From images to clinical insights: an educational review on radiomics in lung diseases

Cheryl Y. Magnin[1,2,5], David Lauer[1,2,5], Michael Ammeter[1,2,3] and Janine Gote-Schniering[1,2,4]

[1]Department of Rheumatology and Immunology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. [2]Lung Precision Medicine (LPM), Department for BioMedical Research (DBMR), University of Bern, Bern, Switzerland. [3]Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland. [4]Department of Pulmonary Medicine, Allergology and Clinical Immunology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. [5]Both authors contributed equally.

Corresponding author: Janine Gote-Schniering (janine.gote-schniering@unibe.ch)

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Radiomics can transform lung disease management by improving diagnosis, prognosis and treatment evaluation. This review discusses radiomics-based image analysis, addressing technical challenges and potential clinical applications in respiratory medicine. https://bit.ly/3VROg5m

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Abstract

Radiological imaging is a cornerstone in the clinical workup of lung diseases. Radiomics represents a significant advancement in clinical lung imaging, offering a powerful tool to complement traditional qualitative image analysis. Radiomic features are quantitative and computationally describe shape, intensity, texture and wavelet characteristics from medical images that can uncover detailed and often subtle information that goes beyond the visual capabilities of radiological examiners. By extracting this quantitative information, radiomics can provide deep insights into the pathophysiology of lung diseases and support clinical decision-making as well as personalised medicine approaches. In this educational review, we provide a step-by-step guide to radiomics-based medical image analysis, discussing the technical challenges and pitfalls, and outline the potential clinical applications of radiomics in diagnosing, prognosticating and evaluating treatment responses in respiratory medicine.

Educational aims

- To learn the fundamental principles of radiomics-based medical image analysis.
- To understand the technical challenges and pitfalls of radiomics and how to overcome them.
- To learn how radiomics can aid diagnosis, prognostication and treatment response evaluation in lung diseases.

Introduction

Radiological imaging, particularly (high-resolution) computed tomography ((HR)CT), is a cornerstone in the routine clinical workup of patients with suspected lung disease due to its unique advantage of enabling noninvasive, spatially and time-resolved visualisation of anatomical structures and pathological changes in the lung [1]. Despite being the clinical gold standard, visual and qualitative image evaluation by radiologists can be challenging, even for experienced professionals, leading to inter-observer variability and diagnostic uncertainty [2]. In addition, reliably detecting subtle changes during disease progression remains a significant challenge [3].

Advances in artificial intelligence (AI) and quantitative computational image analysis have given rise to the field of radiomics, which aims to address current limitations and complement traditional visual image analysis [4]. Introduced in 2012 [5], radiomics follows the principles of high-throughput omics applications in molecular biology (*e.g.* genomics, transcriptomics, proteomics) to extract large amounts of information from an organ or tissue in an unbiased, objective and reproducible manner [6]. The key benefit of radiomics lies in its ability to acquire quantitative tissue information noninvasively from

three-dimensional (3D) images, thereby preserving the full spatial context of the anatomically intact organ. In contrast, liquid and tissue biopsy-derived molecular omics techniques are invasive, require complex processing protocols and do not necessarily represent the pathophysiology of the entire organ. Radiomic features encompass a wide array of quantitative, mathematically defined (handcrafted) imaging characteristics that go beyond what is visible to the naked eye. These features are typically classified into histogram, texture, shape and wavelet categories. More recently, deep learning (DL)-derived radiomic features have emerged as a novel promising class of radiomic variables [7]. The result of the radiomic process is a digital disease fingerprint, which can be leveraged to develop models that support and enhance clinical decision-making, such as predicting or monitoring disease development (figure 1).

This review aims to educate readers on the principles, applications, challenges and future directions of conventional radiomics in lung imaging. DL-based approaches are not the focus of this review and are discussed elsewhere [8, 9].

Radiomics workflow

The process of radiomics analysis begins with the definition of the study aims and clinical question, which will establish the framework for selecting the optimal image modality and protocol, the region of interest (ROI) to be analysed, and ultimately the statistical analysis to build and evaluate the radiomic model. Prior to initiating the study, it is essential to obtain patient consent and ethical approval in accordance with local laws and regulations. Only once the study is clearly defined and regulatory approval is secured can data acquisition and analysis begin. The radiomic workflow typically involves several steps, which are divided into image acquisition, segmentation and processing, followed by feature extraction, selection, and finally, the radiomic model building and testing (figure 2). In the following sections, we provide a step-by-step guide on the principles of how to perform radiomics using CT as an example modality. We also discuss the technical challenges and pitfalls to consider in each step (table 1).

Step 1: image acquisition

Radiomics can in principle be performed with all radiological imaging modalities, for example, CT, magnetic resonance imaging (MRI) and positron emission tomography (PET), and is thus applicable to a wide range of clinical questions and lung diseases. The raw data source for radiomic features is the radiological image itself, making the selection of appropriate image acquisition parameters crucial to ensure the quality of the radiomic features. Important parameters to consider are the scan parameters (*e.g.* resolution, slice thickness, voltage, contrast), the patient's positioning (*e.g.* supine or prone position, inspiration or expiration) and the image reconstruction algorithms, all of which have been shown to greatly affect the reproducibility and robustness of radiomic features [10–13]. For best practice, these parameters should be consistent across the entire study cohort. In the case of prospective (multicentre) studies, the definition of standardised image acquisition protocols and reconstruction parameters can considerably improve study outcomes and reliability [14]. For retrospective studies, which often exhibit greater variability in the dataset, it is usually advisable to establish well-defined inclusion criteria and to perform

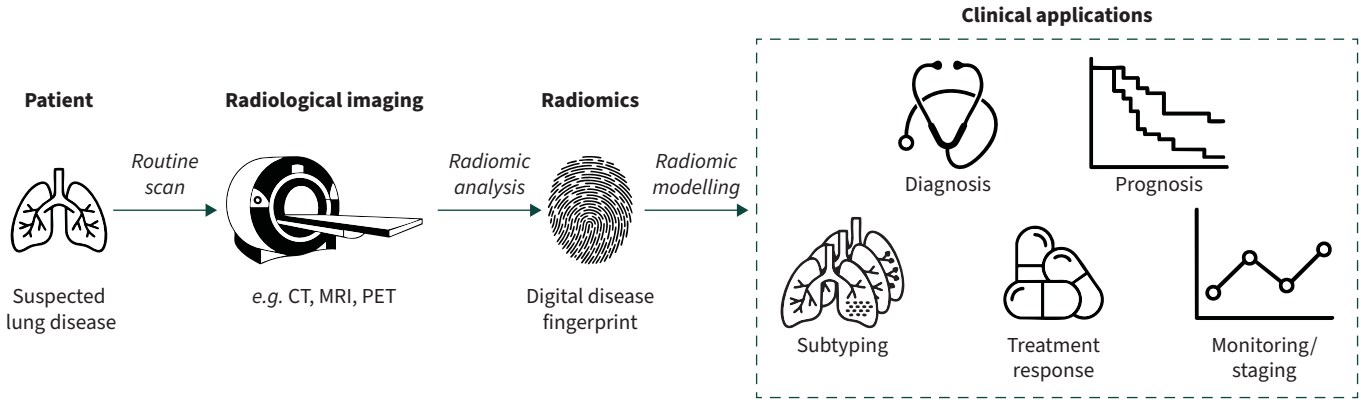

FIGURE 1 Principle of conventional radiomics and potential clinical applications. The imaging data from routine medical imaging scans in patients with suspected lung disease can be used to extract large amounts of quantitative image characteristics to generate a radiomics-based digital disease fingerprint. This information has the potential to support or complement clinical applications such as diagnosis, prediction/prognosis, disease subtyping and evaluation of treatment response as well as disease monitoring. CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography.

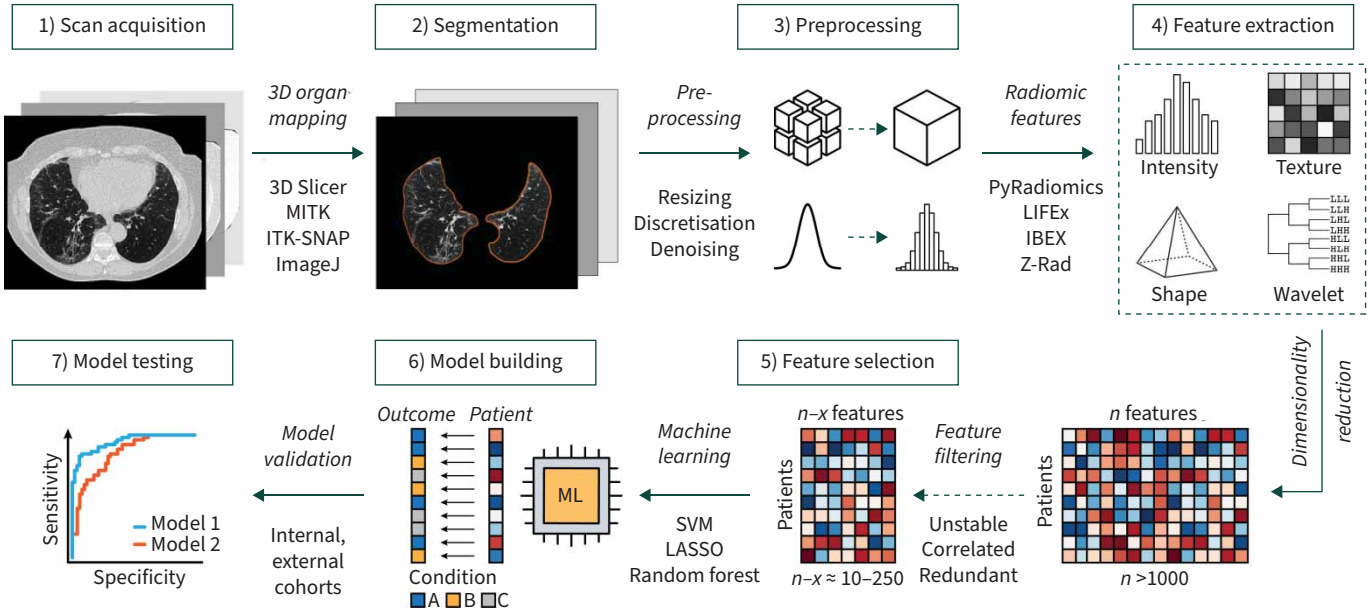

FIGURE 2 Schematic of the main radiomic workflow steps, including scan acquisition, image segmentation, radiomic feature extraction, radiomic feature selection, model building and testing. ML: machine learning; SVM: support vector machine; LASSO: least absolute shrinkage and selection operator.

post-imaging feature harmonisation using batch correction methods such as ComBat or resampling techniques to enhance dataset comparability [15, 16]. Special attention should be given to CT reconstruction parameters, including the reconstruction kernel, which can strongly influence the radiomic fingerprint [12]. The reconstruction kernel affects image output through adjustment of spatial resolution, noise and artefact reduction, tailoring the CT scan to specific diagnostic needs [11]. Typically, reconstruction kernels are divided into sharp (*e.g.* lung, bone) and smooth/soft (*e.g.* soft tissue, brain) kernels. Depending on the research question or the tissue type of interest, different kernels may be appropriate. For instance, when assessing the lung parenchyma, sharp kernels lead to clearer intensity details or textures of the lung tissue [12]. For lung diseases, Denzler *et al.* [12] recently found limited robustness of radiomic features between different kernel types. Thus, if a cohort includes datasets reconstructed with different kernels, their comparability should be carefully evaluated to ensure the reproducibility of radiomic features.

TABLE 1 Challenges and pitfalls in radiomic analyses and how to tackle them

Category	Challenge	Suggested solution
Image acquisition	Variability between scanners, acquisition parameters and reconstruction kernels affect radiomic features and can hamper real-world applicability of radiomic models	Apply predefined patient inclusion criteria to obtain comparable cohorts, standardise image acquisition protocols and/or apply feature harmonisation techniques
Image segmentation	Reader variability in the image segmentation process can impact radiomic outcomes	Use semi-automated or AI-based automated segmentation methods to reduce segmentation bias
Image preprocessing	Image preprocessing settings (resizing, binning, denoising) prior to feature extraction can impact radiomic outcomes	Subject all patient scans to the same preprocessing workflow Adhere to established best-practice guidelines (if available)
Feature extraction	Radiomic features are not fully standardised across different radiomic software tools	Compute radiomic features using IBSI-compliant tools
Model interpretability	Radiomic models can be difficult to interpret	Assess associations between radiomic features and molecular, histopathological and/or clinical data
Model generalisation	Radiomic model performance can be behind expectations in real-world application scenarios, putting their generalisability into question	Evaluate the model on external multicentre cohorts State the radiomics quality score (RQS) of your study Perform subsequent prospective studies to validate the findings

AI: artificial intelligence; IBSI: Image Biomarker Standardisation Initiative.

The medical images used for radiomics analysis are generally provided in DICOM (digital imaging and communications in medicine) format, and are accessible through a clinical picture archiving and communication system (PACS) or publicly available repositories, such as OSIC (Open Source Imaging Consortium) [17] or TCIA (The Cancer Imaging Archive) [18]. Relevant imaging parameters such as slice thickness, kernel and manufacturer are stored in the DICOM metadata and can be accessed. Other than DICOM, formats such as NIfTI (neuroimaging informatics technology initiative) or TIFF (tagged image file format) are typically also compatible with established radiomic software tools.

Step 2: image segmentation

To enable the acquisition of organ-specific radiomic features, the spatial location of the ROI, here the lung, has to be delineated within the scan data. This is achieved through the use of image segmentation tools. Common approaches include manual, semi-automated and fully automated DL-based segmentation algorithms. Importantly, segmentation results can affect radiomic outcomes, as feature calculation considers the full spatial dimension of the underlying structure [19]. In manual segmentation, readers define the outlines of the lung by hand, which is time-consuming and prone to inter- and intra-reader variability [20]. Semi-automated algorithms rely on thresholding, region growing and edge detection, and they represent a reliable and convenient tool to objectively delineate the lung structure. However, visual assessment and minor manual corrections are still usually necessary to ensure the segmented volume matches the lung's anatomical borders accurately. To ensure robustness, multiple operators should delineate the lung structure for the assessment of inter- and intra-reader variability by intraclass correlation coefficient (ICC) analysis [21]. Nonreproducible features should be excluded from follow-up analyses. More recently, DL-based segmentation methods, including nnU-Net models, which run without human intervention, have gained interest for avoiding observer bias and reducing hands-on time [22–24]. However, their use may still require expert implementation and fine-tuning depending on the specific use case [7]. Available open-source and proprietary image segmentation tools include 3D Slicer [25], ITK-SNAP [26], ImageJ/Fiji [27], MITK [28], and MIM software (MIM Software Inc., Cleveland, OH, USA).

Step 3: image processing

As described above, radiomic features depend on imaging acquisition parameters and segmentation quality [10]. Different processing steps, such as resizing, resampling and discretisation, help to assimilate and homogenise the images. The goal is to produce consistent and comparable radiomic features from different scanners and acquisition protocols, as is common in a hospital setting [14]. For 3D radiomic feature calculation, the segmented region is resized into isotropic voxels with identical dimensions in all three axes. Maintaining a consistent voxel size is important to increase comparability between different cohorts and reproducibility of radiomic features [29]. No clear guidelines on the appropriate voxel size are currently available. Different voxel sizes may be suitable depending on the research question, and it is advisable to consult the literature for similar studies to determine the optimal size [30–32]. Range re-segmentation and intensity outlier filtering are techniques to remove outliers from the segmented tissue that fall out of the predefined range of grey levels or intensities measured in Hounsfield units. Another step is discretisation of values, specifically intensities in the ROI. The discretisation is required to make feature calculation feasible [33]. Three parameters can be adjusted: range, bin number and/or bin size. The range is usually kept from the original image. Depending on the research question, the bin size, mainly used for CT scans, or the number of bins, often used in MRI images, can be adjusted. The bin size refers to the interval width used to group continuous intensity values of the image into discrete categories or bins. This acts as a smoothing filter on the data distribution. However, the optimal bin size or number has not yet been clearly established. A bin size that is too small makes distinguishing between information and noise difficult, while a bin size that is too generous carries the risk of losing relevant information [34].

Step 4: feature extraction

The segmented and resized structure can now be used for feature extraction. Radiomic features are based on mathematically defined formulas and can be extracted with dedicated radiomic software. Several open-source radiomics programs are available, including PyRadiomics [35], IBEX [36], LIFEx [37] and Z-Rad (https://github.com/medical-physics-usz/z-rad). It is important to note that feature extraction implementations, including formulas and nomenclature, may differ between software packages, potentially leading to nonidentical results, which have raised concerns about the cross-platform reproducibility of radiomic features [38].

To address these reproducibility issues and facilitate clinical use of radiomic studies, the Image Biomarker Standardisation Initiative (IBSI) [14], and recently IBSI 2 [39], have been initiated. The IBSI aims to standardise radiomic feature definition, nomenclature and extraction, thereby enhancing the comparability of findings across studies and providing standards for objective and reproducible feature generation [39].

For best practice, it is thus highly recommended to follow the IBSI guidelines and use IBSI-compliant radiomics software.

Radiomic features can be divided into different classes: intensity or histogram, texture, shape and wavelet-transformed features [6]. Histogram features describe first-order statistics of the distribution of grey-level voxel intensities (*e.g.* mean, skewness, kurtosis), thus quantifying tissue intensity characteristics. Texture features (*e.g.* entropy, contrast, grey-level co-occurrence matrix, grey-level run-length matrix) provide information on the spatial distribution and inter-relationship between neighbouring voxel intensities, thus describing tissue heterogeneity [40]. Shape features describe the geometry of the ROI, for example, shape, size and surface properties of the tissue. Wavelet features essentially represent histogram, texture and shape characteristics following the application of mathematical filters (*e.g.* wavelet or Gaussian filters), which denoise the imaging data and enhance specific imaging patterns, effectively generating additional analysable information [39]. Unlike handcrafted radiomic features, which are computed on user-defined image segmentations, DL-derived radiomic features utilise convolutional neural networks (CNN) for automated feature extraction directly from images without previous segmentation and the need of pre-defining features [7].

Step 5: feature selection

Hundreds or, depending on the application of statistical filters in the software package used, thousands of features can be calculated from a single ROI. Reducing the dimensionality of this feature space by selecting a set of nonredundant and highly relevant features is essential to mitigate overfitting and build a clinically meaningful model that generalises to perform well on never-before-seen patient data. At this point in the radiomics workflow, feature numbers usually exceed the sample size [41], which is often small in radiomic studies especially when studying rare diseases. This situation of computational imbalance tends to exacerbate overfitting, as learned rules are more based on noise rather than on patterns.

In practice, various methods can be used to reduce feature dimensionality and select radiomic features. At first, simple methods based on a defined threshold can be applied to filter out features, involving for instance elimination of non-stable radiomic features (*e.g.* identified in ICC analysis addressing segmentation variability) and filtering of low variance features to improve model performance and interpretability. Additional filter methods commonly used and which have been shown to perform well in radiomics contexts are analysis of variance (ANOVA) and minimum redundancy maximum relevance [42]. Alternative approaches such as principal component analysis (PCA) transform the feature space into low-dimensional representations, identifying the most informative features. Since the remaining feature subsets might still be collinear and correlating, it is advisable to perform correlation-based filtering removing highly correlated features [34]. Other methods are based on machine learning and rank or select variables, *i.e.* features based on importance metrics, keeping only the most informative features (*e.g.* in random forest algorithms, recursive feature elimination and least absolute shrinkage and selection operator (LASSO) regression). It is important to note that no common guidelines on feature selection methods have been established [42]. Typically, different approaches need to be tested to identify the most suitable method. The methodology used should be precisely outlined in a step-by-step manner, including reporting of intermediate results to improve reproducibility and clinical utility of radiomic studies.

Step 6: model building

The selected radiomic features can be used to build statistical models that facilitate clinical decision-making, such as predicting disease outcome. The choice of the model largely depends on the research question and is further strongly related to the availability of labelled (*i.e.* the target variable is known) or unlabelled data (*i.e.* no pre-assigned output label).

In unsupervised learning, hidden structures or patterns are searched in the data without pre-existing labels. Techniques such as PCA or clustering algorithms, including k-means, hierarchical or consensus clustering, are suitable for identifying homogeneous subgroups within the data (*e.g.* patient subtypes). These subgroups can then be associated with clinical data, thereby enabling disease characterisation and patient (endo-)phenotyping.

In supervised learning, the model is trained to learn rules to optimally predict the target variable from the input data (*e.g.* disease status) and thus needs labelled data. LASSO regression, support vector machines (SVM) and ensemble learning methods such as random forest and gradient boosting are popular choices for building radiomic models. The process of selecting and training machine learning models for radiomics applications has been reviewed extensively in the literature [43, 44]. In the case of DL, the individual tasks of feature extraction, reduction and model building are optimised jointly and automatically during model training [45].

Step 7: model testing and validation

The final and key aspect in the radiomic workflow is the validation of the model. To evaluate the model performance (*i.e.* how well it generalises to new data) the available data should be split into training and internal validation sets, possibly by simple holdout (usually in an 80:20 ratio) or k-fold cross-validation, and most importantly tested on an independent, external validation cohort. Study cohorts should ideally be collected from multiple centres and populations. It is important to assure that target variable classes (*e.g.* disease status or presence) are equally represented in both training and internal validation data. Class-imbalances can be addressed by randomising the internal data before splitting them into training and test sets. Various metrics can be used to evaluate the performance of the model. For instance, in classification problems, where equally likely classes are discriminated, area under the receiver operating characteristic curve (AUC) with sensitivity and specificity are commonly used, while precision and recall are suitable for class-imbalanced problems and multilabel classification tasks. Furthermore, uncertainty measures, such as 95% confidence intervals or standard deviations, should be reported.

The predictive performance of the developed radiomic models should be compared in univariate and multivariate analyses with the current gold standard non-radiomics-based methods to prove its added clinical value. External validation is essential to assess the generalisability and hence clinical utility of a model. However, only 6% of published results have been externally validated [46]. For best practice, the model should finally be validated in a prospectively collected cohort.

To enhance reproducibility and transparency of the radiomics workflow, the Radiomics Quality Score (RQS) was proposed to assess the quality and clinical utility of radiomic studies [47]. The RQS evaluates the study design, image acquisition protocols, statistical data processing, validation of model performance and open science policies using a points system. Although these quality criteria were collectively issued as a means of best practice to support the scientific community, systematic reviews on radiomic studies in lung cancer found overall low RQS, particularly regarding standardisation of radiomic workflow, external validation and prospective study registration [48, 49]. Recently, the METhodological RadiomICs Score (METRICS) was introduced as another tool to assess the quality of radiomics studies and guide the development of clinically useful radiomic models. METRICS provides a flexible evaluation framework for various study designs, ranging from handcrafted radiomic features to DL-based approaches [50]. Adherence to METRICS or RQS can enhance study quality and facilitate translation of radiomics research into clinical use.

Radiomics in lung diseases

Over the past decade, radiomics has gained significant attention for its potential to support clinical decision-making in respiratory disorders. While lung cancer has been the primary focus of radiomic research due to its high incidence and mortality, its potential and success has sparked interest in applying radiomic techniques to other, non-neoplastic respiratory disorders, such as interstitial lung diseases (ILDs), COPD and COVID-19-associated pneumonia. In the following sections, we provide an overview of radiomic studies across various lung diseases, highlighting its potential for diagnosis and staging, outcome prediction, and treatment response evaluation (table 2).

Neoplastic lung diseases

One of the earliest and most significant radiomic studies focused on lung cancer, the most common and leading cause of cancer-related death worldwide. In 2014, Aerts *et al*. [40] conducted a comprehensive radiomic analysis involving over 700 patients with non-small cell lung cancer (NSCLC). This study identified a four-feature radiomic signature predictive of overall survival, demonstrating the prognostic power of radiomic features. In addition, the study revealed that radiomic features are not only associated with cancer outcomes but also linked to tumour gene expression profiles. Since then, numerous studies have highlighted the potential of radiomics for lung cancer prognostication [51–55]; studies have also shown its potential for diagnosis and staging [56–58], evaluation of therapy response [59–62], as well as noninvasive assessment of tumour biology [63–65], including mutation status [66–68] and histopathological subtypes [62, 69, 70].

For cancer diagnosis, several studies have demonstrated the effectiveness of CT-based radiomics in accurately differentiating benign from malignant pulmonary nodules and predicting the risk for malignancy in lung cancer screening programmes [56, 71–73], facilitating early detection and targeted intervention by reducing false-positive results and unnecessary treatments.

Another promising clinical application of radiomics is predicting the response to anti-cancer therapies from pretreatment radiomic data. Recent studies have shown the potential of both whole-tumour and subregional

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TABLE 2 Examples of recent radiomic studies in lung diseases categorised by the field of application

Study, year	Disease	Image modality	Cohort size	Outcome variable	Model building	Model validation	Model AUC	Study description and application
Diagnosis								
Hunter [56], 2023	Lung nodules	CT	810	Diagnosis by radiologist	LASSO regression	Internal and external	0.78	Developed a small nodule radiomics-predictive-vector (SN-RPV) model to assist in lung cancer diagnosis
Amudala Puchakayala [87], 2023	COPD	CT	8878	Diagnosis by PFT	CatBoost	Internal	0.90	Developed a texture- and shape-driven radiomic model for accurate detection of COPD in high- and low-dose CT scans
Wu [57], 2020	Adenocarcinoma	CT	291	Diagnosis by pathologist	Random forest	External	0.98	Developed a radiomic model based on ground-glass and solid features for accurate diagnosis of invasive lung adenocarcinoma in part-solid nodules
Prognostication								
Perez-Johnston [58], 2022	Adenocarcinoma	CT	219	RSS, genomics, histopathology	Consensus clustering	N/A	N/A	Identified associations between radiomic features and genomic, histopathological and clinical outcome variables in stage I lung adenocarcinoma patients
Martini [81], 2021	SSc-ILD	HRCT	60	ILD-GAP staging	Logistic regression	Internal	0.98	Developed a texture-based radiomic model to detect ILD and distinguish disease stages in patients with SSc-ILD
Ryan [83], 2019	Sarcoidosis	HRCT	151	Pulmonary function and Scadding stage	Linear/ functional regression	N/A	N/A	Identified associations between radiomic features and lung function as well as disease stage in sarcoidosis patients
Disease characterisation and staging								
Chen [62], 2023	NSCLC	CE-CT	194	NSCLC diagnosis, PD-L1 expression	Linear regression	Internal and external	0.70	Developed a composite lung cancer immunotherapy-radiomics prediction vector (LCI-RPV) model for prediction of disease-free survival in NSCLC patients
Schniering [31], 2022	SSc-ILD	HRCT	156	Progression-free survival	Cox regression	External	0.71[#]	Developed a quantitative radiomic risk score (qRISSc) for prediction of progression-free survival in SSc-ILD patients
Wu [88], 2020	COVID-19	CT	492	Poor outcome (clinical records)	LASSO+ Fine–Gray regression	Internal and external	0.86	Developed a model (CrrScore) combining radiomic signature (RadScore) and clinical factors to predict poor outcome in COVID-19 patients on early disease onset CT scans
Treatment response								
Lauer [32], 2024	PF-ILD	HRCT	19	Pulmonary function change	K-means clustering	N/A	N/A	Identified delta radiomic signatures correlating with disease-related biological pathway activity in experimental fibrosing ILD, and demonstrated their potential to accurately reflect response to antifibrotic treatment with nintedanib in PF-ILD patients
Peng [59], 2024	NSCLC	CT	264	PD-L1 status, TMB score, progression-free survival	SVM	Internal and external	0.86	Developed a subregional radiomics model (SRRM) for prediction of response to immunotherapy treatment in NSCLC patients, and progression-free survival
Cousin [60], 2023	NSCLC	CE-CT	188	Clinical treatment response status, overall survival	Random forest	Internal and external	0.80	Developed a delta radiomics model for identification of patients with advanced NSCLC who presented a clinical benefit from PD-1/PD-L1 immunotherapy early in the treatment course

AUC: area under the curve; CT: computed tomography; HRCT: high-resolution computed tomography; CE-CT: contrast enhanced computed tomography; ILD-GAP: interstitial lung disease-gender-age-physiology; SVM: support vector machine; NSCLC: non-small cell lung cancer; TMB: tumour mutational burden; SSc-ILD: systemic sclerosis-associated interstitial lung disease; PF-ILD: progressive fibrosing interstitial lung disease; RSS: recurrence-specific survival; LASSO: least absolute shrinkage and selection operator; PFT: pulmonary function test. [#]: C-index (AUC equivalent in Cox regression).

CT radiomic signatures for predicting response in patients with NSCLC undergoing PD-1/PD-L1 immunotherapy [59, 62]. Delta radiomics, which quantifies the feature variation between two or more imaging time points, has emerged as a method to predict and quantify treatment response in various types of cancer, including lung cancer [60, 74–76]. Cousin *et al.* [60] recently showed that delta radiomics could identify patients with advanced NSCLC who presented a clinical benefit from PD-1/PD-L1 immunotherapy early in the treatment course.

Both tumour histology and mutation status are critical determinants for patient prognosis and treatment choice. The key value of radiomics lies in the integrated in-depth analysis of tissue phenotypes across spatial scales conveying not only morphological but also biological tissue information and it can therefore serve as a virtual tissue biopsy [65]. Previously, radiomic features have been found to be predictive of tumour histology. For instance, Wu *et al*. [70] showed that radiomics can reliably predict histopathological NSCLC subtypes. Furthermore, a recent multicentre study showed that a radiomic model combining both ground-glass and solid CT radiomic features of part-solid nodules accurately differentiated invasive from noninvasive or minimally invasive adenocarcinoma subtypes, improving upon current diagnostic methods [57]. Radiogenomics investigates the association between macroscopic radiomic and microscopic gene expression features to define the underlying genetic basis of imaging phenotypes and derive noninvasive imaging surrogates for genetic profiles. Numerous studies have shown the capability of radiomics in predicting tumour mutation status noninvasively [68, 77–79]. For example, Rios Velazquez *et al*. [68] showed that radiomics is able to predict EGFR and KRAS mutations in lung adenocarcinoma. Furthermore, many studies have established links between radiomic features and underlying biological pathways [58, 62–64, 80], including immune activation and cell proliferation. However, while strong correlative relationships between radiomics and tissue-derived molecular omics have been well documented, establishing a direct causal relationship remains a complex area of active research.

Non-neoplastic lung diseases

Although radiomics first found use for oncological (lung) diseases, it is generally applicable to any type of disease that shows phenotypic changes on a radiological level. For lung diseases, comprehensive studies have been conducted for fibrosing ILDs [31, 32, 81–85], COPD [86, 87], and COVID-19-related pneumonia [88–91].

Early and accurate diagnosis is also crucial for non-neoplastic lung diseases to achieve the best possible outcomes. Amudala Puchakayala *et al.* [87] conducted one of the largest studies for early COPD detection in smokers (n=8878), demonstrating highly reliable diagnosis in combined (radiomics, lung function and demographics) models on both standard- and low-dose CT scans. Refaee *et al*. [82] further showed that radiomic models can be applied for disease subtyping in ILD, accurately differentiating idiopathic pulmonary fibrosis (IPF) from non-IPF ILD cases, thereby outperforming visual evaluation by trained clinicians. Interestingly, their models achieved the highest performance when combining both handcrafted and DL-derived radiomic features. Further evidence for the potential of radiomics for lung disease subtyping was provided by Liu *et al*. [90], who established a combined clinico-radiomic model for accurate diagnosis of COVID-19 pneumonia and differentiation from other non-COVID-19-related pneumonia, thereby improving upon established clinical and CO-RADS (COVID-19 reporting and data system) evaluations.

Disease characterisation and staging are important factors in patient management, especially for highly heterogeneous disorders such as ILDs. Martini *et al.* [81] evaluated texture-based radiomic features for distinguishing between ILD-GAP (gender, age, physiology) stages 1 and 2 in systemic sclerosis (SSc)-associated ILD patients, showing that radiomics can detect indicators of disease severity not recognisable by visual analysis. Moreover, Qin *et al.* [85] developed a nomogram, *i.e.* a graphical mathematical tool that can be used for clinical decision-making, to assess the severity and predict the mortality of patients with connective tissue disease-associated ILD. Similar to other studies, their model achieved the highest accuracy when combining radiomic and clinical factors. In the case of pulmonary sarcoidosis, Ryan *et al*. [83] identified associations between radiomics and lung function and demonstrated their usefulness for disease staging.

Besides diagnosis and disease characterisation, individual prognostication plays a crucial role in determining the optimal patient management strategy. Wu *et al*. [88] proposed a clinico-radiomic risk-stratification model that predicts poor outcome in COVID-19 patients at early disease stages, allowing clinicians to adopt precautionary measures for high-risk individuals. Schniering *et al*. [31] developed a composite radiomic risk score (qRISSc) that allows prediction of progression-free survival in patients with SSc-ILD. Notably, evaluation of their radiomic model in an *in vivo* lung fibrosis model demonstrated a

strong correlation with pro-fibrotic pathway activity, thus highlighting the potential of radiomics to serve as a surrogate marker of molecular readouts. Makimoto *et al*. [86] established a clinico-radiomic model consisting of texture-based radiomics, as well as demographic and lung function measurements to identify individuals at risk of progression to COPD.

For many non-neoplastic lung diseases, identification of patients who benefit from therapy can be difficult with established methods such as pulmonary function tests, clinical assessment and radiologic evaluation. Based on the premise that radiomics reflects underlying tissue pathophysiological information, radiomics holds promise to function as a treatment monitoring and response stratification tool. Utilising a quantitative lung fibrosis score, built upon histogram-derived features, Kim *et al*. [92] demonstrated the value of CT-derived quantitative outcomes for treatment response evaluation in IPF patients. More recently, Lauer *et al*. [32] demonstrated that delta radiomic signatures, which were associated with extracellular matrix remodelling in an *in vivo* lung fibrosis model, stratified patients with progressive fibrosing (PF)-ILD undergoing anti-fibrotic treatment according to lung function decline and hence their treatment response.

Taken together, these studies demonstrate that radiomics has shown promise to transform lung disease management by improving diagnosis, prognosis and treatment response evaluation.

Future perspective

The future potential of radiomics lies in its integration with multimodal patient data and other omics biomarkers (figure 3) [93]. This includes clinical (*e.g.* patient demographics, history, lung function, laboratory tests), histopathological and molecular data (*e.g.* proteomics, transcriptomics, genomics) from peripheral body fluids (*e.g.* blood, bronchoalveolar lavage fluid) and/or tissues. In oncology, multivariate machine learning models that combine radiomics with clinical, genomic and pathological information have already demonstrated improved predictive performance and led to a deeper understanding of disease mechanisms [94–96].

Building associations between macroscopic radiomics and microscopic molecular features derived from genomic, transcriptomic or proteomic profiling can aid in defining the underlying biological basis of radiomic profiles and deriving noninvasive imaging surrogates for molecular profiles. The ability to assess distinct pathways and cellular activities noninvasively from standard-of-care lung scans could pave the way towards

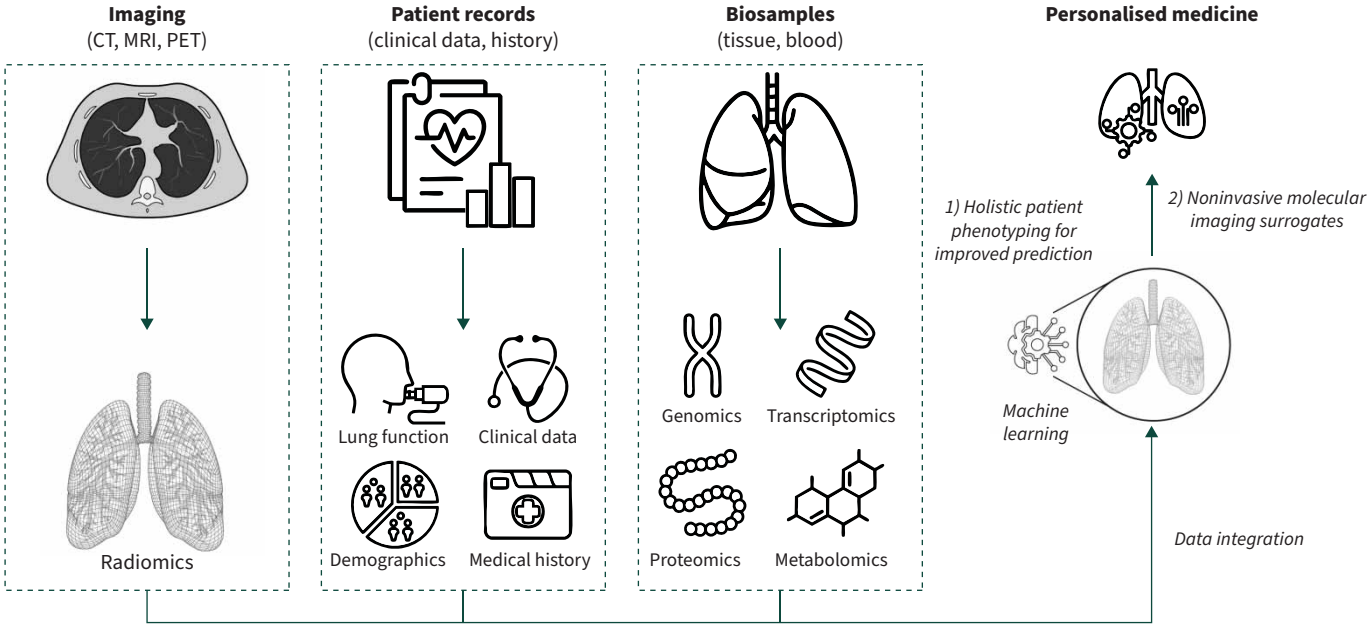

FIGURE 3 Future perspective of radiomics. Multimodal integration could enhance diagnosis, prognosis and treatment response prediction. Linking radiomic and molecular features could further help to functionally characterise radiomic phenotypes and derive noninvasive radiomic surrogates for molecular profiles, paving the way for digital molecular disease fingerprints ("virtual biopsy"). CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography.

digital molecular disease fingerprints overcoming the limitations of invasive tissue biopsies [32]. This could enable noninvasive, molecular-targeted patient stratification for targeted therapies and precision medicine.

As research in this field continues to evolve, addressing the current technical challenges (table 1) and automating the radiomic workflow in user-friendly interfaces will be crucial for the successful integration of radiomics into clinical practice. Implementing open science and fostering collaboration between key stakeholders – including clinicians, biologists, radiologists, medical physicists, data scientists and patients – will be essential. Sharing data across multiple centres and building up international image data repositories will play a critical role in developing robust and generalisable radiomic models [97]. A good example of such collaborative efforts is the European Respiratory Society Clinical Research Collaboration named PROFILE.net (PROgressive Fibrosing Lung diseasEs.network) [98], which aims to build a multidisciplinary network to facilitate the development of clinically applicable decision support tools for diagnosis and prognostication in patients with ILD. In addition, establishing clear ethical and regulatory frameworks, ensuring patient safety, confidentiality and compliance with existing healthcare standards, will be crucial for use of AI in respiratory medicine.

In conclusion, radiomics is poised to play a pivotal role in the future of precision medicine of respiratory diseases. By harnessing the power of advanced imaging technologies, AI and integrative omics approaches, radiomics can provide deeper insights into disease mechanisms, improve patient stratification and guide personalised treatment strategies. Addressing current challenges through standardisation, regulatory frameworks and collaborative efforts will be key to realising the full potential of radiomics in clinical practice.

Key points

- Radiomics describes the quantitative computational analysis of standard-of-care radiological images, resulting in digital disease fingerprints that can aid clinical decision-making and complement visual radiological evaluation.
- Standardisation and optimisation of the radiomics workflow is crucial to facilitate translation of radiomic models into clinical practice.
- Radiomic features were found to reflect the underlying pathophysiology of the organ/tissue of interest, therefore holding great potential to serve as a noninvasive organ-scale virtual tissue biopsy.

Self-evaluation questions

1. What are radiomic features, and how do they differ from traditional image analysis in radiology?
2. Which radiological imaging modalities are suitable for radiomics?
3. Describe the general workflow to establish a radiomic model starting at the radiological image acquisition. Is it possible to include information other than radiomics in your model?
4. Which technical issues are associated with radiomics and need to be considered for clinical implementation?
5. Provide examples of how radiomics can be used in lung diseases for diagnosis, prognosis, characterisation and treatment response prediction.

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Suggested answers

1. Radiomic features are quantitative and computationally describe shape, intensity, texture and wavelet characteristics that can uncover detailed and often subtle information in medical images beyond the visual capabilities of radiological examiners. Conventional radiological evaluation is based on qualitative and visual examination criteria, which rely on the radiologist's visual interpretation. Both approaches have unique strengths and may complement each other to aid radiological evaluations and patient outcomes.
2. Radiomics is applicable to the majority of radiological imaging modalities, including both two- and three-dimensional scans. The most widely used modalities include CT, MRI, and PET. Less frequently used modalities include ultrasound, radiography and single-photon emission computed tomography. Each technique has unique advantages depending on the clinical question, underlying type of tissue and the anatomical ROI.
3. Building a radiomic model follows a systematic approach ensuring the extraction of meaningful radiomic features from medical images and their translation into clinically relevant information. The main steps include: 1) image acquisition, 2) image segmentation, 3) image preprocessing, 4) radiomic feature extraction, 5) radiomic feature selection (*i.e.* dimensionality reduction), 6) model building, and 7) model testing and validation. Notably, radiomic features can be combined with clinical and other disease-related markers for improved model performance.
4. Radiomics holds great promise to advance the field of medical imaging by improving patient outcomes and enabling personalised medicine. However, several technical issues need to be addressed to allow for the integration of radiomics into clinical practice. The most pertinent challenges include the following. 1) To standardise or harmonise imaging acquisition and reconstruction protocols in order to ensure reproducibility and consistency of the resulting radiomic features across different scanners and settings. 2) To advance automated algorithms to reliably segment organs/tissues of interest, thereby reducing segmentation bias and hands-on time. 3) To establish standardised guidelines on image preprocessing to increase radiomic feature reproducibility and study comparability. 4) To standardise radiomic feature nomenclature and calculation algorithms. 5) To adhere to best practice radiomic guidelines, validate models on external cohorts, and report on quality measures (*e.g.* RQS) to increase generalisability of results and credibility.
5. **Diagnosis**: Radiomics can enhance the accuracy of diagnosis by quantifying subtle disease characteristics invisible to the naked eye. For example, radiomics can assist in differentiating benign from malignant tumours in small lung nodules, accurately detect COPD in low-dose CT scans, or identify invasive lung adenocarcinoma in part-solid nodules. **Prognosis**: Radiomics can be used to predict patient outcomes by identifying imaging markers associated with disease progression or survival rates. Examples include the development of radiomic models to predict the progression and overall survival in SSc-ILD and NSCLC patients, respectively, and a model to predict the outcome of COVID-19-related pneumonia.
   Characterisation: Radiomics can help differentiate disease subtypes and stages, and even serve as a surrogate for molecular and clinical phenotypes. Examples include the classification of disease stages in SSc-ILD patients, the association of radiomic features with pulmonary function in sarcoidosis patients, and the associations with genomic, histopathological and clinical outcome variables in lung cancer patients.
   Treatment response: Radiomics can function as a predictor or surrogate of how patients will respond to treatments. Studies demonstrated that delta radiomic features (*i.e.* change of feature between two or more time points) reflected the response to antifibrotic treatment in PF-ILD patients, and showed great potential to early identify NSCLC patients benefiting from immunotherapy. In addition, radiomics was shown to predict response to immunotherapy in NSCLC patients.