Multimodal Machine Learning in Precision Health

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Summary

Background: As machine learning and artificial intelligence are more frequently being leveraged to tackle problems in the health sector, there has been increased interest in utilizing them in clinical decision-support. This has historically been the case in single modal data such as electronic health record data. Attempts to improve prediction and resemble the multimodal nature of clinical expert decision-making this has been met in the computational field of machine learning by a fusion of disparate data. This review was conducted to summarize this field and identify topics ripe for future research.

Methods: We conducted this review in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) extension for Scoping Reviews to characterize multi-modal data fusion in health. We used a combination of content analysis and literature searches to establish search strings and databases of PubMed, Google Scholar, and IEEEXplore from 2011 to 2021. A final set of 125 articles were included in the analysis.

Findings: The most common health areas utilizing multi-modal methods were neurology and oncology. However, there exist a wide breadth of current applications. The most common form of information fusion was early fusion. Notably, there was an improvement in predictive performance performing heterogeneous data fusion. Lacking from the papers were clear clinical deployment strategies and pursuit of FDA-approved tools.

Interpretation: These findings provide a map of the current literature on multimodal data fusion as applied to health diagnosis/prognosis problems. Very few papers compared the outputs of the multimodal approach with unimodal predictions. However, those that did achieved an average increase of 4.2% in predictive accuracy (AUC). Multi-modal machine learning, while more robust in its estimations over unimodal methods, has drawbacks in its scalability and the time-consuming nature of information concatenation.

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Introduction
Clinical decision support has long been an aim for those implementing algorithms and machine learning in the health sphere\(^1\)\(^-\)\(^3\). Examples of algorithmic decision supports utilize lab test values, imaging protocols or clinical (physical exam scores) hallmarks.\(^4\)\(^,\)\(^5\) Some health diagnoses can be made on a single lab and a single threshold. This is the case in diabetes in older adults\(^6\). Other diagnoses made based on a constellation of the signs, symptoms, lab values and/or supportive imaging are referred to as a 'clinical diagnosis'. Oftentimes these clinical diagnoses are based on additive scoring systems that representing a threshold that requires crossing, or a mixture of positive and negative hallmarks required prior to confirmatory labeling. One example of such a diagnostic protocol is with Parkinson’s disease. Two supportive features are required to be included in the diagnosis such as bradykinesia, rigidity, rest tremor or a beneficial response to dopaminergic therapy. Exclusionary criteria for Parkinson’s include but is not limited to; a history of repeated strokes with an associated stepwise Parkinsonian manifestation, or severe autonomic failure (e.g. orthostatic hypotension)\(^7\). This example highlights the expected benefit of leveraging both imaging data (for history of strokes), combined with structured Electronic Health Records (EHR) that provides blood pressure measurements for indicative of orthostatic hypotension and clinical exam findings.

The modus operandi of a clinical diagnosis may fail to consider the importance of relative weighting of these disparate data inputs due to the limitations of human decision-making capacity and potentially non-linear relationships. The strength of algorithmic decision-making support is that it can be used to offload such tasks, ideally yielding a more successful result. This phenomenon has sparked an interest in fusion studies using health care data. The purpose of this study is to highlight the current scope of this research domain.

Undertakings to characterize this literature have been performed by Huang et al.\(^8\), who performed a systematic review of deep learning fusion of imaging and EHR data in health. However, it was limited to EHR and imaging data, where only deep learning applications were shown. In a follow-up paper\(^9\) that included commentary on omics and imaging data fusion. The current study is more inclusive in the breath of the types of machine learning protocols used and attempts to encompass all current modalities.

Data fusion is underpinned by information theory and is the mechanism by which disparate data sources are merged to create an information state based on the sources’ complementarity\(^10\). Data fusion is concisely defined as: “. . . the process of combining data to refine state estimates and predictions.”\(^11\) updating the commonly used definition: ‘A process dealing with the association, correlation, and combination of data and information from single and multiple sources to achieve refined position and identity estimates, and complete and timely assessments of situations and threats, and their significance.’\(^12\).

The hope and expectation in machine learning is that doing so will result in an improvement in predictive power\(^13\),\(^14\) and therefore more reliable results in potentially low validity settings\(^15\).
Data fusion touts the advantage that the results of modeling become inherently more robust, by relying on a multitude of informational factors rather than a single type. However, the methodology of combinatorial information has drawbacks; adding complexity to specifying the model and reducing the interpretability of results\textsuperscript{15,16}.

Successful data fusion is built on the pillar of data harmonization, that is quality control of data performed alongside the models in which it will be implemented. Because data from different sources and file formats are rarely uniform, and this holds true especially for clinical data\textsuperscript{17}. For example, data sets can have different naming conventions, units of measure, represent different local population biases. This feat can be difficult, and a balance is required between efficacious harmonization (information that is similar and works together) and pure (information that corresponds 1:1)\textsuperscript{18}. Care must be taken to search and correct for systematic differences between datasets and assess the degree of interchangeability. For example, Colubri et al. in order to aggregate computed tomography (CT) and PCR labs, they performed an intra-site normalization to ensure that values were comparable across sites and needed to discard several potentially informative clinical variables since they were not available in all datasets\textsuperscript{19}. The clinical field of Heart Failure with preserved ejection fraction (HFpEF) saw novel applications of multiple tensor factorization formulations to integrate the deep phenotypic and trans-omic information\textsuperscript{20}, and this extends to other areas of precision medicine\textsuperscript{21}. To increase the portability of EHR-based phenotype algorithms, the Electronic Medical Records and Genomics (eMERGE) network has adopted common data models (CDMs) and standardized design patterns of the phenotype algorithm logic to integrate EHR data with genomic data and enable generalizability and scalability\textsuperscript{22-25}.

Given the recency of this literature, there is no consensus on the optimal way to combine data. Classification of informational source amalgamation was first posed by Durrant-Whyte\textsuperscript{26}. Incoming data can be complementary; where sources represent different aspects of the entity under investigation, redundant; where sources provide the same information and serve to reinforce the information, and lastly cooperative; where the information is fused to create new information of a higher order. It is this last class or cooperative information that data fusion takes its roots.

There are three main types of data fusion that are used in machine learning; early (data-level), intermediate (joint), and late (decision-level)\textsuperscript{27}. In the case of early fusion, multiple data sources are converted to the same information space. This often results in vectorization or numerical conversion from an alternative state, as performed by Chen et al. via vectorized pathology reports\textsuperscript{28}. Images possess characteristics that can undergo numerical conversion based on area, volume, and/or structural calculations\textsuperscript{29}. These are then concatenated with additional measurements from structured data sources and fed into an individual classifier. Canonical correlation analysis\textsuperscript{30}, non-negative matrix factorization\textsuperscript{31,32}, Independent Component Analysis (ICA) and numerical feature conversion methodologies exist as common options to transform all data into the same feature space\textsuperscript{33}.

Intermediate data fusion occurs inside a step-wise set of models and offers the greatest latitude in model architecture. A 3-stage deep neural learning and fusion model was proposed by Zhou et
al. where stage 1 consists of feature selection by a soft-max classifier for independent modalities. Stage 2 and 3 constitute combining these selected features, establishing a further refined set of features, and feeding these into a Cox-nnet to perform joint latent feature representation for Alzheimer’s diagnosis. In contrast to early fusion, intermediate fusion combines the features that distinguish each type of data to produce a new representation that is more expressive than the separate representations from which it arose.

In late fusion, multiple models are trained, where each model corresponds to an incoming data source. This is akin to ensemble learning, which offer better performance over individual models. Ensemble methods use multiple learning algorithms (typically applied to the same dataset) to obtain better predictive performance than could be obtained from any of the constituent learning algorithms alone. However, in the case of multimodal ML ensemble here can refer to ensemble learning within a data type and across data types. Common ensemble learning methods include bagging, boosting, stacking, random forest, and Bayesian optimal classifier. These takes symbolic representations as sources and combine them to obtain a more accurate decision. Bayesian’s methods are typically employed at this level to support a voting process between the set of models into a global decision. A broad-based schematic for the 3 subtypes of data fusion are presented in Figure 1.

Early and late fusion have the greatest flexibility as to the number of models that can be fused. Early fusion gains this advantage by converting all data into the same feature space that can be classified using simpler models such as support-vector machines or logistic regression. While there inevitably exists a loss of information via dimensionality reduction using this method, it involves a single model and therefore offers a propitious entry point for those wishing to perform fusion for health predictions. Attribute differences and similarities are showcased in Table 1.

![Figure 1: early, intermediate, and late fusion data flow and general structure](image-url)


| Attribute                        | Early | Intermediate/Joint | Late/Decision |
|----------------------------------|-------|--------------------|---------------|
| Ability to handle missing data   | no    | no                 | yes           |
| Scalable                         | no    | yes                | yes           |
| Multiple models needed           | no    | yes                | yes           |
| Improved accuracy                | yes   | yes                | yes           |
| Voting/weighting issues          | no    | yes                | yes           |
| Interaction effects across sources | yes  | yes                | no            |
| Interpretable                    | yes   | no                 | no            |
| Implemented in health            | yes   | yes                | yes           |

Table 1. Comparison of Fusion techniques

Methods

There are several research questions that drove this review:

**RQ1** - What characterizes the published literature using multimodal data fusion in the health sector?

A multiplicity of different lenses will be used to showcase these studies.

**RQ2** - What are the different analysis techniques, methods, and strategies applied to analyze multi-modal health data for diagnosis/prognosis?

In addition to providing a summary of the analytical techniques applied, this RQ aims to explore the challenges and opportunities that researchers have encountered in implementing these techniques.

**RQ3** - What areas of heterogeneous data fusion have had the most impact?

This RQ aims to identify current gaps in the literature that will provide recommendations for future information concatenation in the health sector. Also, how the results of this RQ allow different health care researchers the opportunity to make informed decisions on how to use multi-modal data fusion as part of their studies.

Search Strategy and Selection Criteria

Inclusion requirements are: an original research article published within the last 10 years which inclusively encompassed years 2011-2021, published in English and on the topic of multi-modal or multi-view using machine learning in health for diagnostic or prognostication applications. ’multi-modal’ or ’multi-view’ for our context and sake of brevity is taken to mean data sources not of the same type. For example, a paper using CT and MRI would be considered multi-modal imaging but under our premise was considered to be uni-modal i.e. imaging. Exclusions for these purposes of this review were scientific articles not published in English, commentaries or editorials, other review articles. Papers were also excluded if the data was not human derived. We also excluded papers where the fusion already occurred at the data generation stage, such as spatial transcriptomics producing integrated tissue imaging and transcriptomics data\textsuperscript{37-39}. All papers underwent a 2-person verification for inclusion in the manuscript.
Search strings were established via literature searches, domain expertise. Additional keywords were identified based on keyword co-occurrence matrices established from the abstracts of the previous articles found. Table 2 displays the search strings, where an individual string would include one keyword from each column. For example, “health + heterogeneous data + machine learning” would be one of the search strings for automatic search. This process was repeated until all combinations of search strings were incorporated. An overview of the inclusion/exclusion process is noted in Figure 2 and echoes the standard set by PRISMA extension for scoping reviews. All titles included in this review can be seen in Supplementary material.

| Keyword₁ | Keyword₂ | Keyword₃ |
|----------|----------|----------|
| health | medicine | heterogeneous | fusion | learning [machine, deep] | artificial intelligence |

*Table 2. health-related keyword, Multimodal-related keyword, machine learning-related keywords, | : or*

*Figure 2: Overview of Study Inclusion Process*

Data Analysis

Information garnered from the articles included title, year published, FDA approval of the tool, whether published in a clinical journal, author affiliations, number of authors, locations (continents) and abstract. Health context information extracted included the specific health disease under investigation and the healthcare domain(s) that this fall under. It should be noted that several topics fell into one or more broad based health topics. For example, the specific health care topic might be small-cell lung cancer. The corresponding
health care domains would be respiratory and cancer.

Given the multi-modality aspect of machine learning, we also recorded and extracted the number of different modalities used and the divisions (i.e. text/image vs EHR/genomic/time series). To elucidate this, a paper characterized using lab values (structured EHR) and computed tomography as input into machine learning would be categorized as 'Imaging/EHR' subtype. The objective of each paper was extracted in a 1-2 sentence summary along with the keyword (if available). Patient characterization in the studies noted was performed by ascertaining the number of unique patients leveraged in the cohort and patient sex (i.e. Men/women/both or not mentioned).

Computational information extracted via recording the coding interface(s) used in data processing/analysis, machine learning type, data merging technique (early, intermediate, late) and types of machine learning algorithms used. Validation of the results of any machine learning work is important. Statistical tests run, whether validation was performed (yes/no) and the nature of that validation and other outcomes measures were all recorded for each paper. Validation consisted of leave-one-out cross validation, train-test split, n-fold cross validation. Statistical tests comparing outcomes from varying models included but were not limited to: student’s t-test, Chi-square, ANOVA etc. Outcome measures included accuracy, F1, recall, sensitivity, specificity etc. Assessing the significance, impact and limitations of each paper was extracted by noting their primary findings and individual limitations as noted in the papers.

**Results**

The topic modelling displayed in Figure 3 showcases the category, specific health ailment under investigation and the modality type. Neurology and singularly Alzheimer’s had the most papers published on this topic, accounting for 22 of the publications. Individual health diseases/diagnoses are mapped to all applicable overarching health topic areas as noted previously in the data extraction section above. With the advent of the COVID-19 pandemic, several primary research articles are dedicated, which can be arrived at through respiratory or infectious disease hierarchies. Articles are subsequently mapped back to their multi-modal subtype on the right of the Sankey plot.

This should serve as a resource to fellow researchers to identify areas that lack such saturation, namely dermatology, hematology, medication/drug issues such as alcohol use disorder investigated by Kinreich et al. that may offer new research horizons. A dashboard resource published in conjunction with this review article is available here. This dashboard was created as an interactive infographic-based display of some major findings presented here. To assist and spawn future work, a drop-down menu has been created to help researchers filter our underlying data file of titles based on overarching health topic by selection, so they may more readily find and read the papers as presented whose broader trends are presented here.
Figure 3: Topic and Modality Modeling
Of the models used in the papers, 128/130 explicitly reported performing a validation procedure of their model(s). The most common validation performed were; N-fold cross validation (54), train test split (55), leave one out cross validation (9) and external dataset (10). A cornucopia of machine learning techniques and methods were comprised both within and across articles in this review. They have been summarized in Table 3 noting which fusion umbrella subtype they were implemented in.

### Table 3. Fusion and machine learning methods included in this review

| Fusion Type | Machine learning models/techniques implemented |
|-------------|-----------------------------------------------|
| Early       | SVM\textsuperscript{28-31,33,49,50,52-80}, RF\textsuperscript{28,30,33,66,68-70,72,73,77-79,81-88}, Gaussian process\textsuperscript{33,54}, Bayesian network\textsuperscript{28,89}, NB\textsuperscript{53}, n-grams\textsuperscript{53}, LR\textsuperscript{28,46,50,66-68,78,79,88-94}, ridge regression\textsuperscript{76,86}, multivariate linear regression\textsuperscript{51,76,86,87}, K-means\textsuperscript{74}, DT\textsuperscript{57,28,31,67,68,74,75,78,83,92,95}, MLP\textsuperscript{68}, transfer learning\textsuperscript{47,61,93,98,99}, AutoEncoders\textsuperscript{56,95,100,101}, bag-of-words\textsuperscript{80}, Transformers (BERT, GPT)\textsuperscript{99}, RNN\textsuperscript{96,102}, LASSO\textsuperscript{86,90}, CNN\textsuperscript{47,79,80,93,99}, GNN\textsuperscript{101}, Semantic-embeddings\textsuperscript{102}, DNN\textsuperscript{60}, multitask learning\textsuperscript{61}, gradient boosting classifiers\textsuperscript{70,71,73,92}, Markov model\textsuperscript{105}, bagging\textsuperscript{87}, ensemble learning\textsuperscript{64,87}, KNN\textsuperscript{64,72,74,75,106}, ANN\textsuperscript{72,77}, Adaboost\textsuperscript{67,72,74,78}, tensor decomposition\textsuperscript{73}, SGD\textsuperscript{86}, MARS\textsuperscript{86}, MKL\textsuperscript{63,107}, cox regression\textsuperscript{108}, DUN\textsuperscript{109}, EM\textsuperscript{106}, iMSF\textsuperscript{106}, mixture model\textsuperscript{110}, graph clustering\textsuperscript{105}, network/graphical Lasso\textsuperscript{105}, hierarchical clustering\textsuperscript{105} |
| Intermediate | LR\textsuperscript{111-115}, SVM\textsuperscript{34,58,111,113,114,116-121}, DT\textsuperscript{112,122}, CNN\textsuperscript{41,44,114-119,121-135}, AutoEncoders\textsuperscript{11,134}, multivariate regression\textsuperscript{58,111,120,130,136}, DNN\textsuperscript{34}, n-grams\textsuperscript{114}, MLP\textsuperscript{115,121,124,129,130,135}, LSTM\textsuperscript{112,124,126,128-130,136}, RF\textsuperscript{44,48,58,112,114,115,118,120,134}, Semantic-embeddings\textsuperscript{122}, LASSO\textsuperscript{122,123}, NB\textsuperscript{58}, bi-LSTM\textsuperscript{58,122}, ensemble learning\textsuperscript{126}, gradient boosting\textsuperscript{137}, transfer learning\textsuperscript{128}, multitask learning\textsuperscript{136,138}, linear regression\textsuperscript{118}, XGBoost\textsuperscript{115,121}, Adaboost\textsuperscript{115}, ANN\textsuperscript{118}, word2vec\textsuperscript{132}, bag-of-words\textsuperscript{121}, NLP\textsuperscript{132,139}, ridge regression\textsuperscript{137,140}, SVR\textsuperscript{133}, MKL\textsuperscript{48,133}, LDA\textsuperscript{139}, graph learning\textsuperscript{139} |
| Late        | SVM\textsuperscript{141-146}, RF\textsuperscript{41,43,143-146}, KNN\textsuperscript{43,147}, CNN\textsuperscript{41,43,145,147-152}, LASSO\textsuperscript{146,153}, MLP\textsuperscript{36,42,45}, LSTM\textsuperscript{36,148}, AutoEncoders\textsuperscript{36,41}, DT\textsuperscript{147,152}, LR\textsuperscript{45,143,145,146}, bi-LSTM\textsuperscript{42,152}, mixed effects linear model\textsuperscript{154}, ensemble learning\textsuperscript{155}, multivariate linear regression\textsuperscript{144}, DNN\textsuperscript{143}, NLP\textsuperscript{42,147}, XGBoost\textsuperscript{42,146,156}, NB\textsuperscript{147}, sentiment analysis\textsuperscript{42}, word embedding\textsuperscript{45,147}, word2vec\textsuperscript{45}, GLMNET\textsuperscript{156}, recursive partitioning\textsuperscript{156}, GAM\textsuperscript{156}, graph clustering\textsuperscript{157} |

SVM: support vector machine, RF: random forest, LR: Logistic regression, DT: decision trees, CNN: convolutional neural network, GNN: graph neural network, NB: naive Bayes, KNN: k-nearest neighbors, MKL: Multiple Kernel Learning, DUN: deep unified networks, SGD: stochastic gradient descent, MARS: Multivariate adaptive regression splines, MLP: multilayer perceptron, GLM- NET: Elastic-Net Regularized Generalized Linear Models, NLP: natural language processing, bi-LSTM: bidirectional long short-term memory, DNN: deep neural network, LDA: Latent Dirichlet Allocation, SVR: support vector regression, GAM: generalized additive model, EM: Expectation Maximization, iMSF: incomplete Multi-Source Feature

All papers noted in this review used either two or three disparate data sources when fusing their data. Fusing two data sources, and specifically that of imaging and EHR (n=52) was the most
prevalent as per Table 4. Figure 4 A showcases the relative distributions of preferred interface type and fusion strategy, the most popular being the Python platform and early fusion.

| Number of Modalities | Subtype                          | (# of papers) |
|----------------------|----------------------------------|---------------|
| 2                    | Imaging/EHR                      | 52            |
| 2                    | EHR/Text                         | 21            |
| 2                    | Imaging/Genomic                  | 14            |
| 2                    | Imaging/Time series              | 5             |
| 2                    | Imaging/Text                     | 4             |
| 2                    | EHR/Genomic                      | 4             |
| 2                    | EHR/Time Series                  | 3             |
| 2                    | Genomic/Text                     | 1             |
| 3                    | Genomic/Imaging/EHR              | 13            |
| 3                    | EHR/Imaging/Time series          | 2             |
| 3                    | Text/Imaging/EHR                 | 2             |
| 3                    | EHR/Genomic/Text                 | 2             |
| 3                    | Text/Imaging/Time series         | 1             |
| 3                    | EHR/Text/Time series             | 1             |

*Table 4. Multimodalities and subtypes*
Figure 4: A: Heat map of fusion type broken down into the coding platforms papers reportedly used. B: Totally number of original research papers published in this sphere. C: Continental breakdown of author contributions (note some papers have authors from multiple continents). D: Breakdown of publication type (clinical/non-clinical journal) and sex breakdown of populations studied.
70 papers were published using early fusion. Of those, most were published using imaging and EHR data. Nearly all these papers performed numericalization of their images prior to processing, however two performed matrix factorization. A combination of EHR and text data was noted in 12 papers. Meng et al. created a Bidirectional Representation Learning model used latent Dirichlet allocation (LDA) on clinical notes. Cohen et al. used unigrams and bigrams in conjunction with medication usage. Zeng et al. used concept identifiers from text as input features. Cohen et al. used unigrams and bigrams in conjunction with medication usage. 9 papers used early fusion with imaging, EHR and genomic data. Doan et al. concatenated components derived from images with polygenic risk scores. Lin et al. also created aggregated scores from MRI, cerebral spinal fluid and genetic individually and brought them together into a single cohesive extreme learning machine to predict mild cognitive impairment. 10 papers performed fusion using imaging and genomic data. Three of these generated correlation matrices as features by vectorizing imaging parameters and correlating them with single nucleotide polymorphisms (SNPs) prior to feeding into the model. Both Hernandez and Canni`ere et al. implemented their methods for purposes of cardiac rehabilitation and harnessed the power of support vector machines (SVMs). However, Hernandez preserved time series information by assembling ECG data into tensors that preserve the structural and temporal relationships inherent in the feature space, while Canni`ere performed dimensionality reduction of the time series information using t-SNE plots. Two papers comprised early fusion using imaging and time series. Both Hernandez and Canni`ere et al. implemented their methods for purposes of cardiac rehabilitation and harnessed the power of support vector machines (SVMs). However, Hernandez preserved time series information by assembling ECG data into tensors that preserve the structural and temporal relationships inherent in the feature space, while Canni`ere performed dimensionality reduction of the time series information using t-SNE plots. Two papers comprised early fusion using imaging and time series.

33 papers were published using a form of intermediate data fusion. 14 used imaging and EHR data. Zihni et al. merged the output from a Multilayer Perceptron (MLP) for modeling clinical data and Convolutional Neural Network (CNN) for modeling imaging data into a single full connected final layer to predict stroke. Tang et al. used 3-dimensional CNNs and merged the layers in the last layer. EHR and text data were fused together in 11 papers. Of these, six used long term short term (LSTM) networks, CNNs or knowledge-guided CNNs in their fusion of EHR and clinical notes. Chowdhury et al. used graph neural networks and autoencoders to learn meta-embeddings from structured lab test results and clinical notes. Pivovarov et al. learned probabilistic phenotypes from clinical notes and medication/lab orders (EHR) data. Two models each employing Latent Dirichlet Allocation (LDA) where data type is treated as a bag of elements and brings each and coherence between the two models outlines unique phenotypes. Ye et al. and Shin et al. used concept identifiers via NLP and bag-of-words techniques respectively prior to testing a multitude of secondary models. In general, clinical notes can provide complementary information to structured
EHR data, where natural language processing (NLP) is often needed to extract such information\(^{159-161}\).

A few were published using imaging and genomic\(^{34,118,120}\). Here radiogenomics are used to diagnose attention-deficit/hyperactivity disorder (ADHD), glioblastoma survival and dementia respectively. Polygenic risk scores are combined with MRI by Yoo et al. who used an ensemble of random forests for ADHD diagnosis\(^{120}\). Zhou et al. fused SNPs information together with MRI and positron emission tomography (PET) for dementia diagnosis by learning latent representations (i.e., high-level features) for each modality independently and subsequently learning joint latent feature representations for each pair of modality combination and finally learning the diagnostic labels by fusing the learned joint latent feature representations from the second stage\(^34\). Wijethilake also used MRI and gene expression profiling performing recursive feature elimination prior to merging into multiple models SVM, linear regression, artificial neural network (ANN) where the linear regression model outperformed the other two merged models and any single modality\(^{118}\). Wang et al. and Zhang et al. showcased their work in merging imaging and text information\(^{128,129}\). Both used LSTM for language modeling a CNN to generate embeddings that are joined together in a dual-attention model which is achieved by computing a context vector with attended information preserved for each modality resulting in joint learning. Seldomly were articles published in: (Imaging, EHR, Text)\(^{114}\), (Genomic, Text)\(^{48}\), (imaging, time series)\(^{44}\), ( Imaging, Text, Time series)\(^{136}\), (Imaging, EHR, Genomic)\(^{41}\), (Imaging, EHR, Time series)\(^{117}\), (EHR, Genomic)\(^{134}\), (EHR, text, time series)\(^{126}\).

20 papers currently exist in this sphere having used late fusion. 7 of those performed this using imaging and EHR data types\(^{43,141,142,149,150,155,162}\). Both Xiong et al. and Yin et al. fed outputs into a convolutional neural network to provide a final weighting and decision\(^{149,150}\). 3 papers were published in using a trimodal approach: imaging, EHR and genomic\(^{41,153,156}\).

Xu et al. and Faris et al. published papers using EHR and text data\(^{45,152}\). Faris et al. processed clinical notes using TF-IDF, hashing vectorizer and document embeddings in conjunction with binarized clinical data\(^{45}\). Logistic Regression (LR), Random Forest (RF), Stochastic Gradient Descent Classifier (SGD Classifier), and a Multilayer Perceptron (MLP) were applied to both sets of data independently and final outputs of the two models are combined using different schemes; ranking, summation, and multiplication. 2 articles were published using imaging and time series\(^{148,151}\) both of which employed CNNs, one in video information of neonates\(^{148}\) and the other in chest x-rays\(^{151}\). However, they differ in their processing of the time series data, where Salekin used a bidirectional CNN and Nishimori used a 1-dimensional CNN. Far fewer papers were published using (Imaging, EHR, Text)\(^{42}\), (EHR, Genomic, Text)\(^{147}\), (imaging, EHR, time series)\(^{144}\), (imaging, genomic)\(^{154}\), (EHR, Genomic)\(^{143}\) and (imaging, Text)\(^{36}\).

Two papers performed more than one kind of data fusion architecture\(^{163,164}\). Huang et al. created 7 different fusion architectures, these included early, joint and late fusion. The architecture that performed the best was the late elastic average fusion for the diagnosis of pulmonary embolism using computed tomography and EHR data\(^{163}\). Their Late Elastic Average Fusion leverages an ElasticNet (linear regression with combined L1 and L2 priors that act as regularizers) for EHR variables. El-Sappagh et al. performed early and late fusion to create an interpretable Alzheimer’s diagnosis and progression detection model\(^{164}\). Their best performing model was one
that implemented instance-based explanations of the random forest classifier by using the SHapley Additive exPlanations (SHAP) feature attribution. Despite using clinical, genomic and imaging data, the most influential feature was found to be the Mini-Mental State Examination.

Both men and women were represented relatively equally across papers, however varied in that distribution within an individual studies. Data fusion may help address sex differences and increase population diversity issues (including minority population) in health modeling by creating a more cohesive representative dataset if one datatype contained more of one and the reciprocal true for the other datatype(s). This would also hold true for racial or ethnic diversities. Less than half (37.6%) of the papers were published in a journal intended for a clinical audience. However, none of the papers included in the final cohort of studies had created tools for clinical use that had FDA approval. Figure 4 B contains the breakdown of total number of publications in this field over the last 10 years, and the Figure 4 C continental contributions of authors. Asia and North America had a near equal number of publications 60 and 61 respectively. Note that some titles had repeated counts due to cross-continent collaborations between authors.

Discussion

Returning to our research questions, we outlined from the inception of this work:

**RQ1** - What characterizes the published literature using multi-modal data fusion in the health sector?

The literature published in this area as displayed and characterized in the results’ section is one that has a growing and global interest. It is fueled by a desire to improve predictive capabilities, relying on complimentary and correlative (reinforcing) data. The most common health topic was Neurology, and the second most was cancer. The relative saturation of this field likely reflects the underlying multimodal diagnosis that is present in a clinical counterpart i.e. neuroimaging and EHR (cognitive scores) as well as the number of established and curated databases that lends itself well for multi-modality predictions such as Alzheimer’s Disease Neuroimaging Initiative and The Cancer Genome Atlas Program. Early data fusion methods leveraging imaging and EHR data likely owe their pervasiveness for reasons that are three-fold; 2 modalities over 3 is means less work overall in model building and deployment, EHR and image data do not require as extensive digital conversion for models such as text, and lastly early fusion is built on a single model with a multitude of feature inputs and is typically less computationally complex. Only 4 articles performed comparisons against their human clinician counterparts. Several did perform comparisons between uni-modal and multi-modal predictions, with the majority of those citing an improvement from baseline by incorporating heterogeneous data types. Of the studies that compared predictive performance between multi-modal data and uni-have modal data, there is a consistent citing of improvement in classification accuracy, sensitivity, and specificity. However, this was not seemingly limited to a particular subtype of multi-modal strategy that was detectable in our metadata. We therefore make the overall and general recommendation that multi-modal data integration be attempted to improve performance and better mirror a human expert by creating a higher validity environment from which to make clinical decisions.

**RQ2** - What are the different analysis techniques, methods, and strategies applied to analyze multi-modal health data for diagnosis/prognosis?
The analysis techniques are varied and currently do not showcase a gold standard or ‘best-practice’ in the field. This is likely linked to this being a relatively new and emerging field. Further, while an N-cross fold validation was the most common and a robust estimator in the face of bias within a dataset, strength of generalizability stems from either the dataset set containing multi-site/location patient data to begin with or using an external dataset from a remote location.\textsuperscript{167}

**RQ3- What areas of heterogeneous data fusion have had the most impact?**

Health contexts predominantly impacted by this include Neurology and Cancer predictive modeling, though no domain laid claim to building translation models via FDA (or equivalent) approval for use in clinical circumstances. As multi-modal fusion is touted to be an important fulcrum from which to leverage disparate types of information, there are calls to compare models more readily to physician decision makers.\textsuperscript{168-171} This will guide the validity of the environments suitable to machine learning/artificial intelligence decision makers and hopefully result in the adoption and therefore FDA approval of these tools. In the review performed by Lyell et al.\textsuperscript{172} they outline the methods of clinical decision support (assistive, autonomous information and autonomous decision), and acknowledge FDA approval of ML devices is a recent development. For without deployment, the benefits to these exercises remain minimal and indirect. Information fusion has led to an increase in predictive performances over single modalities.\textsuperscript{52,111,163}

The most common reported limitations in the papers included in the review are:

1) Cohort built on a single site/location: Samples were most often built from a single hospital or academic medical center.\textsuperscript{153} A corollary of this issue is that most studies were based on samples from a single country. Because of the lack of an external cohort, it was difficult to validate and generalize the proposed model across different health systems.
2) Small Sample size: The median number of unique patients reported across the studies was 658 with a standard deviation of, 42600. This suggests that while some studies were able to leverage large and multi-center cohorts, a great many were not able to. Sample size were usually too small to train the model completely and obtain the best performance.\textsuperscript{69,81,120,125}
3) Retrospective data: Are Seldom machine learning investigations performed prospectively, this is endemic to the machine learning field in general.\textsuperscript{83}
4) Imbalanced samples: The imbalance problem in terms of positive and negative samples was usually ignored, which biases the model and is unfair to the validation test samples.\textsuperscript{74,150} It is necessary to address the imbalance problem by adopting techniques such as under- or over-sampling or differential weighting for training samples.
5) Handling of missing data: Missing data were usually ignored by dropping data points or imputing. It is very important to address this issue, if not dealt with appropriately can skew the results due to a biased model.\textsuperscript{67,109,173} More studies need to discuss frequencies and types of missing data, and the imputation method used, if any, to create a full data set.\textsuperscript{174-177} Comparison of different imputation methods on the final results should be part of the reporting process.\textsuperscript{178}
6) Feature engineering: Extracting features completely are important to the predictive or classification model. The features extracted based on feature engineering may not be enough for training models, which is usually time-consuming and dependent on empirical knowledge from experts.\textsuperscript{110} Deep learning-based techniques have been considered by researchers in some previous studies to extract features automatically from a dataset.
7) Confounding factors: When performing statistical analysis, researchers usually ignored
possible confounding factors such as age or gender, which may have major effects on the impact of results\textsuperscript{42}. Such possible confounding effects should either be taken into consideration by the model\textsuperscript{179,180} or adjusted first, prior to reporting model results.

8) Interpretation: Reasonable interpretations of the model and outputs must be presented so that clinicians find the results credible and then use them to provide guidance for treatments. However, most authors did not take the time to interpret the models for clinical audiences, and how the results provide useful tools. Different types of models need different types of explanation\textsuperscript{41,123}. For example, using explainable tools such as Local Interpretation Model-Agnostic and Shapely Additive Explanation would clarify such feature contributions.

Limitations are highlighted ‘where’ in the data processing and modeling building pipeline they exist, as per Figure 5.

\textbf{Figure 5. Limitations to multimodal fusion in health}

To expedite and facilitate this field, we have outlined a number of gaps for future researchers in this field that we have garnered having performed this review. These are listed below, with specific suggestions.

The relative topic saturation showcased in Figure 3 above has highlighted notable places for future work. Two subdivisions that become apparent are; 1) several topics that would benefit from more work in that area, and 2) the need to progress health topics where significant effort has already been made. Medication/drug topics present an underrepresented area, with only two papers being published in this field\textsuperscript{49,65}. Given current issues with drug interaction effects and recommendation guidelines such as the Beer’s criteria\textsuperscript{181} for use in older patients, performing multimodal machine learning may offer an earlier detection of medication misuse that is marked by iatrogenic error, user non-compliance or addiction.
Multimodal investigation may be a key to unlocking early detection, given the manifestations of misuse may be reflected in structured data (EHR) or imaging data. Take, for example, a heart failure patient who has inadvertently taken or been prescribed the wrong dosage of their diuretic\cite{109}. Here this could be reflected in lab values (urine and serum) and systemic opacity on chest x-ray. The opioid crisis is wreaking havoc on the medical system, two hallmarks of which include pinpoint pupils and depressed respiratory status\cite{182}. This also represents an area where image assessment of pupillary status and assessment of vitals (structured) may assist in making the decision to provide naloxone. Awareness of drug interaction effects is a difficult and growing issue\cite{183-186}, particularly in geriatrics, which gave rise to Beer’s criteria. However, this does little to assess real time adverse events and may present another avenue of lucrative health returns if modeled with multimodal machine learning.

Yap et al. published the only dermatology geared paper contained in this review\cite{47}. While some dermatological conditions are self-contained to the skin, many can be linked to gastrointestinal disease, infections or systemic cancer. Digital images of dermatological manifestations combined with lab values and clinical impressions via unstructured text presents a gateway of novel research questions. Therefore, the gauntlet has been thrown for pursuing a multimodal line of inquiry and exploration that could have both diagnostic and potentially screening implications in primary care settings. Similar justifications as outlined above could be applied to other areas seen as ‘lacking’ such as hematology with 1 paper\cite{48} and nephrology having 3\cite{86,108,112}. Conversely, the topics with more corresponding papers may improve their application and cement their gained expertise in our subsequent suggestions.

A multitude and extensive methodological undertaking is evident, characterized in the titles included in our review. While incorporating disparate data does lend itself to seemingly better predictions\cite{142}, our knowledge around certain diseases continue to accumulate and new data modalities continue to emerge. Thus, data fusion in healthcare is an evolving target that calls for machine learning framework to proactively adapt to the dynamic landscape\cite{187}.

It is anticipated this will vary based on the diagnosis or prognosis under investigation. For example, it has been shown in protein-protein interactions that utilization of the XGBoost algorithm reduces noisy features, maintain the significant raw features, and prevent overfitting via average gain\cite{122}. XGBoost is a gradient boosting decision tree using regularized learning and cache-aware block structure tree learning for ensemble learning. The average gain is the total gain of all trees divided by the total number of splits for each feature. The higher the feature importance score of XGBoost is, the more important and effective the corresponding feature is\cite{122}. Similarly, LightGBM is an ensemble algorithm developed by Microsoft that provides an efficient implementation of the gradient boosting algorithm\cite{188}. LightGBM has the advantages of faster training speed, higher efficiency, lower memory usage, better accuracy, being capability for handling large-scale data, and the support of parallel and GPU learning\cite{189}, and has been consistently outperforming other models\cite{190,191}. This represents a possible avenue for the advent of information fusion from disparate data in healthcare.

Augmenting clinical decision-making with ML to improve clinical research and outcomes present positive impacts that have economic, ethical, and moral ramifications as it has the ability
to reduce suffering and save human lives. Multiple studies have pointed to that bias of the underlying data often lead to the bias in the resulting ML models\textsuperscript{192,193}. The ethical imperative now on offer requires overcoming several hurdles with respect to data structure and federated access, clear definition of outcomes, assessment of biases and interpretability/transparency of results and limitations inherent in its predictions\textsuperscript{194}. Future work is subsequently invited on a per-disease basis to characterize the combinatorics (which fusion strategy and set of mixed data types) optimize model performance. Doing so will push individual fields to create recommendations for subsequent real-world implementations.

Continuing in the same vein, model optimization with respect to disease-based predictions is the ease of use when modeling the data and the ensuing interpretability to end users. The extensive preprocessing and transformation inherent in multimodal machine learning create a significant and systemic drawback to its use. Perotte et al.\textsuperscript{108} model was not compared with conventional simpler machine learning classifiers and their vectorization of clinical text required extensive manual work. And collective matrix factorization becomes inherently difficult to interpret\textsuperscript{78}. Contrast this with Fraccaro et al. whose work into macular degeneration noted their white box performed as well as black box methods implementing\textsuperscript{67}.

Trade-offs between increasing accuracy at the expense of complex and time-consuming data transformations may mean the predictive power gained from a multimodal approach is offset by this front-end bottleneck and may mean predictions are no longer temporally relevant or useful. In addition to knowing how the models should be built per disease, we also advocate for pipelines and libraries to speed up data conversion processes via open access to make the technology more widely available\textsuperscript{195,196}.

Going from bench to bedside should be the goal of machine learning in medicine. Otherwise, these become technical exercises without real world impact. While lacking in the reviewed literature, it is understandable given the infancy of the machine learning health data fusion field. As machine learning and multimodal ML become more ubiquitous, there are increased demands for regulation and accountability.

Of crucial importance for uptake is that predictions be patient specific and actionable at a granular level\textsuperscript{197}. For example, Golas et al. created a 30-day readmission prediction algorithm for those with heart failure\textsuperscript{109}. If put into practice, it may serve to inform hospitals about resource management and prompt further lines of research that may decrease the number of patients being re-admitted in that 30 days. Linden et al. developed Deep personalized LOngitudinal convolutional RIsk model—DeepLORI (DeepLORI) capable of creating predictions that can be interpreted on the level of individual patients\textsuperscript{122}. Simpler white-box models should be selected over complex ones if there exist similar performance measures to increase interpretability. Leveraging both and clinical and empirically driven information to create meaningful and usable recommendations\textsuperscript{139} may improve clinician/end user understanding by relating to existing frameworks. Resources such as CRISP-ML provide a framework for moving use cases into more practical applications\textsuperscript{198}, while efforts to vie for Food and drug administration (FDA) approvals as a tool for use are encouraged to increased adoption.

Limitations of this work include that it is not a systematic review. Therefore, it is possible that
some titles that should have been included were missed. However, to mitigate this issue search strings were included based on both empirical knowledge in the field and alternative synonyms and keywords were identified using a literature review and language modelling and lexical analysis to find the context-sensitive terms that present the field. This was performed by using keyword co-occurrence strategy on each paper’s objectives within the abstract of the article. As the primary purpose of this study was to perform scientific paper profiling on multimodal machine learning in health, a critical appraisal of individual methodological quality of the included studies was not performed. However, commentary is provided on the methodological limitations that could have affected their results and impact.

To our knowledge, this is the first review that offers a comprehensive meta-analysis evaluation across health domains, inmaterial to the type of machine learning or the data used. This work serves as both a summary and steppingstone for future research in this field. The topic areas of health that have saturation relative to others were highlighted, which serves to build a foundation for future work. FDA approval and design of the tools for clinical centers also remains a large and outstanding invitation for further research to continue. Multi-site data integration is of the utmost importance for creating models that are generalizable and representative of the populace at large. Comparing developed models against working clinician counterparts would go a long way to effecting meaningful change in the uptake of algorithm-based decision-making models. Unimodal machine learning is inherently in contrast to current routine clinical practice in which imaging, clinical or genomic data are interpreted in unison to inform accurate diagnosis and warrants further work for ease of use and implementation. Overall, it appears justified to claim that multi-modal data fusion increases predictive performance over uni-modal approaches and is warranted where applicable and available results provide tenable models.

**Contributors**
AK lead the review process, performed data extraction, performed the computation analysis, figure generation, writing and dashboard creation. HW, YL, SD, MH performed data extraction. ZX synthesized limitations of the studies. FW and FC performed proof reading and content curation. YL conceived the review, oversaw the review process and provided necessary feedback, proof reading, and content curation.

**Declaration of Interests**
We declare no competing interests.

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**References**
1. Nils BH, Sabine S. The ethics of machine learning-based clinical decision support: an analysis through the lens of professionalisation theory. *BMC Med Ethics* 2021; 22.
2. Sanchez-Pinto LN, Luo Y, Churpek MM. Big Data and Data Science in Critical Care. *Chest* 2018; 154(5): 1239-48.
3. Miotto R, Wang F, Wang S, Jiang X, Dudley JT. Deep learning for healthcare: review, opportunities and challenges. *Brief Bioinform* 2017.
4. Timothy JWD, Antonio De M, Wenzhe S, et al. Machine learning of threedimensional right ventricular motion enables outcome prediction in pulmonary hypertension: A cardiac MR imaging study. *Radiology* 2017; **283**(2): 381-90.

5. Gigi FS, Gregory RH, Bradley JN, Jun D. Predicting breast cancer risk using personal health data and machine learning models. *PLoS One* 2019; **14**.

6. Michael F, Justin BE-T, Elizabeth S. Clinical and public health implications of 2019 endocrine society guidelines for diagnosis of diabetes in older adults. *Diabetes Care* 2020; **43**: 1456-61, pmid:32327419, American Diabetes Association Inc.

7. Ronald BP, Daniela B, Matthew S, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 2015; **30**: 1591-601, pmid:26474316, John Wiley and Sons Inc.

8. Shih Cheng H, Anuj P, Saeed S, Imon B, Matthew PL. Fusion of medical imaging and electronic health records using deep learning: a systematic review and implementation guidelines. *npj Digital Medicine* 2020; **3**.

9. Weixian H, Kaiwen T, Jinlong H, Ziye Z, Shoubin D. A review of fusion methods for omics and imaging data. *IEEE/ACM Trans Comput Biol Bioinform* 2022: 1-, pmid:35044920, Institute of Electrical and Electronics Engineers (IEEE).

10. Federico C. A review of data fusion techniques. *The Scientific World Journal, pmid:24288502, Hindawi Publishing Corporation* 2013; **2013**.

11. Alan NS, Christopher LB, Franklin EW. Revisions to the JDL data fusion model. *Sensor Fusion: Architectures, Algorithms, and Applications III 1999; 3719: 430, SPIE*.

12. White JFE. Data Fusion Lexicon. *Computer Science* 1991: 29-52.

13. Erik M-M-r, Antonio AA, Ramon FB, Enrique G-C. Improved accuracy in predicting the best sensor fusion architecture for multiple domains. *Sensors* 2021; **21**.

14. Ahmad FS, Luo Y, Wehbe RM, Thomas JD, Shah SJ. Advances in Machine Learning Approaches to Heart Failure with Preserved Ejection Fraction. *Heart Fail Clin* 2022; **18**(2): 287-300.

15. Erik B, Tien P, Chee Yee C, et al. Machine Learning/Artificial Intelligence for Sensor Data Fusion-Opportunities and Challenges. *IEEE Aerospace and Electronic Systems Magazine* 2021; **36**: 80-93, Institute of Electrical and Electronics Engineers Inc.

16. Li Y, Wu X, Yang P, Jiang G, Luo Y. Machine Learning Applications in Diagnosis, Treatment and Prognosis of Lung Cancer. *arXiv preprint arXiv:220302794 2022*.

17. Kohane IS, Aronow BJ, Avillach P, et al. What every reader should know about studies using electronic health record data but may be afraid to ask. *J Med Internet Res* 2021; **23**(3): e22219.

18. Afshin J, Jean Pierre P, Johanne M-P. Machine-learning-based patient-specific prediction models for knee osteoarthritis. *Nature Reviews Rheumatology* 2019; **15**: 49-60, pmid:30523334, Nature Publishing Group.

19. Andres C, Mary Anne H, Matthew S, et al. Machine-learning Prognostic Models from the 2014—16 Ebola Outbreak: Data-harmonization Challenges, Validation Strategies, and mHealth Applications. *EclinicalMedicine* 2019; **11**: 54-64, Lancet Publishing Group.

20. Luo Y, Ahmad FS, Shah SJ. Tensor factorization for precision medicine in heart failure with preserved ejection fraction. *J Cardiovasc Transl Res* 2017: 1-8.

21. Luo Y, Wang F, Szolovits P. Tensor factorization toward precision medicine. *Briefings in Bioinformatics* 2016.
22. Rasmussen L, Brandt P, Jiang G, et al. Considerations for Improving the Portability of Electronic Health Record-Based Phenotype Algorithms. Proceedings of 2019 AMIA Annual Symposium; 2019; 2019.

23. Zhong Y, Rasmussen L, Deng Y, et al. Characterizing design patterns of EHR-driven phenotype extraction algorithms. 2018 IEEE International Conference on Bioinformatics and Biomedicine (BIBM); 2018: IEEE; 2018. p. 1143-6.

24. Rasmussen LV, Hoell C, Smith ME, et al. Solutions for Unexpected Challenges Encountered when Integrating Research Genomics Results into the EHR. ACI Open 2020; 4(02): e132-e5.

25. Shang N, Liu C, Rasmussen LV, et al. Making work visible for electronic phenotype implementation: Lessons learned from the eMERGE network. J Biomed Inform 2019; 99: 103293.

26. Durrant-Whyte HF. Sensor models and multisensor integration. International Journal of Robotics Research 1988; 7: 97-113.

27. Dana L, Tulay A, Christian J. Multimodal Data Fusion: An Overview of Methods, Challenges, and Prospects. Proceedings of the IEEE 2015; 103: 1449-77. Institute of Electrical and Electronics Engineers Inc.

28. Wei C, Yungui H, Brendan B, Simon L. The utility of including pathology reports in improving the computational identification of patients. J Pathol Inform 2016; 7.

29. Yubraj G, Ramesh Kumar L, Goo Rak K. Prediction and Classification of Alzheimer’s Disease Based on Combined Features From Apolipoprotein-E Genotype, Cerebrospinal Fluid, MR, and FDG-PET Imaging Biomarkers. Front Comput Neurosci 2019; 13.

30. Xia An B, Xi H, Hao W, Yang W. Multimodal Data Analysis of Alzheimer's Disease Based on Clustering Evolutionary Random Forest. IEEE Journal of Biomedical and Health Informatics 2020; 24: 2973-83, pmid:32071013, Institute of Electrical and Electronics Engineers Inc.

31. Ariana A, Pamela KD, Wesley TK, et al. Non-negative matrix factorization of multimodal MRI, fMRI and phenotypic data reveals differential changes in default mode subnetworks in ADHD. Neuroimage 2014; 102: 207-19, pmid:24361664, Academic Press Inc.

32. Chao G, Luo Y, Ding W. Recent advances in supervised dimension reduction: A survey. Machine learning and knowledge extraction 2019; 1(1): 341-58.

33. Pillai PSLTY. Fusing Heterogeneous Data for Alzheimer's Disease Classification. Stud Health Technol Inform 2015; 216; 731-5.

34. Tao Z, Kim Han T, Xiaofeng Z, Dinggang S. Effective feature learning and fusion of multimodality data using stage-wise deep neural network for dementia diagnosis. Hum Brain Mapp 2019; 40: 1001-16, pmid:30381863, John Wiley and Sons Inc.

35. Robi P. Ensemble based systems in decision making. IEEE Circuits and Systems Magazine 2006; 6: 21-44.

36. Francesco C, Marwa M. Multimodal temporal machine learning for Bipolar Disorder and Depression Recognition. Pattern Analysis and Applications 2021.

37. Marx V. Method of the Year: spatially resolved transcriptomics. Nature methods 2021; 18(1): 9-14.

38. Zeng Z, Li Y, Li Y, Luo Y. Statistical and machine learning methods for spatially resolved transcriptomics data analysis. Genome Biol 2022; 23(1): 1-23.
39. Longo SK, Guo MG, Ji AL, Khavari PA. Integrating single-cell and spatial transcriptomics to elucidate intercellular tissue dynamics. *Nature Reviews Genetics* 2021; **22**(10): 627-44.
40. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Ann Intern Med* 2018; **169**: 467-73, pmid:30178033, American College of Physicians.
41. Janani V, Li T, Hamid Reza H, May DW. Multimodal deep learning models for early detection of Alzheimer’s disease stage. *Sci Rep* 2021; **11**.
42. Wenhuan Z, Anupam G, Daniel HH. On the application of advanced machine learning methods to analyze enhanced, multimodal data from persons infected with covid-19. *Computation* 2021; **9**: 1-15, MDPI AG.
43. Ming X, Liu O, Yan G, et al. Accurately Differentiating COVID-19, Other Viral Infection, and Healthy Individuals Using Multimodal Features via Late Fusion Learning. *J Med Internet Res* 2021; **28**.
44. Jayachitra VP, Nivetha S, Nivetha R, Harini R. A cognitive IoT-based framework for effective diagnosis of COVID-19 using multimodal data. *Biomedical Signal Processing and Control* 2021; **70**.
45. Hossm F, Maria H, Mohammad F, Haya E, Alaa A. An intelligent multimodal medical diagnosis system based on patients’ medical questions and structured symptoms for telemedicine. *Informatics in Medicine Unlocked* 2021; **23**.
46. Tommaso G, Giampaolo B, Elisabetta B, et al. SARS-COV-2 comorbidity network and outcome in hospitalized patients in Crema, Italy. *PLoS One* 2021; **16**.
47. Jordan Y, William Y, Philipp T. Multimodal skin lesion classification using deep learning. *Exp Dermatol* 2018; **27**: 1261-7, pmid:30187575, Blackwell Publishing Ltd.
48. Kai Z, Zhu Hong Y, Lei W, Yong Z, Li Ping L, Zheng Wei L. MLMDA: A machine learning approach to predict and validate MicroRNA-disease associations by integrating of heterogenous information sources. *J Transl Med* 2019; **17**.
49. Sivan K, Jacquelyn LM, Adi M-K, et al. Predicting risk for Alcohol Use Disorder using longitudinal data with multimodal biomarkers and family history: a machine learning study. *Mol Psychiatry* 2021; **26**: 1133-41, pmid:31595034, Springer Nature.
50. Mara Ten K, Alberto R, Enrico P, et al. MRI predictors of amyloid pathology: Results from the EMIF-AD Multimodal Biomarker Discovery study. *Alzheimer's Research and Therapy* 2018; **10**.
51. Isamu H, Hajime Y, Fumitaka I, et al. Radiogenomics predicts the expression of microRNA-1246 in the serum of esophageal cancer patients. *Sci Rep* 2020; **10**.
52. Jesus JC, Jianhua Y, Daniel JM. Enhancing image analytic tools by fusing quantitative physiological values with image features. *J Digit Imaging* 2012; **25**: 550-7, pmid:22246203.
53. Kevin Bretonnel C, Benjamin G, Hansel MG, et al. Methodological Issues in Predicting Pediatric Epilepsy Surgery Candidates through Natural Language Processing and Machine Learning. *Biomedical Informatics Insights* 2016; **8**: BII.S38308, SAGE Publications.
54. Weiming L, Qinquan G, Jiangnan Y, et al. Predicting Alzheimer’s Disease Conversion From Mild Cognitive Impairment Using an Extreme Learning Machine-Based Grading Method With Multimodal Data. *Front Aging Neurosci* 2020; **12**.
55. Micah C, Nils O, Scott C, et al. Predicting rehospitalization within 2 years of initial patient admission for a major depressive episode: a multimodal machine learning approach. *Translational Psychiatry* 2019; **9**.
56. Jongin K, Boreom L. Identification of Alzheimer’s disease and mild cognitive impairment using multimodal sparse hierarchical extreme learning machine. *Hum Brain Mapp* 2018; 39: 3728-41, pmid:29736986, John Wiley and Sons Inc.
57. Hélène De C, Federico C, Christophe JPS, et al. Wearable monitoring and interpretable machine learning can objectively track progression in patients during cardiac rehabilitation. *Sensors (Switzerland)* 2020; 20: 1-15, pmid:32604829, MDPI AG.
58. Tamer A, Shaker E-S, Jose MA. Robust hybrid deep learning models for Alzheimer’s progression detection. *Knowledge-Based Systems* 2021; 213.
59. Jeungchan L, Ishtiaq M, Jieun K, et al. Machine learning-based prediction of clinical pain using multimodal neuroimaging and autonomic metrics. *Pain* 2019; 160: 550-60, pmid:30540621, Lippincott Williams and Wilkins.
60. Uttam K, Goo Rak K, Horacio R-G. An Efficient Combination among sMRI, CSF, Cognitive Score, and APOE ϵ 4 Biomarkers for Classification of AD and MCI Using Extreme Learning Machine. *Computational Intelligence and Neuroscience*, pmid:32565773, Hindawi Limited 2020; 2020.
61. Bo C, Mingxia L, Heung Il S, Dinggang S, Daoqiang Z. Multimodal manifold-regularized transfer learning for MCI conversion prediction. *Brain Imaging and Behavior* 2015; 9: 913-26, pmid:25702248, Springer New York LLC.
62. Kevin H, Ulrike L, Markus M, Katja B-B. Separating generalized anxiety disorder from major depression using clinical, hormonal, and structural MRI data: A multimodal machine learning study. *Brain and Behavior* 2017; 7.
63. Fayao L, Luping Z, Chunhua S, Jianping Y. Multiple kernel learning in the primal for multimodal alzheimer’s disease classification. *IEEE Journal of Biomedical and Health Informatics* 2014; 18: 984-90, pmid:24132030, Institute of Electrical and Electronics Engineers Inc.
64. Diego C-B, Javier R, Fermín S, Francisco JM-M, Diego S-G, Juan MG. Robust Ensemble Classification Methodology for 1123-Ioflupane SPECT Images and Multiple Heterogeneous Biomarkers in the Diagnosis of Parkinson’s Disease. *Front Neuroinform* 2018; 12.
65. Yi Z, Hui P, Xiaocai Z, Zhixun Z, Jie Y, Jinyan L. Predicting adverse drug reactions of combined medication from heterogeneous pharmacologic databases. *BMC Bioinformatics* 2018; 19.
66. Chin Po C, Susan Shur Fen G, Chi Chun L. Toward differential diagnosis of autism spectrum disorder using multimodal behavior descriptors and executive functions. *Computer Speech and Language* 2019; 56: 17-35, Academic Press.
67. Paolo F, Massimo N, Monica B, et al. Combining macula clinical signs and patient characteristics for age-related macular degeneration diagnosis: A machine learning approach Retina. *BMC Ophthalmol* 2015; 15.
68. Benjamin DW, Hansel MG, Tracy AG, et al. Early identification of epilepsy surgery candidates: A multicenter, machine learning study. *Acta Neurol Scand* 2021; 144: 41-50, pmid:33769560, Blackwell Publishing Ltd.
69. Xia An B, Wenyuan Z, Lou L, Zhaoxu X. Detecting Risk Gene and Pathogenic Brain Region in EMCI Using a Novel GERF Algorithm Based on Brain Imaging and Genetic Data. *IEEE Journal of Biomedical and Health Informatics* 2021; 25: 3019-28, pmid:33750717, Institute of Electrical and Electronics Engineers Inc.
70. Prashanth R, Sumantra Dutta R, Pravat KM, Shantanu G. High-Accuracy Detection of Early Parkinson's Disease through Multimodal Features and Machine Learning. *Int J Med Inform* 2016; **90**: 13-21, pmid:27103193, Elsevier Ireland Ltd.

71. Ali A-M, Fernando P-G, Karan D, et al. Machine Learning for Localizing Epileptogenic-Zone in the Temporal Lobe: Quantifying the Value of Multimodal Clinical-Semiology and Imaging Concordance. *Frontiers in Digital Health* 2021; **3**.

72. Baiying L, Yingxia L, Changfeng D, et al. Assessment of liver fibrosis in chronic hepatitis B via multimodal data. *Neurocomputing* 2017; **253**: 169-76, Elsevier B.V.

73. Larry H, Renaid K, Neriman T, et al. Multimodal tensor-based method for integrative and continuous patient monitoring during postoperative cardiac care. *Artif Intell Med* 2021; **113**.

74. Ivo DD, Ben H, Ming T, et al. Predictive big data analytics: A study of Parkinson’s disease using large, complex, heterogeneous, incongruent, multi-source and incomplete observations. *PLoS One* 2016; **11**.

75. Eleftherios T, Ioannis S, Apostolos HK, Kostas M. Deep radiotranscriptomics of non-small cell lung carcinoma for assessing molecular and histology subtypes with a data-driven analysis. *Diagnostics* 2021; **11**.

76. Hua W, Feiping N, Heng H, Shannon LR, Andrew JS, Li S. Identifying disease sensitive and quantitative trait-relevant biomarkers from multidimensional heterogeneous imaging genetics data via sparse multimodal multitask learning. *Bioinformatics* 2012; **28**.

77. Xia B, Xi H, Yiming X, Hao W. A novel CERNNE approach for predicting Parkinson's Disease-associated genes and brain regions based on multimodal imaging genetics data. *Med Image Anal* 2021; **67**.

78. Vijay H, Bapu Koundinya D, Vaibhav R, Sakyajit B, Shourya R, Chandan KR. Predicting Complications in Critical Care Using Heterogeneous Clinical Data. *IEEE Access* 2016; **4**: 7988-8001, Institute of Electrical and Electronics Engineers Inc.

79. Wang H, Li Y, Khan SA, Luo Y. Prediction of breast cancer distant recurrence using natural language processing and knowledge-guided convolutional neural network. *Artif Intell Med* 2020; **110**: 101977.

80. Zeng Z, Yao L, Roy A, et al. Identifying Breast Cancer Distant Recurrences from Electronic Health Records Using Machine Learning. *Journal of Healthcare Informatics Research* 2019: 1-17.

81. Kautzky A, Vanicek T, Philippe C, et al. Machine learning classification of ADHD and HC by multimodal serotonergic data. *Translational Psychiatry* 2020; **10**.

82. Nhat Trung D, Tobias K, Francesco B, et al. Distinct multivariate brain morphological patterns and their added predictive value with cognitive and polygenic risk scores in mental disorders. *NeuroImage: Clinical* 2017; **15**: 719-31, pmid:28702349, Elsevier Inc.

83. Niha B, Jay P, Prateek P, et al. Radiogenomic analysis of hypoxia pathway is predictive of overall survival in Glioblastoma. *Sci Rep* 2018; **8**.

84. Jan CP, Tatyana G, Thomas P, et al. Combining multimodal imaging and treatment features improves machine learning-based prognostic assessment in patients with glioblastoma multiforme. *Cancer Medicine* 2019; **8**: 128-36, pmid:30561851, Blackwell Publishing Ltd.

85. Hao Z, Ken C, Harrison XB, et al. Machine learning reveals multimodal MRI patterns predictive of isocitrate dehydrogenase and 1p/19q status in diffuse low- and high-grade gliomas. *J Neurooncol* 2019; **142**: 299-307, pmid:30661193, Springer New York LLC.

86. Namyoung P, Eunjeong K, Minsu P, et al. Predicting acute kidney injury in cancer patients using heterogeneous and irregular data. *PLoS One* 2018; **13**.
87. Wei Liang T, Chee Kong C, Sim Heng O, Alvin Choong Meng N. Ensemble-based regression analysis of multimodal medical data for osteopenia diagnosis. *Expert Systems with Applications* 2013; **40**: 811-9.

88. Sébastien T, Yasser I-M, José María M-P, Alan CE, Louis De B. Defining a multimodal signature of remote sports concussions. *Eur J Neurosci* 2017; **46**: 1956-67, pmid:28512863, Blackwell Publishing Ltd.

89. Casper R, Evangelia G, Nicole CMV, et al. Preoperative risk stratification in endometrial cancer (ENDORISK) by a Bayesian network model: A development and validation study. *PLoS Med* 2020; **17**.

90. Huan Q, Xianling H, Junfeng Z, et al. Machine-learning radiomics to predict early recurrence in perihilar cholangiocarcinoma after curative resection. *Liver International* 2021; **41**: 837-50, pmid:33040701, Lippincott Williams and Wilkins.

91. Ramon C, Fang Chi H, Kaycee MS, et al. Alzheimer's disease risk assessment using large-scale machine learning methods. *PLoS One* 2013; **8**.

92. Gianluca B, Ulf N, Mustafa AM, et al. Multimodal Predictive Modeling of Endovascular Treatment Outcome for Acute Ischemic Stroke Using Machine-Learning. *Stroke* 2020: 3541-51, pmid:33040701, Lippincott Williams and Wilkins.

93. Aleksei T, Stefan K, Sita MAB-Z, et al. Multimodal Machine Learning-based Knee Osteoarthritis Progression Prediction from Plain Radiographs and Clinical Data. *Sci Rep* 2019; **9**.

94. Michael JD, Gerardo F, Richard S, et al. Development and validation of a novel automated Gleason grade and molecular profile that define a highly predictive prostate cancer progression algorithm-based test. *Prostate Cancer Prostatic Dis* 2018; **21**: 594-603, pmid:30087426, Nature Publishing Group.

95. Yiming X, Xiaohong L, Liyan P, et al. Explainable Dynamic Multimodal Variational Autoencoder for the Prediction of Patients with Suspected Central Precocious Puberty. *IEEE Journal of Biomedical and Health Informatics* 2021: 1-, Institute of Electrical and Electronics Engineers (IEEE).

96. Yanbo X, Siddharth B, Shriprasad RD, Kevin OM, Jimeng S. RAIM: Recurrent attentive and intensive model of multimodal patient monitoring data. *Proceedings of the ACM SIGKDD International Conference on Knowledge Discovery and Data Mining* 2018: 2565-73, Association for Computing Machinery.

97. Vaishnavi S, Minh ND, Tanveer S-M. Multimodal fusion of imaging and genomics for lung cancer recurrence prediction. 2020.

98. Yiwen M, William S, Michael KO, Corey WA. Bidirectional Representation Learning from Transformers Using Multimodal Electronic Health Record Data to Predict Depression. *IEEE Journal of Biomedical and Health Informatics* 2021; **25**: 3121-9, pmid:33661740, Institute of Electrical and Electronics Engineers Inc.

99. Li Y, Wang H, Luo Y. A Comparison of Pre-trained Vision-and-Language Models for Multimodal Representation Learning across Medical Images and Reports. 2020 IEEE International Conference on Bioinformatics and Biomedicine (BIBM); 2020 16-19 Dec. 2020; 2020. p. 1999-2004.

100. Rui Y, Fa Z, Xiaosong R, et al. Richer fusion network for breast cancer classification based on multimodal data. *BMC Med Inform Decis Mak* 2021; **21**.

101. Chowdhury S, Zhang C, Yu PS, Luo Y. Mixed Pooling Multi-View Attention Autoencoder for Representation Learning in Healthcare. *arXiv preprint arXiv:191006456* 2019.
102. Yixue H, Mohd U, Jun Y, Hossain MS, Ahmed G. Recurrent convolutional neural network based multimodal disease risk prediction. *Future Generation Computer Systems* 2019; 92: 76-83, Elsevier B.V.
103. Shinichi G, Keitaro M, Lauren B-N, et al. Artificial intelligence-enabled fully automated detection of cardiac amyloidosis using electrocardiograms and echocardiograms. *Nature Communications* 2021; 12.
104. Chowdhury S, Zhang C, Yu PS, Luo Y. Med2Meta: Learning Representations of Medical Concepts with Meta-Embeddings. *HEALTHINF*; 2020; 2020. p. 369-76.
105. Ilan S, Elizabeth TC, Lei H, et al. An unsupervised learning approach to identify novel signatures of health and disease from multimodal data. *Genome Med* 2020; 12.
106. Lei Y, Yalin W, Paul MT, Vaibhav AN, Jieping Y. Multi-source feature learning for joint analysis of incomplete multiple heterogeneous neuroimaging data. *Neuroimage* 2012; 61: 622-32, pmid:22498655.
107. Michele D, João MM, Massimiliano P, et al. Combining heterogeneous data sources for neuroimaging based diagnosis: re-weighting and selecting what is important. *Neuroimage* 2019; 195: 215-31, pmid:30894334, Academic Press Inc.
108. Perotte A, Ranganath R, Hirsch JS, Blei D, Elhadad N. Risk prediction for chronic kidney disease progression using heterogeneous electronic health record data and time series analysis. *J Am Med Inform Assoc* 2015; 22(4): 872-80.
109. Sara Bersche G, Takuma S, Stephen A, et al. A machine learning model to predict the risk of 30-day readmissions in patients with heart failure: A retrospective analysis of electronic medical records data. *BMCMed Inform Decis Mak* 2018; 18.
110. Alan DK, Qi C, Kadri Adivya M, et al. Mixture Model Framework for Traumatic Brain Injury Prognosis Using Heterogeneous Clinical and Outcome Data. *IEEE Journal of Biomedical and Health Informatics* 2021.
111. Xing T, Xiaopan X, Zhiping H, et al. Elaboration of a multimodal MRI-based radiomics signature for the preoperative prediction of the histological subtype in patients with non-small-cell lung cancer. *BioMedical Engineering Online* 2020; 19.
112. Xu Z, Chou J, Zhang XS, et al. Identification of Predictive Sub-Phenotypes of Acute Kidney Injury using Structured and Unstructured Electronic Health Record Data with Memory Networks. *Journal of Biomedical Informatics* 2019; 102: 103361.
113. Kathleen CF, Kristina Lundholm F, Marie E, Fredrik Ö, Dimitrios K. Predicting MCI status from multimodal language data using cascaded classifiers. *Front Aging Neurosci* 2019; 10.
114. Amir Hossein Y, Mohammad Saeid M, Goonmeet B, et al. Multimodal mental health analysis in social media. *PLoS One* 2020; 15.
115. Ye J, Yao L, Shen J, Janarthanam R, Luo Y. Predicting mortality in critically ill patients with diabetes using machine learning and clinical notes. *BMCMed Inform Decis Mak* 2020; 20(11): 1-7.
116. Xueyi Z, Zhao Y, Yini H, et al. Deep learning radiomics can predict axillary lymph node status in early-stage breast cancer. *Nature Communications* 2020; 11.
117. Juan Camilo V-C, Tomas A-V, Orozco-Arroyave JR, Björn E, Jochen K, Elmar N. Multimodal Assessment of Parkinson's Disease: A Deep Learning Approach. *IEEE Journal of Biomedical and Health Informatics* 2019; 23: 1618-30, pmid:30137018, Institute of Electrical and Electronics Engineers Inc.
118. Navodini W, Mobarakol I, Hongliang R. Radiogenomics model for overall survival prediction of glioblastoma. *Med Biol Eng Comput* 2020; 58: 1767-77, Springer.
119. Ping Z, Rong Z, Lun Y, et al. Deep-Learning Radiomics for Discrimination Conversion of Alzheimer's Disease in Patients With Mild Cognitive Impairment: A Study Based on 18F-FDG PET Imaging. *Front Aging Neurosci* 2021; 13.

120. Jae Hyun Y, Johanna Inhyang K, Bung Nyun K, Bumseok J. Exploring characteristic features of attention-deficit/hyperactivity disorder: findings from multi-modal MRI and candidate genetic data. *Brain Imaging and Behavior* 2020; 14: 2132-47, pmid:31321662, Springer.

121. Shin J, Li Y, Luo Y. Early Prediction of Mortality in Critical Care Setting in Sepsis Patients Using Structured Features and Unstructured Clinical Notes. 2021 IEEE International Conference on Bioinformatics and Biomedicine (BIBM); 2021: IEEE; 2021. p. 2885-90.

122. Cheng C, Qingmei Z, Bin Y, et al. Improving protein-protein interactions prediction accuracy using XGBoost feature selection and stacked ensemble classifier. *Comput Biol Med* 2020; 123.

123. Alan Baronio M, Carla Diniz Lopes B, Silvio Cesar C. Computer-aided diagnosis of hepatocellular carcinoma fusing imaging and structured health data. *Health Information Science and Systems* 2021; 9.

124. Haiyang Y, Li K, Feng Qiang X. Multimodal temporal-clinical note network for mortality prediction. *Journal of Biomedical Semantics* 2021; 12.

125. Cam Hao H, Thien H-T, Kiyoung K, et al. Bimodal learning via trilogy of skip-connection deep networks for diabetic retinopathy risk progression identification. *Int J Med Inform* 2019; 132.

126. Dongdong Z, Changchang Y, Jucheng Z, Xiaohui Y, Ping Z. Combining structured and unstructured data for predictive models: a deep learning approach. *BMC Med Inform Decis Mak* 2020; 20.

127. Yucheng T, Riqiang G, Ho Hin L, et al. Prediction of Type II Diabetes Onset with Computed Tomography and Electronic Medical Records. *Lecture Notes in Computer Science* 2020; 12445: 13-23, Springer Science and Business Media Deutschland GmbH.

128. Xiaosong W, Yifan P, Le L, Zhiyong L, Ronald MS. TieNet: Text-Image Embedding Network for Common Thorax Disease Classification and Reporting in Chest X-Rays. *Proceedings of the IEEE Computer Society Conference on Computer Vision and Pattern Recognition* 2018: 9049-58, IEEE Computer Society.

129. Zizhao Z, Pingjun C, Manish S, Lin Y. TandemNet: Distilling Knowledge from Medical Images Using Diagnostic Reports as Optional Semantic References. 2017; 10435: 320-8, Springer International Publishing.

130. Shaker E-S, Tamer A, Islam SMR, Kyung Sup K. Multimodal multitask deep learning model for Alzheimer's disease progression detection based on time series data. *Neurocomputing* 2020; 412: 197-215, Elsevier B.V.

131. Rui Y, Fei R, Xiaosong R, et al. Integration of Multimodal Data for Breast Cancer Classification Using a Hybrid Deep Learning Method. *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)* 2019; 11643: 460-9, Springer Verlag.

132. Batuhan B, Mehmet T. Improving clinical outcome predictions using convolution over medical entities with multimodal learning. *Artif Intell Med* 2021; 117.

133. Chao T, Baoyu L, Jun L, Zhigao Z. A Deep Automated Skeletal Bone Age Assessment Model with Heterogeneous Features Learning. *J Med Syst* 2018; 42.
134. Thomas L, Johann De J, Chao L, Victor K, Kathrin H, Holger F. An Explainable Multimodal Neural Network Architecture for Predicting Epilepsy Comorbidities Based on Administrative Claims Data. *Frontiers in Artificial Intelligence* 2021; 4.

135. Esra Z, Vince M, Ahmed K, et al. Multimodal fusion strategies for outcome prediction in Stroke. *HEALTHINF 2020 - 13th International Conference on Health Informatics, Proceedings; Part of 13th International Joint Conference on Biomedical Engineering Systems and Technologies, BIOSTEC 2020* 2020: 421-8, SciTePress.

136. Syed Arbaaz Q, Sriparna S, Mohammed H, Gael D, Erik C. Multitask Representation Learning for Multimodal Estimation of Depression Level. *IEEE Intelligent Systems* 2019; 34: 45-52, Institute of Electrical and Electronics Engineers Inc.

137. Solale T, Maryamossadat A, Mohammad E, et al. A distributed multitask multimodal approach for the prediction of Alzheimer's disease in a longitudinal study. *Neuroimage* 2020; 206.

138. Leon MA, Marzia AS, Andre FM, Daniel CA, Sebastien O, Andre A. Modeling longitudinal imaging biomarkers with parametric Bayesian multi-task learning. *Hum Brain Mapp* 2019; 40: 3982-4000, pmid:31168892, John Wiley and Sons Inc.

139. Rimma P, Adler JP, Edouard G, John A, Chris HW, Noémie E. Learning probabilistic phenotypes from heterogeneous EHR data. *Journal of Biomedical Informatics* 2015; 58: 156-65, pmid:26464024, Academic Press Inc.

140. Luo Y, Mao C, Yang Y, et al. Integrating Hypertension Phenotype and Genotype with Hybrid Non-negative Matrix Factorization. *Bioinformatics* 2019; 35(8): 1395-403.

141. Paris Alexandros L, Stephen JW, Lianne S, et al. Heterogeneity and Classification of Recent Onset Psychosis and Depression: A Multimodal Machine Learning Approach. *Schizophr Bull* 2021; 47: 1130-40, pmid:33543752, Oxford University Press.

142. Nikolaos K, Lana K-I, Stephan R, et al. Prediction Models of Functional Outcomes for Individuals in the Clinical High-Risk State for Psychosis or with Recent-Onset Depression: A Multimodal, Multisite Machine Learning Analysis. *JAMA Psychiatry* 2018; 75: 1156-72, pmid:30267047, American Medical Association.

143. Dongdong S, Minghui W, Ao L. A Multimodal Deep Neural Network for Human Breast Cancer Prognosis Prediction by Integrating Multi-Dimensional Data. *IEEE/ACM Trans Comput Biol Bioinform* 2019; 16: 841-50, Institute of Electrical and Electronics Engineers Inc.

144. Karen SA, Martin WS, Jonathan F, et al. A machine-learning framework for robust and reliable prediction of short- and long-term treatment response in initially antipsychotic-naïve schizophrenia patients based on multimodal neuropsychiatric data. *Translational Psychiatry* 2020; 10.

145. Sun M, Baron J, Dighe A, et al. Early Prediction of Acute Kidney Injury in Critical Care Setting Using Clinical Notes and Structured Multivariate Physiological Measurements. *Stud Health Technol Inform* 2019; 264: 368-72.

146. Dennis SR, Simuni T, Luo Y. A Predictive Model for Parkinson’s Disease Reveals Candidate Gene Sets for Progression Subtype. 2020 IEEE International Conference on Bioinformatics and Biomedicine (BIBM); 2020 16-19 Dec. 2020; 2020. p. 417-20.

147. Min C, Yixue H, Kai H, Lin W, Lu W. Disease Prediction by Machine Learning over Big Data from Healthcare Communities. *IEEE Access* 2017; 5: 8869-79, Institute of Electrical and Electronics Engineers Inc.
148. Md. Sirajul S., Ghada Z., Dmitry G., Rangachar K., Thao H., Yu S. Multimodal spatio-temporal deep learning approach for neonatal postoperative pain assessment. *Comput Biol Med* 2021; 129.

149. Jian X., Fei L., Diping S., et al. Multimodal Machine Learning Using Visual Fields and Peripapillary Circular OCT Scans in Detection of Glaucomatous Optic Neuropathy. *Ophthalmology* 2021; 129: 171-80, pmid:34339778, Elsevier Inc.

150. Dai Y., Yiqi Z., Yang W., Wenpu Z., Xiaoming H. Auxiliary diagnosis of heterogeneous data of Parkinson’s disease based on improved convolution neural network. *Multimedia Tools and Applications* 2020; 79: 24199-224, Springer.

151. Makoto N., Kunihiko K., Kunihiro N., et al. Accessory pathway analysis using a multimodal deep learning model. *Sci Rep* 2021; 11.

152. Keyang X., Mike L., Jingzhi P., et al. Multimodal Machine Learning for Automated ICD Coding. *Proceedings of Machine Learning Research* 2019; 106: 1-17.

153. Peng L., Dong Yue W., Ling C., et al. A radiogenomics signature for predicting the clinical outcome of bladder urothelial carcinoma. *Eur Radiol* 2020; 30: 547-57, pmid:31396730, Springer.

154. Md. Ashad A., Hui Yi L., Hong Wen D., Vince DC., Yu Ping W. A kernel machine method for detecting higher order interactions in multimodal datasets: Application to schizophrenia. *J Neurosci Methods* 2018; 309: 161-74, pmid:30184473, Elsevier B.V.

155. Jeremy AT., Kit ML., Marta IG. Multi-dimensional predictions of psychotic symptoms via machine learning. *Hum Brain Mapp* 2020; 41: 5151-63, pmid:32870535, John Wiley and Sons Inc.

156. Liuqing Y., Xifeng W., Qi G., et al. Deep Learning Based Multimodal Progression Modeling for Alzheimer’s Disease. *Statistics in Biopharmaceutical Research* 2021; 13: 337-43, Taylor and Francis Ltd.

157. Luo Y., Eran A., Palmer N., et al. A multidimensional precision medicine approach identifies an autism subtype characterized by dyslipidemia. *Nat Med* 2020; 26: 1375–9.

158. Yao L., Mao C., Luo Y. Clinical text classification with rule-based features and knowledge-guided convolutional neural networks. *BMC Med Inform Decis Mak* 2019; 19(3): 71.

159. Velupillai S., Suominen H., Liakata M., et al. Using clinical Natural Language Processing for health outcomes research: Overview and actionable suggestions for future advances. *J Biomed Inform* 2018; 88: 11-9.

160. Luo Y., Uzuner Ö., Szolovits P. Bridging semantics and syntax with graph algorithms—state-of-the-art of extracting biomedical relations. *Briefings in Bioinformatics* 2016; 18(1): 160-78.

161. Zeng Z., Deng Y., Li X., Naumann T., Luo Y. Natural Language Processing for EHR-Based Computational Phenotyping. *IEEE/ACM Trans Comput Biol Bioinform* 2018; 16(1): 139-53.

162. Nikolaos K., Dominic BD., Franziska D., et al. Multimodal Machine Learning Workflows for Prediction of Psychosis in Patients with Clinical High-Risk Syndromes and Recent-Onset Depression. *JAMA Psychiatry* 2021; 78: 195-209, pmid:33263726, American Medical Association.

163. Shih Cheng H., Anuj P., Roham Z., Imon B., Matthew PL. Multimodal fusion with deep neural networks for leveraging CT imaging and electronic health record: a case-study in pulmonary embolism detection. *Sci Rep* 2020; 10.
164. Shaker E-S, Jose MA, Islam SMR, Ahmad MS, Kyung Sup K. A multilayer multimodal detection and prediction model based on explainable artificial intelligence for Alzheimer’s disease. *Sci Rep* 2021; **11**.

165. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer’s Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology* 2010; **74**(3): 201-9.

166. Weinstein JN, Collisson EA, Mills GB, et al. The cancer genome atlas pan-cancer analysis project. *Nat Genet* 2013; **45**(10): 1113.

167. Christopher JK, Alan K, Mustafa S, Greg C, Dominic K. Key challenges for delivering clinical impact with artificial intelligence. *BMC Med* 2019; **17**.

168. Michael AM, Noel CFC, Stephen WD, et al. Results of the 2016 International Skin Imaging Collaboration International Symposium on Biomedical Imaging challenge: Comparison of the accuracy of computer algorithms to dermatologists for the diagnosis of melanoma from dermoscopic images. *J Am Acad Dermatol* 2018; **78**: 270-7.e1, pmid:28969863.

169. Jannin PGC, Gibaud B. Medical applications of NDT data fusion; 2001.

170. Guang Y, Qinghao Y, Jun X. Unbox the black-box for the medical explainable AI via multi-modal and multi-centre data fusion: A mini-review, two showcases and beyond. *Information Fusion* 2022; **77**: 29-52, Elsevier BV.

171. Radiological images and machine learning: Trends, perspectives, and prospects. *Comput Biol Med* 2019; **108**: 354-70, pmid:31054502, Elsevier Ltd.

172. David L, Enrico C, Jessica C, Parina S, Farah M. How machine learning is embedded to support clinician decision making: An analysis of FDA-approved medical devices. *BMJ Health and Care Informatics* 2021; **28**.

173. Luo Y, Szolovits P, Dighe AS, Baron JM. Using Machine Learning to Predict Laboratory Test Results. *Am J Clin Pathol* 2016; **145**(6): 778-88.

174. Thakur S, Choudhary J, Singh DP. A Survey on Missing Values Handling Methods for Time Series Data. Intelligent Systems: Springer; 2021: 435-43.

175. Luo Y, Szolovits P, Dighe AS, Baron JM. 3D-MICE: integration of cross-sectional and longitudinal imputation for multi-analyte longitudinal clinical data. *Journal of the American Medical Informatics Association (JAMIA)* 2017; **25**(6): 645-53.

176. Xue Y, Klabjan D, Luo Y. Mixture-based Multiple Imputation Model for Clinical Data with a Temporal Dimension. 2019 IEEE International Conference on Big Data (Big Data); 2019: IEEE; 2019. p. 245-52.

177. Cao W, Wang D, Li J, Zhou H, Li L, Li Y. Brits: Bidirectional recurrent imputation for time series. *arXiv preprint arXiv:180510572* 2018.

178. Luo Y. Evaluating the state of the art in missing data imputation for clinical data. *Briefings in Bioinformatics* 2022; **23**(1): bbab489.

179. Zhao Q, Adeli E, Pohl KM. Training confounder-free deep learning models for medical applications. *Nature communications* 2020; **11**(1): 1-9.

180. Luo Y, Mao C. ScanMap: Supervised Confounding Aware Non-negative Matrix Factorization for Polygenic Risk Modeling. Machine Learning for Healthcare Conference; 2020: PMLR; 2020. p. 27-45.

181. Donna MF, Todd PS, Michael S, et al. American Geriatrics Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 2019; **67**: 674-94, pmid:30693946, Blackwell Publishing Inc.
182. Nicole H, Tim S, Debra R, Samuel L, Jane LP. Opioid errors in inpatient palliative care services: A retrospective review. *BMJ Supportive and Palliative Care* 2018; 8: 175-9, pmid:29307863, BMJ Publishing Group.

183. Kalavathy R, Suresh RM. Pharmacovigilance from electronic medical records to report adverse events. *Journal of Chemical and Pharmaceutical Sciences* 2015; 2015-April: 188-91.

184. Luo Y, Thompson W, Herr T, et al. Natural Language Processing for EHR-Based Pharmacovigilance: A Structured Review. *Drug Saf* 2017; (doi: 10.1007/s40264-017-0558-6).

185. Segura Bedmar I, Martínez P, Herrero Zazo M. Semeval-2013 task 9: Extraction of drug-drug interactions from biomedical texts (ddiextraction 2013). 2013: Association for Computational Linguistics; 2013.

186. Hammann F, Drewe J. Data mining for potential adverse drug-drug interactions. *Expert Opinion on Drug Metabolism and Toxicology* 2014; 10(5): 665-71.

187. Luo Y, Wunderink RG, Lloyd-Jones D. Proactive vs Reactive Machine Learning in Health Care: Lessons From the COVID-19 Pandemic. *JAMA* 2022; 327(7): 623-4.

188. Ke G, Meng Q, Finley T, et al. LightGBM: A Highly Efficient Gradient Boosting Decision Tree. *Adv Neural Inf Process Syst* 2017; 30.

189. Derara Duba R, Taye Girma D, Achim I, Worku Gachena N. Diagnosis of diabetes mellitus using gradient boosting machine (Lightgbm). *Diagnostics* 2021; 11.

190. Xiaolei S, Mingxi L, Zeqian S. A novel cryptocurrency price trend forecasting model based on LightGBM. *Finance Research Letters* 2020; 32: 101084.

191. Dongzi J, Yiqin L, Jiancheng Q, Zhe C, Zhongshu M. SwiftIDS: Real-time intrusion detection system based on LightGBM and parallel intrusion detection mechanism. *Comput Secur* 2020; 97: 101984.

192. Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. *Science* 2019; 366(6464): 447-53.

193. Wang H, Li Y, Ning H, Wilkins J, Lloyd-Jones D, Luo Y. Using Machine Learning to Integrate Sociobehavioral Factors in Predicting Cardiovascular-Related Mortality Risk. *Stud Health Technol Inform* 2019; 264: 433-7.

194. Weissler EH, Tristan N, Tomas A, et al. The role of machine learning in clinical research: transforming the future of evidence generation. *Trials* 2021; 22.

195. Christof E. Open source software in industry. *IEEE Software* 2008; 25: 52-3.

196. Robert MS. Why develop open-source software? The role of non-pecuniary benefits, monetary rewards, and open-source licence type. *Oxford Review of Economic Policy* 2007; 23: 605-19, Oxford University Press (OUP).

197. Pratik S, Francis K, Sean K, et al. Artificial intelligence and machine learning in clinical development: a translational perspective. *npj Digital Medicine* 2019; 2.

198. Inna K, Simeon S. Interpretability of Machine Learning Solutions in Public Healthcare: The CRISP-ML Approach. *Frontiers in Big Data* 2021; 4.