IQ-UIP Software

Instructions for Use US

Software Version 2.1.1 and onwards

IQ-UIP Instructions for Use

US

Contents

1 Introduction

1.1 Scope of Manual

This user manual was written for the 4DMedical IQ-UIP software.

IQ-UIP is accessible via multiple deployment options, including various distribution partners or 4DMedical Protected Platform (4DM-PP). Usage of these platforms and deployment options are outside of the scope of this manual. Contact support@4dmedical.com for more information.

1.2 Product Overview

4DMedical's IQ-UIP software device uses a locked artificial intelligence algorithm to automatically analyze a qualifying chest computed tomography (CT) scan. The device performs image classification to identify if a chest CT scan contains findings suspicious for the radiological usual interstitial pneumonia (UIP) pattern and generates a summary output to report positive findings in parallel to and separate from the standard of care radiological image interpretation. The software does not recommend treatment or provide a diagnosis. It is a tool to assist ILD clinics in identification of patients with radiological UIP within their hospital system. The final radiological determination is provided by a thoracic radiologist after reviewing the original scans on the clinical PACS. The final clinical ILD diagnosis and/or treatment strategy is determined after consultation with clinicians from other clinical units, via a multidisciplinary team discussion (MDT/MDD) or other similar process in accordance with the institution's procedures.

IQ-UIP does not interface directly with any CT or data collection equipment, does not require user input, provides no image viewing capabilities, does not route images, and does not annotate images. Instead, the software imports data files previously generated by CT and is designed to function using information entirely derived from the CT images alone.

The IQ-UIP software utilizes high-resolution, non-contrast, inspiration, chest/lung CT images in DICOM format as input to the software.

IQ-UIP software outputs are sent to 4DMedical's web-based Portal, or similar application from commercial distribution partners. An IQ-UIP Report is automatically generated and added to a designated worklist if a scan is flagged as scan containing findings suspicious for UIP Pattern.

The outputs from IQ-UIP software are not to be used in the primary radiology clinical workflow. The standard-of-care radiology workflow (i.e. reviewing and reporting the findings that initiated the request for CT) continues unaffected by the parallel workflow of the lung health program. For clarity, the IQ-UIP device does not flag/prioritize cases within the standard, clinical radiology workflow.

2 Symbols

The meaning of the symbols shown on the labeling and/or instructions for use are as follows:


Consult Electronic Instructions for Use


Manufacturer


Date of Manufacture (YYYY-MM-DD)

Medical Device

Unique Device Identifier

Batch Code (Device Version)


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

3 Indications for Use and Requirements

3.1 Indications for Use

IQ-UIP is a computer-aided software indicated for use in passively notifying specialists associated with the interstitial lung disease (ILD) cernters of radiological findings suggestive of radiological usual intersitial pneumonia (UIP) in non-contrast, chest CT scans of adults. IQ-UIP uses an artificial intelligence algorithm to analyze images and identify positive findings on a worklist application separate from and in parallel to the standard of care radiological image interpretation. Identification of positive findings include summary reports with a clinical guideline reference for the definition of UIP pattern that are meant for informational purposes only. The device does not alter the original medical image and is not intended to be used as a diagnostic device.

The results of IQ-UIP are used to notify specialists at an ILD center of radiological findings that may be consistent with UIP. These specialists are qualified clinicians experienced in evaluating chest CTs for ILD. Input images originate from within the same hospital network associated with the ILD center. The results of IQ-UIP are intended to be used in conjunction with additional patient information and based on the user's professional judgement to assist with the review of medical images. Notified clinicians are responsible for viewing full image series and making final clinical determinations.

3.2 Intended Users

The intended users are thoracic radiologists and pulmonologists experienced in evaluating chest CTs for interstitial lung disease (ILD) and involved in a specialty ILD program/center. The intended use environment is within a specialty ILD program/center. The data analyzed by IQ-UIP may originate from anywhere within the hospital network, at the discretion of the user.

The device is not to be used by physicians with no experience evaluating chest CTs for ILDs.

3.3 Cautions, Warnings, and Contraindications

There are no known contraindications. Known limitations and precautions related to image quality, anatomy, and artefacts are described in Sections 6 and 7.

3.4 Intended Patient Population

Inputs into the IQ-UIP device may originate within a hospital network where chest imaging is performed including a full hospital facility, a standalone imaging clinic, or other network facilities. However, the IQ-UIP device notification output will only be available within a dedicated worklist application accessible by the intended users, as listed above, from a specialty ILD program/center. Therefore, the chest CTs analyzed are any CT scan that fits the input criteria within the hospital network.

3.5 Scan Protocol Requirements

The ability of the IQ-UIP software to analyze an chest CT scan is dependent on the field-of-view and image resolution. Therefore, it is important to analyze the scan's field-of-view and resolution. The field-of-view and 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 4DMedical's required parameters. The scan should also be visually assessed to ensure that there are no artifacts or missing information.

3.5.1 Acquisition Parameter Requirements

The IQ-UIP software will not generate outputs for scans with acquisition parameters that do not meet the requirements as outlined in the table below.

DICOM Tag	Name	Required Value
(0008,0060)	Modality	CT
(0028,0030)	Pixel Spacing	≤ 2.0 x 2.0 mm
(0018,9305)	Revolution Time	≤ 1.0 s (if present)
N/A	Slice Spacing	≤ 3.0 mm
(0018,0050)	Slice Thickness	≤ 3.0 mm
N/A	Field of View	≥ 10.0 x 10.0 x 20.0 cm
(0028,1054)	Rescale Type	HU (if present)
(0020,0032)	Image Position Patient	Present and not empty
(0020,000E)	Series Instance UID	Present and not empty
(0010,1010), or (0010,0030) AND (0008,0020)	Patient Age	≥ 22 years
(0018,0010)	Contrast Bolus Agent	Empty or not present
(0002,0010)	Transfer Syntax UID	≠ 1.2.840.10008.1.2.2 (Explicit VR Big Endian)

3.5.2 Recommended Protocol

For the IQ-UIP software, 4DMedical recommends a 3D volumetric acquisition with pixel spacing less than 1 mm and slice thickness less than 3 mm for the input inspiration scan. 4DMedical also recommends that the patient lies in the supine position. IQ-UIP software will automatically reject contrast enhanced acquisitions. Example protocols are listed in the table below. The protocols accepted by IQ-UIP software are not limited to the scanners and protocols in the table, but the acquisition parameters should be similar. Failure to observe the recommended scan protocol could limit the software's ability to properly segment lungs.

Scanner Make	GE	SIEMENS	PHILIPS	TOSHIBA/CANON
Scanner Model	VCT 64	Sensation-64	64 Slice	Aq64
Scan Type	Helical	Spiral	Helical	Helical
Rotation Time (s)	0.5	0.5	0.5	0.5
Det. Configuration	64 x 0.625	64 x 0.6	64 x 0.625	64 x 0.5
Pitch	0.984	1.0	1.0	0.828
kVp	120	120	120	120
mA	200	200	200	150
Reconstruction				
Kernel	Standard[1]	B35f[1]	B[1]	FC13[1]
Thickness (mm)	0.625	0.75	0.67	1
Spacing (mm)	0.5	0.5	0.5	0.5
DFOV (cm)	Lungs[2]	Lungs[2]	Lungs[2]	Lungs[2]

[1]More reconstruction kernels are considered acceptable than the kernels listed in thistable. See table below listing all recommended and not recommended reconstruction kernels.

[2]Reconstruction field of view should encompass the widest diameter of the lung

3.5.3 Recommended Reconstruction Kernels

4DMedical does not provide an exhaustive list of acceptable reconstruction kernels due to the large number of reconstruction kernels available and the implementation of new kernels. The performance assessment of IQ-UIP software, as further described below in 5.3, primarily utilized datasets with the SOFT (7.8% of test datasets), STANDARD (53.9% of test datasets), BONE (1.7% of test datasets), and LUNG (36.6 of test datasets) reconstruction kernels or equivalent kernels for non-GE vendors.

3.6 Hardware Requirements

Hardware requirements for running IQ-UIP software are as follows:

- 4 CPU Cores
- 8 GB RAM
- 50 GB Storage

4 Quality Assessment / Clinical Workflow

Scan quality and possible artifacts must be assessed before utilizing the results produced by the 4DMedical IQ-UIP software.

This software is designed to run on any input data that satisfies the criteria in 5.3 and it does not perform any additional quality checking. **It is the responsibility of the medical professional who is using the application 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. IQ-UIP software is not intended for use as a primary tool for disease detection and/or diagnosis.

IQ-UIP was designed and validated on adult lungs and has not been validated on children.

4.1 Clinical Workflow

IQ-UIP is intended to analyze chest CT image series that originate from a variety of different clinical scenriors or sources. Some detailed examples will be discussed below. Generally speaking, there is one guiding principle that applies to all cases analyzed with IQ-UIP: the radiology standard-of-care will proceed unaffected without inadvertently biasing clinical radiologist reads.

As shown in the figure below, there are four anticipated clinical scenarios or sources for a qualified chest CT dataset to be processed with IQ-UIP within a hospital system: CTs originating from an (1) ILD Center, (2) other Specialty Care (e.g., nodule follow-up, treatment or surgery planning, etc.), (3) an Emergency Department (ED), or (4) Primary Care (e.g., Lung Cancer Screening (LCS), PCP orders due to symptoms). In all scenarios, the current radiology standard of care occurs in parallel, unaffected by IQ-UIP processing. Chest CTs are programmatically sent to the 4DMedical IQ-UIP algorithm which then populates a worklist application. A specialist at an ILD center can review the worklist application which displays the IQ-UIP output for CT datasets consisted suspicious for UIP pattern.

An example analysis workflow is shown in the figure below where chest CT originate from the four anticipated clinical scenarios. Customers can designate the types of DICOM series sent for IQ-UIP processing via standard DICOM routing procedures. The ability to withhold certain CT scans originating from an ILD Center, aids in reducing the number of subjects with previously identified UIP pattern populating the worklist.

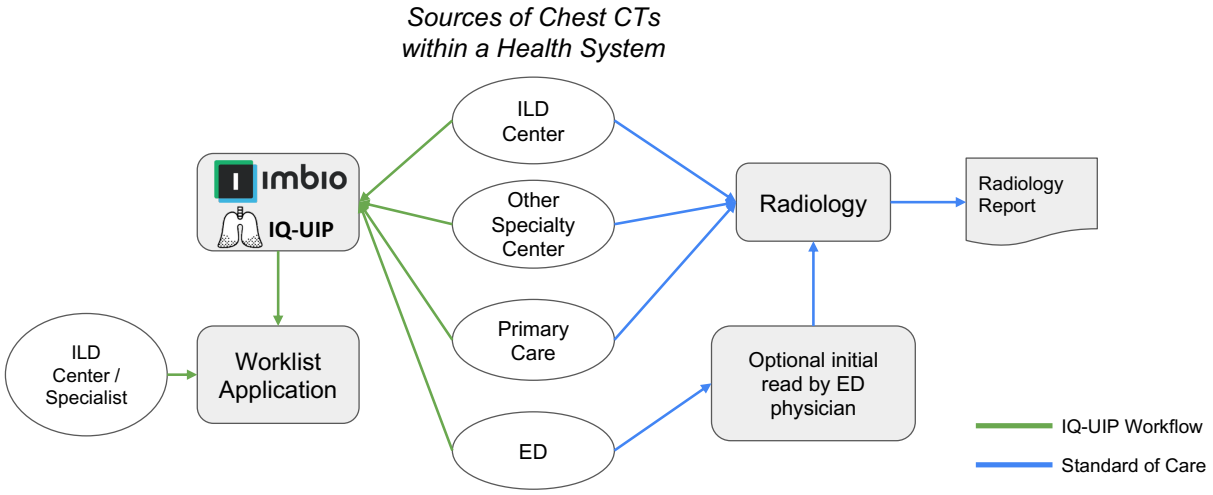


Figure 1: Clinical workflow diagram for sources of chest CTs throughout a hospital system for the 4DMedical IQ-UIP device.

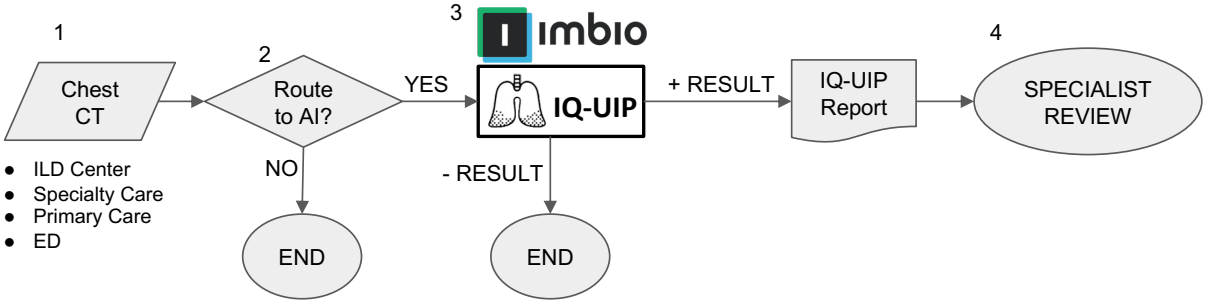


Figure 2: Analysis workflow for chest CT analysis by the 4DMedical IQ-UIP device.

After analysis is performed, nothing happens in the case where there were no findings suspicious for radiological UIP pattern; the workflow for IQ-UIP ends, as shown in step 3. In cases that have findings suspicious for UIP apptern, an IQ-UIP Report is automatically generated and is added to a designated worklist. The worklist application is outside the scope of the IQ-UIP device and could be 4DMedical's Portal or a similar application from commercial distribution partners. The clinical workflow downstream from the creation of the IQ-UIP Report is outlined in the figure below. Regardless of the worklist application used as a follow-up management tool, the user accesses the worklist to see the list of patients for which follow-up is recommended based on findings that are suspicious for radiological UIP pattern. The user would also be able to access the IQ-UIP Report from this application. The specialist, who meets the criteria of the intended users of IQ-UIP, would review the patient's images on a clinical PACS and access any relevant clinical history via the institution's electronic medical record (EMR). If the clinician disagrees with the analysis, the patient is marked as "Review complete", with an indication that the IQ-UIP Report was reviewed and determined to be incorrect and/or a user is able to remove from the worklist application and nothing further is done.

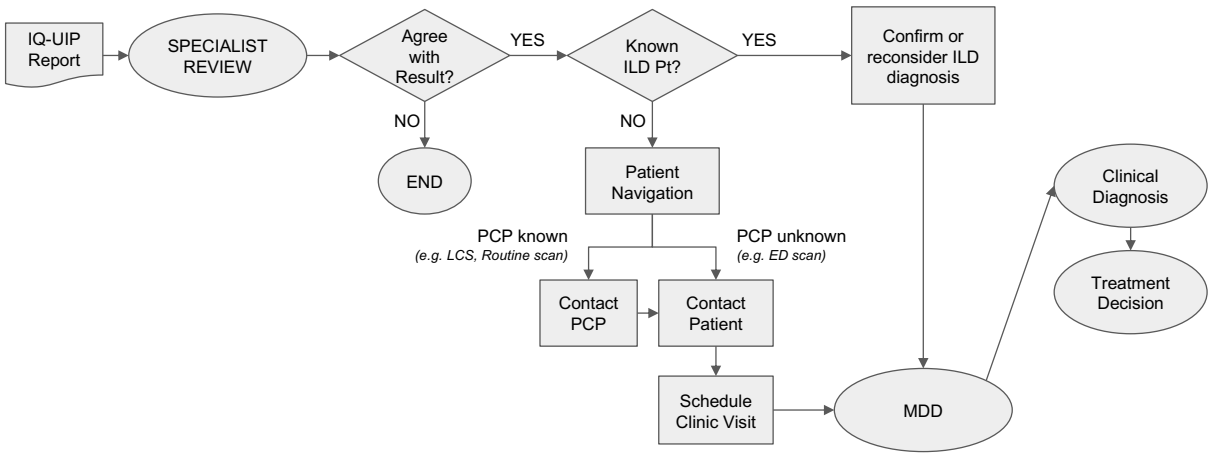


Figure 3: Downstream diagnostic algorithm after IQ-UIP analysis report.

In the event that the user agrees that radiological UIP pattern is present and it is determined that this patient in not a patient previously known to the ILD clinic, the patient would enter a navigation step where someone from the ILD clinic (i.e., dedicated physician, nurse navigator, etc.) would reach out directly to either the patient's PCP or ordering physician if it is a reasonable assumption that the patient has a relationship with the ordering physician (most likely if the CT was routine or screening related). Alternatively, the patient could be contacted directly by the ILD clinic (most likely if the CT originated from an Emergency Department and the PCP is unknown or not a part of the institution).

The goal of the navigation step/patient outreach is to schedule a visit in the ILD clinic for follow up with an ILD specialist. Depending on the history of the patient and the amount of clinical history available, further tests and clinical workup might be needed in conjunction with the initial visit, or they might be postponed until after the initial clinical encounter with the patient. This is at the discretion of the ILD specialist. Only after the clinical encounter with the patient and all necessary tests and workups are complete, would care management and/or therapy be discussed. Also, in accordance with the ATS/ERS/JRS/ALAT Clinical Practice Guidelines [1], patients with UIP or probable UIP should only receive a clinical diagnosis (of IPF or other alternative diagnosis) after an MDT discussion. IQ-UIP does not alter this aspect of the published diagnostic algorithm for IPF, as outlined in downstream diagnostic algorithm figure above.

5 IQ-UIP Software

5.1 Device Input

The 4DMedical IQ-UIP software requires a single DICOM format, non-contrast, chest CT image series as input.

The 4DMedical IQ-UIP software will not generate outputs for scans with acquisition parameters that do not meet the requirements as outlined in 3.5.1.

5.2 Device Outputs

5.2.1 IQUIP Report

When analyzed with appropriate input data, the IQ-UIP Software generates an IQ-UIP Report (as a PDF-formatted file) if, and only if, a CT scan contains features suspicious for radiological UIP pattern. The output IQ-UIP Report is accessible to view within the dedicated worklist application.

IQ-UIP software does not generate outputs if a CT case is not flagged as suspicious for radiological UIP pattern.

The report has been designed to communicate essential information to the user while reducing risks of improper use of the device. Each section of the report will be discussed in detail. An example of the IQ-UIP Report is shown below.

Header: The header section contains patient identifiable data, such as Patient Name, Patient ID, Patient Sex, and Patient Date of Birth, study information such as Study Date and Report Date, along with image acquisition/reconstruction information such as CT Manufacturer, Reconstruction Kernel, Slice Thickness, Tube Current, and kVp as available in the DICOM tags.

Notification Result: A report is only produced in the event that findings suspicious for radiological UIP pattern are identified in the input CT image series. Therefore, all reports will have the following messaging:

```
"Suspicious for UIP Pattern. Review by specialist recommended."
```

This message communicates the results of the IQ-UIP analysis to the user and also drives the intended clinical workflow for users to review the input CT scans for patients with a positive

IQ-UIP result. IQ-UIP is not intended to deliver a final diagnosis or be a sole trigger for initiating additional testing or treatment. It is intended only to identify CT image series that warrant a review by specialized clinicians with experience evaluating CTs for ILDs and who are involved in an ILD specialty clinic. An abbreviated version of the device's indications for use (IFUs) are also included below the notification result.

IQ-UIP Score: The IQ-UIP score is displayed as an integer between 1 and 10 where a score of 1 means very likely UIP negative and a score of 10 means very likely UIP positive. The IQ-UIP score is not a probability of UIP but is intended to be analyzed relative to IQ-UIP scores generated based on the datasets included within the IQ-UIP Standalone Performance Assessment with known ground-truth. The IQ-UIP score, in combination with other information, may be used in the help characterize a dataset as being UIP positive and may be used as one input to clinical decision making when following published clinical guidelines.

The histogram plot displays all IQ-UIP scores in 10 bins for the population in the and relative amounts of ground-truthed UIP+ or UIP- datasets. The performance datasets used to generate the IQ-UIP Score histogram plot were not used in model training and consist of a UIP prevalence of 24%. The highlighting colorization of the bars within the histogram plot coincide with the output IQ-UIP score calculated from the input dataset for easier identification.

Notice: The population used to test the device's performance was enriched for UIP as well as other fibrotic, UIP-mimicking diseases. Users must consider their patient population's UIP prevalence when interpreting the IQ-UIP score. In real-world prevalence(s), which is expected to have a lower UIP prevalence, equivalent IQ-UIP scores may have a lower percentage of true UIP positives.

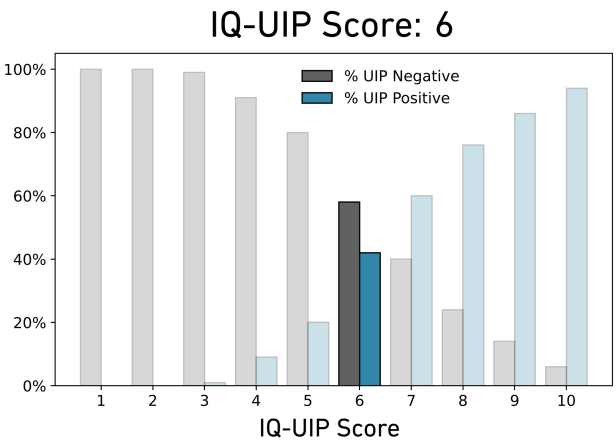
Clinical Guidelines for UIP Pattern: A detailed excerpt from the 2022 clinical guidelines for the definitions of radiological UIP pattern on high-resolution CT is included on the bottom half of the report. The UIP radiological patterns are defined according to the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) publication [1]. The excerpt from the clinical guidelines is meant for informational purposes only and is not intended for diagnostic use. The guidelines explain the four UIP pattern subtypes in terms of confidence level for UIP histology, distribution of findings, and CT features observed in the CT images.

Footer: A report footer contains additional information such as device performance in terms of sensitivity and specificity based on the device's performance assessment along with possible warnings and hyperlinks to the IQ-UIP User Manual.

NAME: **ILD_UIP** SEX: **Female** STUDY DATE: **October 10, 2006**
PATIENT ID: **ILD_UIP** DOB: **July 1, 1951** REPORT DATE: **November 14, 2024**
MANUFACTURER: **SIEMENS** KERNEL: **B46f** SLICE THICKNESS: **1.0** TUBE CURRENT AVG KVP: **311 mA, 120 kV**

Suspicious for UIP pattern.
Review by specialist recommended.

Imbio IQ-UIP is a computer-aided software indicated for use in passively notifying specialists at an ILD center of radiological findings that may be consistent with UIP. The results of Imbio IQ-UIP are intended to be used in conjunction with additional patient information and based on the user's professional judgment, to assist with the review of medical images. Notified clinicians are responsible for viewing full image series and making final clinical determinations.



NOTICE: The patient population's UIP prevalence must be considered when interpreting the IQ-UIP score. The histogram above is based on the device performance test in a ground truth database with UIP prevalence of 24%. See IQ-UIP user manual for additional info.

Excerpt from: **2022 ATS/ERS/JRS/ALAT Clinical Practice Guidelines: High-Resolution CT Scanning Patterns**

	UIP Pattern	Probable UIP Pattern	Indeterminate for UIP	CT Findings Suggestive of an Alternative Diagnosis
Confidence level for UIP histology	Confident (>90%)	Provisional high confidence (70–89%)	Provisional low confidence (51–69%)	Low to very low confidence (<=50%)
Distribution	Subpleural and basal predominant Often heterogeneous (areas of normal lung interspersed with fibrosis) Occasionally diffuse May be asymmetric	Subpleural and basal predominant Often heterogeneous (areas of normal lung interspersed with reticulation and traction bronchiectasis/ bronchiolectasis)	Diffuse distribution without subpleural predominance	Peribronchovascular predominant with subpleural sparing (consider NSIP) Perilymphatic distribution (consider sarcoidosis) Upper or mid lung (consider fibrotic HP, CTD-ILD, and sarcoidosis) Subpleural sparing (consider NSIP or smoking-related IP)
CT Features	Honeycombing with or without traction bronchiectasis/ bronchiolectasis Presence of irregular thickening of interlobular septa Usually superimposed with a reticular pattern, mild GGO May have pulmonary ossification	Reticular pattern with traction bronchiectasis/ bronchiolectasis May have mild GGO Absence of subpleural sparing	CT features of lung fibrosis that do not suggest any specific etiology	Lung findings • Cysts (consider LAM, PLCH, LIP, and DIP) • Mosaic attenuation or three-density sign (consider HP) • Predominant GGO (consider HP, smoking-related disease, drug toxicity, and acute exacerbation of fibrosis) • Profuse centrilobular micronodules (consider HP or smoking-related disease) • Nodules (consider sarcoidosis) • Consolidation (consider organizing pneumonia, etc.) Mediastinal findings • Pleural plaques (consider asbestosis) • Dilated esophagus (consider CTD)

Adapted from: Raghu G, et al. *Am J Respir Crit Care Med*, 2022. **205**(9): p. e18-e47.

Definition of abbreviations: CT = computed tomography; CTD = connective tissue disease; DIP = desquamative interstitial pneumonia; GGO = ground-glass opacity; HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IP = interstitial pneumonia; LAM = lymphangioleiomyomatosis; LIP = lymphoid interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; PLCH = pulmonary Langerhans cell histiocytosis; UIP = usual interstitial pneumonia.

Figure 4: Example IQ-UIP Report

5.2.2 Input Check Failure Report

The Input Check Failure Report can also be output in a DICOM-compatible format. The cause(s) of the input check failure can be identified by the red 'X' mark in the Result column of the Input Check Failure Report. In the figure below, the offending parameters are the modality. Note the yellow triangle warning signs indicate sub-optimal parameters or parameters that are missing from the input meta data (Revolution Time or Rescale Type). These warnings will not result in an input check failure, but should be noted, nonetheless.

ACCESSION NUMBER: **00000001**	STATION NAME: **Unknown**	MANUFACTURER: **SIEMENS**
REPORT DATE: **November 14, 2024**	STUDY DATE: **October 10, 2006**	
IMAGES TOTAL: **143**	SERIES NUMBER: **Unknown**	TUBE CURRENT AVG, KVP: **311 mA, 120 kV**

	Requirement	Value	Result
Series Instance UID	Valid UID	1.3.6.1.4.1.39653.1473456764744878.506	✓
Modality	CT	MR	✗
Revolution Time (s)	<= 1.0	Not Present	⚠
Pixel Spacing (mm)	<= [2.0, 2.0]	[1.0, 1.0]	✓
FOV/ImagePositionPatient (mm)	>= (100, 100, 200)	(270, 270, 287)	✓
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	2.0	✓
Slice Thickness (mm)	<= 3.0	3.0	✓
Rescale Type	HU	Not Present	⚠
Patient Age (years)	>= 22	55	✓
Contrast Bolus Agent	Missing	Missing	✓
Transfer Syntax UID	Non-Big-Endian	OK	✓
Patient Position	Supine	FFS	✓

Figure 5: Example Input Check Failure Report

5.3 Algorithm Performance

The purpose of the device's standalone performance assessment is to demonstrate the effectiveness of the IQ-UIP software compared to a clinically acceptable, reference standard (i.e., ground-truth dataset) to make a binary determination for the presence of the radiological UIP pattern in qualifying chest CT image series.

IQ-UIP software's performance was evaluated on 804 anonymized, chest CT datasets collected from multiple hospitals, clinical imaging centers, and imaging databases, both private and publicly available, to have a representative distribution of varying CT scanner vendors, slice thicknesses, convolution kernels, and lung disease subtypes. All datasets were quarantined from the datasets used in the device's model training and validation (i.e., model tuning). The population of CT datasets was selected to represent a large cross-section of lung disease observed in a screening population. The population is enriched with cases with radiologist-confirmed UIP pattern to more accurately measure the efficacy of the IQ-UIP software.

Datasets with obvious metal or high attenuation artifacts, severe motion artifacts, undergone prior lung transplant or with a missing lung were excluded from the study.

The average age of subjects in the performance dataset was 64.1 +/- 11.9 years including 300 females, 437 males, and 67 subjects with gender unavailable.

The breakdown for the number of datasets from each database and number of clinically diagnosed IPF subjects is included. IPF prevalence was determined to be 29%. All datasets used in the standalone performance assessment were quarantined from model training with no overlap in imaging site or subject ID (i.e., site and subject-level independence).

Database	Datasets (N)	IPF + Datasets (N)
OSIC	242	118
COPDGene	186	0
RIFF	98	98
FocuSSced	20	0
SegMed Insights	59	0
MIDRC RiCORD	16	0
NLST	70	0
UC-Davis	36	18
CCIC	77	0

Important cohorts were subdivided by the dataset's clinical diagnosis label from the associated database into four groups: IPF-only, Non-IPF Fibrotic, Non-Fibrotic, Normal. The cohorts included the following diagnoses:

- **IPF-only:** datasets with an IPF clinical diagnosis label (MDT or pulmonologist determined)
- **Non-IPF Fibrotic:** idiopathic nonspecific interstitial pneumonia (iNSIP), fibrotic NSIP (fNSIP), unclassifiable idiopathic interstitial pneumonia (uIIP), unclassifiable interstitial lung disease (uILD), sarcoidosis, chronic/fibrotic hypersensitivity pneumonitis (cHP/fHP), rheumatoid-arthritis interstitial lung disease (RA-ILD), sarcoidosis, exposure-related ILDs, combined pulmonary fibrosis and emphysema (CPFE).
- **Non-Fibrotic:** emphysema (COPD), bronchitis (COPD), carcinoma, lymphoma, organizing pneumonia (OP), acute HP, pleuroparenchymal fibroelastosis (PPFE), respiratory bronchiolitis ILD (RB-ILD), Systemic sclerosis (SSc), bronchiolitis, pneumonia.
- **Normal:** datasets without any apparent lung abnormalities or pathologies.

5.3.1 Overall Performance

The software's performance was compared against a ground truth determined by majority opinion from five, expert, U.S. board-certified radiologists ("truthers") practicing within the United States. Each truther had a minimum of 5+ years' experience evaluating chest CTs for ILDs and a clinical familiarity with using the ATS/ERS/JRS/ALAT diagnostic categories for radiological UIP pattern. Each truther evaluated and categorized all 804 datasets into 1 of the 4 diagnostic categories (i.e., UIP, Probable UIP, Indeterminant for UIP, and Alternative Diagnosis) for radiological UIP pattern. For analysis, a binary (two-category) radiological UIP pattern ground truth label was generated by defining UIP positive (UIP+) as UIP or Probable UIP and UIP negative (UIP-) as either Indeterminate for UIP or Alternative Diagnosis. The device's overall performance in terms of area-under-the-curve (AUC) of the receiver operating curve (ROC), accuracy, sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) are reported below compared to ground truth labels. Device performance metrics and 95% confidence intervals (CI) are reported for all groups/subgroups unless the number of datasets needed for computation is ≤5, no True Positives (for determining device specificity) are present, or no True Negatives (for determining device sensitivity) datasets are not present. "N/A" will be reported instead in these cases.

Metric	Value	95% CI
AUC ROC (%)	96.6	[95.4, 97.7]
Sensitivity (%) [3]	90.2	[86.2, 94.3]
Specificity (%) [3]	91.5	[89.2, 93.7]
Accuracy (%) [3]	91.2	[89.1, 93.0]
PPV (%) [4]	77.0	[72.2, 82.0]
NPV (%) [4]	96.7	[95.5, 98.1]

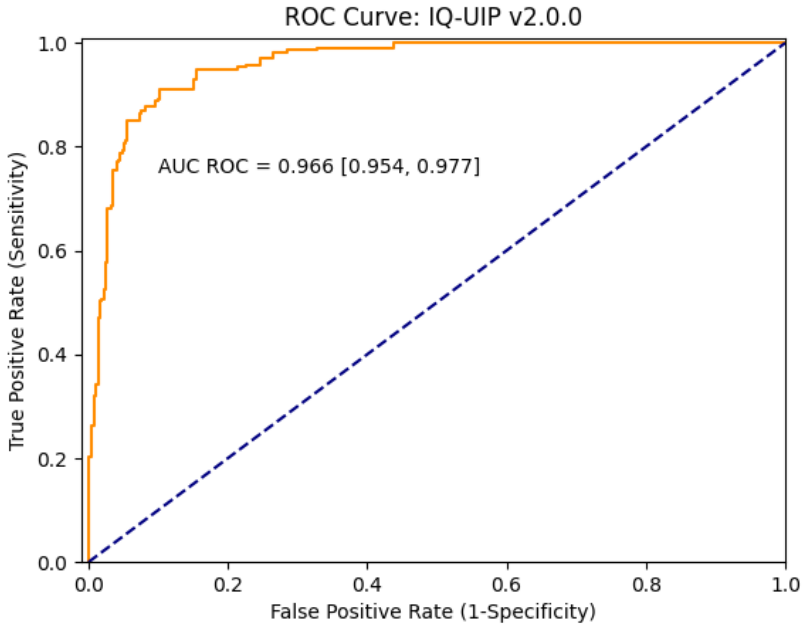


Figure 6: Receiver Operator Curve (ROC) for the IQ-UIP Performance Assessment. AUC = Area-under-curve.

The PPVs and NPVs using the default binary threshold were simulated across all possible UIP disease prevalences ranging from 0 to 100% using the IQ-UIP device's performance. The 95% confidence intervals were estimated using boostrapping with replacement. The simulated curves are shown in the Figure below.

[3]Performance was assessed using IQ-UIP model binary threshold of 0.395. This threshold algorithmically determines the cut-off for decidingbetween UIP+ and UIP-.

[4]Performance was assessed using an ground-truthed UIP+ prevalence of 24% within the assessment cohort.

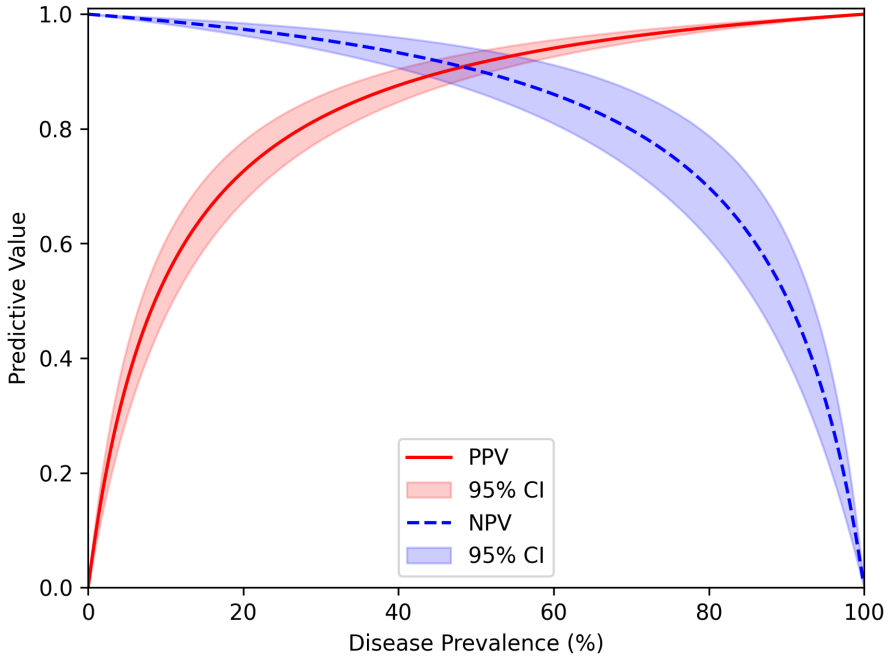


Figure 7: Simulated positive and negative predictive values (PPV, NPV) and their 95% confidence intervals (CI) with varying UIP+ disease prevalences from the IQ-UIP Performance Assessment.

The expected UIP/IPF prevalence were estimated in the following device-use locations: ILD clinic, specialty center, primary care / emergency department and lung cancer screening.

Device Use Locations	Expected UIP Prevalence	PPV (%)	NPV (%)
ILD Clinic [2, 3]	25.0%	77.9 [73.3, 82.8]	96.5 [95.2, 98.0]
Speciality Clinic	10.0%	54.1 [47.8, 61.6]	98.8 [98.4, 99.3]
LCS [4]	1.0%	9.7 [7.7, 12.7]	99.9 [99.8, 99.9]
Primary Care/ED [5]	0.6%	6.0 [4.7, 8.0]	99.9 [99.9, 100]

LCS = Lung Cancer Screening. ED = Emergency Department. 95% CI included for PPV and NPV values.

5.3.2 Subgroup Performance

To understand the generalizability of the device's performance in cohorts and possible confounders, a subgroup analysis was performed to evaluate the device for sensitivity and specificity for across these subgroups including lung disease, manufacturer, reconstruction kernel, and slice thickness. The tables below show the performance across subgroups.

Cohort	IPF-Only	Non-IPF Fibrotic	Non-Fibrotic	Normal
Datasets (N)	234	228	202	140
UIP+ / UIP- (N)	181 / 53	12 / 216	0 / 202	0 / 140
Sensitivity (%)	94.5 [91.1, 97.3]	25.0 [0.0, 53.8]	N/A	N/A
Specificity (%)	41.5 [28.6, 55.1]	92.6 [88.9, 96.2]	97.5 [N/A]	100 [100, 100]
TN, FN, TP, FP (N)	22, 10, 171, 31	200, 9, 3, 16	197, 0, 0, 5	140, 0, 0, 0

Manufacturer	GE Medical	Siemens	Canon/Toshiba	Philips
Datasets (N)	232	296	89	187
UIP+ / UIP- (N)	45 / 187	37 / 259	30 / 59	81 / 106
Sensitivity (%)	82.2 [70.0, 92.9]	89.2 [77.3, 97.6]	90.0 [77.8, 100]	95.1 [89.5, 98.9]
Specificity (%)	94.1 [90.4, 97.3]	93.2 [86.4, 98.4]	77.4 [69.2, 84.7]	77.4 [69.2, 84.7]
TN, FN, TP, FP (N)	176, 8, 37, 11	246, 4, 33, 12	55, 3, 27, 4	82, 4, 77, 24

Notice: User(s) should be aware of performance differences observed in chest CT scans originating from Philips manufacturer as shown in the Manufacturer table above.

Recon. Kernel[5]	SOFT	STANDARD	BONE	LUNG
Datasets (N)	63	433	14	294
UIP+ / UIP- (N)	28 / 35	49 / 384	7 / 7	109 / 185
Sensitivity (%)	89.3 [76.9, 100]	83.7 [72.9, 92.7]	85.7 [55.6, 100]	93.6 [88.9, 98.1]
Specificity (%)	82.9 [69.7, 94.1]	97.4 [95.7, 98.7]	100.0 [100, 100]	80.5 [74.1, 86.2]
TN, FN, TP, FP (N)	29, 3, 25, 6	374, 8, 41, 10	7, 1, 6, 0	149, 7, 102, 36

Slice Thickeness[5]	< 1.5 mm	≥ 1.5 & <3.0 mm	= 3.0 mm
Datasets (N)	664	100	40
UIP+ / UIP- (N)	180 / 484	12 / 88	1 / 39
Sensitivity (%)	91.7 [87.4, 95.4]	75.0 [44.4, 100.0]	0.0 [0.0, 0.0]
Specificity (%)	90.3 [87.6, 93.0]	95.5 [90.8, 98.9]	97.4 [92.1, 100.0]
TN, FN, TP, FP (N)	437, 15, 165, 47	84, 3, 9, 4	38, 1, 0, 1

6 Possible Encountered Exceptions

The IQ-UIP 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.

6.1 Input Errors

`ERROR: Input data invalid`

This error occurs if one or more acquisition parameters do not meet 4DMedical's requirements. For the details on each required parameter, see 3.5.1.

`ERROR: [DIRECTORY] contains more than one series`

This error occurs if the input contains more than one images series.

6.2 General Errors

`ERROR: "No Lungs Detected"`

This error indicates the lungs could not be detected. Possible causes include the input image does not contain the lung, input image is noisy, or there is not coverage of the lungs within the image field-of-view.

[5]Reconstruction kernels across vendors were grouped according to the "GE Medical Equivalent" best match.

7 Considerations to Reduce Risk

4DMedical IQ-UIP does not interface directly with any CT or data collection equipment; instead the software imports data files previously generated by such equipment. Furthermore, IQ-UIP provides no image viewing capabilities. Instead, IQ-UIP writes files out that can be viewed by other commercial viewing applications. The device does not alter the original medical image and is not intended to be used as a diagnostic device.

7.1 Protocol

For optimal results, users should follow the CT protocol as outlined in 3.5. It is important to work with the IT administrator to set up access to the separate, dedicated worklist/workstation; either to the Portal worklist or similar application from 4DMedical's distribution partners.

7.2 Algorithm Limitations

The IQ-UIP software checks input parameters and notifies users with warnings or error messages. Even so, there are a small number of cases where no warning or error is given and the output report is generated with potentially misleading results. The IQ-UIP software should only be used by intended users as specified in 3.2.

Users are responsible for reviewing each exam on a diagnostic viewer according to the current standard of care. IQ-UIP is limited to the notification of specialists associated with ILD Centers of radiological findings suggestive of radiological UIP pattern in chest CT scans of adults. IQ-UIP does not provide any diagnostic information, does not remove or alter original medical images, and should not be used in lieu of full patient evaluation, or relied upon to make or confirm diagnosis.

The results of IQ-UIP are intended to be used in conjunction with other patient information and based on the user's professional judgment, to assist with the review of medical images. Notified clinicians are responsible for viewing full image series and making final clinical determinations.

The outputs from IQ-UIP software are not be used in the primary radiology clinical workflow. The standard-of-care radiology workflow (i.e., reviewing and reporting the findings that initiated the request for CT) continues unaffected by the parallel workflow of the ILD program. For clarity, the IQ-UIP device does not annotate original medical image, make diagnoses, or flag/prioritize cases within the standard, clinical radiology workflow.

7.3 Cybersecurity Recommendations

When deploying systems on which this application will run, please consider the following technical security guidelines:

- Ensure only permitted users are able to sign into the system, using at minimum, a username and strong password.
- Ensure that system firewalls are configured in such a way as to only allow needed traffic to ingress the system.
- Ensure that operating system patches are kept up-to-date, and monitor operating system vendor communications for security and patching-related announcements.

8 Regulatory Information

8.1 Contact 4DMedical

For support, contact 4DMedical using the details below during standard business hours.

Phone: +1 833 877 2267
Address: 21255 Burbank Blvd. Suite 120
Woodland Hills, California
91367
U.S.A
Email: support@4DMedical.com | 4DMedical.com/support

8.2 Software Label

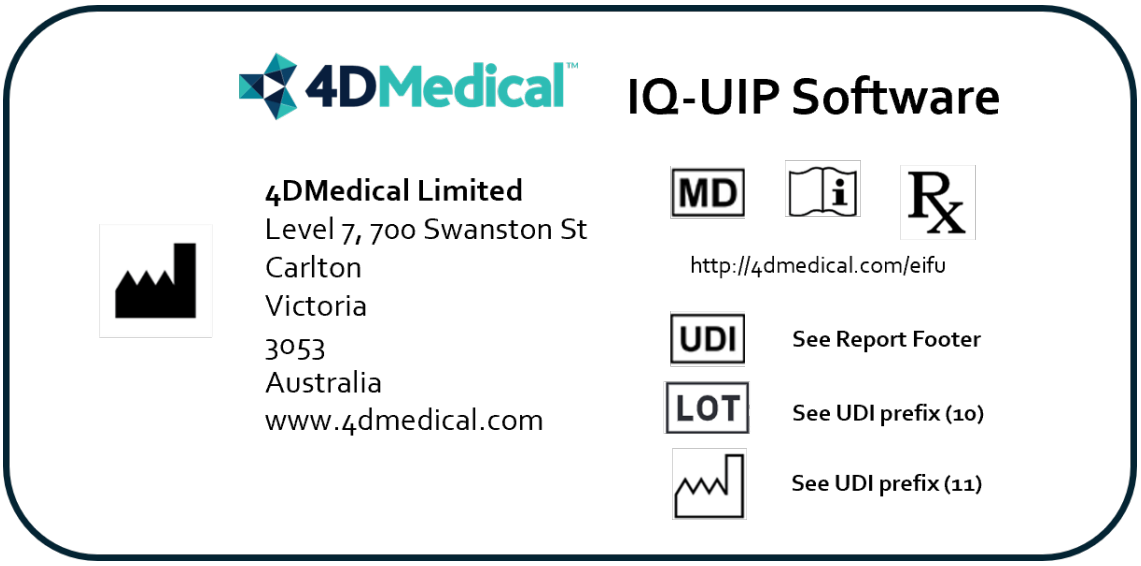


Figure 8: Software Label

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