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REVIEW

Applications of AI/ML in accelerating the development of pulmonary drug delivery system

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KEY WORDS

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Abstract Artificial intelligence (AI) is a transformative technique for drug development, and it has been widely applied in pharmaceutical industry and academia. Pulmonary drug delivery systems (PDDS) are preferred for treating respiratory diseases due to their ability to provide localized and rapid action with fewer side effects. The integration of AI and Machine Learning (ML) has significantly accelerated the development of PDDS by enhancing both respiratory disease detection, and different stages during PDDS development. This paper provides an overview of the present landscape by literature analysis of the key areas of research. This review first introduces the fundamental principles of AI/ML and how they are applied in respiratory disease detection and diagnostics, highlighting FDA-approved software used in this field. Furthermore, we examine the role of AI in different stages during the development of PDDS, from identifying novel drug candidates to optimizing formulations and drug delivery mechanisms. The review also discusses regulatory and ethical considerations, along with existing challenges during AI-driven PDDS development. By addressing these key aspects, we provide insights into the revolutionary potential of AI/ML in advancing pulmonary drug delivery and improving therapeutic outcomes.

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1. Introduction

Respiratory diseases consist of multiple conditions that affect the airways and structures of the lungs[1]. These include chronic obstructive pulmonary disease (COPD), asthma, lung cancer, pneumonia, and bronchitis, which are collectively responsible for high morbidity and mortality rates[2]. Smokers and those occupationally or environmentally exposed to hazardous substances are more susceptible to these diseases, showing the critical role of environmental factors in respiratory health[3]. The symptoms of respiratory diseases can severely restrict daily activities and lead to life-threatening complications. Therefore, there's an urgent need for effective management and treatment strategies.

Diagnostic tests for respiratory diseases involve a series of techniques aimed at identifying and assessing conditions affecting the lungs and airways. The effective diagnosis of respiratory diseases is essential for early intervention and treatment, which can significantly improve patient outcomes[4,5]. Common respiratory disease diagnostic methods involve pulmonary function tests, imaging studies such as chest X-rays and high-resolution computed tomography, and the evaluation of biomarkers[6–8]. These methods enable healthcare providers to identify respiratory diseases. Recent advancements in diagnostic technologies, including rapid point-of-care and advanced imaging techniques, allow for more effective and efficient respiratory disease assessment and evaluation[9,10]. As the landscape of respiratory medicine evolves, Utilization of these diagnostic techniques will be essential for the development of PDDS. Therefore, effective diagnostics are fundamental for optimal and effective treatment, which ensures patients receive better treatment for respiratory diseases.

Effective management of respiratory diseases relies on both accurate and timely diagnostics and innovative treatment modalities. Pulmonary drug delivery is a special route of administration that involves delivering drugs to the lungs directly through inhalation. This delivery method exhibits benefits including rapid onset of therapeutic effect, concentrated drug at the site of action, and reduced systemic exposure and side effects[11]. Multiple respiratory diseases such as asthma, COPD, pulmonary hypertension, cystic fibrosis, and tuberculosis can be treated through the local delivery of therapeutics[12–15]. In addition, the airways are regarded as one of the most optimal routes for systemic drug administration due to a large surface area for absorption, thin absorption membrane and elevated blood flow, and relatively low metabolic activity[16]. Therefore, pulmonary drug delivery can prevent first-pass metabolism and provide opportunity for drugs that will degrade in the gastrointestinal (GI) tract[17]. Moreover, it's a non-invasive route of administration with improved patient compliance than injection and infusion[18]. Drugs are typically delivered to the lungs through inhaler devices, and they can be divided into nebulizers, pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), and soft mist inhalers (SMIs). However, due to the lung anatomy and physiology, inhalation drug products cannot be delivered efficiently to the lung with a low percentage of 15% in some cases[19,20].

Artificial intelligence (AI) and machine learning (ML) are gaining significant attention in pharmaceutical sciences, particularly in drug discovery[21–25], formulation development[26–30], clinical study[31–33], and drug repurposing[34–38]. The definition of AI was initially proposed by John McCarthy as "the science and engineering of making intelligent machines" in 1955. ML is an important subfield of AI, and it involves the utilization of data and algorithms to enable AI to simulate humans' behaviors, such as decision making[39]. As another essential subfield of AI, natural language processing (NLP) has attracted significant interest globally with the development of large language models (LLMs) such as ChatGPT, DeepSeek, BERT, Claude, and Gemini[40–44]. It has been demonstrated that the potential of applying LLMs in drug development[45].

With the increasing demand for more effective treatments for respiratory diseases, there have been significant advances in the development of PDDS in recent years. Incorporation of AI in PDDS development has been extremely promising, with AI-based technologies being investigated for their capability to facilitate drug design, optimize formulations, and streamline manufacturing processes. This review aims to present a comprehensive overview of the application of AI and ML in developing PDDS. In particular, we begin with an examination of existing literature through bibliometric analysis, thereby gaining insight into the scope of research in this area in terms of metrics such as citation counts and the number of publications. Then, in our main review section, we provide a detailed examination of specific applications of AI in PDDS, which can be divided into two key aspects: (1) AI for respiratory diseases detection and diagnostics—including the use of ML algorithms for predicting and visualizing respiratory disease progression, and summarizing FDA-approved software for respiratory disease detection and diagnostics; and (2) AI-assisted design of PDDS, which involves drug discovery, formulation development, process control, manufacturing, and drug delivery. By exploring these two aspects thoroughly, we aim to provide a comprehensive understanding of the current state-of-the-art in AI-driven PDDS development and highlight potential avenues for future research.

2. Bibliometric and visual analysis (2014–2024)

Firstly, we conduct an analysis on a systematic literature search on the Web of Science Core Collection using the Scienced Citation Index-Expanded database. The search was performed on July 16th, 2025, utilizing the Web of Science product. Our search strategy combined relevant keywords related to AI and the development of PDDS, including: (TS = (pulmonary drug delivery) OR TS = (pulmonary drug delivery system) OR TS = (Dry powder inhaler) OR TS = (Inhalation product development) OR TS = (Metered Dose Inhaler) OR TS = (Respiratory disease diagnostic) OR TS = (Pulmonary disease diagnostic)) AND (TS = (AI) OR TS = (ML) OR TS = (Deep Learning) OR TS = (Neural networks)). The search results were filtered by article type and publication year ranging from 2014 to 2024. Despite the existence of earlier research on this topic, we focused our analysis on more recent publications (2014–2024) to capture emerging trends and advancements in the field. After removing duplicate records, a total of 1192 relevant documents were retrieved, which were subsequently exported for further processing.

To provide quantitative insights into our literature survey, we employed various bibliometric analysis tools. Specifically, we utilized Clarivate Analytics[46], VOSviewer[47], and the bibliographic online platform Bibliometric.com[48] to process and visualize the data. Relevant information, including research area, publication year, journal title, country/region, affiliation, author names, and funding agency information, was extracted for analysis. Moreover, we have generated citation reports for selected documents to obtain metrics such as H-index, average citations per item, total number of times cited, and number of citing articles. These

metrics provide a deeper understanding of our literature survey's scope and significance.

The bibliometric analysis resulted in 1192 documents for the applications of AI in the development of PDDS. Fig. 1A displayed the number of publications annually from 2014 to 2024. There were 7 documents in 2014, and the number of publications tended to grow exponentially, reaching 305 in 2024. In addition, there was a significant increase in the number of citations that was seen in the last decade, peaking at 5422 in 2024. The total citations of collected documents were 19,542 from 2014 to 2024, indicating that AI in the development of PDDS has attracted great research interest over the last decade and is prone to continue being a research hotspot (Fig. 1B). The top ten contributing countries/regions of the number of publications was illustrated in Fig. 1C. China (276, 23.15%) and USA (265, 22.23%) were the only two countries/regions crediting over 200 documents. The cooperation relationship between countries/regions was displayed in Fig. 1D. China and the USA are two of the most collaborative countries/regions among all. Co-citation and co-occurrence were two important bibliometric indexes, which characterize the research areas' similarity and research keywords, respectively[49,50]. The co-citation results were visualized in Supporting Information Figs. S1 and S2. Overall, 63 items with three red, green, and blue clusters were displayed. We summarized the results as follows: Red cluster (25 items): studies that investigated ML, deep learning (DL), and computer vision; Green cluster (19 items): studies that investigated respiratory disease detection and diagnostics and ML methodologies; Blue cluster (19 items): studies that investigated the application of ML and DL in respiratory disease detection particularly COVID-19 using medical images. Keywords of the publication play a crucial role in understanding the research topic. Accordingly, 141 of 4930 keywords with a frequency $\geq$10 were extracted for analysis. The visualization of relevant keywords was depicted in Supporting Information Figs. S3−S5. The size of each node in the graph is directly related to the frequency or weight assigned to it based on its appearance, with more prominent nodes indicating greater instances of keywords and *vice versa*. Additionally, a shorter distance between these nodes indicates stronger correlations between select terms. The 141 primary keywords were divided into six clusters: Cluster 1 (red) was the largest one and contained 50 items, which mainly focused on the applications of AI and ML in the development of PDDS. Keywords such as AI, ML, diagnosis, COPD, asthma, pulmonary, prediction, and lung cancer were in this cluster. Cluster 2 (green) is related to the application of deep learning in pulmonary medical image analysis, as evidenced by the keywords: deep learning, convolutional neural networks, image segmentation, medical imaging, and chest radiography. Cluster 3 (blue) primarily focused on the detection of multiple respiratory diseases using computed tomography, indicated by keywords such as computed tomography, idiopathic pulmonary fibrosis, interstitial lung diseases, and lung diseases. Cluster 4 (yellow) mainly referred to the applications of AI in respiratory disease diagnostics and drug development, and contained keywords including pulmonary tuberculosis, asthma, artificial neural network, random forest, support vector machine, and drug delivery. Cluster 5 (purple) focused on COVID-19 and AI's applications in disease diagnosis and treatment, as evidenced by keywords: COVID-19, coronavirus, SARS-CoV-2, radiology, protein, and neural networks. Cluster 6 (light blue) included keywords such as respiratory diseases, algorithm, healthcare, and neural network, which indicated the applications of deep learning algorithms in the respiratory healthcare industry.

Based on the bibliometric results above, AI and ML play a more significant role in respiratory disease detection and

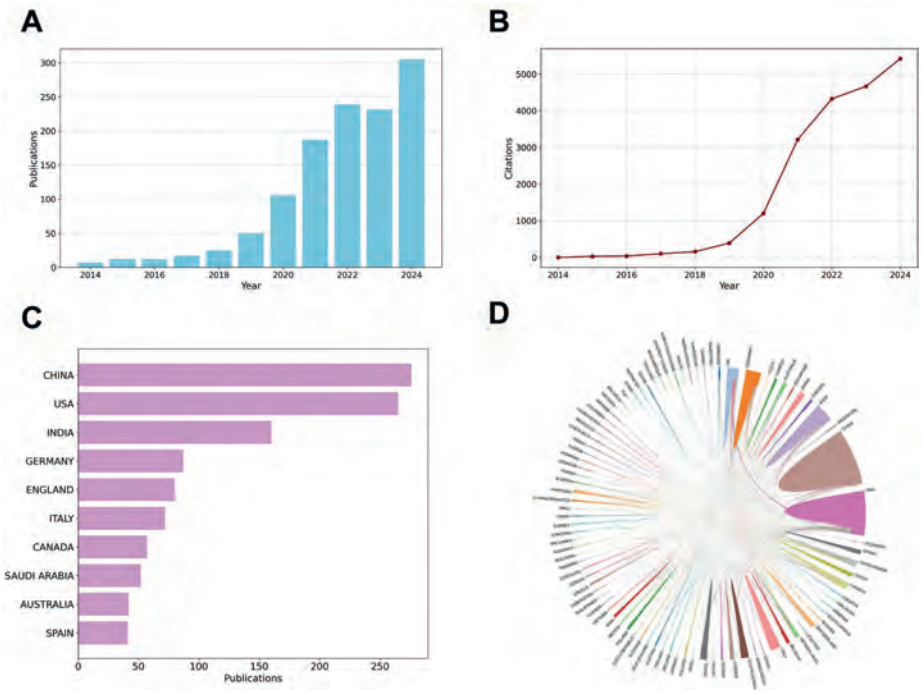

Figure 1 Bibliometric analysis on the development of PDDS using AI from 2014 to 2024. Annual numbers of publication (A). Annual numbers of citations (B). Top ten contributing countries or regions of the publications (C). Network visualization of collaborations between countries or regions (D).

diagnosis, as shown by the increasing numbers of publications and citations. According to the keywords co-occurrence cluster time overlay visualization (Supporting Information Fig. S4), we observed the research tendency shift from older terms such as COPD, asthma, algorithm, drug delivery, and nodules to newer terms such as AI, deep learning, image segmentation, feature extraction, idiopathic pulmonary fibrosis, COVID-19, screening, and bioinformatics. In addition, most of the papers related to this field were published during the COVID-19 pandemic period, and some of the studies reported the use of AI techniques to analyze medical images. Moreover, it's the tendency to utilize advanced AI/ML and bioinformatics techniques for respiratory disease detection and diagnostics rather than traditional mathematical methods. It is believed that such techniques can largely be applied in the drug development process, including drug discovery, formulation screening and optimization, and drug delivery.

In summary, based on the results of the bibliometric analysis, the development of AI-based PDDS has received increasing attention. The bibliometric results also suggest that the application of AI-based PDDS has been widely used across multiple respiratory diseases such as asthma, COPD, COVID-19, lung cancer, and pneumonia. Despite the promising data emerging from published and ongoing research, the challenge of translating these findings into clinical triumphs persists, hindered by the quality and availability of data, the model's interpretability, regulatory approval, and a range of additional obstacles. This bibliometric analysis was based only on the Web of Science Core Collection and may potentially lead to the omission of relevant studies indexed only in Scopus, PubMed, or Embase. It is our future work to incorporate more valuable documents from multiple databases to provide more diverse knowledge domains.

3. Introduction of PDDS

Pulmonary drug delivery has become one of the most important administration routes for local and systemic treatment. Compared to other administration routes, pulmonary drug delivery exhibits several advantages due to the special physiological characteristics of lungs[51]. The lungs serve as an efficient gateway for drugs into the bloodstream, owing to their large surface area for absorption (approximately 100 m^2), the thin absorption membrane (0.1−0.2 μm), and the elevated blood flow (5 L/min), which expeditiously distributes molecules throughout the body[16]. In addition, the lungs demonstrate relatively low local metabolic activities[52]. Unlike oral drug administration, which is susceptible to first-pass metabolism, pulmonary drug delivery bypasses this step and allows for more effective drug delivery and absorption[16]. The noninvasiveness of this drug delivery mode is another advantage since it minimizes discomfort and enhances compliance among patients[53]. Moreover, it enables targeted drug delivery to the site of action, which can lead to a rapid onset of therapeutic effects and reduced side effects compared to systemic administration[18]. For the above-mentioned reasons, pulmonary drug delivery is beneficial for treating patients with respiratory conditions such as pneumonia, asthma, cystic fibrosis, COPD, and lung cancer[15,54−59]. In general, distinctive features of PDDS highlight their transformative potential in contemporary drug therapy to ensure efficient management of respiratory diseases.

PDDS encompass several novel methods aimed at delivering therapeutics directly to the lungs with increased efficacy and reduced systemic side effects. Fig. 2 [60,61] depicts a summary of types of PDDS by different inhaler technologies. pMDIs are among the most commonly used devices that employ pressurized canisters to dispense a defined dose of drug as an aerosol[62]. These devices are portable and user-friendly, making them a staple for conditions like asthma and COPD. In addition, pMDIs exhibit benefits including rapid administration times, sterility and prevention of backflow, and patient familiarity. However, pMDIs have several challenges, such as formulation challenges related to the non-aqueous liquid propellant system[63]. Moreover, pMDIs require proper coordination between actuation of the devices and inhalation by patients, which might be difficult for some patients[64]. pMDIs can be combined with spacers to improve drug delivery efficiency, especially in patients who may struggle with proper inhalation techniques[11]. Nebulizers deliver liquid medications as inhalable fine droplets, enabling patients to inhale treatments for a longer duration, which is particularly favorable for patients who have difficulties with pMDIs or DPIs. However, nebulizers are less portable and typically have longer administration time. Nebulizers can be classified as jet nebulizers, ultrasonic nebulizers, and mesh nebulizers[65]. DPIs have become increasingly attractive for pulmonary drug delivery and consist of a drug formulation in a powdered form and an inhalation device where aerosolization of the powder is mainly driven by patient inspiration through the device. Compared to pMDIs, DPIs require less patient coordination between actuation and inhalation and can be used for biological products that are unstable in liquid form[11]. Drug particles in DPIs must be manufactured within an aerodynamic diameter range between 1 and 5 μm for inhalation[54]. The larger surface area-to-mass ratio of particles within this size, combined with increased surface energy introduced during production processes of these fine powders, usually results in highly cohesive particles and aggregates. The effect can significantly affect the flowability and dispersibility of powders significantly, which are key factors for effective pulmonary drug delivery. Therefore, to overcome cohesive forces and improve flowability and dispersibility, drug can be blended with large carrier particles such as lactose[11].

4. Principles of AI and ML

4.1. AI, ML, and DL

AI has gained significant attention in pharmaceutics, particularly in formulation screening and optimization[26,29,30], process control[66−68], and drug delivery[69−71] areas. AI is simulation of human intelligence processes by machines, mainly computer systems[72]. This broad field involves various techniques and methodologies designed to enable machines to carry out those human intelligence, such as visual perception, speech recognition, and decision-making[73,74]. Within AI, ML is a subset focusing on algorithms that allow computers to learn from data and make predictions. ML emphasizes the ability of machines to improve their performance on a given task by gaining experience, rather than being explicitly programmed for every situation[72]. DL, a more specialized subfield of ML that typically employs neural networks to process large amounts of data, is particularly suited for tasks like image and speech recognition[39]. It has been reported that AI exhibits great potential in pulmonary drug delivery and many cases have shown the feasibility of applying traditional ML and DL algorithms to develop inhalation product[75,76].

4.1.1. Supervised learning

One of the most significant types of ML algorithms is supervised learning, which is used to predict outcomes by means of labeled

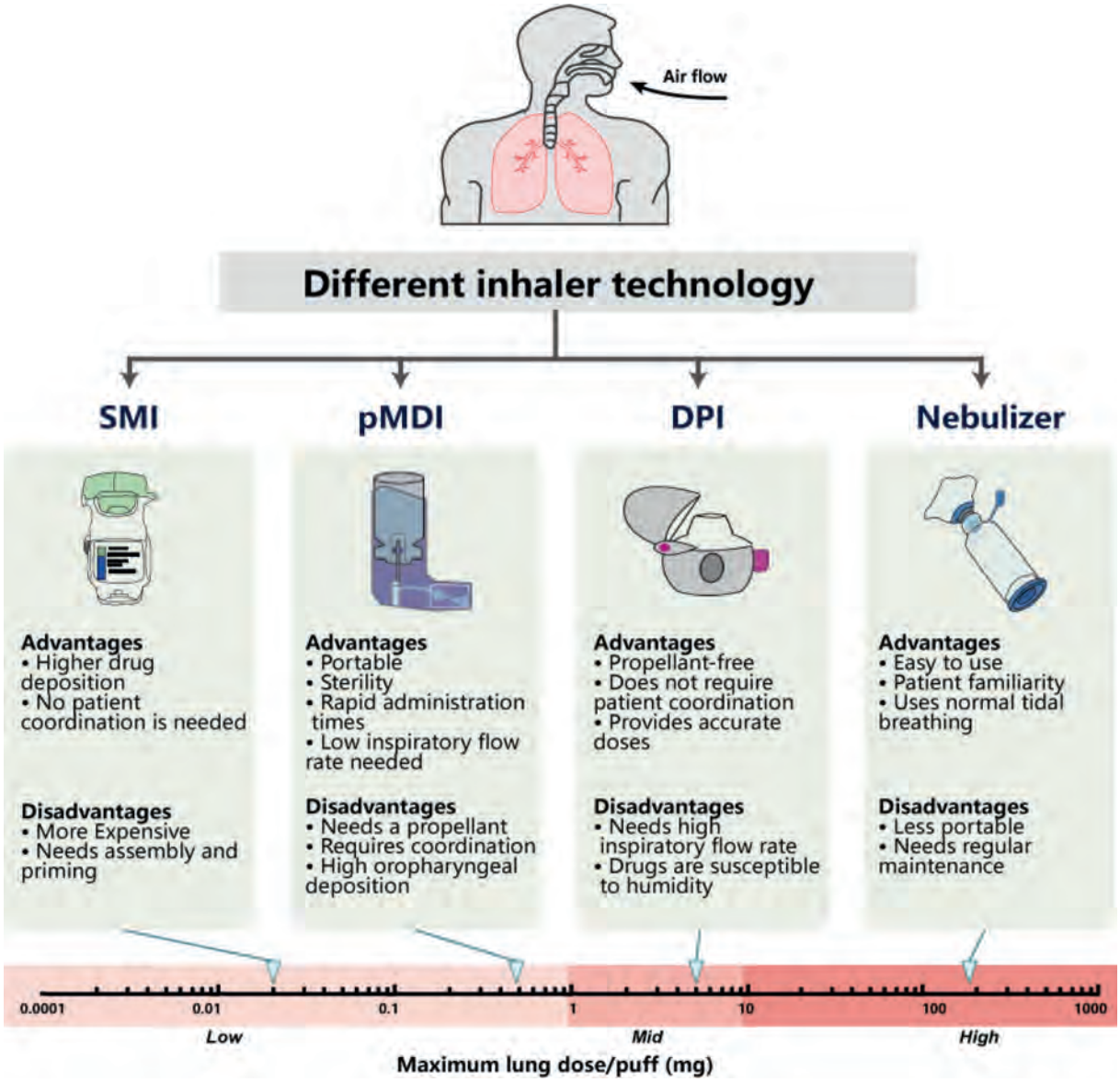

Figure 2 An overview of different inhaler technology. Reprinted with the permission from Refs. 60,61: Copyright © 2022 Frontiers; Copyright © 2023 Elsevier.

datasets. The developed model then learns to associate patterns and correlations between output labels and input features by training on the dataset. There are two main tasks of supervised learning, namely classification and regression. Classification algorithms are implemented when output labels are categorical. Regression algorithms, on the other hand, are used when the output labels are numerical.

Multiple supervised learning algorithms, such as linear regression, logistic regression, decision tree, random forest, gradient boosting machine, support vector machine (SVM), and neural network, have been frequently utilized in the development of PDDS (Fig. 3).

4.1.2. Semi-supervised learning

Semi-supervised learning is a type of ML that includes both supervised and unsupervised learning by integrating labeled and unlabeled data to train the models. This methodology is typically used when the labels in a dataset are incomplete, *e.g.*, only a small amount of data is labeled or images are partially annotated. Therefore, semi-supervised learning is an efficient approach to increase the quantity of the dataset, and it can be utilized to derive knowledge the dataset[77,78]. Common semi-supervised learning techniques include self-training, co-training, graph-based labeling, and consistency regularization, each designed to propagate label information effectively[79]. The use of semi-supervised learning during model development can allow researchers to enhance predictive performance with less dependency on extensive manual labeling.

4.1.3. Unsupervised learning

Unlike supervised learning and semi-supervised learning, unsupervised learning utilizes self-learning algorithms where unlabeled data is provided, and it learns the hidden patterns and insights without human supervision. Unsupervised learning can be

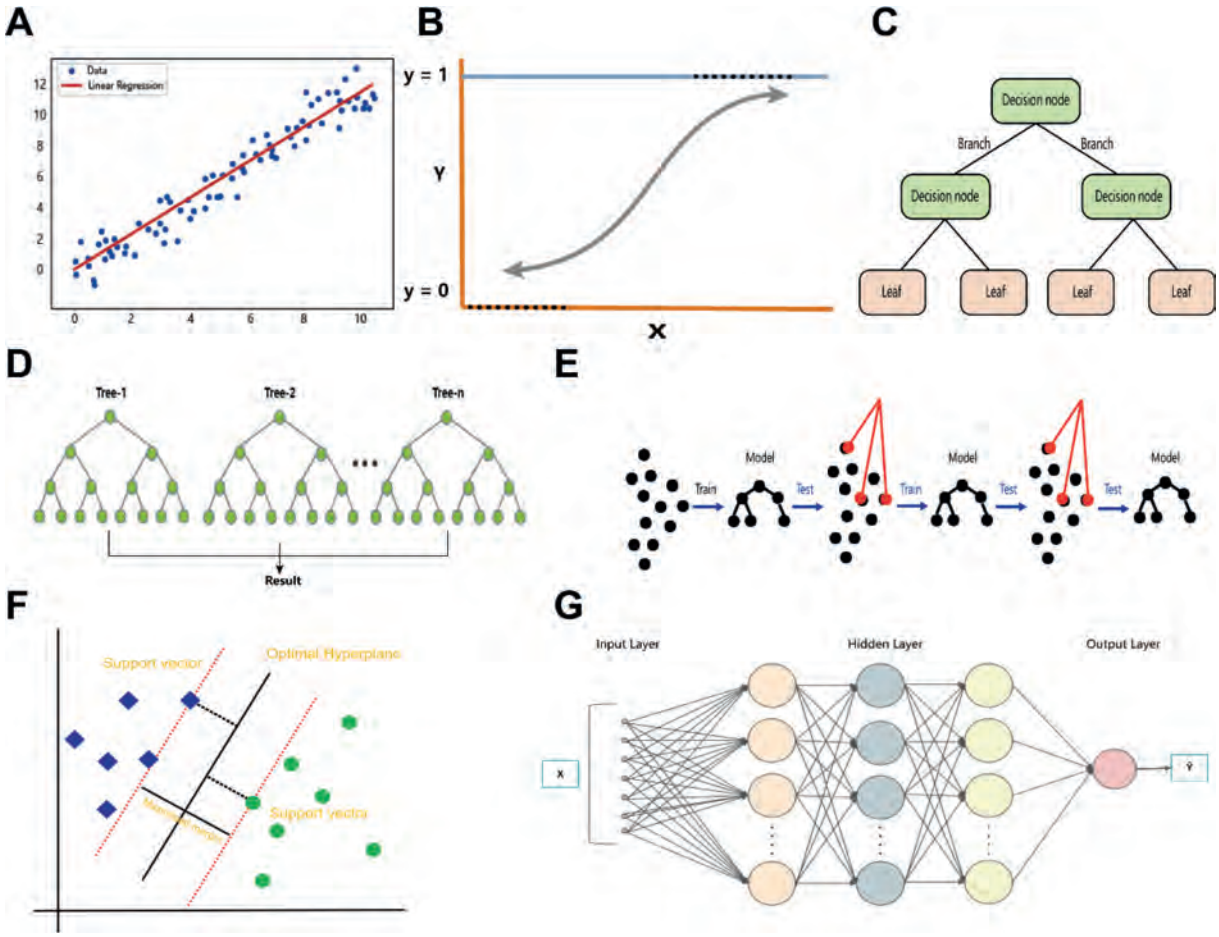

Figure 3 Illustrations of representative ML algorithms. Linear Regression (A). Logistic Regression (B). Decision Tree (C). Random Forest (D). Gradient Boosting Machine (E). Support Vector Machine (F). Artificial Neural Networks (ANN) (G).

classified into different tasks, namely clustering[80,81], dimensionality reduction[82], and association rule learning[83]. In recent years, it has been reported that unsupervised learning has been widely applied to drug development. Specifically, this method shows potential in drug repurposing and identifies new indications against multiple diseases[84].

4.1.4. Deep learning

Deep Learning refers to a subset of ML techniques that employ neural networks with multiple layers to model and simulate patterns and representations within large datasets. The techniques are increasingly significant in a number of applications, *e.g.*, computer vision and NLP, as they learn hierarchical features automatically from raw data. Neural networks consist of a diverse range of architectures, such as Feedforward Neural Network (FNN), Convolutional Neural Networks (CNNs), Recurrent Neural Networks (RNNs), Long Short-Term Memory (LSTM), Generative Adversarial Networks (GANs), and Graph Neural Networks (GNNs), each copes with specific computational challenges (Fig. 4)[85-88]. Each neural network architecture specializes in dealing with specific data types as well as tasks and offers different tools to encompass a broad set of applications from computer vision to natural language processing to other domains.

4.2. Generative AI

Generative AI is now among the most popular research fields following the release of ChatGPT. Generative AI denotes algorithms that can create new content such as images, audio, text, video, and code. There are multiple types of generative AI, including GANs[89], variational autoencoders (VAEs)[90], autoregressive models[91], RNNs[92], and transformer-based models[93].

4.2.1. Generative adversarial networks

Generative adversarial networks were initially proposed by Goodfellow et al.[89] in 2014, and it employs two neural networks that compete against each other to produce more authentic new data from a provided training dataset. In recent years, GANs have garnered significant attention for their capability to generate realistic and diverse data across various domains, such as chemistry, material science, and pharmaceutical science[94–97]. Moreover, GANs have gained significant attention in drug development for various applications, including molecule generation, drug discovery, toxicity prediction, and formulation optimization[86,98–100].

4.2.2. Transformer-based models

Transformer model is a neural network that understands and retains context and meaning by interpreting relationships within sequential data, *e.g.*, the words within this sentence. These models

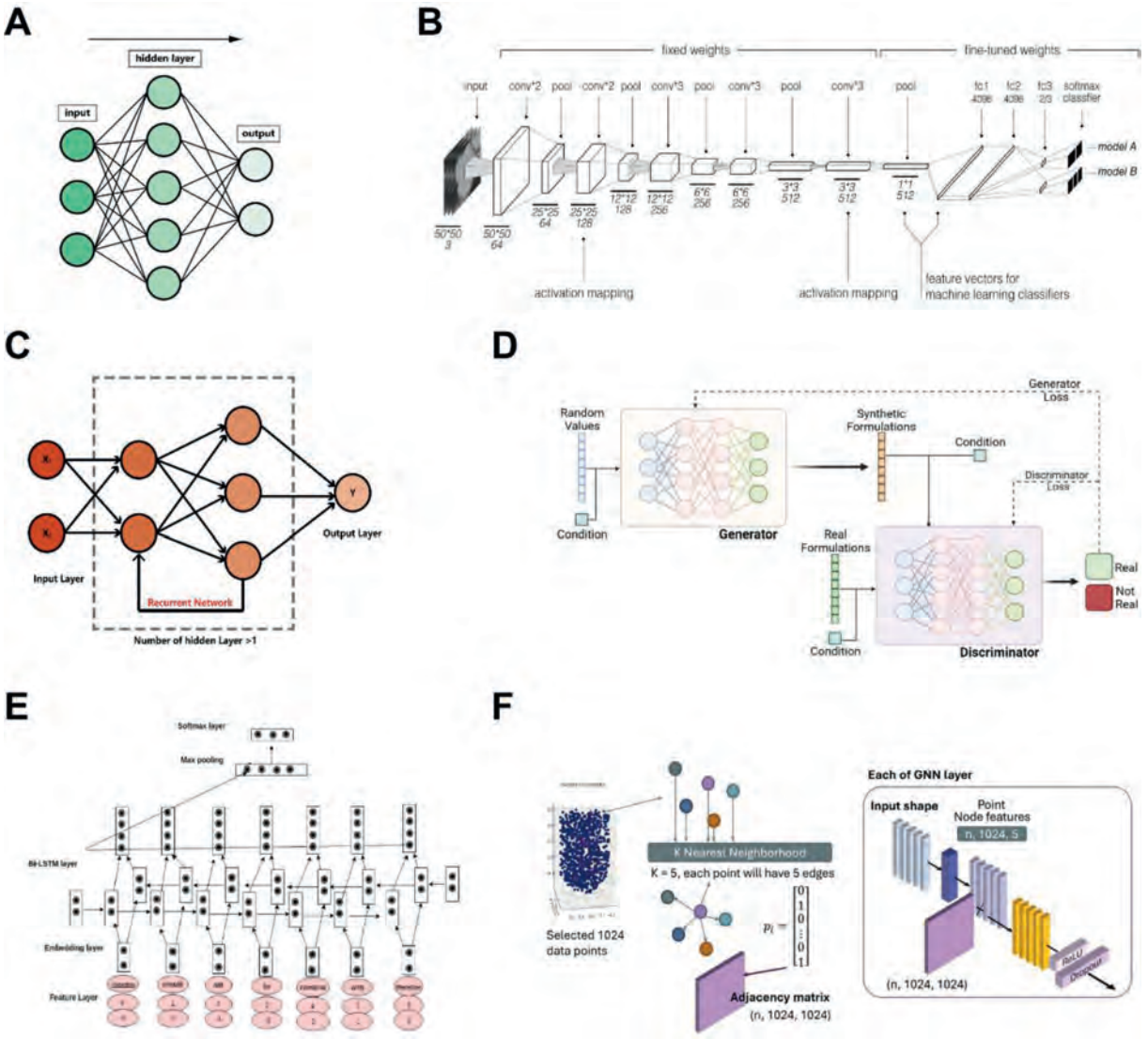

Figure 4 Illustrations of representative DL algorithms. Feedforward Neural Networks (A). Convolutional Neural Networks. Reprinted with the permission from Ref. 85. Copyright © 2021 Springer Nature (B). Recurrent Neural Networks (C). Generative Adversarial Networks. Reprinted with the permission from Ref. 86. Copyright © 2024 Elsevier (D). Long Short-Term Memory. Reprinted with the permission from Ref. 87. Copyright © 2018 Elsevier (E). Graph Neural Networks. Reprinted with the permission from Ref. 88. Copyright © 2023 Elsevier (F).

employ a dynamic set of mathematical techniques called attention or self-attention to recognize the subtle ways in which distant elements within a sequence influence and relate to one another[93]. Transformer-based models have been successfully applied across various fields, including computer vision, audio and speech processing, internet of things, and healthcare[101]. More importantly, transformer-based models have been extensively used in drug development processes such as drug discovery, protein structure prediction, drug synthesis prediction, genomic data analysis, and clinical outcome prediction[102−106].

5. Applications of AI/ML in the development of PDDS

It is reported that AI and ML have been extensively applied to respiratory disease detection and diagnostics[107−110] and the development of PDDS[75,111−113]. In the subsequent sections, we will first review the applications of AI in respiratory disease detection and diagnostics, specifically in the development of AI-directed respiratory disease detection and diagnostics methodologies and FDA-approved software. Subsequently, the development of PDDS, including drug discovery, formulation design and optimization, and drug delivery, will be discussed.

5.1. Respiratory disease detection algorithms

5.1.1. Applications of AI in respiratory disease detection and diagnostics

The integration of AI into respiratory disease detection and diagnostics has revolutionized medical evaluations with enhanced accuracy and efficiency (Fig. 5)[114,115]. ML algorithms, particularly DL algorithms, have shown promise in analyzing medical images such as chest X-rays and CT scans to identify patterns indicative of respiratory diseases like pneumonia, tuberculosis, and COVID-19[116-118]. AI-driven tools can process large amounts of data in real-time to allow radiologists to provide quicker and more precise diagnoses. Furthermore, with digital stethoscopes

and wearable devices, AI can analyze respiratory sounds and provide an early diagnosis[119]. These technologies not only enhance diagnostic accuracy but also support personalized treatment plans by predicting disease progression and patient outcomes. As AI evolves, its effect on respiratory medicine is gaining increasing attention, potentially reducing mortality rates and improving the quality of life for patients.

AI and ML have significantly facilitated lung cancer detection and diagnosis through improved accuracy, efficiency, and increased early identification rates. Using medical imaging data like CT scans[120], X-rays[121], and PET scans[122], alongside clinical[123] and radiomic data[124], ML models are able to accurately predict lung cancer. Talukder et al.[125] employed a hybrid ensemble model to identify lung cancer efficiently. This ensemble model consisted of deep feature extraction, high-performance filtering, and ensemble learning modules. Multiple transfer learning models, such as VGG16, VGG19, MobileNet, and DenseNet, were applied to conduct feature extraction of the LC25000 histopathological data. MobileNet and an ensemble soft voting classifier were integrated as the final model to detect lung cancer. The trained ML model demonstrated good predictive performance with an accuracy of up to 99.05%[125]. As the most common type of lung cancer, non-small cell lung cancer (NSCLC) is the deadliest epithelial cancer, and it involves lung adenocarcinoma and lung squamous cell carcinoma[126]. Kludt et al.[127] developed a NSCLC computational pathology platform to improve patient care and enable various downstream applications. The multi-class tissue segmentation algorithm was trained on a high-quality dataset containing lung adenocarcinoma and squamous cell carcinoma whole-slide images. An NSCLC subtyping algorithm, which was validated by a diverse international cohort (4097 slides from 1527 patients), was successfully developed. Moreover, four explainable AI-derived prognostic parameters were found related to tertiary lymphoid structures and necrosis. These parameters enable precise quantitative analysis of H&E-stained slides and provide effective risk classification for NSCLC patients. In another study, a triage-driven Chinese Lung Nodules Reporting and Data System (C-Lung-RADS) was developed to improve the evaluation of pulmonary nodules detected through low-dose computed tomography (LDCT) screening[128]. With a cohort of 45,064 cases, the system categorized nodules into low-, mid-, high-, and extremely high-risk groups by size and density. It

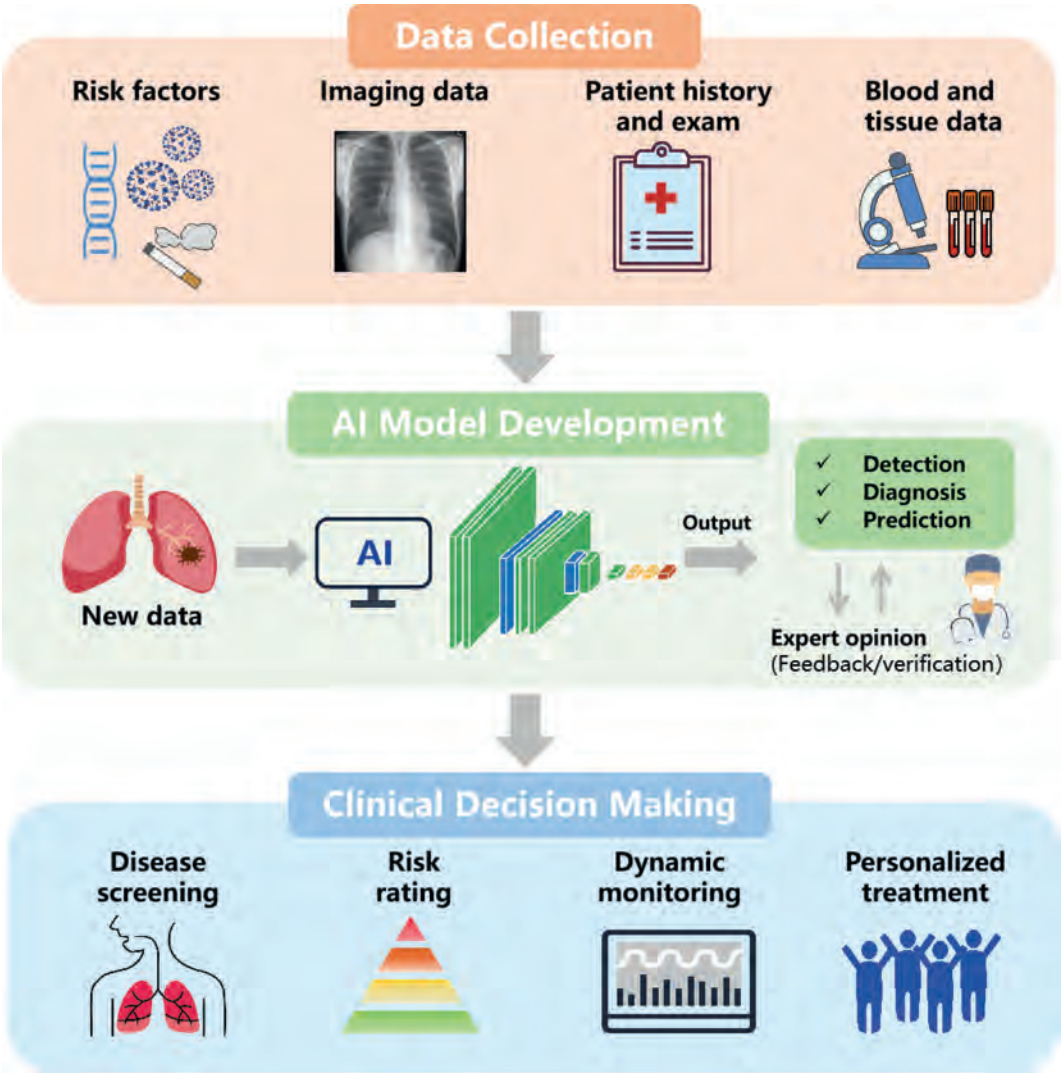

Figure 5 A proposed workflow for applying AI in respiratory diseases detection and diagnostics. Reprinted with the permission from Refs. 114,115: Copyright ©2021 Springer Nature; Copyright © 2023 Springer Nature.

then integrated imaging, demographic, and follow-up data to refine malignancy risk assessment. C-Lung-RADS achieved state-of-the-art performance with an AUC of 0.918, outperforming single-dimensional approaches (AUC of 0.881). In an independent cohort, it presented higher sensitivity (87.1%) than Lung-RADS v2022 (63.3%). The system reduced unnecessary invasive procedures for low-risk categories and recommended timely interventions for nodules with high-risk, which accelerates lung cancer diagnosis efficiency, particularly in resource-limited environments (Fig. 6A)[128].

AI and ML are increasingly reshaping lung infectious disease diagnosis with increased speed, accuracy, and accessibility. Medical imaging data, such as chest X-rays and CT scans can be evaluated by AI-driven systems to identify conditions such as tuberculosis, pneumonia, and COVID-19[129-133]. CNNs are especially efficient at recognizing abnormalities and patterns in these images to enable early and precise detection of pulmonary infections[134]. Moreover, ML models can incorporate clinical data, such as patient history, images, and laboratory findings, to provide a more comprehensive diagnosis[135]. Shao et al.[136] developed a multimodal integration (MMI) pipeline that could distinguish respiratory diseases caused by fungal infections, bacterial infections, as well as by pulmonary tuberculosis and viral pneumonia, using a real-world dataset from 24,107 patients. The MMI-based system integrating clinical text and CT image data obtained an AUC of 0.910 on the internal test dataset and 0.887 on the external test dataset, comparable to the performance of experienced physicians. Moreover, the system can effectively differentiate between viral subtypes with a mean AUC of 0.822 and bacterial subtypes with a mean AUC of 0.803. This MMI approach shows promise for guiding personalized medication recommendations, thereby reducing antibiotic misuse (Fig. 6B) [136].

For chronic respiratory diseases, like asthma and COPD, AI and ML are revolutionizing their management and diagnosis by providing more efficient, precise, and personalized approaches. It is difficult to diagnose respiratory diseases like asthma and COPD because there is an overlap in the symptoms, and there's reliance on patient history, physical exams, pulmonary function tests, and imaging, leading to both underdiagnosis and overdiagnosis[137]. Misdiagnosis can result in inappropriate treatment, for example, the failure to prescribe corticosteroids for asthma and administration of inhaled corticosteroids for COPD patients, which can cause adverse effects, impaired quality of life, and higher expenditures[138,139]. AI techniques can interpret various data

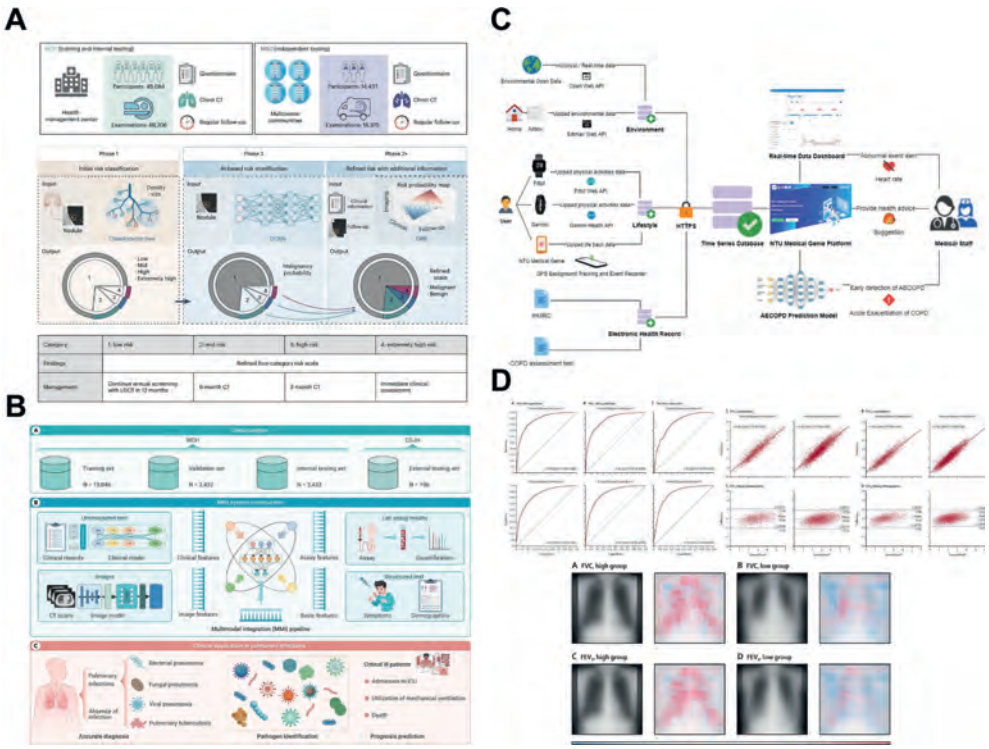

Figure 6 AI-driven techniques in respiratory disease detection and diagnostics. The proposed workflow and pipeline of C-Lung-RADS, a system for lung cancer screening utilizing a medical checkup cohort of 45,064 cases. The system involved three phases: phase I determined the initial risk of nodules based on their size and density using decision tree algorithm, phase II distinguished suspicious malignant nodules by CT images, and phase II + utilize multimodal data fusion for further evaluation. Reprinted with the permission from Ref. 128. Copyright © 2024 Springer Nature (A). The proposed MMI pipeline for pulmonary infectious disease management, which consists of 1. data collection and processing, 2. construction of MMI system using multimodal data such as clinical records, CT scans, lab assay, and demographics, and 3. MMI clinical application development including pulmonary infection diagnostics, pathogen identification, and prognosis prediction. Reprinted with the permission from Ref. 136. Copyright © 2024 Cell Press (B). The developed Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) predictive system based on wearable devices and AI algorithms demonstrated high predictive accuracy in early disease detection within 7 days. Reprinted with the permission from Ref. 140. Copyright © 2021 JMIR (C). AI-driven pulmonary function predictive model for the diagnosis of COPD and asthma achieved robust performance and good interpretability across dataset from multiple institutes. Reprinted with the permission from Ref. 142. Copyright © 2024 Elsevier (D).

sources, including pulmonary function tests, imaging scans, electronic health records, and data from wearable devices (Fig. 6C)[137,140,141]. Ueda et al.[142] developed and validated a DL-based model that predicted two major pulmonary functions, namely forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1), from chest X-rays. Using a dataset of 141,734 X-ray and spirometry pairs across five Japanese institutions, the model was trained with data from three institutions and externally tested in two others. In external testing, the model demonstrated high agreement with spirometry results, achieving high Pearson's correlation coefficients of approximately 0.90 for FVC and FEV1, and intraclass correlation coefficients (ICC) from 0.89 to 0.91. The performance metrics suggested strong predictive accuracy. This AI model presented a viable alternative for predicting pulmonary function in patients are unable to undergo spirometry, potentially improving the diagnosis and management of lung diseases and optimizing imaging protocols (Fig. 6D)[142]. In another study, asthma exacerbations in adult patients can be predicted by ML[143]. The dataset comprised 7001 daily self-monitoring reports, and 7-day window-based models were trained to predict exacerbations on Day 8. Three ML models, a naïve Bayesian classifier, an adaptive Bayesian network, and an SVM, resulted in sensitivities of 0.80, 1.00, and 0.84, respectively. The specificities for these models were 0.77, 1.00, and 0.80, respectively. The study demonstrated the promise of ML technology for personalized decision support for telemonitoring chronic disease.

5.1.2. *Representative software approved by the FDA*

US Food and Drug Administration (FDA) regulates software used in respiratory disease detection and diagnostics to ensure safety, effectiveness, and reliability. This includes software as a medical device (SaMD), such as AI-driven tools that assist in detecting, diagnosing, and managing conditions like asthma, COPD, lung cancer, and lung infections[144]. Several AI software platforms specifically targeting respiratory diagnostics have received FDA clearance. For instance, Brainomix's e-Lung AI software is one of the breakthrough technologies that have recently achieved FDA clearance for its capabilities in pulmonary diagnostics[145]. The FDA's review process emphasizes the importance of diverse study methodologies in determining the appropriateness and applicability of AI and ML technologies in medical devices[146]. This ensures that the AI tools released for use not only meet clinical requirements but also cater to a wide range of scenarios presented in real-world applications.

In recent years, various AI and ML-based medical devices have been approved by the FDA for diagnosis and treatment of respiratory diseases (summarized in Table 1). Chest X-ray (CXR) and computed tomography (CT) images are mainly used with these medical devices. Most of these AI/ML models have been approved as an adjunct to diagnosis and analysis for conditions like lung nodules, pulmonary embolism, pleural effusion, pneumothorax, endotracheal tube localization, lung parenchyma analysis, and lung volume assessment. The last decade witnessed a remarkable rise in medical devices incorporating AI technology. According to the FDA's database by August 7, 2024, a total of 950 AI/ML-enabled devices had been approved. As technology advances further, we expect the expansion of AI-based medical devices with increased functionalities. AI medical devices hold the potential to enhance patient care and outcomes with enhanced engagement of healthcare professionals, increased transparency of AI algorithms, and reformed regulatory frameworks.

5.1.3. *Comparison of conventional methods and AI algorithms*

Here, we present a table of a detailed comparison of conventional methods and AI algorithms applied to diagnose and detect respiratory diseases (Table 2). It displays the main benefits and limitations of each method. It is thought that traditional diagnostic methods are central to clinical practice while AI might be able to improve diagnostic accuracy and speed. Comparing both approaches, this table aims to make healthcare professionals and stakeholders aware of the benefits and limitations of such methods for respiratory disease detection and diagnostics.

5.2. *Pulmonary drug delivery system development using AI*

Application of AI and ML in the development of PDDS is reshaping the field by speeding up discovery and optimization of new therapeutic agents against respiratory diseases. The AI/ML models examine enormous datasets from molecular interactions, formulations, clinical trials, and patient records to screen drug candidates and predict their efficacy and safety profiles. These technologies enable researchers to simulate complex biological processes, uncover potential drug targets, and design molecules with improved pharmacokinetic and pharmacodynamic properties[147]. In this section, we systematically review the applications of AI in the development of PDDS, particularly drug discovery, formulation development and optimization, and drug delivery (Fig. 7)[148-150]. Using AI/ML, pharmaceutical companies may decrease the timelines and costs compared to traditional drug development process and promote the likelihood of success for bringing effective treatments to market.

5.2.1. *Drug discovery*

AI is transforming PDDS in drug discovery by optimizing both *de novo* drug design and the repurposing of existing drugs. For *de novo* drugs, state-of-the-art AI algorithms, such as DL models, analyze vast datasets of molecular properties and biological activities to identify new compounds targeting specific respiratory diseases. For instance, *in silico* medicine discovered and designed INS018_055, a small molecule candidate targeting Traf2-and Nck-interacting kinase (TNIK) and developed for idiopathic pulmonary fibrosis patients, within merely 18 months with the assistance of AI models, including transformer-based models, GANs, and genetic algorithms[151]. More importantly, as of Sep 2024, this first-in-class drug molecule has progressed through Phase IIa clinical testing, and the 12-week study displayed a favorable safety profile and dose-dependent response in lung function in idiopathic pulmonary fibrosis patients, which demonstrated a proof-of-concept success for AI-based drug discovery[152]. Remdesivir, originally developed against the Ebola virus, was rapidly repurposed for coronavirus disease 2019 (COVID-19) with the utilization of AI[153]. COVID-19 is an infectious disease caused by the SARS-CoV-2 virus and is spreading worldwide. Beck et al.[154] successfully developed a molecule Transformer-Drug Target Interaction(MT-DTI) based on a DL model and identified several chemical compounds with inhibitory potency that can potentially be used against the SARS-CoV-2 virus, such as proteinase (94.94 nmol/L), remdesivir (113.13 nmol/L), efavirenz (199.17 nmol/L), ritonavir (204.05 nmol/L), and dolutegravir (336.91 nmol/L) (Fig. 8A)[154]. In addition, Jin et al.[155] successfully developed a DL model to identify synergistic drug combinations against the SARS-CoV-2 virus (Fig. 8B and C)[155]. In this study, researchers proposed a novel neural network framework integrating drug−target interaction and target-disease association

Table 1 US Food and Drug Administration (FDA) approved AI-based medical device for respiratory disease detection and diagnostic.

Indication or function	Modality	Device	Company	FDA approval date	*De novo* or 510 (k) number
Idiopathic pulmonary fibrosis	CT	Fibresolve	Imvaria, Inc.	01/12/2024	DEN220040
Respiratory rate measurement	NIR	Oxehealth Vital Signs	Oxehealth Limited	03/26/2021	DEN200019
	NIR	Gili Pro Biosensor	Continuse Biometrics Ltd.	04/01/2021	DEN200038
Rib fractures	CT	BriefCase	Aidoc Medical, Ltd.	02/01/2023	K230020
Pulmonary nodule	CT	AI-Rad Companion (Pulmonary)	Siemens Healthcare GmbH	03/21/2024	K233753
	CXR	Lung-CAD	Imagen Technologies, Inc.	10/03/2023	K230085
	CT	uOmnispace.CT	Shanghai United Imaging Healthcare Co., Ltd.	05/17/2024	K233209
	CT	AI-Rad Companion (Pulmonary)	Siemens Healthcare GmBh	08/11/2022	K213713
	CT	AVIEW Lung Nodule CAD	Coreline Soft Co., Ltd.	02/24/2023	K221592
	CT	NinesMeasure	Nines, Inc.	02/25/2021	K202990
	MDCT	syngo.CT Lung CAD (Version VD30)	Siemens Healthcare GmbH	07/19/2023	K231157
	CXR	qXR-LN	Qure.AI Technologies	12/22/2023	K231805
	CXR	VisiRad XR	Imidex Inc.	08/03/2023	K223133
Pulmonary embolism	CT	CINA-iPE	Avicenna.AI	03/13/2024	K233968
	CT	Xeleris V Processing and Review System	GE Healthcare	03/01/2023	K221680
	CTPA	Viz RV/LV	Viz.Ai, Inc.	08/29/2022	K221100
	CTPA	BriefCase	Aidoc Medical, Ltd.	08/26/2022	K222277
	CTPA	Rapid PE Triage and Notification	iSchemaView Inc.	05/17/2022	K220499
Pleural effusion and pneumothorax	CXR	Radify Triage	Envisionit DeepAI Ltd.	01/17/2024	K231871
	CXR	BraveCX	Bering Ltd.	11/09/2023	K223754
	CXR	qXR-PTX-PE	Qure.AI Technologies	08/22/2023	K230899
Pleural effusion and pneumoperitoneum	CXR	Annalise Enterprise CXR Triage Trauma	Annalise-AI Pty Ltd.	03/28/2023	K222179
Pleural effusion	CXR	EFAI ChestSuite XR Pleural Effusion Assessment System	Ever Fortune.AI Co., Ltd.	09/08/2022	K222076
Pneumothorax	CXR	Critical Care Suite 2.1,	GE Medical Systems, LLC.	05/25/2023	K223491
	CXR	QOCA image Smart CXR Image Processing System	Quanta Computer Inc.	01/27/2023	K221868
	CXR	ClearRead Xray Pneumothorax	Riverain Technologies, Inc.	03/10/2022	K213566
	CXR	EFAI ChestSuite XR Pneumothorax Assessment System	Ever Fortune.AI Co., Ltd.	11/08/2022	K221552
	CXR	DrAid for Radiology v1	VinBrain Joint Stock Company	09/01/2022	K221241
	CXR	Annalise Enterprise CXR Triage Pneumothorax	Annalise-AI	02/24/2022	K213941
Interstitial lung disease	CT	Brainomix 360 e-Lung	Brainomix Limited	05/13/2024	K233875
Abnormal vertical position of endotracheal tube	CXR	BriefCase	Aidoc Medical, Ltd.	11/18/2022	K221330
Lung parenchyma analysis	CT	LungQ v3.0.0	Thirona BV	01/08/2024	K232412
	CT	VIDAvision	VIDA Diagnostics Inc.	08/07/2020	K200990
Suspicious lesions in the chest region	CXR	DeepTek CXR Analyzer v1.0	DeepTek Medical Imaging Pvt Ltd.	10/05/2023	K231001
Pulmonary segmentation	CT	ClariPulmo	ClariPi Inc.	04/06/2022	K203783
	CT	AI-Rad Companion (Pulmonary)	Siemens Healthcare GmBh	08/11/2022	K213713

CT, computed tomography; NIR, near infrared; CXR, chest X-Ray; MDCT, multi-detector computed tomography; CTPA, computed tomographic pulmonary angiography.

modules by leveraging datasets from drug−target interaction, single agent antiviral activity, and drug−drug combination. Through the *in vitro* experimental validation, remdesivir-reserpine and remdesivir-IQ-1S showed strong antiviral SARS-CoV-2 synergy and can be potentially treated for COVID-19. Therefore, the applications of AI in drug discovery greatly facilitate the development of PDDS by accelerating the process of identifying potent drug molecules for respiratory diseases.

Respiratory toxicity is a critical consideration in the drug discovery and development of PDDS, as inhaled drugs directly target the lungs and are at higher risk of causing local toxicity. It is essential to ensure drug safety and efficacy by understanding and mitigating respiratory toxicity. Jaganathan et al.[156] investigated the application of an explainable ML model to predict the respiratory toxicity of drug molecules. In this study, researchers successfully developed quantitative structure−activity relationship

Table 2 Comparison of conventional methods and AI strategies in detecting and diagnosing respiratory diseases.

Method	Advantage	Disadvantage
Conventional methods	Well-trusted and widely used in clinical settings. Results are interpreted in conjunction with clinical presentation. Generally, conventional methods are less expensive compared to advanced AI techniques. Many healthcare facilities have established systems in place for conventional diagnostics, making them readily available. Many conventional diagnostic methods are approved and recognized by regulatory agencies, ensuring their reliability.	Often requires trained personnel for operation and interpretation. Results can be subject to human error or variability in interpretation. There's variability in protocols, which can lead to inconsistent results across different healthcare settings. Conventional methods may struggle with uncommon or complex respiratory diseases.
AI strategies	Offers rapid detection and diagnosis. Can detect asymptomatic cases and differentiate between multiple pathogens. AI tools can analyze real-time data for ongoing assessment of patient conditions. Can assist in creating personalized treatment plans based on comprehensive patient data analysis.	High sensitivity of patient data raises concerns about security and privacy. AI models may be biased if training data is not representative of the patient population. Poor data input or noise can lead to inaccurate predictions. AI results may require specialized knowledge to interpret correctly and apply clinically.

models associated with respiratory toxicity by applying eight different ML algorithms and multiple feature selection methods. Among all ML models, SVM demonstrated the best predictive performance with an accuracy of 86.2% and a Matthews correlation coefficient of 0.722 in the test dataset. More importantly, by utilizing the Shapley Additive explanations (SHAP) approach, several important chemical properties were identified and analyzed. Overall, this study has shown the potential of applying ML in the early stage of drug discovery for predicting respiratory toxicity of drug molecules (Fig. 8D–F)[156].

5.2.2. *Formulation design and optimization*

Formulation development is one of the most important sectors in the development of PDDS. The FDA encouraged the use of quality by design (QbD) in the pharmaceutical industry[157]. According to the QbD framework, design space is defined as the multidimensional combination and interaction of input variables such as critical material attributes and critical process parameters[158]. It is estimated that the design space of pharmaceutical formulation development is around 10^{25}–10^{30}, which is difficult and almost impossible to optimize the formulations simply by prior knowledge from scientists or researchers[26]. Therefore, with the assistance of novel modeling methods such as AI and ML, scientists can greatly improve the development efficiency compared to conventional trial-and-error experiments. In recent decades, AI has been transforming the field of PDDS by facilitating formulation design and optimization processes. Leveraging ML algorithms, researchers can analyze vast datasets containing drug

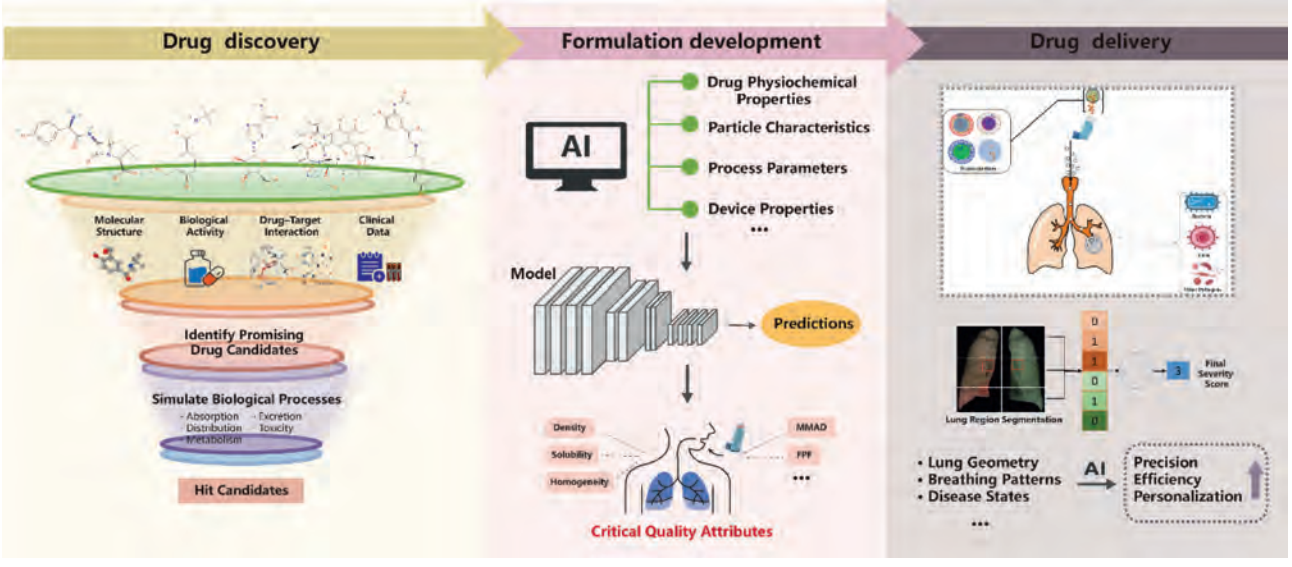

Figure 7 A proposed workflow for applying AI in the development of PDDS. Reprinted with the permission from Refs. 148–150: Copyright © 2019 American Chemical Society; Copyright © 2023 Elsevier; Copyright © 2023 Elsevier.

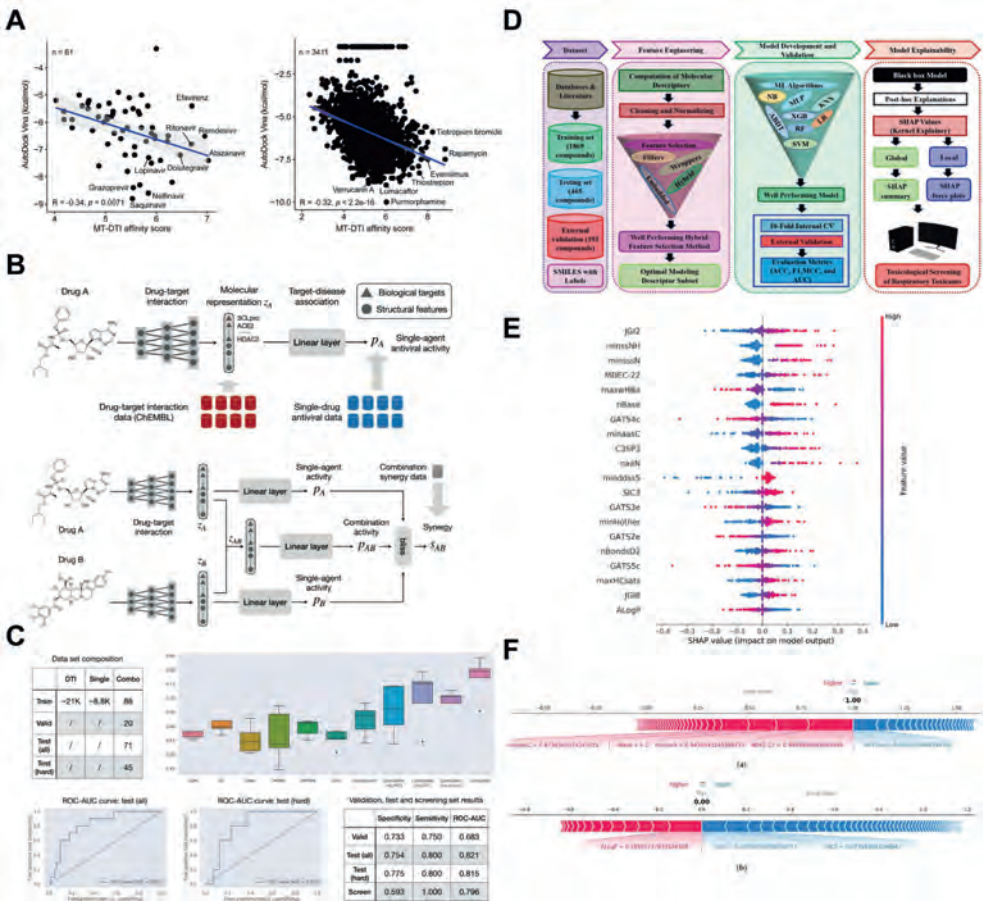

Figure 8 AI used in drug discovery during the development of PDDS. Determination of antiviral drug for SARS-CoV-2 using MT-DTI and AutoDock Vina methods. 3410 FDA-approved drugs were evaluated based on the deep learning affinity score, and remdesivir was selected as a promising candidate for SARS-CoV-2. Reprinted with the permission from Ref. 154. Copyright © 2020 Elsevier (A). The framework of ComboNet for synergistic drug combination discovery, consisting of a drug-target interaction (DTI) and a target-disease association network. Reprinted with the permission from Ref. 155. Copyright © 2021 National Academy of Sciences (B). ComboNet displayed satisfactory predictive performance in training, validation, and testing sets, and was experimentally validated. Reprinted with the permission from Ref. 155. Copyright © 2021 National Academy of Sciences (C). The workflow of respiratory toxicity predictive model. Reprinted with the permission from Ref. 156. Copyright © 2022 MDPI (D). SHAP summary plot for respiratory toxicity predictive model. JGI2 (Mean topological charge index of order 2), minssNH (Minimum atom-type E-State: −NH−), and MDEC-22 (Molecular distance edge between all secondary carbons) were the top three important features for the model. Reprinted with the permission from Ref. 156. Copyright © 2022 MDPI (E). Respiratory toxicity predictive model's local explanation. Reprinted with the permission from Ref. 156. Copyright © 2022 MDPI (F).

physicochemical properties, particle characteristics, process parameters, and device properties to predict optimal performance of drug formulation[75,111,113,159].

ML has been widely used in the formulation development of PDDS. Recent studies have shown that drug combination treatment could benefit patients with COPD and asthma[160]. Specifically, glucocorticoids can be administered with either a long-acting beta-adrenoceptor agonist (LABA) or a long-acting muscarinic antagonist (LAMA)[161]. In addition, short-acting muscarinic receptor antagonists (SAMAs) and short-acting beta adrenoreceptor agonists (SABAs) can be administered jointly for acute asthma attacks and show enhanced bronchodilator response compared to single drugs. The drug combinations can form co-amorphous systems (COAMS) through particle engineering techniques such as milling, spray-drying, freeze-drying, and solvent evaporation. Fink et al.[111] successfully developed an ML predictive model of COAMS from a dataset containing 225 formulations. Among all ML algorithms, XGBoost exhibited the best predictive performance with an overall accuracy of 100% in the training subset. The trained model was evaluated in the test subset by 19 unseen formulations and achieved a satisfactory accuracy of 79%. Lastly, experimental validation was conducted by three drug combination systems, and two COAMS (streptomycin sulphate-glycopyrronium bromide and glycopyrronium bromide-budesonide) were successfully prepared (Fig. 9A)[111]. This study has proven the potential of ML-based formulation development method for inhalation therapy.

DPIs are one of the most widely used dosage forms to treat pulmonary diseases such as asthma and COPD. An aerodynamic size of inhaled particles between 1 and 5 μm is the prerequisite to ensure effective drug deposition in lung[54]. Aerosol performance of DPIs is typically indicated by fine particle fraction (FPF) and mass median aerodynamic diameter (MMAD). A conventional DPI formulation development pathway utilizes trial-and-error experiments, requiring substantial time and workload. To overcome this challenge, researchers have developed ML aerosol performance

predictive models for DPIs[75,162]. Jiang et al.[75] successfully developed the aerosol performance predictive model of DPIs using both formulation tabular data and scanning electron microscopy (SEM) images. Specifically, multiple traditional ML and DL algorithms were applied to build predictive models for aerosol performance, such as ridge regression, random forest, XGBoost, LightGBM, SVM, K-Nearest Neighbors (KNN), ANN, and CNN. A dataset containing 134 DPI formulations was collected to train the ML models, and the formulations were prepared by thin-film-freezing technology. After evaluating the predictive performance of all models, random forest performed the best to predict FPF with a mean absolute error of around 7.25%, and ANN was the best in MMAD prediction with a mean absolute error of around 0.393 μm. Moreover, a CNN was applied to predict aerosol performance based on SEM images and has demonstrated a relatively high accuracy of 83.8% over 316 SEM images (Fig. 9B)[75]. Therefore, ML can greatly improve the development efficiency by reducing the workload.

In formulation manufacturing, particle engineering is critical in optimizing pulmonary drug delivery by enabling scalable production of inhalable drug formulations with precise control over critical attributes like particle size, shape, and density. Techniques such as spray drying and spray freeze-drying are widely adopted to produce porous, flowable particles in a single, continuous process suitable for large-scale production[163,164]. Schimitt et al.[159] studied the impact of formulation and process parameters on particle size of spray dried particles by using ML modeling. Specifically, an ensemble ML model was successfully developed to predict particle size and showed acceptable prediction error between −7.7% and 18.6% (25%/75% percentiles) for the evaluation set. SHAP was also applied to analyze the trained model, and the results were consistent with the mechanistic understanding of the formation of spray-dried particles. This study has demonstrated the feasibility of predicting the particle size of spray-dried powder during the scale-up process and can potentially be adapted to the development of dry powder for inhalation. In addition, other critical quality attributes such as moisture and yield can be predicted by ML models during the spray drying process[165]. Fiedler et al.[165] investigated the application of an ML approach to predict the design space of spray-dried proteins by using lactose as a surrogate material. A design of experiments (DoE) was performed to generate data for ML modeling, followed by a multiple-step ML approach involving XGBoost and ANN. This methodology can effectively optimize the design space of spray-dried powder by saving at least 62% material, resulting in acceptable yields >75% and residual moisture <10% (Fig. 9C)[165]. Surface charge density is a critical attribute for dry particles, particularly for those prepared by fluidized beds. Lu et al.[166] successfully utilized multiple ML models (*i.e.*, kernel ridge regression, support vector machine regression, and multilayer perceptron) to analyze the charging behavior of dry particles in gas-solid fluidized beds with high accuracy (R^2 equal to 0.980 and 0.979), which can potentially be used for the development of DPIs. In summary, AI and ML have been extensively used in the formulation development of PDDS. By applying different ML algorithms, critical quality attributes of the systems can be predicted and optimized with a significant reduction in workload and cost.

In addition, AI and ML have been widely used for image analysis of PDDS. By utilizing AI algorithms, the quality attributes of PDDS, such as aerosol performance and homogeneity, can be characterized with relatively high accuracy and efficiency[75,162,167]. For instance, a DL model was developed to characterize the 3D microstructure of a DPIs using correlative multi-scale XCT[167]. In this study, a carrier-based DPI was first prepared by blending, and then micro-XCT and nano-XCT were employed to analyze the inhalation blend. A deep neural network was subsequently utilized to conduct image segmentation. The results demonstrated that the drug-lactose blend was homogenous on a bulk scale, while it was heterogeneous on an individual particle scale. Moreover, the drug proportions of each cluster can be predicted by a linear relationship between the thickness of the drug-rich phase and the carrier in a cluster (Fig. 9D)[167]. In summary, the application of AI-driven image analysis has shown significant potential in understanding the critical quality attributes of PDDS during formulation development.

5.2.3. Drug delivery

AI is revolutionizing pulmonary drug delivery by enhancing accuracy, efficacy, and personalization of treatment strategies. AI-based models enable the optimization of inhaler designs and formulations to provide effective drug deposition in the targeted regions of the lungs. ML algorithms can be implemented to examine patient-specific parameters such as lung geometry, breathing patterns, and disease progressions to predict drug distribution and absorption and develop tailored therapies[113]. Through integration real-time monitoring and feedback from smart inhalers, AI also improves patient compliance and outcomes, enabling pulmonary drug delivery to be more effective and patient-centric[168].

Effective pulmonary drug delivery aims to provide precise and efficient deposition of aerosolized drug molecules at specific lung sites, enhancing therapeutic outcomes while minimizing systemic side effects and damage to healthy tissues. Recurrent respiratory papillomatosis requires targeted drug delivery to effectively treat papillomata in the larynx and glottis with minimal action on healthy tissues[169]. A study reported incorporating computational fluid particle dynamics (CFPD) and ML to develop a smart inhaler algorithm to optimize nozzle settings and drug release. This computational method is based on patient-specific data with improved drug deposition efficiency at targeted sites. Specifically, the ML algorithm, trained on data from CFPD simulations, adjusted the drug release nozzle with patient-specific breathing profiles and particle characteristics to enhance therapy accuracy. Using AI to individualize inhalation therapy outperforms conventional methods with higher precision in drug delivery and holds promise in managing recurrent respiratory papillomatosis and other respiratory diseases[113]. Additionally, Tree-Based Random Forest Analysis (TBRFA) was developed to accurately predict pulmonary immune responses and lung burden of inhaled nanoparticles (Fig. 10A)[170]. By addressing challenges posed by heterogeneous nanoparticles datasets, TBRFA uses multiway importance analysis to reduce feature importance bias and builds feature interaction networks to improve model interpretability. TBRFA achieved high predictive accuracy with correlation coefficients >0.9 and >0.75 in the training set and half of the test sets, respectively. This framework also explored complex interactions between nanoparticle properties and exposure conditions. Specifically, multiway feature analysis showed that gender is not a significant feature of the IL-4 RF model. Recovery duration is negatively correlated with immune responses. Nanoparticles with a large specific surface area tend to reduce cytokine release while increasing total protein and cell number. In addition, nanoparticles with a small diameter (<100 nm) could achieve cross-organ transportation through penetration of biological membranes.

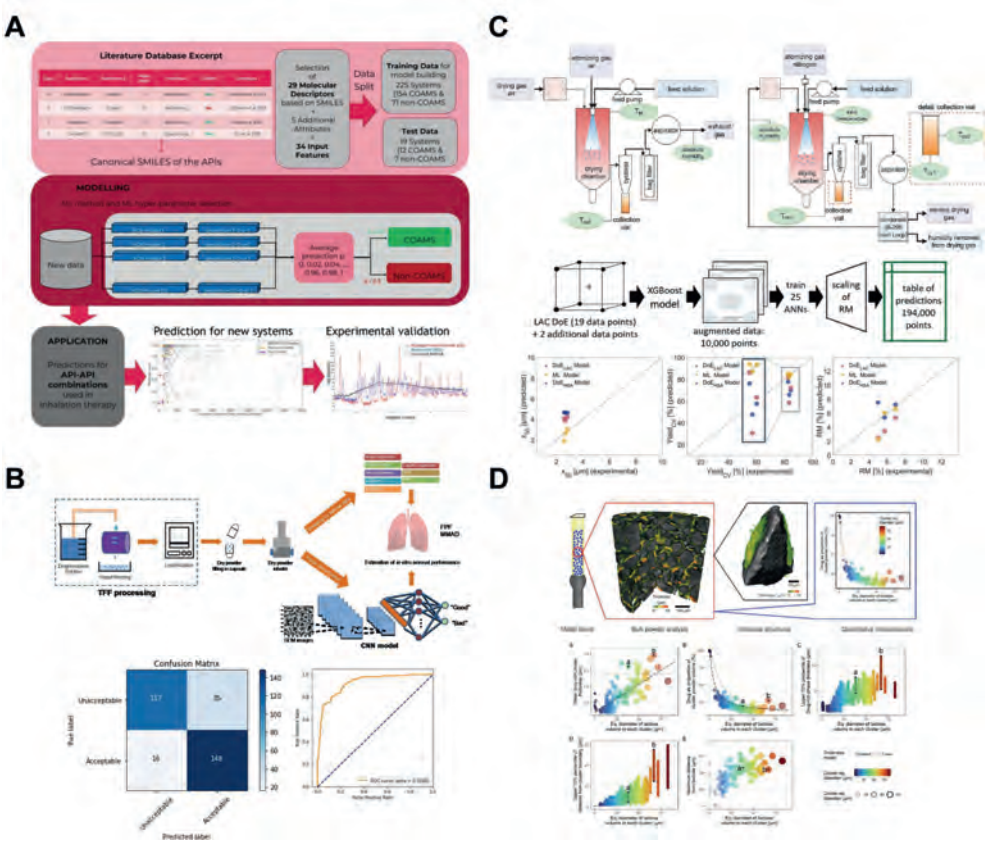

Figure 9 The applications of AI in formulation design and optimization during the development of PDDS. An AI-based COAMS screening system for the development of binary drug inhalation therapy. Reprinted with the permission from Ref. 111. Copyright © 2023 MDPI (A). A hybrid ML model using tabular data and SEM images was developed to predict the aerosol performance of inhaled dry powder prepared by thin-film-freezing, demonstrating an accuracy of 83.86% in SEM image classification. Reprinted with the permission from Ref. 75. Copyright © 2022 Elsevier (B). ML and Design of Experiment (DoE) were integrated to predict critical quality attributes such as yield, residual moisture, preservation of protein conformation during spray drying process, and the experimental validation was conducted with satisfactory outcome. Reprinted with the permission from Ref. 165. Copyright © 2023 Elsevier (C). AI-driven model was applied to investigate the microstructure of inhalation blend characterized by XCT images, and individual clusters were analyzed quantitatively with good correlation. Reprinted with the permission from Ref. 167. Copyright © 2023 Elsevier (D).

Overall, TBRFA and feature importance analysis provided valuable insights for inhaled nanoparticles design and application (Fig. 10B)[170]. Moreover, Huang et al.[171] developed an ML pipeline to identify potent antimicrobial peptides from a virtual library of billions of sequences containing 6−9 amino acids. Using a coarse-to-fine design principle, this pipeline employs sequential ML modules to narrow the search space rapidly. Among the selected candidates, three antimicrobial hexapeptides demonstrated strong activity against multidrug-resistant pathogens. More importantly, aerosolized formulations of these peptides showed therapeutic efficacy comparable to penicillin in bacterial pneumonia in mice, with low toxicity and resistance. This pipeline has demonstrated the promise of ML in accelerating the discovery of antimicrobial peptides for pulmonary drug delivery. Pulmonary gene therapy is gaining attention recently, particularly nonviral messenger RNA (mRNA)[172,173]. Ionizable lipids are essential for lipid nanoparticles and mRNA delivery[174]. To accelerate the process of identifying these lipids, Witten et al.[175] developed a DL approach for lipid optimization. A dataset of over 9000 lipid nanoparticles was used to construct a message-passing neural network to predict nucleic acid delivery for various lipid structures. This model successfully predicted drug delivery both *in vitro* and *in vivo*, even for lipid structures not included in the training data. By screening 1.6 million lipids *in silico*, two promising candidates, FO-35 and FO-32, were identified. These lipids achieved effective mRNA delivery to mouse muscles and nasal tissues. Additionally, FO-32 exhibited equivalent performance of current benchmarks for nebulized mRNA delivery to mouse lungs, and both FO-35 and FO-32 showed the potential of delivering mRNA to ferret lungs. This study demonstrates the potential of DL to enhance the development of lipid nanoparticles for RNA delivery. In addition, ML was successfully employed to predict nanoparticle mobility and fate in the mucus barrier during the pulmonary drug delivery process[176]. Specifically, an ML-based analysis called MotionNet was developed to classify the type of diffusion behavior of particle trajectories. This method was used to predict diffusion and fate of influenza A virus within human mucus and can potentially be used for the evaluation of nanoparticle formulation penetration through mucus in lungs. Recently, Mi et al.[177] studied the tissue distribution and tumor delivery efficiency of nanoparticles in mice using ML models. In this study, a deep neural network (DNN) was constructed to predict tissue

distribution across major tissues (*i.e.*, tumor, heart, liver, spleen, lung, and kidney) and tumor delivery using physicochemical properties of nanoparticles and tumor therapeutic strategies. The trained DNN exhibited high predictive accuracy with $R^2 = 0.87$ for lung tissue distribution, which can potentially be utilized to investigate the PDDS *in vivo* distribution across different tissues.

Last but not least, AI-driven techniques enable precise segmentation and quantification of lung structures from images such as CT and X-rays. They allow for accurate assessment of airway morphology and function[178,179]. Recent studies have demonstrated that AI-based image processing frameworks can reconstruct 3D respiratory geometries from 2D chest X-rays and 3D CT images, predicting regional drug deposition of a nebulizer with a median error of 5% compared to *in vivo* measurements (Fig. 10C–E)[179]. In this study, the researchers first developed a statistical shape and appearance model (SSAM) to reconstruct 3D lung and airway geometry based on 2D images. CNNs and UNet were then employed to conduct image segmentation of lung lobes and airways within the 3D CT images. Image-processing tools were

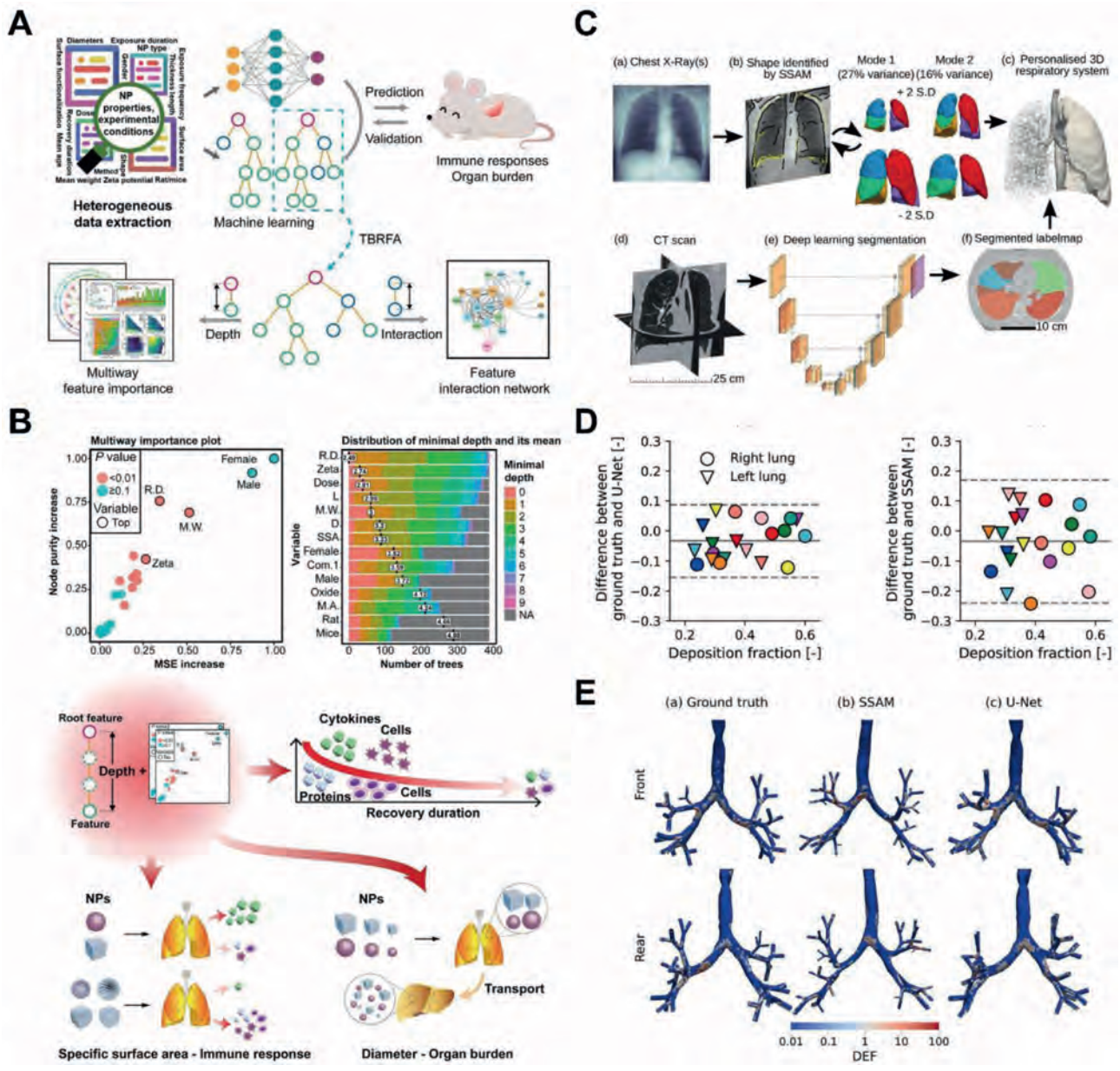

Figure 10 AI used in pulmonary drug delivery. The proposed TBRFA framework to predict the pulmonary immune responses and lung burden of nanoparticles *in vivo*. Reprinted with the permission from Ref. 170. Copyright © 2021 AAAS (A). A comprehensive feature importance analysis of TBRFA elucidated the mechanism of pulmonary drug delivery system *in vivo*. Reprinted with the permission from Ref. 170. Copyright © 2021 AAAS (B). The workflow of evaluating drug delivery process using DL-based 2D and 3D image analysis methods. Reprinted with the permission from Ref. 179. Copyright © 2024 Public Library of Science (C). Pulmonary drug deposition analysis results by U-Net and SSAM. Reprinted with the permission from Ref. 179. Copyright © 2024 Public Library of Science (D). The computation of deposition enhancement factor showed good consistency of U-Net and ground truth. Reprinted with the permission from Ref. 179. Copyright © 2024 Public Library of Science (E).

developed to simulate drug deposition and morphological properties of the airways, and the drug deposition prediction results were validated against experimental data. Furthermore, AI models have been successfully developed to predict and evaluate drug response in patients with cystic fibrosis. In this study, 283 cystic fibrosis patients treated with lumacaftor−ivacaftor for one year showed significant improvements in lung structure, as evidenced by decreased Bhalla scores on chest CT scans. Additionally, an unsupervised ML algorithm identified three distinct morphological clusters, with patients in cluster C more likely to experience a $\geq$5% increase in (forced expiratory volume in 1 s) FEV_1% predicted, suggesting that pre-therapeutic radiomics features may help predict lung function response to treatment[178].

5.2.4. *Comparison of conventional methods and AI strategy*

Traditional PDDS development approaches often focus on empirical trial-and-error experiments wherein formulations and device geometries are optimized subjecting them to *in vitro* and *in vivo* testing, patient response, and professional knowledge. Although such approaches are gold standard, they are generally time-consuming, laborious, and expensive owing to the complex pulmonary system and its variability among different individuals. On the contrary, AI-based approaches show prominence by taking advantage of advanced algorithms and ML models to study large datasets to optimize drug formulations and to estimate patient-specific responses. Particle size distribution, drug deposition, as well as release profiles, can be optimized by processing large amounts of data with the assistance of AI. Furthermore, pulmonary drug delivery can be enhanced by precision medicine with personalization to identify optimal treatment regimens based on patient profiles[180]. Overall, there's no doubt that conventional methods are necessary but with the incorporation of AI to this process there is great potential to revolutionize pulmonary drug delivery with improved efficiency and patient outcomes (Table 3).

6. Challenges and prospects

6.1. *Regulatory and ethical considerations*

In terms of the use of AI in drug development, regulatory frameworks play an essential role in ensuring the safety and efficacy of novel therapies. Regulatory agencies such as the FDA and the European Medicines Agency (EMA) are considering ways to leverage AI-based tools to support various phases of drug development. The current practice at FDA involves reviewing AI-based medical devices through an appropriate premarket clearance, including 510 (k), *de novo*, and premarket approval[181]. The FDA released an AI/ML-based software as a medical device (SaMD) action plan during January 2021, which was intended to promote a multi-faceted approach to optimizing the agency regulation of AI-based medical software[182]. In addition, EMA released a work plan to guide the use of AI in medicines regulation in December 2023[183]. A major breakthrough in addressing the regulatory and ethical considerations surrounding AI in the pharmaceutical industry is the FDA release of a discussion paper titled "Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products"[184]. The paper contains information of the use of AI in drug discovery, preclinical study, and clinical trials as well as prospective best practices for integrating AI and ML into the development process. The action by FDA represents a landmark event for regulating AI-driven innovations in respiratory healthcare. Through understanding the benefits and challenges of drug development by AI, the agency is laying out a path towards future regulatory improvement that may provide new opportunities within this field.

Applications of AI to develop of PDDS raised several ethical issues and considerations, including patient privacy and data security, patient autonomy and informed consent, as well as algorithmic unfairness and bias[185,186]. Specifically, there are significant areas of patient privacy protection of personal information protection since personal data are liable to be examined by AI algorithms. Further, current AI algorithms may inadvertently reinforce pre-existing disparities in health care access and outcomes, leading to unequal treatment and loss of confidence among patients[187]. To overcome such challenges, we should ensure that AI algorithms are developed, implemented, and regulated on ethical grounds by ensuring transparent patterns of decision-making, recognition of potential biases, and promotion of fairness[188]. There is a need to develop and implement AI algorithms with transparency, accountability, and nondiscrimination patterns of action[189]. Moreover, informed consent remains one of the primary ethical considerations to be undertaken. Patients have all the right to receive clear and concise explanations about the extent of usage of AI during their treatment and its potential impacts on their outcomes. The disclosure enables patients to make appropriate decisions on their treatment options by balancing the benefits *versus* drawbacks of AI-driven diagnostics and therapy. For this reason, healthcare professionals should communicate efficiently with clear explanation of AI's role in their diagnostics and therapy and ensure an environment that respects patient autonomy. Through emphasis on informed consent and open explanation, we can ensure to a large extent that patients are well informed of the implications of AI-driven PDDS on their health outcomes.

6.2. *Challenges*

AI-driven PDDS exhibits various challenges on technology, physiology, and regulatory factors. The biggest challenges include data availability and quality as ML modeling mainly is primarily based on reliable experimental data. The quality of the data significantly affects the predictive performance of ML models. Nevertheless, high-quality preclinical and clinical data on lung deposition and efficacy are scarce or limited to access by model development. Additionally, other issues such as data format heterogeneity[190], data ownership issues, and privacy vulnerability are equally challenging[191]. Currently, data interoperability is a major challenge as the medical records or drug formulation data are stored in different electronic health record systems or different institutes[192]. Therefore, data integration or distribution is hindered due to technical as well as policy barriers, and there is a need to develop systematic data sharing framework to accelerate the process[193]. Further, data bias exhibits as a common issue when developing ML models since most researchers and publications tend to report positive results, which will lead to data imbalance[194]. In addition, model interpretability is another challenge because most ML models can be black box, which makes it difficult to understand how they make predictions and potentially limits clinical translation[195]. Physiological complexity is another challenge. Specifically, predicting the drug deposition within the lungs is a complex process and requires extensive computational

Table 3 Comparison of conventional methods and AI strategies in the development of PDDS systems.

Method	Advantage	Disadvantage
Conventional methods	Well-established and widely used. Based on expert knowledge and empirical evidence. Allows for direct testing and validation in real-world conditions.	Time-consuming and costly. Requires large-scale clinical trials and lengthy optimization. Can be inefficient in handling complex data or predicting outcomes accurately. Less personalization for patient-specific treatment.
AI strategies	Can analyze vast amounts of data quickly and accurately. Enables more precise optimization of formulations and device designs. Personalizes drug delivery based on patient-specific data. Reduces development time and costs.	Requires large, high-quality datasets for training models. Potential for model overfitting or lack of generalizability. Dependent on computational resources and expertise. Regulatory challenges and the need for validation in clinical setting.

recourses[196]. Patient variability, such as lung function and inhaler technique, can significantly impact pulmonary drug delivery[197]. Last but not least, some AI medical devices face safety issues, representing 25% of AI/ML-enabled medical devices reported[198]. For example, a patient showed hypokalemic potassium and was transferred to the ICU after using the insulin AI software Monarch Endotool for recommended administration. Therefore, regulatory agencies face challenges in integrating AI while maintaining reliability and safety in clinical trial approvals, drug authorizations, and post-market surveillance. Adapting current frameworks to assess AI-driven models introduces complexities in evaluation and implementation[199].

6.3. Conclusions and prospects

Traditional PDDS development process often applies a trial-and-error approach with much time and laborious workload. The incorporation of AI and ML can significantly ease the PDDS development process with high accuracy, improved efficiency, and increased efficacy, especially in respiratory disease detection and diagnosis, drug discovery, formulation design and optimization, and drug delivery. The software approved by the FDA and specific applications have demonstrated the transformative role of AI/ML to accelerate PDDS development for respiratory diseases.

The future of AI in the development of PDDS exhibits potential to transform therapy for respiratory diseases. Personalized medicine will become commonplace with the use of AI methods. Clinicians will be able to optimize treatment plans based on individual patient data, such as their genetic profiles and environmental factors[200,201]. Personalized medicine is becoming more essential in respiratory diseases, where patients respond differently to therapy as a result of genetic and phenotypic differences. Using varied datasets such as genomic data, proteomic data, patient history, and environmental exposures, AI-based models have the potential to develop individualized therapy plans that enhance efficacy and minimize adverse effects[202]. Moreover, ML-based algorithms permit real-time monitoring of drug delivery efficiency and drug responses at the patient end. The adjustments to therapy plans can be undertaken on a timely basis. For instance, AI can process biomarkers through remote sensors to continuously assess the respiratory status of patients[203].

AI can improve drug formulation and dosing regimen optimization by evaluating large datasets. It can interpret how variations in inhaled formulations can affect therapeutic outcomes. Multifactorial data can be interpreted by ML algorithms to recognize optimal candidates for PDDS. Using AI and ML, researchers can investigate combinations of APIs, excipients, and inhalers and recognize the optimal formulations with high drug delivery efficiency and reduced side effects.

The future of PDDS can be significantly facilitated by incorporating AI and automation to enable more efficient, personalized, and effective respiratory therapy. Automation of processes during manufacturing ensures high accuracy and consistency, which reduces human error and boosts production scalability of drug delivery systems[204]. These advancements are expected to transform pulmonary drug delivery, providing improved therapeutic outcomes.

Overall, these advancements will streamline the product development process of PDDS and revolutionize respiratory disease management by expanding the boundaries of established therapeutic capabilities. Acting on AI's prediction advantage in respiratory disease detection and diagnostics, drug discovery, formulation design optimization, and drug delivery promises remarkable breakthroughs that will transform therapy for patients. Nevertheless, challenges such as data quality and availability, model interpretability, and regulatory clearance can impede clinical translation. Going forward, it will be essential for regulatory frameworks to adapt to such technologies by balancing safety and efficacy while fostering an innovative environment.

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Author contributions

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Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2025.11.028.

References

1. Ferkol T, Schraufnagel D. The global burden of respiratory disease. *Ann Am Thorac Soc* 2014;**11**:404−6.
2. Soriano JB, Kendrick PJ, Paulson KR, Gupta V, Abrams EM, Adedoyin RA, et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990−2017: a systematic analysis for the global burden of disease study 2017. *Lancet Respir Med* 2020;**8**: 585−96.
3. Salvi S. Tobacco smoking and environmental risk factors for chronic obstructive pulmonary disease. *Clin Chest Med* 2014;**35**:17−27.
4. Zemanick ET, Harris JK, Conway S, Konstan MW, Marshall B, Quittner AL, et al. Measuring and improving respiratory outcomes in cystic fibrosis lung disease: opportunities and challenges to therapy. *J Cyst Fibros* 2010;**9**:1−16.
5. MacLeod M, Papi A, Contoli M, Beghé B, Celli BR, Wedzicha JA, et al. Chronic obstructive pulmonary disease exacerbation fundamentals: diagnosis, treatment, prevention and disease impact. *Respirology* 2021;**26**:532−51.
6. Labaki WW, Martinez CH, Martinez FJ, Galbán CJ, Ross BD, Washko GR, et al. The role of chest computed tomography in the evaluation and management of the patient with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017;**196**:1372−9.
7. Trivedi A, Hall C, Hoffman EA, Woods JC, Gierada DS, Castro M. Using imaging as a biomarker for asthma. *J Allergy Clin Immunol* 2017;**139**:1−10.
8. National Academies of Sciences , Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Committee on Identifying New or Improved Diagnostic or Evaluative Techniques. Techniques for respiratory disorders. Advances in the diagnosis and evaluation of disabling physical health conditions, 2023, National Academies Press (US). Available from: https://www.ncbi.nlm.nih.gov/books/NBK593672/
9. Zhang ZW, Ma P, Ahmed R, Wang J, Akin D, Soto F, et al. Advanced point-of-care testing technologies for human acute respiratory virus detection. *Adv Mater* 2022;**34**:2103646.
10. Vliegenthart R, Fouras A, Jacobs C, Papanikolaou N. Innovations in thoracic imaging: CT, radiomics, AIand X-ray velocimetry. *Respirology* 2022;**27**:818−33.
11. Brunaugh AD, Moraga-Espinoza D, Bahamondez-Canas T, Smyth HDC, Williams RO. *Pulmonary drug delivery.* 2024. p. 195−214.
12. Zhou Q, Leung SSY, Tang P, Parumasivam T, Loh ZH, Chan HK. Inhaled formulations and pulmonary drug delivery systems for respiratory infections. *Adv Drug Deliv Rev* 2015;**85**:83−99.
13. Kole E, Jadhav K, Shirsath N, Dudhe P, Verma RK, Chatterjee A, et al. Nanotherapeutics for pulmonary drug delivery: an emerging approach to overcome respiratory diseases. *J Drug Deliv Sci Technol* 2023;**81**:104261.
14. He SQ, Gui JJ, Xiong K, Chen MW, Gao HL, Fu Y. A roadmap to pulmonary delivery strategies for the treatment of infectious lung diseases. *J Nanobiotechnol* 2022;**20**:101.
15. Liang ZL, Ni R, Zhou JY, Mao SR. Recent advances in controlled pulmonary drug delivery. *Drug Discov Today* 2015;**20**:380−9.
16. Pilcer G, Amighi K. Formulation strategy and use of excipients in pulmonary drug delivery. *Int J Pharm* 2010;**392**:1−19.
17. Patton JS, Fishburn CS, Weers JG. The lungs as a portal of entry for systemic drug delivery. *Proc Am Thorac Soc* 2004;**1**:338−44.
18. Gonda I. The ascent of pulmonary drug delivery. *J Pharm Sci* 2000; **89**:940−5.
19. Lavorini F, Pistolesi M, Usmani OS. Recent advances in capsule-based dry powder inhaler technology. *Multidiscip Respir Med* 2017;**12**:1−7. 2017 121.
20. Atkins PJ. Dry powder inhalers: an overview. *Respir Care* 2024;**50**: 1304−12.
21. David L, Thakkar A, Mercado R, Engkvist O. Molecular representations in AI-driven drug discovery: a review and practical guide. *J Cheminf* 2020;**12**:1−22.
22. Qureshi R, Irfan M, Gondal TM, Khan S, Wu J, Hadi MU, et al. AI in drug discovery and its clinical relevance. *Heliyon* 2023;**9**:e17575.
23. Deng JY, Yang ZB, Ojima I, Samaras D, Wang FS. Artificial intelligence in drug discovery: applications and techniques. *Briefings Bioinf* 2022;**23**:bbab430.
24. Jayatunga MKP, Xie W, Ruder L, Schulze U, Meier C. AI in small-molecule drug discovery: a coming wave?. *Nat Rev Drug Discov* 2022;**21**:175−6.
25. Chan HCS, Shan HB, Dahoun T, Vogel H, Yuan SG. Advancing drug discovery *via* artificial intelligence. *Trends Pharmacol Sci* 2019;**40**: 592−604.
26. Wang W, Ye ZYF, Gao HL, Ouyang DF. Computational pharmaceutics—a new paradigm of drug delivery. *J Controlled Release* 2021;**338**:119−36.
27. Vora LK, Gholap AD, Jetha K, Thakur RRS, Solanki HK, Chavda VP. Artificial intelligence in pharmaceutical technology and drug delivery design. *Pharmaceutics* 2023;**15**:1916.
28. Bao ZQ, Bufton J, Hickman RJ, Aspuru-Guzik A, Bannigan P, Allen C. Revolutionizing drug formulation development: the increasing impact of machine learning. *Adv Drug Deliv Rev* 2023; **202**:115108.
29. Bannigan P, Aldeghi M, Bao ZQ, Häse F, Aspuru-Guzik A, Allen C. Machine learning directed drug formulation development. *Adv Drug Deliv Rev* 2021;**175**:113806.
30. Jiang JH, Ma XY, Ouyang DF, Iii ROW. Emerging artificial intelligence (AI) technologies used in the development of solid dosage forms. *Pharmaceutics* 2022;**14**:2257.
31. Aliper A, Kudrin R, Polykovskiy D, Kamya P, Tutubalina ELN, Chen S, et al. Prediction of clinical trials outcomes based on target choice and clinical trial design with multi-modal artificial intelligence. *Clin Pharmacol Ther* 2023;**114**:972−80.
32. Harrer S, Shah P, Antony B, Hu JY. Artificial intelligence for clinical trial design. *Trends Pharmacol Sci* 2019;**40**:577−91.
33. Chen ZY, Liu X, Hogan W, Shenkman E, Bian J. Applications of artificial intelligence in drug development using real-world data. *Drug Discov Today* 2021;**26**:1256−64.
34. Zhou Y, Wang F, Tang J, Nussinov R, Cheng F. Artificial intelligence in COVID-19 drug repurposing. *Lancet Digit Health* 2020;**2**:e667−76.
35. Tanoli Z, Vähä-Koskela M, Aittokallio T. Artificial intelligence, machine learning, and drug repurposing in cancer. *Expert Opin Drug Discov* 2021;**16**:977−89.
36. Wan ZM, Sun XR, Li Y, Chu TY, Hao XY, Cao Y, et al. Applications of artificial intelligence in drug repurposing. *Adv Sci* 2025;**12**: 2411325.
37. Dotolo S, Marabotti A, Facchiano A, Tagliaferri R. A review on drug repurposing applicable to COVID-19. *Briefings Bioinf* 2021;**22**:726−41.
38. Ahmed F, Soomro AM, Chethikkattuveli Salih AR, Samantasinghar A, Asif A, Kang IS, et al. A comprehensive review of artificial intelligence and network based approaches to drug repurposing in COVID-19. *Biomed Pharmacother* 2022;**153**:113350.
39. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature* 2015;**521**: 436−44.
40. ChatGPT. Available from: https://chatgpt.com [accessed March 11, 2025].
41. DeepSeek. Available from: https://www.deepseek.com/[accessed March 11, 2025].

42. Devlin J, Chang MW, Lee K, Toutanova K. *BERT: pre-training of deep bidirectional transformers for language understanding*. 2019.
43. Claude. Available from: https://claude.ai/login?returnTo=%2F%3F [accessed March 11, 2025].
44. Gemini — chat to supercharge your ideas. Gemini. Available from: https://gemini.google.com [accessed March 11, 2025].
45. Elbadawi M, Li HX, Basit AW, Gaisford S. The role of artificial intelligence in generating original scientific research. *Int J Pharm* 2024;**652**:123741.
46. Gates AJ, Ke Q, Varol O, Barabási AL. Nature's reach: narrow work has broad impact. *Nature* 2019;**575**:32−4.
47. van Eck NJ, Waltman L. Visualizing bibliometric networks. In: Ding Y, Rousseau R, Wolfram D, editors. *Measuring scholarly impact: methods and practice*. Cham: Springer International Publishing; 2014. p. 285−320.
48. Cao SM, Huang HH, Xiao MZ, Yan L, Xu WX, Tang XM, et al. Research on safety in home care for older adults: a bibliometric analysis. *Nurs Open* 2021;**8**:1720−30.
49. Boyack KW, Klavans R. Co-citation analysis, bibliographic coupling, and direct citation: which citation approach represents the research front most accurately?. *J Am Soc Inf Sci Technol* 2010;**61**:2389−404.
50. Su HN, Lee PC. Mapping knowledge structure by keyword co-occurrence: a first look at journal papers in technology foresight. *Scientometrics* 2010;**85**:65−79.
51. Groneberg DA, Witt C, Wagner U, Chung KF, Fischer A. Fundamentals of pulmonary drug delivery. *Respir Med* 2003;**97**:382−7.
52. Zeng XM, Martin GP, Marriott C. The controlled delivery of drugs to the lung. *Int J Pharm* 1995;**124**:149−64.
53. Mathias NR, Hussain MA. Non-invasive systemic drug delivery: developability considerations for alternate routes of administration. *J Pharm Sci* 2010;**99**:1−20.
54. Peng TT, Lin SQ, Niu BY, Wang XY, Huang Y, Zhang XJ, et al. Influence of physical properties of carrier on the performance of dry powder inhalers. *Acta Pharm Sin B* 2016;**6**:308−18.
55. Tang J, Ouyang QH, Li YY, Zhang PS, Jin WH, Qu S, et al. Nanomaterials for delivering antibiotics in the therapy of pneumonia. *Int J Mol Sci* 2022;**23**:15738.
56. Andrade F, Rafael D, Videira M, Ferreira D, Sosnik A, Sarmento B. Nanotechnology and pulmonary delivery to overcome resistance in infectious diseases. *Adv Drug Deliv Rev* 2013;**65**:1816−27.
57. Sharma P, Mehta M, Dhanjal DS, Kaur S, Gupta G, Singh H, et al. Emerging trends in the novel drug delivery approaches for the treatment of lung cancer. *Chem Biol Interact* 2019;**309**:108720.
58. Mangal S, Gao W, Li TL, Zhou Q (Tony). Pulmonary delivery of nanoparticle chemotherapy for the treatment of lung cancers: challenges and opportunities. *Acta Pharmacol Sin* 2017;**38**:782−97.
59. Xiong LS, Li XY, Lu XJ, Zhang ZD, Zhang Y, Wu W, et al. Inhaled multilevel size-tunable, charge-reversible and mucus-traversing composite microspheres as Trojan horse: enhancing lung deposition and tumor penetration. *Chin Chem Lett* 2024;**35**:109384.
60. Clark AR. Half a century of technological advances in pulmonary drug delivery: a personal perspective. *Front Drug Deliv* 2022;**2**: 871147.
61. Banat H, Ambrus R, Csóka I. Drug combinations for inhalation: current products and future development addressing disease control and patient compliance. *Int J Pharm* 2023;**643**:123070.
62. Newman SP. Principles of metered-dose inhaler design. *Respir Care* 2005;**50**:1177−90.
63. Smyth HDC. The influence of formulation variables on the performance of alternative propellant-driven metered dose inhalers. *Adv Drug Deliv Rev* 2003;**55**:807−28.
64. Moon C, Smyth HDC, Watts AB, Williams RO. Delivery technologies for orally inhaled products: an update. *AAPS PharmSciTech* 2019;**20**:117.
65. Fink JB, Stapleton KW. Nebulizers. *J Aerosol Med Pulm Drug Deliv* 2024;**37**:140−56.
66. Jiang JH, Lu AQ, Ma XY, Ouyang DF, Williams RO. The applications of machine learning to predict the forming of chemically stable amorphous solid dispersions prepared by hot-melt extrusion. *Int J Pharm X* 2023;**5**:100164.
67. Nagy B, Galata DL, Farkas A, Nagy ZK. Application of artificial neural networks in the process analytical technology of pharmaceutical manufacturing—a review. *AAPS J* 2022;**24**:74.
68. Farkas D, Madarász L, Nagy ZK, Antal I, Kállai-Szabó N. Image analysis: a versatile tool in the manufacturing and quality control of pharmaceutical dosage forms. *Pharmaceutics* 2021;**13**:685.
69. Wang W, Feng S, Ye ZYF, Gao HL, Lin JZ, Ouyang DF. Prediction of lipid nanoparticles for mRNA vaccines by the machine learning algorithm. *Acta Pharm Sin B* 2022;**12**:2950−62.
70. Gao XJ, Ciura K, Ma YJ, Mikolajczyk A, Jagiello K, Wan YX, et al. Toward the integration of machine learning and molecular modeling for designing drug delivery nanocarriers. *Adv Mater* 2024;**36**:2407793.
71. He S, Leanse LG, Feng YF. Artificial intelligence and machine learning assisted drug delivery for effective treatment of infectious diseases. *Adv Drug Deliv Rev* 2021;**178**:113922.
72. What is artificial intelligence (AI)? | IBM. Available from: https://www.ibm.com/topics/artificial-intelligence [accessed December 11, 2024].
73. Yang JC, Wang CG, Jiang B, Song HB, Meng QG. Visual perception enabled industry intelligence: state of the art, challenges and prospects. *IEEE Trans Ind Inf* 2021;**17**:2204−19.
74. Nassif AB, Shahin I, Attili I, Azzeh M, Shaalan K. Speech recognition using deep neural networks: a systematic review. *IEEE Access* 2019;**7**:19143−65.
75. Jiang JH, Peng HH, Yang ZP, Ma XY, Sahakijpijarn S, Moon C, et al. The applications of machine learning (ML) in designing dry powder for inhalation by using thin-film-freezing technology. *Int J Pharm* 2022;**626**:122179.
76. Mendyk A, Szlęk J, Pacławski A, Lau R, Jachowicz R. Empirical modeling of the fine particle fraction for carrier-based pulmonary delivery formulations. *Int J Nanomed* 2015;**10**:801−10.
77. Camacho DM, Collins KM, Powers RK, Costello JC, Collins JJ. Next-generation machine learning for biological networks. *Cell* 2018;**173**:1581−92.
78. Elbadawi M, McCoubrey LE, Gavins FKH, Ong JJ, Goyanes A, Gaisford S, et al. Harnessing artificial intelligence for the next generation of 3d printed medicines. *Adv Drug Deliv Rev* 2021;**175**:113805.
79. Ouali Y, Hudelot C, Tami M. An overview of deep semi-supervised learning. *ArXiv* 2020. Available from: https://doi.org/10.48550/arXiv.2006.05278.
80. Xie JY, Girshick R, Farhadi A. Unsupervised deep embedding for clustering analysis. *Int Conf Mach Learn. PMLR* 2016:478−87.
81. Caron M, Bojanowski P, Joulin A, Douze M. *Deep clustering for unsupervised learning of visual features*. Proceedings of the European Conference on Computer Vision (ECCV), 2018, 132-149.
82. Wang MH, Sha F, Jordan M. Unsupervised kernel dimension reduction. In: *Advances in neural information processing systems*. vol. 23. Curran Associates, Inc.; 2010.
83. Cios KJ, Swiniarski RW, Pedrycz W, Kurgan LA. Unsupervised learning: association rules. In: Cios KJ, Swiniarski RW, Pedrycz W, Kurgan LA, editors. *Data mining: a knowledge discovery approach*. Boston, MA: Springer US; 2007. p. 289−306.
84. Madugula SS, John L, Nagamani S, Gaur AS, Poroikov VV, Sastry GN. Molecular descriptor analysis of approved drugs using unsupervised learning for drug repurposing. *Comput Biol Med* 2021; **138**:104856.
85. Chaunzwa TL, Hosny A, Xu Y, Shafer A, Diao N, Lanuti M, et al. Deep learning classification of lung cancer histology using CT images. *Sci Rep* 2021;**11**:5471.
86. Elbadawi M, Li HX, Sun SY, Alkahtani ME, Basit AW, Gaisford S. Artificial intelligence generates novel 3d printing formulations. *Appl Mater Today* 2024;**36**:102061.
87. Sahu SK, Anand A. Drug−drug interaction extraction from biomedical texts using long short-term memory network. *J Biomed Inf* 2018;**86**:15−24.
88. Chumpu R, Chu CL, Treeratanaphitak T, Marukatat S, Hsu SH. Physics-informed graph neural networks accelerating microneedle

simulations towards novelty of micro-nano scale materials discovery. *Eng Appl Artif Intell* 2023;**126**:106894.
89. Goodfellow IJ, Pouget-Abadie J, Mirza M, Xu B, Warde-Farley D, Ozair S, et al. Generative adversarial networks. *arXiv* 2014. Available from: https://doi.org/10.48550/arXiv.1406.2661.
90. Kingma DP, Welling M. Auto-encoding variational bayes. *arXiv* 2022. Available from: https://doi.org/10.48550/arXiv.1312.6114.
91. Bond-Taylor S, Leach A, Long Y, Willcocks CG. Deep generative modelling: a comparative review of VAEs, GANs, normalizing flows, energy-based and autoregressive models. *IEEE Trans Pattern Anal Mach Intell* 2022;**44**:7327−47.
92. Sherstinsky A. Fundamentals of recurrent neural network (RNN) and long short-term memory (LSTM) network. *Phys Nonlinear Phenom* 2020;**404**:132306.
93. Vaswani A, Shazeer N, Parmar N, Uszkoreit J, Jones L, Gomez AN, et al. Attention is all you need. *arXiv* 2023. Available from: https://doi.org/10.48550/arXiv.1706.03762.
94. Dan YB, Zhao Y, Li X, Li SB, Hu M, Hu JJ. Generative adversarial networks (GAN) based efficient sampling of chemical composition space for inverse design of inorganic materials. *NPJ Comput Mater* 2020;**6**:1−7.
95. Kim S, Noh J, Gu GH, Aspuru-Guzik A, Jung Y. Generative adversarial networks for crystal structure prediction. *ACS Cent Sci* 2020;**6**:1412−20.
96. Mao YW, He Q, Zhao XH. Designing complex architectured materials with generative adversarial networks. *Sci Adv* 2020;**6**: eaaz4169.
97. Kadurin A, Nikolenko S, Khrabrov K, Aliper A, Zhavoronkov A. DruGAN: an advanced generative adversarial autoencoder model for *de novo* generation of new molecules with desired molecular properties *in silico*. *Mol Pharm* 2017;**14**:3098−104.
98. Pang C, Qiao JB, Zeng XX, Zou Q, Wei LY. Deep generative models in *de novo* drug molecule generation. *J Chem Inf Model* 2024;**64**: 2174−94.
99. Tang BW, Ewalt J, Ng HL. *Generative AI models for drug discovery. Biophysical and computational tools in drug discovery.* Cham: Springer International Publishing; 2021. p. 221−43.
100. Chen X, Roberts R, Liu ZC, Tong WD. A generative adversarial network model alternative to animal studies for clinical pathology assessment. *Nat Commun* 2023;**14**:7141.
101. Islam S, Elmekki H, Elsebai A, Bentahar J, Drawel N, Rjoub G, et al. A comprehensive survey on applications of transformers for deep learning tasks. *Expert Syst Appl* 2024;**241**:122666.
102. Honda S, Shi S, Ueda HR. SMILES transformer: pre-trained molecular fingerprint for low data drug discovery. *arXiv* 2019. Available from: https://doi.org/10.48550/arXiv.1911.04738.
103. Wang WK, Peng ZL, Yang JY. Single-sequence protein structure prediction using supervised transformer protein language models. *Nat Comput Sci* 2022;**2**:804−14.
104. Lee AA, Yang Q, Sresht V, Bolgar P, Hou X, Klug-McLeod JL, et al. Molecular transformer unifies reaction prediction and retrosynthesis across pharma chemical space. *Chem Commun* 2019;**55**: 12152−5.
105. Ji YR, Zhou ZH, Liu H, Davuluri RV. DNABERT: pre-trained bidirectional encoder representations from transformers model for DNA-language in genome. *Bioinformatics* 2021;**37**:2112−20.
106. Yang ZC, Mitra A, Liu WS, Berlowitz D, Yu H. TransformEHR: transformer-based encoder−decoder generative model to enhance prediction of disease outcomes using electronic health records. *Nat Commun* 2023;**14**:7857.
107. Zhang GR, Luo L, Zhang LM, Liu Z. Research progress of respiratory disease and idiopathic pulmonary fibrosis based on artificial intelligence. *Diagnostics* 2023;**13**:357.
108. Feng YH, Wang YB, Zeng CF, Mao H. Artificial intelligence and machine learning in chronic airway diseases: focus on asthma and chronic obstructive pulmonary disease. *Int J Med Sci* 2021;**18**: 2871−89.
109. Gonem S, Janssens W, Das N, Topalovic M. Applications of artificial intelligence and machine learning in respiratory medicine. *Thorax* 2020;**75**:695−701.
110. Exarchos KP, Aggelopoulou A, Oikonomou A, Biniskou T, Beli V, Antoniadou E, et al. Review of artificial intelligence techniques in chronic obstructive lung disease. *IEEE J Biomed Health Inform* 2022;**26**:2331−8.
111. Fink E, Brunsteiner M, Mitsche S, Schröttner H, Paudel A, Zellnitz-Neugebauer S. Data-driven prediction of the formation of co-amorphous systems. *Pharmaceutics* 2023;**15**:347.
112. Ahmed F, Samantasinghar A, Bae MA, Choi KH. Integrated ML-based strategy identifies drug repurposing for idiopathic pulmonary fibrosis. *ACS Omega* 2024;**9**:29870−83.
113. Islam MR, Liu CN, Cai CJ, Shah J, Feng Y. A user-centered smart inhaler algorithm for targeted drug delivery in juvenile onset recurrent respiratory papillomatosis treatment integrating computational fluid particle dynamics and machine learning. *Phys Fluids* 2024;**36**: 021912.
114. Majumder J, Minko T. Recent developments on therapeutic and diagnostic approaches for COVID-19. *AAPS J* 2021;**23**:14.
115. Ullah Z, Usman M, Latif S, Gwak J. Densely attention mechanism based network for COVID-19 detection in chest X-rays. *Sci Rep* 2023;**13**:261.
116. Sharma S, Guleria K. A deep learning based model for the detection of pneumonia from chest X-ray images using VGG-16 and neural networks. *Procedia Comput Sci* 2023;**218**:357−66.
117. Sharma V, Nillmani Gupta SK, Shukla KK. Deep learning models for tuberculosis detection and infected region visualization in chest X-ray images. *Intell Med* 2024;**4**:104−13.
118. Aggarwal P, Mishra NK, Fatimah B, Singh P, Gupta A, Joshi SD. COVID-19 image classification using deep learning: advances, challenges and opportunities. *Comput Biol Med* 2022;**144**:105350.
119. Honkoop P, Usmani O, Bonini M. The current and future role of technology in respiratory care. *Pulm Ther* 2022;**8**:167−79.
120. Sk L, Mohanty SN, K S, N A, Ramirez G. Optimal deep learning model for classification of lung cancer on CT images. *Future Gener Comput Syst* 2019;**92**:374−82.
121. Ausawalaithong W, Thirach A, Marukatat S, Wilaiprasitporn T. Automatic lung cancer prediction from chest X-ray images using the deep learning approach. In: *2018 11th biomedical engineering international conference (BMEiCON)*; 2018. p. 1−5.
122. Hyun SH, Ahn MS, Koh YW, Lee SJ. A machine-learning approach using pet-based radiomics to predict the histological subtypes of lung cancer. *Clin Nucl Med* 2019;**44**:956.
123. Lai YH, Chen WN, Hsu TC, Lin C, Tsao Y, Wu S. Overall survival prediction of non-small cell lung cancer by integrating microarray and clinical data with deep learning. *Sci Rep* 2020;**10**:4679.
124. Le NQK, Kha QH, Nguyen VH, Chen YC, Cheng SJ, Chen CY. Machine learning-based radiomics signatures for EGFR and KRAS mutations prediction in non-small-cell lung cancer. *Int J Mol Sci* 2021;**22**:9254.
125. Talukder MdA, Islam MdM, Uddin MA, Akhter A, Hasan KF, Moni MA. Machine learning-based lung and colon cancer detection using deep feature extraction and ensemble learning. *Expert Syst Appl* 2022;**205**:117695.
126. Zhang YT, Vaccarella S, Morgan E, Li MM, Etxeberria J, Chokunonga E, et al. Global variations in lung cancer incidence by histological subtype in 2020: a population-based study. *Lancet Oncol* 2023;**24**:1206−18.
127. Kludt C, Wang Y, Ahmad W, Bychkov A, Fukuoka JY, Gaisa NDN, et al. Next-generation lung cancer pathology: development and validation of diagnostic and prognostic algorithms. *Cell Rep Med* 2024; **5**:101697.
128. Wang CD, Shao J, He YC, Wu JJ, Liu XT, Yang LQ, et al. Data-driven risk stratification and precision management of pulmonary nodules detected on chest computed tomography. *Nat Med* 2024;**30**: 3184−95.

129. Gao XW, Qian Y. Prediction of multidrug-resistant TB from CT pulmonary images based on deep learning techniques. *Mol Pharm* 2017;**5**:4326−35.
130. Rahman T, Khandakar A, Kadir MA, Islam KR, Islam KF, Mazhar R, et al. Reliable tuberculosis detection using chest X-ray with deep learning, segmentation and visualization. *IEEE Access* 2020;**8**: 191586−601.
131. Bhattacharya S, Reddy Maddikunta PK, Pham QV, Gadekallu TR, Krishnan SSR, Chowdhary CL, et al. Deep learning and medical image processing for coronavirus (COVID-19) pandemic: a survey. *Sustain Cities Soc* 2021;**65**:102589.
132. Jaiswal AK, Tiwari P, Kumar S, Gupta D, Khanna A, Rodrigues JJPC. Identifying pneumonia in chest X-rays: a deep learning approach. *Measurement* 2019;**145**:511−8.
133. Saygılı A. A new approach for computer-aided detection of coronavirus (COVID-19) from CT and X-ray images using machine learning methods. *Appl Soft Comput* 2021;**105**:107323.
134. Jin G, Liu CC, Chen X. An efficient deep neural network framework for COVID-19 lung infection segmentation. *Inf Sci* 2022;**612**: 745−58.
135. Shiri I, Sorouri M, Geramifar P, Nazari M, Abdollahi M, Salimi Y, et al. Machine learning-based prognostic modeling using clinical data and quantitative radiomic features from chest CT images in COVID-19 patients. *Comput Biol Med* 2021;**132**:104304.
136. Shao J, Ma JC, Yu YZ, Zhang S, Wang WY, Li WM, et al. A multimodal integration pipeline for accurate diagnosis, pathogen identification, and prognosis prediction of pulmonary infections. *Innovation* 2024;**5**:100648.
137. Kaplan A, Cao H, FitzGerald JM, Iannotti N, Yang E, Kocks JWH, et al. Artificial intelligence/machine learning in respiratory medicine and potential role in asthma and COPD diagnosis. *J Allergy Clin Immunol Pract* 2021;**9**:2255−61.
138. Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma. *Respir Med* 2006;**100**:1307−17.
139. Griffith MF, Feemster LC, Zeliadt SB, Donovan LM, Spece LJ, Udris EM, et al. Overuse and misuse of inhaled corticosteroids among veterans with COPD: a cross-sectional study evaluating targets for de-implementation. *J Gen Intern Med* 2020;**35**: 679−86.
140. Wu CT, Li GH, Huang CT, Cheng YC, Chen CH, Chien JY, et al. Acute exacerbation of a chronic obstructive pulmonary disease prediction system using wearable device data, machine learning, and deep learning: development and cohort study. *JMIR mHealth uHealth* 2021;**9**:e22591.
141. Jabbour S, Fouhey D, Kazerooni E, Wiens J, Sjoding MW. Combining chest X-rays and electronic health record (EHR) data using machine learning to diagnose acute respiratory failure. *J Am Med Inform Assoc JAMIA* 2022;**29**:1060−8.
142. Ueda D, Matsumoto T, Yamamoto A, Walston SL, Mitsuyama Y, Takita H, et al. A deep learning-based model to estimate pulmonary function from chest X-rays: multi-institutional model development and validation study in Japan. *Lancet Digit Health* 2024;**6**:e580−8.
143. Finkelstein J, Jeong I Cheol. Machine learning approaches to personalize early prediction of asthma exacerbations. *Ann N Y Acad Sci* 2017;**1387**:153−65.
144. Milam ME, Koo CW. The current status and future of FDA-approved artificial intelligence tools in chest radiology in the United States. *Clin Radiol* 2023;**78**:115−22.
145. Brainomix. Brainomix achieves breakthrough with FDA clearance of e-Lung AI software. Available from:: https://www.prnewswire.com/news-releases/brainomix-achieves-breakthrough-with-fda-clearance-of-e-lung-ai-software-302144832.html [accessed December 11, 2024].
146. Artificial intelligence and machine learning (AI/ML)-Enabled medical devices. FDA. Available from:: https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices [accessed December 11, 2024].
147. Obrezanova O. Artificial intelligence for compound pharmacokinetics prediction. *Curr Opin Struct Biol* 2023;**79**:102546.
148. Lim J, Ryu S, Park K, Choe YJ, Ham J, Kim WY. Predicting drug−target interaction using a novel graph neural network with 3d structure-embedded graph representation. *J Chem Inf Model* 2019; **59**:3981−8.
149. Kumar M, Hilles AR, Almurisi SH, Bhatia A, Mahmood S. Micro and nano-carriers-based pulmonary drug delivery system: their current updates, challenges, and limitations — a review. *JCIS Open* 2023;**12**:100095.
150. Khan AM, Akram MU, Nazir S, Hassan T, Khawaja SG, Fatima T. Multi-head deep learning framework for pulmonary disease detection and severity scoring with modified progressive learning. *Biomed Signal Process Control* 2023;**85**:104855.
151. First generative AI drug begins phase II trials with patients | Insilico Med. Available from: https://insilico.com/blog/first_phase2 [accessed October 31, 2024].
152. Insilico medicine reports positive phase IIa results for ISM001-055, a novel first-in-class drug treatment for idiopathic pulmonary fibrosis (IPF) designed using generative AI. BioSpace. Available from:: https://www.biospace.com/press-releases/insilico-medicine-reports-positive-phase-iia-results-for-ism001-055-a-novel-first-in-class-drug-treatment-for-idiopathic-pulmonary-fibrosis-ipf-designed-using-generative-ai [accessed October 31, 2024].
153. Zhou YD, Wang F, Tang J, Nussinov R, Cheng FX. Artificial intelligence in COVID-19 drug repurposing. *Lancet Digit Health* 2020;**2**: e667−76.
154. Beck BR, Shin B, Choi Y, Park S, Kang K. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug−target interaction deep learning model. *Comput Struct Biotechnol J* 2020;**18**:784−90.
155. Jin W, Stokes JM, Eastman RT, Itkin Z, Zakharov AV, Collins JJ, et al. Deep learning identifies synergistic drug combinations for treating COVID-19. *Proc Natl Acad Sci U S A* 2021;**118**:e2105070118.
156. Jaganathan K, Tayara H, Chong KT. An explainable supervised machine learning model for predicting respiratory toxicity of chemicals using optimal molecular descriptors. *Pharmaceutics* 2022;**14**:832.
157. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, et al. Understanding pharmaceutical quality by design. *AAPS J* 2014;**16**: 771−83.
158. Q8(R2) pharmaceutical development. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q8r2-pharmaceutical-development [accessed April 12, 2025].
159. Schmitt JM, Baumann JM, Morgen MM. Predicting spray dried dispersion particle size *via* machine learning regression methods. *Pharm Res* 2022;**39**:3223−39.
160. Page C, Cazzola M. Bifunctional drugs for the treatment of asthma and chronic obstructive pulmonary disease. *Eur Respir J* 2014;**44**:475−82.
161. Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. *Respir Res* 2013;**14**:1−13.
162. Farizhandi AAK, Alishiri M, Lau R. Machine learning approach for carrier surface design in carrier-based dry powder inhalation. *Comput Chem Eng* 2021;**151**:107367.
163. Iskandar F, Nandiyanto ABD, Widiyastuti W, Young LS, Okuyama K, Gradon L. Production of morphology-controllable porous hyaluronic acid particles using a spray-drying method. *Acta Biomater* 2009;**5**:1027−34.
164. Maa YF, Nguyen PAT, Hsu SW. Spray-drying of air−liquid interface sensitive recombinant human growth hormone. *J Pharm Sci* 1998;**87**: 152−9.
165. Fiedler D, Fink E, Aigner I, Leitinger G, Keller W, Roblegg E, et al. A multi-step machine learning approach for accelerating qbd-based process development of protein spray drying. *Int J Pharm* 2023; **642**:123133.
166. Lu JY, Duan CL, Zhao YM. Machine learning approach to predict the surface charge density of monodispersed particles in gas−solid fluidized beds. *ACS Omega* 2022;**7**:9879−90.

167. Gajjar P, Styliari ID, Legh-Land V, Bale H, Tordoff B, Withers PJ, et al. Microstructural insight into inhalation powder blends through correlative multi-scale X-ray computed tomography. *Eur J Pharm Biopharm* 2023;**191**:265−75.
168. Chan AHY, Pleasants RA, Dhand R, Tilley SL, Schworer SA, Costello RW, et al. Digital inhalers for asthma or chronic obstructive pulmonary disease: a scientific perspective. *Pulm Ther* 2021;**7**:345−76.
169. Derkay CS. Recurrent respiratory papillomatosis. *Laryngoscope* 2001;**111**:57−69.
170. Yu FB, Wei CH, Deng P, Peng T, Hu XG. Deep exploration of random forest model boosts the interpretability of machine learning studies of complicated immune responses and lung burden of nanoparticles. *Sci Adv* 2021;**7**:eabf4130.
171. Huang JJ, Xu YC, Xue YF, Huang Y, Li X, Chen XH, et al. Identification of potent antimicrobial peptides *via* a machine-learning pipeline that mines the entire space of peptide sequences. *Nat Biomed Eng* 2023;**7**:797−810.
172. Choi SH, Engelhardt JF. Gene therapy for cystic fibrosis: lessons learned and paths forward. *Mol Ther* 2021;**29**:428−30.
173. Ruigrok MJR, Frijlink HW, Melgert BN, Olinga P, Hinrichs WLJ. Gene therapy strategies for idiopathic pulmonary fibrosis: recent advances, current challenges, and future directions. *Mol Ther Methods Clin Dev* 2021;**20**:483−96.
174. Hou XC, Zaks T, Langer R, Dong YZ. Lipid nanoparticles for mRNA delivery. *Nat Rev Mater* 2021;**6**:1078−94.
175. Witten J, Raji I, Manan RS, Beyer E, Bartlett S, Tang YH, et al. Artificial intelligence-guided design of lipid nanoparticles for pulmonary gene therapy. *Nat Biotechnol* 2024:1−10.
176. Kaler L, Joyner K, Duncan GA. Machine learning-informed predictions of nanoparticle mobility and fate in the mucus barrier. *APL Bioeng* 2022;**6**:026103.
177. Mi K, Chou WC, Chen QR, Yuan L, Kamineni VN, Kuchimanchi Y, et al. Predicting tissue distribution and tumor delivery of nanoparticles in mice using machine learning models. *J Control Release* 2024;**374**:219−29.
178. Campredon A, Battistella E, Martin C, Durieu I, Mely L, Marguet C, et al. Using chest computed tomography and unsupervised machine learning for predicting and evaluating response to lumacaftor−ivacaftor in people with cystic fibrosis. *Eur Respir J* 2022;**59**: 2101344.
179. Williams J, Ahlqvist H, Cunningham A, Kirby A, Katz I, Fleming J, et al. Validated respiratory drug deposition predictions from 2d and 3d medical images with statistical shape models and convolutional neural networks. *PLoS One* 2024;**19**:e0297437.
180. Franssen FM, Alter P, Bar N, Benedikter BJ, Iurato S, Maier D, et al. Personalized medicine for patients with COPD: where are we?. *Taylor Francis* 2019;**14**:1465−84.
181. Artificial intelligence and machine learning in software as a medical device. FDA. Available from:: https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device [accessed December 6, 2024].
182. Proposed regulatory framework for modifications to artificial intelligence/machine learning (AI/ML)-Based software as a medical device (SaMD)-Discussion paper and request for feedback. Available from:: https://www.fda.gov/files/medical20devices/published/US-FDA-Artificial-Intelligence-and-Machine-Learning-Discussion-Paper.pdf.
183. Artificial intelligence workplan to guide use of AI in medicines regulation | European Medicines Agency (EMA). Available from:: https://www.ema.europa.eu/en/news/artificial-intelligence-workplan-guide-use-ai-medicines-regulation [accessed December 6, 2024].
184. https://www.fda.gov/media/167973/download.
185. Williamson SM, Prybutok V. Balancing privacy and progress: a review of privacy challenges, systemic oversight, and patient perceptions in AI-driven healthcare. *Appl Sci* 2024;**14**:675.
186. Chen ZS. Ethics and discrimination in artificial intelligence-enabled recruitment practices. *Humanit Soc Sci Commun* 2023;**10**:1−12.
187. Paulus JK, Kent DM. Predictably unequal: understanding and addressing concerns that algorithmic clinical prediction may increase health disparities. *Npj Digit Med* 2020;**3**:1−8.
188. Dhudum R, Ganeshpurkar A, Pawar A. Revolutionizing drug discovery: a comprehensive review of AI applications. *Drugs Drug Candidates* 2024;**3**:148−71.
189. Johnson Oyeniyi. The role of AI and mobile apps in patient-centric healthcare delivery. *World J Adv Res Rev* 2024;**22**:1897−907.
190. Severson K, VanAntwerp JG, Natarajan V, Antoniou C, Thömmes J, Braatz RD. Elastic net with monte carlo sampling for data-based modeling in biopharmaceutical manufacturing facilities. *Comput Chem Eng* 2015;**80**:30−6.
191. Liu XM, Xie LH, Wang YP, Zou J, Xiong JB, Ying ZB, et al. Privacy and security issues in deep learning: a survey. *IEEE Access* 2021;**9**: 4566−93.
192. Li YH, Li YL, Wei MY, Li GY. Innovation and challenges of artificial intelligence technology in personalized healthcare. *Sci Rep* 2024;**14**:18994.
193. van Panhuis WG, Paul P, Emerson C, Grefenstette J, Wilder R, Herbst AJ, et al. A systematic review of barriers to data sharing in public health. *BMC Public Health* 2014;**14**:1144.
194. Castro BM, Elbadawi M, Ong JJ, Pollard T, Song Z, Gaisford S, et al. Machine learning predicts 3d printing performance of over 900 drug delivery systems. *J Controlled Release* 2021;**337**:530−45.
195. Kelly CJ, Karthikesalingam A, Suleyman M, Corrado G, King D. Key challenges for delivering clinical impact with artificial intelligence. *BMC Med* 2019;**17**:195.
196. Darquenne C, Fleming JS, Katz I, Martin AR, Schroeter J, Usmani OS, et al. Bridging the gap between science and clinical efficacy: physiology, imaging, and modeling of aerosols in the lung. *J Aerosol Med Pulm Drug Deliv* 2016;**29**:107−26.
197. Newman SP. Drug delivery to the lungs: challenges and opportunities. *Ther Deliv* 2017;**8**:647−61.
198. Handley JL, Krevat SA, Fong A, Ratwani RM. Artificial intelligence related safety issues associated with FDA medical device reports. *NPJ Digit Med* 2024;**7**:351.
199. Oualikene-Gonin W, Jaulent MC, Thierry JP, Oliveira-Martins S, Belgodère L, Maison P, et al. Artificial intelligence integration in the drug lifecycle and in regulatory science: policy implications, challenges and opportunities. *Front Pharmacol* 2024;**15**:1437167.
200. Schork NJ. Artificial intelligence and personalized medicine. In: Von Hoff DD, Han HY, editors. *Precision medicine in cancer therapy.* Cham: Springer International Publishing; 2019. p. 265−83.
201. Johnson KB, Wei W, Weeraratne D, Frisse ME, Misulis K, Rhee K, et al. Precision medicine, ai, and the future of personalized health care. *Clin Transl Sci* 2021;**14**:86−93.
202. Exarchos KP, Beltsiou M, Votti CA, Kostikas K. Artificial intelligence techniques in asthma: a systematic review and critical appraisal of the existing literature. *Eur Respir J* 2020;**56**:2000521.
203. Walter JR, Lee JY, Yu L, Kim B, Martell K, Opdycke A, et al. Use of artificial intelligence to develop predictive algorithms of cough and PCR-confirmed COVID-19 infections based on inputs from clinical-grade wearable sensors. *Sci Rep* 2024;**14**:8072.
204. Bao ZQ, Yung F, Hickman RJ, Aspuru-Guzik A, Bannigan P, Allen C. Data-driven development of an oral lipid-based nanoparticle formulation of a hydrophobic drug. *Drug Deliv Transl Res* 2024;**14**: 1872−87.