Explainable artificial intelligence supports pulmonologists in the accurate interpretation of pulmonary function tests.

Supplemental document

S1: Centre participation in P1 and P2

S2: Informed consent for clinical participants

S3: Tutorial task for the clinical participants

S4: Participant Demographics in P1 and P2

S5: Preferential and differential diagnostic performance of the XAI model across different disease cohorts

S6: Comparison of preferential and differential diagnostic performance between XAI as stand-alone, control (individual pulmonologists) and intervention (pulmonologists and explainable AI (XAI)) in P1 and P2

S7: Interventional diagnostic performance stratified on years of experience and baseline enthusiasm of clinicians in AI applications in P2 study

S8: Table showing diagnostic performance of clinicians whenever XAI's preferential diagnosis was incorrect (Automation bias)

Supplement table S1

Table showing centre wise participation

P1 (N=16)	
Centre	**N**
UZ Leuven	16
P2 (N=62)	
Centre	**N**
AZ Sint-Jan Brugge-Oostende	4
CHU Charleroi	2
Cochin Hospital Paris	4
Hospital Clinic de Barcelona	2
Imperial College London	4
LungenClinic Grosshansdorf	4
Maastricht UMC	2
National Pirogov Memorial Medical University	6
Nottingham University Hospitals NHS	4
Royal Brompton Hospital	5
University of Ferrara Italy	2
University of Leicester	5
UZ Brussels	2
UZ Gent	16

Informed Consent

Title of the study:
Diagnosing respiratory diseases with artificial intelligence

Research organisation - Sponsor:
KU Leuven, Belgium

Medical Ethics Committee: University Hospital Leuven, Belgium

Local investigators:
Dr. Nilakash Das
Post-doc scientist
Laboratory of respiratory diseases and thoracic surgery
KU Leuven, Belgium
neel.das@kuleuven.be

Sofie Happaerts
Clinical resident
Faculty of medicine
KU Leuven, Belgium
University Hospital Leuven
sofie.happaerts@uzleuven.be

Prof. Dr. Wim Janssens
Principal investigator
Laboratory of respiratory diseases and thoracic surgery
KU Leuven, Belgium
University Hospital Leuven
wim.janssens@uzleuven.be

I Information vital to your decision to take part

Introduction

You are invited to participate in a study on how artificial intelligence (AI) and clinicians can collaborate on diagnosing respiratory diseases. In order to help you decide whether or not to take part in this study, please take the time to review the following information for participants so that you can make an informed decision. This is called "informed consent".

We ask you to read the following information carefully. If you have any questions, please contact the researcher.

This page consists of essential information that you need to make your decision, and an option to provide your consent digitally.

This page consists of essential information that you need to make your decision, and an option to provide your consent digitally.

If you are participating in this study, you should know that:

1. This study was drawn up after evaluation by the Ethical Committee (EC) Research UZ/KU Leuven.
2. Your participation is voluntary; there can be no question of coercion. Your signed consent is required for participation. Even after you have signed, you can let the researcher know that you want to stop your participation without giving any reason.
3. The information collected within the framework of your participation is confidential. Your anonymity is guaranteed when the results are published.
4. If you would like additional information, you can always contact the researchers.

Objectives and conduct of the study

In this retrospective study, we want to assess **how AI and clinicians can collaborate together in diagnosing respiratory diseases using pulmonary function tests (PFT) reports**. We invite you to participate in this study because you are an expert in the field of the respiratory medicine and experienced in interpreting pulmonary function test reports.

Specifically, we will request you to **perform a series of 24 PFT report interpretations in two parts, first without the aid of AI and then with the aid of AI**. We will record your responses like your preferred diagnoses, and your confidence in diagnosis on a likert scale. Filling out these responses will take around 2-3 minutes of your time for each interpretation. However, there is no time limitation and you can provide all your responses within a week or two.

Description of the risks and benefits

Your participation in this study **does not present any risk to subjects**. The subjects will be anonymized and your responses will not be used to interfere with their current clinical strategy.

Your participation will be beneficial in understanding the interaction between AI and clinicians.

Privacy and security

Your **responses will be anonymized** and downloaded on a KU Leuven hard-drive prior to data analysis. Afterwards, they will be deleted from the servers of the online platform. Aggregated data reports will be provided per participating center.

Publication policy

You will be invited to contribute as co-authors to the manuscript that is written as outcome of this research project in accordance with **ICMJE guidelines**.

Withdrawal of your consent

It is up to you to decide whether you want to take part in the study. **Participation is voluntary**. If you decide not to participate, you do not need to do anything else. You do not have to sign anything. You also do not have to say why you do not want to participate.

If you do participate, you can always change your mind and still stop, even during the study. You do not have to give a reason for this.

No new data will be collected and that if consent to participate in the study is withdrawn, the coded data already collected before withdrawal will be retained.

If you wish to participate in this study

We would like to **request you to cooperate fully** to ensure the proper conduct of the study.

Contact

If you require additional information or have any concerns, or if you encounter any problems, you can contact Dr. Nilakash Das (neel.das@kuleuven.be, +32 484576481) or Prof.Dr.Wim Janssens, (wim.janssens@kuleuven.be, +32 16377265).

II Informed consent

☐ I declare that I have been informed of the nature of the study, its purpose, its duration, the possible side effects and what is expected of me. I have taken note of the information document and the appendices to this document.

I have had the opportunity to ask any questions that came to mind and have obtained a favorable response to my questions.

I understand that data about me will be collected throughout my participation in this study and that the investigator and the sponsor of the study will guarantee the confidentiality of these data in accordance with applicable European and Belgian legislation. I understand that the performance of this study by UZ Leuven serves the general interest and that the processing of my personal data is necessary for the performance of this study.

I have received a copy of the information to the participant and the informed consent form.

Investigator

I, **Wim Janssens**, the principal investigator of this study, confirm that no pressure was applied to persuade the participants to agree to take part in the study and that I am willing to answer any additional questions if required.

I confirm that I operate in accordance with the ethical principles set out in the latest version of the "Helsinki Declaration", the "Good Clinical Practices" and the Belgian Law of 7 May 2004 related to experiments on humans.

III Supplementary information

Supplementary information on the organization of the study

The study involves retrospective evaluation of PFT cases using an online platform

Supplementary information on the risks associated with participation in the study

Not applicable

Supplementary information on the protection and rights of the participant in a clinical study

Ethics Committee
This study has been reviewed by an independent Ethics Committee, namely the Ethics Committee of UZ Leuven. It is the task of the Ethics Committees to protect people who take part in a clinical trial. They make sure that your rights as a patient and as a participant in a clinical study are respected, that based on current knowledge, the study is scientifically relevant and ethical.

You should not under any circumstances take the favorable opinion of the Ethics Committee as an incentive to take part in this study.

Voluntary participation
Before signing, do not hesitate to ask any questions you feel are appropriate. Take the time to discuss matters with a trusted person if you so wish.

Your participation in the study is voluntary and must remain free of any coercion: this means that you have the right not to take part in the study or to withdraw without giving a reason, even if you previously agreed to take part. Your decision will not affect your relationship with the investigator or the quality of your future therapeutic care.

If you agree to take part in this study, you will sign the informed consent form. The investigator will also sign this form to confirm that he/she has provided you with the necessary information about the study. You will receive a copy of the form.

Costs associated with your participation

You will not receive any compensation for your participation in this study. Furthermore, the study will not involve any additional costs for you.

Guarantee of confidentiality

Your participation in the study means that you agree to the investigator collecting data about you and to the study sponsor using these data for research purposes and in connection with scientific and medical publications.

The processing of your personal data is necessary to achieve the scientific research purposes as set out herein. The conduct of scientific research is one of the core missions of UZ Leuven as defined by law. As a university hospital, part of KU Leuven, UZ Leuven is indeed required to support research and education in the public interest. We would therefore like to inform you that the necessity of the processing for the conduct of scientific research as a task of public interest constitutes the lawful basis on which we process your information in the context of the study in which you are participating. UZ Leuven is also subject to specific legal requirements which require the processing of your personal in the context of safety reporting (such as for example the notification of adverse events to the regulatory authorities).

Your data will be processed in accordance with the European General Data Protection Regulation (GDPR) and Belgian framework law. The sponsor UZ Leuven is responsible for the data collection with Data protection officer (DPO) contact: DPO - UZ Leuven, Herestraat 49, 3000 Leuven, Belgium e-mail: dpo@uzleuven.be. Data will be kept secured for a minimal period of 20 years.

You are entitled to ask the investigator what data are being collected about you and what is their use in connection with the study. This data concerns your current clinical situation but also some of your background, the results of examinations carried out within the context of care of your health in accordance with current standards. You have the right to inspect these data and correct them if they are incorrect.

The investigator has a duty of confidentiality vis-à-vis the data collected. This means that he/she undertakes not only never to reveal your name in the context of a publication or conference but also that he/she will encode your data before sending them to the manager of the database of collected data (Laboratory of respiratory diseases and thoracic surgey, CHROMETA department, KU Leuven).

The investigator and his team will therefore be the only ones to be able to establish a link between the data transmitted throughout the study and your medical records.

The personal data transmitted will not contain any combination of elements that might despite everything allow you to be identified.
For the study data manager designated by the sponsor, the data transmitted will not allow you to be identified. The latter is responsible for collecting the data gathered by all investigators taking part in the study, processing them and protecting them in accordance with the requirements of the Belgian law on the protection of privacy.

These (encoded) data will be able to be sent to Belgian or other regulatory authorities, to the relevant ethics committees, to other doctors and/or to organisations working in collaboration with the sponsor.

The sponsor will use the data collected within the context of the study in which you are taking part, but would also like to be able to use them in connection with other research concerning the same disease as yours and its treatment. Any use of your data outside the context described in this document is only possible with the approval of the ethics committee.

If you withdraw your consent to take part in the study, to guarantee the validity of the research, the data encoded up to the point at which you withdraw will be retained. No new data may be sent to the sponsor.

If you have any questions relating to how your data are being processed, you may contact the investigator. The data protection officer in your hospital can be contacted as well: DPO - UZ Leuven, Herestraat 49, 3000 Leuven, e-mail dpo@uzleuven.be.

Finally, if you have a complaint concerning the processing of your data, you can contact the Belgian supervisory authority who ensures that privacy is respected when personal data are processed.

The Belgian supervisory authority is called:
Data Protection Authority (DPA)
Drukpersstraat 35,

1000 Brussels, Belgium
Tel. +32 2 274 48 00
Email: contact@apd-gba.be
Website: https://www.dataprotectionauthority.be

Next

1000 Brussels, Belgium
Tel. +32 2 274 48 00
Email: contact@apd-gba.be
Website: https://www.dataprotectionauthority.be

About you

Please answer the following questions about you

Your years of experience as a physician

Please Select... ⌄

Have you worked with AI-based decision support systems before?

○ Yes
○ No

On a scale from 1 (least) to 5 (most), are you enthusiastic about AI for clinical outcomes in general?

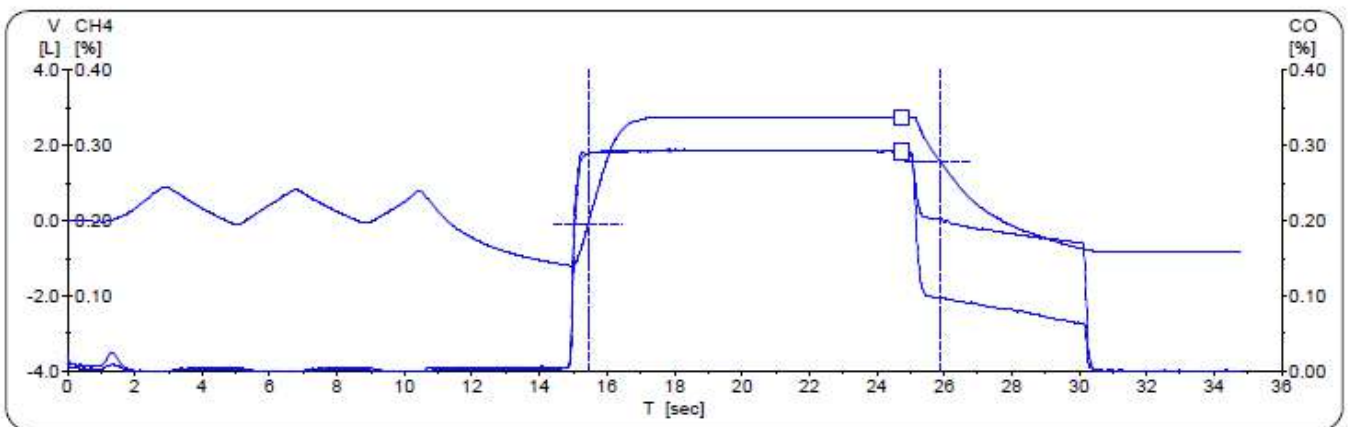| 1	2	3	4	5

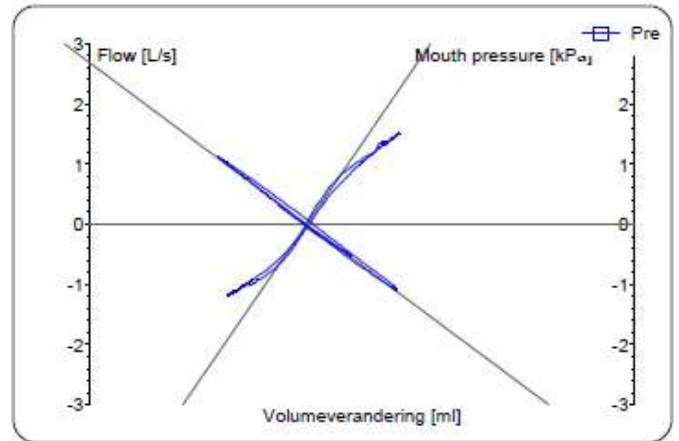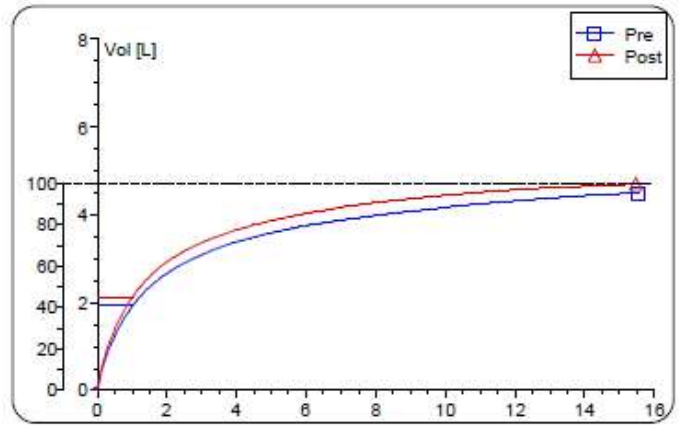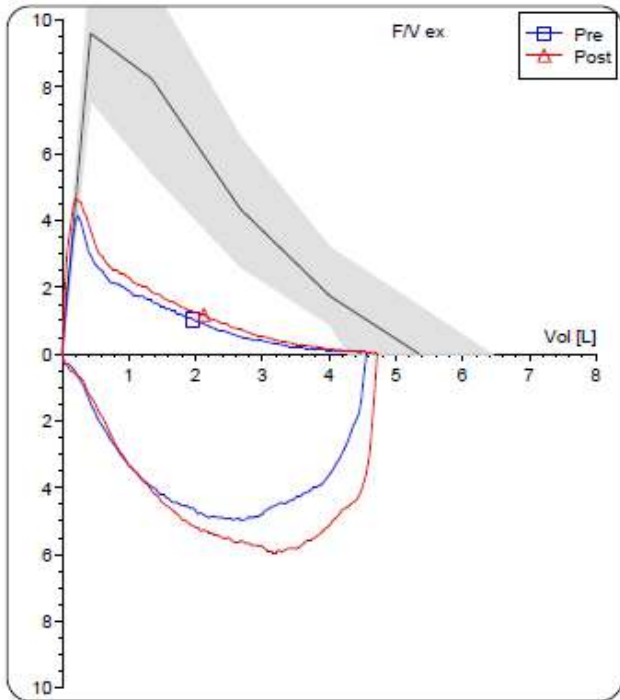Next

☰

Tutorial task 1a

Instruction The following is a PFT report with clinical characteristics, flow-volume and volume-time curves from spirometry, resistance curves from body-plethysmography, volume-time and CO concentration-time curves from diffusion capacity test.

Please scroll down to view the entire PFT report. At the end, we will ask your responses.

To improve visibility, press *Ctrl and scroll* to zoom in or out.

Sex: Male   **Age**: 34   **Height**: 178 cm   **Weight**: 74 kg   **BMI**: 23 kg/m²   **Race**: Caucasian   **Smoking**: 10 PY
Case: Male 34yo, heavy-smoker, complaints of dyspnoea, cough and sputum production

		Refer...	Pred	Pre	%Pred	Z-Score	Post Ven...	%Pred	%Chg	Z-Score	Z-Score
Substantie											
Spirometrie											
Meas time				14:41			15:29				
FVC	L	Quanj...	5.35	4.47	84	-1.35	4.68	88	5	-1.02	-1.02
FEV 1	L	Quanj...	4.36	1.92	44	-4.27	2.10	48	9	-3.99	-3.99
FEV 1 % FVC	%	Quanj...	81.80	43.03	53	-4.49	44.79	55	4	-4.37	-4.37
PEF	L/s	ECCS...	9.60	4.27	45	-4.40	4.68	49	10	-4.06	-4.06
FEF 25	L/s	ECCS...	8.25	1.76	21	-3.79	2.03	25	15	-3.64	-3.64
FEF 50	L/s	Quanj...	4.34	0.79	18	-4.23	0.95	22	19	-3.93	-3.93
FEF 75	L/s	Quanj...	1.73	0.23	14	-4.41	0.28	16	18	-4.08	-4.08
MFEF	L/s	Quanj...	4.34	0.63	15	-4.56	0.75	17	18	-4.32	-4.32
FIF50	L/s			4.88			5.47		12		
FET100	sec			15.45			15.39		-0		
Longvolumes Plethysmografisch											
VC	L	ECCS...	5.24	4.56	87	-1.21					
RV	L	ECCS...	1.85	2.41	131	1.38					
ITGV	L	ECCS...	3.37	4.84	143	2.44					
RV%TLC	%	ECCS...	27.22	34.61	127	1.35					
TLC	L	ECCS...	7.12	6.97	98	-0.21					
Diffusie											
DLCO_SB mmol/(min*kPa)		ECCS...	11.47	8.28	72	-2.26					
KCO mmol/(min*kPa*L)		ECCS...	1.61	1.62	101	0.05					
Hb g(Hb)/dL				14.20							
DLCOcSB mmol/(min*kPa)		ECCS...	11.47	8.38	73	-2.19					
KCOc mmol/(min*kPa*L)		ECCS...	1.61	1.64	102	0.13					
VA_SB	L	JAEG...	6.97	5.10	73						
Weerstandsmeting											
R mid	kPa/(L/s)	ECCS...	0.30	0.47	158						
sG mid	1/(kPa*s)	ECCS...	0.85	0.41	48						

Your preferred diagnosis?

Please Select...

Second diagnosis? (Optional)

None

Third diagnosis? (Optional)

None

Fourth diagnosis? (Optional)

None

Your overall confidence in diagnosis from 1(least) to 5 (most)?

1	2	3	4	5

Any comments? (Optional)

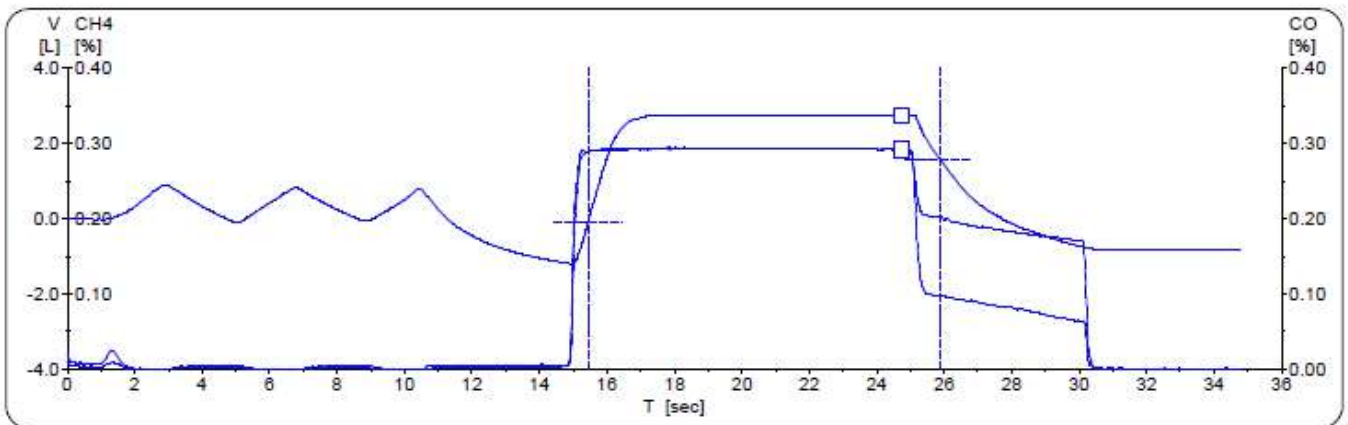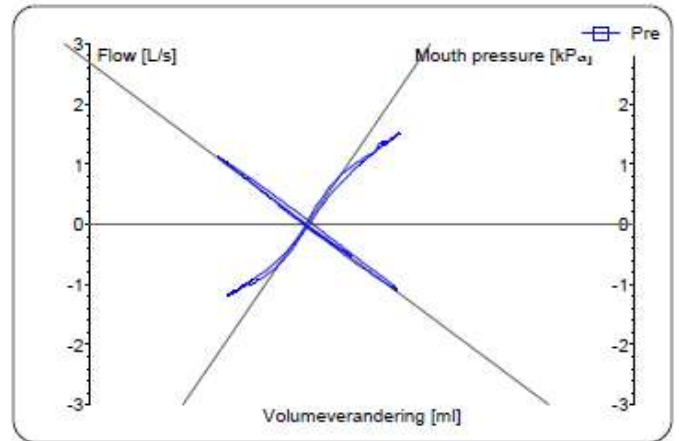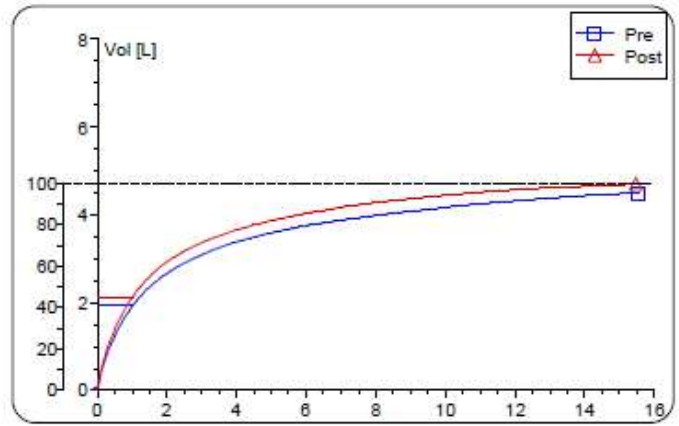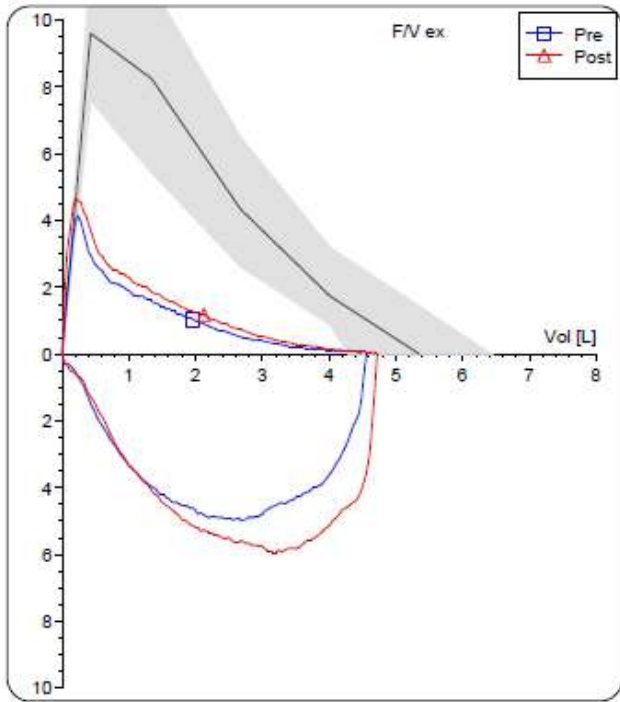**Instruction** Please click Next to proceed to tutorial task 1b

Back   Next

=

Tutorial task 1b

Instruction The same PFT report from the task a is displayed here, but now the suggestions of AI are included at the end of the report.

Please scroll down to view the PFT report and AI's suggestions

Sex: Male **Age**: 34 **Height**: 178 cm **Weight**: 74 kg **BMI**: 23 kg/m² **Race**: Caucasian **Smoking**: 10 PY															
Case: Male 34yo, heavy-smoker, complaints of dyspnoea, cough and sputum production															

		Refer...	Pred	Pre	%Pred	Z-Score -3--2	Z-Score2 3	Post	%Pred	%Chg	Z-Score -3--2	Z-Score2 3	Z-Score
Substantie								Ven...					
Spirometrie													
Meas time				14:41				15:29					
FVC	L	Quanj...	5.35	4.47	84	-1.35	●	4.68	88	5	-1.02	●	-1.02
FEV 1	L	Quanj...	4.36	1.92	44	-4.27 ▶		2.10	48	9	-3.99 ▶		-3.99
FEV 1 % FVC	%	Quanj...	81.80	43.03	53	-4.49 ▶		44.79	55	4	-4.37 ▶		-4.37
PEF	L/s	ECCS...	9.60	4.27	45	-4.40 ▶		4.68	49	10	-4.06 ▶		-4.06
FEF 25	L/s	ECCS...	8.25	1.76	21	-3.79 ▶		2.03	25	15	-3.64 ▶		-3.64
FEF 50	L/s	Quanj...	4.34	0.79	18	-4.23 ▶		0.95	22	19	-3.93 ▶		-3.93
FEF 75	L/s	Quanj...	1.73	0.23	14	-4.41 ▶		0.28	16	18	-4.08 ▶		-4.08
MFEF	L/s	Quanj...	4.34	0.63	15	-4.56 ▶		0.75	17	18	-4.32 ▶		-4.32
FIF50	L/s			4.88				5.47		12			
FET100	sec			15.45				15.39		-0			
Longvolumes Plethysmografisch													
VC	L	ECCS...	5.24	4.56	87	-1.21	●						
RV	L	ECCS...	1.85	2.41	131	1.38	●						
ITGV	L	ECCS...	3.37	4.84	143	2.44	●						
RV%TLC	%	ECCS...	27.22	34.61	127	1.35	●						
TLC	L	ECCS...	7.12	6.97	98	-0.21	●						
Diffusie													
DLCO_SB mmol/(min*kPa)		ECCS...	11.47	8.28	72	-2.26 ●							
KCO mmol/(min*kPa*L)		ECCS...	1.61	1.62	101	0.05	●						
Hb g(Hb)/dL				14.20									
DLCOcSB mmol/(min*kPa)		ECCS...	11.47	8.38	73	-2.19 ●							
KCOc mmol/(min*kPa*L)		ECCS...	1.61	1.64	102	0.13	●						
VA_SB	L	JAEG...	6.97	5.10	73								
Weerstandsmeting													
R mid	kPa/(L/s)	ECCS...	0.30	0.47	158								
sG mid	1/(kPa*s)	ECCS...	0.85	0.41	48								

Interpretation by AI

Suggested diagnoses in order: COPD, OBD

Asthma	COPD	OBD
19.6%	38.5%	21.7%

Legend: Asthma, COPD, OBD, Healthy, ILD, NMD, PVD, TD

COPD

Smoking	10 pack years
Age	34 years
FEV1/FVC	45 %
TLC	98 %pred
KCO	101 %pred

<-Against Evidence For->

OBD

Smoking	10 pack years
Age	34 years
FEF25-75%	17 %pred
KCO	101 %pred
DLCO	72 %pred

<-Against Evidence For->
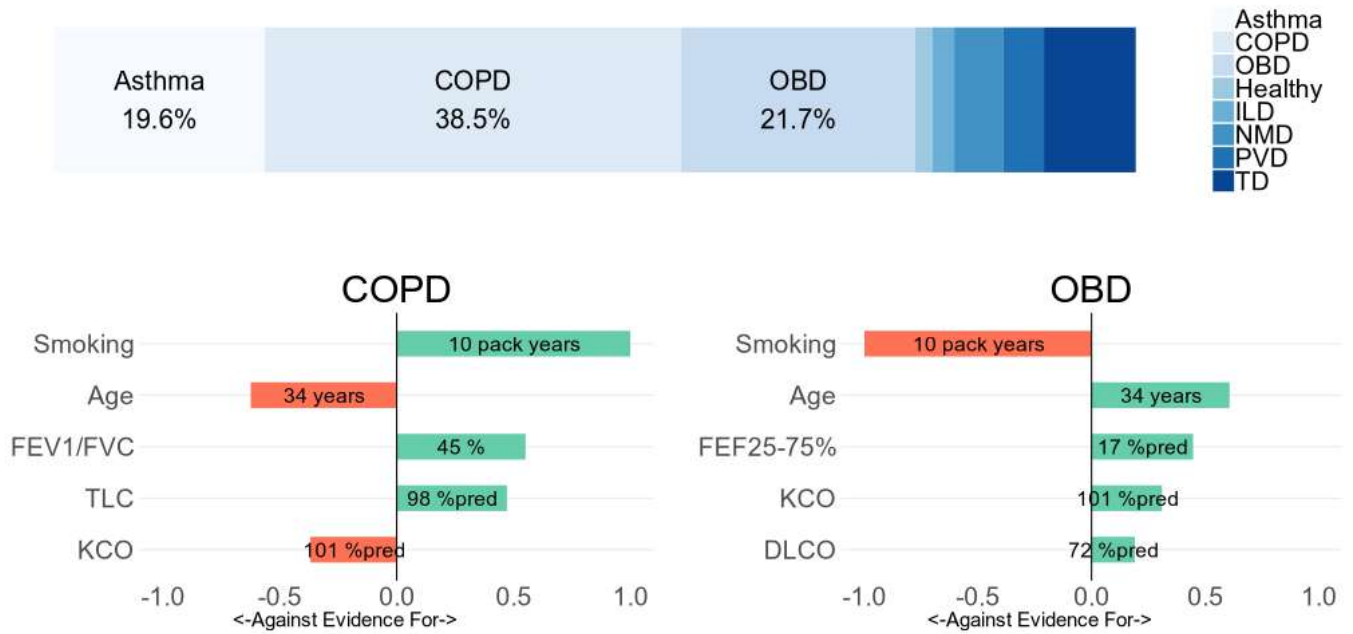
Instruction Key points to note

1. AI's disease suggestions are based on a descending order of predicted probabilities (bar plot) , and the suggestions are limited to two diseases.

2. The evidence plots show the relative evidence of the top 5 PFT report parameters towards AI's suggestions. The parameter with the highest evidence has a magnitude of 1.

3. Evidence can be **positive** implying supporting evidence, or **negative** implying counter-evidence

Abbreviations
COPD: Chronic obstructive pulmonary disease
OBD: Other obstructive disease
ILD: Interstitial lung disease
NMD: Neuromuscular disease
PVD: Pulmonary vascular disease
TD: Thoracic deformity

Your preferred diagnosis?

Please Select...

Second diagnosis? (Optional)

None

Third diagnosis? (Optional)

None

Fourth diagnosis? (Optional)

None

Your overall confidence in your diagnosis from 1(least) to 5 (most)?

1	2	3	4	5

Do you agree with the suggestions and the evidence provided by AI?

Strongly disagree	Disagree	Neutral	Agree	Strongly agree

Any comments? (Optional)

Instruction Please click Next to conclude the tutorial

Back   Next

☰

Supplement Table S4

Participant demographics in phase P1 and P2 studies

|	P1	P2
N	16	62
Enrolment	Monocentric	Multicentric
Years of experience > 5 years	75%	81%
Past experience with AI	56%	11%
Mean baseline enthusiasm in AI on Likert Scale (1-least, 5-most)*	3.56 (0.96)	3.92 (0.93)

Supplement Table S5

Preferential and differential diagnostic performance of the explainable artificial intelligence (XAI) model across different disease cohorts.

	P1 study								
	Overall	Healthy	COPD	Asthma	ILD	NMD	OBD	TD	PVD
N	24	4	4	4	4	2	2	2	2
Preferential diagnosis (disease with maximum probability) = GS	15	2	4	2	4	2	1	0	0
Differential diagnosis (preferential + second suggestion if probability > 15%) includes GS	22	4	4	4	4	2	2	1	1

	P2 study								
	Overall	Healthy	COPD	Asthma	ILD	NMD	OBD	TD	PVD
N	24	4	4	4	4	2	2	2	2
Preferential diagnosis (disease with maximum probability) = GS	15	2	3	3	4	2	1	0	0
Differential diagnosis (preferential + second suggestion if probability > 15%) includes GS	21	4	4	4	4	2	1	1	1

Abbreviations: GS= Gold standard; NMD = neuromuscular disease; ILD = interstitial lung diseases; PVD = pulmonary vascular diseases; OBD = other obstructive diseases; TD = Thoracic deformity/ Pleural diseases; COPD = chronic obstructive pulmonary disease

(a) P1 with 16 pulmonologists
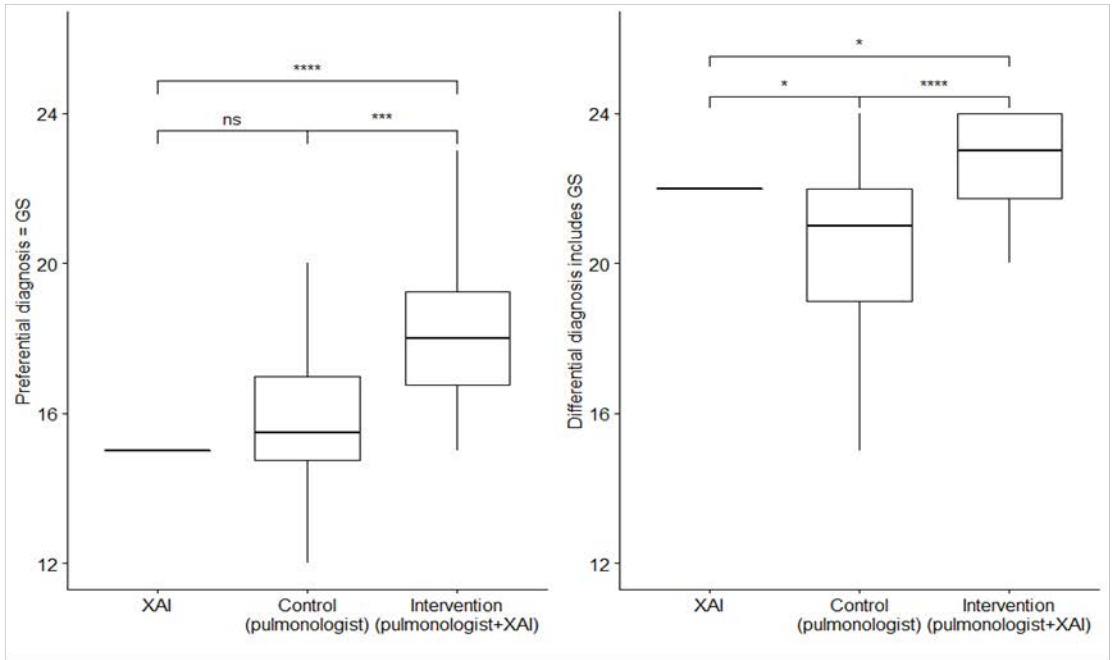
(b) P2 with 62 pulmonologists
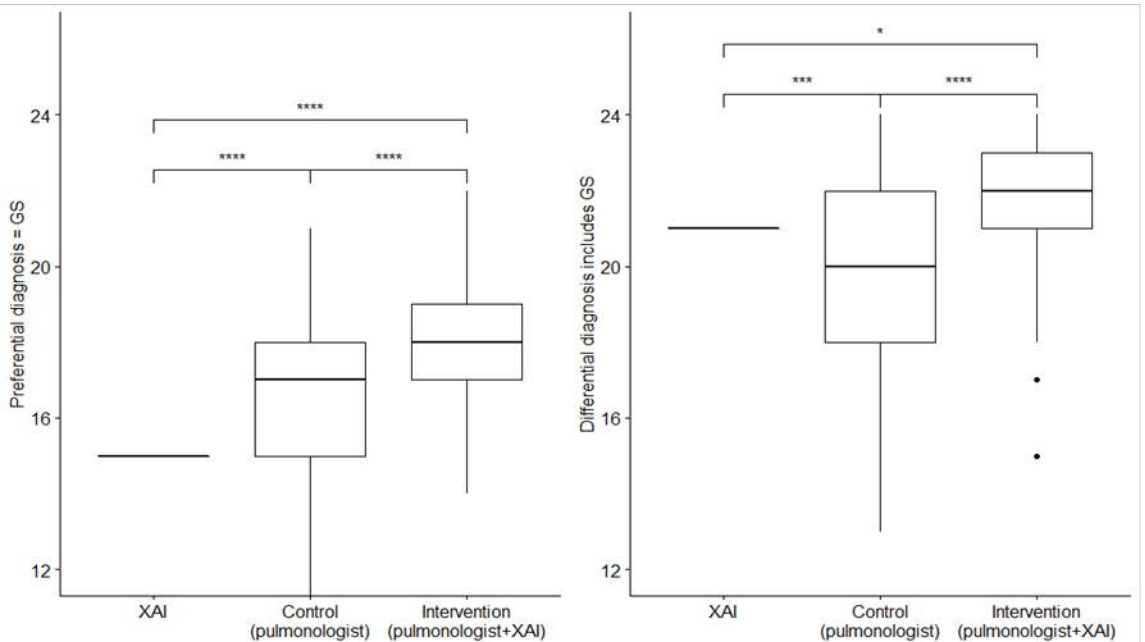
Supplement S7

Table : Interventional diagnostic performance stratified on years of experience and baseline enthusiasm in AI applications in P2 study (N=62 pulmonologists)

Diagnostic performance based on years of experience (pulmonologist + XAI, N = 62)			
	< 5 years (N=12)	> 5 years (N=50)	p
Preferential diagnosis= GS	18.42 (1.93)	17.82 (1.79)	0.34
Differential diagnosis includes GS	22 (1.81)	21.62 (2.18)	0.54
Diagnostic performance based on baseline enthusiasm in AI applications measured on Likert Scale (LS) (pulmonologist + XAI, N=62)			
	LS > 3 (N=42)	LS <= 3 (N=20)	p
Preferential diagnosis= GS	17.69 (1.83)	18.45 (1.73)	0.12
Differential diagnosis includes GS	21.23 (2.31)	22.65 (1.14)	0.06

Supplement S8

Table showing how pulmonologists' diagnostic performance whenever XAI's preferential diagnosis was incorrect.

	P1 study (16 pulmonologists)					
	XAI's preferential diagnosis was incorrect (N=9)			XAI's preferential diagnosis was correct (N=15)		
	Control (pulmonologist)	Intervention (pulmonologist + XAI)	p	Control (pulmonologist)	Intervention (pulmonologist + XAI)	p
Preferential diagnosis= GS	5.94 (1.44)	5.5 (1.55)	0.032	9.69 (1.08)	12.62 (1.89)	<0.0001
Mean level of agreement with XAI on Likert scale	3.47 (0.43)			4.07 (0.13) (p<0.0001)		

	P2 study (62 pulmonologists)					
	XAI's preferential diagnosis was incorrect (N=9)			XAI's preferential diagnosis was correct (N=15)		
	Control (pulmonologist)	Intervention (pulmonologist + XAI)	p	Control (pulmonologist)	Intervention (pulmonologist + XAI)	p
Preferential diagnosis= GS	6.45 (1.29)	5.47 (1.64)	<0.0001	10.19 (1.49)	12.47 (1.26)	<0.0001
Mean level of agreement with XAI on Likert Scale	2.95 (0.52)			3.75 (0.06) (p<0.00001)		

Abbreviations: GS= Gold standard; XAI: Explainable AI