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Artificial Intelligence: Exploring the Future of Innovation in Allergy Immunology

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Abstract

Purpose of Review Artificial intelligence (AI) has increasingly been used in healthcare. Given the capacity of AI to handle large data and complex relationships between variables, AI is well suited for applications in healthcare. Recently, AI has been applied to allergy research.

Recent Findings In this article, we review how AI technologies have been utilized in basic science and clinical allergy research for asthma, atopic dermatitis, rhinology, adverse reactions to drugs and vaccines, food allergy, anaphylaxis, urticaria, and eosinophilic gastrointestinal disorders. We discuss barriers for AI adoption to improve the care of patients with atopic diseases.

Summary These studies demonstrate the utility of applying AI to the field of allergy to help investigators expand their understanding of disease pathogenesis, improve diagnostic accuracy, enable prediction for treatments and outcomes, and for drug discovery.

Keywords Artificial intelligence · Allergy · Immunology · Machine learning · Neural network · Algorithmic bias

Introduction

Artificial intelligence (AI) has been adopted in many industries outside of the healthcare field. AI is the harnessing of advanced computational algorithms to model complex human cognitive capabilities by learning and adapting to data that is collected. The study and application of AI in healthcare have increased rapidly in the last decade [1•, 2]. Within the field of allergy and immunology, early work has largely focused on inborn errors of immunity, asthma, and atopic dermatitis, but few applications have been broadly implemented [3••, 4]. Traditional statistics has not adequately tackled complex datasets in medicine given the interdependent nonlinear relationships in a dataset [5]. Several domains of AI, including machine learning (ML), deep learning (DL), and natural language processing (NLP), have significant potential to improve both diagnostic and therapeutic capabilities, as well as improve efficiency for clinicians and the healthcare system [6–8] (Table 1).

Interest in applying AI to other allergy and immunology diagnostic and predictive applications is expanding (Fig. 1) while also balancing the risks and benefits of adoption [9, 10]. A recent study from Mayo Clinic evaluating clinicians' adherence to asthma guidelines with AI illustrates some of these concepts. Clinical notes from 300 asthma patients were selected for analysis, 200 for a training set and 100 for a test set [11•]. With ML, the model must first be trained on a representative set of data and then validated with a test set of unseen data. The learning process on the training set can be supervised, in which the data are labeled, or unsupervised, in which the data are unlabeled and the algorithm analyzes the data without human intervention [12]. In this study, the investigators used natural language processing (NLP) to analyze and extract data from text in clinician notes. NLP, sometimes referred to as text mining, is a method of computer-based analysis of unstructured text [3••]. It utilizes deep

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Table 1 AI terminology

Artificial intelligence (AI) Automated systems that perform tasks that mimic human intelligence				
Machine learning (ML) The process of developing systems with the ability to learn from data and make predictions without prespecified programming [3••, 7, 12]				
Elastic net regression A regularized logistic regression ML for the classification of problems with more variables than classification items [17, 18]	Decision tree analysis (DTA) A ML method used to make predictions based on prior observations [3••, 32, 78]	Support vector machine (SVM) A ML method that uses labeled data to train models for classification or regression [32, 34]	Random forest (RF) A ML method that uses multiple decision trees for classification or regression (18)	K-nearest neighbor (KNN) A ML method used for classification based on similarities between features [32]
Deep learning (DL) A subset of ML that uses layers of neural networks to process complex data [8]				
Natural language processing (NLP) A method of computer-based analysis of unstructured text [3••, 8]				
Artificial neural network (ANN) A collection of interconnected nodes, inspired by biological neural networks, designed to recognize complex patterns in data to solve similar problems in the future [32, 61]	Convolutional neural network (CNN) A class of ANN designed to process data from multiple arrays, often applied to the analysis of images [32]		Recurrent neural network (RNN) A type of ANN in which connections between nodes create cycles where a node's output affects future inputs and outputs [14]	
Receiver operator curve (ROC) A graphical representation of the performance of a model that depicts the true positive rate, or sensitivity, as a function of the false positive rate, or 1-specificity, along a curve		Area under the ROC curve (AUC ROC) A numeric measure of the performance of a model by its ability to separate or distinguish between measures or tests		

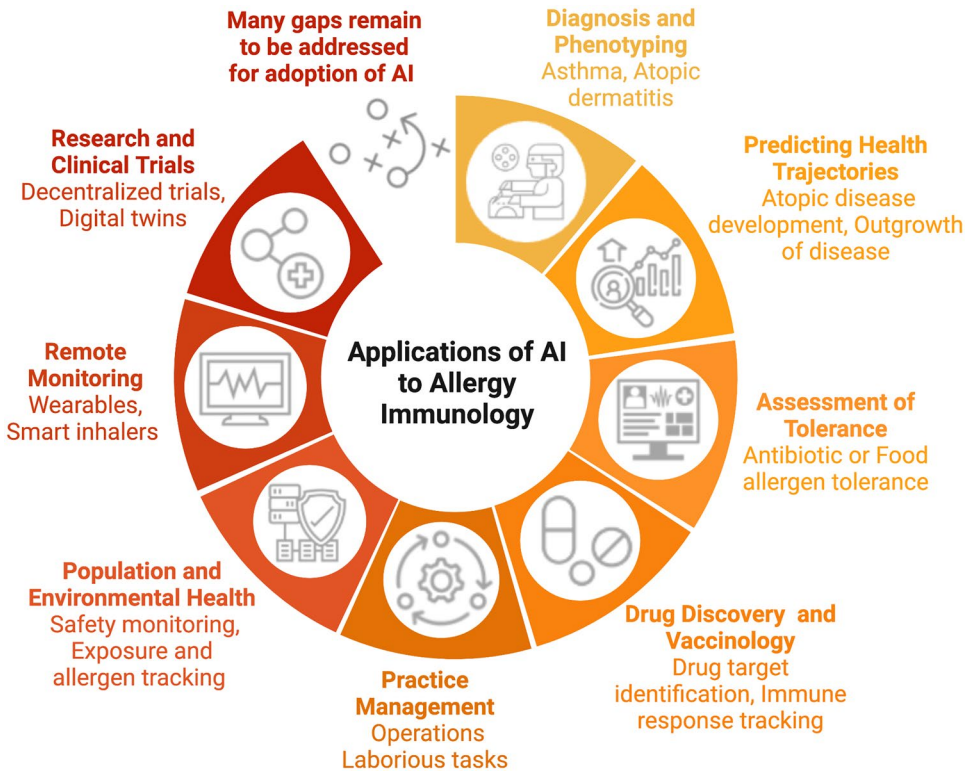

Fig. 1 Example applications and use cases of AI for allergy immunology. (created with Biorender)

learning (DL), a branch of ML in which a computer learns complex concepts by learning multiple simple concepts through multi-layered networks. The NLP model that the investigators used to evaluate clinicians' adherence to asthma guidelines utilized a rules-based algorithm that utilizes inputted knowledge about language and how facts are stated [13]. In this case, the algorithm was taught the 2007 National Asthma Education and Prevention Program guidelines to assess guideline-congruent elements described in free text from clinical notes. The model found that the clinicians' adherence to guidelines in primary care was low, and the investigators concluded that AI can be helpful in evaluating clinician performance compared to standards of care [11•].

AI can be harnessed to better understand the increasingly complex and large datasets of electronic health record (EHR) information including laboratory results, clinical notes, imaging, and genetic testing. Clinically, AI has the potential to provide decision support to clinicians to decrease delays in diagnosis. The study of AI in allergy and immunology is in its nascency, and further research and approaches for implementation are still in development. Challenges such as ethical, privacy, legal, and regulatory processes will need to be addressed before AI can be widely adopted and incorporated into clinical practice. Clinicians will also need to be trained to understand AI principles and ML models.

Key Clinical Applications of AI in Allergy

Asthma

Within the field of allergy, AI investigation and application have most frequently been applied to asthma due to the large population affected as well as healthcare utilization and costs associated with poorly controlled or severe asthma. Proposed benefits of AI for asthma include the prediction of future development of asthma, more accurate diagnosis, prediction of asthma exacerbations, evaluation of clinician adherence to asthma guidelines, and classifying asthma endotypes for optimal therapeutic intervention [11•, 14–23].

When the diagnosis of asthma is uncertain, ML can play a role in identifying which patients with respiratory symptoms indeed have asthma. ML models applied to data extracted from medical databases have been shown to accurately distinguish patients with asthma from other potential respiratory diagnoses, and further similar work has been proposed to strengthen such models [14, 15]. For children less than 5 years old, asthma diagnoses are often uncertain. Some clinicians are hesitant to apply an asthma diagnosis too early as many children will experience symptom resolution. ML models trained on clinical and demographic data from children diagnosed with

asthma between two and five years old within the Children's Hospital of Philadelphia Care Network were used to predict asthma persistence with up to 81% accuracy [24].

Once a diagnosis of asthma is clearly established, the prediction of asthma exacerbations is a clinical conundrum that could impact therapeutic decisions. ML models have been developed using factors such as environmental, clinical, and demographic data to predict exacerbations with an AUC greater than 0.7. These studies have been performed in a variety of patient populations from children to adults presenting for routine or emergency asthma encounters, and in different regional locations [16–18]. ML has also been used to identify which clinical and laboratory characteristics are most associated with a future exacerbation in adult patients presenting to the ED with an asthma exacerbation [19]. A peripheral blood eosinophil count was unsurprisingly found to have a prognostic role in predicting the risk of severe asthma exacerbations. New approaches such as "wearables" or remote patient monitoring (RPM) have allowed the evaluation of patterns by analyzing data from electronic inhalers [25]. Inhaler usage, peak inspiratory flow (PIF), time to PIF, inhalation volume, and inhalation duration were assessed [20]. The resulting ML model predicted asthma exacerbation in the next 5 days in individuals with an AUC of 0.83, representing successful prediction ability with clear clinical utility. Future ML application for asthma exacerbation prediction has been proposed using data from smart peak flow meters, smartwatches, and indoor air quality monitors, though real-world applicability of these methods will be dependent on cost, coverage, and availability of the technology [21, 22]. Given the volume and complexity of electronic monitoring device data and the growth of the digitally connected drug delivery market for inhalers, ML will be an essential tool for the utilization of RPM [26].

For optimal treatment of asthma, ML approaches to multi-omics datasets have been proposed to better understand asthma endotypes using predictive biomarkers [23]. The heterogeneity of asthma belies even standard biomarker approaches with patients exhibiting differential responses to the same monoclonal agent despite similar biomarker profiles. ML integration of high-dimensional "omics" data paired with clinical characteristics or "non-omics" represents an opportunity to increase precision and personalization in asthma care in the future [23]. The significant cost of asthma therapeutics, including biologic agents and inhalers, represents an opportunity for AI to reduce healthcare costs with quicker and more precise identification of responders to specific drugs. Given the multitude of complex data associated with an asthma diagnosis, prediction, and classification, AI has begun to be utilized more in asthma research with future clinical applicability.

Atopic Dermatitis

Given the high prevalence of atopic dermatitis in the general population, the quantity of data generated in claims databases lends itself to analysis with AI methods. Recently, AI has been applied to AD diagnosis, severity prediction and scoring, omics analysis, and treatment response prediction. AI in AD has been previously reviewed; however, the field remains active with research [4, 27–29].

AD may be diagnosed by different specialties with disparate approaches to the diagnosis of AD. Recent publications have demonstrated that photographic images of skin lesions can be analyzed using DL algorithms including deep convolutional neural network (CNN) and hybrid deep neural networks to accurately distinguish AD from other common skin conditions [30–32]. Data from other imaging modalities using ultrasound or dermal imaging have been proposed as potential avenues to improve diagnostic accuracy regardless of the specialist involved. Some examples include multiphoton tomography for noninvasive subcellular 3D-resolved imaging and Raster-scanning optoacoustic mesoscopy images that use DL CNN to diagnose AD based on their prior success in psoriasis diagnosis [33–35].

Beyond diagnosing AD, AI is useful in assessing and scoring the severity of AD. SCORing Atopic Dermatitis (SCORAD) is a commonly used clinical tool to measure AD severity; however, it is time-consuming and interobserver reliability is inconsistent [36]. Automatic SCORAD uses DL with CNN to measure AD severity accurately, rapidly, and without interobserver variability [37]. ML models trained on patient-reported data or serum biomarker measurements have been used to predict future AD severity with SCORAD [38–40]. Researchers have employed ML to identify which clinical and demographic characteristics are most associated with severe AD to better understand which patients are at the highest risk [41].

ML models and more complex datasets that incorporate transcripts, microbiota, metabolomic, and exposure data can help researchers to better understand AD pathogenesis [42–44]. For example, studies have associated pollution exposures with AD disease prevalence [45]. Similarly, AD flares have been associated with wildfires [46].

An important area of clinical interest in severe AD is determining which treatment options are best suited for individual patients as new therapies are discovered. A ML model using serum cytokines and chemokine data collected from patients prior to treatment with azathioprine or methotrexate was not able to successfully predict therapeutic response to these drugs [47]. However, a ML model trained on demographic and clinical variables of patients initiating dupilumab therapy for AD was able to predict non-response to dupilumab with 69% accuracy [48]. Predicting treatment response to AD therapeutics represents an important area for future application of AI.

Rhinology

AI strategies have been studied within the field of otolaryngology, including rhinosinusitis classification, image processing for diagnostic capabilities, treatment outcome prediction, and optimization of surgery. Rhinologists have assessed ML and DL algorithms in surgical planning using DL models to classify anatomic structures and to diagnose sinusitis [49–51]. A DL algorithm was developed to diagnose maxillary sinusitis on panoramic radiography with good sensitivity and specificity for the diagnosis of sinusitis, on par with the performance of radiologists and dental residents [52].

One of the challenges in treating CRS (chronic rhinosinusitis with nasal polyps, CRSwNP, or without CRSsNP) relates to the heterogeneity of presentations, as well as disparate responses to therapy in more refractory cases. AI has also been used to better understand CRS endotypes through ML clustering approaches [53]. A recent study used ANN modeling to distinguish an eosinophilic endotype of CRSwNP using clinical biomarkers. Clinical features included nasal nitric oxide levels, peripheral absolute eosinophil count, total IgE, and CT sinus scores. Two AAN models to predict eosinophilic CRSwNP outperformed logistic regression modeling with the AUC ROC of 0.976 vs 0.902 ($p = 0.048$) and 0.970 vs. 0.845 ($p = 0.011$) [54•]. Moving beyond disease subtypes of CRS to endotypes categorized by molecular and inflammatory profiles using algorithms for imaging as well as immune signatures may help determine more personalized and targeted diagnostic and management strategies. In the future, AI offers the promising opportunity to identify which CRS patients may respond to specific drugs as well as to aid in consideration of those who may most benefit from sinus surgery.

Adverse Reactions to Drugs

Drug allergy represents a significant public health issue with 7% of adults reporting a drug allergy, with an even higher prevalence of reported penicillin allergy among hospitalized patients [55, 56]. Classification of adverse drug reactions can be difficult with both inappropriate diagnoses as well as missed diagnoses. Indeed, less than 10% of patients who report a history of penicillin allergy have a positive skin test [57, 58]. Having a penicillin allergy label is associated with higher healthcare resource utilization, emphasizing the need for accurate diagnosis and labeling [59]. ML has been used to risk stratify, and potentially de-label penicillin allergy with medical record analysis playing a key role in addressing drug allergy at a population level [60, 61, 62•, 63, 64].

Hypersensitivity to NSAIDs or aspirin represents the most common drug hypersensitivity with broad implications, but little is known about its pathogenesis and aspirin-exacerbated respiratory disease (AERD) can be challenging to diagnose [65]. An ANN trained on demographic and laboratory data from a subset of asthma patients with and without AERD was able to diagnose AERD with 85% accuracy on a larger cohort of asthma patients [66]. In order to further understand the mechanisms of NSAID-induced urticaria/angioedema, an ML model was trained to distinguish between pre-dose and post-dose mRNA transcripts of patients undergoing aspirin desensitization in the setting of coronary artery disease from controls to identify differences in pathway enrichment before and after desensitization. The ML model found that the IL-22 pathway was most upregulated in the pre-desensitized patients [67].

In contrast to NSAIDs and ASA, skin testing and drug challenges are the mainstay for the evaluation of IgE-mediated penicillin allergy. However, the need for urgent drug administration or lack of appropriate specialists may impede appropriate evaluation [55, 68]. In these situations, AI may serve a role in identifying immediate IgE-mediated allergy in patients with a reported history of penicillin intolerance. An ANN trained on clinical data from patients with and without confirmed beta-lactam allergy at a single center was able to prospectively predict beta-lactam allergy with an AUC of 0.939 [61]. Another ANN trained on EHR data from patients with labeled penicillin allergy was able to distinguish between true allergy and intolerance with an AUC of 0.994 when compared with expert criteria and manual chart review [60].

Inaccuracies in documented drug allergies in the EHR are common and can be classified using AI. In one example, NLP algorithms were found to be more accurate in identifying and classifying drug reactions than ICD diagnostic codes review or equally as accurate to manual classification by pharmacists [62•, 63]. Even patients who have demonstrated tolerance to a prior listed allergy with a drug challenge continue to be labeled as allergic in the EHR. An NLP algorithm was developed to detect discrepancies between EHR-listed allergies and the results of drug challenges [64]. Such an approach could be used to ensure accurate categorization and alter prescribing in real time. These studies in aggregate demonstrate the potential utility of AI in identifying mechanisms of drug allergy, as well as identifying true IgE-mediated reactions by reported history; however, clinical validation and real-world clinical performance data in larger studies that include drug challenges will be needed prior to adoption.

Adverse Reactions to Vaccines

The development of SaRS-CoV2 mRNA vaccines heightened the focus on vaccine adverse events. With the initial reports of vaccine allergic reactions, a focus on polyethylene glycol (PEG) as a potential culprit component of mRNA COVID-19 vaccines

was raised as a cause of allergic and anaphylactic reactions. One study utilized an ML algorithm to evaluate EHR text for allergy documentation of clinician-reported PEG or vaccine allergy [69]. Another group trained an ML algorithm with demographics and clinical variables (allergic history, COVID-19 history, vaccine manufacturer, time of day of vaccination) from patients receiving COVID-19 mRNA vaccination to predict allergic and non-allergic symptoms 3 days after vaccination based on the patient report [70]. Despite the fact that ML has been proposed to analyze Vaccine Adverse Events Reporting System (VAERS) data in the US, the data structure, validity, and comprehensiveness of data entered are highly variable, as unstructured patient and clinician reporting occur [71]. One NLP model was developed to distinguish between adverse events and misinformation or false information reported in VAERS to extract the incidence of specific symptoms such as flu-like symptoms and arm-soreness with moderate to high accuracy, suggesting that this approach could be applied in the allergic context using different terms [72]. Although free-text data is ripe for AI, in reality, controlled studies of vaccine reactions may be better suited to discern reaction profiles such as "immunization-stress related response" as was found in one study [73]. Understanding the prevalence of and predicting specific vaccine adverse events in concert with controlled studies can help inform vaccine design.

Food Allergy

AI has been used to predict which pediatric patients will develop or have persistence of food allergies. A DL framework, specifically using long short-term memory (LSTM), was proposed to predict milk, egg, and peanut allergy in infants from birth to 3 years old in Russia, Finland, and Estonia using gut microbiome profiles and food allergen-specific serum IgE from the DIABIMMUNE dataset. The DL tool performance was compared to clinical responses to food allergen exposure and had an AUC ROC of 0.69 in predicting clinical food allergy status. High-risk infants from the Consortium of Food Allergy Researchers (CoFAR2) study were evaluated. Investigators prospectively measured and collected peanut-specific and epitope-specific IgE and IgG4, total IgE, and SPT results, demographics, and clinical history in 293 children [74]. A random forest ML algorithm trained on these data was able to predict the development of peanut allergy after 4 years from data collected at various ages (AUC 0.84–0.87) with good accuracy [75]. In the LEAP study, clinical data including biomarkers of IgE and IgG4 to 64 sequential epitopes of Ara h 1–3 proteins were assessed in an elastic-net algorithm to predict peanut allergy at 5 years of age with accuracy ranges of 64–83% depending on the amount of data used [76•].

In addition to diagnosis, prediction of tolerance of oral food challenge (OFC) and response to OIT is a pressing need. Structured data from one retrospective study of pediatric patients who had completed OFC to cooked egg were used to train an ML model using demographics, total IgE, IgE to egg white, egg yolk, and ovomucoid and demonstrated an AUC ROC of 0.83 for predicting OFC success [77]. An ML decision tree analysis (DTA) similarly evaluated diagnostic OFC outcomes and then retrospectively assessed demographics, clinical history, IgE, and SPT results to predict the likelihood of OFC outcomes with NPV and PPV of > 96% [78]. Both these studies were conducted in single centers and generalizability to other settings requires further study. Few studies have investigated OIT outcomes using AI. In patients aged 7 to 35 receiving milk oral immunotherapy (OIT) for cow's milk allergy had IgE and IgG4 to sequential milk protein epitopes measured before and after milk OIT in a study assessing the efficacy of omalizumab for milk OIT tolerance. ML was used to identify baseline variables that predicted sustained unresponsiveness with 87% accuracy [79]. These preliminary studies demonstrate the utility of AI in the early identification of OIT outcomes and OFC results in patients with food allergies.

Emerging Areas: Anaphylaxis, Urticaria, and EGIDs

Anaphylaxis

Understanding accurate anaphylaxis diagnosis and incidence is important for patient care and surveillance of foods and medicines. In a manual review of medical records at Kaiser Permanente in Washington, only 64% of inpatient, outpatient, or emergency room encounters with a diagnostic code of anaphylaxis met the criteria for anaphylaxis [80]. The investigators found that a ML model trained to identify anaphylaxis from medical records had an AUC of 0.62, and when NLP was incorporated, the AUC increased to 0.70 for anaphylaxis identification [81]. AI and ML models may also have a role in identifying proteins capable of causing an allergic reaction. With the genetic engineering of foods and the development of new biological and peptide agents, there is the potential for the creation of novel or cross-reactive antigens capable of allergic or immunologic responses. An ML model was trained on proteins known to cause allergic reactions. When applied to a validation set of proteins, the model had 97% accuracy in discriminating between allergenic and non-allergic antigens [82]. Ultimately, AI modalities can be useful in tracking the incidence of anaphylaxis to food and drugs and other potential triggers, as well as predicting the allergenicity of new products or medicinal compounds.

Chronic Spontaneous Urticaria

ML methods can be helpful in understanding the pathophysiology of chronic spontaneous urticaria (CSU) and making clinical predictions to guide management. Using CSU gene

expression data from the Gene Expression Omnibus database, investigators used ANN and sampling-based ML methods to implicate active pathways in CSU, identify potential drug targets, and then link these targets to CSU processes such as mast cell activation and degranulation [83]. A random survival forest ML model was trained on clinical and demographic features of CSU patients available at the time of diagnosis to predict clinical remission. The model also identified non-modifiable risk factors, such as age and presence of comorbidities, as well as modifiable risk factors, such as smoking and elevated BMI, as risk factors for a longer time to clinical remission [84]. Using SVM and k-nearest neighbors ML models, CSU patients were evaluated to predict response to omalizumab. Demographics and laboratory features were collected prior to treatment, and patients were assessed at specific time points for clinical control of CSU after starting omalizumab. The ML models were able to predict response to omalizumab at 1, 3, and 5 months with accuracy up to 77% [85]. Such prediction would allow clinicians to identify which patients would most benefit from omalizumab, saving cost and avoiding the risk of potential adverse events associated with trialing the drug in nonresponders. These studies demonstrate the range of applications of ML to decipher mechanisms of disease and drug targets, identify predictors for remission, and predict response to therapies such as omalizumab.

Eosinophilic Gastrointestinal Disorders (EGID)

Eosinophilic gastrointestinal disorders (EGID), specifically eosinophilic esophagitis (EoE), pose diagnostic challenges to clinicians due to poor inter-observer agreement among endoscopists as well as subjectivity in pathologists' interpretation and reporting of histopathologic findings. ML modalities have been utilized to diagnose and classify disease severity. Using mRNA transcript data from esophageal biopsies, a ML model was trained to establish an EoE diagnostic probability score with a sensitivity of 90.9% and specificity of 93.2% [86]. Endoscopic images from patients with active EoE were used to train a CNN to diagnose EoE. When evaluated on a validation test set, the model correctly diagnosed EoE in 94.7% of images [87]. Counting eosinophils in multiple biopsies throughout the gastrointestinal tract, and reporting multiple high-power fields is time-consuming, resource-intensive, and consequently not performed universally by pathologists. Furthermore, increased research has pointed to additional histopathologic features in making an accurate diagnosis. ML models have been designed to alleviate slide and image analysis [88]. Deep learning modalities have also been used to analyze histology in patients with EoE to determine severity and predict disease activity [89, 90]. It is increasingly evident that AI/ML can serve an important role in EGID diagnosis and healthcare utilization. As with all models ensuring transferability and application beyond single-center use is needed.

Challenges and Barriers to Adoption of AI

Bias, Harm, and Ethical Considerations

There are many elements of bias, ethics, and harm that can be inappropriately incorporated at many levels of AI and ML creation. Consideration of fairness, transparency, explainability, and other ethical attributes are necessary to prevent harm during healthcare delivery (Fig. 2). Health equity must be at the forefront of consideration when evaluating the role of AI in healthcare. Algorithmic bias is the incorporation of human biases into computer models. When inferring data elements, including demographic attributes such as biological sex, gender, race, and behavioral predictions into algorithms, the risk of further worsening health equity exists. The sources of algorithmic bias originate in

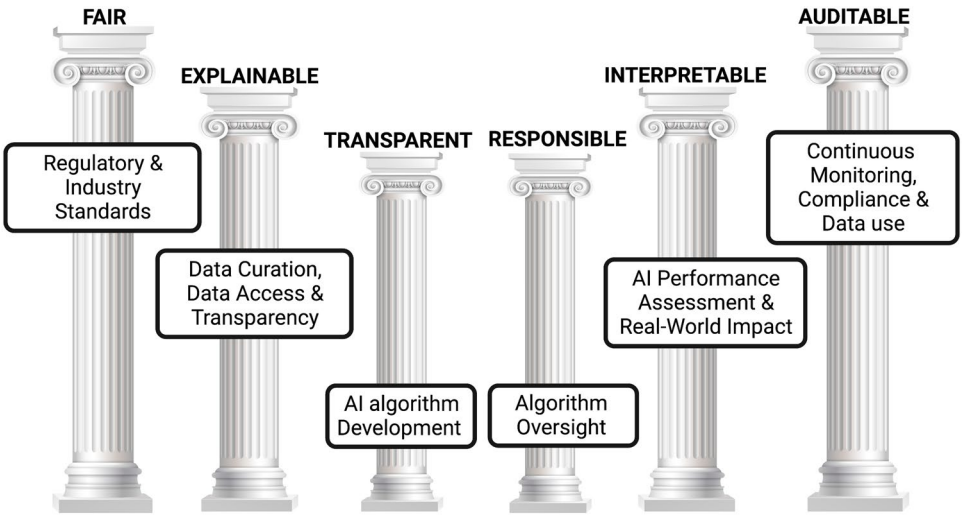

Fig. 2 Pillars of ethical AI delivery are shown. Requirements to prevent introduction of bias or harms for each pillar or stage of Ethical AI delivery are shown in boxes. (created with Biorender)

the early stages of development when individual or historic biases are replicated, even unintentionally, into computer programs. The lack of diversity in training data sets themselves may also recapitulate biases and produce disparate healthcare outcomes for underrepresented groups when they are implemented at a population level. The data sources may also be problematic if structural competency and social determinants are not considered at the point of data curation. It is well known that a lack of diverse representation exists in data scientists, first and last authors of AI publications, and creators of AI [91]. Clinicians can help mitigate inappropriate model development by serving as experts during the conception of the clinical problem as well as interpretation and implementation to assure algorithmic fairness. Similarly, assuring the involvement of the population under study, other key stakeholders, and the inclusion of diverse disciplines such as social scientists to assure algorithmic fairness, is important [92]. Models can, and should, be trained responsibly, including on data that is representative of the entire population, with broad racial, ethnic, and sociodemographic representation. Additionally, developers of algorithms should report on how programs were designed, including a description of elements of CONSORT-AI, for full transparency. Regulation and auditing of AI should be planned and iterative to assure compliance with fair principles [93••]. Ultimately, multiple layers of oversight are needed to prevent bias and harm to patients from inappropriate use.

Implementation, Governance, and Adoption of AI

Many barriers exist to implementing AI/ML including regulatory considerations, explainability, and reproducibility of algorithmics, as well as privacy, data, and legal constraints (Table 2). Regulatory barriers include the process of approval of the technology via FDA processes that categorize software as a medical device (SaMD) [94, 95]. FDA regulation requires that SaMD serve a medical purpose to diagnose, treat, prevent disease, or inform clinical management. In order to submit a market application for SaMD, a clear description of the patient population for the application and the intended users of the SaMD must be provided. SaMD must demonstrate a valid clinical association, in addition to analytical and clinical validation. Akin to Good Medical Practice, a similar framework is applied to Good Machine Learning Practice (GMLP). A human-centered approach and the conduct of clinical trials to assess effectiveness or real-world performance (RWP) prior to full-scale adoption is recommended. Certain AI models encounter implementation barriers for incorporation into routine clinical practice in medicine [96]. The efficacy and safety of ML algorithms need to be rigorously evaluated. Patient privacy and the protection of personal health information remain at the forefront of the focus of efforts, yet data access can also create challenges for aggregating quality data across health systems for optimal algorithm creation [97]. Studies examining AI in one system or with small datasets may not be replicated easily and interpretability carries risks that may only be identified once an AI algorithm is in use. Given the high-profit potential as well as downstream risks, legal considerations for both healthcare providers as well as health systems may restrict adoption. As an inevitably expanding field, clinicians in allergy immunology will need to be aware of how AI is developed, where it is being utilized, and how it provided a particular explanation or result for a diagnostic or treatment question. The full scope of potential harms and ethical considerations is beyond the scope of this review but has been reviewed extensively elsewhere [92, 96, 98–101, 102•, 103]. As with any new tool, clinicians need to understand the inherent limitations and potential drawbacks of AI.

Table 2 Governance of AI implementation

Challenges	Recommendations	Resources
Appropriate regulation of software as a medical device (SaMD)	SaMD must be clinically validated, generate reliable outputs, and achieve its intended purpose in the context of clinical care	FDA SaMD Clinical Evaluation Guidance Document
Adherence to good machine learning practices (GMLP)	AI/ML technologies in healthcare must adopt and apply practices that have been proven in other sectors as well as create new practices to promote safe, effective, and high-quality products	FDA SaMD – Digital Health Center of Excellence
Assurance of patient privacy and safety	Developers of AI/ML must commit to protecting the public from unsafe or ineffective systems, algorithmic discrimination, and abusive data practice	White House Blueprint for an AI Bill of Rights

Conclusion

The application of AI to clinical questions in allergy immunology offers the potential to improve diagnostic accuracy, therapeutic approaches, and overall clinical care. The majority of ML learning models in allergy immunology thus far have focused on inborn errors of immunity, asthma, and atopic dermatitis, though other domains are being explored. Although AI has developed to the point of being incorporated for direct use in other fields such as radiology where a number of software applications have been approved by the FDA as medical devices, equivalent allergy-immunology approaches are in nascent stages. Several areas that impact clinical immunology include the use of systems biology approaches and AI for drug development and precision diagnostics. These may translate more readily into applications for therapeutic approaches and the discovery of pathogenesis at an individual level. Given the diagnostic challenges often faced by our patients and also the expanding landscape of biologics and targeted therapeutics, there are incredible opportunities for the application of AI/ML to deliver personalized medicine. As the field of AI research rapidly expands, there are many opportunities to implement AI to better understand and characterize allergic disease processes to deliver personalized care.

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Compliance with Ethical Standards

Conflict of Interest Derek MacMath, Meng Chen, and Paneez Khoury declare that they have no conflict of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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