Review

Evolving Applications of Artificial Intelligence and Machine Learning in Infectious Diseases Testing

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BACKGROUND: Artificial intelligence (AI) and machine learning (ML) are poised to transform infectious disease testing. Uniquely, infectious disease testing is technologically diverse spaces in laboratory medicine, where multiple platforms and approaches may be required to support clinical decision-making. Despite advances in laboratory informatics, the vast array of infectious disease data is constrained by human analytical limitations. Machine learning can exploit multiple data streams, including but not limited to laboratory information and overcome human limitations to provide physicians with predictive and actionable results. As a quickly evolving area of computer science, laboratory professionals should become aware of AI/ML applications for infectious disease testing as more platforms are become commercially available.

CONTENT: In this review we: (*a*) define both AI/ML, (*b*) provide an overview of common ML approaches used in laboratory medicine, (*c*) describe the current AI/ML landscape as it relates infectious disease testing, and (*d*) discuss the future evolution AI/ML for infectious disease testing in both laboratory and point-of-care applications.

SUMMARY: The review provides an important educational overview of AI/ML technique in the context of infectious disease testing. This includes supervised ML approaches, which are frequently used in laboratory medicine applications including infectious diseases, such as COVID-19, sepsis, hepatitis, malaria, meningitis, Lyme disease, and tuberculosis. We also apply the concept of "data fusion" describing the future of laboratory testing where multiple data streams are integrated by AI/ML to provide actionable clinical knowledge.

Introduction

Infectious disease testing is one of the most technologically diverse spaces in laboratory medicine. Beginning with Koch's postulates published in 1890, infectious disease testing has evolved from simple microscopy and microbiological culture to modern techniques ranging from immunoassays (e.g., direct pathogen detection, serology) and MALDI–TOF–MS, to molecular diagnostics (Fig. 1) (1–3). In some cases, several tests may be used in combination to produce definitive results (e.g., blood culture → MALDI–TOF–MS → antimicrobial susceptibility testing) (4).

In the 21st century, infectious disease testing has heavily leveraged information technology (5). Both laboratory and point-of-care (POC) platforms quickly transmit results to electronic medical record (EMR) systems to integrating other data streams (e.g., vitals monitors, imaging systems, home testing devices) to help physicians determine the best course of action. By having all medical data stored in the EMR, it was hoped clinical decision-making would become more efficient (6). Unfortunately, this digitization of medical data has created a state of "information overload" for healthcare professionals (7) — causing data to be unintentionally ignored, misinterpreted, and/or potentially masking clinically significant patterns.

On average, humans can comfortably interpret and integrate up to 4 variables at a time (8) — limiting the value of EMR data. For example, the number of variables used for sepsis prediction, can range from a few simple parameters (e.g., heart rate, white blood cell [WBC] count, respiratory rate [RR], and body temperature) to hundreds of time-series measurements which could quickly overwhelm an individual (9–12). Computers do not share these limitations since they can handle a wider range of variables simultaneously and recognize patterns that are not apparent to the human eye. Thus, the use of predictive analytics via artificial intelligence (AI)/machine learning (ML) could
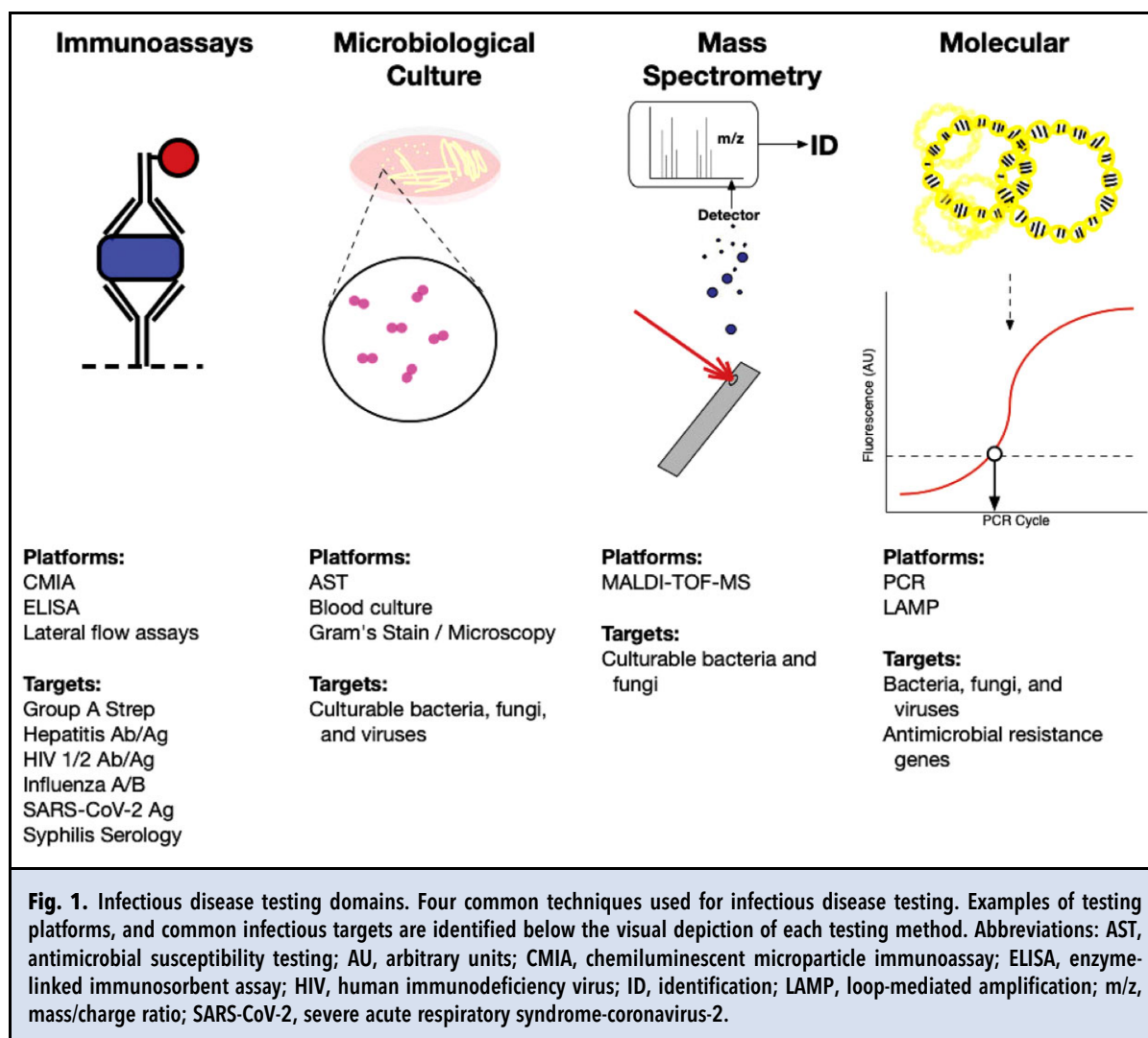
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Fig. 1. Infectious disease testing domains. Four common techniques used for infectious disease testing. Examples of testing platforms, and common infectious targets are identified below the visual depiction of each testing method. Abbreviations: AST, antimicrobial susceptibility testing; AU, arbitrary units; CMIA, chemiluminescent microparticle immunoassay; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; ID, identification; LAMP, loop-mediated amplification; m/z, mass/charge ratio; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

enhance our ability to identify clinically significant patterns, including those for infectious diseases (13).

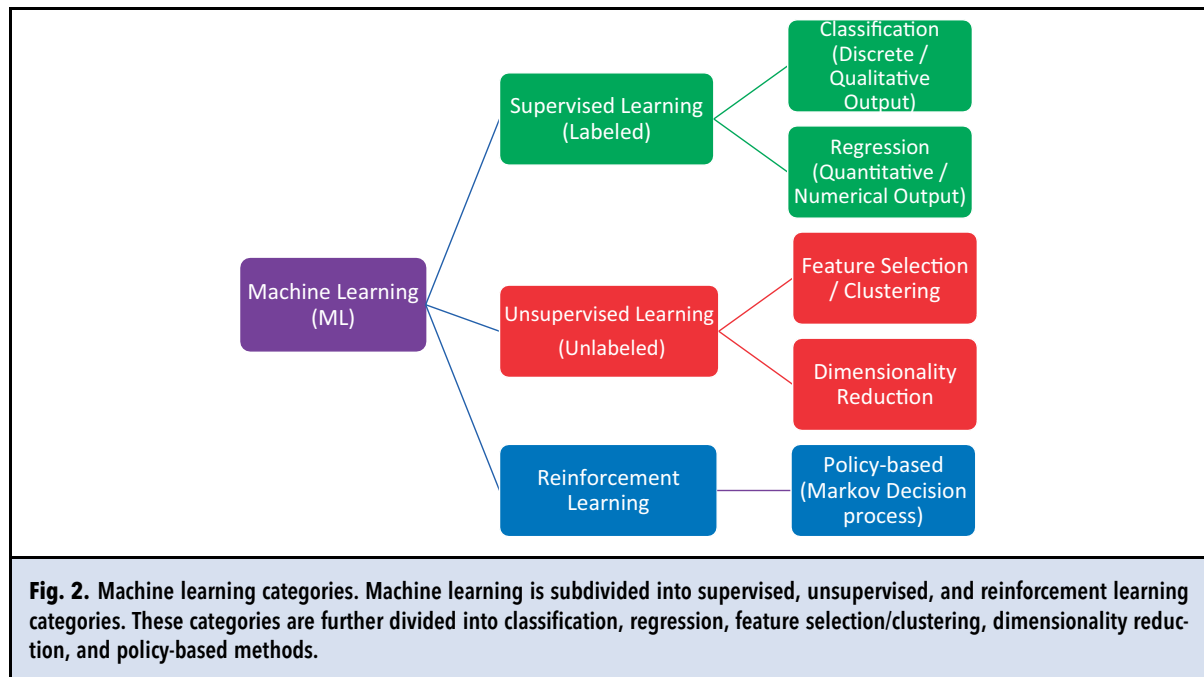## Artificial Intelligence and Machine Learning

Artificial intelligence is a rapidly evolving field of computer science and statistics aimed at producing systems that mimic human behavior (14, 15). In contrast, ML is an application of AI that enables systems to automatically learn from new data without explicit programming. Machine learning algorithms ultimately enable one to improve the predictive analytic performance for a given task and/or acquire new skills over time when trained with more data. Classically, ML is grouped into 3 major categories discussed in this review (14–24): (*a*) supervised learning, including classification and regression approaches, (*b*) unsupervised learning, and (*c*)

reinforcement learning (Fig. 2). Here we provide a general overview of ML techniques with emphasis on applications for infectious disease testing. For more detailed discussion on AI/ML theory and techniques, we refer the reader to other publications (16–24).

MACHINE LEARNING TECHNIQUES
Laboratory medicine data often favor the use of supervised learning for ML applications largely due to the large amount of information and types of data (e.g., image versus numerical values versus text) available in this discipline (11, 14, 16, 25, 26). It must be noted, however, that as more studies use AI/ML, and computing power and portability increases, these predictive analytics will quickly evolve over time.

The type of data also influences which ML methods are used (14). Example of ML methods include

Fig. 2. Machine learning categories. Machine learning is subdivided into supervised, unsupervised, and reinforcement learning categories. These categories are further divided into classification, regression, feature selection/clustering, dimensionality reduction, and policy-based methods.

parametric techniques such as logistic regression, while nonparametric methods include neural network and non-neural network approaches such as linear regression, logistic regression, naïve Bayes, gradient boosting machine/decision tree, k-nearest neighbor (k-NN), support vector machine (SVM), and random forest (RF) (Fig. 3).

Machine Development Tools

Traditional AI/ML development requires substantial expertise and time. Programming languages used for various AI/ML tools include Python and R (1, 11, 14, 25, 26). Often, developers may take months to train and test a single supervised algorithm. This process could be further prolonged if there is a need to determine the best feature combinations to include or exclude in their models. Additionally, given the rapidly moving AI/ML landscape, not all data scientists may be comfortable with all methods. For example, some data scientists may prefer one technique versus another (e.g., SVM vs neural networks)—potentially creating bias and/or limiting the potential for discovery of better performing ML algorithms. Alternately, a priori determination of feature set combinations impacts ML model performance.

Due to these potential limitations, automated ML platforms have gained popularity (11, 25, 26). These "Auto-ML" platforms allow users to import train and test data, which are then automatically run through the whole process of feature selection, model building, and

validation. An AI/ML programming task that could take a single data scientist months now takes a few hours. Examples of automated ML platforms include H2OAI AutoML, Microsoft ML.NET, Tree-based Pipeline Optimization Tool, Machine Intelligence Learning Optimizer, and AutoSKLearn (11, 17, 25).
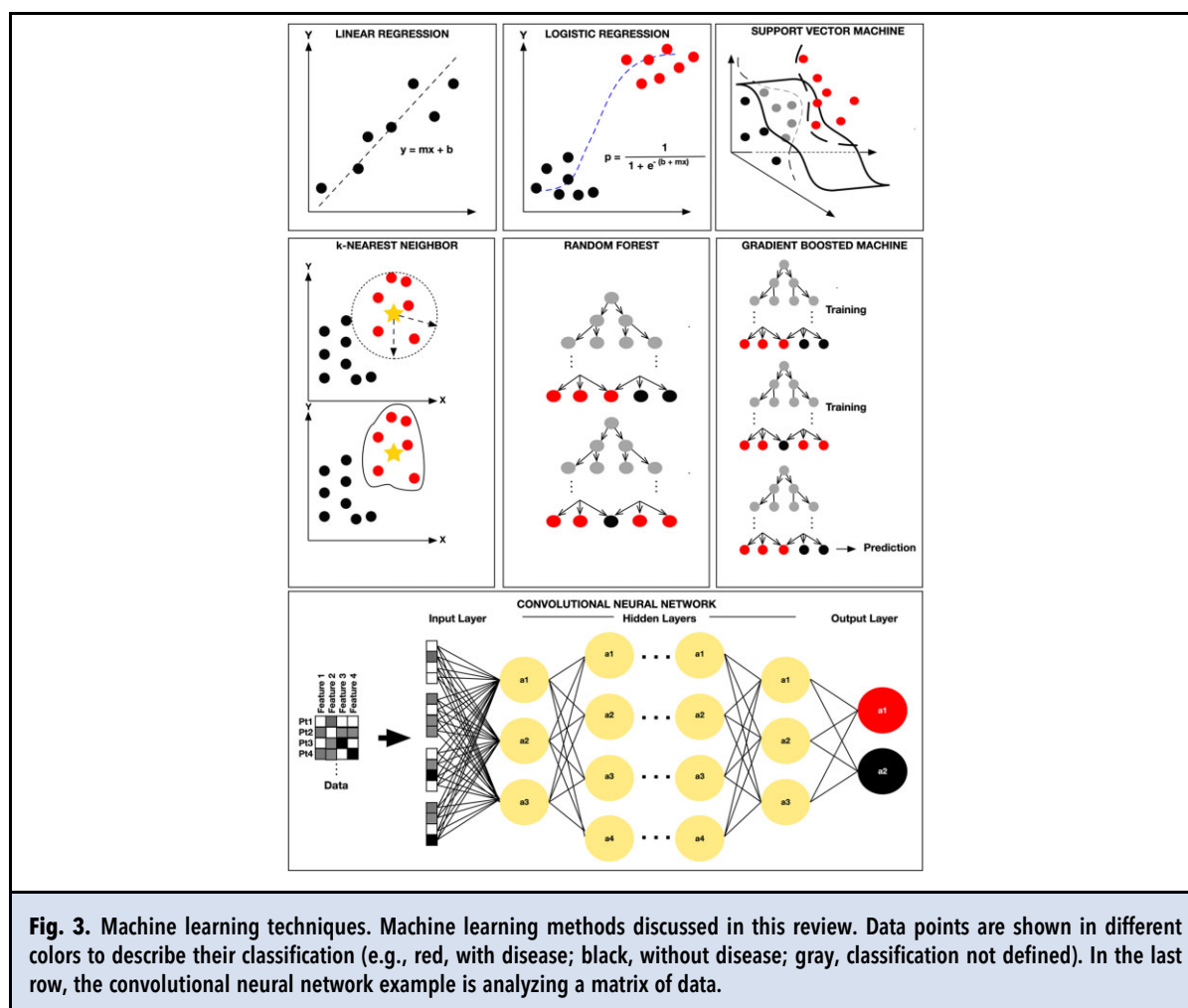
Machine Learning Applications for Infectious Disease Testing

AI/ML is poised to transform not only bedside medicine, but also the field of infectious disease testing. In particular, infectious disease testing has seen a surge in miniaturization, automation, and increasing computing power, creating a unique opportunity to exploit AI/ML. We can categorize the applications into 3 categories: (a) laboratory diagnostics, (b) clinical prognosis, and (c) clinical diagnostics. Application examples are discussed next.

LABORATORY DIAGNOSTICS
Novel 2019 coronavirus infectious disease (COVID-19). The COVID-19 pandemic resulted in a substantial demand for molecular testing in the USA (27, 28). Early in the pandemic, molecular capacity was not sustainable and impacted the US response in controlling the spread of severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 infections. Asymptomatic spread of COVID-19 further increased demand for testing (29).

Alternative testing approaches using MALDI–TOF–MS have been proposed as a low-cost, rapid, and

Fig. 3. Machine learning techniques. Machine learning methods discussed in this review. Data points are shown in different colors to describe their classification (e.g., red, with disease; black, without disease; gray, classification not defined). In the last row, the convolutional neural network example is analyzing a matrix of data.

high-throughput solution to alleviate demand on molecular testing (26, 30). Briefly, MALDI–TOF–MS detects ionizable proteins from respiratory samples such as anterior nares swabs, producing hundreds or even thousands of MS spectra peaks per samples. The use of AI/ML provides means to identify MALDI–TOF–MS profiles specific to COVID-19. Recent studies have used a neural network approach to analyze MALDI–TOF–MS spectra that achieved a sensitivity and specificity of 100% and 96%, respectively, with an area under the receiver operating characteristic (ROC) curve of 0.99 when using 487 peaks that span 1993.91 to 199 590.89 *m/z* (26). It must be also noted that these published MALDI–TOF–MS methods currently detect the host response to COVID-19, rather than the virus itself.

Antimicrobial susceptibility testing (AST). Antimicrobial resistance is one of the top 10 global public health threats defined by the World Health Organization (31).

The inappropriate use of antimicrobial therapy fuels the persistence of existing drug resistant organisms, and the development of multidrug resistant strains. Currently, detection of resistant organisms relies on microdilution in vitro AST or molecular approaches (32). Microdilution AST involves exposing a known concentration of cultured microbes to antimicrobials to determine a minimum inhibitory concentration. Molecular approaches target specific genes to rapidly determine genotypic resistance rather than determining in vitro susceptibility to antimicrobials.

The application of AI/ML for AST has been reported for MALDI–TOF–MS techniques (32). For MALDI–TOF–MS, ML (e.g., neural networks, SVM, RF, *k*-NN) is used to analyze spectra representing ionizable proteins (mostly ribosomal proteins) from cultured bacteria. In one study, SVM was used to differentiate methicillin resistant *Staphylococcus aureus* versus methicillin sensitive *S. aureus* with an accuracy of 85% (33).

In another study, 5 different ML algorithms (*k*-NN, RF, SVM, naïve Bayes, and logistic regression) were used to identify carbapenem resistant versus sensitive *Klebsiella pneumonia* MALDI–TOF–MS spectra, achieving an accuracy of over 93% (34).

Malaria. Detection of *Plasmodium* species remains challenging due to the unique nature of the parasite (35). Microscopic examination with thin and thick smears requires experienced personnel. Rapid antigen testing is available but may not detect or easily differentiate between *Plasmodium* subspecies. Machine learning techniques have been proposed to microscopically analyze blood smears, including at the point of care via smartphone-based applications. In a study using neural network, SVM, and *k*-NN approaches, the investigators were able to produce models that achieved a sensitivity and specificity as high as 99.5% and 99.1% with an accuracy of 99.2% using a smartphone based slide imaging software (35).

Lyme disease. Lyme disease is the most common vector-borne infectious disease in North America and Europe (36). Timely diagnosis is necessary to prevent progression, especially if the early disease presentation is missed. Current Lyme disease tests, however, exhibit poor sensitivity (<50%) for early presenters. One group has proposed a multiplex POC sero-diagnostic test targeting antigens OspC, BmpA, P41, ErpD, Crasp1, OspA, DbpB, VlsE, P35, and Mod-C6 enhanced by ML to improve clinical performance, with a reported sensitivity of 90.5% and specificity of 87.0% (37).

CLINICAL PROGNOSIS

Hepatitis B virus infection. Hepatitis B virus has resulted in over 250 million chronically infected individuals worldwide (38). At present, hepatitis B surface antigen and hepatitis B core antigen are the primary biomarkers for predicting virological relapse. Unfortunately, these methods still exhibit poor performance. The use of ML to predict early virological relapse following discontinuation of therapy has shown promise. A supervised ML approach has been used to predict early virological relapse using soluble immune markers profiles (39). Optimal ML models using a combination of interleukin-2, monocyte induced interferon gamma, regulation on activation normal T-cell expressed and secreted, stem cell factor, and tumor necrosis factor related apoptosis-inducing ligand produced the highest predictive values for early virological relapse following treatment cessation.

Hepatitis C virus (HCV) infection. Serology and molecular approaches remain the gold standard for HCV screening. Detection of strains resistant to direct-acting antivirals, however, as well as predicting chronic HCV infection progression, has proven challenging (40). In one study, SVM was used to analyze HCV genomes to determine which patients could produce sustained viral response, producing an accuracy 95.4% (40). Another study employed longitudinal ML models incorporating laboratory (i.e., albumin, platelet, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, alpha fetoprotein), and existing scoring (i.e., MELD, Ishak) data to predict chronic HCV infection progression (41). The area under the ROC curve for optimal RF models predicting fibrosis progression was 0.79, while models predicting clinical progression achieved an area under the ROC curve of 0.86.

CLINICAL DIAGNOSTICS

Meningitis. Meningitis results in 36 000 hospitalizations annually in the USA, costing between $234 and $310 million per year (42). Detection and differentiation of viral versus bacterial meningitis has been augmented by molecular platforms. Unfortunately, molecular tests still rely on invasive collection of cerebrospinal fluid (CSF). More traditional tests including CSF Gram stain and measurement of CSF WBC, glucose, and protein concentrations can provide rapid results, but are not always sensitive or specific. Several investigators have studied the use of AI/ML to enhance detection of meningitis (43, 44). One of these studies described a neural network-based approach based on 6 features including lymphocyte count, blood glucose, and age that produced an accuracy of 86.3% (44). The second study reported improved performance using naïve Bayes, neural network, and genetic programming techniques with age, race, sex, WBC, blood glucose, CSF glucose/protein/leukocytes (if available) as features (43). Naïve Bayes and neural network techniques exhibited sensitivity/specificity of 98%/98% and 99%/100%, respectively. The AI/ML approach produced an algorithm that achieved a sensitivity of 100% and 99%.

Sepsis. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (45). Early recognition of sepsis is critical to survival (46). Unfortunately, parameters for recognizing sepsis are not always sensitive nor specific. The systemic inflammatory response syndrome criteria introduced in 1992 is a major foundation of both past and present sepsis criteria (47). Although updated in more recent times (48, 49), the systemic inflammatory response syndrome criteria remain the same and focus on abnormal body temperature, RR, HR, and WBC count: parameters that are hardly specific for infection. Subsequent sepsis criteria have attempted to improve specificity by including other elements such as indicators of organ

dysfunction, but resulted in far too many variables to account for by a single human.

Electronic Health Record sepsis ML algorithms: Since EMR systems serve as the central repository of data, the use of AI/ML and statistical algorithms have been used to predict sepsis (49, 50). Sensitivity and specificity are reported to be 87% for statistical (non-AI/ML) algorithms with an area under the ROC curve of 0.94 when using 15 features (i.e., age, gender, blood pressure, HR, temperature, oxygen saturation, RR, WBC count, microbiological culture results, lactate, high sensitivity C-reactive protein, procalcitonin, arterial blood gas, use of vasopressors, and use of antibiotics). Application of AI/ML in sepsis has improved prediction performance (51, 52) including its use in more challenging populations such as burn patients (53, 54). Using heart rate, body temperature, hemoglobin, blood urea nitrogen, and total CO_2 as features with k-NN, sensitivity, and specificity was observed to be 95.8% and 87.8%, respectively, with an area under the ROC curve of 0.96 for predicting burn sepsis (53).

Sepsis host-response ML approaches: Expanding from traditional indicators of sepsis, other investigators have used ML to predict sepsis using a multi-RNA host-response approach. One study described a 29-host-mRNA based blood test that combined ML with a less than 30-min turnaround time POC test (55). This technique used a neural network based that achieved an area under the ROC curve of 0.92 and 0.91 for identifying individuals enrolled within 36 h of admission with bacterial or viral infections, respectively (56).

Tuberculosis. Tuberculosis remains a global healthcare problem. The use of AI/ML techniques has been studied for over a decade to aid in the diagnosis of tuberculosis, including the use of neural networks and SVM (57, 58). Support vector machines incorporating CD4 counts, human immunodeficiency virus status, purified protein derivative status, chest pain, weight loss, coughs, night sweats, fever, shortness of breath, total hemoglobin, platelet count, WBC count, neutrophil count, lymphocyte count, erythrocyte sedimentation rate, alanine aminotransferase, alkaline phosphatase, and lactate dehydrogenase concentration as features have exhibited 100% sensitivity and specificity (58). The investigators leading these studies, however, concede that future investigations are needed to determine the generalizability of this technique given the sample size.
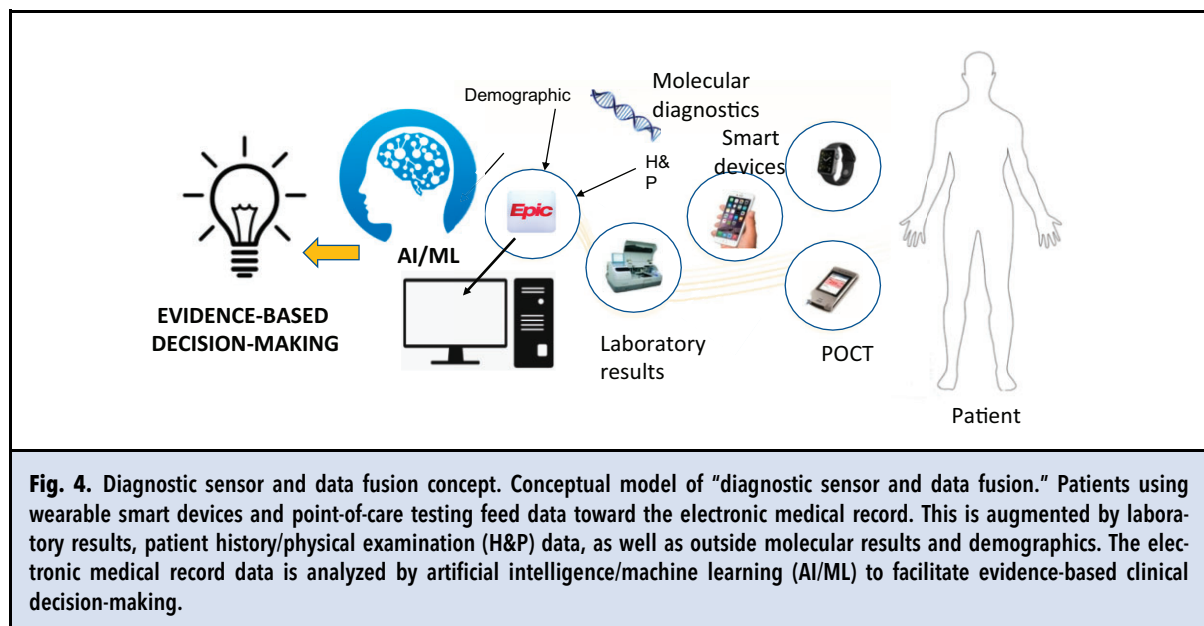
Machine Learning Best Practices

Machine learning algorithm performance is dependent on the quality of data used for training and testing.

Challenges include the ability for laboratories and/or clinical services to generate, collect, standardize, and quality control data that can be used in AI/ML. Overcoming these challenges will pave the way for optimal training and testing of candidate ML algorithms with datasets to increase overall performance. Developers and investigators also should be not tied to a single ML method or even particular features since this can bias analyses. A stepwise approach to develop ML for laboratory medicine applications has been discussed (16). Step 1 involves assessing the quality and accessibility of the data, followed by Step 2, which requires method validation to identify optimal AI/ML model(s). Once optimal AI/ML models have been identified, Step 3 involves determining their ability to work for other secondary and tertiary datasets (generalizability). Finally, Step 4 involves evaluating the data in more "real world" conditions to further assess performance and refine (go back to Step 2) as needed to achieve a desirable outcome.

Future Applications

The future of infectious disease diagnostics will involve the fusion of multiple data streams (i.e., vital signs, host-response biomarkers, traditional laboratory tests, etc.) with AI/ML to produce high quality clinically actionable results. This concept of "data fusion" is not new and is already prevalent in normal everyday life. Data fusion (in contrast to data integration) is the process of gathering data from multiple sources to produce more sophisticated models and better understand a disease or problem (59, 60). For example, data fusion of data from geofenced and connected smart devices (e.g., watches, tablets, cellular phones, etc.) provide a means to enhance the user experience while helping them to predict customer needs (60). Semiautonomous and autonomous vehicles also leverage this concept (61). In the context of infectious disease testing, AI/ML could enhance clinician and patient experience through integrating in vitro diagnostic testing with information from the EMR, in the form of data fusion, to facilitate predictive analytics (Fig. 4).

POC infectious disease testing represents another potential area that could be transformed by AI/ML By design, POC devices reside in a decentralized ecosystem—necessitating operation in a network-centric manner to gather a substantial amount of medical information (62). Wearable POC devices (e.g., smart watches), in particular, can now monitor oxygen saturation, and provide one-lead electrocardiogram and heart rate. Diabetics are now able to directly record discrete or continuous blood glucose concentrations, body weight, and blood pressure into their smart phones (63), stored in a centralized application (e.g., Apple HealthKit,

Fig. 4. Diagnostic sensor and data fusion concept. Conceptual model of "diagnostic sensor and data fusion." Patients using wearable smart devices and point-of-care testing feed data toward the electronic medical record. This is augmented by laboratory results, patient history/physical examination (H&P) data, as well as outside molecular results and demographics. The electronic medical record data is analyzed by artificial intelligence/machine learning (AI/ML) to facilitate evidence-based clinical decision-making.

Google Fit), and upload their data to compatible EMR, producing a valuable collection of persistent patient data that could be analyzed by AI/ML to predict disease. Such an example has been employed through the recent FDA emergency use authorization of the COVID Plus Monitor (Tiger Tech Solutions) that identifies patients who may exhibit signs of SARS-CoV-2 infection (64).

Conclusion

Artificial intelligence and ML will transform infectious disease testing. The use of AI/ML for sepsis management highlights the power of this technology for mining EMR data and prompting clinical action with better sensitivity and specificity compared to traditional approaches. Machine learning shows promise for a range of infectious disease applications such as COVID-19, hepatitis, malaria, Lyme disease, and tuberculosis. However, AI/ML should be implemented in a systematic and rational way to ensure data quality is not compromised, and model development is performed with minimal bias. The use of automated ML platforms is also an exciting development where thousands of candidate models could be automatically trained and tested across a range of feature combinations and allowing developers to quickly identify optimal algorithms for further development. Ultimately, the future of AI/ML infectious disease testing may revolve around concepts of "data fusion" to not only integrate multiple data streams, but also convert vast amounts of heterogenous data into actionable knowledge.

Review

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