imbio

LUNG DENSITY ANALYSIS™

v5.1.1

SOFTWARE USER MANUAL

Imbio Document Number: UM-164 v1.0

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1 Introduction

1.1 Scope of Manual

This user manual was written for the Imbio CT Lung Density Analysis™ (LDA) Software. Guidance for using the Imbio Core Computing Platform (CCP) is not included in this document.

The Imbio CCP includes a cloud platform which is a subscription-based, scalable software-as-a-service product which allows customers to run computationally-intensive image algorithms in the cloud, on infrastructure maintained by Imbio. The Imbio CCP is also available as an on-premise hosted product, targeted at those organizations which desire to keep their image data in-house. This enterprise version of CCP provides a system by which customers can still benefit from image processing job automation, while integrating with native DICOM tools and workflows. The Imbio CCP with cloud and enterprise options is a separate product developed by Imbio.

1.2 Product Overview

Imbio's CT Lung Density Analysis™ Software is a set of image post-processing algorithms designed to help radiologists and pulmonologists determine the location and extent of tissue damage in patients with COPD, by providing visualization and quantification of areas with abnormal CT tissue density. The LDA Software runs automatically on the input CT series, with no user input or intervention. The LDA Software consists of the Functional Assessment and the Inspiration Assessment.

The Imbio CT Lung Density Analysis™ Functional Assessment performs image segmentation, registration, thresholding, and classification on CT images of human lungs. The Functional Assessment performs the four algorithms sequentially on two CT scans (inspiration and expiration lung datasets).

The purpose of the segmentation algorithm is to automatically identify and separate the two lungs from the rest of the body. An optional feature of the segmentation algorithm is the ability to label the individual lobes of the lungs. The purpose of the registration algorithm is to map one lung image onto another, so that a pairwise mapping comparison between lung images can be done. The purpose of the thresholding algorithm is to identify voxels above and below a given threshold for the inspiration series and to identify voxels above and below a given threshold for the expiration series. The purpose of the classification algorithm is to compare inspiration and expiration lung images that have been registered and have gone through thresholding. Further description of this component is in the Functional Assessment section of the document (Section 4.1).

The Imbio CT Lung Density Analysis™ Inspiration Assessment is a component for users who only acquire inspiration datasets. The Inspiration Assessment performs image segmentation and thresholding on an inspiration CT scan. Volumetric percentages of the lung tissue below the user configurable threshold are calculated. Further description of this component is in the Inspiration Assessment section of the document (Section 4.2).

The Imbio CT Lung Density Analysis™ Software utilizes DICOM format high resolution CT lung inspiration and expiration data sets as input to the software. The specific requirements are given in the Scan Protocol section of this document (Section 2.2).

The output provided by the Imbio CT Lung Density Analysis™ Software is a RGB lung image series in DICOM format and a DICOM summary report (Encapsulated-PDF SOPClass or Secondary Capture Image Storage SOPClass).

1.3 Hardware Requirements

Hardware requirements for running LDA are as follows:

1.3.1 Inspiration Assessment LDA

- 4 CPU Cores
- 8 GB RAM
- 50 GB

1.3.2 Functional Assessment LDA

- 8 CPU Cores
- 32 GB RAM
- 50 GB

1.4 Contact Imbio

Imbio Inc.
1015 Glenwood Avenue Floor 4
Minneapolis, MN 55405
United States
www.imbio.com

2 Indications for Use and Requirements

The Imbio CT Lung Density Analysis™ Software provides reproducible CT values for pulmonary tissue, which is essential for providing quantitative support for diagnosis and follow up examinations. The Imbio CT Lung Density Analysis™ Software can be used to support the physician in the diagnosis and documentation of pulmonary tissue images (e.g., abnormalities) from CT thoracic datasets. Three-D segmentation and isolation of sub-compartments, volumetric analysis, density evaluations, and reporting tools are provided.

2.1 Intended Users

The intended user base for the Imbio CT Lung Density Analysis™ Software is Pulmonologists, Radiologists, and Radiology Technicians under the supervision of a Pulmonologist or Radiologist.

2.2 Scan Protocol Requirements

The ability to segment and register the scans is dependent on the resolution of the scan; therefore, it is important to analyze the scan resolution. The resolution can be determined by assessing the acquisition protocols from the DICOM data as well as visually assessing the images themselves. The DICOM data provides information on the basic acquisition parameters used and can be compared with Imbio's required parameters. The scan should also be visually assessed to ensure that there are not contraindications or missing information.

2.2.1 Imbio Acquisition Parameters

The Imbio CT Lung Density Analysis™ Software will not generate outputs for scans with acquisition parameters that do not meet the requirements as outlined in the Table 1 below. In addition, Imbio CT Lung Density Analysis™ Software will not generate outputs unless DICOM Patient Image Orientation (DICOM tag 0020,0037) can be rounded to [+/-1,0,0,0,+/-1,0].

DICOM Tag	Name	Required Value
(0008,0060)	Modality	CT
(0028,0030)	Pixel Spacing	$\leq$ 2.0 x 2.0 mm^2
(0018,9305)	Revolution Time	$\leq$ 1.0 s (if present)
N/A	Slice Spacing	$\leq$ 3.0 mm
(0018,0050)	Slice Thickness	$\leq$ 3.0 mm
N/A	Field of View	$\geq$ 10.0 x 10.0 x 20.0 cm^3
N/A	Number of Slices	$\leq$ 1024
(0010,1010)*	Patient's Age	$\geq$ 18 (if present)
(0028,1054)	Rescale Type	HU (if present)
(0018,0010)	Contrast Bolus Agent	Not present

Table 1: Required CT Scan Parameters

* Patient's Age will be calculated from PatientBirthDate (0010,0030) and StudyDate (0008,0020) if (0010,1010) is not populated.

Recommended Convolution Kernels

⚠ Imbio recommends using only inputs of images reconstructed with non-edge enhancing kernels. Sharp kernels are not appropriate for Imbio CT Lung Density Analysis™ Software. Below is a list of kernels that are acceptable for use.

GE: standard
PHILIPS: B
TOSHIBA: FC01
SIEMENS: B31f, B35f, Qr40, Qr40d, Br40, Br40d

Below is a list of kernels that are not recommended for Imbio CT Lung Density Analysis™ Software. If an image with a kernel in the following list (or not in the list of approved kernels) is passed to the software, the analysis will run but a warning will be issued and displayed in the report footer.

GE: bone, bone+, edge, lung
PHILIPS: D
TOSHIBA: FC30, FC31, FC50, FC51, FC52, FC53, FC54, FC55, FC56, FC57, FC58, FC59, FC80, FC81, FC82
SIEMENS: Kernels belonging to the 'Head' family (e.g. H31f), vascular or pediatric groups (e.g. Bp31f, e.g. Bv31f), or having sharpness greater than or equal to 60 (e.g. B60f).

2.2.2 Imbio Recommended Protocol

For the Imbio CT Lung Density Analysis™ Software, Imbio recommends a 3D volumetric acquisition with pixel spacing less than 1 mm and slice thickness less than 3.0 mm for both inspiration and expiration scans. The images should be reconstructed with a soft tissue/smoothing algorithm without high spatial frequency enhancement. Imbio Lung Density Analysis™ Imbio does not recommend a contrast enhanced acquisition. Example protocols are listed in the table below. The protocols accepted by Imbio CT LDA Software are not limited to the scanners and protocols in Table 2, but the acquisition parameters should be similar. Failure to observe the recommended scan protocol could limit the software's ability to properly segment and register lungs.

Scanner Make	GE	SIEMENS	PHILIPS 64
Scanner Model	VCT 64	Sensation-64	64 Slice
Scan Type	VCT Helical	Spiral	Axial Helix
Rotation Time (S)	See mA	0.5	0.5
Det. Configuration	64 x 0.625	64 x 0.6	64 x 0.625
Pitch	1.375	1.1	0.923
Speed (mm/rot)	13.75	21.1	0.5
kVp	120	120	120
mA	400 @ 0.5s (Ins) 100 @ 0.5s (Exp)	Effective mAs: 200 (Ins) Effective mAs: 50 (Exp)	200 mAs (Ins) 50 mAs (Exp)
Dose modulation	Off	CARE Dose 4D Off	Off
Reconstruction			
Algorithm	Standard	B31f	B
Thickness (mm)	0.625	0.75	0.9
Interval (mm)	0.625	0.5	0.45
DFOV(cm)	Lungs*	Lungs*	Lungs*

Table 2: Recommended protocol for full-dose CT scans

*Reconstruction field of view should encompass the widest diameter of the lung.

2.2.3 Imbio Recommended Protocol for Low-dose Images

Due to increased image noise, it is especially important that images from low-dose CT scans should be reconstructed using a soft tissue/smoothing kernel OR an iterative reconstruction algorithm. If available, fully iterative reconstructions should be used with the Imbio post-processing filter turned OFF. If iterative reconstructions are not available, the post-processing filter should be turned ON to reduce the effects of noise on LDA measures. For more information on Imbio's post-processing filter, see section 4.3.1. An example low-dose protocol is shown in the Table 3 below. Please note that the software operator should be familiar with the effects of x-ray dose and slice-thickness on LDA measurements.

Scanner Make	GE	SIEMENS	PHILIPS 64
Scanner Model	VCT 64	Sensation-64	64 Slice
Scan Type	VCT Helical	Spiral	Axial Helix
Rotation Time (S)	See mA	0.5	0.5
Det. Configuration	64 x 0.625	64 x 0.6	64 x 0.625
Pitch	1.375	1.1	0.923
Speed (mm/rot)	13.75	21.1	0.5
kVp	120	120	120
mA	80-160 @ 0.5s (Ins) 100 @ 0.5s (Exp)	Effective mAs: 40-80 (Ins) Effective mAs: 50 (Exp)	40-80 mAs (Ins) 50 mAs (Exp)
Dose modulation	On	On	On
Reconstruction			
Algorithm	Standard*	B31f*	B*
Thickness (mm)	2-3	2-3	2-3
Interval (mm)	2	2	2
DFOV(cm)	Lungs‡	Lungs‡	Lungs‡

Table 3: Recommended protocol for low-dose CT scans

*Fully iterative reconstructions are recommended if available. Otherwise, LDA should be run with the "Filter-ON" option to reduce the impact of quantum noise.

‡ Reconstruction field of view should encompass the widest diameter of the lung.

2.2.4 Breathing Instructions

The patient should be coached to achieve and hold full inspiration, with several practice attempts prior to scan acquisition. If the patient is unable to hold their breath for the scan period, such as the case for a severely ill patient, a faster scanner needs to be utilized. The scan protocol remains the same for expiratory scanning. The patient should be coached for full expiration holds and be capable of retaining the hold for the duration of the scan. Below is a suggested script of how to coach a patient for the inspiratory and expiratory scans.

Breathing Instructions Script
Inspiratory CT
For the first part of this scan, I am going to ask you to take a deep breath in and hold it
First let's practice:
    Take a deep breath in
    Hold it - do not breathe
    Breathe and relax
Take a deep breath in
    Let it out
Take a deep breath in
    Let it out
Breath all the way IN...IN...IN...
    Keep holding your breath - DO NOT BREATHE!
    At end of scan: Breathe and relax
Start scan at bottom of lungs; end at top of lungs

Expiratory CT
For the second part of this scan, I am going to ask you to breathe out and hold it out.
First let's practice:
    Take a deep breath in
    Breath out and hold it - do not breathe
    Breathe and relax
Take a deep breath in
    Let it out
Take a deep breath in
    Let it out
Take another deep breath in
    Let it out and hold it out
    Keep holding your breath - DO NOT BREATHE!
    At end of scan: Breathe and relax
Start scan at bottom of lungs; end at top of lungs

3 Quality Assessment

The scan quality and possible contraindications must be assessed before executing the Imbio CT Lung Density Analysis™ Software.

3.1 Scan Quality

Lung density values from a CT scan may vary due to different acquisition parameters thus causing variation in LDA results. Sources of variation include but are not limited to dose, reconstruction kernel, slice thickness, scanner calibration and respiratory cycle. Users should not compare LDA results across acquisitions with different acquisition parameters.

Refer to Table 4 for scan quality issues that may generate errors:

Scan Quality Component	Result
Noise	The airway segmentation in a noisy scan may fail if the lung tissue is not distinguishable from other tissue.
Missing slices	If slices within the tissue containing lung are missing, the resultant Lung Density Analysis™ map and report could be inaccurate.
Entire lung not included	If scan does not fully contain the lungs, segmentation of the lungs will fail.
Intubation	If the patient is intubated during the scan, the lung segmentation will fail.
Motion Artifact	If the patient does not execute a full breath hold and/or moves during the scan, motion artifacts may be present in the scan that will cause segmentation and/or registration to fail or affect the classification results.

Table 4: Potential causes of image processing and analysis failures

3.2 Contraindications

This software is designed to run on any input data that satisfies the criteria in Section 2.2.1 and does not perform any additional quality checking. **It is the responsibility of the medical professional who is using the application (i.e., the Radiologist, Pulmonologist or Radiology Technologist) to ensure that the input data is of adequate quality.** If the input data is not of adequate quality, the application's results should be disregarded. Imbio's CT Lung Density Analysis™ Software is not intended for use as a primary tool for disease detection and/or diagnosis.

3_QUALITY ASSESSMENT

Areas of the lung where comorbidities or anomalous pathologies are present may give unpredictable results, and the Lung Density Analysis™ results should be interpreted with a knowledge of the location and extent of any comorbidities or anomalous pathologies.

Lung Density Analysis™ was designed and validated on adult lungs and has not been validated on children. The software is not cleared by the FDA for use in a pediatric setting.

4 Components

The Imbio CT Lung Density Analysis™ Software has two components for processing data, the Functional Assessment and the Inspiration Assessment. Output Reports and Assessment Maps generated by Imbio CT Lung Density Analysis™ Software are DICOM compatible.

NOTE: The outputs from each component of Imbio CT LDA Software have the following DICOM tags populated according to the Coordinated Universal Time (UTC):

DICOM Tag	Name
(0008,0021)	Series Date
(0008,0023)	Content Date
(0008,0031)	Series Time
(0008,0033)	Content Time
(0040,a032)	Observation Date Time

4.1 Functional Assessment

The Functional Assessment takes two CT scans as input, an inspiration and an expiration scan. The process performs segmentation on both images and then registers the inspiration image to the expiration. Thresholding is applied to the images and then each voxel pair is classified. The process outputs an RGB image with color overlay classifying each lung voxel as either "Normal", "Functional Low Density Area" or "Persistent Low Density Area". In addition, a Functional Assessment Report is generated summarizing results, for more details see Section 5.5.

4.2 Inspiration Assessment

The Inspiration Assessment takes one CT scan as input, a full inspiration scan. The process performs segmentation on the inspiration image and then thresholding. The output image is an RGB image with color overlay classifying lung voxels above and below the inhalation threshold. In addition, a report is generated summarizing results.

4.3 Optional Features

Both Functional Assessment and Inspiration Assessment have the following additional features for processing; filtering, adjustable thresholding, selectable report format and personalizing report with an institution logo.

Inspiration Assessment has two optional features not available for Functional Assessment: adjustable percentile and an additional LungMap™ report.

Both Functional and Inspiration Assessment have the option of labeling and computing lung density statistics on the upper right, middle right, lower right, upper left, and lower left lung lobes. Alternatively, Functional and Inspiration Assessment can be run with segmentation of only the left and right lungs, in which case the statistics will be computed over three equally spaced vertical partitions of each lung (i.e. "thirds"). The quality of the lobar or lungs-only segmentation must be assessed by the user visually using RGB output image (see Section 8.3).

Important Note: If Imbio CT LDA Software is installed with the Imbio Cloud Platform or the Imbio Enterprise Platform, user preferences for optional features are set only at installation.

4.3.1 Filtering

If both RevolutionTime (0018,9305) and XRayTubeCurrent (0018,1151) are present in the input metadata and the average series mAs is < 80 mAs, a noise reducing filter is applied to the lung datasets before classification. Filtering options can be configured at installation or upon request.

There are tradeoffs between the two options, unfiltered and filtered. Filtering before classification allows for robust classification of low signal-to-noise ratio (SNR) images (high specificity) at the expense of missing small areas of low attenuation (reduced sensitivity). Not filtering before classification allows for identification of small areas of low attenuation areas (high sensitivity) at the expense of small erroneous classifications of low attenuation areas in noisy images (reduced specificity).

The user is allowed to determine if filtering is appropriate for classification for the input images based on the patient of interest and the noise level of the scans.

4.3.2 Adjustable Thresholds

The inhalation threshold and exhalation threshold (if applicable) may be determined by the user and provided as inputs to the LDA Software. Values for thresholds are given in Hounsfield units (HU) and are allowed in the range of -1024 HU and 0 HU.

The default inhalation threshold is -950 HU and the default exhalation threshold is -856 HU (Nature Medicine, Volume 18, Number 11, November 2012, Pages 1711-1715.).

4.3.3 Report Format

The format of the output report can be selected by the user. The two SOPClasses currently supported for the output report are Encapsulated PDF Report and Secondary Capture Image Storage. The user may select either one of these formats to be generated or both formats to be generated as output. The default format for the report is Encapsulated PDF Report.

4.3.4 Institution Logo

The LDA summary reports display the Imbio logo in the upper left corner of the report. This logo can be replaced with an alternate logo from the user's institution. The maximum logo size is 1.4 cm height by 6.0 cm width. Minimum resolution is 300 dots per inch (dpi). Given these requirements, either square or horizontal shaped logos are recommended, vertical oriented (tall) logos will not elegantly fit in the report header. The logo format can be either PNG or JPEG.

4.3.5 Multiple Thresholds (Insp. Assessment Feature Only)

Inspiration Assessment can be configured such that the RGB output image can display multiple thresholds as different color overlays. The Report will only report statistics on the primary thresholds provided to the algorithm as reflected in the report. In Figure 1, the color scheme has been configured as follows:

RED - **Below -950 HU**
YELLOW - **Between -950 and -900 HU**
GREEN - **Between -900 and -875 HU**
PURPLE - **Betwen -700 and -200 HU**
BLUE - **Above -200 HU**

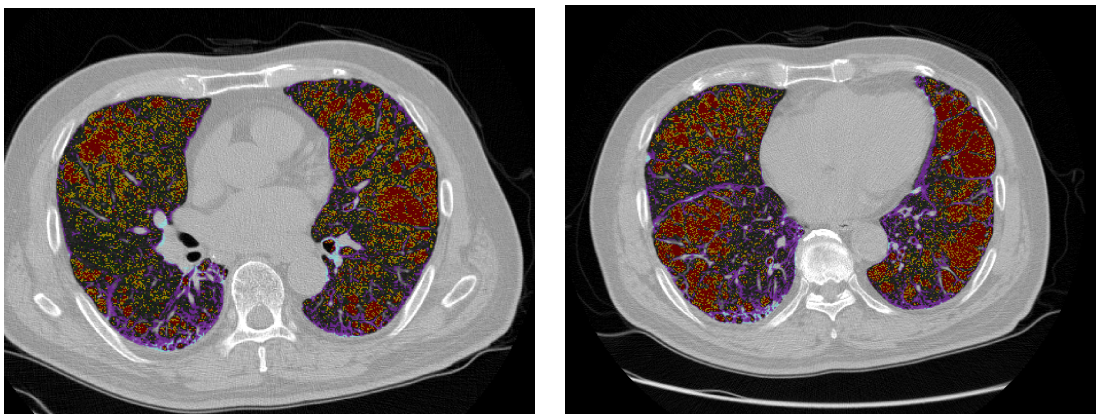


Figure 1: Slices of Inspirational Assessment Map with multiple thresholds configured.

4.3.6 Additional LungMap Report (Insp. Assessment Feature Only)

The Inspiration Assessment can output an additional report, the LungMap™ Report. This report simplifies the Inspiration Assessment Report results and is available in two versions: one that contains information about general benefits of smoking cessation and another that contains peer-reviewed, published statistics that may help motivate former smokers to stay off tobacco. For more information on the contents of the LungMap™ Report, see Section 6.5.

4.3.7 DICOM Structured Report (SR)

The user can optionally select to include the output of a DICOM structured report (SR) document that includes the algorithm's quantitative metrics. The DICOM SR document has a SOP class of Enhanced SR (1.2.840.10008.5.1.4.1.1.88.22). The DICOM SR ContentSequence (0040,A730) metadata tag encodes the structured content.

5 Functional Assessment

The Functional Assessment generates two main outputs; a Functional Assessment Map and a Functional Assessment Report.

5.1 Inputs

The LDA Functional Assessment takes two CT scans from the same exam as input, one taken during inspiration and the other during expiration. The input datasets must have the same Patient Name, Patient ID, and Study ID. The user may also input an inspiration HU threshold, an expiration HU threshold, select the registration direction and/or turn filtering off. For more information on optional inputs, see Section 4.3.

5.2 Functional Assessment Map

The Functional Assessment Map is a DICOM Secondary Capture Image with voxel data that is the original expiration image with an RGB overlay. The RGB overlay color codes each lung tissue voxel, identifying the lung tissue as one of three classification categories. The classification categories are defined by an inhalation threshold (in HU), an exhalation threshold (in HU), lower limit threshold of -1024 HU and an upper limit threshold of 0 HU. See Section 4.3.2 for more information on input thresholds. Below are the definitions of the classification categories and the corresponding color of the Functional Assessment Map voxel data.

GREEN - **Normal**
Voxels with HU higher than inspiration threshold and higher than expiration threshold

YELLOW - **Functional Low Density Area**
Voxels with HU higher than inspiration threshold and lower than expiration threshold

RED - **Persistent Low Density Area**
Voxels with HU lower than inspiration threshold and lower than expiration threshold

Example axial slices from the Functional Assessment Map are shown below in Figure 2.

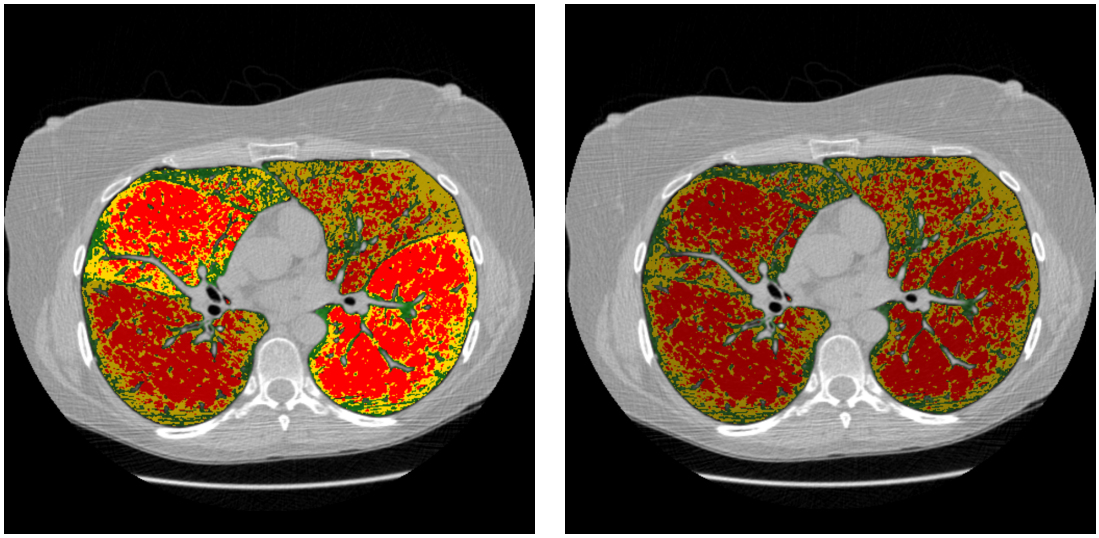


Figure 2: Slice of Functional Assessment Map: Lobar segmentation activated (left) and de-activated (right).

5.3 Segmentation Map

Imbio CT LDA Software produces a segmentation DICOM series so that users can assess the quality of segmentation. If lobar segmentation is NOT activated, the left and right lungs are labeled. If lobar segmentation is activated, the upper right, middle right, lower right, upper left, and lower left lobes are labeled: See Figure 3 for example segmentation DICOM series images and section 8.3 for more details on how to interpret the images.

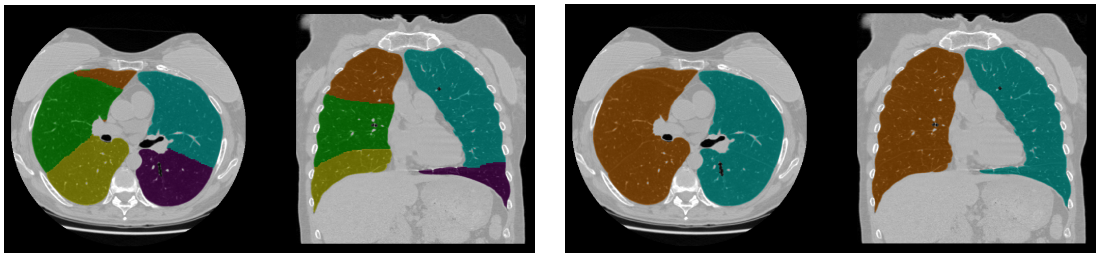


Figure 3: Example segmentation maps: Lobar segmentation activated (left) and lobar segmentation de-activated.

5.4 Registration Map

Imbio CT Lung Density Analysis™ (LDA) Software generates a "warped" inspiration map that helps visualize the registration process that is part of the Functional Assessment algorithm. Figure 4 shows an example of this output side by side with a corresponding expiration image. Please see section 8.5 for more details on how to interpret this image.

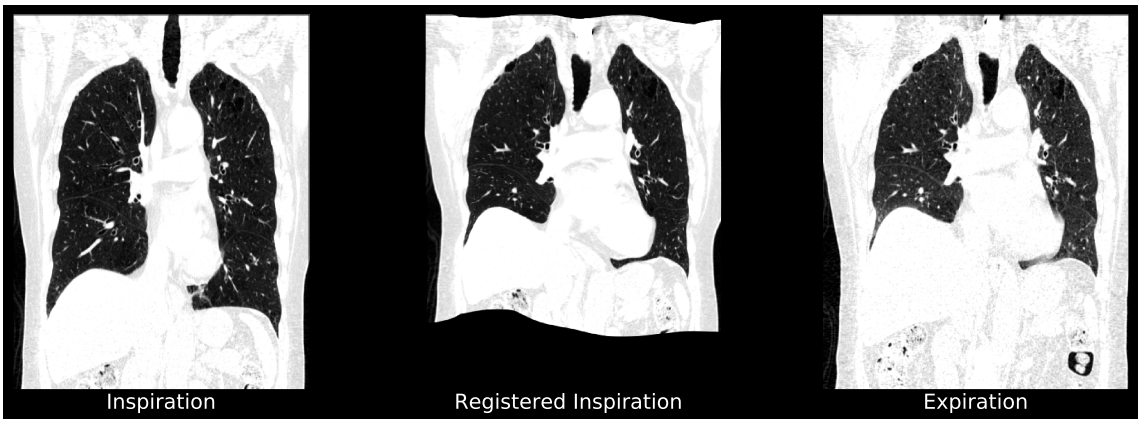
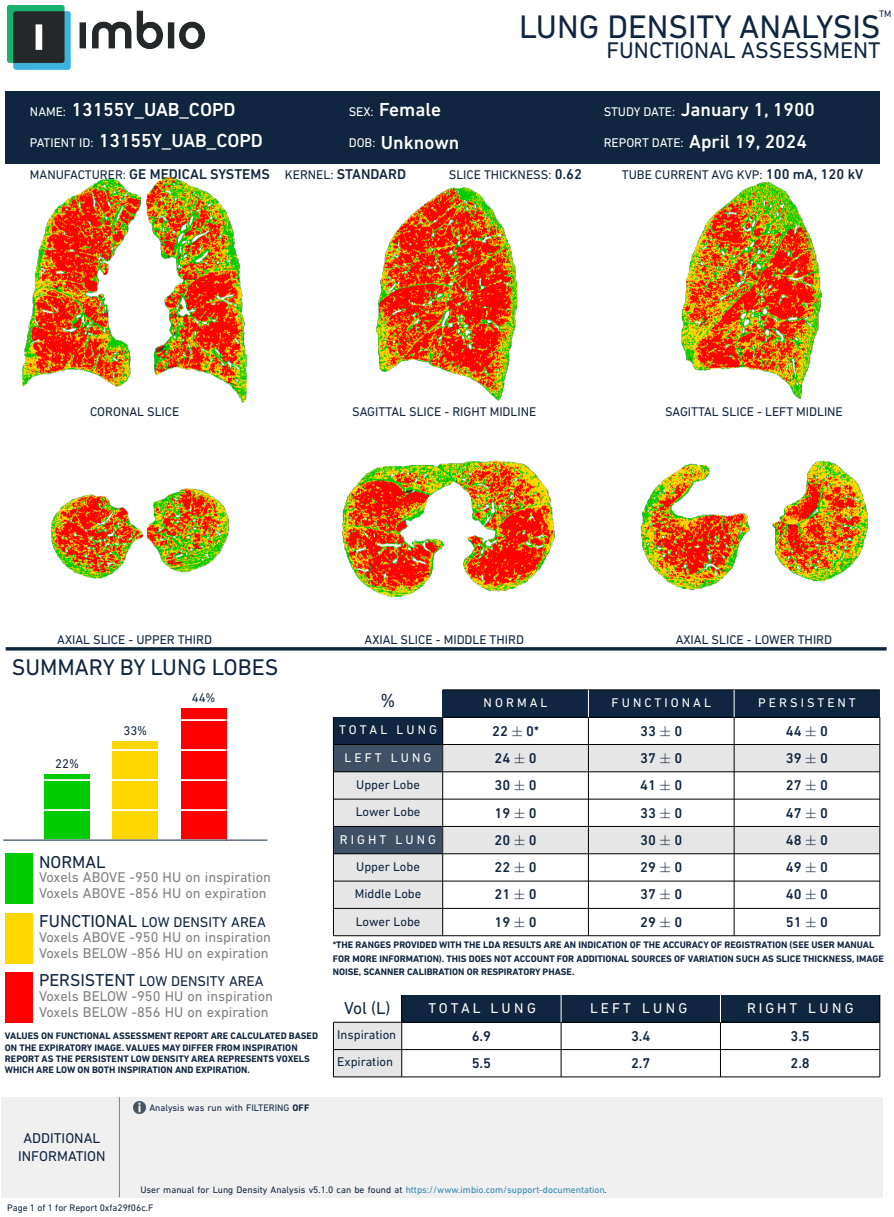


Figure 4: Inspiratory phase CT scan registered to the expiratory phase CT scan.

5.5 Functional Assessment Report

The Functional Assessment Report is a DICOM compatible format. It is either a Encapsulated PDF Report SOPClass or Secondary Capture Image Storage SOPClass. The report summarizes the results of the Functional Assessment Map. It contains patient information, lung slice images, and tables displaying results. An example report is shown below in Figure 5.



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LUNG DENSITY ANALYSIS™
FUNCTIONAL ASSESSMENT

NAME: 13155Y_UAB_COPD SEX: Female STUDY DATE: January 1, 1900
PATIENT ID: 13155Y_UAB_COPD DOB: Unknown REPORT DATE: April 19, 2024

MANUFACTURER: GE MEDICAL SYSTEMS KERNEL: STANDARD SLICE THICKNESS: 0.62 TUBE CURRENT AVG KVP: 100 mA, 120 kV

CORONAL SLICE
SAGITTAL SLICE - RIGHT MIDLINE
SAGITTAL SLICE - LEFT MIDLINE
AXIAL SLICE - UPPER THIRD
AXIAL SLICE - MIDDLE THIRD
AXIAL SLICE - LOWER THIRD

SUMMARY BY LUNG LOBES

22% 33% 44%

NORMAL
Voxels ABOVE -950 HU on inspiration
Voxels ABOVE -856 HU on expiration

FUNCTIONAL LOW DENSITY AREA
Voxels ABOVE -950 HU on inspiration
Voxels BELOW -856 HU on expiration

PERSISTENT LOW DENSITY AREA
Voxels BELOW -950 HU on inspiration
Voxels BELOW -856 HU on expiration

VALUES ON FUNCTIONAL ASSESSMENT REPORT ARE CALCULATED BASED ON THE EXPIRATORY IMAGE. VALUES MAY DIFFER FROM INSPIRATION REPORT AS THE PERSISTENT LOW DENSITY AREA REPRESENTS VOXELS WHICH ARE LOW ON BOTH INSPIRATION AND EXPIRATION.

%	NORMAL	FUNCTIONAL	PERSISTENT
TOTAL LUNG	22 ± 0*	33 ± 0	44 ± 0
LEFT LUNG	24 ± 0	37 ± 0	39 ± 0
Upper Lobe	30 ± 0	41 ± 0	27 ± 0
Lower Lobe	19 ± 0	33 ± 0	47 ± 0
RIGHT LUNG	20 ± 0	30 ± 0	48 ± 0
Upper Lobe	22 ± 0	29 ± 0	49 ± 0
Middle Lobe	21 ± 0	37 ± 0	40 ± 0
Lower Lobe	19 ± 0	29 ± 0	51 ± 0

*THE RANGES PROVIDED WITH THE LDA RESULTS ARE AN INDICATION OF THE ACCURACY OF REGISTRATION (SEE USER MANUAL FOR MORE INFORMATION). THIS DOES NOT ACCOUNT FOR ADDITIONAL SOURCES OF VARIATION SUCH AS SLICE THICKNESS, IMAGE NOISE, SCANNER CALIBRATION OR RESPIRATORY PHASE.

Vol (L)	TOTAL LUNG	LEFT LUNG	RIGHT LUNG
Inspiration	6.9	3.4	3.5
Expiration	5.5	2.7	2.8

ADDITIONAL INFORMATION

Analysis was run with FILTERING OFF

User manual for Lung Density Analysis v5.1.0 can be found at https://www.imbio.com/support-documentation.

Page 1 of 1 for Report 0xfa29f06c.F

Figure 5: Functional LDA report

Report Header
Of particular importance in the report header are the reconstruction kernel, slice thickness, and x-ray tube current. These parameters affect either the effective resolution of the CT image and/or the dose, which in turn affect repeatability of lung density measurements. When comparing follow-up lung density measurements, it is important that changes in these parameters are observed and accounted for during assessment.

Report Statistics
The results summarized within the report include the percent of lung tissue identified as Normal, Functional Low Density Area and Persistent Low Density Area for right, left and total lung. A small percentage of voxels do not fit into well-defined physiologic categories (below -950 HU on inspiration and above -856 on expiration) and thus are not reported. For this reason, the reported category percentages may not add up to 100%. If lobar segmentation is enabled, the text "SUMMARY BY LUNG LOBES" is displayed along with percentages for the upper, middle, and lower right and upper and lower left lobes. If lobar segmentation is NOT enabled, the text "SUMMARY BY LUNG THIRDS" is displayed along with percentages for three equally sized regions of both lungs.

Percentages are presented with estimated variations. The values are based off of the estimated accuracy of the registration algorithm. Large estimated variations typically reflect a nonuniform density pattern that is sensitive to registration accuracy. If the density patterns are uniform and insensitive to registration accuracy, the estimated variations will be small. Therefore, the estimated variations can be thought of as a measure of confidence in the reported values based on the expected accuracy of the registration process.

The Imbio registration algorithm will not produce a perfect registration between the inspiration and expiration images. The effect of the registration accuracy was assessed by comparing the automated Imbio registration to a perfect registration found through manual landmark definition. LDA percentages were calculated for the automated Imbio registration and for the perfect registration for multiple subjects. It was found the LDA percentages for the automated Imbio registration all fell within the variation of the LDA percentages for the perfect registration.

Volumes of the segmented inspiration and expiration lungs are also reported. Total lung volumes are given as well as the volumes for the right and left lung.

NOTE: Report summary statistics are rounded to the nearest integer. Thus, values less than 0.5% will be displayed as 0%.

Report Graphics
The report displays six images, displaying slices of the Functional Assessment Map in different orientations. The six images include, one coronal slice, mid sagittal slice of the right lung, mid sagittal slice of the left lung, and three axial slices, the middle of the lower, middle and upper third of the lungs. Below is an example of the images found in the report (Fig. 6).

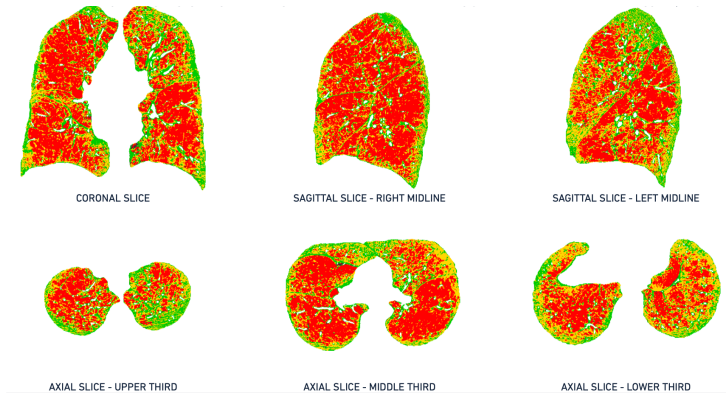


Figure 6: Example of lung images found in Functional Assessment Report

6 Inspiration Assessment

The Inspiration Assessment of the LDA Software generates two main outputs; the Inspiration Assessment Map and the Inspiration Assessment Report.

6.1 Inputs

The Inspiration Assessment component only takes an inspiration scan as input. In addition, the user may input inhalation thresholds, create the additional LungMap™ Report and/or turn filtering off. For more information on optional inputs, see Section 4.3. For the version of LungMap targeting former smokers, the Patient Sex DICOM attribute (0x0010,0x0040) must be present and contain an "M" or "F" value.

6.2 Inspiration Assessment Map

The Inspiration Assessment Map is a DICOM Secondary Capture Image with voxel data that is the original expiration image with an RGB overlay. The RGB overlay color codes each lung tissue voxel, identifying the lung tissue as one of three classification categories. Below are the definitions of the classification categories and the corresponding color of the Inspiration Assessment Map voxel data.

BLUE - **Very High Density Area**
Voxels with HU higher than -200 HU

PURPLE - **High Density Area**
Voxels with HU higher than -700 HU
and lower than -200 HU

RED - **Low Density Area**
Voxels with HU lower than -950 HU

The default settings for the thresholds can be changed. Contact Imbio Support for more information.

6_INSPIRATION ASSESSMENT

An example of a slice from the Inspiration Assessment Map is shown below in Figure 7.

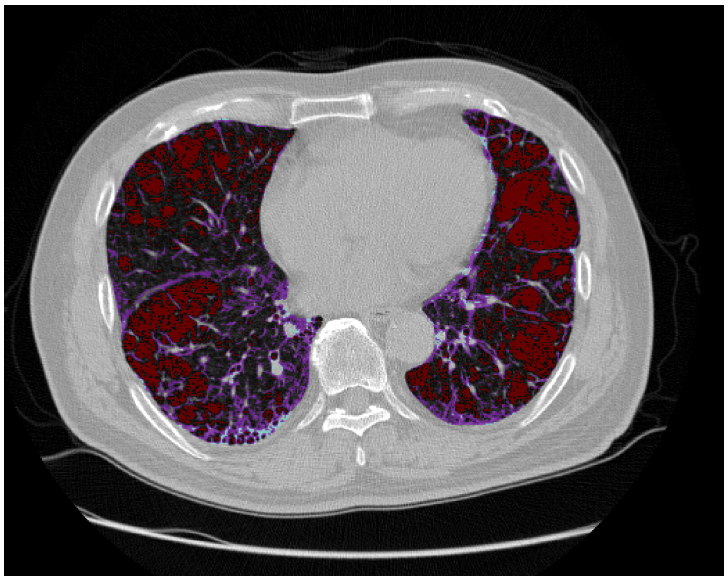


Figure 7: Slice of Inspiration Assessment Map

6.3 Segmentation Map

Imbio CT LDA Inspiration Assessment Software produces a segmentation DICOM series so that users can assess the quality of segmentation. For more details, please refer to sections 5.3 and 8.3.

6.4 Inspiration Assessment Report

The Inspiration Assessment Report contains the results from the LDA Inspiration Software analysis. It can be provided in several formats: PDF file, DICOM encapsulated PDF, or a DICOM Secondary Capture Storage. As explained in Section 5.5, it is important to note the image acquisition parameters. Please see Section 5.5 for more details.

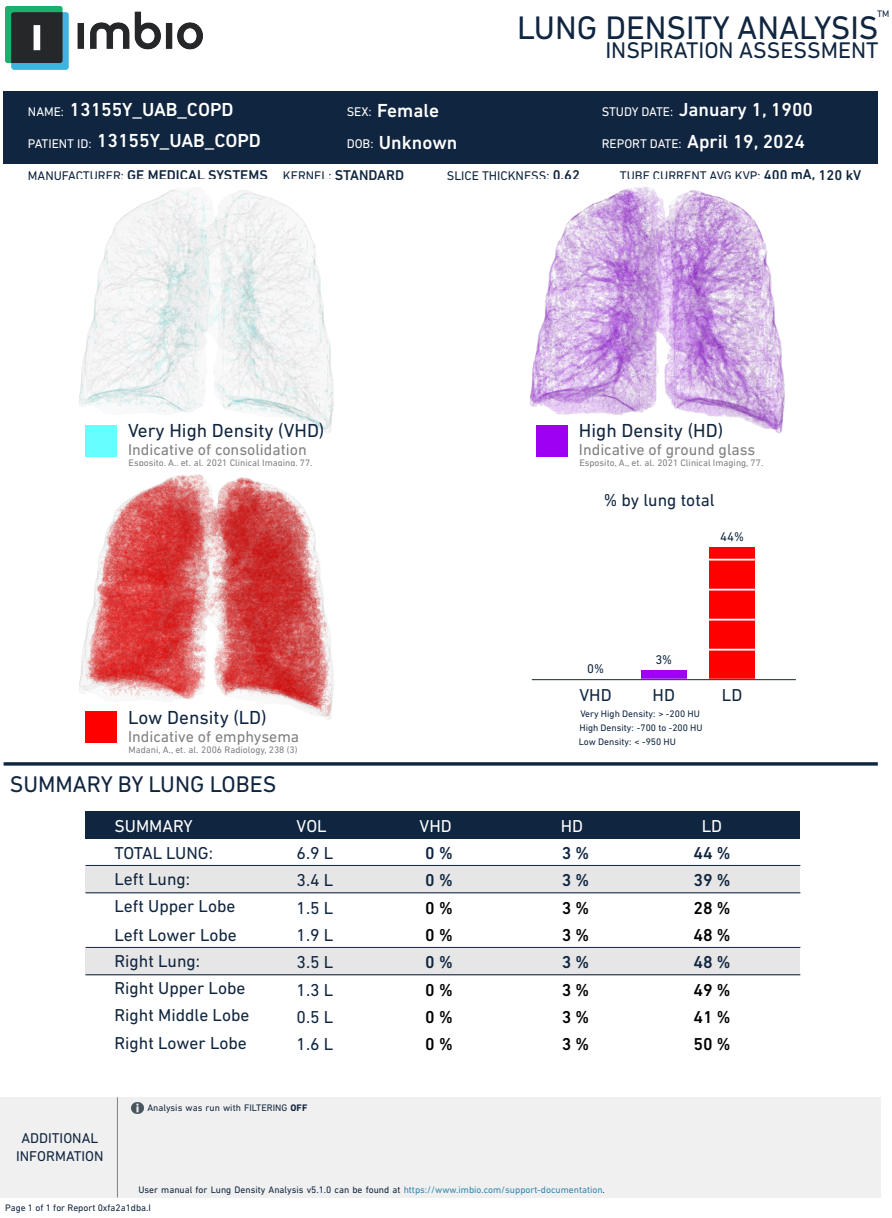
The three key density measures reported in the LDA Inspiration Assessment report include:

- **Very High Density (VHD)**: Percent of tissue above a threshold of -200 HU. Has been shown to be indicative of consolidation. [2].

- **High Density (HD)**: Percent of tissue above a threshold of -700 HU and below a threshold of -200 HU. Has been shown to be indicative of ground glass. [2].

- **Low Density (LD)**: Percent of tissue below a threshold of -950 HU. Has been shown to be indicative of emphysema. [3].

The default settings for the thresholds can be changed. Contact Imbio Support for more information.



SUMMARY	VOL	VHD	HD	LD
TOTAL LUNG:	6.9 L	0 %	3 %	44 %
Left Lung:	3.4 L	0 %	3 %	39 %
Left Upper Lobe	1.5 L	0 %	3 %	28 %
Left Lower Lobe	1.9 L	0 %	3 %	48 %
Right Lung:	3.5 L	0 %	3 %	48 %
Right Upper Lobe	1.3 L	0 %	3 %	49 %
Right Middle Lobe	0.5 L	0 %	3 %	41 %
Right Lower Lobe	1.6 L	0 %	3 %	50 %

Figure 8: Inspiration LDA report

Report Statistics

The key metrics for each lung are displayed in a table on the report, along with lung volumes. If lobar segmentation is enabled, the text "SUMMARY BY LUNG LOBES" is displayed along with percentages for the upper, middle, and lower right and upper and lower left lobes. If lobar segmentation is NOT enabled, the text "SUMMARY BY LUNG THIRDS" is displayed along with percentages for three equally sized regions of both lungs.

NOTE: Report summary statistics are rounded to the nearest integer. Thus, values less than 0.5% will be displayed as 0%.

Report Graphics
The report includes 3D renderings showing the distribution of each density measure and a plot of percentages by lung total. See figure 9

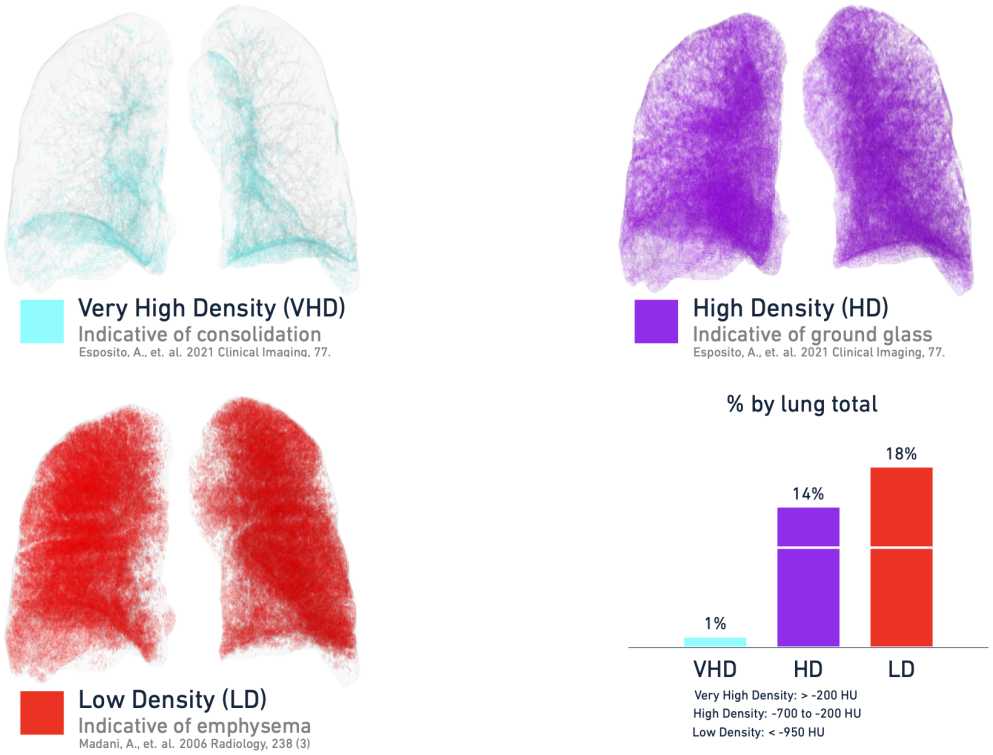


Figure 9: 3D renderings of each density measure.

6.5 LungMap™ Report

The LungMap™ Report is an optional report that is generated in addition to the Inspiration Assessment Map and the Inspiration Assessment Report. The LungMap™ Report is a DICOM compatible format. It is either a Encapsulated PDF Report SOPClass or Secondary Capture Image Storage SOPClass. The report contains the percentages of lung volume below and above the inspiration threshold, the most affected lobe or third of the lung and is corresponding percent below threshold, and an image of the lung and a table listing the potential benefits of smoking cessation. An example report is shown below in Figure 10.

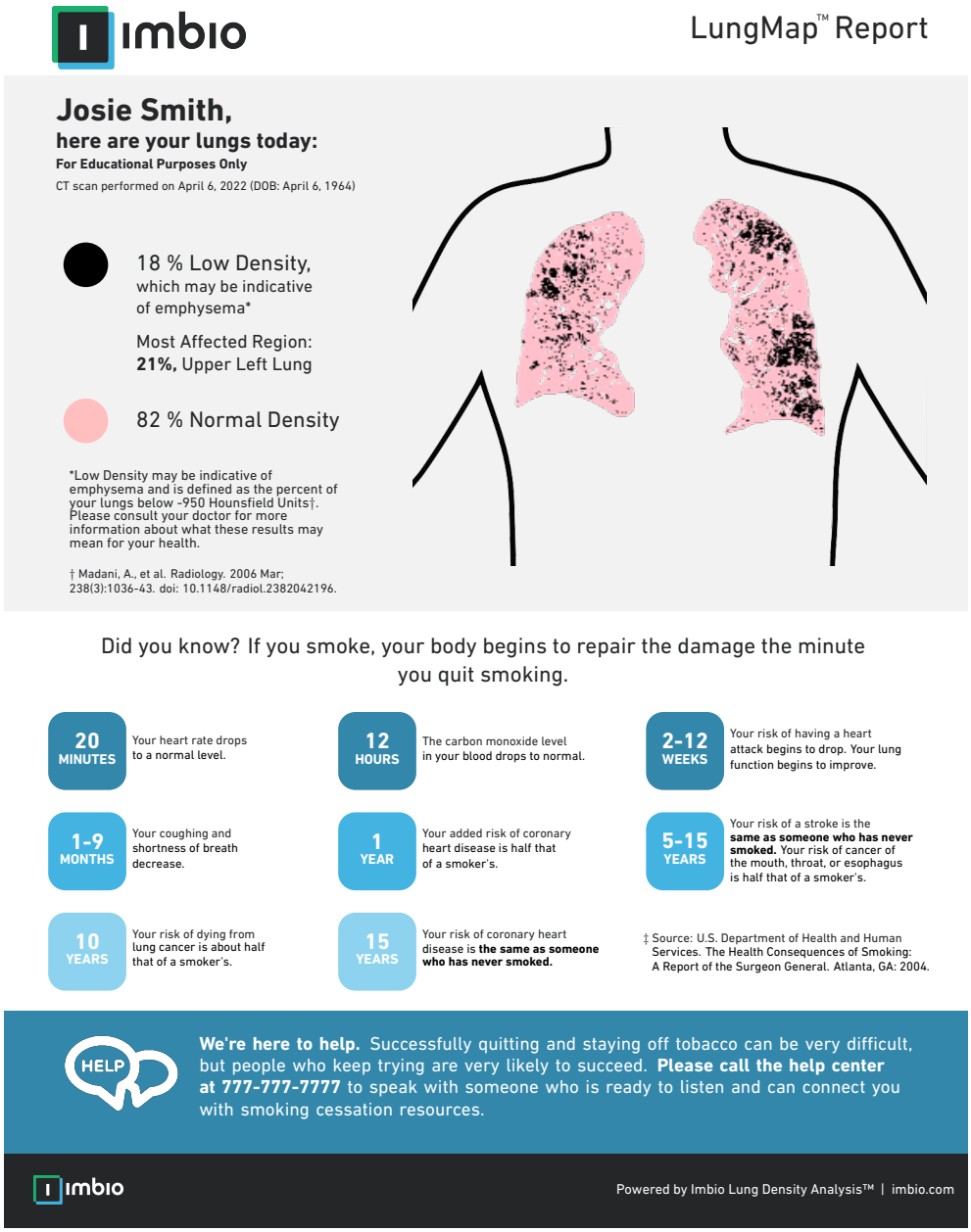


Figure 10: Example LungMap™ Report for current smokers

Another version of the LungMap™ Report for former smokers is also available. Instead of a table listing the potential benefits of smoking cessation, a figure showing decreasing relative risk of lung cancer over time after quitting tobacco compared to never-smokers is displayed. Statistics are taken from a peer-reviewed article [1] and are personalized based on the patient's gender. An example report is shown below in Figure 11.

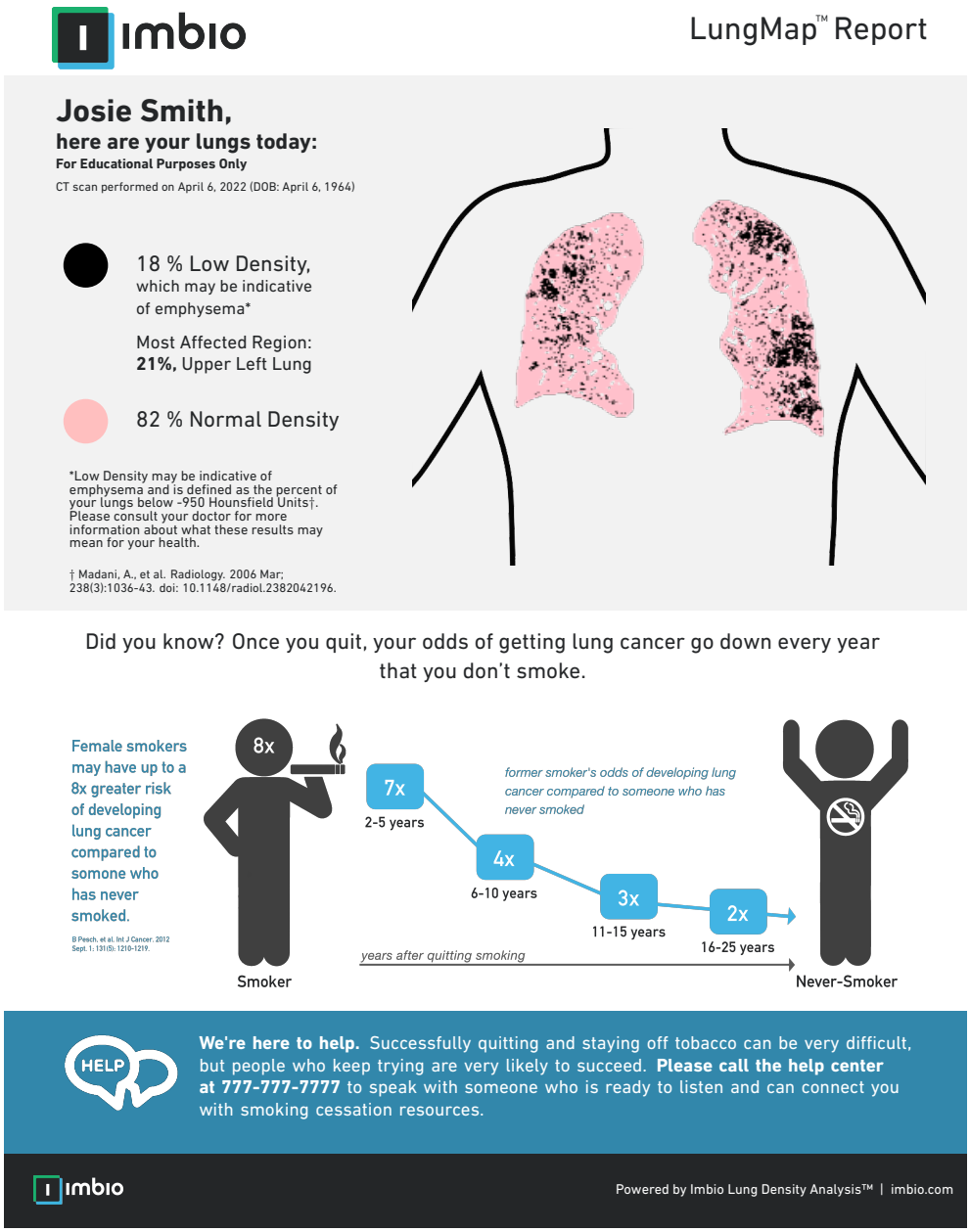


Figure 11: Example LungMap™ Report for former smokers

A customizable version of the LungMap™ Report is also available. This version allows for a custom header and footer to be used instead of the default header and footer. Custom report options can be configured at installation or upon request.

Report Statistics

The statistics within the report are the total percentages of lung volume below and above the inspiration threshold, as well the most affected region with it's corresponding percentage below the threshold. The most affected region refers to the lobe or third with the highest percentage of voxels below the specified threshold. Unlike the Inspiration Assessment Report, the lung volumes are not included in the LungMap™ Report.

Report Graphics

The LungMap™ report displays an image of a coronal slice of the Inspiration Assessment Map towards the center of the lungs that has percentage of pixels below the threshold similar to the percentage below the threshold for the entire lung. The color of the lung pixels on this image slice imitates the colors of the physical lung; pink for normal density tissue and black for low density tissue. The image has an outline of the body outside of the lungs to give a clearer picture of the orientation and position of the lungs in the patient's body. Below is an example of the image slice found in the report (Fig. 12).

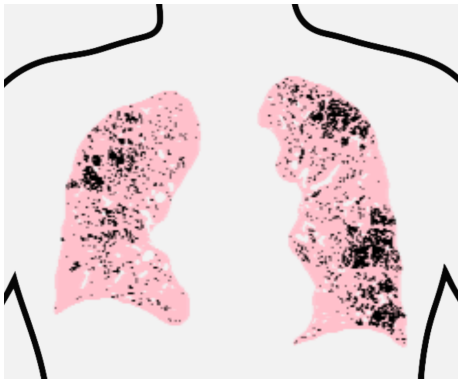


Figure 12: Example of lung image in LungMap™ Report

The other graphic in the current smoker report is a table of smoking cessation benefits (Figure 13). This table remains the same and does not change on a patient-to-patient basis.

The other graphic in the former smoker report is the figure showing the relative risk of lung cancer diagnosis as a function of time after quitting tobacco (Figure 14). This figure is personalized based on whether or not the patient is male (Fig. 14) or female (Fig. 15). Please see Table 4 from [1].

20 MINUTES	Your heart rate drops to a normal level.
12 HOURS	The carbon monoxide level in your blood drops to normal.
2-12 WEEKS	Your risk of having a heart attack begins to drop. Your lung function begins to improve.
1-9 MONTHS	Your coughing and shortness of breath decrease.
1 YEAR	Your added risk of coronary heart disease is half that of a smoker's.
5-15 YEARS	Your risk of a stroke is the **same as someone who has never smoked.** Your risk of cancer of the mouth, throat, or esophagus is half that of a smoker's.
10 YEARS	Your risk of dying from lung cancer is about half that of a smoker's.
15 YEARS	Your risk of coronary heart disease is **the same as someone who has never smoked.**

‡ Source: U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, GA: 2004.

Figure 13: Table of Smoking Cessation Benefits

Did you know? Once you quit, your odds of getting lung cancer go down every year that you don't smoke.

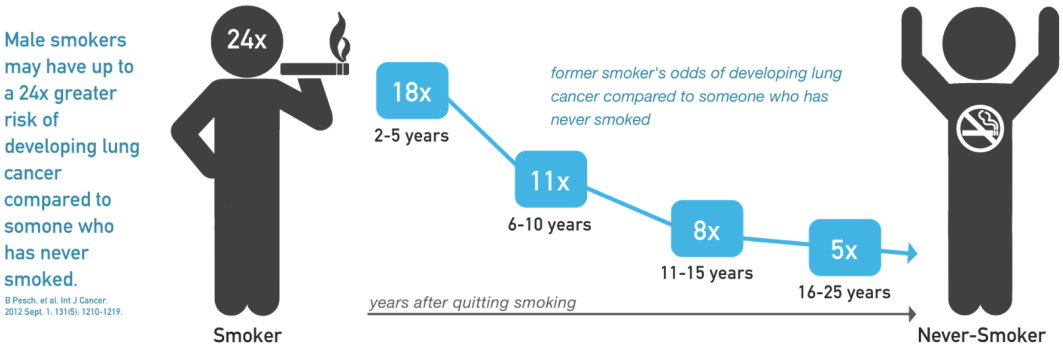


Figure 14: Figure showing the decreasing relative risk of lung cancer diagnosis compared to never-smokers for males.

Did you know? Once you quit, your odds of getting lung cancer go down every year that you don't smoke.

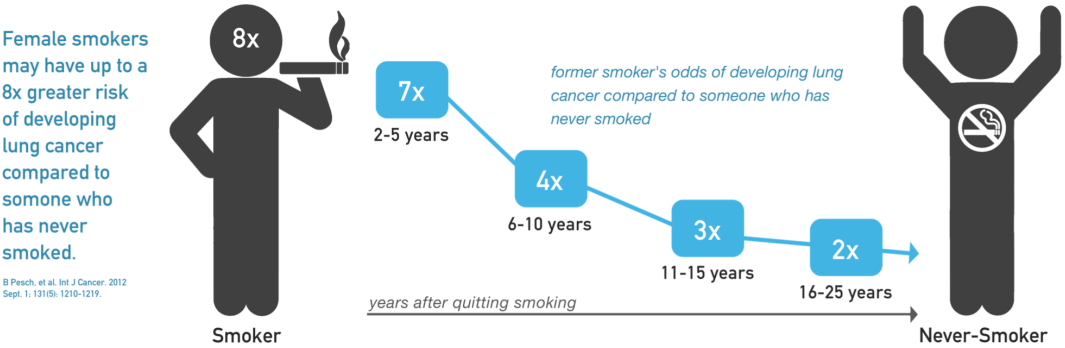


Figure 15: Figure showing the decreasing relative risk of lung cancer diagnosis compared to never-smokers for females.

7 Possible Encountered Exceptions

The Imbio CT Lung Density Analysis™ Software produces notifications and errors when an exception is encountered within the algorithm. Below are possible errors generated by the software with further descriptions and probable causes of the exceptions.

7.1 Input Errors

`ERROR: Invalid input data |`
This error occurs if the data provided do not meet Imbio's requirements. For example, the path provided contains more than one DICOM series. For the details on each required parameter, see Section 2.2.1.

`ERROR: Unacceptable input data |`
This error occurs if the image acquisition parameters fo not meet Imbio's requirements. For the deatils on each required parameter, see Secion 2.2.1.

In the event that this error occurs, the algorithm will output and Input Check Failure Report indicating the reason why the input data was deemed unacceptable. An examle Input Check Dailure Report for the Inspiration Assessment is shown in Figure 16. The cause(s) of the input check failure can be identified by the red 'X' mark in the Result column. In Figure 16, the offending parameter is the slice thickness. Note the yellow triangle warning signs indicate sub-optimal parameters (Convolution Kernel) or parameters that are missing from the input meta data (Revolution Time). These warnings will not result in an input check failure, but should be noted nonetheless.

`ERROR: Input images have same Series Instance UID`
This error occurs when both input images have the same Series Instance UID. The Series Instance UIDs must be unique for each input image. Check the DICOM attributes of the uploaded series.

7.2 Segmentation Errors

```
ERROR: Could not extract airways
ERROR: Could not separate lungs
ERROR: Could not find trachea
ERROR: No lungs found
```

These errors indicate an exception in the segmentation step of the Imbio CT Lung Density Analysis™ Software. Possible causes include:

- Patient body motion or breathing during the scan.
- Tracheomalacia or very narrow major bronchi.
- Scanning more than a few centimeters above the apex of the lung.
- Lungs are not contained with the field of view of the image.

imbio

LUNG DENSITY ANALYSIS™
INPUT CHECK REPORT

ACCESSION NUMBER: **6789** STATION NAME: **Unknown** MANUFACTURER: **GE** TUBE CURRENT AVG KVP: **300 mA, 140 kV**

Series Description: ER AAA 3.0 B30f - THICK
Series Instance UID: 1.3.6.1.4.1.19291.2.1.2.16413
Series Number: 5348

	Requirement	Value	Result
Modality	CT	CT	✓
Revolution Time (s)	<= 1.0	Not Present	⚠
Pixel Spacing (mm)	<= [2.0, 2.0]	[0.607, 0.607]	✓
FOV (mm)	>= (100, 100, 200)	(311, 311, 295)	✓
Image Orientation	(±1,0,0,0,±1,0)	(1.0, 0.0, 0.0, 0.0, 1.0, 0.0)	✓
Slice Spacing (mm)	<= 3.0	2.5	✓
Slice Thickness (mm)	<= 3.0	5.0	✗
Rescale Type	HU	HU	✓
Patient Age (years)	>= 18	52	✓
Convolution Kernel	Non-edge-enhancing	BONE	⚠
Contrast Bolus Agent	Missing	Missing	✓
Transfer Syntax UID	Non-Big-Endian	OK	✓

Figure 16: Example of an Input Check Failure Report

- The input image does not contain lungs or the input image is noisy.

```
ERROR: Lung larger than the expected size range
ERROR: Lung smaller than the expected size range
```

These errors indicate that the segmented lungs do not fall within the expected range of volumes. This could be due to a poor segmentation where non lung tissue was misidentified as lung or lung tissue was excluded from the segmentation. These errors could also be a result of a patient with anomalous anatomy.

```
ERROR: Airways larger than the expected size range
ERROR: Airways smaller than the expected size range
```

These errors indicate that the segmented airways do not fall within the expected range of volumes. This could be due to a poor segmentation where airways bled into the lung or only the trachea was able to be identified. These errors could also be a result of a patient with anomalous anatomy.

7.3 Registration Errors

```
ERROR: Borders metric indicates poor registration
ERROR: Similarity metric indicates poor registration
```

These errors indicate that the registered image does not meet the required Imbio standards. A poor registration could be due to a large difference in size between the two input images or a poor segmentation.

8 Considerations to Reduce Risk

8.1 Protocol

Users must follow CT protocol as seen in Section 2.2.

8.2 Expected Performance

The accuracy of the LDA Functional Assessment measurements is primarily determined by the quality of the image registration. An estimate of the accuracy of the measurements is given in the form of a range for each measurement on the output report (Figure 17).

%	NORMAL	FUNCTIONAL	PERSISTENT
TOTAL LUNG	22 ± 0*	33 ± 0	44 ± 0
LEFT LUNG	24 ± 0	37 ± 0	39 ± 0
Upper Lobe	30 ± 0	41 ± 0	27 ± 0
Lower Lobe	19 ± 0	33 ± 0	47 ± 0
RIGHT LUNG	20 ± 0	30 ± 0	48 ± 0
Upper Lobe	22 ± 0	29 ± 0	49 ± 0
Middle Lobe	21 ± 0	37 ± 0	40 ± 0
Lower Lobe	19 ± 0	29 ± 0	51 ± 0

Figure 17: Chart of LDA measurements on the Functional Assessment Report.The arrows indicate the estimated variation of the LDA measurement.

These ranges of values represent an estimate of how the measurement values would change if the images were translated in all directions within the range of the estimated accuracy of the image registration process. Note that the Imbio LDA algorithm is deterministic, meaning that the LDA measurements will be identical for repeated analyses on the same input data set. Therefore, the major determinant of measurement precision is the noise level in the input images. The noise level of the input images should be considered when comparing measurements from multiple acquisitions.

8.3 Lung Segmentation Quality Assessment

8.3.1 Introduction

The Imbio CT Lung Density Analysis™ (LDA) Software uses advanced image processing techniques to segment the lungs from thoracic CT images so that density analysis can be performed. The software produces a segmentation DICOM series so that users can

assess the quality of segmentation. If lobar segmentation is NOT activated, the left and right lungs are labeled. If lobar segmentation is activated, the upper right, middle right, lower right, upper left, and lower left lobes are labeled: See Figure 18 for a list of the colors used for anatomical labeling and Figures 19 and 20 for example segmentation DICOM series images.

Left/Right Lung Segmentation		Lung Lobe Segmentation	
Right Lung		Upper Right	
Left Lung		Middle Right	
		Lower Right	
		Upper Left	
		Lower Left	

Figure 18: Lung Segmentation label colors.

In order to detect segmentation errors, LDA software checks input parameters and lung segmentation statistics, and notifies users with warning or error messages if potential problems are discovered. Even so, there may be a small number of cases where poor segmentation quality is not automatically detected and the output report is generated with potentially misleading results. These cases can be categorized as one of the following:

- Lung inclusion errors. This includes but is not limited to the following:
  - Air outside of the body is categorized as lung.
  - Air in the gut is categorized as lung.
  - Air in the esophagus is categorized as lung.
- Lung exclusion errors. This includes but is not limited to the following:
  - Part of the lung is categorized as belonging to the airway tree, removing that part of the lung from the analysis.
  - The apex of the lung is categorized as part of the trachea.
  - High-density areas of the lung parenchyma are excluded from the segmentation.
- Left/right lung labeling error.
  - Part of the left lung is incorrectly classified as belonging to the right lung, or vice versa.
  - Either the left or right lung is excluded from the segmentation.

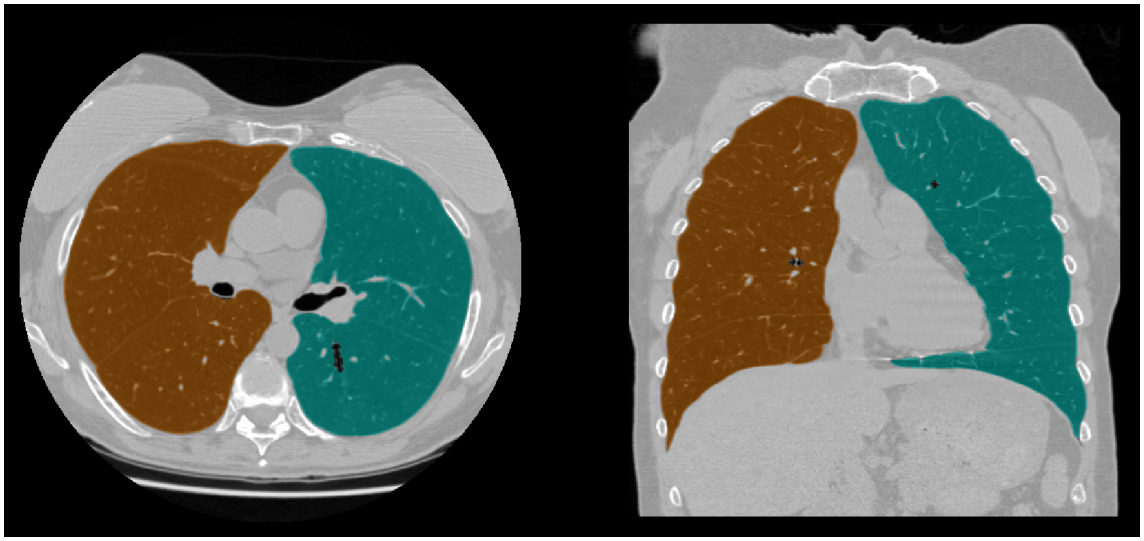


Figure 19: Example lung segmentation.

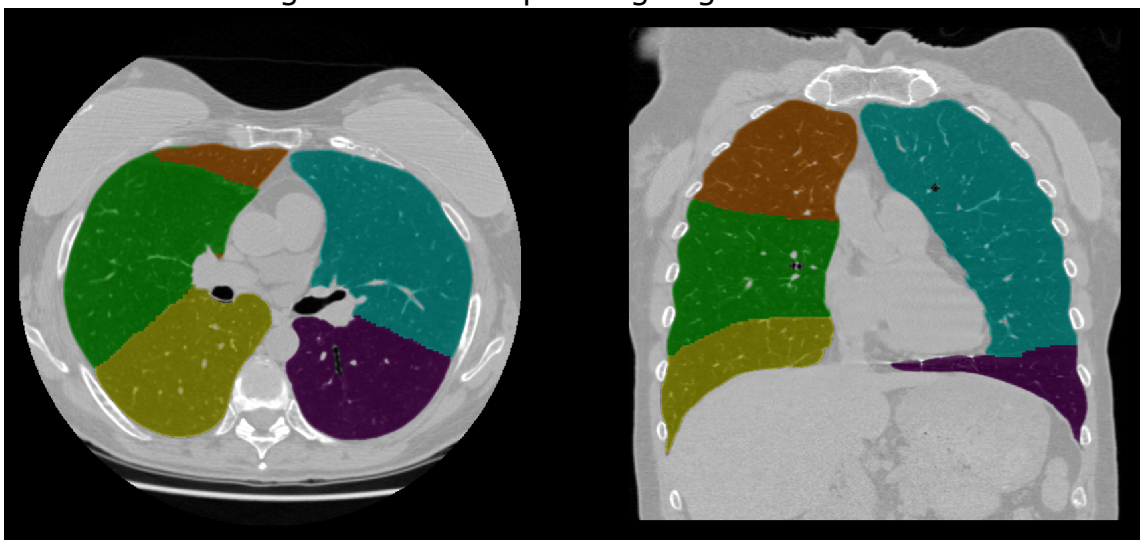


Figure 20: Example lobar segmentation.

The following section contains figures that illustrate examples of segmentation errors that may generate misleading results. Users of the software should look for this type of output and, if present, the results should not be used. The Imbio CT Lung Density Analysis™ Software should only be used by Pulmonologists, Radiologists, and Radiology Technicians under the supervision of a Pulmonologist or Radiologist.

8.3.2 Examples of Lung Segmentation Errors

1. Outside inclusion. In certain cases, the air outside of the body may be incorrectly labeled as part of the left or right lung.

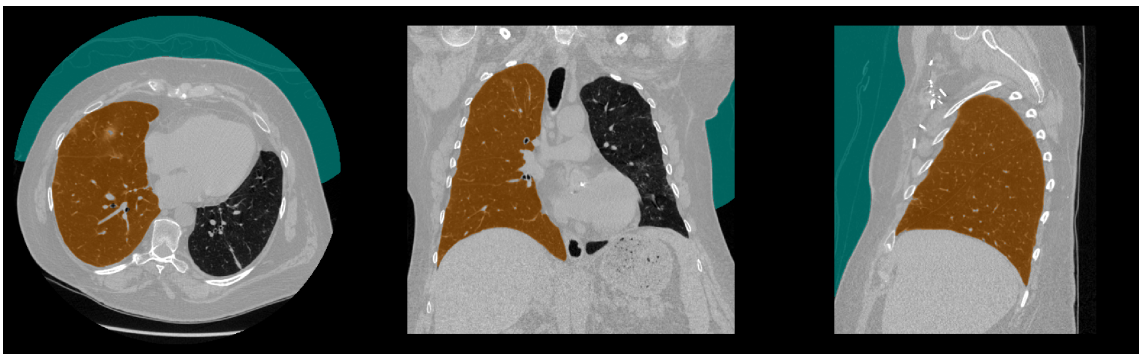


Figure 21: Segmentation overlay showing outside air inclusion error.

2. Gut inclusion. If air is present in the transverse colon, the colon may incorrectly be labeled as part of the lung. This is more common when the input CT image has a slice thicknesses greater than 2 cm.

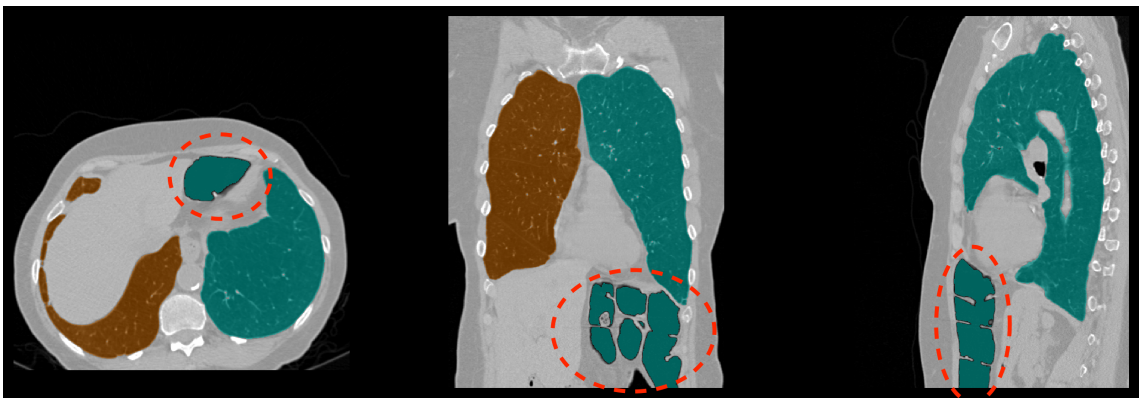


Figure 22: Segmentation overlay showing gut air inclusion error.

3. Esophagus inclusion. A dilated esophagus may accidentally be labeled as part of the lungs. This type of error may result in a few percentage point over-estimation of persistent (Functional LDA) or percent below threshold (Inspiration LDA).

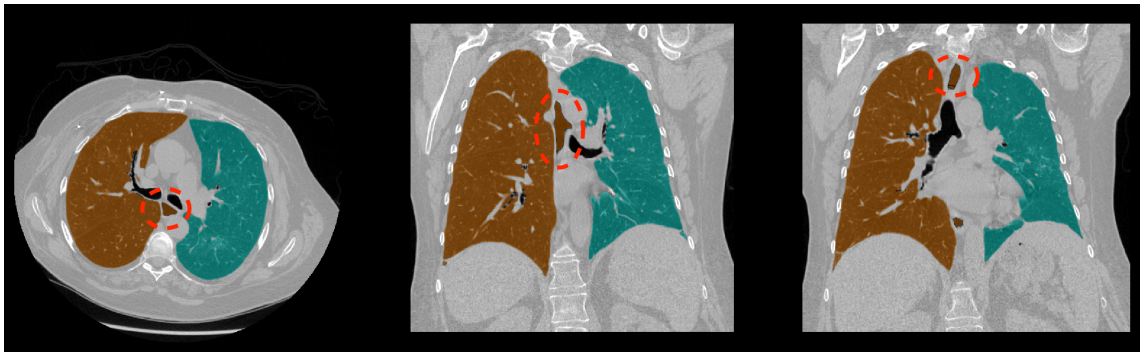


Figure 23: Segmentation overlay showing gut air inclusion error.

4. Lung exclusion due to mislabeled airways. In some cases, parts of the lung parenchyma may be accidentally classified as distal airways. In other cases, the apex of the lung may be mis-identified as part of the trachea, leading to a lung exclusion error and mis-labeling of the trachea as part of the lungs.

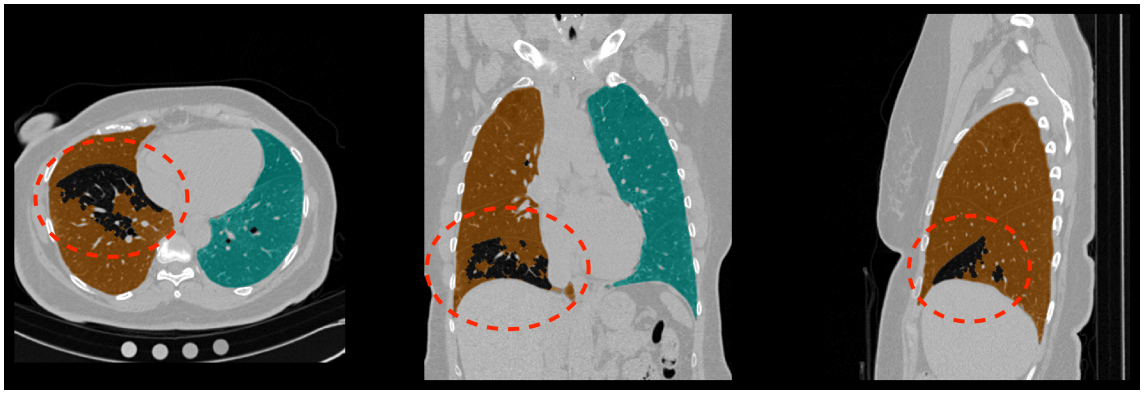


Figure 24: Segmentation overlay showing airway leak into lung parenchyma.

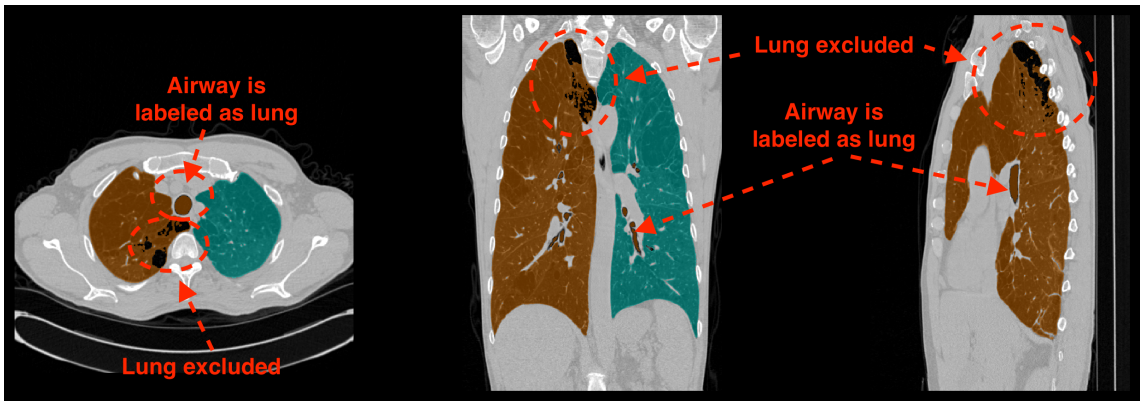


Figure 25: Segmentation overlay showing lung apex classified as trachea.

4. Exclusion due to dependent atelectasis.

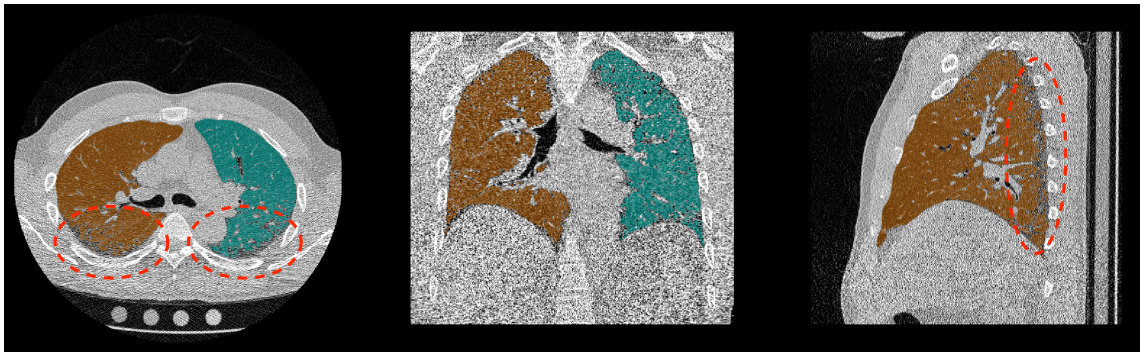


Figure 26: Segmentation overlay lung exclusion due to depenent atelectasis.

5. Left/right lung labeling error.

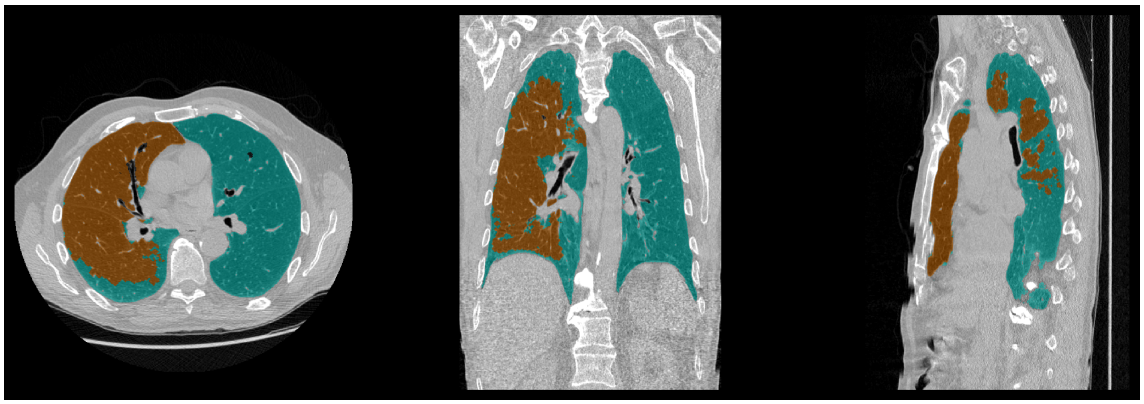


Figure 27: Segmentation overlay showing left/right lung mislabeling.

6. Left/right lung exclusion error. This occurs more often in expiration scans when the major airways are occluded or have collapsed.

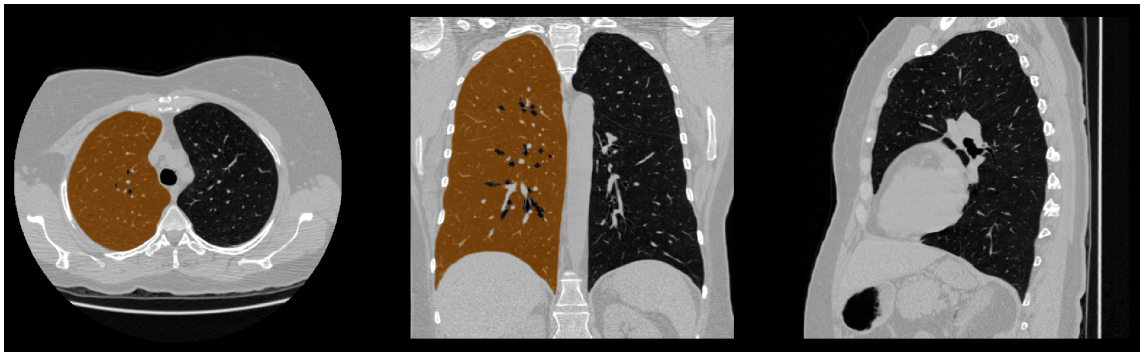


Figure 28: Segmentation overlay showing left lung exclusion.

8.4 Lobe Segmentation Quality Assessment

8.4.1 Introduction

As an optional feature, Imbio CT Lung Density Analysis™ Software is able to perform lobar segmentation of the lungs. Lobar segmentation divides the right lung into the upper, middle, and lower right lobes and the left lung into the upper and lower left lobes. In some cases, a lung lobe may be missing from the segmentation, or the segmentation may be of low quality, both of which may lead to misleading results. The segmentation overlay series should be used to assure that the lobar segmentation accurately represents the underlying lobar anatomy. NOTE: Viewing the lobar segmentation in the sagittal plane maybe be especially helpful for detecting segmentation errors.

Examples of poor lobar segmentations are illustrated in the following figures:

8.4.2 Examples of Lobe Segmentation Errors

1. Missing lobe. In some cases, an entire lobe or most of a lobe may be missing from the segmentation. This most often occurs with the middle right lobe.

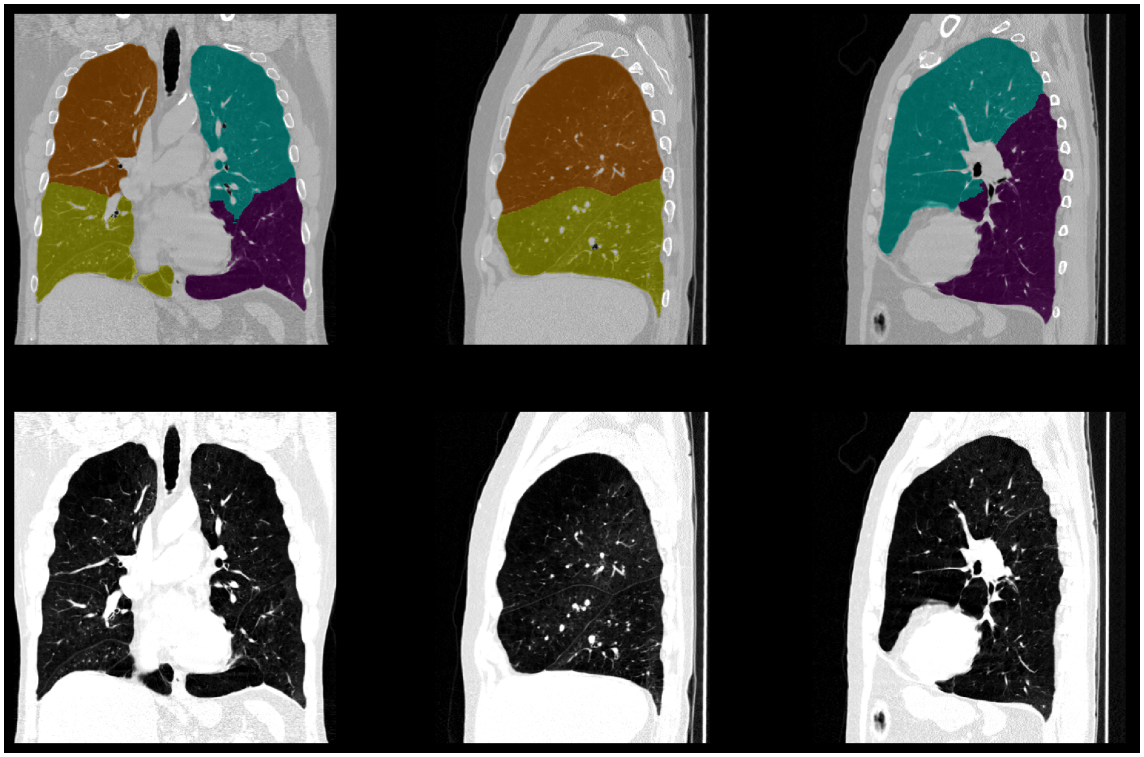


Figure 29: Segmentation showing a missing middle right lobe.

2. Poor quality lobe labeling. In some cases, the lobe segmentation may not agree with a visual assessment of the location of lobe fissures and/or may have a geometry that is unlikely from an anatomical standpoint. A side-by-side comparison of the segmentation overlay with the original CT image can be used to help confirm a poor segmentation.

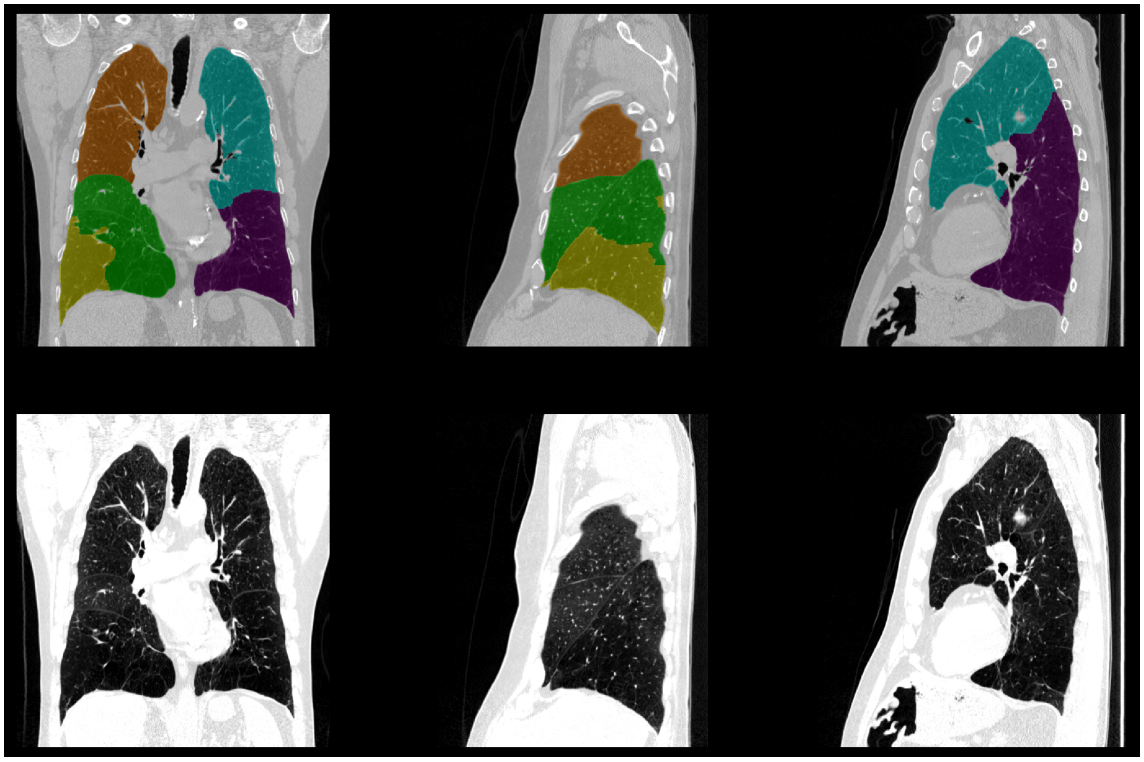


Figure 30: Lobe borders in segmentation are not correctly aligned with fissures.

8.5 Image Registration Quality Assessment

8.5.1 Introduction

Imbio CT Lung Density Analysis™ (LDA) Software uses advanced image processing techniques to spatially "register" two CT images of the lungs. When two images are spatially registered, one of the images is "warped" so that the anatomical landmarks shared by the images are spatially aligned, establishing a one-to-one correspondence between the voxels in each image. Figure 31 shows an example of this process.

Figure 31: Inspiratory phase CT scan registered to the expiratory phase CT scan.

In order to detect errors, LDA software checks lung registration statistics, and notifies users with warning or error messages if potential problems are discovered. However, there may be a small number of cases where poor registration quality is not automatically detected and the output report is generated with potentially misleading results.

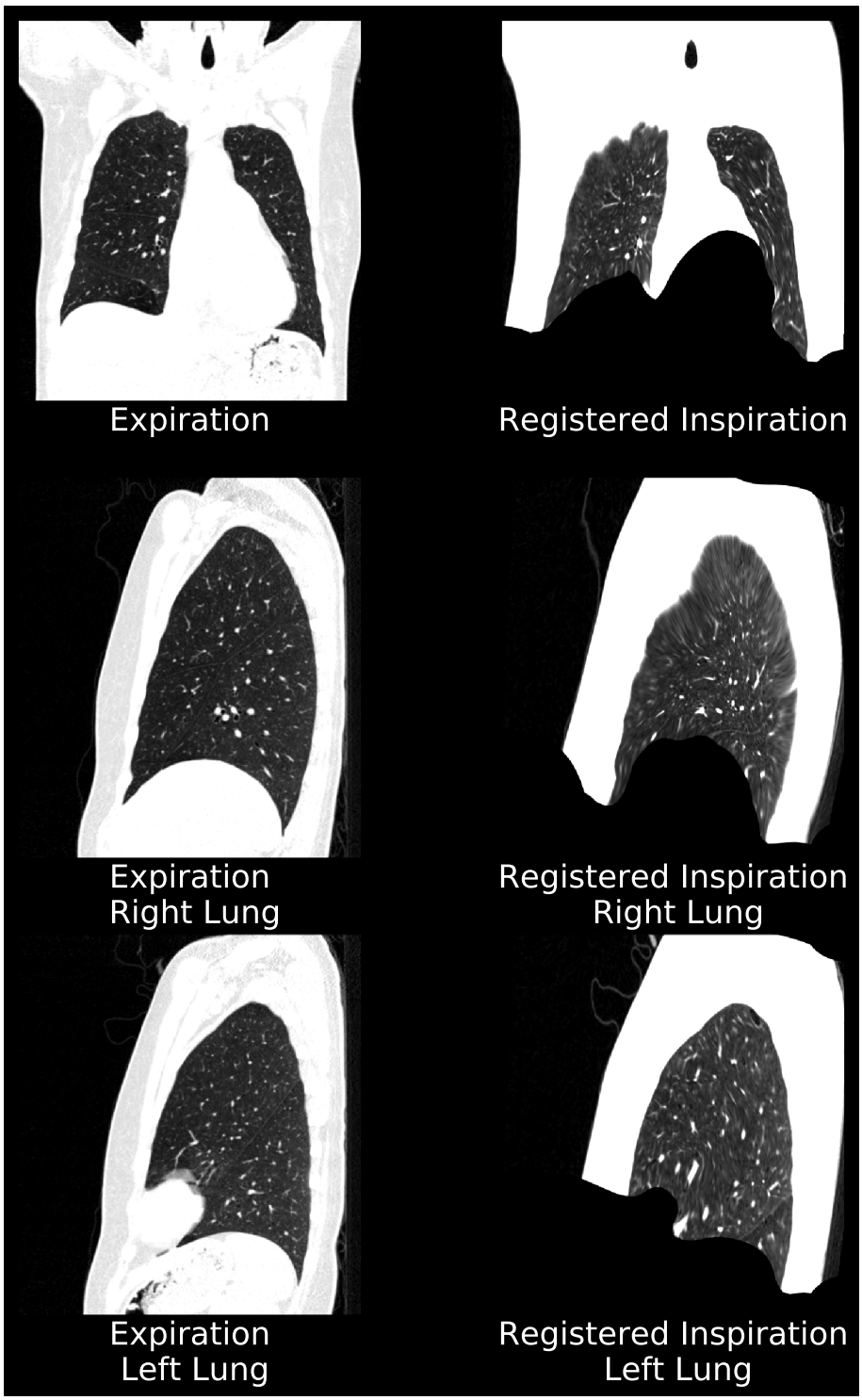
Image registration is never perfect, and most registrations will have minor errors. However, extensive registration errors that occur over large areas of the lung may cause LDA to produce misleading results. To help users to detect these kinds of errors, a registered inspiration DICOM series is provided.

Registration errors can be detected by visually comparing the warped inspiration image to the original expiration CT image. The lung borders and other anatomical features inside the lung should appear in roughly the same position on both images. Systematic anatomical misalignments greater than 1.5 cm may generate misleading results. It should be noted that anatomical features outside of the lung will not necessarily be well-registered; this should be ignored as it does not affect LDA classification results.

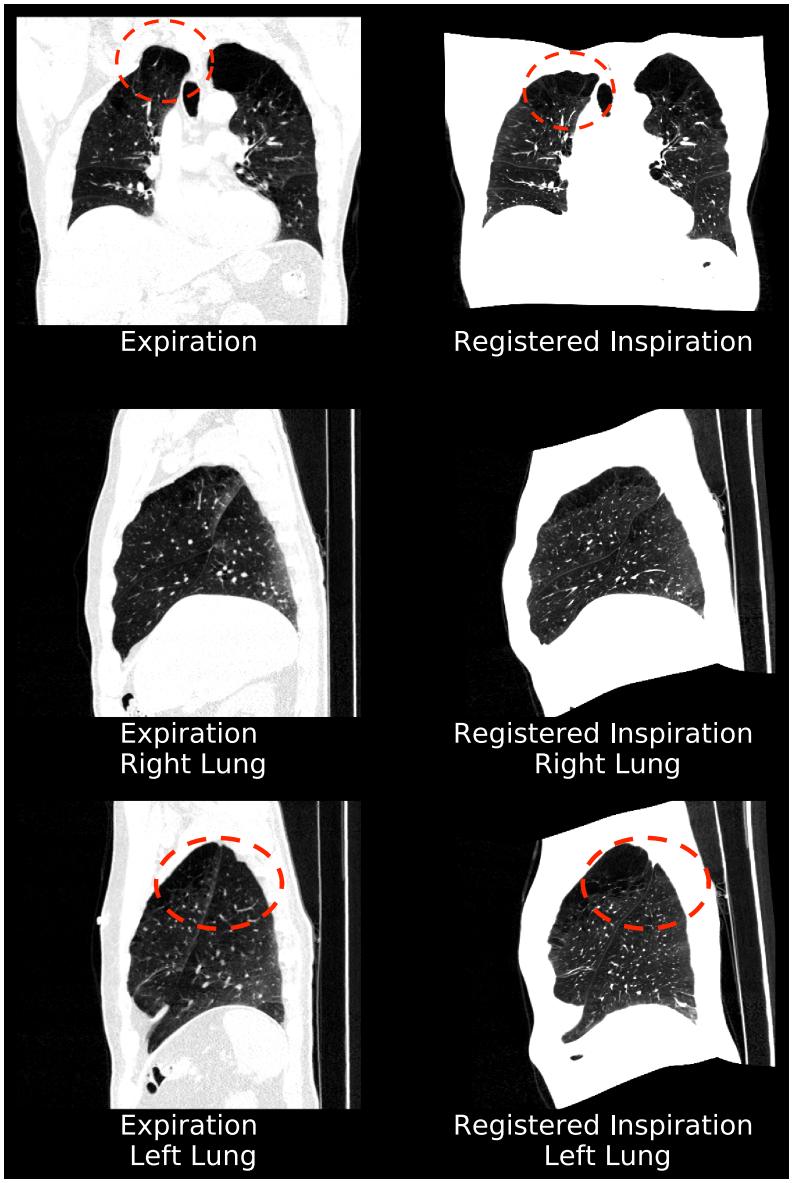
8.5.2 Examples of Registration Errors

This section contains figures that illustrate examples of unacceptable registration errors. Users of the software should look for this type of output and, if present, the results should not be used. The Imbio CT Lung Density Analysis™ Software should only be used by Pulmonologists, Radiologists, and Radiology Technicians under the supervision of a Pulmonologist or Radiologist.

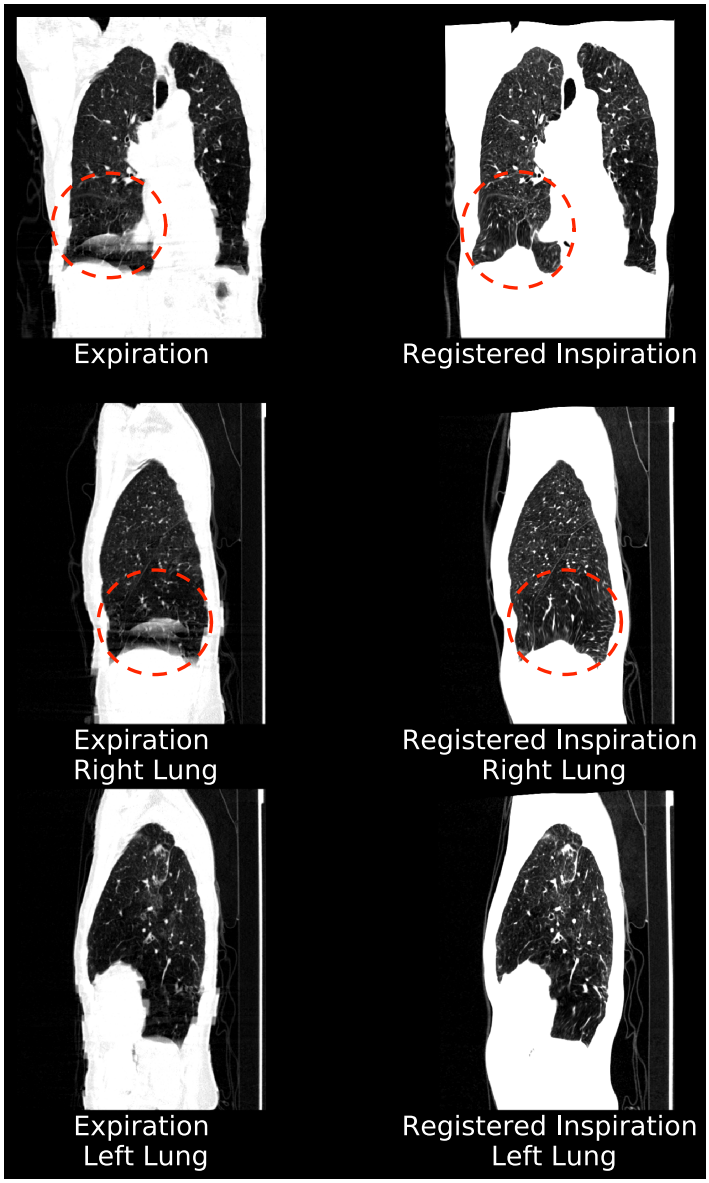
1. Lobe borders are poorly registered and the edges of the registered inspiration image have a blurred appearance. Additionally, internal landmarks are poorly aligned.



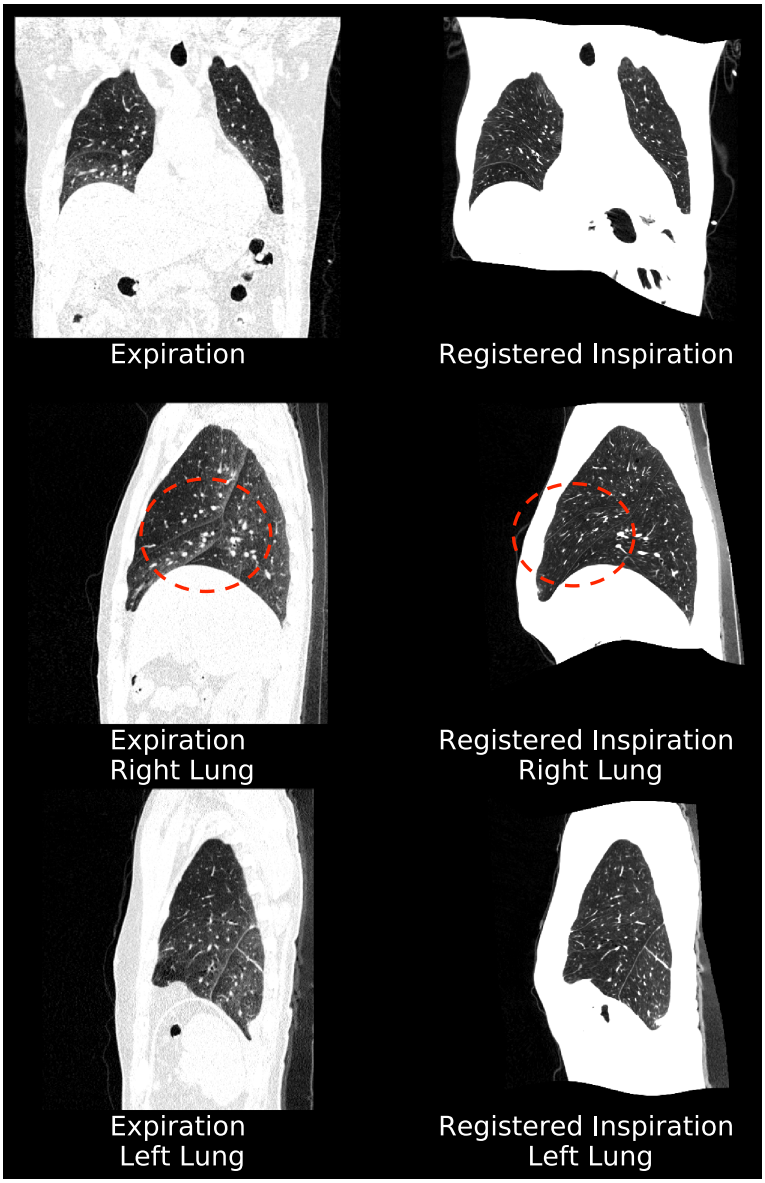
2. Superior lung borders of the right lung are not aligned. Additionally, lobe fissure in the left lung are not well-aligned.



3. Poor registration of the inferior border of the right lung due to respiratory motion during the expiration acquisition. The left lung registration is acceptable.



4. Internal anatomy poorly registered. Visualization of the lobar fissures in the right lung sagittal view indicates poor alignment of internal anatomical structures. The left lung registration is acceptable.



8.5.3 Examples of Acceptable Registrations

For reference, this section contains figures that illustrate examples of acceptable registrations.

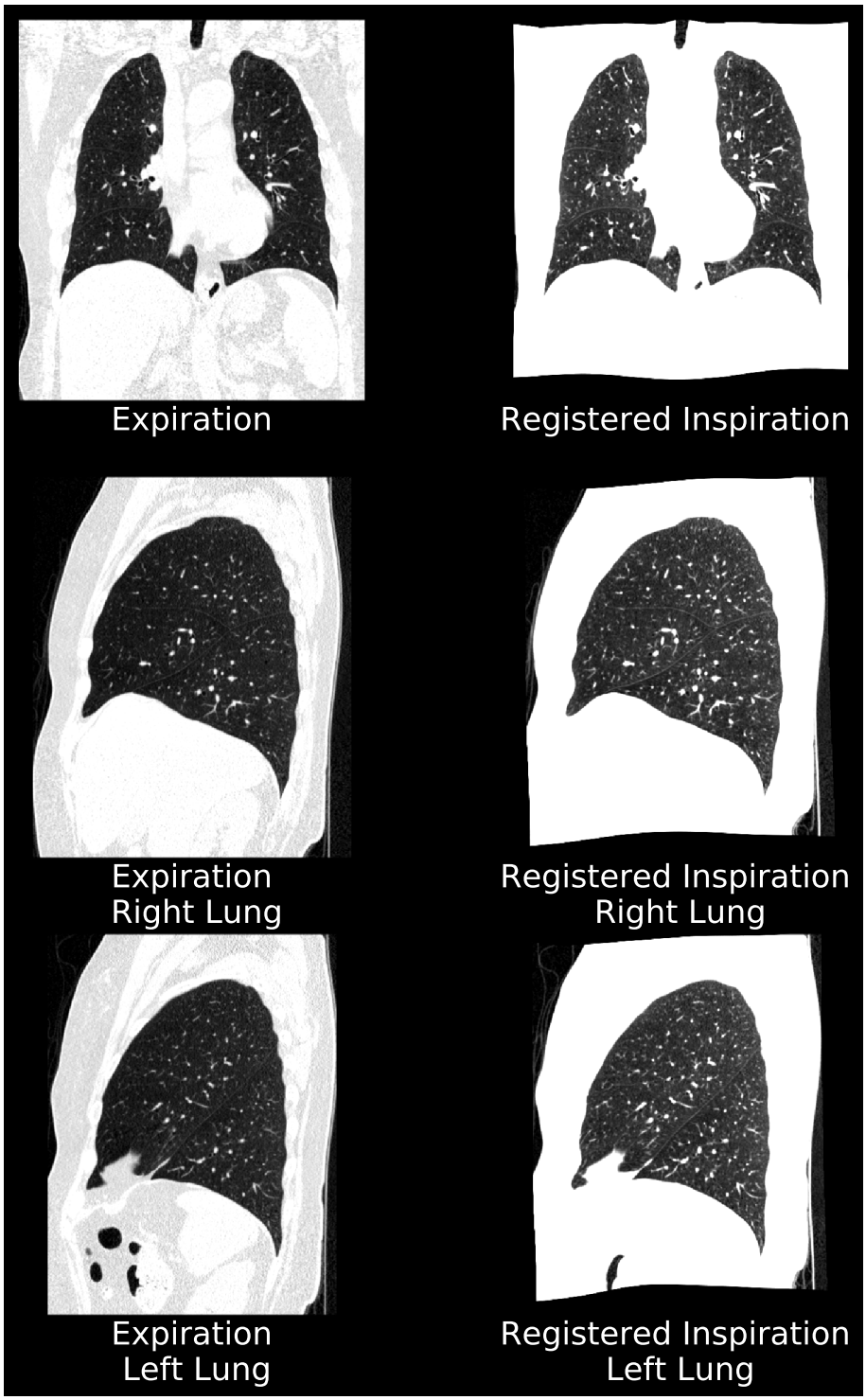


Figure 32: Acceptable registration example 1.

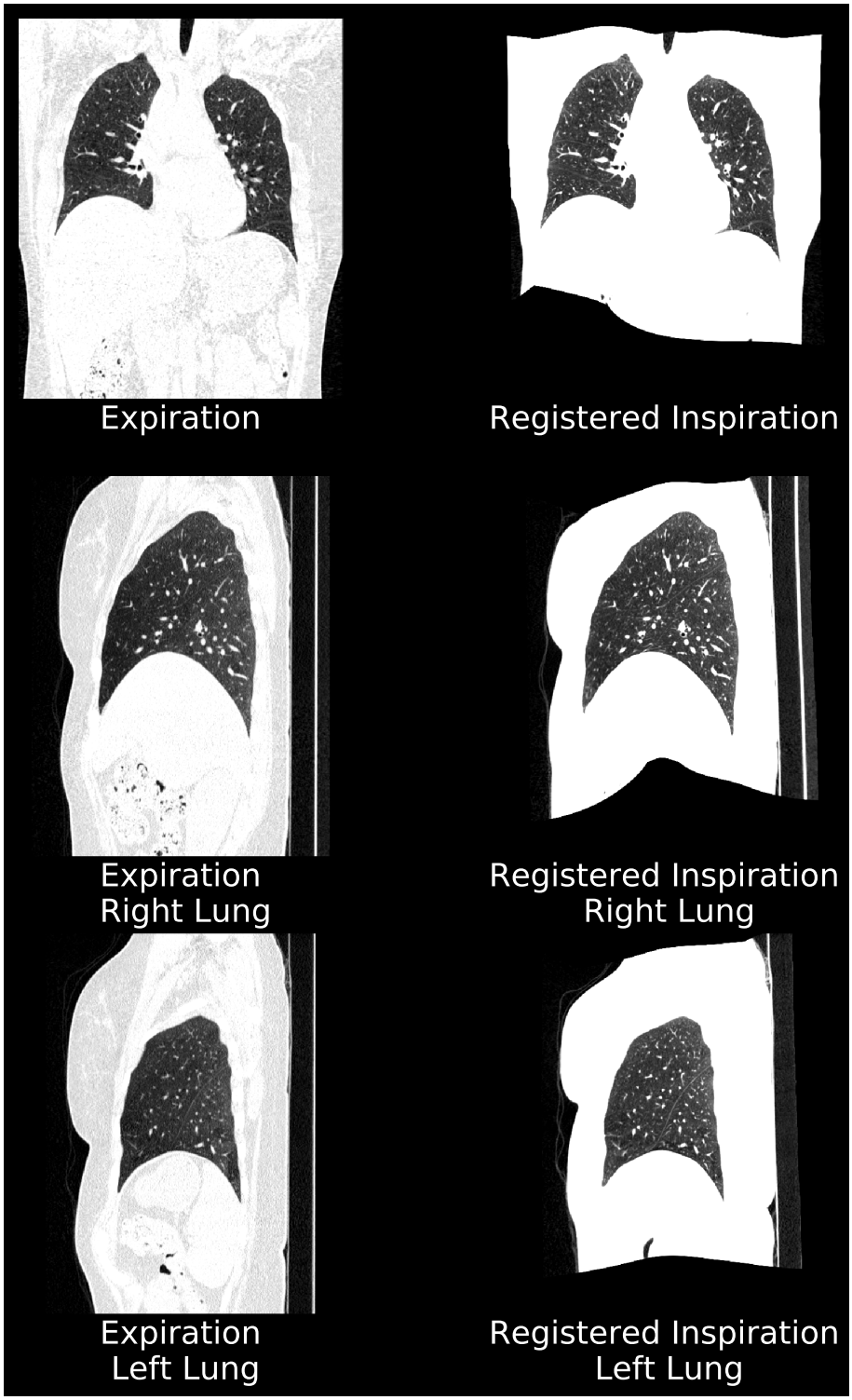


Figure 33: Acceptable registration example 2.

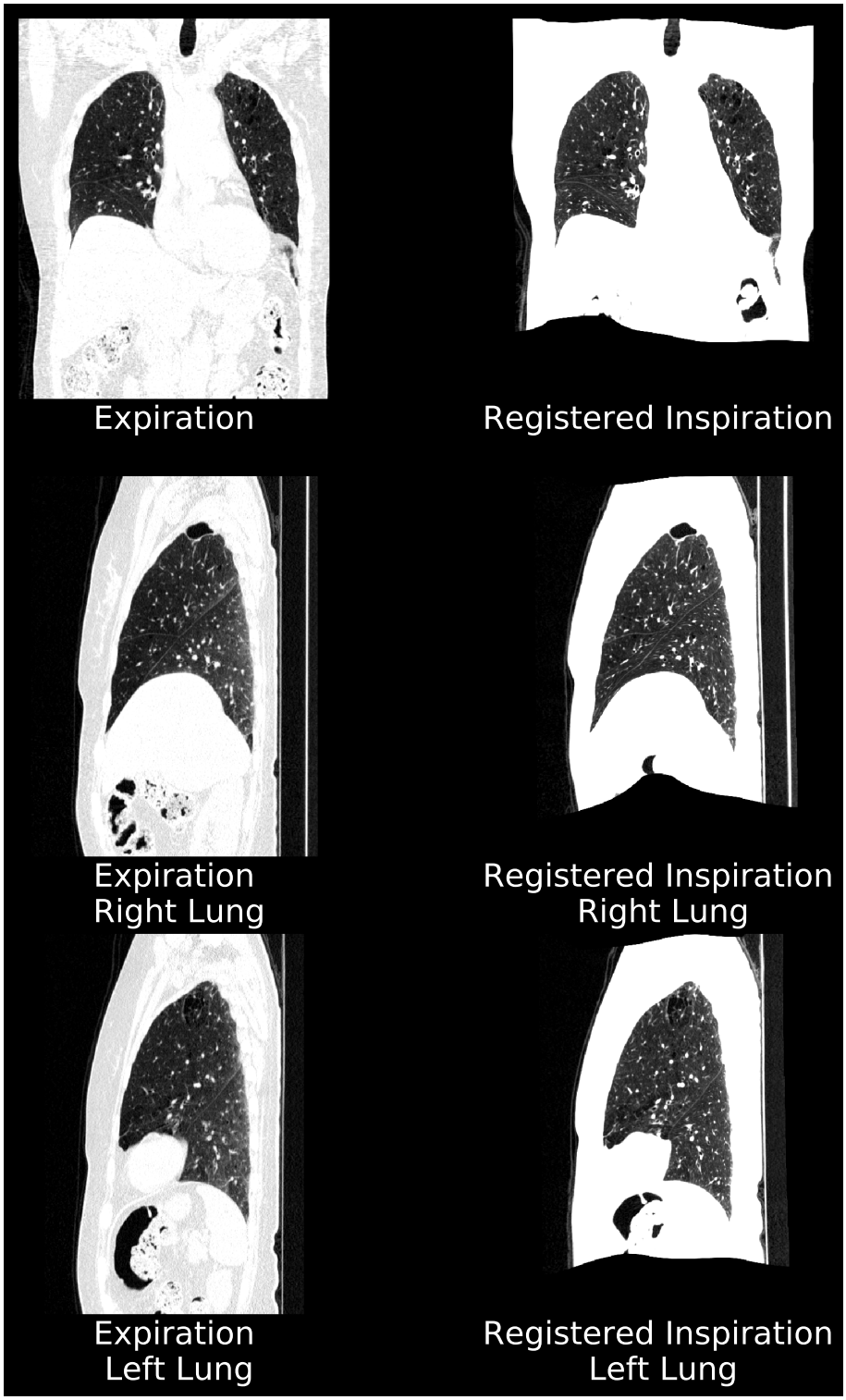


Figure 34: Acceptable registration example 3.

9 Unique Device Identification

9.1 Overview

The FDA has established a unique device identification system to adequately identify medical devices through their distribution and use. Therefore the label of Imbio's devices include a unique device identifier (UDI) in human- and machine-readable form.

9.2 Printing the Label

Printing barcode symbols is a very complex process. There are many variables that can affect the quality and readability of your printed barcode symbols, from the quality of the ink and paper stock, to printer resolution, to something as small as lint on the imaging wire of a laser printer; therefore, we highly recommend that you engage a certified barcode print vendor to ensure the quality and readability of your barcode.

10 Software Label

CT Lung Density Analysis Software
Version 5.1.1

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