Machine learning in rare disease

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Synopsis

(Instructions: Describe the background, basic structure of the article, list material to be covered indicating depth of coverage, how they are logically arranged, include recent pubs in the area, 300-500 words)

The advent of high-throughput profiling methods such as genomics, transcriptomics, and other technologies has accelerated basic research and made deep characterization of patient samples routine. These approaches provide a rich portrait of genes, cellular pathways, and cell types involved in complex phenotypes. Machine learning is often a perfect fit for extracting disease-relevant patterns from these high dimensional datasets. Often, machine learning methods require many samples to identify recurrent and biologically meaningful patterns. With rare diseases, biological specimens, and consequently data, are limited due to the rarity of the condition. In this perspective, we outline the challenges and emerging solutions for using machine learning in rare disease settings. We also note that precision medicine presents a similar challenge, in which a common disease is partitioned into small subsets of patients with shared etiologies and treatment strategies. Advances from rare disease research are likely to be highly informative for other applications as well, and we propose that the methods community should prioritize the development of machine learning techniques for rare disease research.

Introduction

Rare disease research is increasingly dependent on high-throughput profiling of samples and would greatly benefit from machine learning (ML) analytics. Machine learning algorithms are computational methods that can identify patterns in data, and can use information about these patterns to perform tasks (e.g., pick out important data points or predict outcomes when they are not yet known, among other tasks). A systematic review of application of ML in rare disease uncovered 211 human data studies that used ML to study 74 different rare diseases over the last 10 years [1]. Indeed, ML can be a powerful tool in biomedical research but it does not come without pitfalls [TODO: ref], some of which are magnified in a rare disease context. In this perspective, we will focus our discussion on considerations for two types of ML in the context of the study of rare diseases: supervised and unsupervised learning.

Supervised algorithms require training data with specific phenotype labels (e.g., responder vs. non-responder) and learn correlations of features with the phenotype labels to predict the phenotype labels of unseen or new test data (e.g., predicting which new patient would or would not respond to treatment). If the goal of a study is to classify patients with a rare disease into molecular subtypes based on high-throughput profiling, researchers would select a supervised ML algorithm to carry out this task. A supervised ML model is of limited utility if it can only accurately predict phenotype labels in the data it was trained on (this is called *overfitting*); instead, it's more beneficial to develop models that *generalize* or maintain performance when applied to new data that has not yet been "seen" by the model. In later sections, we'll discuss regularized models, a strategy for reducing overfitting that can be useful for rare disease datasets.

Unsupervised algorithms can learn patterns or features from *unlabeled* training data. Examples of unsupervised learning include principal component analyses (PCA), k-means or hierarchical clustering, or t-distributed stochastic neighbor embedding (t-SNE). In the absence of known molecular subtypes, unsupervised ML approaches can be applied to identify groups of samples that are similar and may have distinct patterns of pathway activation [TODO: ref]. Unsupervised approaches can also extract combinations of features (e.g., genes) that are indicative of a certain cell type or pathway. Often, too few samples (not enough data) leads to challenges in successfully training a model, or in identifying signals that are useful for biological discovery.

Though researchers strive to train useful and informative models, there are challenges inherent to applying ML to rare disease datasets. For example, training supervised models requires datasets where the phenotype labels have very little uncertainty (or "label-noise") [2] – termed "gold standard" datasets – but rare disease datasets often come with significant label-noise (e.g., *silver standard* datasets) due to limits in the current understanding of underlying biology and evolving clinical definitions of many rare diseases. Label-noise can decrease prediction accuracy and require larger samples sizes during training [3]. ML methods also benefit from using large datasets, but analyzing high dimensional data from rare diseases datasets that typically contain 20 to 99 samples is challenging [1,4]. Small datasets lead to a lack of statistical power and magnify the susceptibility of ML methods to misinterpretation and unstable performance.

While we expect ML in rare disease research to continue to increase in popularity, specialized computational methods that can learn patterns from small datasets and can generalize to newly acquired data are required for rare disease applications [5]. In this perspective, we first highlight ML approaches that address or better tolerate the limitations of rare disease data, and then discuss the future of ML applications in rare disease.

Constructing machine learning-ready rare disease datasets

High-throughput 'omic' data methods generate high-dimensional data or data with many features, regardless of the underlying disease or condition being assayed. A typical rare disease dataset is comprised of a small number of samples [1]. A lack of samples gives rise to the "curse of dimensionality" (i.e., few samples but many features), which can contribute to the poor performance of models [6] [TODO: reference new figure as appropriate #186]. More features often means increased missing observations (*sparsity*), more dissimilarity between samples (*variance*), and increased redundancy between individual features or combinations of features (*collinearity*) [7], all of which contribute to a challenging prediction problem.

If a small sample size compromises an ML model's performance, then two approaches can be taken to improve the outcome: 1) increase the number of samples to reduce sparsity, variance, and collinearity, 2) improve the quality of samples to account for sparsity, variance, and collinearity. In the first approach, appropriate training, evaluation, and held-out validation sets could be constructed by combining multiple small individual rare disease cohorts [TODO: Link to experimental design box #185]. In fact, this is often required for the study of rare diseases in the authors' experience. In doing so, special attention should be directed towards harmonization since data collection can differ from cohort to cohort. Without careful selection of aggregation methods, one may introduce technical variability into the aggregated dataset which can negatively impact the ML model's ability to learn or detect meaningful signal. Steps such as reprocessing the data using a single pipeline, using batch correction methods [8,9], and normalizing raw values [10] may be necessary to mitigate unwanted technical variability.

In the second approach, small but meaningfully generated datasets can greatly enhance the performance of ML models in the context of rare disease. Specifically, improving labeling of data is critical in accounting for sparsity and variance in the data. In our experience, collaboration with domain experts has proved to be critical in gaining insight into potential sources of variation in the datasets. An anecdotal example from the authors' personal experience: conversations with a rare disease clinician revealed that samples in a particular tumor dataset were collected using vastly different surgical techniques (laser ablation and excision vs. standard excision). This information was not readily available to non-experts, but was obvious to the clinician. Addition of this kind of important metadata or labels to the samples can greatly help ML models become more effective in extracting biologically relevant patterns. Such instances underline the fact that continuous collaboration with domain experts and the sharing of well-annotated data is needed to generate robust datasets in the future. Ideally, structure in the composite datasets under study will be aligned with variables of interest, such as phenotype labels if available; if instead samples from the same cohort tend to group together regardless of phenotype, revisiting the construction of the dataset is warranted. In the next section, we will discuss approaches that can aid in identifying and visualizing structure in datasets.

Box 1: Understanding experimental design of machine learning to inform requirements for data

Components of ML experiments

Machine learning algorithms identify patterns that explain or fit a given dataset. Every machine learning algorithm goes through a *training* phase where it identifies underlying patterns in a given dataset to create a "trained" algorithm (a *model*) , and a *testing* phase where the model applies the identified patterns to unseen data points. Typically, a machine learning algorithm is provided with the following fundamental parts as input: 1. a *training dataset* , 2. an *evaluation dataset* , 3. a *held-out validation dataset* . These input data can be images, text, numbers, or other types of data which are typically encoded as a numerical representation of the input data. A *training dataset* is used to expose the model to underlying patterns among the features present in the data of interest. An *evaluation dataset* is a small test dataset which is used during the training phase to help the model iteratively

update its parameters (i.e., *hyperparameter_tuning* or *model tuning*). In many cases, a large training set may be subdivided to form a smaller training dataset and the evaluation dataset, both of which are used to train the model (see next section for more details on cross-validation). In the testing phase, a new or unseen test dataset or *held-out validation set* is used to test whether the patterns learned by the model hold true in new data (are *generalizable*). While the evaluation dataset helps the model iteratively update its parameters to learn important patterns in the training data, the held-out validation set helps test the generalizability of the model. Generalizability of a model is its ability to recognize patterns that can help predict the class or an outcome for previously unseen data. High generalizability of a model on previously unseen data suggest that the model has identified fundamental patterns in the data that may also inform our knowledge regarding the question of interest for which the experiment was designed. Generalizability can be affected if *data leakage* occurs during training of the model, i.e., if a model is exposed to the same or similar data points in both the training set and the held-out test set. Ensuring absence of any overlap or relatedness among data points or samples (e.g., samples with familial relationship, samples from same patient) used in the training set and held-out test set is important to avoid *data leakage* during model training. Specifically in cases of rare genetic diseases where many samples can contain familial relationships, special care should be taken while crafting the training and testing sets to ensure that no data leakage occurs and the trained model has high generalizability.

Training and testing

The implementation of a machine learning experiment begins with splitting a single dataset of interest such that 90% of the data is used for training (generally subdivided into the *training dataset* and the *evaluation dataset*), and remaining 10% of the data is used for testing or validation (as the *held-out validation dataset*). This makes sure that all the datasets involved in training and testing a model maintain uniformity in the features. In case of rare diseases where multiple datasets may be combined to make a large enough training dataset, special care is taken to standardize the features and the patterns therein. The iterative training stage helps the model learn important patterns in the training dataset and then use the evaluation dataset to test for errors in prediction and update its learning parameters (*hyperparameter tuning*). The method by which the evaluation dataset tests the performance of the trained model and helps update the hyperparameters is called *cross-validation*. To maximally utilize the available data for cross-validation, there can be multiple approaches to form the training and evaluation datasets e.g. leave-p-out cross-validation, leave-one-out cross-validation, k-fold cross-validation, Monte-Carlo random subsampling cross-validation [11]. In case of k-fold cross-validation, a given dataset is shuffled randomly and split into *k* parts. One of the *k* parts is reserved as the *evaluation dataset* and the rest are cumulatively used as the *training dataset*. In the next iteration, a different part is used as the *evaluation dataset*, while the rest are used for training. Once the model has iterated through all *k* parts of the training and evaluation datasets, it is ready to be tested on the *held-out validation* dataset.

The held-out validation dataset is exposed to the model only once to estimate the accuracy of the model. High accuracy of a model on the training dataset but low accuracy on the held-out dataset is a sign that the model has become overfit to the training set and has low generalizability. If this is encountered, the experimenter is advised to revisit the dataset construction to make sure they meet the best practices outlined above.

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Figure 1: Combining datasets to increase training data

Learning representations from rare disease data

Dimensionality reduction methods can help 'compress' information from a large number of features into a smaller number of features in an unsupervised manner [12,13,14] (Figure 1C). An example of a method that is commonly used for dimensionality reduction is principal components analysis (PCA). PCA identifies new features or dimensions, termed principal components (PCs), that are combinations of original features. The PCs are calculated in a way that maximizes the amount of information (*variance*) they contain and ensures that each PC is uncorrelated with the other PCs [13]. In practice, researchers often use the first few PCs to reduce the dimensionality without removing what may be important or informative variability in the data, though PCs are obtained without regard for labels (e.g., disease vs. control or dataset of origin). Beyond reducing the number of features in various types of data [16,17], dimensionality reduction can also be used to visualize structure or artifacts in the data (e.g., [18]), to define sample subgroups (e.g., [19], or for feature selection and extraction during application of specific machine learning models [20] (Figure 1D).

Methods like PCA, multidimensional scaling (MDS), t-distributed stochastic neighbor embedding (t-SNE), and uniform manifold approximation and projection (UMAP) can help researchers successfully identify useful patterns in the original data, though t-SNE and UMAP may require adjusting the hyperparameters – values used to set up a model that can be specified by a user, rather than learned from the data – that may effect the output [14,21]. Testing multiple dimensionality reduction methods, rather than a single method, may be necessary to obtain a more comprehensive portrait of the data [22]. Nguyen and Holmes discuss additional important considerations for using dimensionality reduction methods such as selection criteria and interpretation of results [23]. Beyond dimensionality reduction, other unsupervised learning approaches such as k-means clustering or hierarchical clustering have been used to characterize the structure present in genomic or imaging data [24,25].

Representation learning approaches, of which dimensionality reduction methods are a subset, learns low-dimensional representations (composite features) from the raw data. For example, representation learning through matrix factorization can extract features from transcriptomics datasets that are made of combinations of gene expression values found in the training data [26], and use them to interpret test data [22,27]. To ensure that the learned representations are generalizable to other data, the features learned by the model can be constrained through methods like regularization [28]. Representation learning generally requires many samples when applied to complex biological systems and therefore may appear to aggravate the curse of dimensionality. However, it can be a powerful tool to learn low-dimensional patterns from large datasets and then find those patterns in smaller, related datasets. In later sections, we will discuss this method of leveraging large datasets to reduce dimensionality in smaller datasets, also known as feature-representation-transfer learning.

Figure 2: Representation learning can extract useful features from high dimensional data. a) The data (e.g., transcriptomic data) are highly dimensional, having thousands of features (displayed as Fa-Fz). Samples come from two

separate classes (purple and green row annotation). b) In the original feature space, Fa and Fb do not separate the two classes (purple and green) well. c) A representation learning approach learns new features (e.g., New Feature 1, a combination of Fa, Fb …. Fz, and New Feature 2, a different combination of Fa, Fb …. Fz). New Feature 2 distinguishes class, whereas New Feature 1 may capture some other variable such as batch (not represented). New features from the model can be used to interrogate the biology of the input samples, develop classification models, or use other analytical techniques that would have been more difficult with the original dataset dimensions.

Reducing misinterpretation of model output with statistical techniques

Machine learning methods are generally accompanied by a few critical assumptions. First, ML methods often work best on datasets that contain equal number of samples for all categories (no "class imbalance"). Second, the dataset is complete; all samples have measurements for all variables in the dataset (i.e., the dataset is not "sparse", meaning that it is not missing data for some samples). Third, there is no ambiguity about the labels for the samples in the dataset (i.e. no "label-noise").

Rare disease datasets, however, violate many of these assumptions. There is generally a high *class imbalance* due to small number of samples for specific classes (e.g., only a few patients with a particular rare disease in a health records dataset), the data are often *sparse,* and there may be abundant *label-noise* due to incomplete understanding of the disease. All of these contribute to low signal to noise ratio in rare disease datasets. Thus, applying ML to rare disease data without any accommodations for the above shortcomings may lead to models that lack stability required for reproducibility or simplicity required for interpretation. In this section, we highlight a few ML techniques that can help manage the challenges in applying ML models applied to rare disease data.

Class imbalance in datasets can be addressed using decision tree-based ensemble learning methods (Figure[3]A-B) to increase the stability of ML predictions. Random forests use resampling (with replacement) based techniques to form a consensus about the important predictive features identified by the decision trees[30,31,32,33,34]. Additional approaches like combining random forests with resampling without replacement can generate confidence intervals for the model predictions by iteratively exposing the models to incomplete datasets, mimicking real world cases where most rare disease datasets are incomplete [35]. Resampling approaches are most helpful in constructing confidence intervals for algorithms that generate the same outcome every time they are run (i.e., deterministic models). For decision trees that choose features at random for selecting a path to the outcome (i.e., are non-deterministic), resampling approaches can be helpful in determining robustness or stability of the model.

Recent studies suggest that there are limitations to decision tree-based ensemble methods when applied to rare disease datasets, leading to adoption of cascade learning, a variant of ensemble learning [36,37]. In cascade learning, multiple methods leveraging distinct underlying assumptions are used in tandem to capture stable patterns existing in the dataset [**???**,38,39]. For example, a cascade learning approach for identifying rare disease patients from electronic health record data utilized independent steps for feature extraction (word2vec [40]), followed by preliminary prediction with ensembled decision trees, and then prediction refinement using data similarity metrics [37]. Combining these three unrelated methods resulted in better overall prediction when implemented on a silver standard dataset, than other methods applied in isolation. In addition to cascade learning, other approaches that better represent rare classes like inverse class weighting and oversampling [doi:10.1613/jair.953] may also improve ML models that use rare disease data.

The presence of label-noise and sparsity in the data can also lead to overfitting of models to the training data, meaning that the models show high prediction accuracy on the training data but low prediction accuracy (and large prediction errors) on new evaluation data. Overfit models tend to rely on variables that are unique to the training data (for example, the calibration of the instrument that

was used to generate the training data), and not generalizable to new data (e.g., data generated on the same instrument that has been recalibrated). [41] In such cases, regularization can not only protect ML models from poor generalizability caused by overfitting, but also reduce model complexity by reducing the feature space available for training. (Figure[3]C) Regularization is an approach by which a penalty is added to the model to avoid making large prediction errors. Some examples of regularization approaches include ridge regression, LASSO regression, and Elastic-net regression, among others. Regularization is often used in rare variant discovery and immune cell signature discovery studies which are useful examples that also need to accommodate sparsity of data like rare diseases. For example, among various regularization methods hybrid applications of LASSO for capturing combinations of rare and common variants associated with specific traits have proven beneficial [42]. In this example, applying LASSO regularization reduced the number of common variants included as features in the final analysis generating a simpler model while reducing error in the association of common and rare variants with a specific trait. In the context of rare immune cell signature discovery, variations of elastic-net regression were found to outperform other regression approaches [43,44,45]. Thus regularization methods like LASSO or elastic-net have been methods of choice while working with rare observations.[28] Furthermore, in applications of neural network based methods on data from rare diseases like acute myeloid luekemia (AML) or tuberous sclerosis (TS), other methods of regularization like Kullback–Leibler divergence (KL divergence) and dropout have been used respectively. In a study using a variational auto encoder (VAE) for dimensionality reduction in gene expression data from AML samples, the KL divergence between the input data and its low dimensional representation provided the regularizing penalty for the model.[46,47] In a study using a convolutional neural network (CNN) to identify tubers in MRI images from TS patients, overfitting was minimized using the dropout method which removed randomly chosen network nodes in each iteration of the CNN model generating simpler models in each iteration.[48] Thus depending on the learning method of choice, use of appropriate regularization approaches should be considered when working with rare disease datasets.

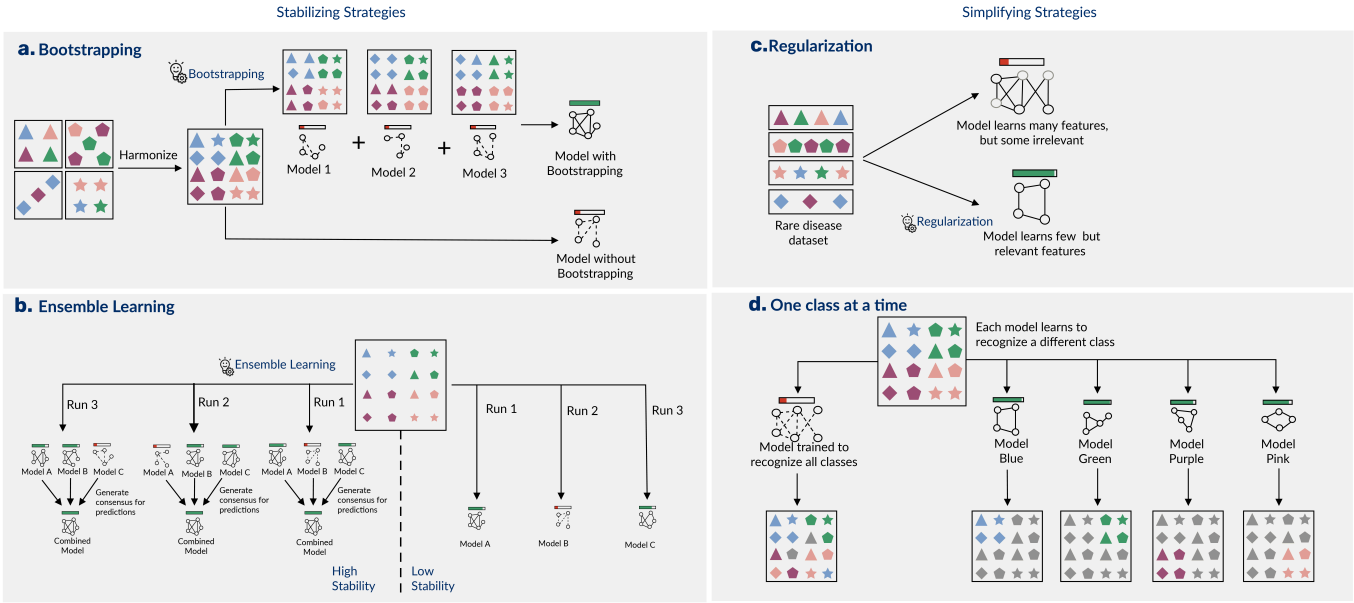

Figure 3: OLD FIGURE (new figure still WIP) Strategies to simplify models and stabilize predictions preserve the value of machine learning in rare disease. A-B) Strategies to build confidence in model predictions; A) A schematic showing the concept of bootstrap, B) A schematic showing the concept of ensemble learning to converge on reliable models; C-D) Strategies to simplify models by penalizing complexity in ML models; C) A schematic showing the concept of regularization to selectively learn relevant features, D) A schematic showing the concept of one-class-at-a-time learning to select few features at a time. Horizontal bars represent health of a model, models are represented as a network of nodes (features) and edges (relationships), nodes with solid edges represent real patterns, nodes with broken edges represent spurious patterns

Build upon prior knowledge and indirectly related data

Rare diseases often lack large, normalized datasets, limiting our ability to study key attributes of these diseases. One strategy to overcome this is to integrate and explore rare disease information alongside other knowledge by combining a variety of different data types. By using several data modalities (such as curated pathway, genetic data, or other data types), it may be possible to gain a better understanding of rare diseases (e.g., identifying novel genotype-phenotype relationships or opportunities for drug repurposing). Knowledge graphs (KGs) which integrate related-but-different data types, create a rich multimodal data source (e.g., Monarch Graph Database [49], hetionet [50], PheKnowLator [51], and the Global Network of Biomedical Relationships [52], Orphanet [53]). These graphs connect genetic, functional, chemical, clinical, and ontological data to enable the exploration of relationships of data with disease phenotypes through manual review [54] or computational methods [55,56]. (Figure[??]a) KGs may include links or nodes that are specific to the rare disease of interest (e.g., an FDA approved treatment would be a specific disease-compound link in the KG) as well as links that are more generalized (e.g., gene-gene interactions noted in the literature for a different disease).

Rare disease researchers can repurpose general (i.e., not rare disease-specific) biological or chemical knowledge graphs to answer rare disease-based research questions [57]. There are a variety of tactics to sift through the large amounts of complex data in knowledge graphs. One such tactic is to calculate the distances between nodes of interest (e.g., diseases and drugs to identify drugs for repurposing in rare disease [57]); this is often done by determining the "embeddings" (linear representations of the position and connections of a particular point in the graph) for nodes in the knowledge graph, and calculating the similarity between these embeddings. Testing a variety of different methods to calculate node embeddings that can generate actionable insights for rare diseases is an active area of research [57], and an opportunity for continued research. Another application of KGs is to augment or refine a dataset [58]. For example, Li et. al.[56] used a KG to identify linked terms in a medical corpus from a large number of patients, some with rare disease diagnoses. They were able to augment their text dataset by identifying related terms in the clinical text to map them to the same term - e.g., mapping "cancer" and "malignancy" in different patients to the same clinical concept. With this augmented and improved dataset, they were able to train and test a variety of text classification algorithms to identify rare disease patients within their corpus. Finally, another possible tactic for rare disease researchers is to take a knowledge graph, or an integration of several knowledge graphs, and apply neural network-based algorithms optimized for graph data, such as a graph convolutional neural network. Rao and colleagues [59] describe the construction of a KG using phenotype information (Human Phenotype Ontology) and rare disease information (Orphanet) and curated gene interaction/pathway data (Lit-BM-13, WikiPathways) [TODO: citations for other resources - HPO, etc]. They then trained a spectral graph convolution neural network on this KG to identify and rank potentially causal genes for the Orphanet rare diseases, and were able to use this model to predict causal genes for a ground truth dataset of rare diseases with known causal genes. While several groups have already published on the use of KGs to study rare diseases, we expect that the growth of multi-modal datasets and methods to analyze KGs will make them a more popular and important tool in the application of ML in rare disease.

Another approach that builds on prior knowledge and large volumes of related data is transfer learning. Transfer learning leverages shared features, e.g., normal developmental processes that are aberrant in disease or an imaging anomaly present in both rare and common diseases, to advance our understanding of rare diseases. Transfer learning, where a model trained for one task or domain (source domain) is applied to another related task or domain (target domain), can be supervised or unsupervised. Among various types of transfer learning, feature-representation-transfer approaches learn representations from the source domain and apply them to a target domain [60] (Figure[??]b). That is, representation learning, as discussed in an earlier section, does not need to be applied only to describe the dataset on which the algorithm was trained – it can also be used to elucidate signals in

sufficiently similar data. For instance, low-dimensional representations can be learned from tumor transcriptomic data and transferred to describe patterns associated with genetic alterations in cell line data [22]. In the next section, we will summarize specific instances of applying transfer learning, along with other techniques described herein, to the study of rare diseases.

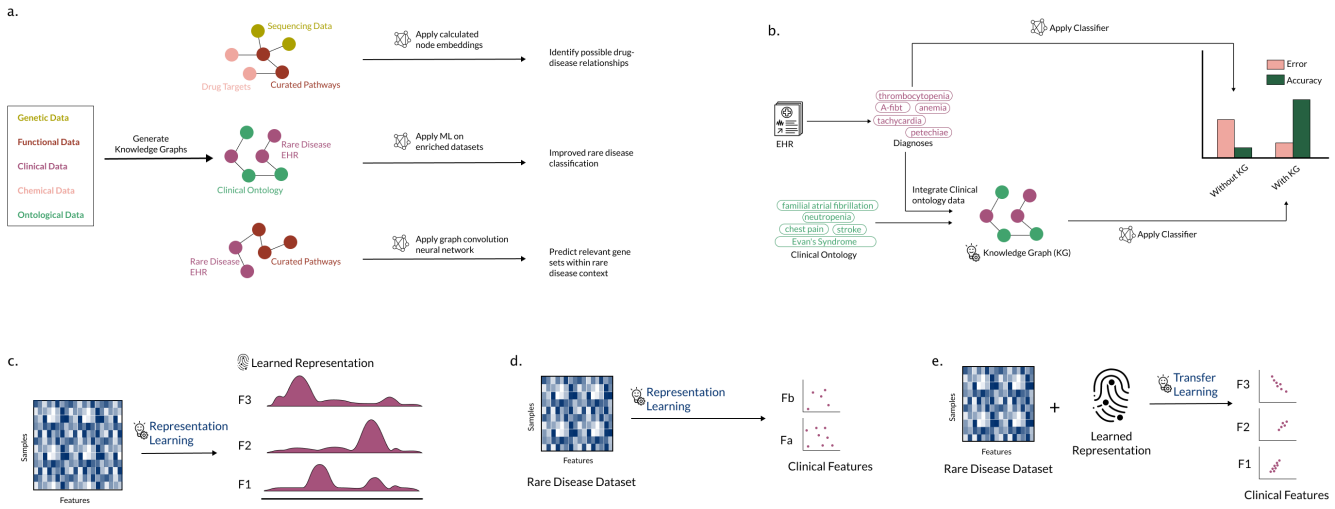

Figure 4: Strategies that build upon prior knowledge help ML models learn patterns in rare disease datasets. A) Knowledge graphs integrate different data types and may allow models to learn from connections that are rare disease-specific or happen in many biomedical contexts. B) Transfer learning is when a model trained in for one task or domain is applied to another, related task.

Combining approaches is required for the successful application of machine learning to rare diseases

We have described multiple approaches for maximizing the success of ML applications in rare disease, but it is rarely sufficient to use any of these techniques in isolation. Below, we highlight two recent works in the rare disease domain that draw on concepts of feature-representation-transfer, use of prior data, and regularization.

A large public dataset of acute myeloid leukemia (AML) patient samples with no drug response data and a small *in vitro* experiment with drug response data form the basis of our first example [61]. Training an ML model on the small *in vitro* dataset alone faced the *curse of dimensionality* and the dataset size prohibited representation learning. Dincer et al. trained a variational autoencoder on the large AML patient dataset (VAE; see definitions) to learn meaningful representations in an approach termed DeepProfile [46] (Figure[5]a). The representations or *encodings* learned by the VAE were then *transferred* to the small *in vitro* dataset reducing it's number of features from thousands to eight, and improving the performance of the final LASSO linear regression model. In addition to improvement in performance, the *encodings* learned by the VAE captured more biological pathways than PCA, which may be attributable to the constraints on the encodings imposed during the training process (see definitions). Similar results were observed for prediction of histopathology in another rare cancer dataset [46].

While DeepProfile was centered on training on an individual disease and tissue combination, some rare diseases affect multiple tissues that a researcher may be interested in studying together for the purpose of biological discovery. Studying multiple tissues poses significant challenges and a cross-tissue analysis may require comparing representations from multiple models. Models trained on a low number of samples may learn representations that "lump together" multiple biological signals, reducing the interpretability of the results. To address these challenges, Taroni et al. trained a

Pathway-Level Information ExtractoR (PLIER) (a matrix factorization approach that takes prior knowledge in the form of gene sets or pathways) on a large generic collection of human transcriptomic data [62]. PLIER used constraints (regularization) that learned *latent variables* aligned with a small number of input gene sets, making it suitable for biological discovery or description of rare disease data. The authors *transferred* the representations or *latent variables* learned by the model to describe transcriptomic data from the unseen rare diseases antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and medulloblastoma in an approach termed MultiPLIER [63]. (Figure[5]b) MultiPLIER used one model to describe multiple datasets instead of reconciling output from multiple models, thus making it possible to identify commonalities among disease manifestations or affected tissues.

DeepProfile [46] and MultiPLIER [63] exemplify modeling approaches that can incorporate prior knowledge – thereby constraining the model space according to plausible or expected biology – or that can share information across datasets. These two methods capitalize on the fact that similar biological processes are observed across different biological contexts and that the methods underlying the approaches can effectively learn about those processes.

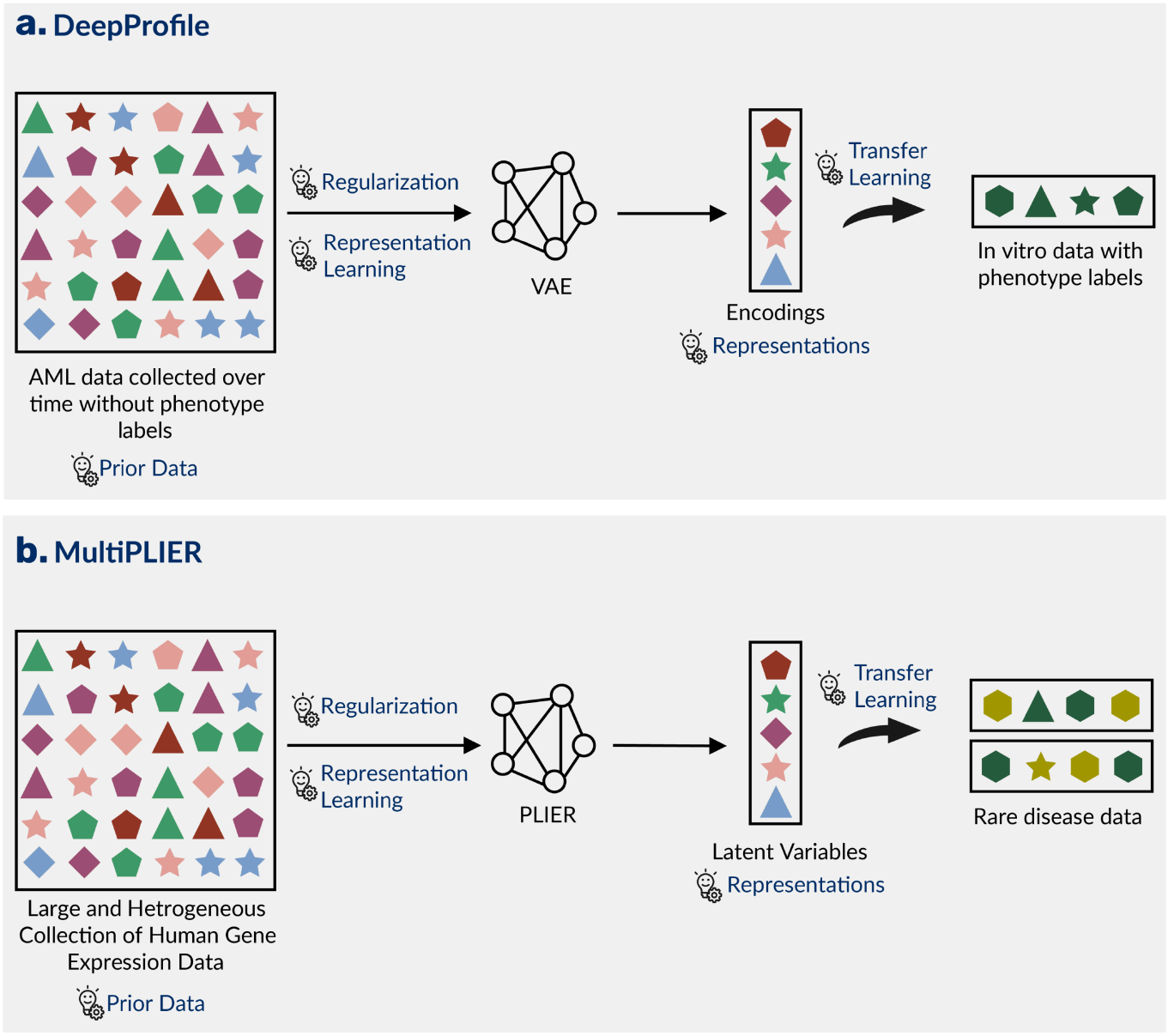

Figure 5: Combining multiple strategies strengthens the performance of ML models in rare disease. A) The authors of DeepProfile trained a variational autoencoder (VAE) to learn a representation from acute myeloid leukemia data without phenotype labels, transferred those representations to a small dataset with phenotype labels, and found that it improved prediction performance [46]. B) The authors of MultiPLIER trained a Pathway-Level Information ExtractoR

(PLIER) model on a large, heterogeneous collection of expression data and transferred the representations to multiple datasets from unseen rare diseases [62].

Outlook

Throughout this perspective, we highlighted various challenges in applying ML methods to rare disease data as well as examples of approaches that address these challenges. Small sample size, while significant, is not the only roadblock towards application of ML in rare disease data. The high dimensionality of modern data requires creative approaches, such as learning new representations of the data, to manage the curse of dimensionality. Leveraging prior knowledge and transfer learning methods to appropriately interpret data is also required. Furthermore, we posit that researchers applying machine learning methods on rare disease data should use techniques that increase confidence (i.e., bootstrapping) and penalize complexity of the resultant models (i.e., regularization) to enhance the generalizability of their work.

All of the approaches highlighted in this perspective come with weaknesses that may undermine investigators' confidence in using these techniques for rare disease research. We believe that the challenges in applying ML to rare disease are opportunities for data generation and method development going forward. In particular, we identify the following two areas as important for the field to explore to increase the utility of machine learning in rare disease.

Emphasis on not just "more n" but "more meaningful n"

Mindful addition of data is key for powering the next generation of analysis in rare disease data. While there are many techniques to collate rare data from different sources, low-quality data may hurt the end goal even if it adds to the size of the dataset. In our experience, collaboration with domain experts has proved to be critical in gaining insight into potential sources of variation in the datasets. An anecdotal example from the authors' personal experience: conversations with a rare disease clinician revealed that samples in a particular tumor dataset were collected using vastly different surgical techniques (laser ablation and excision vs standard excision). This information that was not readily available to non-experts, but was obvious the clinician. Such instances underline the fact that continuous collaboration with domain experts and the sharing of well-annotated data is needed to generate robust datasets in the future.

In addition to sample scarcity, there is a dearth of comprehensive phenotypic-genotypic databases in rare disease. While rare disease studies that collect genomic and phenotypic data are becoming more common [64,65,66], an important next step is to develop comprehensive genomics-based genotype-phenotype databases that prioritize clinical and genomics data standards in order to fuel interpretation of features extracted using ML methods. Finally, mindful sharing of data with proper metadata and attribution to enable prompt data reuse is of utmost important in building datasets that can be of great value in rare disease [67].

Development of methods that reliably support mechanistic interrogation of specific rare diseases

The majority of ML methods for rare disease that we have investigated are applied to classification tasks. Conversely, we've found few examples of methodologies that interrogate biological mechanisms of rare diseases. This is likely a consequence of a dearth of methods that can tolerate the constraints imposed by rare disease research such as phenotypic heterogeneity and limited data. An intentional push towards developing methods or analytical workflows that address this will be critical to apply machine learning approaches to rare disease data.

Method development with rare disease applications in mind requires the developers to bear the responsibility of ensuring that the resulting model is trustworthy. The field of natural language

processing has a few examples of how this can be achieved [68]. One way to increase trust in a developed model is by helping users understand the behavior of the developed model through providing explanations regarding why a certain model made certain predictions [68]. Another approach is to provide robust *error analysis* for newly developed models to help users understand the strengths and weaknesses of a model [69,70,71]. Adoption of these approaches into biomedical ML is quickly becoming necessary as machine learning approaches become mainstream in research and clinical settings.

Finally, methods that can reliably integrate disparate datasets will likely always remain a need in rare disease research. To facilitate such analyses in rare disease, methods that rely on finding structural correspondences between datasets ("anchors") may be able to transform the status-quo of using machine learning methods in rare disease [72,73,74]. We speculate that this an important and burgeoning area of research, and we are optimistic about the future of applying machine learning approaches to rare diseases.

Definitions

VAE:

Variational Autoencoders or VAEs are unsupervised neural networks that use hidden layers to learn or encode representations from available data while mapping the input data to the output data. VAEs are distinct from other autoencoders since the distribution of the encodings are regularized such that they are close to a normal distribution, which may contribute to learning more biologically relevant signals [22].

References

1. **The use of machine learning in rare diseases: a scoping review**
   Julia Schaefer, Moritz Lehne, Josef Schepers, Fabian Prasser, Sylvia Thun
   Orphanet Journal of Rare Diseases (2020-12) https://doi.org/ghb3wx
   DOI: 10.1186/s13023-020-01424-6 · PMID: 32517778 · PMCID: PMC7285453

2. **Learning statistical models of phenotypes using noisy labeled training data**
   Vibhu Agarwal, Tanya Podchiyska, Juan M Banda, Veena Goel, Tiffany I Leung, Evan P Minty, Timothy E Sweeney, Elsie Gyang, Nigam H Shah
   Journal of the American Medical Informatics Association (2016-11-01) https://doi.org/f9bxf9
   DOI: 10.1093/jamia/ocw028 · PMID: 27174893 · PMCID: PMC5070523

3. **Classification in the Presence of Label Noise: A Survey**
   Benoit Frenay, Michel Verleysen
   IEEE Transactions on Neural Networks and Learning Systems (2014-05) https://doi.org/f5zdgq
   DOI: 10.1109/tnnls.2013.2292894 · PMID: 24808033

4. https://www.fda.gov/media/99546/download

5. **Looking beyond the hype: Applied AI and machine learning in translational medicine**
   Tzen S. Toh, Frank Dondelinger, Dennis Wang
   EBioMedicine (2019-09) https://doi.org/gg9dcx
   DOI: 10.1016/j.ebiom.2019.08.027 · PMID: 31466916 · PMCID: PMC6796516

6. **The properties of high-dimensional data spaces: implications for exploring gene and protein expression data**
   Robert Clarke, Habtom W. Ressom, Antai Wang, Jianhua Xuan, Minetta C. Liu, Edmund A. Gehan, Yue Wang
   Nature Reviews Cancer (2008-01) https://doi.org/ffksnf
   DOI: 10.1038/nrc2294 · PMID: 18097463 · PMCID: PMC2238676

7. **The curse(s) of dimensionality**
   Naomi Altman, Martin Krzywinski
   Nature Methods (2018-06) https://doi.org/ghrqhp
   DOI: 10.1038/s41592-018-0019-x · PMID: 29855577

8. **Adjusting batch effects in microarray expression data using empirical Bayes methods**
   W. Evan Johnson, Cheng Li, Ariel Rabinovic
   Biostatistics (2007-01-01) https://doi.org/dsf386
   DOI: 10.1093/biostatistics/kxj037 · PMID: 16632515

9. **svaseq: removing batch effects and other unwanted noise from sequencing data**
   Jeffrey T. Leek
   Nucleic Acids Research (2014-12-01) https://doi.org/f8k8kf
   DOI: 10.1093/nar/gku864 · PMID: 25294822 · PMCID: PMC4245966

10. **A scaling normalization method for differential expression analysis of RNA-seq data**
    Mark D Robinson, Alicia Oshlack
    Genome Biology (2010) https://doi.org/cq6f8b
    DOI: 10.1186/gb-2010-11-3-r25 · PMID: 20196867 · PMCID: PMC2864565

11. **Applied Predictive Modeling**
Max Kuhn, Kjell Johnson
Springer New York (2013) https://doi.org/c432
DOI: 10.1007/978-1-4614-6849-3 · ISBN: 9781461468486

12. **Handbook of Data Visualization**
Chun-houh Chen, Wolfgang Härdle, Antony Unwin
Springer Berlin Heidelberg (2008) https://doi.org/ckmkfp
DOI: 10.1007/978-3-540-33037-0 · ISBN: 9783540330363

13. **Principal component analysis: a review and recent developments**
Ian T. Jolliffe, Jorge Cadima
Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences (2016-04-13) https://doi.org/gcsfk7
DOI: 10.1098/rsta.2015.0202 · PMID: 26953178 · PMCID: PMC4792409

14. **UMAP: Uniform Manifold Approximation and Projection for Dimension Reduction**
Leland McInnes, John Healy, James Melville
arXiv:1802.03426 [cs, stat] (2020-09-17) http://arxiv.org/abs/1802.03426

15. **Visualizing Data using t-SNE**
Laurens van der Maaten, Geoffrey Hinton
Journal of Machine Learning Research (2008) http://jmlr.org/papers/v9/vandermaaten08a.html

16. **Automatic detection of rare pathologies in fundus photographs using few-shot learning**
Gwenolé Quellec, Mathieu Lamard, Pierre-Henri Conze, Pascale Massin, Béatrice Cochener
Medical Image Analysis (2020-04) https://doi.org/ggsrc7
DOI: 10.1016/j.media.2020.101660 · PMID: 32028213

17. **Sensitive detection of rare disease-associated cell subsets via representation learning**
Eirini Arvaniti, Manfred Claassen
Nature Communications (2017-04) https://doi.org/gf9t7w
DOI: 10.1038/ncomms14825 · PMID: 28382969 · PMCID: PMC5384229

18. **The art of using t-SNE for single-cell transcriptomics**
Dmitry Kobak, Philipp Berens
Nature Communications (2019-12) https://doi.org/ggdrfz
DOI: 10.1038/s41467-019-13056-x · PMID: 31780648 · PMCID: PMC6882829

19. **Dimensionality reduction by UMAP to visualize physical and genetic interactions**
Michael W. Dorrity, Lauren M. Saunders, Christine Queitsch, Stanley Fields, Cole Trapnell
Nature Communications (2020-12) https://doi.org/ggqcqp
DOI: 10.1038/s41467-020-15351-4 · PMID: 32210240 · PMCID: PMC7093466

20. **Feature Selection**
Rama Chellappa, Pavan Turaga
Computer Vision (2020) https://doi.org/ghgqb9
DOI: 10.1007/978-3-030-03243-2_299-1 · ISBN: 9783030032432

21. **How to Use t-SNE Effectively**
Martin Wattenberg, Fernanda Viégas, Ian Johnson
Distill (2016-10-13) https://doi.org/gffk7g
DOI: 10.23915/distill.00002

22. **Compressing gene expression data using multiple latent space dimensionalities learns complementary biological representations**
Gregory P. Way, Michael Zietz, Vincent Rubinetti, Daniel S. Himmelstein, Casey S. Greene
Genome Biology (2020-12) https://doi.org/gg2mjh
DOI: 10.1186/s13059-020-02021-3 · PMID: 32393369 · PMCID: PMC7212571

23. **Ten quick tips for effective dimensionality reduction**
Lan Huong Nguyen, Susan Holmes
PLOS Computational Biology (2019-06-20) https://doi.org/gf3583
DOI: 10.1371/journal.pcbi.1006907 · PMID: 31220072 · PMCID: PMC6586259

24. **Clustering cancer gene expression data: a comparative study**
Marcilio CP de Souto, Ivan G Costa, Daniel SA de Araujo, Teresa B Ludermir, Alexander Schliep
BMC Bioinformatics (2008-12) https://doi.org/dqqbn6
DOI: 10.1186/1471-2105-9-497 · PMID: 19038021 · PMCID: PMC2632677

25. **Removing Batch Effects From Histopathological Images for Enhanced Cancer Diagnosis**
Sonal Kothari, John H. Phan, Todd H. Stokes, Adeboye O. Osunkoya, Andrew N. Young, May D. Wang
IEEE Journal of Biomedical and Health Informatics (2014-05) https://doi.org/gdm9jd
DOI: 10.1109/jbhi.2013.2276766 · PMID: 24808220 · PMCID: PMC5003052

26. **Deriving disease modules from the compressed transcriptional space embedded in a deep autoencoder**
Sanjiv K. Dwivedi, Andreas Tjärnberg, Jesper Tegnér, Mika Gustafsson
Nature Communications (2020-12) https://doi.org/gg7krm
DOI: 10.1038/s41467-020-14666-6 · PMID: 32051402 · PMCID: PMC7016183

27. **CoGAPS: an R/C++ package to identify patterns and biological process activity in transcriptomic data**
Elana J. Fertig, Jie Ding, Alexander V. Favorov, Giovanni Parmigiani, Michael F. Ochs
Bioinformatics (2010-11-01) https://doi.org/cwqsv4
DOI: 10.1093/bioinformatics/btq503 · PMID: 20810601 · PMCID: PMC3025742

28. **Regularized Machine Learning in the Genetic Prediction of Complex Traits**
Sebastian Okser, Tapio Pahikkala, Antti Airola, Tapio Salakoski, Samuli Ripatti, Tero Aittokallio
PLoS Genetics (2014-11-13) https://doi.org/ghrqhq
DOI: 10.1371/journal.pgen.1004754 · PMID: 25393026 · PMCID: PMC4230844

29. **Review and evaluation of penalised regression methods for risk prediction in low-dimensional data with few events**
Menelaos Pavlou, Gareth Ambler, Shaun Seaman, Maria De Iorio, Rumana Z Omar
Statistics in Medicine (2016-03-30) https://doi.org/ggn9zg
DOI: 10.1002/sim.6782 · PMID: 26514699 · PMCID: PMC4982098

30. https://doi.org/10.1023/A:1010933404324

31. **Evaluating predictive modeling algorithms to assess patient eligibility for clinical trials from routine data**
Felix Köpcke, Dorota Lubgan, Rainer Fietkau, Axel Scholler, Carla Nau, Michael Stürzl, Roland Croner, Hans-Ulrich Prokosch, Dennis Toddenroth
BMC Medical Informatics and Decision Making (2013-12) https://doi.org/f5jqvh
DOI: 10.1186/1472-6947-13-134 · PMID: 24321610 · PMCID: PMC4029400

32. **Analyzing bagging**
Peter Bühlmann, Bin Yu
The Annals of Statistics (2002-08-01) https://doi.org/btmtjp
DOI: 10.1214/aos/1031689014

33. **Utilising artificial intelligence to determine patients at risk of a rare disease: idiopathic pulmonary arterial hypertension**
David G. Kiely, Orla Doyle, Edmund Drage, Harvey Jenner, Valentina Salvatelli, Flora A. Daniels, John Rigg, Claude Schmitt, Yevgeniy Samyshkin, Allan Lawrie, Rito Bergemann
Pulmonary Circulation (2019-10) https://doi.org/gg4jc7
DOI: 10.1177/2045894019890549 · PMID: 31798836 · PMCID: PMC6868581

34. **Double-bagging: combining classifiers by bootstrap aggregation**
Torsten Hothorn, Berthold Lausen
Pattern Recognition (2003-06) https://doi.org/btzfh6
DOI: 10.1016/s0031-3203(02)00169-3

35. **Integrative Analysis Identifies Candidate Tumor Microenvironment and Intracellular Signaling Pathways that Define Tumor Heterogeneity in NF1**
Jineta Banerjee, Robert J Allaway, Jaclyn N Taroni, Aaron Baker, Xiaochun Zhang, Chang In Moon, Christine A Pratilas, Jaishri O Blakeley, Justin Guinney, Angela Hirbe, … Sara JC Gosline
Genes (2020-02-21) https://doi.org/gg4rbj
DOI: 10.3390/genes11020226 · PMID: 32098059 · PMCID: PMC7073563

36. **Enhancing techniques for learning decision trees from imbalanced data**
Ikram Chaabane, Radhouane Guermazi, Mohamed Hammami
Advances in Data Analysis and Classification (2020-09) https://doi.org/ghz4sz
DOI: 10.1007/s11634-019-00354-x

37. **Learning to Identify Rare Disease Patients from Electronic Health Records.**
Rich Colbaugh, Kristin Glass, Christopher Rudolf, Mike Tremblay Volv Global Lausanne Switzerland
AMIA … Annual Symposium proceedings. AMIA Symposium (2018-12-05)
https://www.ncbi.nlm.nih.gov/pubmed/30815073
PMID: 30815073 · PMCID: PMC6371307

38. **Component-based face detection**
B. Heiselet, T. Serre, M. Pontil, T. Poggio
Proceedings of the 2001 IEEE Computer Society Conference on Computer Vision and Pattern Recognition. CVPR 2001 (2001) https://doi.org/c89p2b
DOI: 10.1109/cvpr.2001.990537 · ISBN: 9780769512723

39. **The Architecture of the Face and Eyes Detection System Based on Cascade Classifiers**
Andrzej Kasinski, Adam Schmidt
Computer Recognition Systems 2 (2007) https://doi.org/cbzq9n
DOI: 10.1007/978-3-540-75175-5_16 · ISBN: 9783540751748

40. **Efficient Estimation of Word Representations in Vector Space**
Tomas Mikolov, Kai Chen, Greg Corrado, Jeffrey Dean
arXiv (2013-09-10) https://arxiv.org/abs/1301.3781

41. **Definitions, methods, and applications in interpretable machine learning**
W. James Murdoch, Chandan Singh, Karl Kumbier, Reza Abbasi-Asl, Bin Yu

Proceedings of the National Academy of Sciences (2019-10-29) https://doi.org/ggbhmq
DOI: 10.1073/pnas.1900654116 · PMID: 31619572 · PMCID: PMC6825274

42. **Comparison of statistical approaches to rare variant analysis for quantitative traits**
Han Chen, Audrey E Hendricks, Yansong Cheng, Adrienne L Cupples, Josée Dupuis, Ching-Ti Liu
BMC Proceedings (2011-12) https://doi.org/b9mf4x
DOI: 10.1186/1753-6561-5-s9-s113 · PMID: 22373209 · PMCID: PMC3287837

43. **Regularization and variable selection via the elastic net**
Hui Zou, Trevor Hastie
Journal of the Royal Statistical Society: Series B (Statistical Methodology) (2005-04)
https://doi.org/b8cwwr
DOI: 10.1111/j.1467-9868.2005.00503.x

44. **Regularized logistic regression with adjusted adaptive elastic net for gene selection in high dimensional cancer classification**
Zakariya Yahya Algamal, Muhammad Hisyam Lee
Computers in Biology and Medicine (2015-12) https://doi.org/f73xvj
DOI: 10.1016/j.compbiomed.2015.10.008 · PMID: 26520484

45. **An elastic-net logistic regression approach to generate classifiers and gene signatures for types of immune cells and T helper cell subsets**
Arezo Torang, Paraag Gupta, David J. Klinke
BMC Bioinformatics (2019-12) https://doi.org/gg5hmj
DOI: 10.1186/s12859-019-2994-z · PMID: 31438843 · PMCID: PMC6704630

46. **DeepProfile: Deep learning of cancer molecular profiles for precision medicine**
Ayse Berceste Dincer, Safiye Celik, Naozumi Hiranuma, Su-In Lee
Bioinformatics (2018-03-08) https://doi.org/gdj2j4
DOI: 10.1101/278739

47. **Auto-Encoding Variational Bayes**
Diederik P Kingma, Max Welling
arXiv (2013) https://doi.org/gpp5xv
DOI: 10.48550/arxiv.1312.6114

48. **Deep learning in rare disease. Detection of tubers in tuberous sclerosis complex**
Iván Sánchez Fernández, Edward Yang, Paola Calvachi, Marta Amengual-Gual, Joyce Y. Wu, Darcy Krueger, Hope Northrup, Martina E. Bebin, Mustafa Sahin, Kun-Hsing Yu, … on behalf of the TACERN Study Group
PLOS ONE (2020-04-29) https://doi.org/gpp5xt
DOI: 10.1371/journal.pone.0232376 · PMID: 32348367 · PMCID: PMC7190137

49. **The Monarch Initiative: an integrative data and analytic platform connecting phenotypes to genotypes across species**
Christopher J. Mungall, Julie A. McMurry, Sebastian Köhler, James P. Balhoff, Charles Borromeo, Matthew Brush, Seth Carbon, Tom Conlin, Nathan Dunn, Mark Engelstad, … Melissa A. Haendel
Nucleic Acids Research (2017-01-04) https://doi.org/f9v7bz
DOI: 10.1093/nar/gkw1128 · PMID: 27899636 · PMCID: PMC5210586

50. **Systematic integration of biomedical knowledge prioritizes drugs for repurposing**
Daniel Scott Himmelstein, Antoine Lizee, Christine Hessler, Leo Brueggeman, Sabrina L Chen, Dexter Hadley, Ari Green, Pouya Khankhanian, Sergio E Baranzini

eLife (2017-09-22) https://doi.org/cdfk
DOI: 10.7554/elife.26726 · PMID: 28936969 · PMCID: PMC5640425

51. **A Framework for Automated Construction of Heterogeneous Large-Scale Biomedical Knowledge Graphs**
Tiffany J. Callahan, Ignacio J. Tripodi, Lawrence E. Hunter, William A. Baumgartner
Bioinformatics (2020-05-02) https://doi.org/gg338z
DOI: 10.1101/2020.04.30.071407

52. **A global network of biomedical relationships derived from text**
Bethany Percha, Russ B Altman
Bioinformatics (2018-08-01) https://doi.org/gc3ndk
DOI: 10.1093/bioinformatics/bty114 · PMID: 29490008 · PMCID: PMC6061699

53. **Orphanet** https://www.orpha.net/consor/cgi-bin/index.php

54. **Structured reviews for data and knowledge-driven research**
Núria Queralt-Rosinach, Gregory S Stupp, Tong Shu Li, Michael Mayers, Maureen E Hoatlin, Matthew Might, Benjamin M Good, Andrew I Su
Database (2020-01-01) https://doi.org/ggsdkj
DOI: 10.1093/database/baaa015 · PMID: 32283553 · PMCID: PMC7153956

55. **Learning Drug-Disease-Target Embedding (DDTE) from knowledge graphs to inform drug repurposing hypotheses**
Changsung Moon, Chunming Jin, Xialan Dong, Saad Abrar, Weifan Zheng, Rada Y. Chirkova, Alexander Tropsha
Journal of Biomedical Informatics (2021-07) https://doi.org/gmpgs6
DOI: 10.1016/j.jbi.2021.103838 · PMID: 34119691

56. **Improving rare disease classification using imperfect knowledge graph**
Xuedong Li, Yue Wang, Dongwu Wang, Walter Yuan, Dezhong Peng, Qiaozhu Mei
BMC Medical Informatics and Decision Making (2019-12) https://doi.org/gg5j65
DOI: 10.1186/s12911-019-0938-1 · PMID: 31801534 · PMCID: PMC6894101

57. **A Literature-Based Knowledge Graph Embedding Method for Identifying Drug Repurposing Opportunities in Rare Diseases**
Daniel N. Sosa, Alexander Derry, Margaret Guo, Eric Wei, Connor Brinton, Russ B. Altman
Biocomputing 2020 (2019-12) https://doi.org/gmpgs7
DOI: 10.1142/9789811215636_0041 · ISBN: 9789811215629

58. **Rare disease knowledge enrichment through a data-driven approach**
Feichen Shen, Yiqing Zhao, Liwei Wang, Majid Rastegar Mojarad, Yanshan Wang, Sijia Liu, Hongfang Liu
BMC Medical Informatics and Decision Making (2019-12) https://doi.org/gm48cq
DOI: 10.1186/s12911-019-0752-9 · PMID: 30764825 · PMCID: PMC6376651

59. **Phenotype-driven gene prioritization for rare diseases using graph convolution on heterogeneous networks**
Aditya Rao, Saipradeep Vg, Thomas Joseph, Sujatha Kotte, Naveen Sivadasan, Rajgopal Srinivasan
BMC Medical Genomics (2018-12) https://doi.org/gnb3q7
DOI: 10.1186/s12920-018-0372-8 · PMID: 29980210 · PMCID: PMC6035401

60. **A Survey on Transfer Learning**
Sinno Jialin Pan, Qiang Yang
IEEE Transactions on Knowledge and Data Engineering (2010-10) https://doi.org/bc4vws
DOI: 10.1109/tkde.2009.191

61. **A machine learning approach to integrate big data for precision medicine in acute myeloid leukemia**
Su-In Lee, Safiye Celik, Benjamin A. Logsdon, Scott M. Lundberg, Timothy J. Martins, Vivian G. Oehler, Elihu H. Estey, Chris P. Miller, Sylvia Chien, Jin Dai, ... Pamela S. Becker
Nature Communications (2018-12) https://doi.org/gcpx72
DOI: 10.1038/s41467-017-02465-5 · PMID: 29298978 · PMCID: PMC5752671

62. **Pathway-level information extractor (PLIER) for gene expression data**
Weiguang Mao, Elena Zaslavsky, Boris M. Hartmann, Stuart C. Sealfon, Maria Chikina
Nature Methods (2019-07) https://doi.org/gf75g6
DOI: 10.1038/s41592-019-0456-1 · PMID: 31249421 · PMCID: PMC7262669

63. **MultiPLIER: A Transfer Learning Framework for Transcriptomics Reveals Systemic Features of Rare Disease**
Jaclyn N. Taroni, Peter C. Grayson, Qiwen Hu, Sean Eddy, Matthias Kretzler, Peter A. Merkel, Casey S. Greene
Cell Systems (2019-05) https://doi.org/gf75g5
DOI: 10.1016/j.cels.2019.04.003 · PMID: 31121115 · PMCID: PMC6538307

64. **Rare-disease genetics in the era of next-generation sequencing: discovery to translation**
Kym M. Boycott, Megan R. Vanstone, Dennis E. Bulman, Alex E. MacKenzie
Nature Reviews Genetics (2013-10) https://doi.org/ghvhsd
DOI: 10.1038/nrg3555 · PMID: 23999272

65. **Paediatric genomics: diagnosing rare disease in children**
Caroline F. Wright, David R. FitzPatrick, Helen V. Firth
Nature Reviews Genetics (2018-05) https://doi.org/gcxbr8
DOI: 10.1038/nrg.2017.116 · PMID: 29398702

66. **Next-Generation Sequencing to Diagnose Suspected Genetic Disorders**
David R. Adams, Christine M. Eng
New England Journal of Medicine (2018-10-04) https://doi.org/gf49m7
DOI: 10.1056/nejmra1711801 · PMID: 30281996

67. **Responsible, practical genomic data sharing that accelerates research**
James Brian Byrd, Anna C. Greene, Deepashree Venkatesh Prasad, Xiaoqian Jiang, Casey S. Greene
Nature Reviews Genetics (2020-10) https://www.nature.com/articles/s41576-020-0257-5
DOI: 10.1038/s41576-020-0257-5

68. **"Why Should I Trust You?": Explaining the Predictions of Any Classifier**
Marco Ribeiro, Sameer Singh, Carlos Guestrin
Proceedings of the 2016 Conference of the North American Chapter of the Association for Computational Linguistics: Demonstrations (2016) https://doi.org/gg8ggh
DOI: 10.18653/v1/n16-3020

69. **Errudite: Scalable, Reproducible, and Testable Error Analysis**
Tongshuang Wu, Marco Tulio Ribeiro, Jeffrey Heer, Daniel Weld
Proceedings of the 57th Annual Meeting of the Association for Computational Linguistics (2019)

https://doi.org/ggb9kk
DOI: 10.18653/v1/p19-1073

70. https://direct.mit.edu/coli/article/37/4/657/2124/Towards-Automatic-Error-Analysis-of-Machine

71. **Recognizing names in biomedical texts: a machine learning approach**
G. Zhou, J. Zhang, J. Su, D. Shen, C. Tan
Bioinformatics (2004-05-01) https://doi.org/bxts7r
DOI: 10.1093/bioinformatics/bth060 · PMID: 14871877

72. **Domain Adaptation with Structural Correspondence Learning**
John Blitzer, Ryan McDonald, Fernando Pereira
Proceedings of the 2006 Conference on Empirical Methods in Natural Language Processing (2006-07) https://aclanthology.org/W06-1615

73. **Heterogeneous domain adaptation using manifold alignment**
Chang Wang, Sridhar Mahadevan
Proceedings of the Twenty-Second international joint conference on Artificial Intelligence - Volume Volume Two (2011-07-16) https://dl.acm.org/doi/10.5555/2283516.2283652
ISBN: 9781577355144

74. **Comprehensive Integration of Single-Cell Data**
Tim Stuart, Andrew Butler, Paul Hoffman, Christoph Hafemeister, Efthymia Papalexi, William M. Mauck, Yuhan Hao, Marlon Stoeckius, Peter Smibert, Rahul Satija
Cell (2019-06) https://doi.org/gf3sxv
DOI: 10.1016/j.cell.2019.05.031 · PMID: 31178118 · PMCID: PMC6687398