do not exhibit biases, which can contribute to or exacerbate health inequities. Researchers must develop techniques that optimize prediction performance and provide insights into the learned representations and decision-making processes, enabling clinicians and researchers to validate and understand a model's outcomes. Most graph representation methods that explicitly handle issues of fairness directly borrow techniques (as well as inductive biases) from nongraph domains. However, these approaches do not consider how sensitive information and associated biases can be propagated through the network during feature propagation. Even after a model has been developed, researchers must be vigilant about model auditing and postmarket surveillance. Because medical data are recorded in a dynamic, nonstationary environment, dataset shifts constitute a major concern because these distributional changes can lead to unexpected biases or errors after a model has been deployed. Given that multiple modalities are often used in graph AI models, monitoring dataset shifts and the interaction between shifts across modalities is even more complex.

The fast-evolving landscapes of graph representation learning and digital health present exciting future opportunities in clinical AI. Clinical prediction tasks are inherently complex, given the nature of the tasks and the availability of only a few (if any) accompanying labeled data points from each task. However, with advances in ultralarge prediction models with billions of parameters, machine learning is shifting from single-task-oriented models to generalist models that can solve diverse tasks. Models that are trained on broad datasets and later adapted for more specialized tasks are referred to as foundation models (152). Using unlabeled data and then employing techniques in self-supervised or semisupervised learning are crucial to this approach. This process eliminates the need for large quantities of labeled data, which are particularly expensive and time-consuming to collect in the medical domain.

Foundation models naturally fit within the pretraining and fine-tuning paradigm, where a base model is first pretrained on a large, broad dataset. Then, typically, a subset of the base

model parameters is updated to adapt the model to an array of clinical tasks. Graphs naturally allow the integration of multiple data modalities and fusion techniques through heterogeneous graph representations (107). Additionally, knowledge graph–based foundation models could infuse medical knowledge in pretrained models, allowing them to perform predictions in a few-shot or zero-shot manner with minimal or no fine-tuning. As the field moves toward constructing such large, multipurpose models, techniques for learning more expressive, explainable, and compelling representations will continue to develop.

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