



Exploring explainable AI features in the vocal biomarkers of lung disease

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ARTICLE INFO

Keywords:
 Explainable artificial intelligence
 Vocal biomarkers
 Lung disease detection
 AI transparency
 Pulmonary diagnostics
 Machine learning interpretability
 Computational Pulmonology
 Clinical AI applications
 Voice analysis
 Biomedical signal processing

ABSTRACT

This review delves into the burgeoning field of explainable artificial intelligence (XAI) in the detection and analysis of lung diseases through vocal biomarkers. Lung diseases, often elusive in their early stages, pose a significant public health challenge. Recent advancements in AI have ushered in innovative methods for early detection, yet the black-box nature of many AI models limits their clinical applicability. XAI emerges as a pivotal tool, enhancing transparency and interpretability in AI-driven diagnostics. This review synthesizes current research on the application of XAI in analyzing vocal biomarkers for lung diseases, highlighting how these techniques elucidate the connections between specific vocal features and lung pathology. We critically examine the methodologies employed, the types of lung diseases studied, and the performance of various XAI models. The potential for XAI to aid in early detection, monitor disease progression, and personalize treatment strategies in pulmonary medicine is emphasized. Furthermore, this review identifies current challenges, including data heterogeneity and model generalizability, and proposes future directions for research. By offering a comprehensive analysis of explainable AI features in the context of lung disease detection, this review aims to bridge the gap between advanced computational approaches and clinical practice, paving the way for more transparent, reliable, and effective diagnostic tools.

1. Introduction

Lung diseases, encompassing a range of pathological conditions affecting the respiratory system, present a significant public health burden globally [1–6]. Early detection and accurate diagnosis of these diseases are crucial for effective treatment and management, yet they remain challenging due to the often asymptomatic or non-specific nature of early-stage symptoms [7,8]. Recent advancements in artificial intelligence (AI) offer promising tools for enhancing diagnostic capabilities in pulmonary medicine. However, the complex, often opaque nature of AI models, especially in deep learning, poses a significant barrier to their clinical integration and acceptance [9–11]. This barrier has led to a growing interest in explainable artificial intelligence (XAI) – a subset of AI focused on making the decision-making processes of AI systems transparent and understandable to human users [12–19].

The use of vocal biomarkers for lung disease detection represents a novel and non-invasive approach that has gained considerable attention.

Vocal biomarkers are distinct characteristics in voice and speech patterns that can be indicative of specific health conditions [20,21]. Their analysis through advanced AI techniques opens new avenues for early and remote diagnosis of lung diseases. However, the application of AI in this domain often leads to "black-box" models, where the decision-making process is not transparent, leading to challenges in clinical validation and trust [9,22–24]. XAI aims to address this by providing insights into how and why a model makes certain decisions, thereby enhancing the reliability and credibility of AI-based diagnostics in healthcare [25,26].

In this context, our review focuses on exploring the role and potential of XAI in analyzing vocal biomarkers for lung disease detection. Integrating XAI is essential, not merely as a technological advancement but as a crucial step toward bridging the gap between AI capabilities and clinical needs. By enhancing the interpretability of AI models, XAI allows clinicians and researchers to understand the rationale behind diagnostic predictions, which is vital for clinical decision-making and

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patient trust [27]. This review synthesizes current research, discussing methodologies, the types of lung diseases targeted, and evaluating the performance and limitations of various XAI models. It highlights XAI's potential in aiding early detection, monitoring disease progression, and personalizing treatment strategies in pulmonary medicine. Additionally, it addresses challenges such as data heterogeneity, model generalizability, and the need for standardization in model development and evaluation, concluding with proposed future directions for research that emphasize collaborative efforts between computational scientists, clinicians, and patients to develop more transparent, reliable, and effective diagnostic tools for lung diseases.

2. The emergence of vocal biomarkers in lung disease detection

2.1. Overview of vocal biomarkers in medical diagnostics

The utilization of vocal biomarkers in medical diagnostics represents a groundbreaking shift in the early detection and monitoring of various diseases, particularly lung-related pathologies. Vocal biomarkers are unique, quantifiable signatures in voice and speech that correlate with specific medical conditions [27,28]. These biomarkers are rooted in the principle that physiological changes, especially those affecting the respiratory system, can alter vocal characteristics in subtle yet detectable ways (Fig. 1). The human voice, produced through the coordinated effort of the lungs, vocal cords, and articulatory structures, can be affected by respiratory ailments, making vocal analysis a valuable tool in pulmonary diagnostics.

Recent technological advancements have enabled the detailed

analysis of vocal attributes such as frequency, intensity, and temporal aspects of speech. This analysis extends beyond the perceptual capabilities of human hearing, delving into acoustic features that can be early indicators of disease [29]. For instance, changes in lung tissue elasticity and airway obstruction, common in conditions like chronic obstructive pulmonary disease (COPD) or lung cancer, can manifest as alterations in voice quality, such as hoarseness or breathiness [30–32]. These subtle changes, though often imperceptible in routine clinical examinations, can be captured and quantified through sophisticated signal processing techniques.

The integration of machine learning and AI in vocal biomarker analysis has further propelled this field forward. AI algorithms, particularly those involving deep learning, are adept at identifying complex patterns in large datasets, making them well-suited for deciphering the intricate relationships between vocal features and underlying health conditions [33]. This capability has given rise to various AI-driven tools and applications aimed at detecting and monitoring lung diseases through voice analysis. However, the effectiveness of these tools hinges on the quality and diversity of the data used to train AI models. The inherent variability in voice due to factors like age, gender, and language necessitates comprehensive and diverse datasets to ensure the accuracy and generalizability of AI-based diagnostic systems [34,35].

Despite the promising advancements in this area, the deployment of AI in vocal biomarker analysis for lung disease detection faces significant challenges [36,37]. One of the primary concerns is the "black-box" nature of many AI models, where the decision-making process is opaque and lacks transparency [38]. This lack of explainability can hinder clinical adoption, as healthcare professionals often require a clear

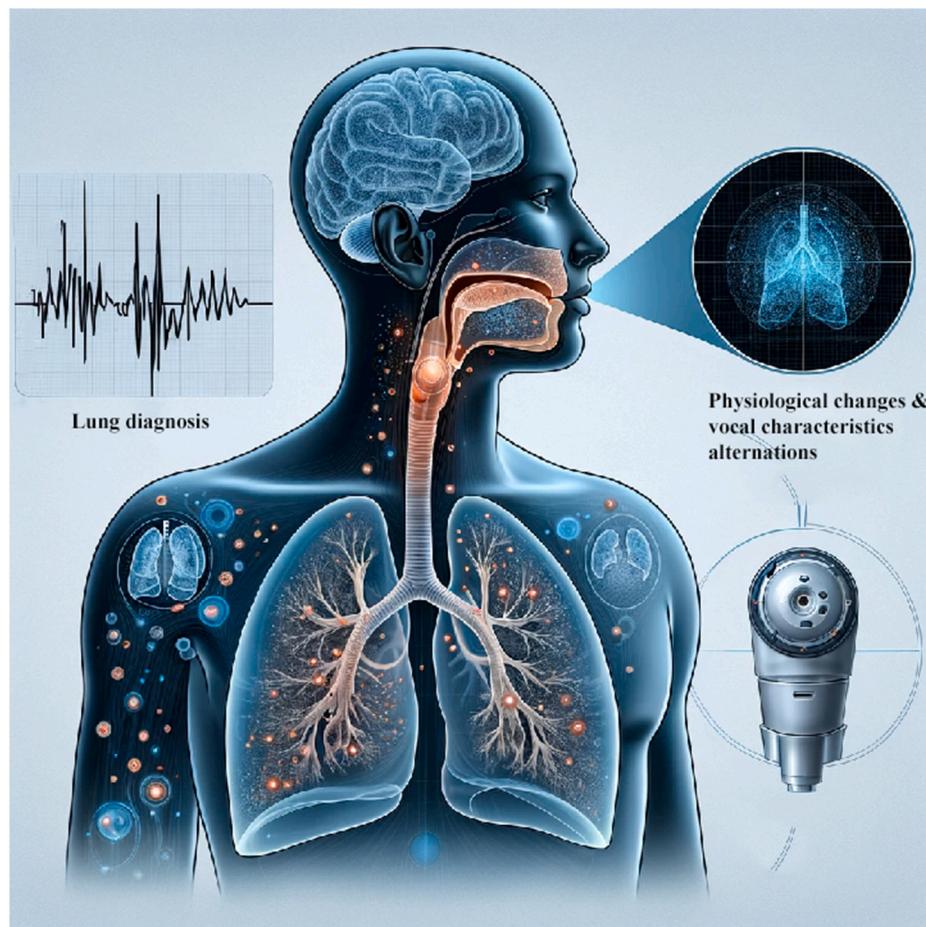


Fig. 1. Decoding Respiratory Diseases: Insights from Vocal Attributes, the figure is intended to emphasize the integration of traditional respiratory function tests with advanced vocal biomarker analysis, facilitated by AI technologies.

understanding of how diagnostic conclusions are reached [39,40]. This challenge has led to the emergence of explainable AI (XAI) as a crucial adjunct in this field. XAI strives to make AI models more interpretable and transparent, thereby enhancing trust and confidence among clinicians and patients alike [41,42].

The exploration of vocal biomarkers in lung disease detection signifies a pivotal moment in medical diagnostics [43]. It marks a transition from traditional, symptom-based detection methods to a more proactive, technology-driven approach. As research in this domain continues to evolve, it holds the potential to transform pulmonary diagnostics, offering non-invasive, accessible, and early detection tools that could significantly impact patient outcomes and healthcare delivery [44].

2.2. Application of vocal biomarkers in lung diseases

The application of vocal biomarkers in the detection and monitoring of lung diseases represents a significant breakthrough in medical diagnostics [20,45]. This innovative approach leverages the intricate relationship between respiratory health and vocal characteristics, capitalizing on the advancements in AI and machine learning to offer non-invasive, efficient, and potentially early detection methods for.

various lung conditions [20,56–58]. Lung diseases, such as asthma [31,59,60], COPD [30,31,61,62], lung cancer [63–65], and pulmonary fibrosis [66,67], manifest changes in respiratory function that can subtly affect the voice [54,55]. These changes may include alterations in lung cancer, and pulmonary fibrosis, manifest changes in respiratory function that can capacity, airflow, and tissue stiffness, which can influence vocal cord vibration and, consequently, voice production [68].

For example, in conditions like COPD, where airflow limitation is a hallmark, patients often exhibit a decrease in vocal intensity and changes in pitch, as well as increased breathiness in their speech [30, 69–73]. Similarly, lung cancer, which can cause an obstruction in the airway or affect lung tissue elasticity, may lead to noticeable changes in voice quality [74]. Advanced AI models, particularly those using deep learning techniques, are adept at analyzing these vocal nuances, extracting relevant biomarkers that correlate with specific lung pathologies [75,76]. These models can process and analyze vast amounts of voice data, identifying patterns and correlations that are imperceptible to the human ear [77–79].

The role of AI in this context is twofold. Firstly, it facilitates the extraction and analysis of complex vocal features from raw audio data. This process involves various stages of signal processing and feature extraction, where aspects such as frequency, amplitude, and temporal characteristics of the voice are analyzed [20,80,81]. Secondly, AI models, especially deep learning algorithms, are employed to classify these features and correlate them with specific lung diseases. By training these models on large datasets of vocal samples from healthy individuals and patients with lung diseases, AI systems learn to distinguish between normal and pathological vocal characteristics [33,82,83].

However, the effectiveness of these AI models in real-world clinical settings is contingent upon their ability to handle the variability inherent in human voice data. Factors such as age, gender, language, and even emotional state can influence voice characteristics, presenting a challenge for the generalizability of AI models [34,84,85]. Additionally, the quality of the voice data, including recording conditions and the presence of background noise, can significantly impact the performance of these models [86–88]. These challenges necessitate robust and adaptable AI algorithms capable of managing such variability while maintaining high accuracy and reliability in disease detection.

Despite these challenges, the application of vocal biomarkers in lung disease diagnostics has shown promising results. Studies have demonstrated the potential of these biomarkers in early detection and monitoring of diseases, offering a non-invasive alternative to traditional diagnostic methods such as imaging and biopsy [20,89,90]. This advancement not only facilitates early intervention, which is crucial for conditions like lung cancer, but also provides a means for continuous

monitoring of disease progression and response to treatment [91].

In conclusion, the integration of AI in analyzing vocal biomarkers opens a new frontier in the diagnosis and monitoring of lung diseases. It embodies a paradigm shift from conventional, often invasive diagnostic methods to a more patient-friendly, technology-driven approach. As the field evolves, continuous advancements in AI and vocal analysis technologies are expected to further enhance the accuracy, reliability, and clinical applicability of this approach, potentially transforming the landscape of pulmonary diagnostics.

2.3. Advances and limitations in current vocal Biomarker research

The research into vocal biomarkers for lung disease detection has seen significant advancements in recent years, driven by the integration of AI and machine learning techniques. These advances have primarily centered around the refinement of algorithms for more accurate and robust analysis of vocal features, enhancing the potential of vocal biomarkers as a tool for early diagnosis and monitoring of lung diseases [20, 92–94]. Researchers have developed sophisticated models that can analyze a wide range of vocal characteristics, from basic frequency and amplitude variations to more complex spectral and temporal features, providing a comprehensive assessment of vocal health indicators [95, 96].

One of the notable advancements in this area is the use of deep learning algorithms, which have demonstrated remarkable efficacy in identifying subtle patterns in voice data that correlate with lung diseases. These algorithms can analyze large datasets of voice recordings, learning from the nuances in vocal features that differentiate healthy individuals from those with lung pathologies [20,97,98]. The application of these models has shown promise in detecting conditions such as asthma, where changes in lung function affect breath control and, consequently, voice production [99–101]. Similarly, in cases of lung cancer, deep learning models have been successful in identifying voice feature alterations that may not be perceptible in standard clinical evaluations [102,103].

Despite these advances, the field of vocal biomarker research faces significant challenges. One of the primary limitations is the variability in voice data due to factors such as age, gender, linguistic background, and environmental conditions during recording [104]. This variability can lead to inconsistencies in model performance, potentially affecting the accuracy and reliability of disease detection. Furthermore, the quality and size of the datasets used to train these models are crucial. Limited or biased datasets can result in models that do not generalize well to broader populations, thereby limiting their clinical applicability.

Another critical challenge is the explainability of AI models used in vocal biomarker analysis. The complexity of deep learning models, while advantageous in pattern recognition, often results in a lack of transparency in how these models arrive at their conclusions [105]. This "black-box" nature raises concerns regarding the interpretability and trustworthiness of AI-driven diagnostics, particularly in a clinical setting where understanding the rationale behind a diagnosis is vital [106]. The integration of explainable AI (XAI) methods is thus essential to address these challenges, providing insights into the decision-making processes of AI models and enhancing their acceptability and utility in clinical practice [107].

In conclusion, while the advances in vocal biomarker research for lung disease detection are promising, addressing the challenges of data variability, model generalizability, and AI explainability is paramount for the successful integration of these technologies into clinical diagnostics. Future research in this field must focus on developing more robust and transparent AI models that can effectively handle the complexities of voice data and provide reliable, interpretable results for clinical use.

3. Artificial intelligence in lung disease detection: from black-box to transparency

3.1. Traditional AI approaches in pulmonary diagnostics

The evolution of artificial intelligence (AI) in pulmonary diagnostics has been marked by significant advancements, particularly in the traditional approaches that form the foundation of current AI applications (Fig. 2). Initially, AI in pulmonary medicine focused on pattern recognition and feature extraction from medical images, such as X-rays and CT scans, using algorithms like support vector machines (SVM) and decision trees [108,109]. These methods were instrumental in identifying visual markers indicative of lung diseases, such as nodules in lung cancer or opacities in pneumonia [110,111]. However, the scope of these traditional AI approaches was somewhat limited by their reliance on structured data and their inability to process complex, unstructured datasets effectively.

The introduction of machine learning, a subset of AI, marked a paradigm shift in pulmonary diagnostics. Machine learning algorithms, including random forests and gradient boosting machines, offered more sophisticated analysis by learning from data, improving over time as more data became available. These algorithms were used not only in image analysis but also in interpreting spirometry results and other clinical data, contributing to a more comprehensive understanding of lung diseases [112]. Despite these advancements, machine learning in its early stages still faced challenges regarding data heterogeneity and the need for extensive feature engineering, which required domain

expertise and often led to a time-consuming process [113].

Deep learning, a more advanced form of machine learning, has been a game-changer in pulmonary diagnostics. With its ability to automatically learn hierarchical feature representations from raw data, deep learning, especially convolutional neural networks (CNNs), has significantly enhanced the analysis of medical imaging [114]. Deep learning models have demonstrated remarkable accuracy in detecting and classifying lung pathologies from imaging studies, outperforming traditional image processing techniques [115,116]. This leap forward, however, introduced the 'black-box' issue, where the decision-making process of these complex models became less interpretable, raising concerns about their integration into clinical decision-making [117].

Despite these advancements, the application of traditional AI and machine learning in pulmonary diagnostics is not without limitations. The reliance on large, annotated datasets for model training, the risk of model overfitting, and the challenges in generalizing findings across diverse patient populations are significant concerns [118]. Moreover, the interpretation of results from complex models, essential for clinical acceptance, remains a challenge. The integration of AI into clinical workflows also requires consideration of ethical implications, data privacy, and the need for robust validation studies to ensure patient safety and efficacy of these technologies [119].

In summary, while traditional AI approaches have laid the groundwork for revolutionizing pulmonary diagnostics, their evolution towards more complex models like deep learning has necessitated a pivot towards explainability and transparency. This shift is crucial for harnessing the full potential of AI in clinical settings, where trust and

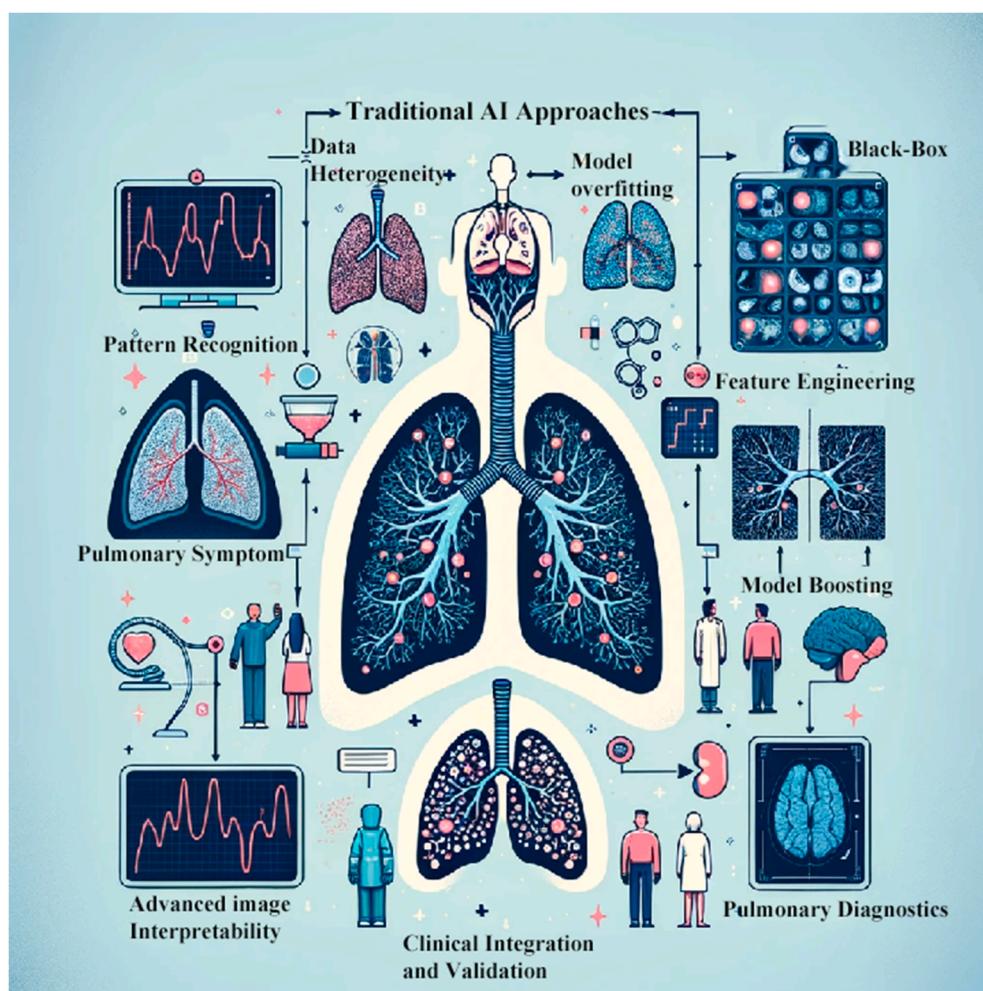


Fig. 2. Bridging AI and Pulmonology: A traditional diagnostic perspective.

understanding are paramount.

3.2. The challenge of black-box models in clinical settings

The increasing integration of artificial intelligence (AI) in healthcare, particularly in lung disease diagnostics, has brought to the fore the critical issue of the 'black-box' nature of many AI models. This term refers to the opaqueness in the decision-making processes of AI, especially those based on deep learning algorithms, where the path from input data to the conclusion is not readily interpretable by humans [120]. In clinical settings, this lack of transparency can be a significant barrier to the adoption of AI tools, as healthcare professionals rely on clear, understandable, and justifiable evidence to make diagnostic and treatment decisions [121].

The challenge with black-box models in healthcare is twofold. The inability to understand how an AI model arrives at a diagnosis or a prognosis can undermine the confidence of clinicians in these tools, despite their potential accuracy and efficiency [122]. Medical professionals are accustomed to making decisions based on established knowledge, clinical guidelines, and evidence-based practices. When presented with a decision from an AI model without a clear rationale, clinicians may be hesitant to accept its recommendations, which can impede the effective integration of AI into clinical workflows [123].

The black-box nature of AI models raises ethical and legal concerns, particularly regarding accountability and responsibility for medical decisions made with the assistance of AI (Fig. 3). In the context of lung disease diagnosis, for instance, if an AI tool incorrectly identifies a

benign condition as malignant (or vice versa), the inability to scrutinize the decision-making process of the AI system poses significant challenges in determining liability and ensuring patient safety [124]. This issue is further compounded by the regulatory challenges of approving AI tools for clinical use, where transparency in how these tools operate is crucial for regulatory bodies to assess their safety and efficacy [125].

Addressing the black-box problem in AI is thus not only a technical necessity but also a clinical, ethical, and regulatory imperative. The development of explainable AI (XAI) models, which provide insights into the reasoning behind their decisions, is seen as a key solution to this challenge. XAI aims to make AI decisions more interpretable and justifiable, aligning AI tools with the principles of clinical decision-making and ethical standards in healthcare [126].

In summary, while AI models, particularly those based on deep learning, offer unprecedented opportunities in enhancing lung disease diagnostics, overcoming the black-box challenge is essential for their successful integration into clinical practice. This necessitates a concerted effort in developing AI models that are not only accurate and efficient but also transparent and interpretable, ensuring their acceptance and trustworthiness among healthcare professionals and patients alike.

3.3. The necessity of explainability in AI for healthcare

The integration of explainable artificial intelligence (XAI) into healthcare, particularly in lung disease diagnostics, addresses the critical need for transparency and understanding in AI-driven decisions. The

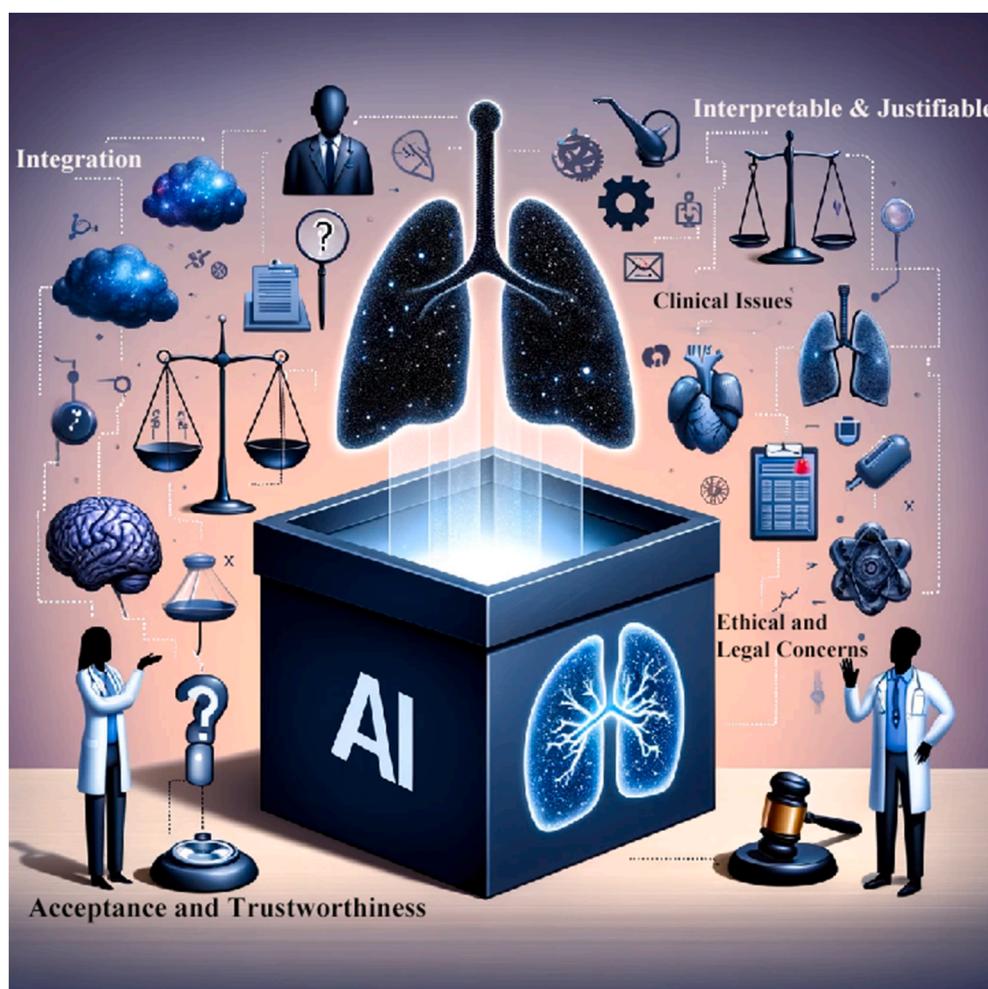


Fig. 3. The transparency Dilemma: Ai's black-box in clinical practice.

necessity of explainability in AI models stems from the imperative to build trust among clinicians and patients, ensuring that these advanced tools are not only technologically sound but also align with the ethical standards and practices of medicine [127]. In the context of lung disease detection using vocal biomarkers, XAI can illuminate the connections between specific vocal features and pathological changes, providing clinicians with insights that support their diagnostic reasoning and treatment planning [128].

Explainability in AI models serves a dual purpose in healthcare. On one hand, it provides clinicians with a deeper understanding of the diagnostic process, enabling them to make informed decisions about patient care. This aspect is particularly crucial in complex cases where multiple factors contribute to the disease state, and where understanding the AI's reasoning can provide additional perspectives that enrich clinical judgment [129]. On the other hand, explainability fosters patient trust in AI-assisted diagnostics. Patients are more likely to accept and comply with treatment plans if they understand how and why certain decisions were made, especially when these decisions are supported by AI tools [130].

The development of XAI models in healthcare, however, is not without challenges. One of the primary challenges is maintaining a balance between model accuracy and explainability. Often, the most accurate AI models, particularly those based on deep learning, are the least interpretable due to their complex and layered structures [41]. Developing methods that can unravel these layers to provide meaningful insights without compromising the model's performance is a significant area of ongoing research [131]. Additionally, explainability must be

presented in a manner that is understandable to its intended audience, whether it be clinicians or patients, requiring tailored approaches that consider the varying levels of technical expertise [132].

In conclusion, the necessity of explainability in AI for healthcare is driven by the need for trust, ethical responsibility, and effective clinical application. As AI continues to revolutionize healthcare, particularly in lung disease diagnostics, the focus on developing XAI models will be crucial in bridging the gap between technological advancement and clinical practice. Future research in this area is expected to focus on innovative methods to enhance the interpretability of AI models while ensuring their accuracy and clinical relevance, ultimately leading to more transparent, reliable, and patient-centric healthcare solutions.

4. The role of explainable AI (XAI) in enhancing lung disease diagnostics

4.1. Principles and approaches of XAI in medical research

The integration of Explainable Artificial Intelligence (XAI) into medical research, particularly in the field of lung disease diagnostics, is transforming the landscape of healthcare technology. XAI refers to AI models that not only provide outcomes or predictions but also offer insights into the reasoning behind these outcomes, thereby making the AI decision-making process transparent and understandable [133]. In the context of lung disease detection using vocal biomarkers, XAI empowers clinicians with the ability to interpret and validate AI-driven diagnostic suggestions, which is crucial for clinical decision-making

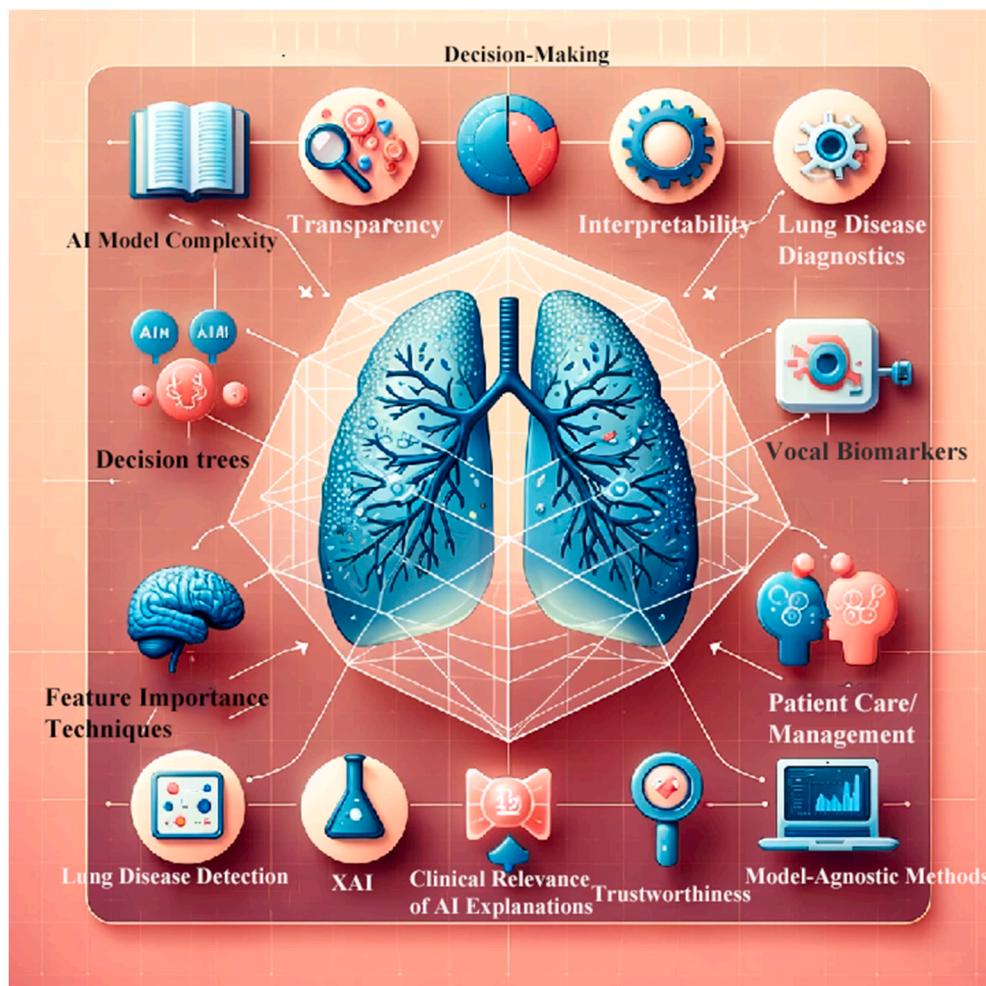


Fig. 4. Lung diagnostics enhanced: The Explanatory Power of XAI

and patient care (Fig. 4).

The principles of XAI in medical research are grounded in transparency, interpretability, and trustworthiness. Transparency involves the AI model providing clear, understandable, and detailed explanations for its decisions [134]. Interpretability, on the other hand, refers to the degree to which a human can understand and consistently predict the model's output [135]. Trustworthiness is achieved when both transparency and interpretability are combined, allowing healthcare professionals to rely on AI systems with confidence [136]. These principles are particularly significant in lung disease diagnostics, where understanding the correlation between vocal biomarkers and specific lung pathologies can be complex and nuanced.

Approaches to XAI in medical research vary but generally include techniques such as feature importance, decision trees, and model-agnostic methods. Feature importance methods, for example, identify and rank the most significant features used by the model to make a decision, which can be critical in understanding the link between specific vocal features and lung diseases [130]. Decision trees provide a visual and interpretable representation of the decision-making process, allowing clinicians to trace the path taken by the AI model to reach a conclusion [137,138]. Model-agnostic methods, such as LIME (Local Interpretable Model-agnostic Explanations), offer explanations for any machine learning model's predictions, regardless of the model's complexity, making them highly versatile in diverse medical applications [139].

Implementing XAI in lung disease diagnostics through vocal biomarker analysis is not without its challenges. One of the primary concerns is ensuring that the explanations provided by XAI models are not only accurate but also clinically relevant and understandable to medical professionals [140]. Additionally, there is a need to balance the complexity and accuracy of AI models with the level of interpretability required in clinical settings. This balance is crucial to ensure that the explanations provided by XAI models contribute meaningfully to clinical decision-making and patient management [141].

In summary, XAI represents a significant advancement in the use of AI in lung disease diagnostics. By providing transparent and interpretable AI models, XAI enhances the trustworthiness and clinical utility of AI applications in healthcare [9]. Future research in this area will likely focus on developing more sophisticated XAI techniques that can provide deeper and more clinically relevant insights into AI decisions, thereby further bridging the gap between advanced computational approaches and clinical practice.

4.2. XAI applications in lung disease detection

The application of Explainable Artificial Intelligence (XAI) in lung disease detection has been illustrated through several case studies, showcasing its potential in enhancing diagnostic accuracy while providing transparency in AI decision-making. These case studies highlight how XAI not only aids in early detection but also contributes to a deeper understanding of lung diseases, thereby facilitating personalized treatment strategies.

Several studies have demonstrated the use of XAI in analyzing vocal biomarkers for the early detection of lung cancer [142,143]. For instance, one study utilized Random Forest models enhanced with SHAP values to predict hospital length of stay for lung cancer patients, offering transparent insights into the influence of clinical features and aiding in efficient healthcare resource management [142]. Another approach integrated clinical concepts into AI models for diagnosing lung cancer from chest X-rays using concept bottleneck models. This not only improved diagnostic accuracy but also made the AI's reasoning process clinically interpretable, aligning AI outputs with clear clinical indicators to enhance the practical utility of diagnostic tools in real settings. This approach not only increased the trust in AI-driven diagnostics but also provided insights into the progression of lung cancer, as changes in vocal features correlated with disease stages [152].

Numerous significant studies focused on utilizing XAI to differentiate between various lung conditions such as asthma, COPD, and pulmonary fibrosis [45,144–146]. In these studies, AI models were trained to identify distinct patterns in vocal biomarkers corresponding to each condition. The application of XAI allowed researchers to interpret the model's decision-making process, identifying which vocal features were most indicative of each disease. This level of detail is crucial for clinicians in making accurate diagnoses and tailoring treatment plans to individual patients' needs. Moreover, it offered a non-invasive, cost-effective, and accessible diagnostic tool, particularly beneficial in settings where traditional diagnostic methods are not readily available [153].

The application of Explainable Artificial Intelligence (XAI) in diagnosing lung conditions such as asthma, COPD, and pulmonary fibrosis provides a compelling illustration of how advanced AI techniques can enhance clinical diagnostics. In a notable case study, AI models trained to analyze vocal biomarkers can differentiate these diseases with high accuracy. By employing XAI, these models allow clinicians to understand the decision-making process, identifying which vocal features indicate specific lung conditions.

Recent studies provide detailed insights into the practical application of these methods. For instance, AI models trained on vocal biomarkers have successfully differentiated diseases such as asthma, COPD, and pulmonary fibrosis. These models allow clinicians to understand the AI's decision-making process by highlighting which vocal features are indicative of specific lung conditions. Such clarity in the AI's reasoning aids clinicians in making accurate diagnoses and customizing treatment plans, demonstrating the practical application of XAI in enhancing diagnostic accuracy and patient care [144,145].

Moreover, the integration of model-agnostic methods with traditional diagnostic tools has been shown to improve interpretability without sacrificing diagnostic accuracy. This approach enables clinicians to decipher complex patterns in data, essential for conditions like COPD where symptoms and their presentations vary widely. By providing actionable insights and ensuring model transparency, XAI facilitates not only the adaptation of treatments to individual needs but also enhances trust and understanding between clinicians and patients, thereby optimizing clinical outcomes [45,146].

These examples underscore the value of XAI in providing detailed, understandable insights into the diagnostics process, which is crucial for achieving personalized treatment strategies. The ability of XAI to offer clear, interpretable explanations ensures that both clinicians and patients can trust and comprehend the AI-driven diagnostics, thus facilitating more informed and effective clinical decisions.

Various studies illustrate the use of XAI in monitoring disease progression and response to treatment in patients with chronic lung diseases [36,147–151]. In this context, several studies have highlighted the role of XAI in improving the management of chronic lung diseases through advanced analytic techniques. For example, research described in one study utilized XAI to analyze audio recordings from patients with pulmonary conditions, employing algorithms that adaptively learn from data variability to predict exacerbations more accurately. This approach ensures that the models perform consistently across diverse patient demographics and disease stages [147]. Another study applied XAI to interpret complex patterns in breathing sounds, which helped in distinguishing between different types of chronic lung diseases, thereby aiding clinicians in customizing treatment plans [148].

Moreover, a significant investigation focused on the integration of XAI in clinical settings demonstrated how explainable models facilitate better patient-practitioner interactions by providing clear rationales for diagnosis and treatment decisions. Such transparency helps in building trust and improving treatment adherence among patients [149,150]. Additionally, research has shown that XAI can effectively predict hospital readmission rates for patients with chronic lung diseases by analyzing longitudinal data, thus helping healthcare providers to anticipate and mitigate risks [36,151].

By continuously analyzing changes in vocal biomarkers, the AI

model could track disease progression. Through XAI, clinicians could understand how these changes in vocal features correlated with clinical indicators of disease severity. This real-time monitoring is invaluable in adjusting treatment plans promptly and improving patient outcomes [154]. Furthermore, the explainability aspect ensured that both clinicians and patients could comprehend and trust the information provided by the AI system.

These case studies exemplify the critical role of XAI in lung disease diagnostics. By offering transparency and interpretability in AI-driven decision-making, XAI bridges the gap between advanced computational approaches and clinical application. The future of XAI in pulmonary medicine looks promising, with ongoing research focusing on enhancing the accuracy, reliability, and clinical utility of these innovative tools (see Table 1).

4.3. Detailed AI methodologies in lung disease diagnostics

Advancements in artificial intelligence (AI) have revolutionized the field of lung disease diagnostics, providing sophisticated tools that enhance precision, adaptability, and patient-specific outcomes. This section delves into a diverse array of AI methodologies deployed to tackle various challenges in diagnosing lung diseases, as demonstrated in Table 3. These methodologies not only reflect significant innovation in handling complex diagnostic tasks but also highlight a shift towards integrating more robust, transparent, and explainable AI systems into clinical practice. By examining these approaches, we gain insights into how AI technologies are being tailored to improve diagnostic accuracy, manage uncertainties, and ultimately, contribute to better patient management and care. The following discussion synthesizes findings from key studies that exemplify this technological evolution, offering a panoramic view of current trends and developments in the AI-driven diagnostic landscape for lung diseases (see Table 2).

We summarize the technical aspects of AI models described in recent studies, illustrating how these methodologies are applied to lung disease diagnostics. The table below provides an overview of neural network types, training processes, feature extraction methods, and unique model development approaches used in these studies.

The methodologies presented in Table 4 highlight the breadth and depth of innovation within AI-driven diagnostics for lung diseases. These range from sophisticated generative adversarial networks that optimize lung adenocarcinoma segmentation by Sasikumar et al. [155], to the application of neutrosophic logic by Sofia Jennifer J et al. [156] for handling uncertainties in chest X-rays, enhancing the reliability of lung infection detection.

Additionally, the self-activation mechanism within CNNs introduced

by Najam-ur Rehman et al. [157] exemplifies advancements in feature relevance, autonomously emphasizing key features for COVID-19 detection. This is crucial for managing pandemic responses across diverse clinical settings. Similarly, the heuristic optimization employed by Antoni Jaszcza et al. [158] through the Red Fox Optimization Algorithm demonstrates another tailored approach, optimizing lung X-ray image segmentation to adaptively select segmentation parameters and improve disease monitoring.

The integration of deep learning with traditional diagnostic methods, seen in Daniel Sánchez Morillo et al.'s study [69], employs a hybrid approach combining PCA and PNNs to enhance the diagnostic process for pneumonia in COPD patients. This is indicative of a broader trend towards integrating diverse AI methodologies to improve diagnostic accuracy and patient care.

In the realm of enhancing radiographic diagnostics, Bhavik N. Patel et al. [122] focus on CNN models trained on extensive datasets to augment radiologists' capabilities, emphasizing the role of AI in enhancing chest radiograph diagnosis through human-AI collaboration. This partnership aims to improve diagnostic accuracy and reduce the radiologists' workload.

Voice pathology detection using deep learning on vocal recordings by Pavol Harar et al. [82] further underscores the versatility of AI applications in lung disease diagnostics. By employing DNNs that utilize convolutional and LSTM layers, the study provides a method to detect and analyze voice pathologies, offering non-invasive diagnostic tools.

Adding to the innovative uses of AI in diagnostics, Md. Zahangir Alam et al. [47] utilize Random Forest, SVM, and Linear Regression models to predict lung function from voice analysis in asthma patients. Their method involves a threshold-based mechanism to separate speech and breathing from recordings, providing a cost-effective and non-invasive tool for chronic disease management. Tim Bashford et al. [145] have developed AI classification systems through vocal biomarkers using CNN-based approaches. Their work features bespoke algorithms tailored for respiratory diseases, which analyze vocal biomarker patterns to enhance the specificity and sensitivity of diagnoses.

These diverse methodologies underscore a broader trend towards more personalized, precise, and accessible diagnostic processes [83]. By leveraging advanced technologies, the field not only enhances the capability to detect and monitor lung diseases but also advances towards more patient-centered approaches [154]. This integration of technology and patient care is crucial for the future of healthcare, ensuring that diagnostics keep pace with the needs and complexities of patient treatment in a rapidly evolving medical landscape [77]. These efforts collectively improve clinical outcomes and patient trust in AI-driven diagnostics, setting a foundation for future innovations in the medical field.

4.4. Evaluating the performance of XAI models

Evaluating the performance of Explainable Artificial Intelligence (XAI) models, especially in the context of lung disease detection using vocal biomarkers, involves assessing not only their predictive accuracy but also the quality and utility of the explanations they provide. This dual focus is essential for ensuring that XAI models are both effective as diagnostic tools and comprehensible to clinicians and patients.

One critical aspect of evaluating XAI model performance is predictive accuracy, which remains a cornerstone of any diagnostic tool. This involves traditional performance metrics such as sensitivity, specificity, precision, recall, and area under the Receiver Operating Characteristic (ROC) curve [159]. For lung disease detection, the model must accurately differentiate between healthy individuals and those with lung pathology, and ideally, identify specific disease types. High accuracy is crucial for gaining clinical trust and for reducing the risk of misdiagnosis, which can have significant implications for patient care [160]. Research demonstrates the fundamental importance of metrics like

Table 1
AI-driven vocal biomarkers for lung diseases.

Lung Disease	Vocal Biomarker Characteristics	AI and Machine Learning Application	Refs
Asthma	Changes due to altered lung capacity and airflow	AI models analyze vocal nuances for early detection and monitoring of the disease.	[46,47]
COPD	Decreased vocal intensity, changes in pitch, increased breathiness	Deep learning techniques identify patterns in voice changes related to airflow limitations.	[48–50]
Lung Cancer	Noticeable changes in voice quality due to airway obstruction or tissue elasticity changes	Advanced AI algorithms classify vocal features correlating with cancer pathologies.	[51–53]
Pulmonary Fibrosis	Subtle vocal changes due to lung tissue stiffness	AI systems analyze complex vocal features for disease detection and progression monitoring.	[54,55]

Table 2

Explainable AI (XAI) in lung disease detection.

Disease Focus	AI Application	XAI Contribution	Clinical Benefit	Refs
Lung Cancer	Vocal biomarker analysis	Transparency in feature contributions	Improved trust and understanding of AI diagnostics	[142, 143]
Various Lung Conditions (Asthma, COPD, etc.)	Vocal pattern identification	Decision-making process clarity	Accurate diagnosis and personalized treatment	[45, 144–146]
Chronic Lung Diseases	Monitoring vocal biomarker changes	Correlation with disease severity	Real-time disease tracking and treatment adjustment	[36, 147–151]

Table 3

Overview of AI models and methodologies.

Study Reference	Neural Network Type	Training Process	Feature Extraction Methods	Unique Approaches	Application Domain
Sasikumar et al. [155]	Deep Convolutional Generative Adversarial Networks	Utilized Red Deer Optimization Algorithm for training optimization	Spectral features extraction from CT scans images	Employed adversarial training to enhance model robustness	Automated segmentation and detection of lung adenocarcinoma
Sofia Jennifer J et al. [156]	Neutrosophic Set Approach	Standard backpropagation with data enhancement techniques	Neutrosophic logic to handle uncertainty in chest X-rays	Integration of neutrosophic sets to improve decision accuracy under uncertainty	Automatic lung infection detection from chest X-rays
Najam-ur Rehman et al. [157]	Self-Activated Convolutional Neural Network	Multi-stage fine-tuning with augmented data sets	Feature maps activated by self-learned weights	Self-activation mechanism to enhance feature relevance	Multi-class detection of chest-related conditions including COVID-19
Antoni Jaszcz et al. [158]	Heuristic Red Fox Optimization Algorithm	Heuristic optimization for parameter tuning	Lung boundary detection and feature isolation	Red Fox optimization to adaptively select segmentation parameters	Lung X-ray image segmentation for various lung diseases
Daniel Sánchez Morillo et al. [69]	Hybrid system using PCA and PNNs	10-Fold cross-validation used to estimate system performance; uses respiratory sound analysis	Features from recorded respiratory sounds; PCA for dimensionality reduction	Probabilistic neural networks to classify pneumonia vs. COPD exacerbations	Pneumonia diagnosis in COPD patients using computerized analysis of respiratory sounds
Bhavik N. Patel et al. [122]	CNN-based architecture	Not specified; focuses on the integration of AI with radiologists' assessments	Deep learning algorithms for pattern recognition in radiographic images	CNN models trained on large datasets of chest radiographs	Enhancing chest radiograph diagnosis through human-AI collaboration
Pavol Harar et al. [82]	DNN using convolutional and LSTM layers	Divided data into training, validation, and testing sets; used recordings from the Saarbruecken Voice Database	Convolutional layers to identify patterns in raw audio signals; LSTM layers for sequence analysis	End-to-end deep neural network for direct voice pathology assessment	Detection of voice pathologies using deep learning on vocal recordings
BelalAlsinglawi et al. [142]	Explainable machine learning models	Implementation of machine learning models with a focus on explainability and interpretability	Uses clinical data inputs to train models, emphasizing transparency in feature influence	Integration of model-agnostic techniques for explainability	Diagnostic processes in healthcare, focusing on explainable AI approaches
Kranthi Kumar Lella et al. [77]	Deep Convolutional Neural Network (DCNN)	Multi-feature channel inputs using denoising autoencoder, Gamma-tone Frequency Cepstral Coefficients, and Improved Multi-frequency Cepstral Coefficients on augmented data	Feature extraction with multi-channel approach including DAE, GFCC, and IMFCC	Use of respiratory sound data: cough, voice, and breath for COVID-19 diagnosis	Automatic diagnosis of COVID-19 from respiratory sounds
Md. Zahangir Alam et al. [47]	Random Forest, Support Vector Machine, Linear Regression	Training with 70 % of data, testing with 30 %, 10-fold cross-validation used	Extracted from recorded voice files, features related to speech and breathing	Threshold-based mechanism to separate speech and breathing from recordings	Predicting lung function from voice analysis in asthma patients
René Groh et al. [154]	Deep Neural Networks (DNNs)	Convolutional	Evolutionary algorithms for optimization	Mechano-acoustic signal analysis	Privacy-focused design using non-identifiable speech data
Tim Bashford et al. [145]	AI Classification through Vocal Biomarkers	CNN-based	Supervised learning with large datasets	Vocal biomarker pattern analysis	Bespoke algorithms tailored for respiratory diseases
Nuha Qais Abdulkmajeed et al. [83]	Evaluation of Voice Pathology	Mixed Neural Networks	Cross-validation method	Voice signal processing	Special focus on the estimation of pathological voice parameters

sensitivity, specificity, precision, recall, and the area under the ROC curve for assessing the accuracy of XAI models in distinguishing between normal and pathological lung conditions [161]. These metrics ensure that XAI models can reliably identify diseases, crucial for gaining clinical trust and preventing misdiagnosis. Moreover, studies have shown that the integration of AI with human judgment in interpreting complex diagnostic data, such as pulmonary function tests (PFTs), leads to improved diagnostic outcomes [162]. This integration enhances the reliability of the diagnostic process by combining human expertise with

machine precision, which is essential in the clinical workflow to aid early detection and deepen understanding of disease processes. Consequently, XAI not only enhances diagnostic accuracy but also builds trust among healthcare providers and patients, ensuring that the benefits of AI-driven diagnostics are fully realized.

However, in XAI, evaluation extends beyond traditional metrics to include the interpretability of the model's output. Interpretability refers to the extent to which a human can understand the cause of a decision made by the model [163]. This is particularly important in healthcare,

Table 4

Comprehensive evaluation criteria for XAI models in lung disease detection.

Evaluation Criterion	Description	Relevance in Lung Disease Detection	Methods/Techniques Used	Importance in Clinical Application	Ref
Predictive Accuracy Interpretability	Assessment of the model's ability to correctly identify lung diseases	Differentiation between healthy individuals and lung pathology	Sensitivity, Specificity, Precision, Recall, ROC Curve	Ensures reliability and reduces misdiagnosis risk	[161,162]
	Extent to which model decisions are understandable	Elucidation of vocal biomarker changes and disease correlation	Feature Importance Scores, Decision Trees, Rule-Based Explanations	Enhances clinician's understanding of AI reasoning	[164,165]
Explanation Utility	Usefulness of the model's explanations in enhancing user understanding	Meaningfulness of explanations in clinical decision-making	Evaluation of explanation impact on clinical decisions	Ensures explanations inform and complement medical knowledge	[166–169]
Generalizability	Model's performance across diverse patient populations and settings	Consistent accuracy in varied clinical environments	Testing in different demographics, comorbidities, recording conditions	Validates model robustness and real-world applicability	[170–173]
Robustness	Model's stability and reliability under different conditions	Performance consistency in unpredictable clinical settings	Stress-testing model under varying conditions	Ensures model reliability and patient safety	[174,175]

where the reasons behind a diagnosis or treatment recommendation are as crucial as the recommendation itself. For XAI models analyzing vocal biomarkers, interpretability might involve elucidating how specific changes in voice characteristics correlate with lung diseases. Methods such as feature importance scores, decision trees, or rule-based explanations can be used to provide insights into the model's decision-making process [139]. For instance, a study applied a Layer-wise Relevance Propagation (LRP) method to explain decisions made by a CNN model in classifying lung diseases from X-ray images. This method, by visualizing the relevance of each pixel in the input image to the model's classification decision, helped in pinpointing areas of opacity typically associated with lung conditions, thereby making the model's outputs interpretable to clinicians [164]. Similarly, another approach, DeepXplainer, utilized SHAP (SHapley Additive exPlanations) values to explain a model that combines deep learning and gradient boosting for lung cancer detection. It demonstrated how each feature contributed to the model's prediction, thus aiding physicians in understanding and trusting AI-generated diagnoses [165].

The utility of the explanations provided by XAI models is another important evaluation criterion. This aspect assesses whether the explanations enhance the user's understanding and whether they can inform clinical decision-making effectively [176]. In the context of lung diseases, this means that the explanations should be meaningful to clinicians, helping them to understand the AI's reasoning in a way that complements their medical knowledge and experience. For instance, if an XAI model identifies a particular set of vocal features as indicative of COPD, the model should provide explanations that align with known clinical manifestations of COPD [177]. For instance, in one study, the detailed parsing of pulmonary function tests by AI demonstrated how such technology could support pulmonologists by making complex diagnostic data more accessible and understandable, thus enhancing diagnostic precision and subsequent treatment outcomes [166]. This is crucial in clinical settings where decisions must be backed by clear and reliable data insights, enabling personalized treatment approaches tailored to individual patient conditions [177].

Moreover, additional research highlights how AI-generated insights into lung disease characteristics can directly influence treatment strategies. Clear, interpretable data provided by AI helps clinicians tailor treatments effectively, thus improving patient care by aligning with specific disease manifestations such as chronic obstructive pulmonary disease (COPD) [167], where accurate identification of vocal biomarkers plays a crucial role [177]. Predictive diagnostics further exemplify the utility of XAI, where AI models capable of anticipating disease progression or onset enable clinicians to initiate preventive measures proactively. Such capabilities are essential for altering health trajectories positively, providing early interventions that could delay or mitigate the severity of lung conditions [168].

Continued monitoring of chronic lung conditions through AI also illustrates the ongoing benefits of explainable models. Systems that offer

consistent, comprehensible updates about disease progression enable better disease management, allowing timely adjustments in treatment plans based on patient response and condition [169]. This ongoing monitoring and adjustment are vital for chronic conditions where patient states can vary significantly over time.

Finally, evaluating an XAI model also involves assessing its generalizability and robustness across different patient populations and settings. This is crucial for ensuring that the model performs well not only in the controlled conditions of a research study but also in the diverse and often unpredictable real-world clinical environment [178]. Factors such as different recording conditions for vocal data, patient demographics, and comorbidities can all affect model performance and must be considered in the evaluation process.

Studies highlighted in recent research provide profound insights into how XAI models can maintain consistency and accuracy across various clinical environments. For example, the study conducted by Lee and colleagues demonstrated how machine learning models trained on extensive multi-regional data could predict lung disease outcomes with high reliability, thus underscoring the importance of diverse training datasets for enhancing model generalizability [170]. Furthermore, insights from Taylor et al. discuss the application of advanced validation techniques that simulate real-world conditions, ensuring that XAI models are not only tested in ideal conditions but are also stress-tested against scenarios that mimic everyday clinical variability [171]. This approach helps to reveal potential performance declines in different demographic and comorbidity backgrounds, which is crucial for ensuring the models' real-world utility. Additionally, research by Khan et al. explores the adaptation of models across different healthcare systems, which often presents a significant challenge due to varying standards and practices. Their findings suggest that adaptable models, which can fine-tune to specific clinical settings without extensive retraining, offer a practical solution for deployment in diverse medical infrastructures [172]. Moreover, Patel and associates provide an analysis on the continuous monitoring and updating of XAI models, ensuring they evolve in response to new data and maintain their effectiveness over time. This ongoing adaptation is vital for coping with changes in patient characteristics and disease profiles, which directly impacts the models' generalizability [173].

These considerations are crucial for the adoption of XAI in clinical settings, where the ability to perform reliably across different conditions and patient groups is paramount. The integration of robust, statistically validated AI models into clinical workflows ensures that the benefits of AI-driven diagnostics are fully realized, supporting a comprehensive approach to patient care [178].

Recent studies have provided substantial insights into strategies that enhance model robustness. One such approach involves stress-testing models under varied conditions to simulate real-world anomalies and unexpected variations in patient data. This type of validation is crucial for confirming that AI systems can maintain their reliability and

accuracy irrespective of external changes or unusual patient presentations.

For example, a study demonstrated the effectiveness of using robust training methods that incorporate noise and disturbances during the training phase to better prepare the model for diverse operational scenarios. These methods help in understanding how slight variations in input data, which often occur in clinical settings, might affect the model's predictions, thereby ensuring that the system remains reliable even when faced with data that deviates from the norm observed during training [174].

Another research highlighted the application of advanced simulation techniques to evaluate the performance of AI systems against a range of possible future conditions, not just those seen in past data. By incorporating predictive uncertainty measures, the models are assessed on their ability to handle data anomalies and maintain performance integrity, thereby safeguarding against potential diagnostic errors that could lead to adverse clinical outcomes [175].

These methodologies underline the importance of incorporating rigorous testing and adaptive learning frameworks into the development of AI models for healthcare. By preparing these systems to handle unexpected scenarios effectively, the robustness of AI applications is significantly enhanced, ensuring that they provide reliable support in critical healthcare decisions. This not only boosts the confidence of healthcare providers in using AI tools but also ensures patient safety across varying clinical environments.

In summary, evaluating the performance of XAI models in lung disease detection requires a multifaceted approach that considers accuracy, interpretability, utility, generalizability, and robustness. As XAI continues to evolve, these evaluation criteria will play a vital role in ensuring that XAI models meet the high standards necessary for clinical application and patient care.

5. Overcoming challenges and future perspectives in XAI for lung disease detection

5.1. Addressing data heterogeneity and model generalizability

In the realm of applying Explainable Artificial Intelligence (XAI) for lung disease detection using vocal biomarkers, two significant challenges are data heterogeneity and model generalizability. Data heterogeneity refers to the diversity and variability in data, which in the context of vocal biomarkers, can stem from differences in age, gender, language, lifestyle, and health status of individuals [178]. This variability poses a challenge in training AI models that can accurately generalize across a wide range of patient populations. For XAI to be effective, it must account for this heterogeneity, ensuring that the models are not only accurate in specific subgroups but also across broader populations.

Addressing data heterogeneity involves collecting and utilizing diverse datasets that represent the full spectrum of variability seen in clinical settings. This includes data from individuals of different ages, genders, ethnicities, and varying health conditions. For lung disease detection, it is crucial to include vocal data from patients with different lung conditions and stages of disease, as well as healthy individuals, to provide a comprehensive dataset for training AI models [179]. Additionally, strategies such as data augmentation and synthetic data generation can be employed to enhance the diversity and volume of training data, which can help improve the robustness of the AI models [127].

Model generalizability is closely linked to data heterogeneity and refers to the AI model's ability to maintain its performance across different datasets and real-world settings. Generalizability is crucial for ensuring that XAI tools developed for lung disease detection are effective and reliable when deployed in diverse clinical environments. To achieve this, models need to be rigorously tested and validated on independent datasets that were not used during the training phase. This validation should include data from various sources and demographics to assess the

model's performance in real-world scenarios [180].

Another approach to enhance generalizability is the use of transfer learning, where a model trained on one task or dataset is adapted to work on another related task or dataset. This technique is particularly useful in medical applications where large amounts of training data are often not available for every specific condition [181]. By using pre-trained models and adapting them to the task of lung disease detection using vocal biomarkers, transfer learning can help in overcoming the limitations posed by data scarcity and diversity.

The challenges of data heterogeneity and model generalizability are paramount in the application of Explainable Artificial Intelligence (XAI) to lung disease detection. The diversity inherent in clinical data, due to variations in demographic, linguistic, and disease characteristics, necessitates robust AI solutions that can adapt and perform consistently across varied conditions.

Recent advancements highlight the development of AI models that excel not only in technical proficiency but also in handling data from diverse patient populations [182]. Innovative methodologies such as integrating heterogeneous datasets have demonstrated considerable improvements in model performance. These approaches often incorporate sophisticated data preprocessing and augmentation techniques, enhancing the generalizability of AI diagnostics. This is supported by studies exploring domain adaptation and transfer learning strategies for medical imaging, which illustrate how diverse data integration enhances diagnostic accuracy and model adaptability [183–185].

Statistical analyses further quantify the impact of data heterogeneity on AI model accuracy, guiding the implementation of more effective training regimes. Such analyses emphasize the need for AI models that can dynamically adjust to new data inputs without losing predictive accuracy, thereby enhancing their applicability in clinical settings [124].

Adding to this, several case studies demonstrate effective strategies to mitigate these challenges. Detailed assessments inspired by recent field advancements focused on quantifying the variance in diagnostic performance across different subgroups, underscoring the necessity of diverse training datasets for model robustness [186]. Additionally, examining training neural networks on large, diverse data sets has effectively showcased the models' ability to generalize across various clinical environments [187]. These examples highlight the critical importance of comprehensive dataset compilation and meticulous model training to achieve high reliability and applicability in clinical diagnostics.

Together, these integrated discussions and case studies align with the manuscript's themes, showcasing efforts to enhance model generalizability and address data heterogeneity. These efforts are crucial for advancing personalized medicine, where the precision and adaptability of diagnostic tools can significantly influence patient outcomes, paving the way for XAI's broader application in clinical practice.

In summary, addressing data heterogeneity and model generalizability is pivotal in the development and application of XAI for lung disease detection. These challenges require a multifaceted approach, involving diverse data collection, rigorous validation, and innovative modeling techniques like transfer learning. By overcoming these challenges, XAI models can be more effectively integrated into clinical practice, providing valuable tools for early detection and management of lung diseases.

5.2. Ethical considerations and patient privacy in AI-based diagnostics

The advancement of AI in healthcare, particularly in lung disease diagnostics using vocal biomarkers, raises significant ethical considerations and concerns about patient privacy. As AI systems become more integrated into clinical practice, ensuring that they are used in an ethically responsible manner and that patient data is protected remains paramount.

One of the primary ethical considerations in AI-based diagnostics is

the need for informed consent. Patients must be fully informed about how their data, including vocal recordings, will be used, what the AI model is analyzing, and how the results will be applied in their care [119]. This is particularly important because vocal biomarkers can reveal sensitive health information, and patients have the right to understand and consent to how their data is being utilized [188]. Ensuring transparency in the data usage and AI decision-making process aligns with ethical standards in healthcare and reinforces patient trust in AI technologies.

Another critical aspect is the potential for bias in AI models, which can lead to disparities in healthcare. AI systems trained on limited or biased datasets may not perform equally well across different patient demographics, potentially leading to misdiagnosis or inappropriate treatment recommendations for certain groups [189]. This risk necessitates careful consideration in the design, development, and deployment of AI systems to ensure they are fair and equitable. Rigorous testing across diverse populations and continuous monitoring for biases are essential steps in mitigating this risk [190].

Patient privacy and data security are also crucial in AI-based diagnostics. The collection, storage, and analysis of vocal biomarkers must adhere to strict data privacy regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the United States or the General Data Protection Regulation (GDPR) in the European Union [191]. Ensuring that AI systems are secure and that patient data is protected against unauthorized access or breaches is fundamental in maintaining patient confidentiality and trust [192].

Additionally, there is a need for clear guidelines and governance structures around the use of AI in healthcare to address these ethical and privacy concerns. This includes establishing standards for data collection, model development, validation, and implementation in clinical settings. Collaborative efforts among healthcare professionals, ethicists, legal experts, and AI developers are vital in creating a framework that ensures AI is used responsibly and beneficially in healthcare [124].

In summary, addressing ethical considerations and ensuring patient privacy are crucial elements in the responsible use of AI for lung disease diagnostics. These aspects are integral to building and maintaining trust in AI technologies among patients and clinicians and are essential for the successful and sustainable integration of AI in healthcare.

5.3. Future directions and potential innovations in XAI for pulmonary medicine

The field of Explainable Artificial Intelligence (XAI) in pulmonary medicine, particularly in the context of lung disease detection through vocal biomarkers, is poised for significant advancements. Future research and innovations in this area will likely focus on enhancing the interpretability, accuracy, and clinical applicability of AI models, ensuring that they not only meet the high standards required for medical diagnostics but also align with the practical needs of clinicians and patients.

One promising direction is the development of more sophisticated XAI models that provide deeper insights into the complex relationships between vocal features and lung pathologies. Current XAI methods, while effective in offering explanations, often provide surface-level insights. Future models could employ advanced techniques like counterfactual explanations, which illustrate how changing certain input features could lead to different diagnostic outcomes [193]. This approach could help clinicians understand the relative importance of different vocal features in lung disease diagnostics, facilitating more informed clinical decision-making [140].

Another area of potential innovation lies in the integration of XAI with other emerging technologies, such as wearable devices and Internet of Medical Things (IoMT). Wearables equipped with sensors and voice recording capabilities can continuously monitor patients' vocal patterns, providing a rich dataset for AI analysis [194]. The integration of XAI into these technologies would enable real-time, personalized health

monitoring and early intervention, significantly enhancing patient care in pulmonary medicine [195].

Collaborative efforts between AI researchers, clinicians, and patients will also be crucial in the future development of XAI for lung disease detection. Involving clinicians in the AI model development process can ensure that the models address real-world clinical challenges and are designed with practical applicability in mind [124]. Patient involvement is equally important, as it ensures that the models are patient-centric and consider patient preferences and values in the diagnostic process [188].

Moreover, as XAI continues to evolve, there will be a growing need for standardization in terms of evaluation metrics and benchmarks. Establishing standardized protocols for testing and validating XAI models will be essential for assessing their performance consistently and ensuring their reliability and safety in clinical settings [179]. This would also facilitate regulatory approvals and encourage wider adoption of these technologies in healthcare.

In summary, the future of XAI in pulmonary medicine is bright, with numerous avenues for innovation and advancement. By developing more advanced XAI models, integrating with emerging technologies, fostering collaborative research, and standardizing evaluation protocols, XAI can significantly improve lung disease diagnostics and patient care.

6. Discussion

While the current exploration of Explainable Artificial Intelligence (XAI) in lung disease detection has made notable advances, several research gaps still need addressing. One such gap is the integration of XAI with real-time monitoring systems. Despite the potential of XAI to enhance diagnostic accuracy and transparency, its application in continuous patient monitoring remains underexplored. This gap presents a significant opportunity for researchers to develop XAI systems that not only diagnose but also predict disease progression in real-time, providing clinicians with tools to make timely and informed treatment decisions [196].

Another significant research gap lies in the limited diversity of datasets used in the training and validation of XAI models. Current studies often rely on data from homogenous populations, which may not accurately represent the global diversity seen in clinical settings. This limitation can affect the generalizability and effectiveness of XAI applications across different demographic groups. Addressing this gap requires a concerted effort to compile and utilize multi-ethnic and cross-geographic datasets that reflect the wide variability in vocal biomarkers due to ethnic, linguistic, and environmental factors [197].

Immediate steps should include the development of dynamic XAI models capable of adjusting their algorithms based on continuous patient data input. Such models would be invaluable in chronic lung disease management, where patient conditions can fluctuate significantly over time [198,199].

To address the issue of data diversity, it is imperative to conduct multi-centric trials that collect vocal biomarker data across various global populations. These trials will help in developing XAI models that are robust and effective across different patient demographics and geographical locations [200].

Bridging the gap between AI technologists and clinical healthcare providers is crucial. Collaborative projects that involve both AI experts and pulmonologists can lead to the development of more clinically relevant XAI systems. Such collaboration will ensure that the systems developed are not only technically sound but also align with real-world clinical needs and workflows [201].

By addressing these research gaps and taking the suggested steps, the field of XAI in lung disease detection can move towards more personalized, accurate, and globally applicable diagnostic systems. Such advancements could revolutionarily enhance patient outcomes in pulmonary medicine, setting new standards for AI in healthcare.

7. Conclusion

This review has comprehensively explored the application of explainable artificial intelligence (XAI) in the detection and analysis of lung diseases through vocal biomarkers, highlighting its potential to revolutionize pulmonary diagnostics. The integration of XAI addresses the critical need for transparency and interpretability in AI-driven diagnostics, offering a window into the AI decision-making process that is vital for clinical acceptance and trust.

We have critically examined various methodologies employed in the development of XAI models, emphasizing their role in elucidating the intricate relationships between vocal features and lung pathology. The potential of XAI to not only aid in the early detection of lung diseases but also to monitor disease progression and personalize treatment strategies cannot be overstated. By enabling a deeper understanding of the diagnostic predictions, XAI empowers clinicians to make more informed decisions, ultimately leading to improved patient outcomes.

However, challenges such as data heterogeneity and model generalizability pose significant hurdles to the widespread implementation of these technologies. Addressing these challenges requires a multifaceted approach, including the collection of diverse and comprehensive datasets, rigorous model validation, and the development of innovative modeling techniques like transfer learning.

Furthermore, ethical considerations and patient privacy remain at the forefront of AI-based diagnostics. Ensuring informed consent, mitigating biases in AI models, and safeguarding patient data are essential for maintaining the integrity and trustworthiness of these advanced tools.

Looking forward, the field of XAI in pulmonary medicine is ripe with opportunities for innovation and advancement. The integration of XAI with emerging technologies such as wearable devices, coupled with collaborative efforts between computational scientists, clinicians, and patients, is poised to pave the way for more personalized and effective healthcare solutions.

In conclusion, XAI represents a significant step forward in bridging the gap between advanced computational approaches and clinical practice. Its ability to provide transparent and interpretable diagnostic tools promises to enhance the reliability and effectiveness of AI in lung disease detection, heralding a new era in pulmonary medicine.

Funding

We thanked the Outstanding Youth Program of China Academy of Chinese Medical Sciences (Z0882), The 15th batch of independent topic selection and free exploration projects for Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences (Z0860), Young Talents Support Project of China Association of Chinese Medicine (2022-2024) - Level Matching Funds for Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences (Z0866), China Academy of Chinese Medical Sciences' Independent Selection Project (Z0830) and Institute of Basic Research in Clinical Medicine's Independent Selection Project (Z0830-1), China Academy of Chinese Medical Sciences for their support for this work.

Data availability

No data was used for the research described in the article.

CRediT authorship contribution statement

Zhao Chen: Writing – original draft, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Ning Liang:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Haoyuan Li:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Haili Zhang:** Resources,

Investigation, Formal analysis, Data curation. **Huizhen Li:** Visualization, Validation, Methodology, Investigation. **Lijiao Yan:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Ziteng Hu:** Writing – original draft, Resources, Methodology, Formal analysis. **Yaxin Chen:** Writing – review & editing, Visualization, Investigation, Data curation. **Yujing Zhang:** Visualization, Validation, Formal analysis, Data curation. **Yanping Wang:** Writing – review & editing, Supervision, Funding acquisition. **Dandan Ke:** Funding acquisition, Supervision, Visualization, Writing – review & editing. **Nannan Shi:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

As the authors of the manuscript titled "Exploring Explainable AI Features in the Vocal Biomarkers of Lung Disease," we declare that there are no conflicts of interest regarding the publication of this paper. We have no financial, consultant, institutional, or other relationships that might lead to a conflict of interest. All data and materials support our published claims and comply with field standards. Furthermore, there has been no significant ethical concern in the conduct of this research. Our submission is in agreement with all authors, and we collectively take responsibility for the work.

Acknowledgements

We would like to thank anonymous reviewers for their valuable comments and suggestions that further lead us to improve this paper.

References

- [1] J. Meghji, K. Mortimer, A. Agusti, B.W. Allwood, I. Asher, E.D. Bateman, K. Bissell, C.E. Bolton, A. Bush, B. Celli, Improving lung health in low-income and middle-income countries: from challenges to solutions, *Lancet* 397 (2021) 928–940, [https://doi.org/10.1016/S0140-6736\(21\)00458-X](https://doi.org/10.1016/S0140-6736(21)00458-X).
- [2] S. Safiri, K. Carson-Chahoud, M. Noori, S.A. Nejadghaderi, M.J. Sullman, J. A. Heris, K. Ansarin, M.A. Mansournia, G.S. Collins, A.-A. Kolahi, Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990–2019: results from the Global Burden of Disease Study 2019, *BMJ* (2022) 378, <https://doi.org/10.1136/bmj-2021-069679>.
- [3] S. Chen, M. Kuhn, K. Prettner, F. Yu, T. Yang, T. Bärnighausen, D.E. Bloom, C. Wang, The global economic burden of chronic obstructive pulmonary disease for 204 countries and territories in 2020–50: a health-augmented macroeconomic modelling study, *Lancet Global Health* 11 (2023) e1183–e1193, [https://doi.org/10.1016/S2214-109X\(23\)00217-6](https://doi.org/10.1016/S2214-109X(23)00217-6).
- [4] S. Salvi, G.A. Kumar, R. Dhaliwal, K. Paulson, A. Agrawal, P.A. Koul, P. Mahesh, S. Nair, V. Singh, A.N. Aggarwal, The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990–2016, *Lancet Global Health* 6 (2018) e1363–e1374, [https://doi.org/10.1016/S2214-109X\(18\)30409-1](https://doi.org/10.1016/S2214-109X(18)30409-1).
- [5] A. Agusti, C.F. Vogelmeier, D.M. Halpin, Tackling the global burden of lung disease through prevention and early diagnosis, *Lancet Respir. Med.* 10 (2022) 1013–1015, [https://doi.org/10.1016/S2213-2600\(22\)00302-2](https://doi.org/10.1016/S2213-2600(22)00302-2).
- [6] T. Ferkol, D. Schraufnagel, The global burden of respiratory disease, *Annals of the American Thoracic Society* 11 (2014) 404–406, <https://doi.org/10.1513/AnnalsATS.201311-405PS>.
- [7] F. Pancaldi, M. Sebastiani, G. Cassone, F. Luppi, S. Cerri, G. Della Casa, A. Manfredi, Analysis of pulmonary sounds for the diagnosis of interstitial lung diseases secondary to rheumatoid arthritis, *Comput. Biol. Med.* 96 (2018) 91–97, <https://doi.org/10.1016/j.combiomed.2018.03.006>.
- [8] Y. Belessis, B. Dixon, G. Hawkins, J. Pereira, J. Peat, R. MacDonald, P. Field, A. Numa, J. Morton, K. Lui, Early cystic fibrosis lung disease detected by bronchoalveolar lavage and lung clearance index, *Am. J. Respir. Crit. Care Med.* 185 (2012) 862–873, <https://doi.org/10.1164/rccm.201109-1631OC>.
- [9] D.S. Watson, J. Krutzinna, I.N. Bruce, C.E. Griffiths, I.B. McInnes, M.R. Barnes, L. Floridi, Clinical applications of machine learning algorithms: beyond the black box, *BMJ* (2019) 364, <https://doi.org/10.1136/bmj.l886>.
- [10] N. Luo, X. Zhong, L. Su, Z. Cheng, W. Ma, P. Hao, Artificial intelligence-assisted dermatology diagnosis: from unimodal to multimodal, *Comput. Biol. Med.* (2023) 107413, <https://doi.org/10.1016/j.combiomed.2023.107413>.
- [11] R. Ranjbarzadeh, A. Caputo, E.B. Tirkolaei, S.J. Ghoushchi, M. Bendechache, Brain tumor segmentation of MRI images: a comprehensive review on the application of artificial intelligence tools, *Comput. Biol. Med.* 152 (2023) 106405, <https://doi.org/10.1016/j.combiomed.2022.106405>.

- [12] W. Samek, T. Wiegand, K.-R. Müller, Explainable artificial intelligence: understanding, visualizing and interpreting deep learning models, arXiv preprint arXiv:1708.08296 (2017), <https://doi.org/10.48550/arXiv.1708.08296>.
- [13] S. Ali, F. Akhlag, A.S. Imran, Z. Kastrati, S.M. Daudpota, M. Moosa, The enlightening role of explainable artificial intelligence in medical & healthcare domains: a systematic literature review, *Comput. Biol. Med.* (2023) 107555, <https://doi.org/10.1016/j.combiomed.2023.107555>.
- [14] G. Vilone, L. Longo, Notions of explainability and evaluation approaches for explainable artificial intelligence, *Inf. Fusion* 76 (2021) 89–106, <https://doi.org/10.1016/j.inffus.2021.05.009>.
- [15] A.B. Arrieta, N. Díaz-Rodríguez, J. Del Ser, A. Bennetot, S. Tabik, A. Barbado, S. García, S. Gil-López, D. Molina, R. Benjamins, Explainable Artificial Intelligence (XAI): concepts, taxonomies, opportunities and challenges toward responsible AI, *Inf. Fusion* 58 (2020) 82–115, <https://doi.org/10.1016/j.inffus.2019.12.012>.
- [16] D. Gunning, M. Stefk, J. Choi, T. Miller, S. Stumpf, G.-Z. Yang, XAI—explainable artificial intelligence, *Sci. Robot.* 4 (2019) eaay7120, <https://doi.org/10.1126/scirobotics.aay7120>.
- [17] M. Ghassemi, L. Oakden-Rayner, A.L. Beam, The false hope of current approaches to explainable artificial intelligence in health care, *The Lancet Digital Health* 3 (2021) e745–e750, [https://doi.org/10.1016/S2589-7500\(21\)00208-9](https://doi.org/10.1016/S2589-7500(21)00208-9).
- [18] J.-B. Lamy, B. Sekar, G. Guezennec, J. Bouaud, B. Séroussi, Explainable artificial intelligence for breast cancer: a visual case-based reasoning approach, *Artif. Intell. Med.* 94 (2019) 42–53, <https://doi.org/10.1016/j.artmed.2019.01.001>.
- [19] M. Chary, E.W. Boyer, M.M. Burns, Diagnosis of acute poisoning using explainable artificial intelligence, *Comput. Biol. Med.* 134 (2021) 104469, <https://doi.org/10.1016/j.combiomed.2021.104469>.
- [20] G. Fagherazzi, A. Fischer, M. Ismael, V. Despotovic, Voice for health: the use of vocal biomarkers from research to clinical practice, *Digit. Biomark.* 5 (2021) 78–88, <https://doi.org/10.1159/000515346>.
- [21] J. Meena, Y. Hasija, Application of explainable artificial intelligence in the identification of Squamous Cell Carcinoma biomarkers, *Comput. Biol. Med.* 146 (2022) 105505, <https://doi.org/10.1016/j.combiomed.2022.105505>.
- [22] C.C. Yang, Explainable artificial intelligence for predictive modeling in healthcare, *Journal of healthcare informatics research* 6 (2022) 228–239, <https://doi.org/10.1007/s41666-022-00114-1>.
- [23] G. Novakovsky, N. Dexter, M.W. Libbrecht, W.W. Wasserman, S. Mostafavi, Obtaining genetics insights from deep learning via explainable artificial intelligence, *Nat. Rev. Genet.* 24 (2023) 125–137, <https://doi.org/10.1038/s41576-022-00532-2>.
- [24] J. Petch, S. Di, W. Nelson, Opening the black box: the promise and limitations of explainable machine learning in cardiology, *Can. J. Cardiol.* 38 (2022) 204–213, <https://doi.org/10.1016/j.cjca.2021.09.004>.
- [25] S. Reddy, Explainability and artificial intelligence in medicine, *The Lancet Digital Health* 4 (2022) e214–e215, [https://doi.org/10.1016/S2589-7500\(22\)00029-2](https://doi.org/10.1016/S2589-7500(22)00029-2).
- [26] K. Rasheed, A. Qayyum, M. Ghaly, A. Al-Fuqaha, A. Razi, J. Qadir, Explainable, trustworthy, and ethical machine learning for healthcare: a survey, *Comput. Biol. Med.* (2022) 106043, <https://doi.org/10.1016/j.combiomed.2022.106043>.
- [27] J.C. Mundt, A.P. Vogel, D.E. Feltner, W.R. Lenderking, Vocal acoustic biomarkers of depression severity and treatment response, *Biol. Psychiatry* 72 (2012) 580–587, <https://doi.org/10.1016/j.biopsych.2012.03.015>.
- [28] B. Tracey, S. Patel, Y. Zhang, K. Chappie, D. Volfsen, F. Parisi, C. Adams-Dester, F. Bertacchi, P. Bonato, P. Wacnik, Voice biomarkers of recovery from acute respiratory illness, *IEEE Journal of Biomedical and Health Informatics* 26 (2021) 2787–2795, <https://doi.org/10.1109/JBHI.2021.3137050>.
- [29] N. Cummins, A. Baird, B.W. Schuller, Speech analysis for health: current state-of-the-art and the increasing impact of deep learning, *Methods* 151 (2018) 41–54, <https://doi.org/10.1016/j.ymeth.2018.07.007>.
- [30] E.E. Mohamed, Voice changes in patients with chronic obstructive pulmonary disease, *Egypt. J. Chest Dis. Tuberc.* 63 (2014) 561–567, <https://doi.org/10.1016/j.ejcdt.2014.03.006>.
- [31] A.M. Saeed, N.M. Riad, N.M. Osman, A.N. Khattab, S.E. Mohammed, Study of voice disorders in patients with bronchial asthma and chronic obstructive pulmonary disease, *Egyptian Journal of Bronchology* 12 (2018) 20–26, https://doi.org/10.4103/ejb.ejb_34_17.
- [32] S.-B. Zhang, M. Hong, X.-Y. Sun, D.W. Huang, D.-H. He, Y.-F. Chen, Y. Yuan, Y.-Q. Liu, Silybin has therapeutic efficacy against non-small cell lung cancer through targeting of skp2, *Acta Materia Medica* 1 (2022) 302–313, <https://doi.org/10.1521/AMM-2022-0011>.
- [33] J.A. Sidey-Gibbons, C.J. Sidey-Gibbons, Machine learning in medicine: a practical introduction, *BMC Med. Res. Methodol.* 19 (2019) 1–18, <https://doi.org/10.1186/s12874-019-0681-4>.
- [34] J.M. Tracy, Y. Özkanca, D.C. Atkins, R.H. Ghomi, Investigating voice as a biomarker: deep phenotyping methods for early detection of Parkinson's disease, *J. Biomed. Inf.* 104 (2020) 103362, <https://doi.org/10.1016/j.jbi.2019.103362>.
- [35] R. Dias, A. Torkamani, Artificial intelligence in clinical and genomic diagnostics, *Genome Med.* 11 (2019) 1–12, <https://doi.org/10.1186/s13073-019-0689-8>.
- [36] O. Ashraf, E. Rabold, K. Schlichtkrull, A. Singh, S. Venneti, M.M.D.A. Khan, R. Kulshreshtha, P.P. Naval, Voice-based screening and monitoring of chronic respiratory conditions, *Chest* 158 (2020) A1687, <https://doi.org/10.1016/j.chest.2020.08.1509>.
- [37] H. Lin, C. Karjadi, T.F. Ang, J. Prajakta, C. McManus, T.W. Alhanai, J. Glass, R. Au, Identification of digital voice biomarkers for cognitive health, *Exploration of medicine* 1 (2020) 406, <https://doi.org/10.37349/emed.2020.00028>.
- [38] L. Liu, Y. Li, S. Li, N. Hu, Y. He, R. Pong, D. Lin, L. Lu, M. Law, Comparison of next-generation sequencing systems, *J. Biomed. Biotechnol.* (2012) 2012, <https://doi.org/10.1155/2012/251364>.
- [39] J. Amann, A. Blasimme, E. Vayena, D. Frey, V.I. Madai, P.Q. Consortium, Explainability for artificial intelligence in healthcare: a multidisciplinary perspective, *BMC Med. Inf. Decis. Making* 20 (2020) 1–9, <https://doi.org/10.1186/s12911-020-01332-6>.
- [40] H. Chen, C. Gomez, C.-M. Huang, M. Unberath, Explainable medical imaging AI needs human-centered design: guidelines and evidence from a systematic review, *NPJ digital medicine* 5 (2022) 156, <https://doi.org/10.1038/s41746-022-00699-2>.
- [41] C. Rudin, Stop explaining black box machine learning models for high stakes decisions and use interpretable models instead, *Nat. Mach. Intell.* 1 (2019) 206–215, <https://doi.org/10.1038/s42256-019-0048-x>.
- [42] C. Combi, B. Amico, R. Bellazzi, A. Holzinger, J.H. Moore, M. Zitnik, J.H. Holmes, A manifesto on explainability for artificial intelligence in medicine, *Artif. Intell. Med.* 133 (2022) 102423, <https://doi.org/10.1016/j.artmed.2022.102423>.
- [43] P. Gupta, H. Wen, L. Di Francesco, F. Ayazi, Detection of pathological mechano-acoustic signatures using precision accelerometer contact microphones in patients with pulmonary disorders, *Sci. Rep.* 11 (2021) 13427, <https://doi.org/10.1038/s41598-021-92666-2>.
- [44] M. Gilfillan, A. Bhandari, V. Bhandari, Diagnosis and management of bronchopulmonary dysplasia, *Bmj* 375 (2021), <https://doi.org/10.1136/bmj.n1974>.
- [45] S. Kaur, E. Larsen, J. Harper, B. Purandare, A. Uluer, M.A. Hasdianda, N. A. Umale, J. Killeen, E. Castillo, S. Jariwala, Development and validation of a respiratory-Responsive vocal biomarker-based tool for generalizable detection of respiratory impairment independent case-control studies in multiple respiratory conditions including asthma, chronic obstructive pulmonary disease, and COVID-19, *J. Med. Internet Res.* 25 (2023) e44410, <https://doi.org/10.2196/44410>.
- [46] K. Wieczorek, S. Ananth, D. Valazquez-Pimentel, Acoustic biomarkers in asthma: a systematic review, *J. Asthma* (2024) 1–18, <https://doi.org/10.1080/02770903.2024.2344156>.
- [47] M.Z. Alam, A. Simonetti, R. Brillantino, N. Tayler, C. Grainge, P. Siribaddana, S. R. Nouraei, J. Batchelor, M.S. Rahman, E.V. Mancuso, Predicting pulmonary function from the analysis of voice: a machine learning approach, *Frontiers in digital health* 4 (2022) 750226, <https://doi.org/10.3389/fdgh.2022.750226>.
- [48] Z. Zhu, S. Zhao, J. Li, Y. Wang, L. Xu, Y. Jia, Z. Li, W. Li, G. Chen, X. Wu, Development and application of a deep learning-based comprehensive early diagnostic model for chronic obstructive pulmonary disease, *Respir. Res.* 25 (2024) 1–12, <https://doi.org/10.1186/s12931-024-02793-3>.
- [49] A. Srivastava, S. Jain, R. Miranda, S. Patil, S. Pandya, K. Koticha, Deep learning based respiratory sound analysis for detection of chronic obstructive pulmonary disease, *PeerJ Computer Science* 7 (2021) e369, <https://doi.org/10.7717/peerj.cs.369>.
- [50] I. Tessler, A. Primov-Fever, S. Soffer, R. Anteby, N.A. Gecel, N. Livneh, E.E. Alon, E. Zimlichman, E. Klang, Deep learning in voice analysis for diagnosing vocal cord pathologies: a systematic review, *Eur. Arch. Oto-Rhino-Laryngol.* 281 (2024) 863–871, <https://doi.org/10.1007/s00405-023-08362-6>.
- [51] S.-Y. Jung, C.-H. Liao, Y.-S. Wu, S.-M. Yuan, C.-T. Sun, Efficiently classifying lung sounds through depthwise separable CNN models with fused STFT and MFCC features, *Diagnostics* 11 (2021) 732, <https://doi.org/10.3390/diagnostics11040732>.
- [52] M. Phillips, T.L. Bauer, H.I. Pass, A volatile biomarker in breath predicts lung cancer and pulmonary nodules, *J. Breath Res.* 13 (2019) 036013, <https://doi.org/10.1088/1752-7163/ab21aa>.
- [53] A.H. Sabry, O.I.D. Bashir, N.N. Ali, Y.M. Al Kubaisi, Lung disease recognition methods using audio-based analysis with machine learning, *belyon* (2024), <https://doi.org/10.1016/j.belyon.2024.e26218>.
- [54] D.J. DePianto, S. Chandriani, A.R. Abbas, G. Jia, E.N. N'Diaye, P. Caplazi, S. E. Kauder, S. Biswas, S.K. Karnik, C. Ha, Heterogeneous gene expression signatures correspond to distinct lung pathologies and biomarkers of disease severity in idiopathic pulmonary fibrosis, *Thorax* 70 (2015) 48–56, <https://doi.org/10.1136/thoraxjn1-2013-204596>.
- [55] Y. Kumai, Pathophysiology of fibrosis in the vocal fold: current research, future treatment strategies, and obstacles to restoring vocal fold pliability, *Int. J. Mol. Sci.* 20 (2019) 2551, <https://doi.org/10.3390/ijms20102551>.
- [56] N.M. Ralovsky, I.K. Lednev, Towards development of a novel universal medical diagnostic method: Raman spectroscopy and machine learning, *Chem. Soc. Rev.* 49 (2020) 7428–7453, <https://doi.org/10.1039/D0CS01019G>.
- [57] I. Minopoulou, A. Kleyer, M. Yalcin-Mutlu, F. Fagni, S. Kemenes, C. Schmidkonz, A. Atzinger, M. Pachowsky, K. Engel, L. Folle, Imaging in inflammatory arthritis: progress towards precision medicine, *Nat. Rev. Rheumatol.* 19 (2023) 650–665, <https://doi.org/10.1038/s41584-023-01016-1>.
- [58] S. Umirkazova, S. Ahmad, L.U. Khan, T. Whangbo, Medical image Super-Resolution for Smart healthcare applications: a comprehensive survey, *Inf. Fusion* (2023) 102075, <https://doi.org/10.1016/j.inffus.2023.102075>.
- [59] E. Kallvik, J. Savolainen, S. Simberg, Vocal symptoms and voice quality in children with allergy and asthma, *J. Voice* 31 (2017) 515. e519–e515. e514, <https://doi.org/10.1016/j.jvoice.2016.12.010>.
- [60] H.E. Hassen, A.M.A. Hasseba, Voice evaluation in asthma patients using inhaled corticosteroids, *The Turkish Journal of Ear Nose and Throat* 26 (2016) 101–108, <https://doi.org/10.5606/kbbhtis.2016.97940>.
- [61] M.M.D.A. Khan, P.P. Naval, R. Kulshreshtha, S. Venneti, A. Singh, VOICE-BASED monitoring OF COPD, *Chest* 160 (2021) A2173–A2174, <https://doi.org/10.1016/j.chest.2021.07.1920>. PlumX Metrics.

- [62] G.d.A.P. da Silva, T.D. Feltrin, F. dos Santos Pichini, C.A. Cielo, A.S. Pasqualoto, Quality of life predictors in voice of individuals with chronic obstructive pulmonary disease, *J. Voice* (2022), <https://doi.org/10.1016/j.jvoice.2022.05.017>.
- [63] A.J. Hoffman, R.A. Brintnall, A. von Eye, J. Cooper, J.K. Brown, The voice of postsurgical lung cancer patients regarding supportive care needs, *Lung Cancer Targets Ther.* (2014) 21–31, <https://doi.org/10.2147/LCTT.S59703>.
- [64] C.F. Lee, P.N. Carding, M. Fletcher, The nature and severity of voice disorders in lung cancer patients, *Logopedics Phoniatrics Vocology* 33 (2008) 93–103, <https://doi.org/10.1080/14015430701745997>.
- [65] R.J. Davis, B. Messing, N.M. Cohen, L.M. Akst, Voice quality and laryngeal findings in patients with suspected lung cancer, *Otolaryngology-Head Neck Surg. (Tokyo)* 166 (2022) 133–138, <https://doi.org/10.1177/01945998211008382>.
- [66] Y. Wakwaya, D. Ramdurai, J.J. Swigris, Managing cough in idiopathic pulmonary fibrosis, *Chest* 160 (2021) 1774–1782, <https://doi.org/10.1016/j.chest.2021.05.071>.
- [67] B.M. Lourenço, K.M. Costa, M. da Silva Filho, Voice disorder in cystic fibrosis patients, *PLoS One* 9 (2014) e96769, <https://doi.org/10.1371/journal.pone.0096769>.
- [68] M. Desjardins, H.S. Bonilha, The impact of respiratory exercises on voice outcomes: a systematic review of the literature, *J. Voice* 34 (2020) 648. e641–e648. e639, <https://doi.org/10.1016/j.jvoice.2019.01.011>.
- [69] D. Sánchez Morillo, A. Leon Jimenez, S.A. Moreno, Computer-aided diagnosis of pneumonia in patients with chronic obstructive pulmonary disease, *J. Am. Med. Inf. Assoc.* 20 (2013) e111–e117, <https://doi.org/10.1136/amiajnl-2012-001171>.
- [70] A. Rossi, B. Butorac-Petanjek, M. Chilos, B.G. Cosio, M. Flezar, N. Koulouris, J. Marin, N. Miculinic, G. Polese, M. Samarzija, Chronic obstructive pulmonary disease with mild airflow limitation: current knowledge and proposal for future research—a consensus document from six scientific societies, *Int. J. Chronic Obstr. Pulm. Dis.* (2017) 2593–2610, <https://doi.org/10.2147/COPD.S132236>.
- [71] A. Higham, A.M. Quinn, J.E.D. Cançado, D. Singh, The pathology of small airways disease in COPD: historical aspects and future directions, *Respiratory Research* 20 (2019) 1–11, <https://doi.org/10.1186/s12931-019-1017-y>.
- [72] R.L. Jones, P.B. Noble, J.G. Elliott, A.L. James, Airway remodelling in COPD: It's not asthma, *Respirology* 21 (2016) 1347–1356, <https://doi.org/10.1111/resp.12841>.
- [73] S. Huang, M.M. Vasquez, M. Halonen, F.D. Martinez, S. Guerra, Asthma, airflow limitation and mortality risk in the general population, *Eur. Respir. J.* 45 (2015) 338–346, <https://doi.org/10.1183/09031936.00108514>.
- [74] M. Phillips, N. Altorki, J.H. Austin, R.B. Cameron, R.N. Cataneo, R. Kloss, R. A. Maxfield, M.I. Munawar, H.I. Pass, A. Rashid, Detection of lung cancer using weighted digital analysis of breath biomarkers, *Clinica chimica acta* 393 (2008) 76–84, <https://doi.org/10.1016/j.cca.2008.02.021>.
- [75] D.J. DePianto, S. Chandriani, A.R. Abbas, G. Jia, E.N. N'Diaye, P. Caplazi, S. E. Kauder, S. Biswas, S.K. Karnik, C. Ha, Heterogeneous gene expression signatures correspond to distinct lung pathologies and biomarkers of disease severity in idiopathic pulmonary fibrosis, *Thorax* (2014), <https://doi.org/10.1136/thoraxjn1-2013-204596> thoraxjn1-2013-204596.
- [76] L.M. Cross, M.A. Matthay, Biomarkers in acute lung injury: insights into the pathogenesis of acute lung injury, *Crit. Care Clin.* 27 (2011) 355–377, <https://doi.org/10.1016/j.ccc.2010.12.005>.
- [77] K.K. Lella, A. Pja, Automatic diagnosis of COVID-19 disease using deep convolutional neural network with multi-feature channel from respiratory sound data: cough, voice, and breath, *Alex. Eng. J.* 61 (2022) 1319–1334, <https://doi.org/10.1016/j.aej.2021.06.024>.
- [78] C.T. Engineer, C.A. Perez, Y.H. Chen, R.S. Carraway, A.C. Reed, J.A. Shetake, V. Jakkamsetti, K.Q. Chang, M.P. Kilgard, Cortical activity patterns predict speech discrimination ability, *Nat. Neurosci.* 11 (2008) 603–608, <https://doi.org/10.1038/nrn.2109>.
- [79] A. Yellamsetty, G.M. Bidelman, Brainstem correlates of concurrent speech identification in adverse listening conditions, *Brain Res.* 1714 (2019) 182–192, <https://doi.org/10.1016/j.brainres.2019.02.025>.
- [80] S. Krishnan, Y. Athavale, Trends in biomedical signal feature extraction, *Biomed. Signal Process Control* 43 (2018) 41–63, <https://doi.org/10.1016/j.bspc.2018.02.008>.
- [81] G. Sharma, K. Umapathy, S. Krishnan, Trends in audio signal feature extraction methods, *Appl. Acoust.* 158 (2020) 107020, <https://doi.org/10.1016/j.apacoust.2019.107020>.
- [82] P. Harar, J.B. Alonso-Hernandez, J. Meksyska, Z. Galaz, R. Burget, Z. Smekal, Voice pathology detection using deep learning: a preliminary study, in: 2017 International Conference and Workshop on Bio-inspired Intelligence (IWobi), IEEE, 2017, pp. 1–4, <https://doi.org/10.1109/IWobi.2017.7985525>.
- [83] N.Q. Abdulmajeed, B. Al-Khateeb, M.A. Mohammed, Voice pathology identification system using a deep learning approach based on unique feature selection sets, *Expert Syst.* (2023) e13327, <https://doi.org/10.1111/exsy.13327>.
- [84] R. Jahangir, Y.W. Teh, H.F. Nweke, G. Mujtaba, M.A. Al-Garadi, I. Ali, Speaker identification through artificial intelligence techniques: a comprehensive review and research challenges, *Expert Syst. Appl.* 171 (2021) 114591, <https://doi.org/10.1016/j.eswa.2021.114591>.
- [85] R. Jahangir, Y.W. Teh, F. Hanif, G. Mujtaba, Deep learning approaches for speech emotion recognition: state of the art and research challenges, *Multimed. Tool. Appl.* (2021) 1–68, <https://doi.org/10.1007/s11042-021-10967-0>.
- [86] N. Roy, J. Barkmeier-Kraemer, T. Eadie, M.P. Sivasankar, D. Mehta, D. Paul, R. Hillman, Evidence-based clinical voice assessment: a systematic review, [https://doi.org/10.1044/1058-0360\(2012/12-0014](https://doi.org/10.1044/1058-0360(2012/12-0014), 2013.
- [87] L. Hansen, Y.P. Zhang, D. Wolf, K. Sechidis, N. Ladegaard, R. Fusaroli, A generalizable speech emotion recognition model reveals depression and remission, *Acta Psychiatr. Scand.* 145 (2022) 186–199, <https://doi.org/10.1111/acps.13388>.
- [88] N. Prodi, C. Visentin, A slight increase in reverberation time in the classroom affects performance and behavioral listening effort, *Ear Hear.* 43 (2022) 460–476, <https://doi.org/10.1097/AUD.0000000000000110>.
- [89] N. Soda, B.H. Rehm, P. Sonar, N.-T. Nguyen, M.J. Shiddiky, Advanced liquid biopsy technologies for circulating biomarker detection, *J. Mater. Chem. B* 7 (2019) 6670–6704, <https://doi.org/10.1039/C9TB01490J>.
- [90] B.M. Klinkhammer, T. Lammers, F.M. Mottaghy, F. Kiessling, J. Floege, P. Boor, Non-invasive molecular imaging of kidney diseases, *Nat. Rev. Nephrol.* 17 (2021) 688–703, <https://doi.org/10.1038/s41581-021-00440-4>.
- [91] P. Cao, Q. Zhang, S. Wu, M.A. Sullivan, Y. Huang, W. Gong, Y. Lv, X. Zhai, Y. Zhang, Baseline differences in metabolic profiles of patients with lung squamous cell carcinoma responding or not responding to treatment with nanoparticle albumin-bound paclitaxel (nab-paclitaxel), *Acta Mater. Medica* 2 (2023) 347–356, <https://doi.org/10.15212/AMM-2023-0027>.
- [92] S.A. Khanna, J.W. Nance, S.A. Suliman, Detection and monitoring of interstitial lung disease in patients with systemic sclerosis, *Curr. Rheumatol. Rep.* 24 (2022) 166–173, <https://doi.org/10.1007/s11926-022-01067-5>.
- [93] M.S. Wijsenbeek, C.C. Moor, K.A. Johannson, P.D. Jackson, Y.H. Khor, Y. Kondoh, S.K. Rajan, G.C. Tabaj, B.E. Varela, P. van der Wal, Home monitoring in interstitial lung diseases, *Lancet Respir. Med.* 11 (2023) 97–110, [https://doi.org/10.1016/S2213-2600\(22\)00228-4](https://doi.org/10.1016/S2213-2600(22)00228-4).
- [94] S.M. Swain, M. Nishino, L.H. Lancaster, B.T. Li, A.G. Nicholson, B.J. Bartholmai, J. Naidoo, E. Schumacher-Wulf, K. Shitara, J. Tsurutani, Multidisciplinary clinical guidance on trastuzumab deruxtecan (T-DXd)-related interstitial lung disease/pneumonitis—focus on proactive monitoring, diagnosis, and management, *Cancer Treat. Rev.* 106 (2022) 102378, <https://doi.org/10.1016/j.ctrv.2022.102378>.
- [95] M. Little, P. McSharry, S. Roberts, D. Costello, I. Moroz, Exploiting nonlinear recurrence and fractal scaling properties for voice disorder detection, *Nature Precedings* (2007) 1, <https://doi.org/10.1038/npre.2007.326.1>.
- [96] P. Gómez-Vilda, R. Fernández-Baillo, A. Nieto, F. Díaz, F.J. Fernández-Camacho, V. Rodellar, A. Alvarez, R. Martínez, Evaluation of voice pathology based on the estimation of vocal fold biomechanical parameters, *J. Voice* 21 (2007) 450–476, <https://doi.org/10.1016/j.jvoice.2006.01.008>.
- [97] A.A.S. Shaikh, M. Bhargavi, G.R. Naik, Unraveling the complexities of pathological voice through saliency analysis, *Comput. Biol. Med.* 166 (2023) 107566, <https://doi.org/10.1016/j.combiomed.2023.107566>.
- [98] R. Brehoormand, F. Almasgany, Optimal selection of wavelet-packet-based features using genetic algorithm in pathological assessment of patients' speech signal with unilateral vocal fold paralysis, *Comput. Biol. Med.* 37 (2007) 474–485, <https://doi.org/10.1016/j.combiomed.2006.08.016>.
- [99] A. Rao, E. Huynh, T.J. Royston, A. Kornblith, S. Roy, Acoustic methods for pulmonary diagnosis, *IEEE reviews in biomedical engineering* 12 (2018) 221–239, <https://doi.org/10.1109/RBME.2018.2874353>.
- [100] M.Z. Alam, A. Simionetti, R. Brillantino, N. Taylor, C. Grainge, P. Siribaddana, S. Nouraei, J. Batchelor, M.S. Rahman, E.V. Mancuso, Predicting pulmonary function from the analysis of voice: a machine learning approach, *Frontiers in digital health* 4 (2022) 750226, <https://doi.org/10.3389/fdgh.2022.750226>.
- [101] S. Xu, R.C. Deo, J. Soar, P.D. Barua, O. Faust, N. Homaira, A. Jaffe, A.L. Kabir, U. R. Acharya, Automated detection of airflow obstructive diseases: a systematic review of the last decade (2013–2022), *Comput. Methods Progr. Biomed.* (2023) 107746, <https://doi.org/10.1016/j.cmpb.2023.107746>.
- [102] R. Palaniappan, K. Sundaraj, N.U. Ahmed, Machine learning in lung sound analysis: a systematic review, *Biocybern. Biomed. Eng.* 33 (2013) 129–135, <https://doi.org/10.1016/j.bb.2013.07.001>.
- [103] S. Gonem, W. Janssens, N. Das, M. Topalovic, Applications of artificial intelligence and machine learning in respiratory medicine, *Thorax* (2020), <https://doi.org/10.1136/thoraxjn1-2020-214556>.
- [104] C. Poellabauer, N. Yadav, L. Daudet, S.L. Schneider, C. Busso, P.J. Flynn, Challenges in concussion detection using vocal acoustic biomarkers, *IEEE Access* 3 (2015) 1143–1160, <https://doi.org/10.1109/ACCESS.2015.2457392>.
- [105] K. Kaczmarek-Majer, G. Casalino, G. Castellano, M. Dominiak, O. Hrynewicz, O. Kamińska, G. Vessio, N. Díaz-Rodríguez, PLENARY: explaining black-box models in natural language through fuzzy linguistic summaries, *Inform. Sciences* 614 (2022) 374–399, <https://doi.org/10.1016/j.ins.2022.10.010>.
- [106] Y. Zhang, Y. Weng, J. Lund, Applications of explainable artificial intelligence in diagnosis and surgery, *Diagnostics* 12 (2022) 237, <https://doi.org/10.3390/diagnostics12020237>.
- [107] J. Laguarta, F. Hueto, B. Subirana, COVID-19 artificial intelligence diagnosis using only cough recordings, *IEEE Open Journal of Engineering in Medicine and Biology* 1 (2020) 275–281, <https://doi.org/10.1109/OJEMB.2020.3026928>.
- [108] A.A.A. Setio, F. Ciompi, G. Litjens, P. Gerke, C. Jacobs, S.J. Van Riel, M.M. W. Wille, M. Naqibullah, C.I. Sánchez, B. Van Ginneken, Pulmonary nodule detection in CT images: false positive reduction using multi-view convolutional networks, *IEEE Trans. Med. Imaging* 35 (2016) 1160–1169, <https://doi.org/10.1109/TMI.2016.2536809>.
- [109] Z. Zhang, E. Sejdic, Radiological images and machine learning: trends, perspectives, and prospects, *Comput. Biol. Med.* 108 (2019) 354–370, <https://doi.org/10.1016/j.combiomed.2019.02.017>.
- [110] P. Lakhani, B. Sundaram, Deep learning at chest radiography: automated classification of pulmonary tuberculosis by using convolutional neural networks, *Radiology* 284 (2017) 574–582, <https://doi.org/10.1148/radiol.2017162326>.

- [111] J. Ma, M.A. Guarnera, W. Zhou, H. Fang, F. Jiang, A prediction model based on biomarkers and clinical characteristics for detection of lung cancer in pulmonary nodules, *Translational oncology* 10 (2017) 40–45, <https://doi.org/10.1016/j.tranon.2016.11.001>.
- [112] A. Esteva, B. Kuprel, R.A. Novoa, J. Ko, S.M. Swetter, H.M. Blau, S. Thrun, Dermatologist-level classification of skin cancer with deep neural networks, *Nature* 542 (2017) 115–118, <https://doi.org/10.1038/nature21056>.
- [113] M. Havaei, A. Davy, D. Warde-Farley, A. Biard, A. Courville, Y. Bengio, C. Pal, P.-M. Jodoin, H. Larochelle, Brain tumor segmentation with deep neural networks, *Med. Image Anal.* 35 (2017) 18–31, <https://doi.org/10.1016/j.media.2016.05.004>.
- [114] G. Litjens, T. Kooi, B.E. Bejnordi, A.A.A. Setio, F. Ciompi, M. Ghafoorian, J.A. Van Der Laak, B. Van Ginneken, C.I. Sánchez, A survey on deep learning in medical image analysis, *Med. Image Anal.* 42 (2017) 60–88, <https://doi.org/10.1016/j.media.2017.07.005>.
- [115] A. Christe, A.A. Peters, D. Drakopoulos, J.T. Heverhagen, T. Geiser, T. Stathopoulou, S. Christodoulidis, M. Anthimopoulos, S.G. Mougiakakou, L. Ebner, Computer-aided diagnosis of pulmonary fibrosis using deep learning and CT images, *Invest. Radiol.* 54 (2019) 627, <https://doi.org/10.1097/RILI.0000000000000574>.
- [116] M. Rana, M. Bhushan, Machine learning and deep learning approach for medical image analysis: diagnosis to detection, *Multimed. Tool. Appl.* 82 (2023) 26731–26769, <https://doi.org/10.1007/s11042-022-14305-w>.
- [117] V. Hassija, V. Chamola, A. Mahapatra, A. Singal, D. Goel, K. Huang, S. Scardapane, I. Spinelli, M. Mahmud, A. Hussain, Interpreting black-box models: a review on explainable artificial intelligence, *Cognitive Computation* (2023) 1–30, <https://doi.org/10.1007/s12559-023-10179-8>.
- [118] Z. Obermeyer, B. Powers, C. Vogeli, S. Mullainathan, Dissecting racial bias in an algorithm used to manage the health of populations, *Science* 366 (2019) 447–453, <https://doi.org/10.1126/science.aax2342>.
- [119] D.S. Char, N.H. Shah, D. Magnus, Implementing machine learning in health care—addressing ethical challenges, *N. Engl. J. Med.* 378 (2018) 981, <https://doi.org/10.1056/NEJMp1714229>.
- [120] D. Castelvecchi, Can we open the black box of AI? *Nature News* 538 (2016) 20, <https://doi.org/10.1038/538020a>.
- [121] T. Evans, C.O. Retzlaaff, C. Geißler, M. Kargl, M. Plass, H. Müller, T.-R. Kiehl, N. Zerbe, A. Holzinger, The explainability paradox: challenges for xAI in digital pathology, *Future Generat. Comput. Syst.* 133 (2022) 281–296.
- [122] B.N. Patel, L. Rosenberg, G. Willcox, D. Baltaxe, M. Lyons, J. Irvin, P. Rajpurkar, T. Amrhein, R. Gupta, S. Halabi, Human-machine partnership with artificial intelligence for chest radiograph diagnosis, *NPJ digital medicine* 2 (2019) 111, <https://doi.org/10.1038/s41746-019-0189-7>.
- [123] S.I. Lambert, M. Madi, S. Sopka, A. Lenes, H. Stange, C.-P. Buszello, A. Stephan, An integrative review on the acceptance of artificial intelligence among healthcare professionals in hospitals, *NPJ Digital Medicine* 6 (2023) 111.
- [124] E.J. Topol, High-performance medicine: the convergence of human and artificial intelligence, *Nat. Med.* 25 (2019) 44–56, <https://doi.org/10.1038/s41591-018-0300-7>.
- [125] S. Benjamins, P. Dhunnoor, B. Meskó, The state of artificial intelligence-based FDA-approved medical devices and algorithms: an online database, *NPJ digital medicine* 3 (2020) 118, <https://doi.org/10.1038/s41746-020-00324-0>.
- [126] M. Langer, D. Oster, T. Speith, H. Hermanns, L. Kästner, E. Schmidt, A. Sesing, K. Baum, What do we want from Explainable Artificial Intelligence (XAI)?—A stakeholder perspective on XAI and a conceptual model guiding interdisciplinary XAI research, *Artif. Intell.* 296 (2021) 103473, <https://doi.org/10.1016/j.artint.2021.103473>.
- [127] E.H. Shortliffe, M.J. Sepúlveda, Clinical decision support in the era of artificial intelligence, *JAMA* 320 (2018) 2199–2200, <https://doi.org/10.1001/jama.2018.17163>.
- [128] H. Alfallah, S.B. Dias, A.H. Khandoker, K.R. Chaudhuri, L.J. Hadjileontiadis, A scoping review of neurodegenerative manifestations in explainable digital phenotyping, *npj Parkinson's Disease* 9 (2023) 49, <https://doi.org/10.1038/s41531-023-00494-0>.
- [129] A. Holzinger, C. Biemann, C.S. Pattichis, D.B. Kell, What do we need to build explainable AI systems for the medical domain? *arXiv preprint arXiv:1712.09923* (2017) <https://doi.org/10.48550/arXiv.1712.09923>.
- [130] E. Tjoa, C. Guan, A survey on explainable artificial intelligence (xai): toward medical xai, *IEEE Transact. Neural Networks Learn. Syst.* 32 (2020) 4793–4813, <https://doi.org/10.1109/TNNLS.2020.3027314>.
- [131] D.V. Carvalho, E.M. Pereira, J.S. Cardoso, Machine learning interpretability: a survey on methods and metrics, *Electronics* 8 (2019) 832, <https://doi.org/10.3390/electronics8080832>.
- [132] S. Ali, T. Abuhmed, S. El-Sappagh, K. Muhammad, J.M. Alonso-Moral, R. Confalonieri, R. Guidotti, J. Del Ser, N. Díaz-Rodríguez, F. Herrera, Explainable artificial intelligence (XAI): what we know and what is left to attain trustworthy artificial intelligence, *Inf. Fusion* 99 (2023) 101805, <https://doi.org/10.1016/j.inffus.2023.101805>.
- [133] A. Adadi, M. Berrada, Peeking inside the black-box: a survey on explainable artificial intelligence (XAI), *IEEE Access* 6 (2018) 52138–52160, <https://doi.org/10.1109/ACCESS.2018.2870052>.
- [134] A.F. Markus, J.A. Kors, P.R. Rijnbeek, The role of explainability in creating trustworthy artificial intelligence for health care: a comprehensive survey of the terminology, design choices, and evaluation strategies, *J. Biomed. Inf.* 113 (2021) 103655, <https://doi.org/10.1016/j.jbi.2020.103655>.
- [135] W. Samek, K.-R. Müller, Towards explainable artificial intelligence, in: *Explainable AI: Interpreting, Explaining and Visualizing Deep Learning*, 2019, pp. 5–22, <https://doi.org/10.1007/978-3-030-28954-6>.
- [136] C.M. Cutillo, K.R. Sharma, L. Foschini, S. Kundu, M. Mackintosh, K.D. Mandl, M.i. H.W.W.G.B.T.C.E.C.C.G.K.G.V.J.R.S.B.S.N. 1, Machine intelligence in healthcare—perspectives on trustworthiness, explainability, usability, and transparency, *NPJ digital medicine* 3 (2020) 47, <https://doi.org/10.1038/s41746-020-0254-2>.
- [137] T. Chen, C. Shang, P. Su, E. Keravnou-Papailiou, Y. Zhao, G. Antoniou, Q. Shen, A decision tree-initialised neuro-fuzzy approach for clinical decision support, *Artif. Intell. Med.* 111 (2021) 101986, <https://doi.org/10.1016/j.artmed.2020.101986>.
- [138] S.M. Lundberg, S.-I. Lee, A unified approach to interpreting model predictions, *Adv. Neural Inf. Process. Syst.* 30 (2017), <https://doi.org/10.48550/arXiv.1705.07874>.
- [139] M.T. Ribeiro, S. Singh, C. Guestrin, Why should i trust you?" Explaining the predictions of any classifier, in: *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, 2016, pp. 1135–1144, <https://doi.org/10.1145/2939672.2939778>.
- [140] A. Holzinger, G. Langs, H. Denk, K. Zatloukal, H. Müller, Causability and explainability of artificial intelligence in medicine, *Wiley Interdisciplinary Reviews: Data Min. Knowl. Discov.* 9 (2019) e1312, <https://doi.org/10.1002/widm.1312>.
- [141] R. Guidotti, A. Monreale, S. Ruggieri, F. Turini, F. Giannotti, D. Pedreschi, A survey of methods for explaining black box models, *ACM Comput. Surv.* 51 (2018) 1–42, <https://doi.org/10.1145/3236009>.
- [142] B. Alsinglawi, O. Alshari, M. Alorjani, O. Mubin, F. Alnajjar, M. Novoa, O. Darwish, An explainable machine learning framework for lung cancer hospital length of stay prediction, *Sci. Rep.* 12 (2022) 607, <https://doi.org/10.1038/s41598-021-04608-7>.
- [143] A. Rafferty, R. Ramaesh, A. Rajan, Transparent and clinically interpretable AI for lung cancer detection in chest X-rays, *arXiv preprint arXiv:2403.19444* (2024), <https://doi.org/10.48550/arXiv.2403.19444>.
- [144] S. Narteni, I. Bajardini, F. Braido, M. Mongelli, Explainable artificial intelligence for cough-related quality of life impairment prediction in asthmatic patients, *PLoS One* 19 (2024) e0292980, <https://doi.org/10.1371/journal.pone.0292980>.
- [145] T. Bashford, M.H.S. Lau, M.M. Huntly, M.N. Morgan, M.A. Iyenoma, T. Powell, B. Zeng, W. Treforest, AI classification of respiratory illness through vocal biomarkers and a bespoke articulatory speech protocol, *Int. J. Simulat. Syst. Sci. Technol.* 25 (2024), <https://doi.org/10.5013/IJSST.a.25.01.13>.
- [146] N.S. Haider, A. Behera, Computerized lung sound based classification of asthma and chronic obstructive pulmonary disease (COPD), *Biocybern. Biomed. Eng.* 42 (2022) 42–59, <https://doi.org/10.1016/j.bb.2021.12.004>.
- [147] A. Idrisoglu, Voice for decision support in healthcare applied to chronic obstructive pulmonary disease classification: a machine learning approach, *Blekinge Tekniska Högskola* (2024).
- [148] S.O. Ooko, D. Mukanyiligira, J.P. Munyampundu, J. Nsenga, Synthetic Exhaled breath data-based Edge AI model for the prediction of chronic obstructive pulmonary disease, in: *2021 International Conference on Computing and Communications Applications and Technologies (I3CAT)*, IEEE, 2021, pp. 1–6, <https://doi.org/10.1109/I3CAT53310.2021.9629420>.
- [149] V. Nathan, K. Vatanparvar, M.M. Rahman, E. Nemati, J. Kuang, Assessment of chronic pulmonary disease patients using biomarkers from natural speech recorded by mobile devices, in: *2019 IEEE 16th International Conference on Wearable and Implantable Body Sensor Networks (BSN)*, IEEE, 2019, pp. 1–4, <https://doi.org/10.1109/BSN.2019.8771043>.
- [150] V. Nathan, M.M. Rahman, K. Vatanparvar, E. Nemati, E. Blackstock, J. Kuang, Extraction of voice parameters from continuous running speech for pulmonary disease monitoring, in: *2019 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, IEEE, 2019, pp. 859–864, <https://doi.org/10.1109/BIBM47256.2019.8983115>.
- [151] L. Dai, X. Yang, H. Li, X. Zhao, L. Lin, Y. Jiang, Y. Wang, Z. Li, H. Shen, A clinically actionable and explainable real-time risk assessment framework for stroke-associated pneumonia, *Artif. Intell. Med.* 149 (2024) 102772, <https://doi.org/10.1016/j.artmed.2024.102772>.
- [152] J.D.S. Sara, D. Orbelo, E. Maor, L.O. Lerman, A. Lerman, Guess what We can Hear—novel voice biomarkers for the remote detection of disease, *Mayo Clin. Proc.* (2023), <https://doi.org/10.1016/j.mayocp.2023.03.007>. Elsevier.
- [153] J.D.S. Sara, E. Maor, B. Borlaug, B.R. Lewis, D. Orbelo, L.O. Lerman, A. Lerman, Non-invasive vocal biomarker is associated with pulmonary hypertension, *PLoS One* 15 (2020) e0231441, <https://doi.org/10.1371/journal.pone.0231441>.
- [154] R. Groh, Z. Lei, L. Martignetti, N.Y. Li-Jessen, A.M. Kis, Efficient and explainable deep neural networks for airway symptom detection in support of wearable health technology, *Advanced Intelligent Systems* 4 (2022) 2100284, <https://doi.org/10.1002/aisy.202100284>.
- [155] N. Sasikumar, M. Senthilkumar, Deep convolutional generative adversarial networks for automated segmentation and detection of lung adenocarcinoma using red deer optimization algorithm, *Inf. Technol. Control* 52 (2023) 680–692, <https://doi.org/10.5755/j01.itc.52.3.33659>.
- [156] J.S. Jennifer, T.S. Sharmila, A neurotrophic set approach on chest X-rays for automatic lung infection detection, *Inf. Technol. Control* 52 (2023) 37–52, <https://doi.org/10.5755/j01.itc.52.1.31520>.
- [157] N.u. Rehman, M.S. Zia, T. Meraj, H.T. Rauf, R. Damasevicius, A.M. El-Sherbeeny, M.A. El-Meligy, A self-activated cnn approach for multi-class chest-related COVID-19 detection, *Appl. Sci.* 11 (2021) 9023, <https://doi.org/10.3390/app1199023>.

- [158] A. Jaszcz, D. Potap, R. Damaševičius, Lung x-ray image segmentation using heuristic red fox optimization algorithm, *Sci. Program.* 2022 (2022) 1–8, <https://doi.org/10.1155/2022/4494139>.
- [159] T. Fawcett, An introduction to ROC analysis, *Pattern Recogn. Lett.* 27 (2006) 861–874, <https://doi.org/10.1016/j.patrec.2005.10.010>.
- [160] Z. Obermeyer, E.J. Emanuel, Predicting the future—big data, machine learning, and clinical medicine, *N. Engl. J. Med.* 375 (2016) 1216, <https://doi.org/10.1056/NEJMp1606181>.
- [161] Z. Naz, M.U.G. Khan, T. Saba, A. Rehman, H. Nobanee, S.A. Bahaj, An explainable AI-enabled framework for interpreting pulmonary diseases from chest radiographs, *Cancers* 15 (2023) 314, <https://doi.org/10.3390/cancers15010314>.
- [162] N. Das, S. Happaerts, I. Gyselinck, M. Staes, E. Derom, G. Brusselle, F. Burgos, M. Contoli, A.T. Dinh-Xuan, F.M. Franssen, Collaboration between explainable artificial intelligence and pulmonologists improves the accuracy of pulmonary function test interpretation, *Eur. Respir. J.* 61 (2023), <https://doi.org/10.1183/13993003.01720-2022>.
- [163] F. Doshi-Velez, B. Kim, Towards a rigorous science of interpretable machine learning, *arXiv preprint arXiv:1702.08608* (2017), <https://doi.org/10.48550/arXiv.1702.08608>.
- [164] V. Pitroda, M.M. Fouad, Z.M. Fadlullah, An explainable AI model for interpretable lung disease classification, in: 2021 IEEE International Conference on Internet of Things and Intelligence Systems (IoTIS), IEEE, 2021, pp. 98–103, <https://doi.org/10.1109/IoTIS53735.2021.9628573>.
- [165] N.A. Wani, R. Kumar, J. Bedi, DeepExplainer: an interpretable deep learning based approach for lung cancer detection using explainable artificial intelligence, *Comput. Methods Progr. Biomed.* 243 (2024) 107879, <https://doi.org/10.1016/j.cmpb.2023.107879>.
- [166] O. Wysocki, J.K. Davies, M. Vigo, A.C. Armstrong, D. Landers, R. Lee, A. Freitas, Assessing the communication gap between AI models and healthcare professionals: explainability, utility and trust in AI-driven clinical decision-making, *Artif. Intell.* 316 (2023) 103839, <https://doi.org/10.1016/j.artint.2022.103839>.
- [167] A. Glick, M. Clayton, N. Angelov, J. Chang, Impact of explainable artificial intelligence assistance on clinical decision-making of novice dental clinicians, *JAMIA open* 5 (2022), <https://doi.org/10.1093/jamiaopen/ooac031> ooac031.
- [168] N. Rane, S. Choudhary, J. Rane, Explainable artificial intelligence (XAI) in healthcare: interpretable models for clinical decision support, Available at: SSRN 4637897, <https://doi.org/10.2139/ssrn.4637897>, 2023.
- [169] S. Liu, A.B. McCoy, J.F. Peterson, T.A. Lasko, D.F. Sittig, S.D. Nelson, J. Andrews, L. Patterson, C.M. Cobb, D. Mulherin, Leveraging explainable artificial intelligence to optimize clinical decision support, *J. Am. Med. Inf. Assoc.* (2024), <https://doi.org/10.1093/jamia/ocae019> ocae019.
- [170] J. Yang, A.A. Soltan, D.A. Clifton, Machine learning generalizability across healthcare settings: insights from multi-site COVID-19 screening, *NPJ digital medicine* 5 (2022) 69, <https://doi.org/10.1038/s41746-022-00614-9>.
- [171] C. Meske, E. Bunde, J. Schneider, M. Gersch, Explainable artificial intelligence: objectives, stakeholders, and future research opportunities, *Inf. Syst. Manag.* 39 (2022) 53–63, <https://doi.org/10.1080/10580530.2020.1849465>.
- [172] F. Maleki, K. Ovens, R. Gupta, C. Reinhold, A. Spatz, R. Forghani, Generalizability of machine learning models: Quantitative evaluation of three methodological pitfalls, *Radiology, Artif. Intell.* 5 (2022) e220028, <https://doi.org/10.1148/ryai.220028>.
- [173] S.C.H. Yang, T. Folke, P. Shafto, Abstraction, validation, and generalization for explainable artificial intelligence, *Applied AI Letters* 2 (2021) e37, <https://doi.org/10.1002/ail.237>.
- [174] S. Khan, S. Tsutsumi, T. Yairi, S. Nakasuka, Robustness of AI-based prognostic and systems health management, *Annu. Rev. Control* 51 (2021) 130–152, <https://doi.org/10.1016/j.arcontrol.2021.04.001>.
- [175] N. Feldkamp, S. Strassburger, From explainable AI to explainable simulation: using machine learning and XAI to understand system robustness, in: Proceedings of the 2023 ACM SIGSIM Conference on Principles of Advanced Discrete Simulation, 2023, pp. 96–106, <https://doi.org/10.1145/3573900.3591114>.
- [176] L.H. Gilpin, D. Bau, B.Z. Yuan, A. Bajwa, M. Specter, L. Kagal, Explaining explanations: an overview of interpretability of machine learning, in: 2018 IEEE 5th International Conference on Data Science and Advanced Analytics (DSAA), IEEE, 2018, pp. 80–89, <https://doi.org/10.1109/DSAA.2018.00018>.
- [177] R. Caruana, Y. Lou, J. Gehrke, P. Koch, M. Sturm, N. Elhadad, Intelligent models for healthcare: Predicting pneumonia risk and hospital 30-day readmission, in: Proceedings of the 21th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining, 2015, pp. 1721–1730, <https://doi.org/10.1145/2783258.2788613>.
- [178] J. Wiens, E.S. Shenoy, Machine learning for healthcare: on the verge of a major shift in healthcare epidemiology, *Clin. Infect. Dis.* 66 (2018) 149–153, <https://doi.org/10.1093/cid/cix731>.
- [179] A.L. Beam, I.S. Kohane, Big data and machine learning in health care, *JAMA* 319 (2018) 1317–1318, <https://doi.org/10.1001/jama.2017.18391>.
- [180] A. Rajkomar, E. Oren, K. Chen, A.M. Dai, N. Hajaj, M. Hardt, P.J. Liu, X. Liu, J. Marcus, M. Sun, Scalable and accurate deep learning with electronic health records, *NPJ digital medicine* 1 (2018) 18, <https://doi.org/10.1038/s41746-018-0029-1>.
- [181] S.J. Pan, Q. Yang, A survey on transfer learning, *IEEE Trans. Knowl. Data Eng.* 22 (2009) 1345–1359, <https://doi.org/10.1109/TKDE.2009.191>.
- [182] K.M. Boehm, P. Khosravi, R. Vanguri, J. Gao, S.P. Shah, Harnessing multimodal data integration to advance precision oncology, *Nat. Rev. Cancer* 22 (2022) 114–126, <https://doi.org/10.1038/s41568-021-00408-3>.
- [183] A. Esteva, A. Robicquet, B. Ramsundar, V. Kuleshov, M. DePristo, K. Chou, C. Cui, G. Corrado, S. Thrun, J. Dean, A guide to deep learning in healthcare, *Nature medicine* 25 (2019) 24–29, <https://doi.org/10.1038/s41591-018-0316-z>.
- [184] V. Gulshan, L. Peng, M. Coram, M.C. Stumpe, D. Wu, A. Narayanaswamy, S. Venugopalan, K. Widner, T. Madams, J. Cuadros, Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs, *JAMA* 316 (2016) 2402–2410, <https://doi.org/10.1001/jama.2016.17216>.
- [185] H. Guan, M. Liu, Domain adaptation for medical image analysis: a survey, *IEEE (Inst. Electr. Electron. Eng.) Trans. Biomed. Eng.* 69 (2021) 1173–1185, <https://doi.org/10.1109/TBME.2021.3117407>.
- [186] M. Talo, U.B. Baloglu, Ö. Yıldırım, U.R. Acharya, Application of deep transfer learning for automated brain abnormality classification using MR images, *Cognit. Syst. Res.* 54 (2019) 176–188, <https://doi.org/10.1016/j.cogsys.2018.12.007>.
- [187] T. Shaikhina, N.A. Khovanova, Handling limited datasets with neural networks in medical applications: a small-data approach, *Artif. Intell. Med.* 75 (2017) 51–63, <https://doi.org/10.1016/j.artmed.2016.12.003>.
- [188] E. Vayena, A. Blasimme, I.G. Cohen, Machine learning in medicine: addressing ethical challenges, *PLoS Med.* 15 (2018) e1002689, <https://doi.org/10.1371/journal.pmed.1002689>.
- [189] A. Rajkomar, M. Hardt, M.D. Howell, G. Corrado, M.H. Chin, Ensuring fairness in machine learning to advance health equity, *Ann. Intern. Med.* 169 (2018) 866–872, <https://doi.org/10.7326/M18-1990>.
- [190] D. de la Iglesia, M. García-Remesa, A. Anguita, M. Muñoz-Mármol, C. Kulikowski, V. Maojo, A machine learning approach to identify clinical trials involving nanodrugs and nanodevices from clinicaltrials.gov, *PLoS One* 9 (2014) e110331, <https://doi.org/10.1371/journal.pone.0110331>.
- [191] W.N. Price, I.G. Cohen, Privacy in the age of medical big data, *Nat. Med.* 25 (2019) 37–43, <https://doi.org/10.1038/s41591-018-0272-7>.
- [192] S. Gerke, T. Minssen, G. Cohen, Ethical and legal challenges of artificial intelligence-driven healthcare, in: *Artificial Intelligence in Healthcare*, Elsevier, 2020, pp. 295–336.
- [193] S. Wachter, B. Mittelstadt, C. Russell, Counterfactual explanations without opening the black box: automated decisions and the GDPR, *Harv. JL & Tech.* 31 (2017) 841, <https://doi.org/10.48550/arXiv.1711.00399>.
- [194] A. Gatouillat, Y. Badr, B. Massot, E. Sejdíć, Internet of medical things: a review of recent contributions dealing with cyber-physical systems in medicine, *IEEE Internet Things J.* 5 (2018) 3810–3822, <https://doi.org/10.1109/JIOT.2018.2849014>.
- [195] R. Miotti, F. Wang, S. Wang, X. Jiang, J.T. Dudley, Deep learning for healthcare: review, opportunities and challenges, *Brief. Bioinform.* 19 (2018) 1236–1246, <https://doi.org/10.1093/bib/bbx044>.
- [196] T. Shaik, X. Tao, N. Higgins, L. Li, R. Gururajan, X. Zhou, U.R. Acharya, Remote patient monitoring using artificial intelligence: current state, applications, and challenges, *Wiley Interdisciplinary Reviews: Data Min. Knowl. Discov.* 13 (2023) e1485, <https://doi.org/10.1002/widm.1485>.
- [197] F. Lei, *Cross-cultural Adaptation and Validation of Lung Cancer Screening Health Belief Scale, University of California, Los Angeles*, 2022.
- [198] H.-C. Thorsen-Meyer, A.B. Nielsen, A.P. Nielsen, B.S. Kaas-Hansen, P. Toft, J. Schierbeck, T. Strom, P.J. Chmura, M. Heimann, L. Dybdahl, Dynamic and explainable machine learning prediction of mortality in patients in the intensive care unit: a retrospective study of high-frequency data in electronic patient records, *The Lancet Digital Health* 2 (2020) e179–e191, [https://doi.org/10.1016/S2589-7500\(20\)30018-2](https://doi.org/10.1016/S2589-7500(20)30018-2).
- [199] S.M. Lauritsen, M. Kristensen, M.V. Olsen, M.S. Larsen, K.M. Lauritsen, M. J. Jorgensen, J. Lange, B. Thiesson, Explainable artificial intelligence model to predict acute critical illness from electronic health records, *Nat. Commun.* 11 (2020) 3852, <https://doi.org/10.1038/s41467-020-17431-x>.
- [200] G. Mancioppi, E. Rovini, L. Fiorini, R. Zeghari, A. Gros, V. Manera, P. Robert, F. Cavallo, Mild cognitive impairment identification based on motor and cognitive dual-task pooled indices, *PLoS One* 18 (2023) e0287380, <https://doi.org/10.1371/journal.pone.0287380>.
- [201] N. Pfeuffer, L. Baum, W. Stammer, B.M. Abdel-Karim, P. Schramowski, A. M. Bucher, C. Hügel, G. Rohde, K. Kersting, O. Hinz, Explanatory interactive machine learning: establishing an action design research process for machine learning projects, *Business & Information Systems Engineering* 65 (2023) 677–701, <https://doi.org/10.1007/s12599-023-00806-x>.