

imbio

LUNG DENSITY ANALYSIS™

IMBIO CT LUNG DENSITY ANALYSIS™ USER MANUAL

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1 Introduction

1.1 Prescription Use Statement

Caution: Federal Law restricts this device to sale by or on the order of a physician.

1.2 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.

1.3 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

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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).

1.4 Contact Imbio



Imbio LLC
807 Broadway St NE, Suite 350
Minneapolis, MN 55413
United States
www.imbio.com

1.5 EU Declaration of Conformity

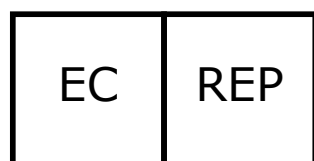
Imbio declares that this product conforms to the following Standard:



0086

The product complies with the Essential Requirements laid down in Annex I and is CE marked in accordance with Annex II of the European Medical Devices Directive 93/42/EEC as modified by 2007/47/EC.

The authorized representative for CE-Marking is Emergo Europe.



Emergo Europe
Prinsessegracht 20
2514 AP, The Hague
The Netherlands

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.

Please note that Imbio CT Lung Density Analysis™ Software does NOT currently support DICOM Files with JPEG2000 compression.

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) is equal to [1,0,0,0,1,0]. This typically will screen out scans performed while the patient is in a prone position.

*Imbio limits the inputs to images reconstructed with non-edge enhancing kernels. Sharp kernels are not appropriate for Lung Density Analysis. For an exhaustive list of prohibited kernels, see list below.

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DICOM Tag	Name	Required Value
(0008,0060)	Modality	CT
(0028,0030)	Pixel Spacing	$\leq 2.0 \times 2.0 \text{ mm}^2$
(0018,9305)	Revolution Time	$\leq 1.0 \text{ s}$ (if present)
N/A	Slice Spacing	$\leq 4.0 \text{ mm}$
(0018,0050)	Slice Thickness	$\leq 4.0 \text{ mm}$
N/A	Field of View	$\geq 10.0 \times 10.0 \times 20.0 \text{ cm}^3$
(0018,1210)	Convolution Kernel	Not an edge enhancing kernel*

Table 1: Required CT Scan Parameters

Unacceptable Kernels

Below is a list of kernels that are not acceptable for Imbio CT Lung Density Analysis™ Software. If an image with one of the following kernels is passed to the software, an error will be raised and the analysis will not run.

GE: bone+, edge, lung

PHILIPS: D

TOSHIBA: FC30, FC31, FC80, FC81, FC82

SIEMENS:[B/S/U][6-8][0-5][s/f/h], [C/D/H/T][2-8][0-5][s/f/h]*

*This notation is meant to simplify the combination of kernel names. This notation expanded would be the following: B60s, B60f, B60h, B61s, B61f, B61h, B62s, B62f, B62h, B63s, B63f, B63h, B64s, B64f, B64h, B65s, B65f, B65h, B70s, B70f, B70h, B71s, B71f, B71h,...,B80s, B80f, B80h, B81s, B81f, B81h,...,S60s, S60f, S60h, S61s, S61f, S61h... etc.

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 2.5 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™ Software also requires that the patient lies in the supine position rather than the prone position during scanning. 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.

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

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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)	<i>Effective mAs: 200 (Ins)</i> <i>Effective mAs: 50 (Exp)</i>	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

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.

*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.

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2_INDICATIONS FOR USE AND REQUIREMENTS

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. Configura- tion	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)	<i>Effective mAs:</i> 40- 80 (Ins) <i>Effec-</i> <i>tive mAs:</i> 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

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...

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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

Breathe 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 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.

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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.

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).

4_COMPONENTS

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

Before classification, a noise reducing filter is applied to the lung datasets by default. This filtering can be turned off by the user.

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

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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 Adjustable Percentile (Insp. Assessment Feature Only)

The Inspiration Assessment calculates PercX (where "X" corresponds to the desired percentile), the HU value corresponding to the Xth percentile of lung intensity values. The percentile used to compute the percentile low attenuation area can be adjusted to be any value between 0 and 100. The default value for X is 15.

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 version: 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 Additional Patient Information

Both the Inspiration and Functional Assessment Reports can be generated with an optional second page containing a list of additional information about the patient and their CT scan. The list is customizable and can display any information that is contained within the CT DICOM image meta-data.

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 coronal slices from the Functional Assessment Map with lobar segmentation enabled (left) and not enabled (right) are shown below in Figure 1.

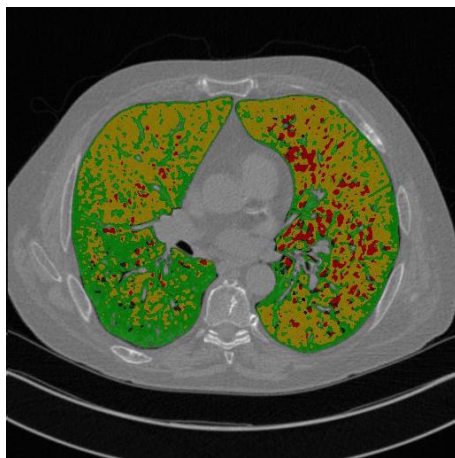


Figure 1: Slice of Functional Assessment Map

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 2 for example segmentation DICOM series images and section 8.3 for more details on how to interpret the images.

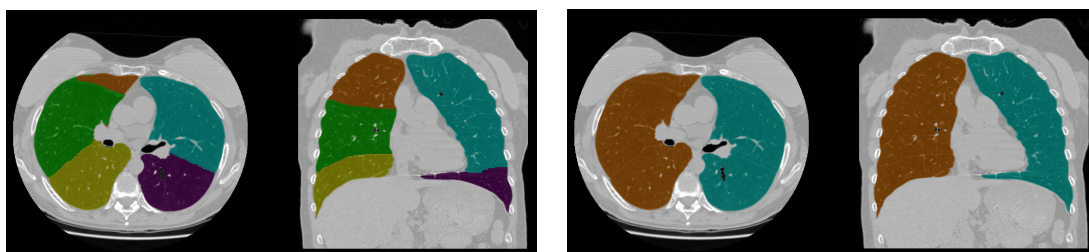


Figure 2: Example segmentation maps: Lobar segmentation activated (left) and lobar segmentation de-activated.

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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 3 shows an example of this output side by side with a corresponding expiration image. Please see section 8.6 for more details on how to interpret this image.

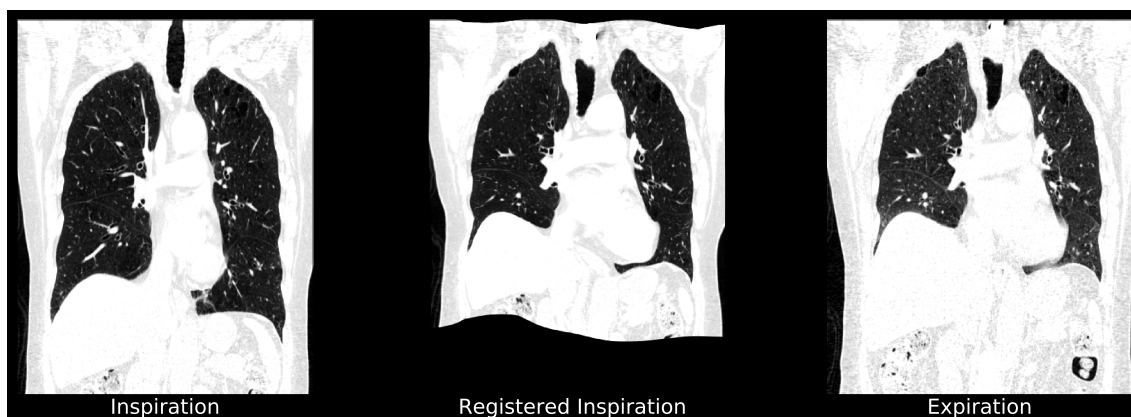
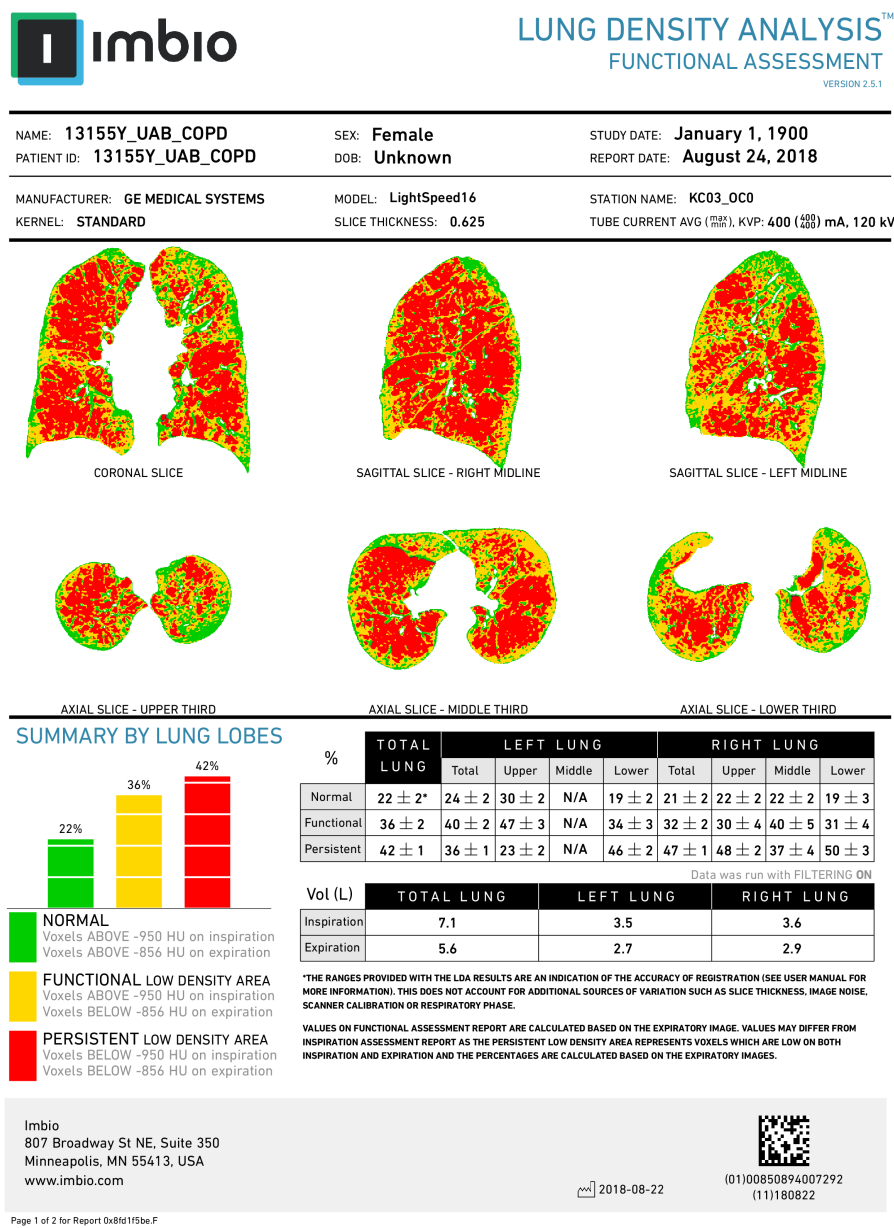


Figure 3: Inspiratory phase CT scan registered to the expiratory phase CT scan.

5_FUNCTIONAL ASSESSMENT

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 4.



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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. 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.

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. 5).

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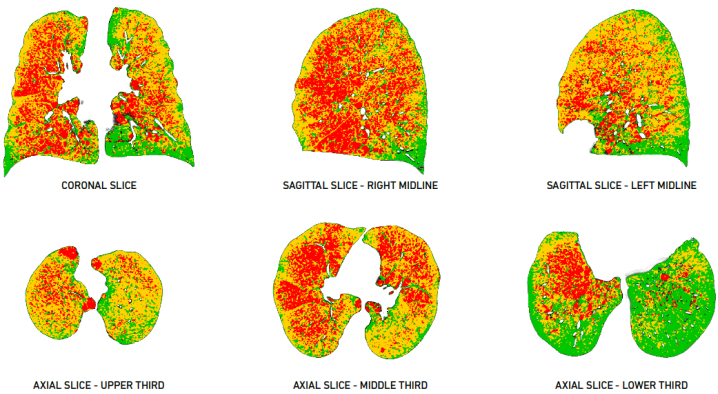


Figure 5: Example of lung images found in Functional Assessment Report

Additional Patient Information

An optional second page containing additional patient information can be added to the functional report. Any information stored within the CT DICOM image metadata can be added to the list on the second page of the report. An example showing the Institution Name, Referring Physician Name, and Product Name is shown below (Fig. 6).


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LUNG DENSITY ANALYSIS™
 ADDITIONAL STUDY INFORMATION
VERSION 2.5.1

NAME: 13155Y_UAB_COPD	SEX: Female	STUDY DATE: January 1, 1900
PATIENT ID: 13155Y_UAB_COPD	DOB: Unknown	REPORT DATE: August 24, 2018

Manufacturer:	GE MEDICAL SYSTEMS
Institution Name:	The Kirklin Clinic
Product Name:	Imbio LDA Functional Assessment 2.5.1

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01090008F4007292
(11180822)

Figure 6: Example of the optional second page of the LDA 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 an inhalation threshold, input a percentile for PercX calculation, 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 inspiration image with an RGB overlay. The RGB overlay identifies two classes of tissue. First, voxels that are labeled as lung tissue by the segmentation algorithm and have a HU value equal to or above the inhalation threshold are identified by a translucent blue color. The blue voxels can be used to assess the quality of the lung segmentation. Second, voxels that are labeled as lung tissue by the segmentation algorithm and have a HU value below the inhalation threshold are identified by an opaque red color. The inhalation threshold may be determined by the user and provided as inputs to the Imbio CT Lung Density Analysis™ Software. If thresholds are not defined by the user, the inhalation threshold defaults to -950 HU.

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

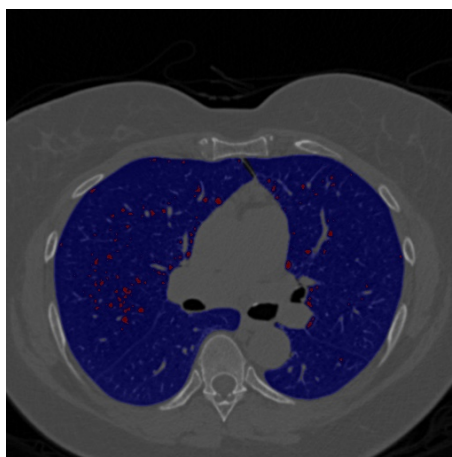


Figure 7: Slice of Inspiration Assessment Map

6.3 Segmentation Map

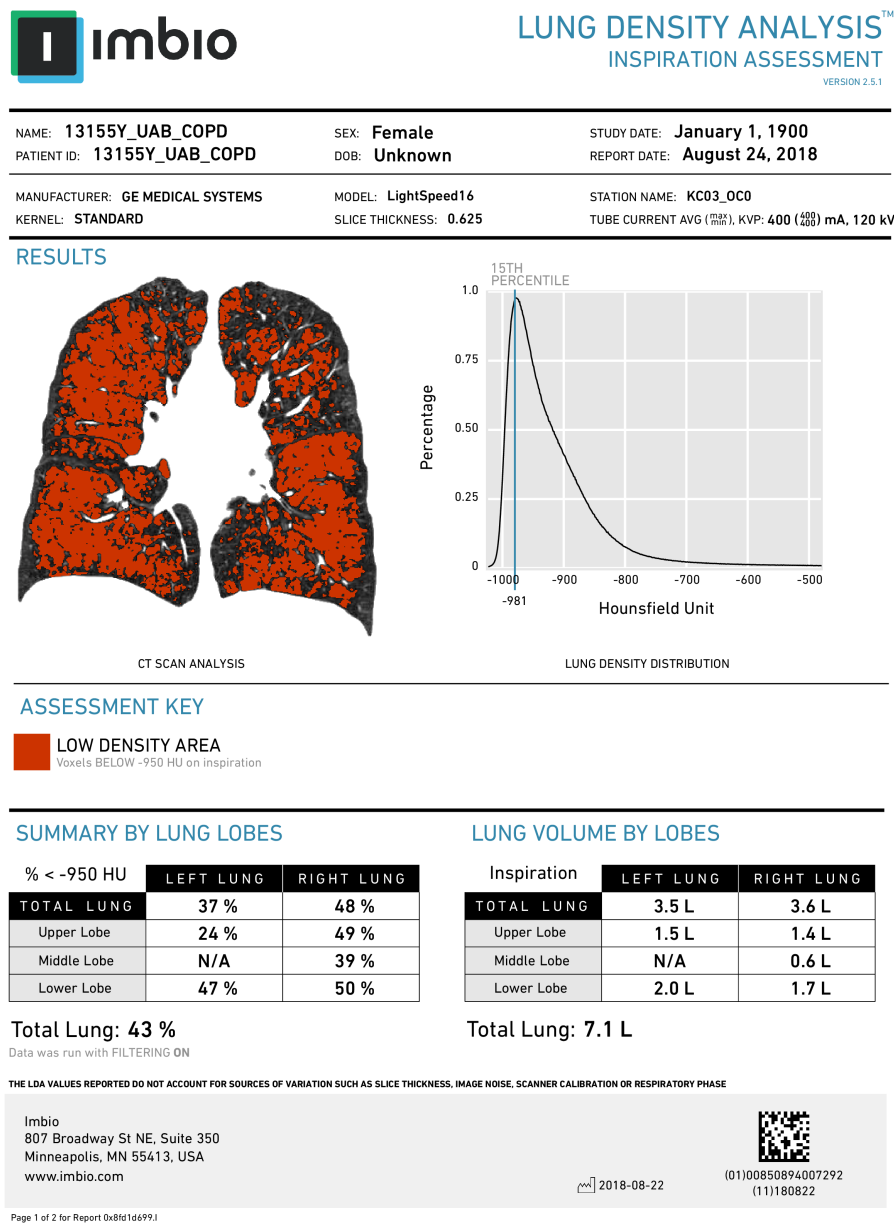
Imbio CT LDA Inspiration Assessment Software produces a segmentation DICOM series so that users can assess the quality of segmentation. For more details, please refer to sections 5.3 and 8.3.

6.4 Inspiration Assessment Report

The Inspiration Assessment Report 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 Inspiration Assessment Map. It contains patient information, lung slice images, charts and tables displaying results. An example report is shown below in Figure 8. As explained in Section 5.5, it is important to note the image acquisition parameters. Please see Section 5.5 for more details.

IMBIO CT LUNG DENSITY ANALYSIS™ USER MANUAL

6_INSPARATION ASSESSMENT



6_INSPARATION ASSESSMENT

Report Graphics

The report displays an image of the mid coronal slice of the Inspiration Assessment Map. In the image shown in the report, only the voxels that are labeled as lung tissue by the segmentation algorithm and have a HU value below the inhalation threshold are shown. Below is an example of the image found in the report (Fig. 9) .

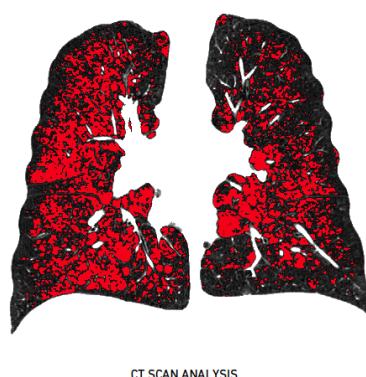


Figure 9: Example of lung image in Inspiration Assessment Report

The other graphic in the report is the Density Histogram. This plot visually displays the percentage of lung voxel density at each Hounsfield Unit for both lungs. In addition, a line corresponding to the PercX measurement (see Section 4.3.5 for details about PercX) is shown on the histogram. Below is an example of the image found in the report (Fig 10).

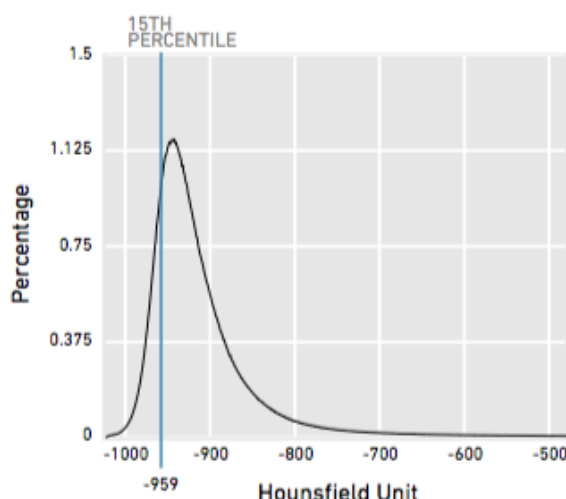


Figure 10: Example of Density Histogram in Inspiration Assessment Report

6_INSPARATION ASSESSMENT

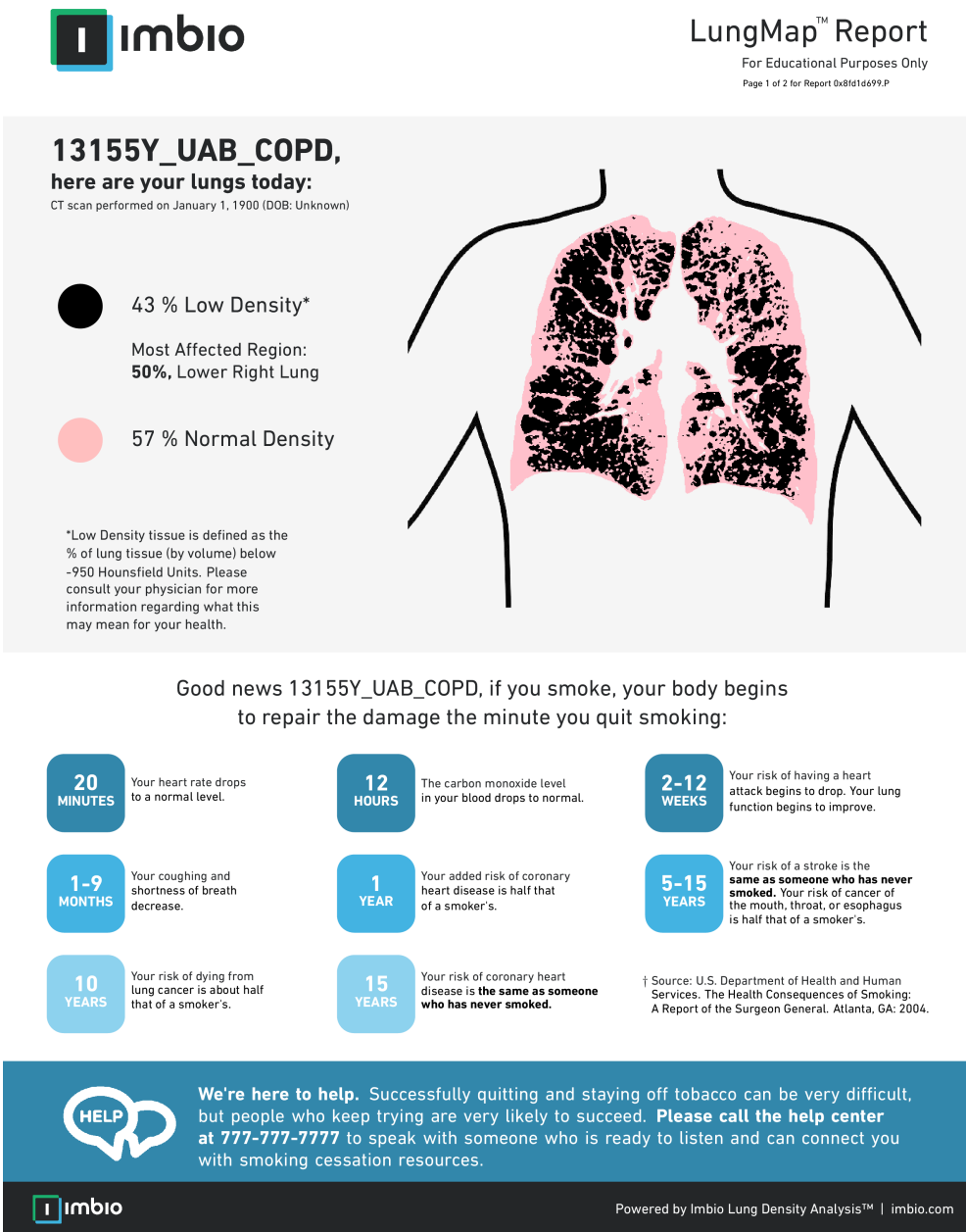
Additional Patient Information

An optional second page containing additional patient information can be added to the inspiration report. As it does not differ from the second page of the functional report, please refer to section 5.5 and Fig. 6 for more details.

6_INSPARATION ASSESSMENT

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 11.



IMBIO CT LUNG DENSITY ANALYSIS™ USER MANUAL

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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 12.

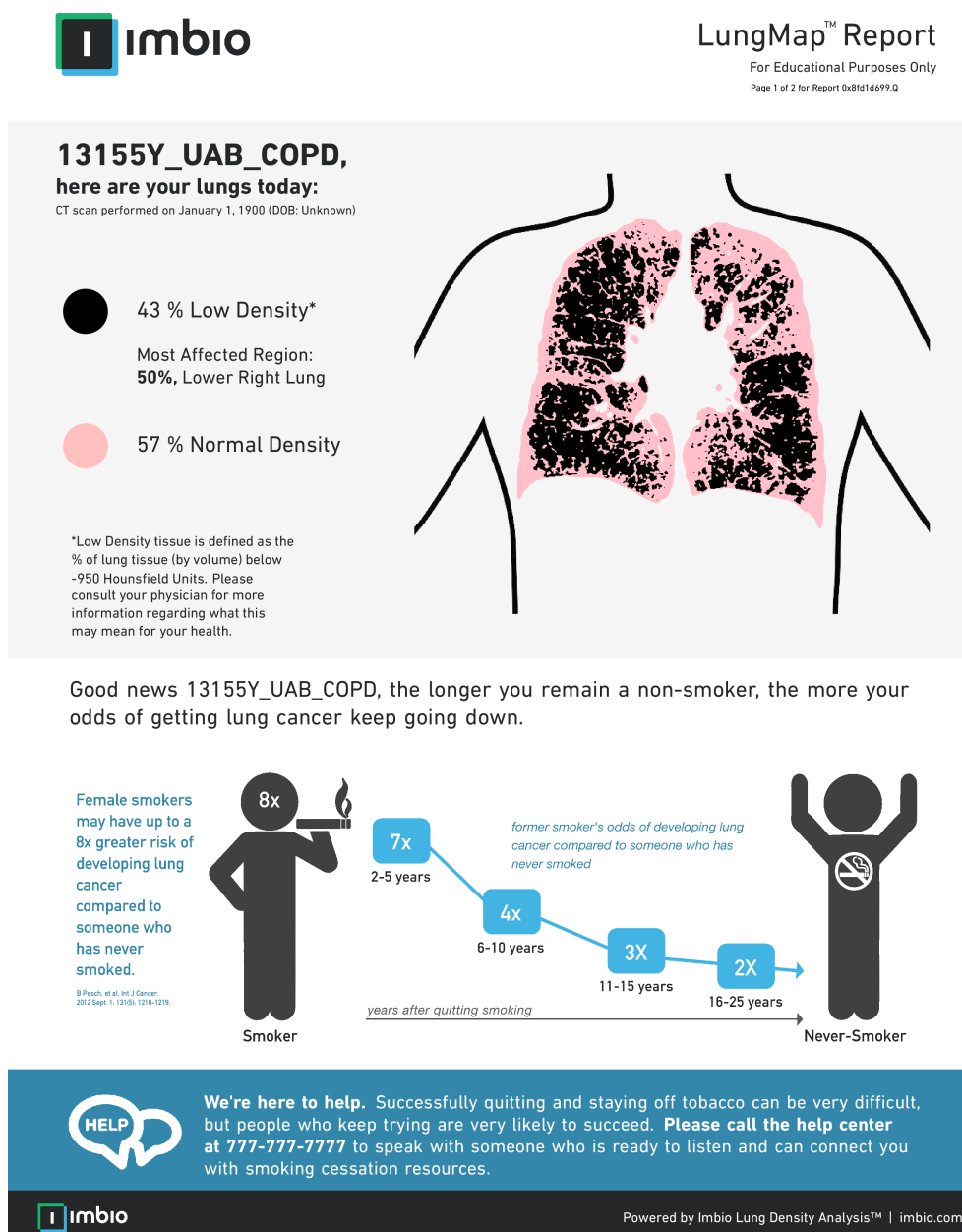


Figure 12: Example LungMap™ Report for former smokers

6_INSPARATION ASSESSMENT

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. 13).

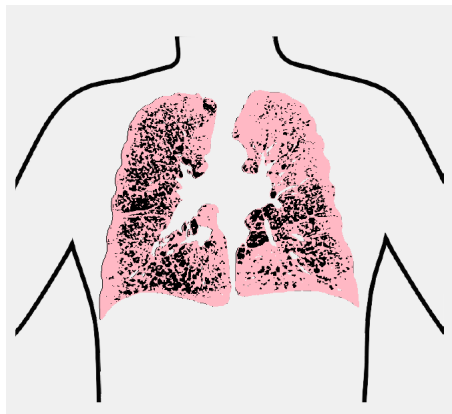


Figure 13: Example of lung image in LungMap™ Report

The other graphic in the current smoker report is a table of smoking cessation benefits (Figure 14). 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 15). This figure is personalized based on whether or not the patient is male (Fig. 15) or female (Fig. 16). Please see Table 4 from [1].

6_INSPARATION ASSESSMENT

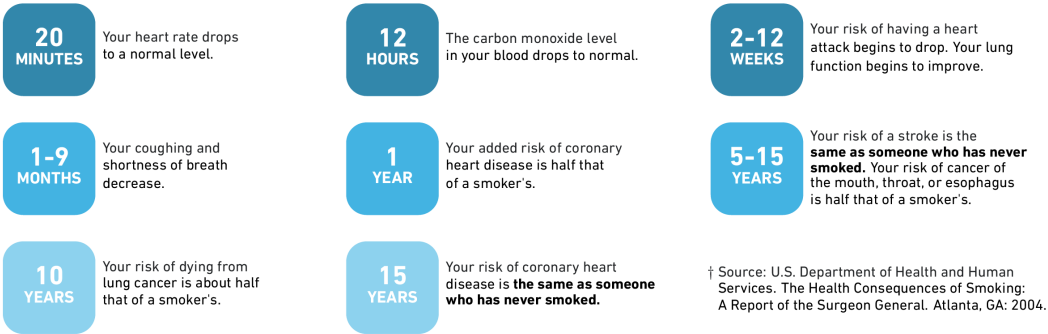


Figure 14: Table of Smoking Cessation Benefits

Good news 10170F_NJC_COPD, the longer you remain a non-smoker, the more your odds of getting lung cancer keep going down.

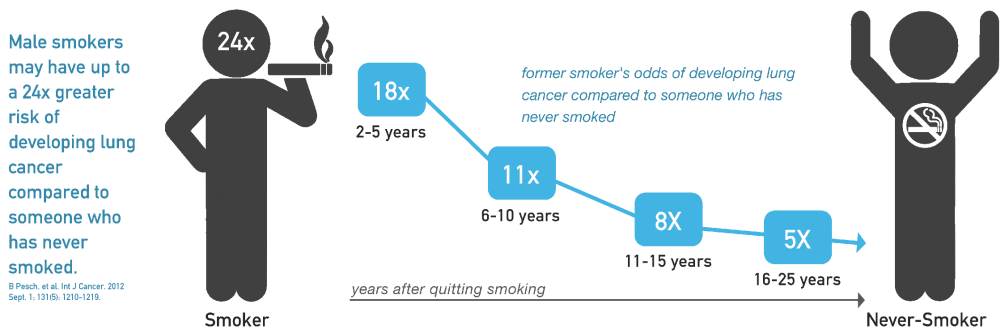


Figure 15: Figure showing the decreasing relative risk of lung cancer diagnosis compared to never-smokers for males.

Good news 13155Y_UAB_COPD, the longer you remain a non-smoker, the more your odds of getting lung cancer keep going down.

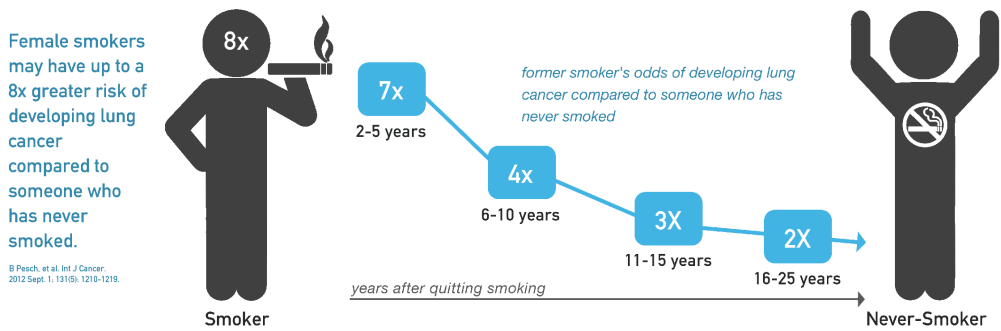


Figure 16: Figure showing the decreasing relative risk of lung cancer diagnosis compared to never-smokers for females.

7_POSSIBLE ENCOUNTERED EXCEPTIONS

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: Input data invalid::`

This error occurs if one or more acquisition parameters do not meet Imbio's requirements. For the details on each required parameter, see Section 2.2.1.

`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 within the field of view of the image.

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`

7_POSSIBLE ENCOUNTERED EXCEPTIONS

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 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).

%	TOTAL LUNG	LEFT LUNG				RIGHT LUNG			
		Total	Upper	Middle	Lower	Total	Upper	Middle	Lower
Normal	24 ± 2*	27 ± 2	23 ± 2	16 ± 1	48 ± 3	21 ± 2	15 ± 2	12 ± 1	34 ± 3
Functional	50 ± 1	51 ± 2	61 ± 3	56 ± 2	37 ± 4	49 ± 2	57 ± 3	51 ± 2	41 ± 4
Persistent	25 ± 1	20 ± 1	15 ± 1	27 ± 2	14 ± 2	30 ± 1	27 ± 2	36 ± 2	24 ± 1

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.

8_CONSIDERATIONS TO REDUCE RISK

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.

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.

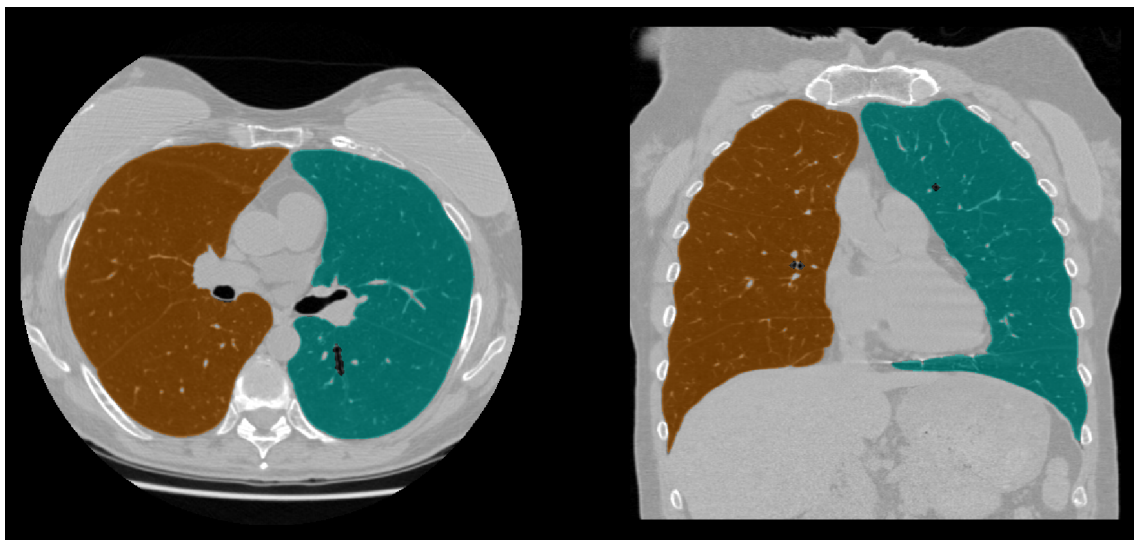


Figure 19: Example lung segmentation.

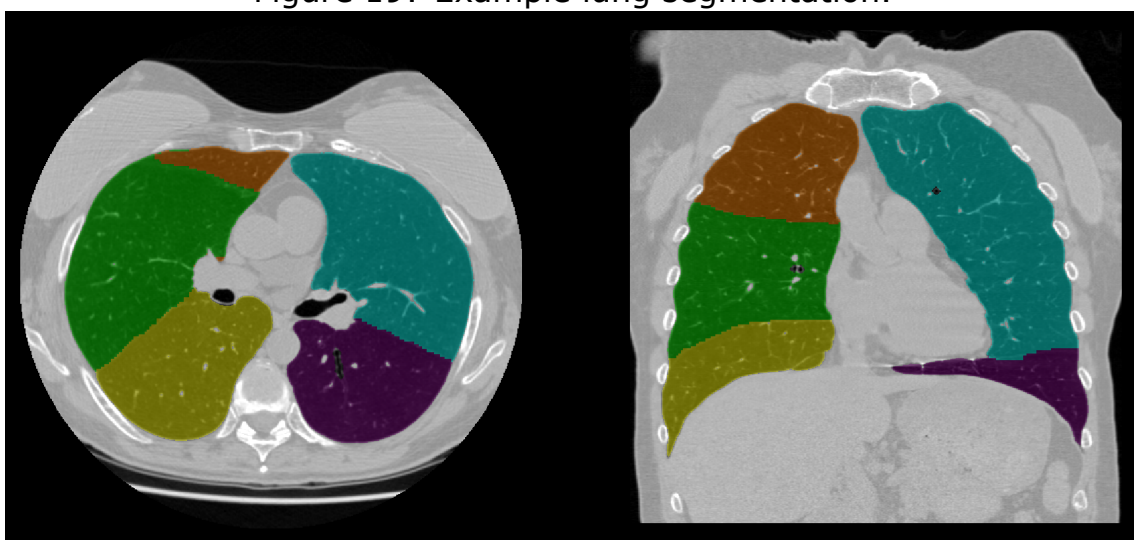


Figure 20: Example lobar segmentation.

8_CONSIDERATIONS TO REDUCE RISK

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.

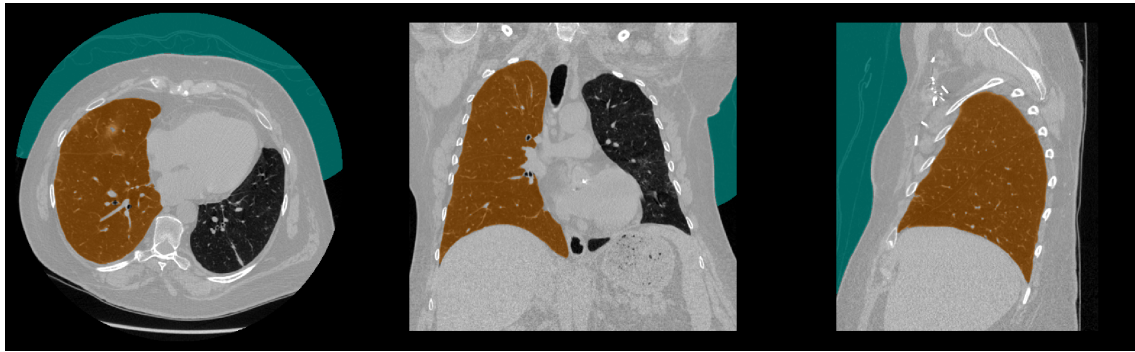


Figure 21: Segmentation overlay showing outside air inclusion error.

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.

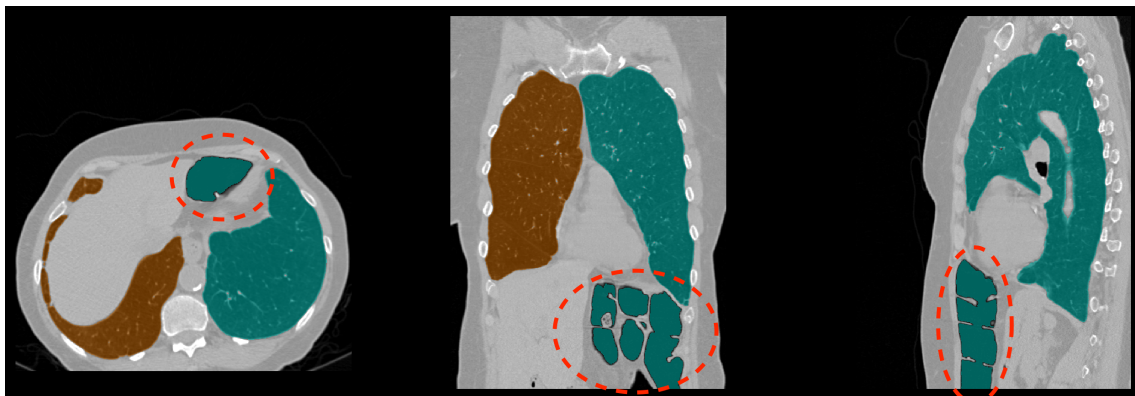


Figure 22: Segmentation overlay showing gut air inclusion error.

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).
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.
4. Exclusion due to dependent atelectasis.

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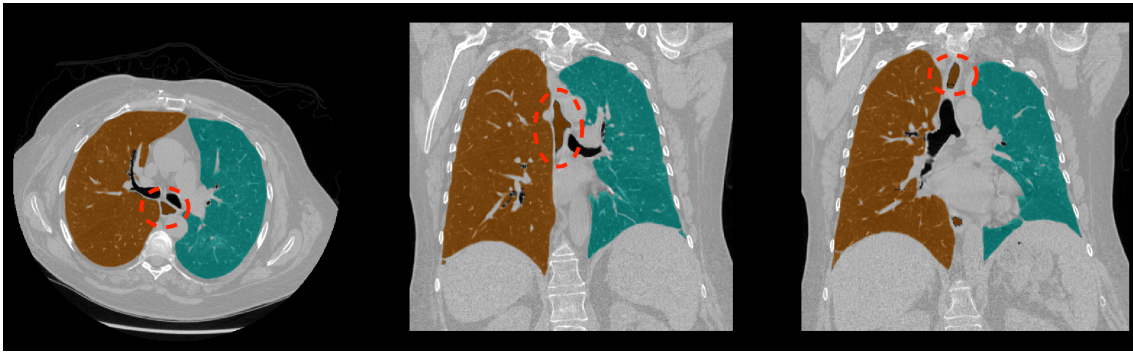


Figure 23: Segmentation overlay showing gut air inclusion error.

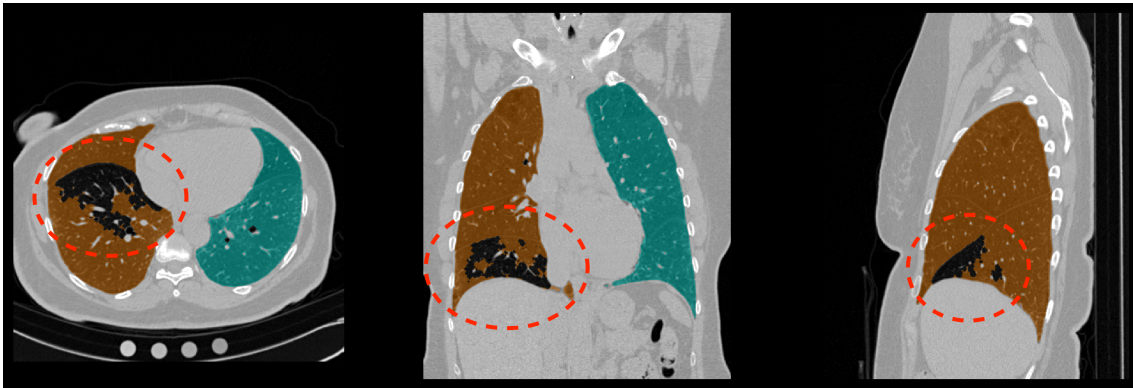


Figure 24: Segmentation overlay showing airway leak into lung parenchyma.

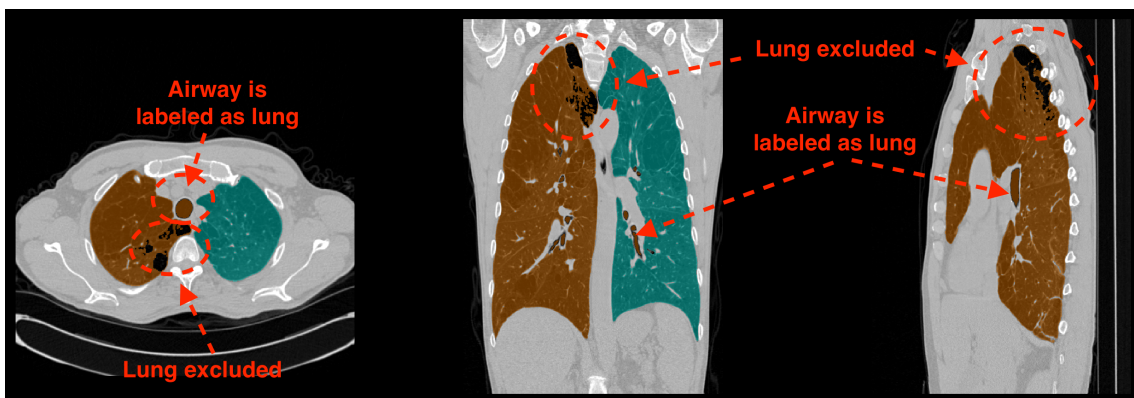


Figure 25: Segmentation overlay showing lung apex classified as trachea.

5. Left/right lung labeling error.

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

8_CONSIDERATIONS TO REDUCE RISK

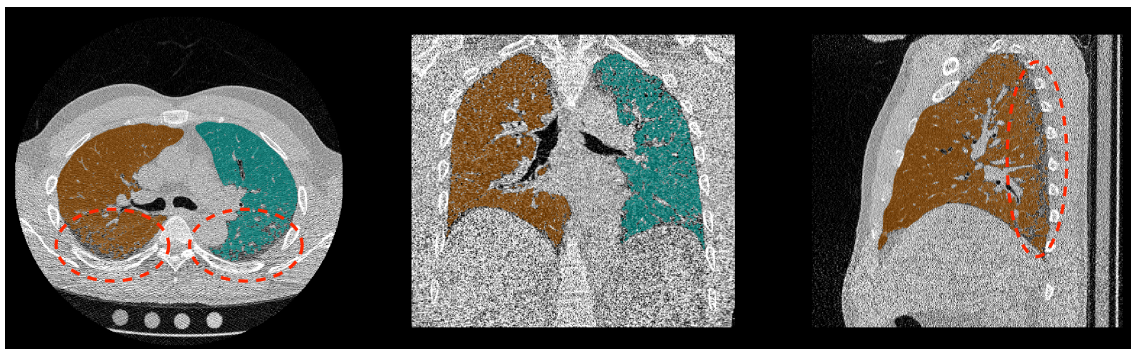


Figure 26: Segmentation overlay lung exclusion due to dependent atelectasis.

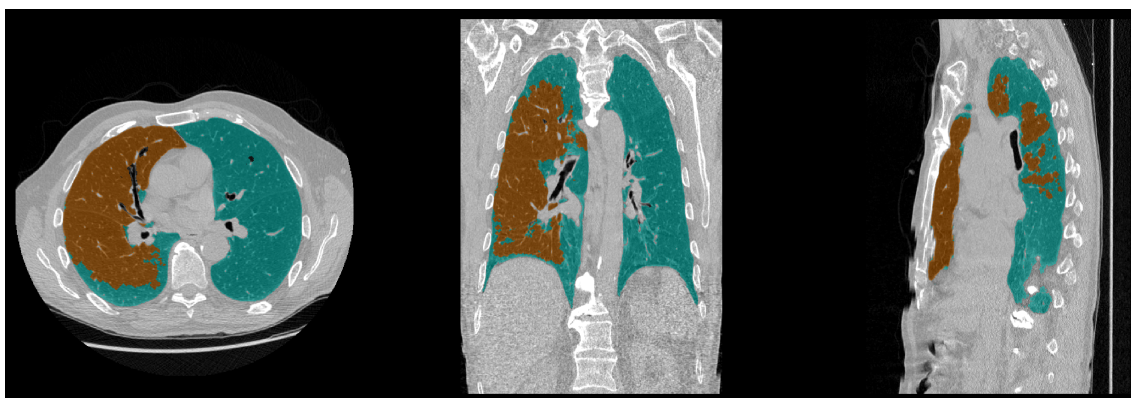


Figure 27: Segmentation overlay showing left/right lung mislabeling.

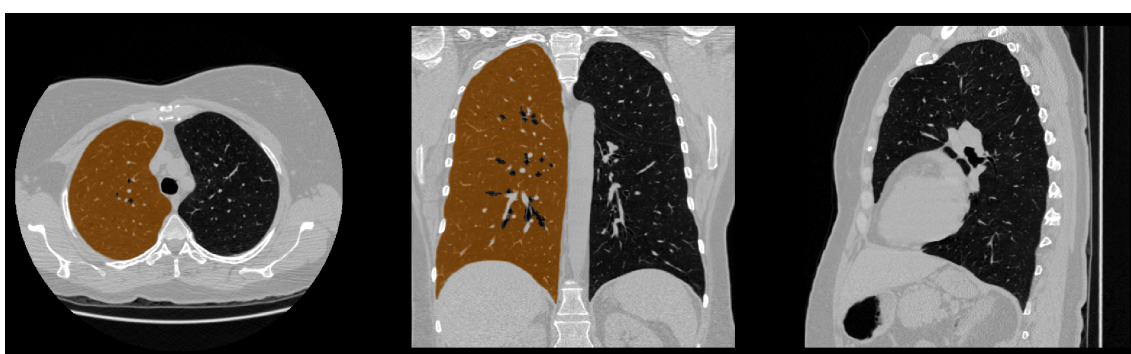


Figure 28: Segmentation overlay showing left lung exclusion.

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

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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 may be especially helpful for detecting segmentation errors.

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

8.5 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.

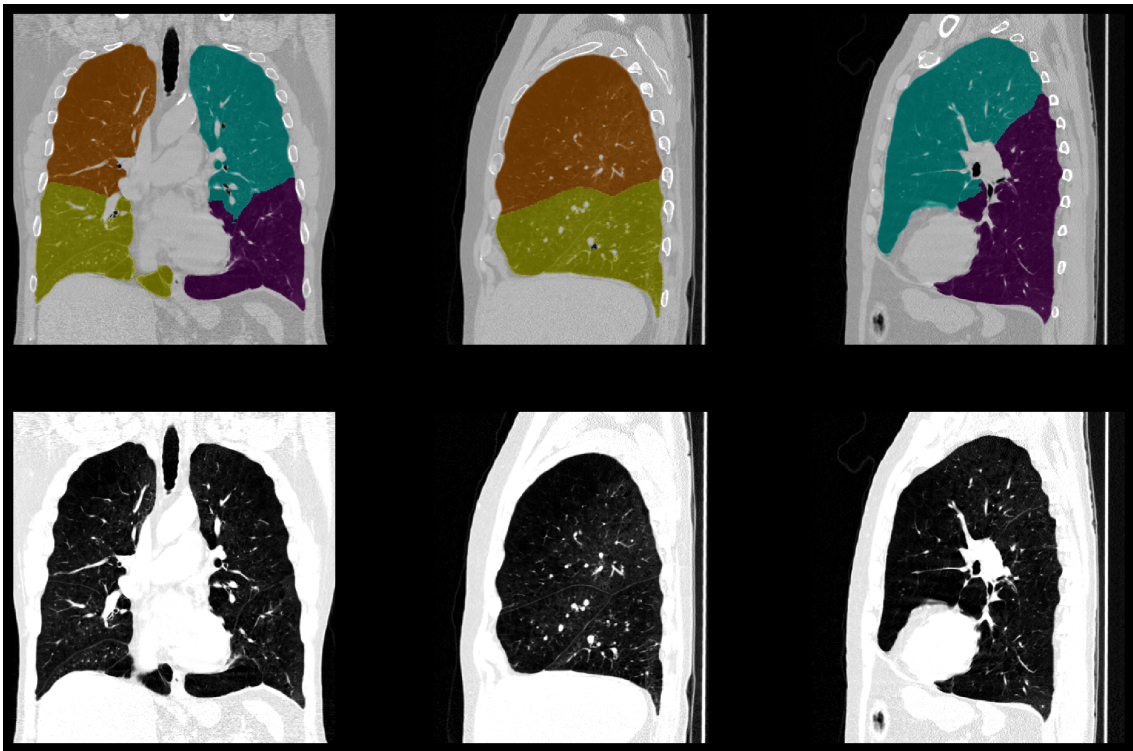


Figure 29: Segmentation showing a missing middle right lobe.

8_CONSIDERATIONS TO REDUCE RISK

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.

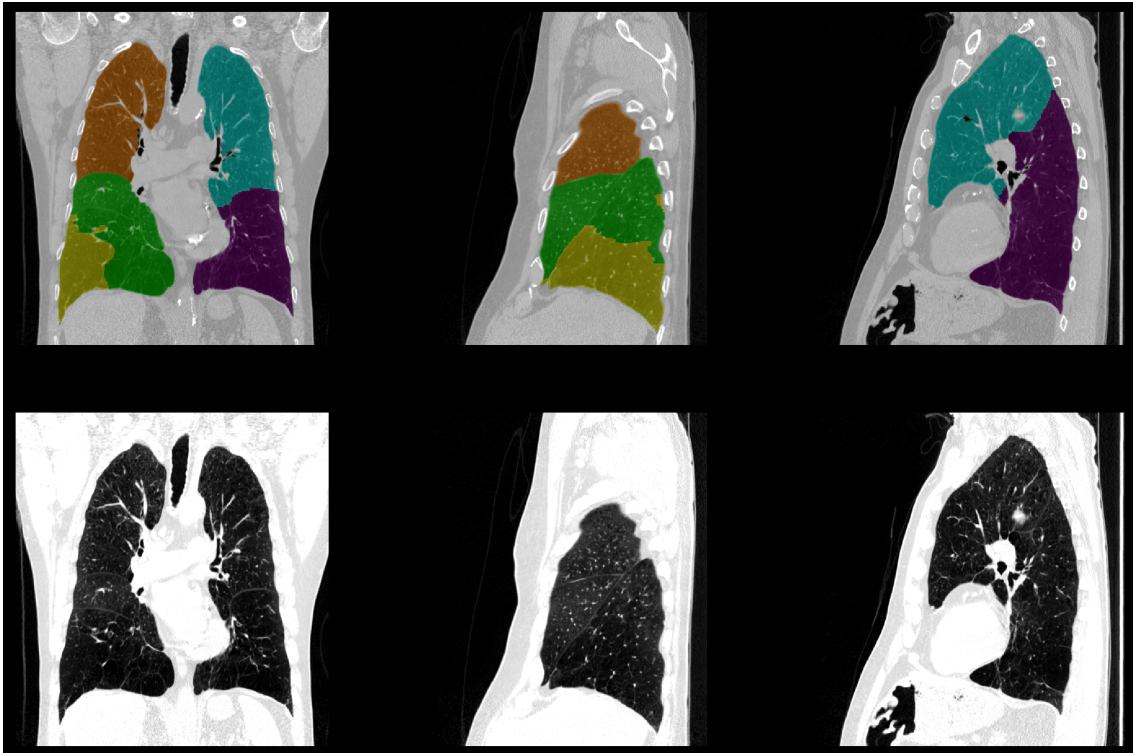


Figure 30: Lobe borders in segmentation are not correctly aligned with fissures.

8_CONSIDERATIONS TO REDUCE RISK

8.6 Image Registration Quality Assessment

8.6.1 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.

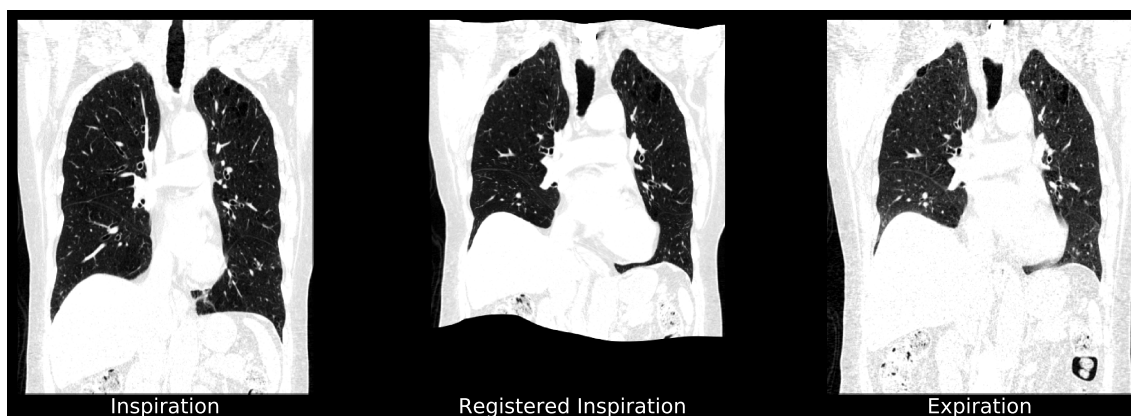


Figure 31: Inspiratory phase CT scan registered to the expiratory phase CT scan.

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.

8.6.2 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

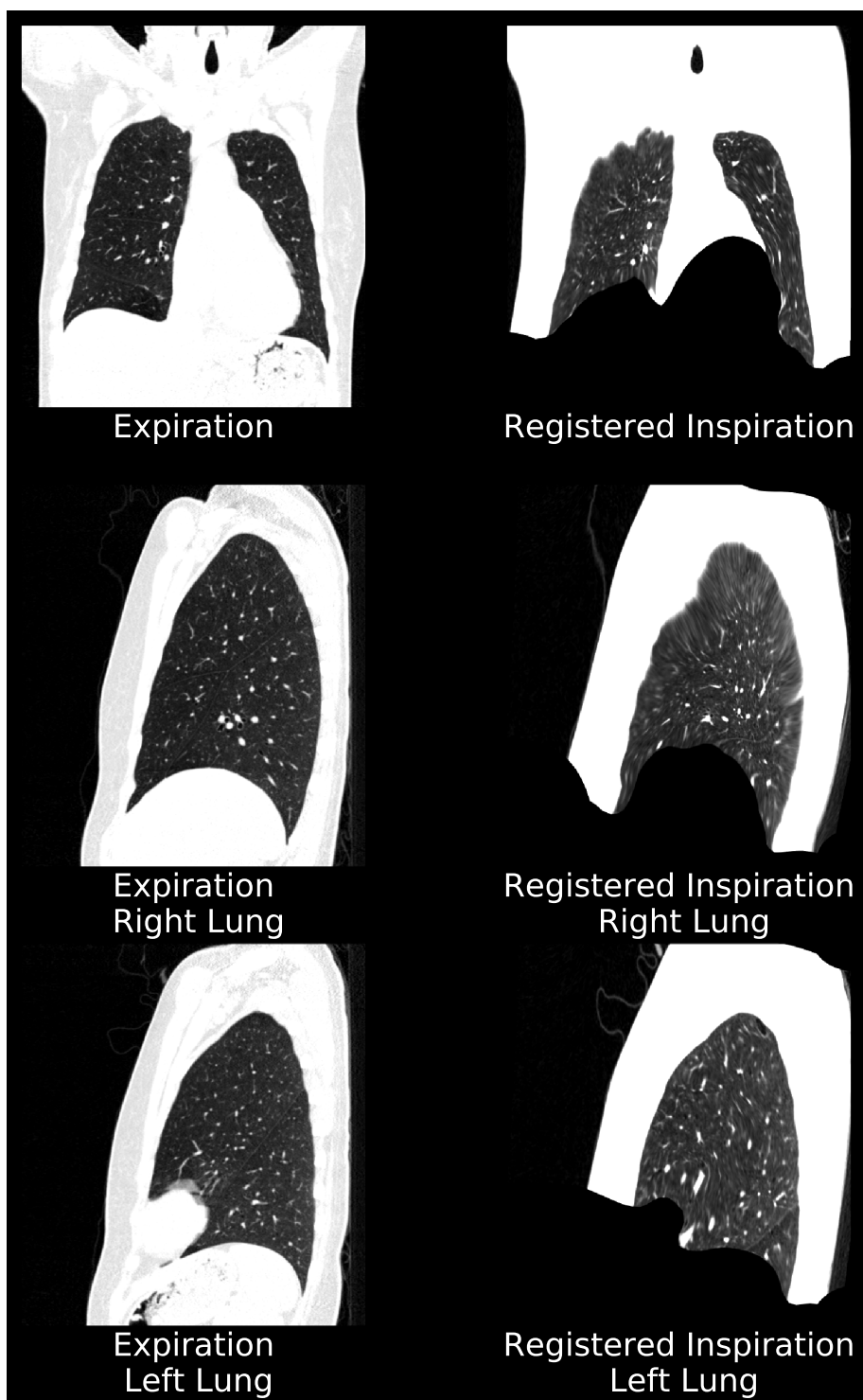
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by Pulmonologists, Radiologists, and Radiology Technicians under the supervision of a Pulmonologist or Radiologist.

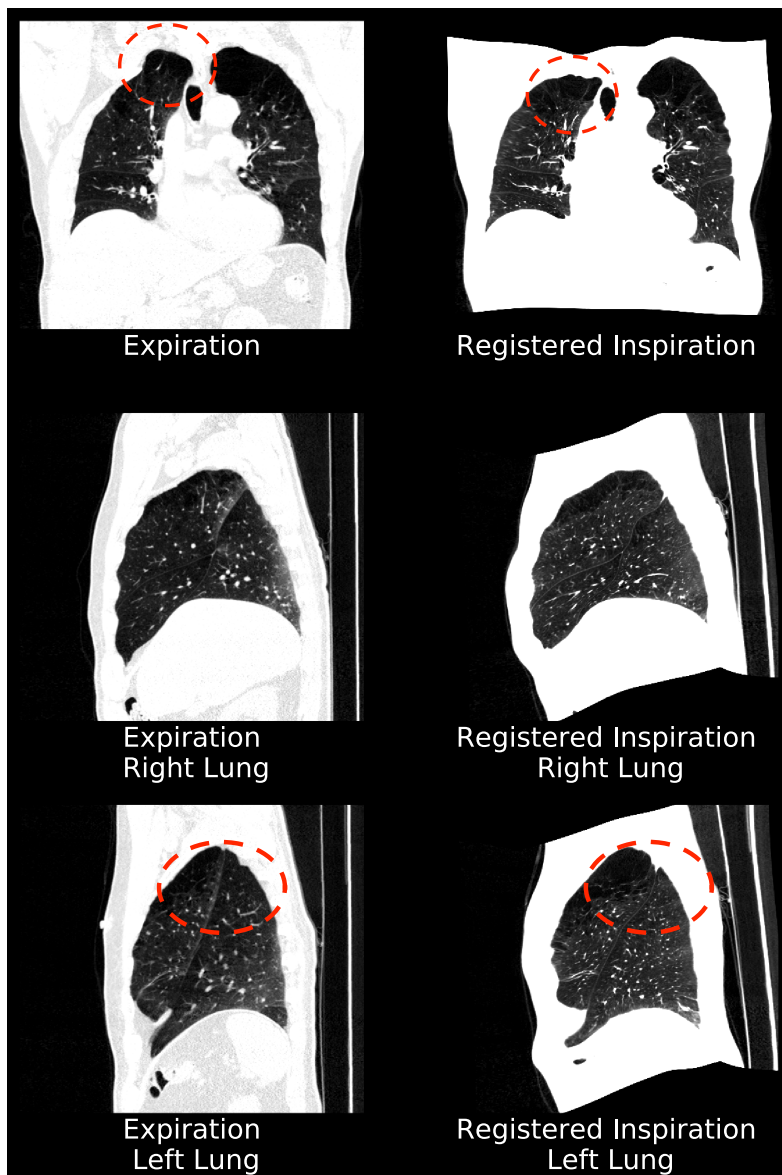
8_CONSIDERATIONS TO REDUCE RISK

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



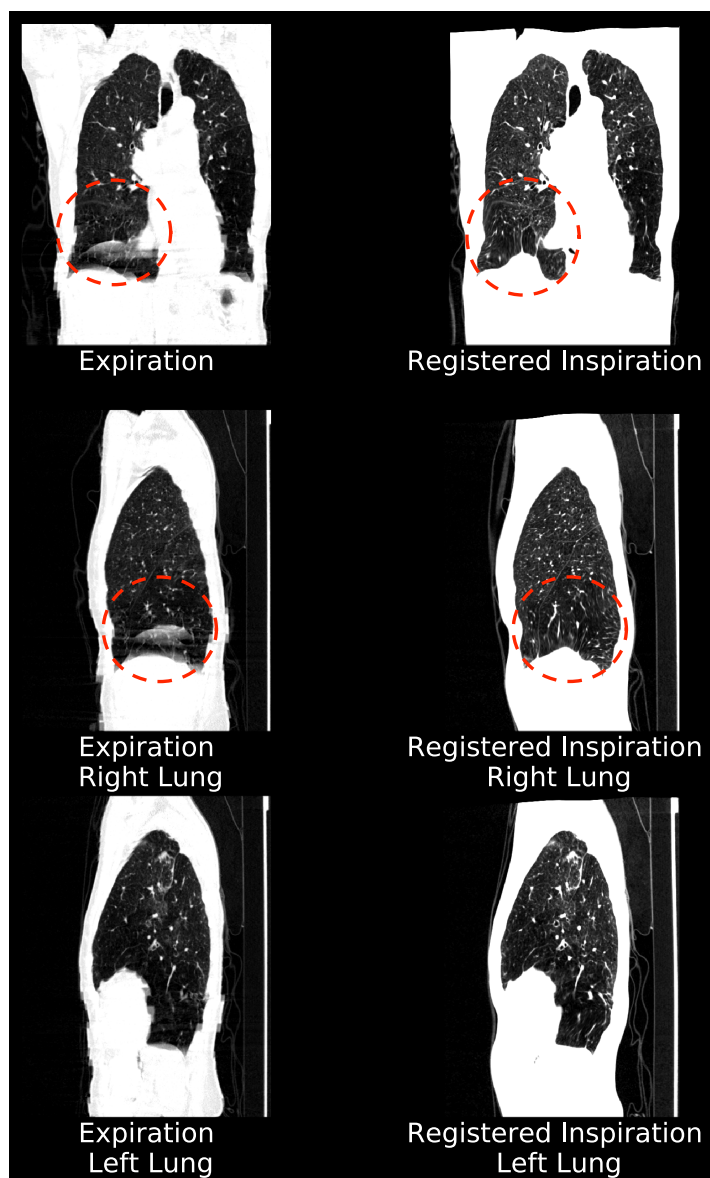
8_CONSIDERATIONS TO REDUCE RISK

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



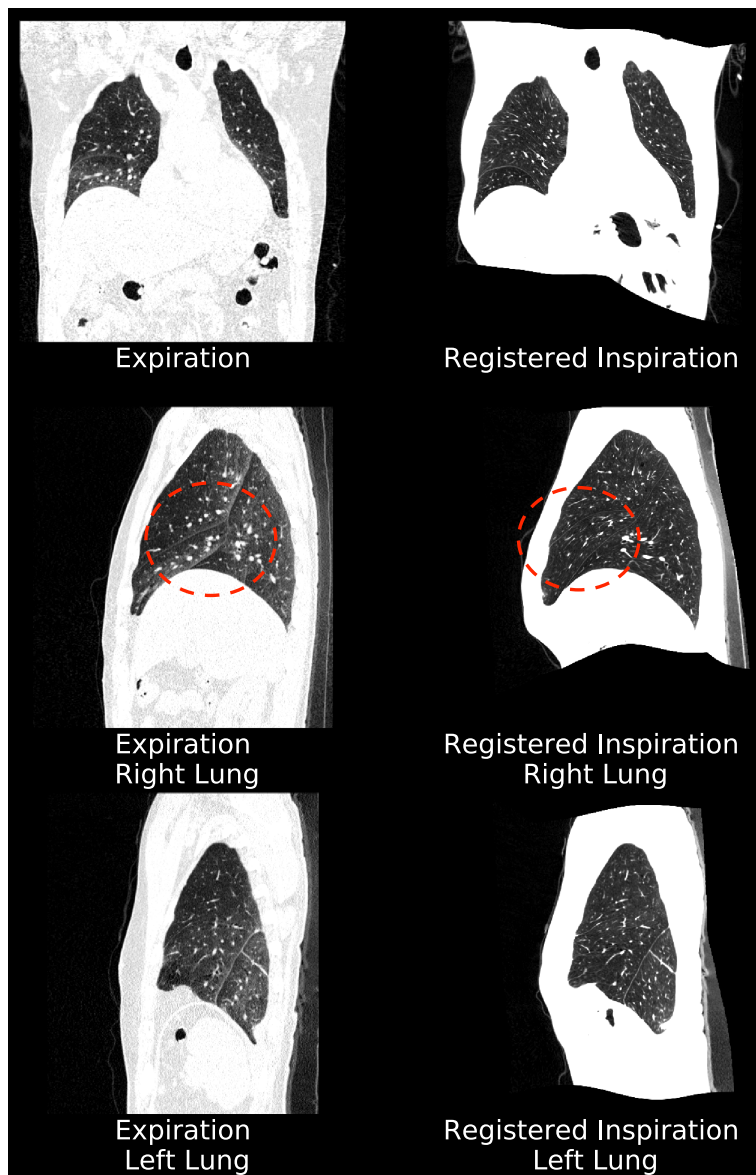
8_CONSIDERATIONS TO REDUCE RISK

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.



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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.



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8.6.3 Examples of Acceptable Registrations

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

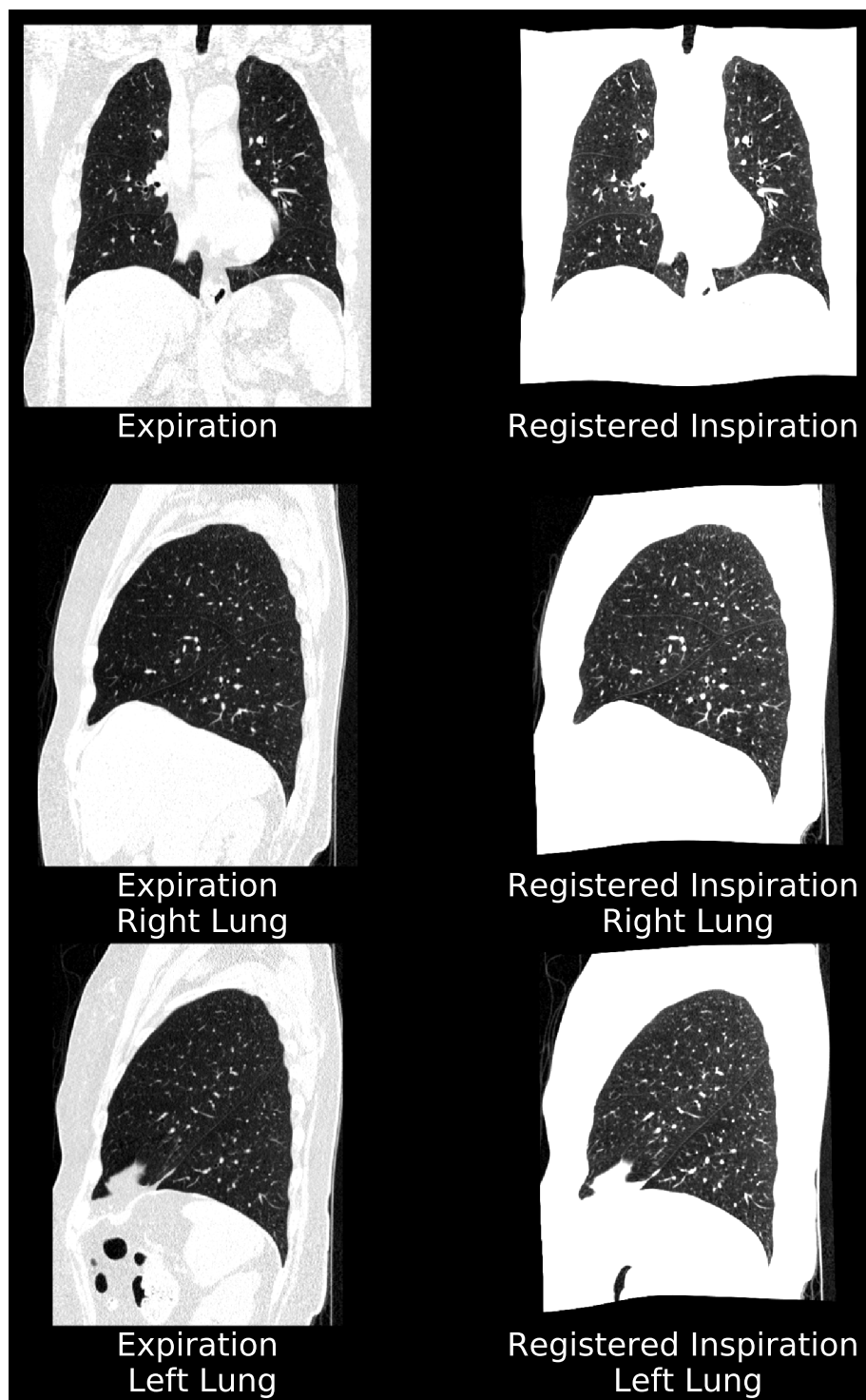


Figure 32: Acceptable registration example 1.

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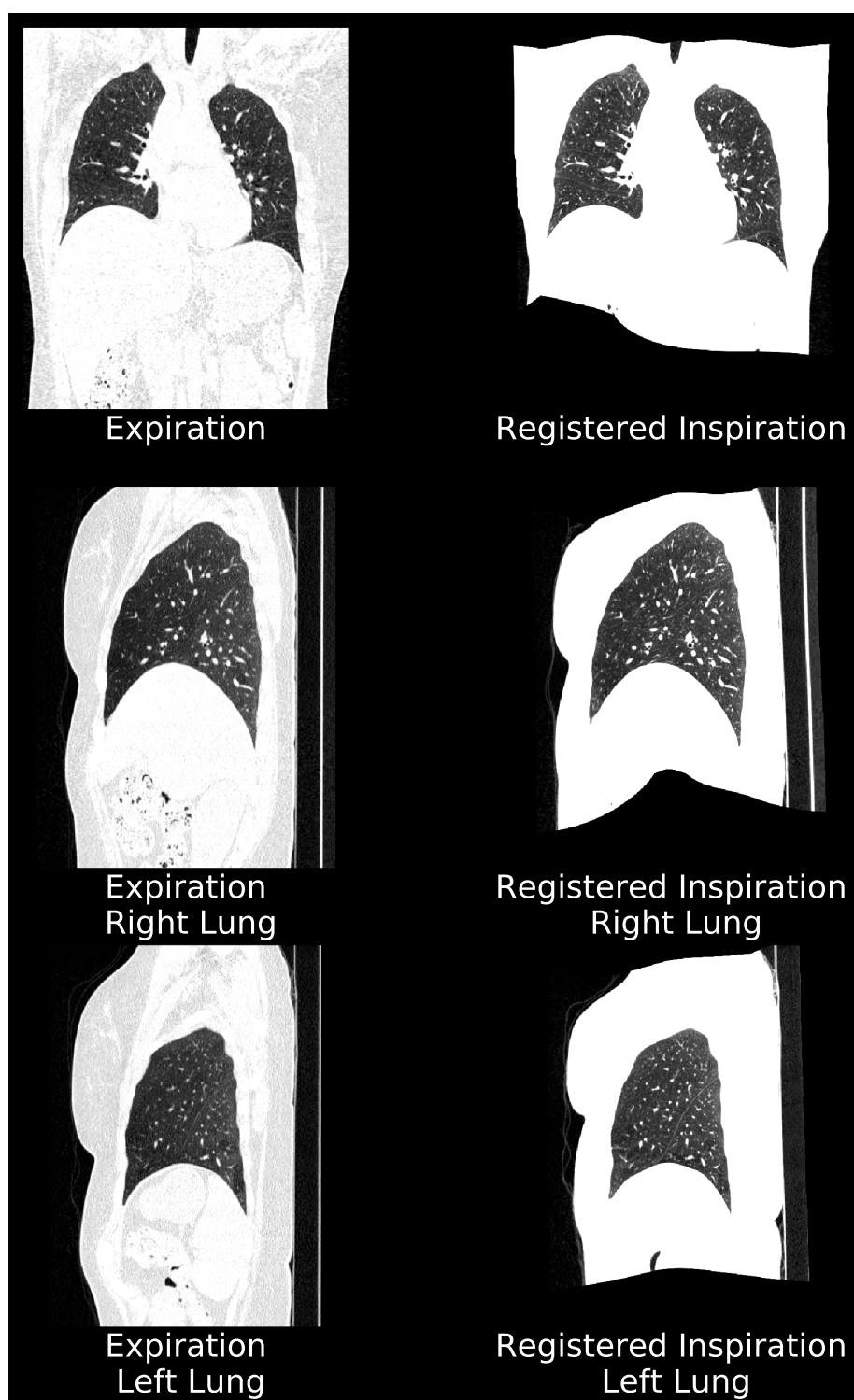


Figure 33: Acceptable registration example 2.

8_CONSIDERATIONS TO REDUCE RISK

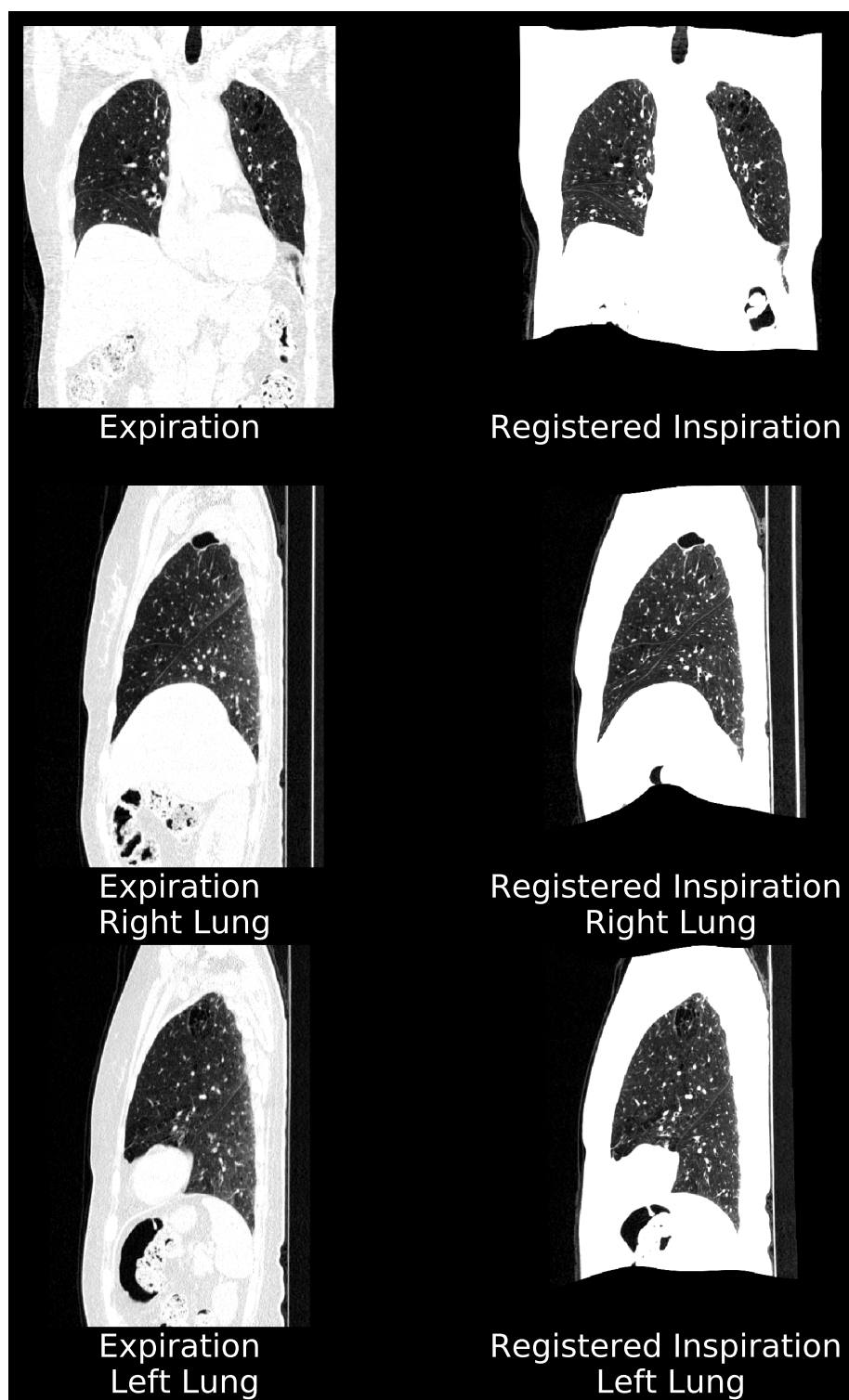


Figure 34: Acceptable registration example 3.

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

Imbio
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Minneapolis, MN 55413, USA
www.imbio.com

 2018-08-22



(01)00850894007292
(11)180822

11 References

- [1] Pesch, Beate and Kendzia, Benjamin and Gustavsson, Per and Jöckel, Karl-Heinz and Johnen, Georg and Pohlabein, Hermann and Olsson, Ann and Ahrens, Wolfgang and Gross, Isabelle Mercedes and Bröske, Irene and others. *Cigarette smoking and lung cancer – relative risk estimates for the major histological types from a pooled analysis of case-control studies*. International journal of cancer. Vol 131, Issue 5, pp 1210–1219. 2012.