Opportunities in Machine Learning for Healthcare

Marzyeh Ghassemi

Massachusetts Institute of Technology, Verily Cambridge, MA 02139 mghassem@mit.edu, marzyeh@google.com

Tristan Naumann

Massachusetts Institute of Technology Cambridge, MA 02139 tjn@mit.edu

Peter Schulam

Johns Hopkins University Baltimore, MD 21218 pschulam@cs.jhu.edu

Andrew L. Beam

Harvard Medical School Boston, MA 02115 andrew_beam@hms.harvard.edu

Rajesh Ranganath

New York University New York, NY 10011 rajeshr@cims.nyu.edu

Abstract

Healthcare is a natural arena for the application of machine learning, especially as modern electronic health records (EHRs) provide increasingly large amounts of data to answer clinically meaningful questions. However, clinical data and practice present unique challenges that complicate the use of common methodologies. This article serves as a primer on addressing these challenges and highlights opportunities for members of the machine learning and data science communities to contribute to this growing domain.

1 Introduction

Health problems are foundational issues in human lives. When medical care is given, care staff collect clinical data about the particular patient being seen, and leverage knowledge from the general population, to determine how to treat the patient. Data thus plays a fundamental role in addressing health problems, and improved information extraction is a crucial part of better treating patients.

Using data, machine learning has driven advances in many domains including computer vision, natural language processing (NLP), and automatic speech recognition (ASR) to deliver powerful systems (e.g., driverless cars, voice activated personal assistants, automated translation). Machine learning's ability to extract information from data, paired with the centrality of data in healthcare, makes research in machine learning for healthcare crucial.

Interest in machine learning for healthcare has grown immensely, including work in diagnosing diabetic retinopathy (Gulshan et al., 2016), detecting lymph node metastases from breast pathology (Golden, 2017), autism subtyping by clustering comorbidities (Doshi-Velez et al., 2014), and large-scale phenotyping from observational data (Pivovarov et al., 2015). Despite these advances, direct application of machine learning to healthcare remains fraught with many pitfalls. Many of these challenges stem from the nominal goal in healthcare to make personalized predictions using large amounts of noisy and biased data. However, the opportunity to create high-impact solutions presents technical opportunities that are likely to be meaningful.

In this paper we present the unique challenges, and the ensuing technical and clinical opportunities, inherent to clinical data. In Sections 2 and 3, we provide an overview of clinical data types, and cover the unique technical challenges that should be considered in machine learning systems for healthcare tasks. The failure to carefully consider these challenges can hinder the validity and utility of machine learning methods. In Section 4, we present a hierarchy of clinical opportunities, organized into the following general categories: automating clinical tasks, providing clinical support, and expanding clinical capacities. Finally, in Section 5 we outline the novel opportunities for new research machine

learning that have particular relevance in healthcare: accommodating shifts in data sources and mechanisms, ensuring models are interpretable, and identifying good representations.

2 The Promise and Perils of Clinical Data

Clinical data comes in a variety of forms which can be relevant to understanding patient health (Weber et al., 2014). We focus on the electronic health record (EHR) that documents care delivered. EHRs are primarily designed to support day-to-day operational needs such as tracking care and revenue cycle management (i.e., billing and payments), and contain heterogeneous data types. In acute care, they range from high-frequency data sampled hundreds of times per second, to vital signs that are noted hourly, to laboratory tests that are recorded when the clinicians order them, to notes that are written every twelve hours, to more static demographic data. These large differences in data type, time scale, and sampling rates make modeling challenging. Clinical data is almost exclusively documented without machine learning in mind, and are collected under a policy of interventions to improve patients' health. Each data type comes with its own challenges, some of which we outline below.

High-frequency monitors record real-time data at a patient's bedside. High-frequency monitors record clinical signals data like oxygen saturation. These signals have frequent artifact corruption (e.g., from sensors falling off), and must be aggregated, filtered, or discarded to remove artifacts prior to any learning or feature extraction. For example, electrocardiogram (ECG) signal acquired in the US must be be filtered at 60 Hz to remove power grid electrical interference (Nimunkar and Tompkins, 2007). While clinical signals can be collected with minimal human interaction, they provide only a narrow view of patient state.

Vitals and labs measure biomarkers of a patient's state. Vital signs, laboratory tests, and other numerical measurements that are noted by clinical staff are often irregularly ordered and subject to sporadic over-sampling. Non-invasive values can conflict with the high-frequency invasive data (Li-wei et al., 2013), or staff may feel that they have a general sense of patient state, and preferentially record results that are consistent with that understanding (Hug et al., 2011). Moreover, clinicians order laboratory tests related to the amount of variability they expect in the test (Hripcsak et al., 2015). For example, the *absolute time* that a laboratory measurement occurs can be more predictive of patient health than the *value* of the test (Weber and Kohane, 2013; Agniel et al., 2018); e.g., a clinician will probably only wake you at 2 am to perform a blood test if you are very ill.

Notes record the interaction between a patient and the healthcare team. The narrative in the clinical notes, recorded by expert care staff, is designed to provide trained professionals a quick glance into the most important aspects of a patient's clinical condition. However, standard natural language processing tasks such as sentiment analysis and word sense disambiguation are difficult in clinical notes, which are misspelled, acronym-laden, and copy-paste heavy (Cohen et al., 2013, 2014). Even clinical NLP packages designed to process clinical text can be misled (Savova et al., 2010). For example, a clinical NLP tool trained on a large corpus of medical text may incorrectly identify many autistic patient records with cancer. This is because the term "T2" is the clinical term for a stage of cancer progression (Winawer et al., 1997), but "T2" also describes one output modality of MRI that is used to diagnose autism in children (Courchesne et al., 2001).

3 Unique Technical Challenges in Healthcare Tasks

In tackling healthcare tasks, there are important factors that should be considered carefully in the design and evaluation of machine learning projects, causality, missingness, and outcome definition. These considerations are important across both modeling frameworks (e.g., supervised vs. unsupervised), and learning targets (e.g., classification vs. regression).

3.1 Understanding Causality is Key

Many of the most important and exciting problems in healthcare require algorithms that can answer *causal*, "what if?" questions about what will happen if a doctor administers a treatment. These

questions are beyond the reach of classical learning algorithms because they require a formal model of interventions. Instead, we need to reason about and learn from data through the lens of *causal models* (e.g., see Pearl 2009). Learning from data to answer causal questions is most challenging when the data are collected *observationally*; that is, it *may* have been influenced by the actions of an agent whose policy for choosing actions is not known.

In healthcare, learning is done almost exclusively using observational data, which poses a number of challenges to building models that can answer causal questions. For instance, Simpson's paradox describes the observation that the relationship between two variables can change directions if more information is included in the model (Pearl, 2009). To better understand this issue, consider prior work in which researchers found that asthmatic patients who were admitted to the hospital for pneumonia were more aggressively treated for the infection, lowering the subpopulation mortality rate (Cooper et al., 2005). A model that predicts death from asthma will learn that asthma is protective. If, however, an additional variable to account for the level of care is included, the model may instead find that having asthma increases the risk of death. To account for these challenges, strong assumptions must be made that cannot be statistically checked or validated; i.e., gathering more data will not help (Greenland et al., 1999). The shortcomings of classical statistical learning when answering causal questions are discussed in greater detail by Pearl (2018).

3.2 Models in Health Must Consider Missingness

Even if all important variables are included in a healthcare dataset, it is likely that many observations will be missing. Truly complete data is often impractical due to cost and volume. Learning from incomplete, or *missing*, data has received relatively little attention in the machine learning community (exceptions include, e.g., Marlin et al. 2011; Mohan et al. 2013; McDermott et al. 2018), but is an actively studied topic in statistics (e.g., Ding and Li 2018).

There are three widely accepted classifications of *missing data mechanisms*; i.e., the measurement mechanism determining whether a value is recorded or not (Little and Rubin, 2014). The first, *missing completely at random* (MCAR), posits a fixed probability of missingness. In this case, dropping incomplete observations — known as complete case analysis — is commonly used (albeit naively), and will lead to unbiased results. Second, the data may be *missing at random* (MAR), where the probability of missingness is random conditional on the observed variables. In this case, common methods include re-weighting data with methods like inverse probability of censoring weighting or using multiple imputations to in-fill (Robins, 2000; Robins et al., 2000). Finally, data may be *missing not at random* (MNAR), where the probability of missingness depends on the missing variable itself, or other missing and unobserved variables. This setting requires strong assumptions about the measurement policy to successfully circumvent (Little and Rubin, 2002).

In designing a learning algorithm in a healthcare setting, the sources of missingness must be carefully understood. For example, lab measurements are typically ordered as part of a diagnostic work-up, meaning that the presence of a datapoint conveys information about the patient's state. Consider a hospital where clinical staff measures patient lactate level. If a power outage led to a set of lactate levels being lost, the data are MCAR. If nurses are less likely to measure lactate levels in patients with traumatic injury, and we record whether patients were admitted with trauma, the data are MAR. However, if nurses are less likely to measure lactate levels in patient who they believe have low levels, then the lactate measures themselves are MNAR, and the measurement of the signal itself is meaningful. The key feature of missing data is that there may be information conveyed by the absence of an observation, and ignoring this dependence may lead to models that make incorrect, and even harmful, predictions.

3.3 Make Careful Choices in Defining Outcomes

Obtaining reliable outcomes for learning is an important step in defining tasks. Outcomes are often used to create the gold-standard labels needed for supervised prediction tasks, but are crucial in other settings as well, e.g., to ensure a well-defined cohorts in a clustering task. There are three key factors to consider with outcome definitions: creating reliable outcomes, understanding the relevance of an outcome clinically, and the subtlety of label leakage in clinical data.

Create reliable outcomes from heterogeneous source data. Multiple data sources should be considered when creating labels in healthcare because EHRs often lack precise structured labels. Or, in some cases, structured labels may be available, but unreliable (O'malley et al., 2005). For example, a diagnostic clinical code for pneumonia could mean a patient was *screened* for pneumonia rather than that they *actually had* pneumonia, e.g., a 2013 study found that sensitivity and specificity for a community-acquired pneumonia diagnostic code could be as low as 60% and 75%, respectively (Williams et al., 2013). Machine learning methods to pool different data types and obtain a more reliable label is known as *phenotyping* (Richesson et al., 2013), and is an important subfield of machine learning in healthcare (Halpern et al., 2016; Yu et al., 2017). Recent work has emphasized the need to integrate the rich information available in clinical notes, and building natural language processing pipelines to extract information from unstructured clinical text accurately is an active subject of research (Savova et al., 2010).

Understand the outcome in context of a healthcare system. Medical definitions are working models using the current scientific understanding of a disease. As the field's understanding evolves, so does the definition. The implication for machine learning is that good predictive performance on labels based on such definitions is only as good as the underlying criteria. For example, acute kidney injury (AKI) is an important critical illness with two recent definitions: RIFLE and KDIGO (Ricci et al., 2008; Khwaja, 2012). Another condition, septic shock, has received considerable attention from machine learning researchers (e.g., Henry et al. 2015; Futoma et al. 2017), and has been redefined several times over the last two decades (Levy et al., 2003; Dellinger et al., 2013; Singer et al., 2016). Similarly, it is tempting to use the actual behavior of clinicians as correct labels, but it is important to remember that they may not be. For example, work that targets prediction of clinical actions must carefully consider whether the treatments are good labels, and whether "incorrect predictions" are in fact forecasting treatments that would have been given by other clinicians rather than treatments that would optimally treat the patient (Ghassemi et al., 2016, 2017; Suresh et al., 2017).

Beware of label leakage. The information collected in an individual's hospital encounter is tightly coupled across time, and this can result in information about the targeted task outcome leaking back into possible features (e.g., Razavian et al. 2016). While exploiting such relationships between features and targets is a goal of learning, information leakage can render a prediction useless. For example, consider predicting mortality of hospital patients using all available data up until their time of death. Such a task could lead to a pathological prediction rule — "if the ventilator is turned off in the preceding hour, predict death." This commonly happens when patients and their families decide to withdraw care at a terminal stage of illness. A machine learning algorithm trained naively on this signal would have extremely high predictive performance by nearly any metric, yet would have absolutely no clinical utility.

4 Addressing a Hierarchy of Healthcare Opportunities

There are many high-impact opportunities in healthcare, and before fitting models, goals should be clearly identified and validated as worth solving. Here, we frame potential healthcare opportunities into three high-level categories: automating clinical tasks, providing clinical support, and expanding clinical capacities. We note that the details of how a technical solution is deployed can change its intent, (e.g., from automation to support) and that it is therefore crucial to engage clinical stakeholders early on.

4.1 Clinical Task Automation: Automating clinical tasks during diagnosis and treatment

There are many tasks currently performed by clinicians that present low-hanging fruit for machine learning researchers. Clinical task automation encompasses a class of work that clinicians currently do. These tasks are well-defined (i.e., known input and output spaces), and thus require the least amount of domain adaptation and investment. The evaluation of task replacement is also straightforward — models map directly onto a task or decision that clinicians are currently capable of doing with a high degree of accuracy, and performance should be measured against existing standards. We emphasize that algorithms should replace clinical staff, but rather be used to optimize the clinical workflow. Clinical roles will likely evolve as these techniques improve, empowering staff to spend more time on patient interaction and well-being (Jha and Topol, 2016).

Automating medical image evaluation. Medical imaging is a natural opportunity for machine learning because clinicians undergo intensive training to map from a fixed input space (e.g. the images) to an output (e.g. the diagnosis). There have been several recent successes in applying deep learning to medical imaging tasks. For example, physician-level parity in the detection of diabetic retinopathy (Gulshan et al., 2016), distinguishing between malignant and non-malignant skin lesions using in dermatoscopic images (Esteva et al., 2017), detecting lymph node metastases from breast pathology slides (Golden, 2017), and detecting hip fractures in x-ray images (Gale et al., 2017).

Automating routine processes. Similarly, automating routine clinical processes stands to reduce the burden place on clinical staff who are already pressed for time. For example, prioritizing triage order in the emergency department is often left to staff (Ieraci et al., 2008), but could be done algorithmically. Likewise, summarizing the contents of patients' medical records (McCoy et al., 2018) is a time-consuming, but valuable, task. For example, when hospital staff are unsure about patient's disease status, they may call for an infectious disease consultation in which a specialist meticulously reviews all the available patient data, and manually summarizes disparate sources into a series of recommended tests and treatments (Forsblom et al., 2012).

4.2 Clinical Support and Augmentation: Optimizing clinical decision and practice support

Another set of opportunities focus on supporting and augmenting clinicians as they provide care. Rather than replacing a well-defined task, support requires understanding clinical pain points and working with clinical staff to understand appropriate input data, output targets and evaluation functions. The opportunities for support in healthcare focus on work that often suffers due to real-world constraints on time and resources, often leading to information loss and errors (e.g., mistaken patient identification, flawed interpretations, or incorrect recall (Shneiderman et al., 2013)). In this setting, it is most appropriate to evaluate how models improve downstream outcomes in tandem with clinical input rather than head-to-head comparisons to clinical staff (Pivovarov et al., 2016).

Standardizing clinical processes. Variations in clinical training and experience lead to ranges of treatment choices that may not be optimal for targeting the underlying maladies of a patient's state. For example, clinical staff may be unsure which medication sets or doses are most appropriate for a patient (Fishbane et al., 2007). To support such needs, past work has examined recommending both standardized order sets to help care staff quickly assess what medications they may have missed (Halpern, 2016) and default dosages to avoid dangerous dosing (Bates and Gawande, 2003).

Integrating fragmented records. Finite resources can also lead to a lack of communication and coordination, affecting patient care. For example, because healthcare delivery is often fragmented, it can take years to identify domestic abuse survivors because any single clinical visit in isolation will be consistent with many other likely causes (e.g. admission to an emergency department due to bruising is consistent with a spontaneous fall). Only a thorough review of a patient's record will demonstrate the pattern of repeated admissions and other indicators (Kyriacou et al., 1999) (e.g., parters' alcohol abuse). While possible without support systems in principle, machine learning can be a powerful tool in aiding clinical staff by identifying patients with high risk, e.g., identifying domestic abuse up to 30 months in advance of the healthcare system (Reis et al., 2009).

4.3 Expanding Clinical Capacities: New horizons in screening, diagnosis and treatment.

As healthcare records become increasingly digitized, clinicians are faced with an ever-increasing amount of novel data for patients and populations. In this explosion of availability, there is an opportunity to give the healthcare system a new set of capacities that deliver healthcare in better and smarter ways. Importantly, creating new capacities require the most involvement with clinical collaborators; as researchers work to create new tools using previously unavailable or unused data, impact should be measured both in innovation and clinical value.

Expanding the coverage of evidence. While healthcare is an inherently data-driven field, most clinicians operate with limited evidence guiding their decisions. Randomized trials estimate average treatment effects for a trial population, but numerous day-to-day clinical decisions are not based on high-quality randomized control trials (RCTs) (Landoni et al., 2015). For example, the majority of commonly used ICU treatments are not rigorously empirically validated (McGinnis et al.,

2013); some analysts have estimated that only 10–20% (Mills et al., 2013) of treatments are backed by an RCT. Even in settings where an RCT exists, the trial population tends to be a narrow, focused subgroup defined by the trial's inclusion criteria (Travers et al., 2007), but that cohort may not be representative of the much more heterogeneous population to which trial results are then applied (Phillips and Hamberg, 2016). Finally, RCT results cannot reflect the complexity of treatment variation because, in practice, patient care plans are highly individualized. Prior work found that approximately 10% of diabetes and depression patients and almost 25% of hypertension patients had a unique treatment pathway (i.e., zero nearest neighbors) in a cohort of 250 million patients (Hripcsak et al., 2016). One way forward would be to leverage this naturally occurring heterogeneity to design natural experiments (Angrist and Pischke, 2008) that approximate the results of an RCT using fewer resources, thereby allowing a much larger set of clinical questions to be investigated.

Moving towards continuous behavioral monitoring. Phenotyping is an important goal in health-care (Richesson et al., 2013), and *wearable data* provides an ongoing way for devices to collect continuous non-invasive data and provide meaningful classifications or alerts when the patient is in need of clinical attention. Recent work has focused on predicting such varied outcomes as heart attack from routinely collected data (Weng et al., 2017) and hydrocephalus from fetal MRI (Pisapia et al., 2017). There are further settings where non-invasive monitoring may be the only practical way to provide detection. For example, automatic fall detection for geriatric patients, or enforcing hand washing compliance in a clinical setting (Haque et al., 2017). Importantly, prior challenges identified in label leakage, soft labels, confounding and missingness must be considered very carefully. In the case of phenotyping chronic conditions, patients with a disease are often already being treated for that disease, and so early *detection* may sometimes amount to identifying an existing treatment—e.g. looking at longitudinal patterns of heart rate data to detect hypertension may really be detecting the use of beta blockers (used to treat hypertension) (Ballinger et al., 2018).

Precision medicine for early individualized treatment. Precision medicine seeks to individualize the treatment of each patient; this is particularly important in the case of syndromes — medical conditions defined by a collection of symptoms whose causes are unknown (Council, 2011). For instance, acute kidney injury (AKI) is defined by a collection of symptoms characterizing kidney failure, not an underlying cause (Kellum and Prowle, 2018). Two individuals may have developed AKI for different reasons because there are many reasons that kidneys can fail. More measurements of the two individuals could reveal the difference in cause, which may in turn suggest alternative treatment strategies (Alge and Arthur, 2014). By personalizing over time, one can learn individualspecific treatment effects that address the cause of the syndrome (Xu et al., 2016; Schulam and Saria, 2017) in a particular individual. This relates to the ideas from "N=1" crossover studies in experimental design (Araujo et al., 2016). Personalized treatment is enabled by growing repositories of longitudinal data, where long-term progressions of an individual's health are available. However, new memory models are needed for sequence prediction tasks, because such records are not evenly spaced, can cover very long durations, and early events can affect patient state many years later. Personalized patient models that target improved early stage of prediction could also leverage population level information, drawing on work in "cold starting" recommendation systems (Park and Chu, 2009).

5 Opportunities for New Research in Machine Learning

Addressing the hierarchy of opportunities in healthcare creates numerous technical opportunities for innovation. Importantly, clinical staff and machine learning researchers often have complementary sets of skills, and many high-impact problems can only be tackled by collaborative efforts. Further, many of the inherent properties that are highly desirable in healthcare (e.g., interpretability) are likely to be important in other domains. Here we note several promising directions of research in machine learning for healthcare, specifically highlighting those that address issues of data non-stationarity, model interpretability, and discovering appropriate representations.

5.1 Accommodating Data and Practice Non-stationarity in Learning and Deployment

In most existing work, models are trained on the largest dataset possible and assumed to be fit for deployment, i.e., once the model is in production, it does not keep learning. This is particularly

problematic in clinical settings, because patient populations and recommended treatment procedures will change over time, resulting in degraded predictive performance as the statistical properties of the target change. For example, clinicians previously assumed that estrogen was cardioprotective in menopausal women (Gabriel Sanchez et al., 2005) and hormone therapy was routinely prescribed as a preventative measure until large trials reported either no benefit or an increase in adverse cardiac events (Prentice et al., 2006). In developing new models for healthcare, models must be made robust to these changes, or acknowledge their mis-calibration for the new population (Tsymbal, 2004).

Internal Validity - Shift over time. In a notable example of concept drift, Google Flu Trends persistently overestimated flu due to shifts in search behaviors (Lazer et al., 2014). In this case, the initial model was a great success, leveraging Google search data to predict flu incidence; however, without update the model began to overestimate flu incidence in subsequent years as user search behaviors had shifted. While the drift in this case was unintentional, the example serves to motivate the need for models that continually update as population characteristics naturally evolve over time.

External Validity - Shift over sources. There is also no reason to believe *a priori* that a model learned from one hospital will generalize to a new one. Many factors impact generalizability, including local hospital practices, different patient populations, available equipment, and even the specific kind of EHR each uses. Even within the same hospital, transitions from one medical record system to another create non-obvious feature mapping problems, which themselves warrant machine learning (Gong et al., 2017). This issue will remain until infrastructure to easily test across multiple sites and health systems becomes prevalent. The absence of such standardization creates opportunities with respect to data normalization, the development of models that are robust to — and potentially able to exploit — differences in data collection at different sites.

Creating models robust to feedback loops. Models that learn from existing clinical practice are susceptible to amplifying the biases endemic to modern healthcare. While not yet observed in healthcare, such feedback loops have been noted in the deployment of predictive policing (Lum and Isaac, 2016). Such biases reflected in deployed predictions can propagate into future training data, effectively creating a feedback loop that causes further bias (Dressel and Farid, 2018). While still in its infancy, work in algorithmic fairness should be considered as it motivates the need for systems that are sufficiently aware that they can alert us to such unwanted behavior.

5.2 Creating interpretable models and recommendations

In a clinical setting, black box methods present new challenges. Traditionally, quantitative training has not been emphasized in a physician's extensive medical training (Obermeyer and Lee, 2017) and most physicians do not have a robust understanding of rubrics such as positive predictive value (Manrai et al., 2014). Models cannot be deployed "in the wild" at a low cost, and clinical staff must justify deviations in treatment to satisfy both clinical and legal requirements.

Defining what interpretibility means. There are many possible ways to interpretability, e.g., through feature space minimization, model regularization, or a preference for particular classes of models that have well-known post-hoc analysis methods (Doshi-Velez and Kim, 2017). For example, providing a posterior distribution over possible decision lists (e.g., "if hemiplegia and age > 60 then stroke risk is 58.9%, else if...") (Letham et al., 2015). Such lists can provide a natural way for clinicians to think about the relative risks of their patient's condition.

Moving from interpretation to justification. In other domains, many forms of interpretability rely on human expertise in the subject matter, e.g., a model may highlight a single sentence from a user review ("The coffee is wonderful.") as the rationale for a review prediction. Clinicians are unlikely to have a similar contextual framework, and it is unlikely to be obvious what a particular pattern of lab measurements that maximally activates a models means, biologically or clinically (Suresh et al., 2017). We argue that models should instead provide "justifiability"; beyond explaining a specific prediction, models should strive towards justifying the predictive path itself. For example, global decision boundaries are often non-linear and complex, but recent work has proposed that locally-interpretable results can be presented for each individual prediction (Ribeiro et al., 2016). Another possibility is learning influence functions to trace a model's prediction through the learning algorithm and back to its training data, thereby identifying training points most responsible for

a given prediction (Koh and Liang, 2017). Outside of reassuring end users, justifying a machine learning algorithm's decision is also important for security concerns. It has recently been argued that medicine may be uniquely vulnerable to "adversarial attacks" (Finlayson et al., 2018), thus it is crucial that algorithms justify their outputs to help identify if a system is being compromised.

Adding interaction to machine learning and evaluation. Machine learning work in healthcare has an opportunity to create systems that interact and collaborate with human experts. Clinical staff provide more than their expertise; they also act as caregivers, and empathy is recognized as an important element of clinical practice (e.g. Charon 2001; Stewart 2003). Building *collaborative* systems can leverage the complementary strengths of physicians and learning systems. There are many threads of research in the machine learning literature that can serve as a foundation for such systems. In active learning, for example, the goal is to leverage an *oracle* in order to learn using fewer samples (Settles, 2012). Apprenticeship learning is another related set of ideas (e.g. Abbeel and Ng 2004). The study of collaborative systems, where the human and machine work together, is still in its early stages. Examples of such systems include content creation algorithms that alternate back and forth between human and machine proposals (Cho, 2002), and intelligent, data-driven operations for drawing software (Zhu et al., 2016).

5.3 Identifying Representations in a Large, Multi-source, Network

Representation learning has prompted great advances in machine learning; for example, the lower dimensional, qualitatively meaningful representations of imaging datasets learned by convolutional neural networks. Healthcare data lacks such obviously natural structures, and investigations into appropriate representations should include multi-source integration, and learning domain appropriate representations.

Integrating predictions from multi-source high-dimensional data. Individual patient data has ballooned to include many sources and modalities, making integration more challenging in systems currently struggling with overload (Obermeyer and Lee, 2017; Beam and Kohane, 2018). Using high-dimensional data to make well-calibrated predictions of established risks is a way that researchers can contribute. For example, inferring drug-resistance status in tuberculosis from whole-genome sequencing data (Chen et al., 2018), predicting cardiovascular risk from EHR data (Ranganath et al., 2016; Weng et al., 2017), readmission and mortality risk from longitudinal EHR data (Rajkomar et al., 2018; Harutyunyan et al., 2017), prediction of hydrocephalus from fetal MRI (Pisapia et al., 2017), and predicting cardiovascular risk from retinal images (Poplin et al., 2018).

Learning meaningful representations for the domain. Learning meaningful state representations that provide both good predictive performance in diverse tasks, and understand many conditional relationships of interest, is an important area of focus in healthcare. Dealing with representations explicitly may be advantageous because they can conveniently express general priors that are not specific to a single predictive task (Bengio et al., 2013), and this is particularly important for zero-shot learning (Socher et al., 2013) in unseen categories. There are several potential opportunities to address in representations for a clinical setting. First, a single patient input (e.g., physiological data) can correspond to many possible correct outputs (e.g., diagnostic codes), and this must be possible in the representations we explore. Additionally, there is likely value in incorporating structure and domain knowledge into representation learning. There has also been some initial exploration into learning representations of other data types that simultaneously capture hierarchy and similarity (Nickel and Kiela, 2017), and recent work has examined using diagnostic code ontologies to aid prediction (Choi et al., 2017), and adding nodes to the hidden layer of neural network models based on known biological relationships between genes (Lin et al., 2017).

6 Conclusion

The effective use of machine learning in healthcare presents many challenges and opportunities for researchers, and the potential impact is vast. In this work, we give a practical guide that researchers can engage with as they begin work in healthcare. We emphasize that there are many opportunities

https://jods.mitpress.mit.edu/pub/issue3-case

for machine learning researchers to collaborate with clinical staff, and encourage researchers to engage with clinical experts early on as they identify and tackle important problems.

Acknowledgements

We would like to thank several colleagues who contributed to our thoughts in this paper; specifically, Matthew BA McDermott, Alex Wiltschko, Paul Varghese, David Adams, Yoni Halpern, Peter Szolovits, Katherine Evans, Finale Doshi-Velez and Jesse Johnson.

References

- P. Abbeel and A.Y. Ng. 2004. Apprenticeship learning via inverse reinforcement learning. In *Proceedings of the twenty-first international conference on Machine learning*. ACM, 1.
- D. Agniel, I.S. Kohane, and G.M. Weber. 2018. Biases in electronic health record data due to processes within the healthcare system: retrospective observational study. *BMJ* 361 (2018), k1479.
- J.L. Alge and J.M. Arthur. 2014. Biomarkers of AKI: a review of mechanistic relevance and potential therapeutic implications. *Clinical Journal of the American Society of Nephrology* (2014).
- J.D. Angrist and J. Pischke. 2008. Mostly harmless econometrics: An empiricist's companion. Princeton university press.
- A. Araujo, S. Julious, and S. Senn. 2016. Understanding variation in sets of N-of-1 trials. *PloS one* (2016).
- B. Ballinger, J. Hsieh, A. Singh, N. Sohoni, J. Wang, G.H. Tison, G.M. Marcus, J.M. Sanchez, C. Maguire, J.E. Olgin, and others. 2018. DeepHeart: Semi-Supervised Sequence Learning for Cardiovascular Risk Prediction. *arXiv preprint arXiv:1802.02511* (2018).
- D.W. Bates and A.A. Gawande. 2003. Improving safety with information technology. *New England journal of medicine* 348, 25 (2003), 2526–2534.
- A.L. Beam and I.S. Kohane. 2018. Big data and machine learning in health care. *JAMA* (2018). DOI:http://dx.doi.org/10.1001/jama.2017.18391
- Y. Bengio, A. Courville, and P. Vincent. 2013. Representation learning: A review and new perspectives. *IEEE transactions on pattern analysis and machine intelligence* 35, 8 (2013), 1798–1828.
- R. Charon. 2001. Narrative medicine: a model for empathy, reflection, profession, and trust. *Journal of the American Medical Association* 286, 15 (2001), 1897–1902.
- M.L. Chen, A. Doddi, J. Royer, L. Freschi, M. Schito, M. Ezewudo, I.S. Kohane, A. Beam, and M. Farhat. 2018. Deep Learning Predicts Tuberculosis Drug Resistance Status from Whole-Genome Sequencing Data. *bioRxiv* (2018), 275628.
- S. Cho. 2002. Towards creative evolutionary systems with interactive genetic algorithm. *Applied Intelligence* 16, 2 (2002), 129–138.
- E. Choi, M.T. Bahadori, L. Song, W.F. Stewart, and J. Sun. 2017. GRAM: Graph-based attention model for healthcare representation learning. In *International Conference on Knowledge Discov*ery and Data Mining (KDD). ACM, 787–795.
- R. Cohen, I. Aviram, M. Elhadad, and N. Elhadad. 2014. Redundancy-aware topic modeling for patient record notes. *PloS one* 9, 2 (2014), e87555.
- R. Cohen, M. Elhadad, and N. Elhadad. 2013. Redundancy in electronic health record corpora: analysis, impact on text mining performance and mitigation strategies. *BMC bioinformatics* 14, 1 (2013), 10.
- G.F. Cooper, V. Abraham, C.F. Aliferis, J.M. Aronis, B.G. Buchanan, R. Caruana, M.J. Fine, J.E. Janosky, G. Livingston, T. Mitchell, and others. 2005. Predicting dire outcomes of patients with community acquired pneumonia. *Journal of biomedical informatics* 38, 5 (2005), 347–366.

- National Research Council. 2011. Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease. National Academies Press.
- E. Courchesne, C.M. Karns, H.R. Davis, R. Ziccardi, R.A. Carper, Z.D. Tigue, H.J. Chisum, P. Moses, K. Pierce, C. Lord, and others. 2001. Unusual brain growth patterns in early life in patients with autistic disorder an MRI study. *Neurology* 57, 2 (2001), 245–254.
- R.P. Dellinger, M.M. Levy, A. Rhodes, D. Annane, H. Gerlach, S.M. Opal, J.E. Sevransky, C.L. Sprung, I.S. Douglas, R. Jaeschke, and others. 2013. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive care medicine* 39, 2 (2013), 165–228.
- P. Ding and F. Li. 2018. Causal inference: A missing data perspective. *Statist. Sci.* 33, 2 (2018), 214–237.
- F. Doshi-Velez, Y. Ge, and I. Kohane. 2014. Comorbidity clusters in autism spectrum disorders: an electronic health record time-series analysis. *Pediatrics* 133, 1 (2014), e54–e63.
- F. Doshi-Velez and B. Kim. 2017. Towards a rigorous science of interpretable machine learning. (2017).
- J. Dressel and H. Farid. 2018. The accuracy, fairness, and limits of predicting recidivism. Science Advances 4, 1 (2018), eaao5580.
- A. Esteva, B. Kuprel, R. A. Novoa, J. Ko, S. M. Swetter, H. M. Blau, and S. Thrun. 2017. Dermatologist-level classification of skin cancer with deep neural networks. *Nature* 542, 7639 (2017), 115.
- S.G. Finlayson, I.S. Kohane, and A.L. Beam. 2018. Adversarial Attacks Against Medical Deep Learning Systems. *arXiv preprint arXiv:1804.05296* (2018).
- S. Fishbane, M.S. Niederman, C. Daly, A. Magin, M. Kawabata, A. de Corla-Souza, I. Choudhery, G. Brody, M. Gaffney, S. Pollack, and others. 2007. The impact of standardized order sets and intensive clinical case management on outcomes in community-acquired pneumonia. *Archives of internal medicine* 167, 15 (2007), 1664–1669.
- E. Forsblom, E. Ruotsalainen, J. Ollgren, and A. Järvinen. 2012. Telephone consultation cannot replace bedside infectious disease consultation in the management of Staphylococcus aureus bacteremia. *Clinical infectious diseases* 56, 4 (2012), 527–535.
- J. Futoma, S. Hariharan, and K. Heller. 2017. Learning to detect sepsis with a multitask gaussian process rnn classifier. In *International Conference on Machine Learning (ICML)*.
- R. Gabriel Sanchez, L.M. Sanchez Gomez, L. Carmona, M. Roqué i Figuls, and X. Bonfill Cosp. 2005. Hormone replacement therapy for preventing cardiovascular disease in post-menopausal women. *The Cochrane Library* (2005).
- W. Gale, L. Oakden-Rayner, G. Carneiro, A. P. Bradley, and L. J. Palmer. 2017. Detecting hip fractures with radiologist-level performance using deep neural networks. arXiv preprint arXiv:1711.06504 (2017).
- M. Ghassemi, M. Wu, M. Feng, L.A. Celi, P. Szolovits, and F. Doshi-Velez. 2016. Understanding vasopressor intervention and weaning: Risk prediction in a public heterogeneous clinical time series database. *Journal of the American Medical Informatics Association* (2016), ocw138.
- M. Ghassemi, M. Wu, M. Hughes, and F. Doshi-Velez. 2017. Predicting Intervention Onset in the ICU with Switching State Space Models. In *Proceedings of the AMIA Summit on Clinical Research Informatics (CRI)*, Vol. 2017. American Medical Informatics Association.
- J. A. Golden. 2017. Deep Learning Algorithms for Detection of Lymph Node Metastases From Breast Cancer: Helping Artificial Intelligence Be Seen. *Jama* 318, 22 (2017), 2184–2186.
- J.J. Gong, T. Naumann, P. Szolovits, and J.V. Guttag. 2017. Predicting Clinical Outcomes Across Changing Electronic Health Record Systems. In *International Conference on Knowledge Discovery and Data Mining (KDD)*. ACM, 1497–1505.

- S. Greenland, J.M. Robins, and J. Pearl. 1999. Confounding and collapsibility in causal inference. *Statistical science* (1999), 29–46.
- V. Gulshan, L. Peng, M. Coram, M.C. Stumpe, D. Wu, A. Narayanaswamy, S. Venugopalan, K. Widner, T. Madams, J. Cuadros, and others. 2016. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *Jama* 316, 22 (2016), 2402–2410.
- Y. Halpern. 2016. Semi-Supervised Learning for Electronic Phenotyping in Support of Precision Medicine. Ph.D. Dissertation. New York University.
- Y. Halpern, S. Horng, Y. Choi, and D. Sontag. 2016. Electronic medical record phenotyping using the anchor and learn framework. *Journal of the American Medical Informatics Association* 23, 4 (2016), 731–740.
- A. Haque, M. Guo, A. Alahi, S. Yeung, Z. Luo, A. Rege, J. Jopling, L. Downing, W. Beninati, A. Singh, and others. 2017. Towards Vision-Based Smart Hospitals: A System for Tracking and Monitoring Hand Hygiene Compliance. *arXiv preprint arXiv:1708.00163* (2017).
- H. Harutyunyan, H. Khachatrian, D. C. Kale, and A. Galstyan. 2017. Multitask Learning and Benchmarking with Clinical Time Series Data. *arXiv* preprint arXiv:1703.07771 (2017).
- K.E. Henry, D.N. Hager, P.J. Pronovost, and S. Saria. 2015. A targeted real-time early warning score (TREWScore) for septic shock. *Science translational medicine* 7, 299 (2015), 299ra122– 299ra122.
- G. Hripcsak, D.J. Albers, and A. Perotte. 2015. Parameterizing time in electronic health record studies. *Journal of the American Medical Informatics Association* 22, 4 (2015), 794–804.
- G. Hripcsak, P.B. Ryan, J.D. Duke, N.H. Shah, R.W. Park, V. Huser, M.A. Suchard, M.J. Schuemie, F.J. DeFalco, A. Perotte, and others. 2016. Characterizing treatment pathways at scale using the OHDSI network. *Proceedings of the National Academy of Sciences* 113, 27 (2016), 7329–7336.
- C.W. Hug, G.D. Clifford, and A.T. Reisner. 2011. Clinician blood pressure documentation of stable intensive care patients: an intelligent archiving agent has a higher association with future hypotension. *Critical care medicine* 39, 5 (2011), 1006.
- S. Ieraci, E. Digiusto, P. Sonntag, L. Dann, and D. Fox. 2008. Streaming by case complexity: evaluation of a model for emergency department fast track. *Emergency Medicine Australasia* 20, 3 (2008), 241–249.
- S. Jha and E.J. Topol. 2016. Adapting to artificial intelligence: radiologists and pathologists as information specialists. *Jama* 316, 22 (2016), 2353–2354.
- J.A. Kellum and J.R. Prowle. 2018. Paradigms of acute kidney injury in the intensive care setting. *Nature Reviews Nephrology* (2018).
- A. Khwaja. 2012. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clinical Practice* 120, 4 (2012), c179–c184.
- P.W. Koh and P. Liang. 2017. Understanding black-box predictions via influence functions.
- D. N. Kyriacou, D. Anglin, E. Taliaferro, S. Stone, T. Tubb, J. A. Linden, R. Muelleman, E. Barton, and J. F. Kraus. 1999. Risk factors for injury to women from domestic violence. *New England journal of medicine* 341, 25 (1999), 1892–1898.
- G. Landoni, M. Comis, M. Conte, G. Finco, M. Mucchetti, G. Paternoster, A. Pisano, L. Ruggeri, G. Alvaro, M. Angelone, and others. 2015. Mortality in multicenter critical care trials: an analysis of interventions with a significant effect. *Critical care medicine* 43, 8 (2015), 1559–1568.
- D. Lazer, R. Kennedy, G. King, and A. Vespignani. 2014. The parable of Google Flu: traps in big data analysis. *Science* 343, 6176 (2014), 1203–1205.

- B. Letham, C. Rudin, T. H. McCormick, D. Madigan, and others. 2015. Interpretable classifiers using rules and bayesian analysis: Building a better stroke prediction model. *The Annals of Applied Statistics* 9, 3 (2015), 1350–1371.
- M.M. Levy, M.P. Fink, J.C. Marshall, E. Abraham, D. Angus, D. Cook, J. Cohen, S.M. Opal, J. Vincent, G. Ramsay, and others. 2003. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Intensive care medicine* 29, 4 (2003), 530–538.
- H.L. Li-wei, M. Saeed, D. Talmor, R. Mark, and A. Malhotra. 2013. Methods of blood pressure measurement in the ICU. *Critical care medicine* 41, 1 (2013), 34.
- C. Lin, S. Jain, H. Kim, and Z. Bar-Joseph. 2017. Using neural networks for reducing the dimensions of single-cell RNA-Seq data. *Nucleic acids research* 45, 17 (2017), e156–e156.
- R. Little and D. Rubin. 2002. Statistical Analysis with Missing Data. Wiley.
- R.J.A. Little and D.B. Rubin. 2014. Statistical analysis with missing data. Vol. 333. John Wiley & Sons.
- K. Lum and W. Isaac. 2016. To predict and serve? Significance 13, 5 (2016), 14–19.
- A. K. Manrai, G. Bhatia, J. Strymish, I. S. Kohane, and S. H. Jain. 2014. Medicine's uncomfortable relationship with math: calculating positive predictive value. *JAMA internal medicine* 174, 6 (2014), 991–993.
- B.M. Marlin, R.S. Zemel, S.T. Roweis, and M. Slaney. 2011. Recommender systems, missing data and statistical model estimation. In *International Joint Conference on Artificial Intelligence (IJCAI)*, Vol. 22. 2686.
- T.H. McCoy, S. Yu, K.L. Hart, V.M. Castro, H.E. Brown, J.N. Rosenquist, A.E. Doyle, P.J. Vuijk, T. Cai, and R.H. Perlis. 2018. High throughput phenotyping for dimensional psychopathology in electronic health records. *Biological psychiatry* (2018).
- M.B.A. McDermott, T. Yan, T. Naumann, N. Hunt, H. Suresh, P. Szolovits, and M. Ghassemi. 2018. Semi-supervised Biomedical Translation with Cycle Wasserstein Regression GANs. In *Association for the Advancement of Artificial Intelligence*. New Orleans, LA.
- J.M. McGinnis, L. Stuckhardt, R. Saunders, and M. Smith. 2013. *Best care at lower cost: the path to continuously learning health care in America*. National Academies Press.
- E.J. Mills, K. Thorlund, and J.P.A. Ioannidis. 2013. Demystifying trial networks and network meta-analysis. *Bmj* 346 (2013), f2914.
- K. Mohan, J. Pearl, and J. Tian. 2013. Graphical models for inference with missing data. In *Neural Information Processing Systems (NIPS)*.
- M. Nickel and D. Kiela. 2017. Poincar\'e Embeddings for Learning Hierarchical Representations. *arXiv* preprint arXiv:1705.08039 (2017).
- A.J. Nimunkar and W.J. Tompkins. 2007. EMD-based 60-Hz noise filtering of the ECG. In Engineering in Medicine and Biology Society, 2007. EMBS 2007. 29th Annual International Conference of the IEEE. IEEE, 1904–1907.
- Z. Obermeyer and T. H. Lee. 2017. lost in Thought—The Limits of the Human Mind and the Future of Medicine. *New England Journal of Medicine* 377, 13 (2017), 1209–1211.
- K.J. O'malley, K.F. Cook, M.D. Price, K.R. Wildes, J.F. Hurdle, and C.M. Ashton. 2005. Measuring diagnoses: ICD code accuracy. *Health Services Research* 40, 5p2 (2005), 1620–1639.
- S.T. Park and W. Chu. 2009. Pairwise preference regression for cold-start recommendation. In *ACM Conference on Recommender Systems*. ACM.
- J. Pearl. 2009. Causality: models, reasoning, and inference. Cambridge University Press.

- J. Pearl. 2018. Theoretical Impediments to Machine Learning With Seven Sparks from the Causal Revolution. arXiv preprint arXiv:1801.04016 (2018).
- S.P. Phillips and K. Hamberg. 2016. Doubly blind: a systematic review of gender in randomised controlled trials. *Global health action* 9, 1 (2016), 29597.
- J. M. Pisapia, H. Akbari, M. Rozycki, H. Goldstein, S. Bakas, S. Rathore, J. S. Moldenhauer, P. B. Storm, D. M. Zarnow, R. C. Anderson, and others. 2017. Use of fetal magnetic resonance image analysis and machine learning to predict the need for postnatal cerebrospinal fluid diversion in fetal ventriculomegaly. *JAMA pediatrics* (2017).
- R. Pivovarov, Y.J. Coppleson, S.L. Gorman, D.K. Vawdrey, and N. Elhadad. 2016. Can Patient Record Summarization Support Quality Metric Abstraction?. In AMIA Annual Symposium Proceedings, Vol. 2016. American Medical Informatics Association, 1020.
- R. Pivovarov, A.J. Perotte, E. Grave, J. Angiolillo, C.H. Wiggins, and N. Elhadad. 2015. Learning probabilistic phenotypes from heterogeneous EHR data. *Journal of biomedical informatics* 58 (2015), 156–165.
- R. Poplin, A.V. Varadarajan, K. Blumer, Y. Liu, M.V. McConnell, G.S. Corrado, L. Peng, and D.R. Webster. 2018. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. *Nature Biomedical Engineering* (2018), 1.
- R.L. Prentice, R.D. Langer, M.L. Stefanick, B.V. Howard, M. Pettinger, G.L. Anderson, D. Barad, J.D. Curb, J. Kotchen, L. Kuller, and others. 2006. Combined analysis of Women's Health Initiative observational and clinical trial data on postmenopausal hormone treatment and cardiovascular disease. *American Journal of Epidemiology* 163, 7 (2006), 589–599.
- A. Rajkomar, E. Oren, K. Chen, A.M. Dai, N. Hajaj, P.J. Liu, X. Liu, M. Sun, P. Sundberg, H. Yee, and others. 2018. Scalable and accurate deep learning for electronic health records. *arXiv* preprint *arXiv*:1801.07860 (2018).
- R. Ranganath, A. Perotte, N. Elhadad, and D. Blei. 2016. Deep Survival Analysis. In *Machine Learning for Healthcare Conference*. 101–114.
- N. Razavian, J. Marcus, and D. Sontag. 2016. Multi-task prediction of disease onsets from longitudinal lab tests. *arXiv preprint arXiv:1608.00647* (2016).
- B. Y. Reis, I. S. Kohane, and K.D. Mandl. 2009. Longitudinal histories as predictors of future diagnoses of domestic abuse: modelling study. *Bmj* 339 (2009), b3677.
- M.T. Ribeiro, S. Singh, and C. Guestrin. 2016. Why should i trust you?: Explaining the predictions of any classifier. In *International Conference on Knowledge Discovery and Data Mining (KDD)*. ACM, 1135–1144.
- Z. Ricci, D. Cruz, and C. Ronco. 2008. The RIFLE criteria and mortality in acute kidney injury: a systematic review. *Kidney International* 73, 5 (2008), 538–546.
- R.L. Richesson, W.E. Hammond, M. Nahm, D. Wixted, G.E. Simon, J.G. Robinson, A.E. Bauck, D. Cifelli, M.M. Smerek, J. Dickerson, and others. 2013. Electronic health records based phenotyping in next-generation clinical trials: a perspective from the NIH Health Care Systems Collaboratory. *Journal of the American Medical Informatics Association* 20, e2 (2013), e226–e231.
- J.M. Robins. 2000. Robust estimation in sequentially ignorable missing data and causal inference models. In *Proceedings of the American Statistical Association*, Vol. 1999. 6–10.
- J.M. Robins, A. Rotnitzky, and D.O. Scharfstein. 2000. Sensitivity analysis for selection bias and unmeasured confounding in missing data and causal inference models. In *Statistical models in epidemiology, the environment, and clinical trials*. Springer, 1–94.
- G.K. Savova, J.J. Masanz, P.V. Ogren, J. Zheng, S. Sohn, K.C. Kipper-Schuler, and C.G. Chute. 2010. Mayo clinical Text Analysis and Knowledge Extraction System (cTAKES): architecture, component evaluation and applications. *Journal of the American Medical Informatics Association* 17, 5 (2010), 507–513.

- P. Schulam and S. Saria. 2017. Reliable decision support using counterfactual models. In *Neural Information Processing Systems (NIPS)*.
- B. Settles. 2012. Active learning. Synthesis Lectures on Artificial Intelligence and Machine Learning 6, 1 (2012), 1–114.
- B. Shneiderman, C. Plaisant, and B.W. Hesse. 2013. Improving healthcare with interactive visualization. *Computer* 46, 5 (2013), 58–66.
- M. Singer, C.S. Deutschman, C.W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, R. Bellomo, G.R. Bernard, J. Chiche, C.M. Coopersmith, and others. 2016. The third international consensus definitions for sepsis and septic shock (sepsis-3). *Journal of the American Medical Association (JAMA)* 315, 8 (2016), 801–810.
- R. Socher, M. Ganjoo, C.D. Manning, and A. Ng. 2013. Zero-shot learning through cross-modal transfer. In *Advances in Neural Information Processing Systems (NIPS)*. 935–943.
- M. Stewart. 2003. *Patient-centered medicine: transforming the clinical method*. Radcliffe Publishing.
- H. Suresh, N. Hunt, A. Johnson, L.A. Celi, P. Szolovits, and M. Ghassemi. 2017. Clinical Intervention Prediction and Understanding with Deep Neural Networks. In *Machine Learning for Healthcare Conference*. 322–337.
- J. Travers, S. Marsh, M. Williams, M. Weatherall, B. Caldwell, P. Shirtcliffe, S. Aldington, and R. Beasley. 2007. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? *Thorax* 62, 3 (2007), 219–223.
- A. Tsymbal. 2004. The problem of concept drift: definitions and related work. *Computer Science Department, Trinity College Dublin* 106, 2 (2004).
- G.M. Weber and I.S. Kohane. 2013. Extracting physician group intelligence from electronic health records to support evidence based medicine. *PloS one* 8, 5 (2013), e64933.
- G. M. Weber, K.D. Mandl, and I. S. Kohane. 2014. Finding the missing link for big biomedical data. *Jama* 311, 24 (2014), 2479–2480.
- S. F. Weng, J. Reps, J. Kai, J. M. Garibaldi, and N. Qureshi. 2017. Can machine-learning improve cardiovascular risk prediction using routine clinical data? *PloS one* 12, 4 (2017), e0174944.
- D. J. Williams, S. S. Shah, A. Myers, M. Hall, K. Auger, M. A. Queen, K. E. Jerardi, L. McClain, C. Wiggleton, and J. S. Tieder. 2013. Identifying pediatric community-acquired pneumonia hospitalizations: accuracy of administrative billing codes. *JAMA pediatrics* 167, 9 (2013), 851–858.
- S.J. Winawer, R.H. Fletcher, L. Miller, F. Godlee, M.H. Stolar, C.D. Mulrow, S.H. Woolf, S.N. Glick, T.G. Ganiats, J.H. Bond, and others. 1997. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* 112, 2 (1997), 594–642.
- Y. Xu, Y. Xu, and S. Saria. 2016. A Bayesian nonparametric approach for estimating individualized treatment-response curves. In *Machine Learning for Healthcare Conference (MLHC)*.
- S. Yu, Y. Ma, J. Gronsbell, T. Cai, A.N. Ananthakrishnan, V.S. Gainer, S.E. Churchill, P. Szolovits, S.N. Murphy, I.S. Kohane, and others. 2017. Enabling phenotypic big data with PheNorm. *Journal of the American Medical Informatics Association* 25, 1 (2017), 54–60.
- J. Zhu, P. Krähenbühl, E. Shechtman, and A.A. Efros. 2016. Generative visual manipulation on the natural image manifold. In *European Conference on Computer Vision*. Springer, 597–613.