Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

RESEARCH QUESTION: Among patients suspected to have COVID-19, should breath tests be used to diagnose COVID-19 infection?

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
There is insufficient evidence to recommend the use of breath test in detecting COVID-19 Infection.	Low	-

Consensus Issues
The Panel considers that it is too premature to make a recommendation on Breath Testing as the technology is not available in the Philippines and the information on its use in other countries is not extensive.

KEY FINDINGS

- This review has a total of 11 cross-sectional studies on the use of breath tests in the diagnosis of COVID-19 infection.
- The overall accuracy of breath tests was high, with pooled sensitivity of 95% (95% CI 0.90-0.97) and pooled specificity of 93% (95% CI 0.86-0.97). However, the overall certainty of evidence was low due to issues of risk of bias and significant heterogeneity. This heterogeneity may be attributed to the different mechanisms of the devices despite using the same idea of breath testing. Further evidence is recommended.
- Currently, there are no available forms of breath testing sold locally and information about cost and resource requirements are limited.

WHAT'S NEW IN THIS VERSION?

- Five new cross-sectional studies were added.
- Additional breath tests include the use of spectroscopy which could also detect semi- and non-volatile organic compounds, aside from VOCs (Volatile Organic Compounds) detected from spectrometry, rapid antigen, and olfactory technology.

PREVIOUS RECOMMENDATIONS
As of 29 November 2021

There is insufficient evidence to recommend the use of breath test in detecting COVID-19 infection. *(Low certainty of evidence)*

Consensus Issues
Despite the addition of five new studies since the previous recommendation, insufficient evidence remains to recommend for or against breath tests. The diagnostic accuracy of breath tests cannot be ascertained due to the heterogeneity across studies. The panel also raised concerns on the availability and accessibility of the test, its cost, and ease of use.

INTRODUCTION

Reverse transcription polymerase chain reaction (RT-PCR) remains to be the gold standard for SARS-CoV-2 testing. Collection of specimens for RT-PCR requires time-consuming invasive procedures which also entail biohazard exposure to health personnel acquiring the sample [1,2]. Breath testing, a novel method, addresses these concerns as samples are obtained via non-invasive sampling and results are usually rapidly acquired with a turnover time of 60 seconds to ten minutes [3]. Testing usually requires the individual blowing or breathing into a disposable mouthpiece that is connected to a breath sampler. The information is fed into an analyzer, which then produces the result.

Breath testing analyzes the concentrations of either volatile organic compounds (VOCs) such as ketones and aldehydes, semi-volatile compounds (steric acid), non-volatile compounds (CRP, IL-6), or antigen to confirm the presence of a medical condition or an infection [3- 5]. Metabolic changes from respiratory viral infection leads to changes in breath profiles, suggesting that infection-associated components of breath may be used to develop non-invasive diagnostic modalities through breath analyzers [6,7].

Common methods of breath tests include gas chromatography with mass spectrometry (GC-MS), as it is capable of quantifying VOC concentrations and analyzing VOC breath patterns, as well as other forms of spectrometry and spectroscopy. However these machines' bulkiness, high cost, need of trained personnel, and the need of pre-concentration methods for VOCs with low baseline concentrations in the breath limit them from being used as point-of-care diagnostic methods [8].

Electronic noses (e-Noses) with their sensors then became a promising inexpensive, simple, and portable option for breath analysis. Some e-Nose sensors (most commonly Metal-Oxide-Semiconductor sensors) react with a single pertinent VOC and derive its concentration based on measuring the chemical changes observed on the sensors themselves. Some e-Noses on the other hand have multiple sensors that detect a unique gas pattern, which consists of multiple VOCs in breath that are associated with a disease. The latter method is made possible through pattern-recognition using machine-learning algorithms [8].

These e-Noses, along with more portable and commercialized forms of spectrometry, spectroscopy, and breath tests such as rapid antigen test via exhaled breath concentrate is now being tested for their ability to detect COVID-19. Portable breath analyzers are currently being tested by the US, Finland, Singapore, India, and Israel for their capability to be accurate and affordable mass screening tools for COVID -19 [6,7].

This study updates the previous evidence reviewed by Epetia et al. 2021 on the diagnostic accuracy of breath tests [9].

REVIEW METHODS

Literature search was done for articles that investigated the utility of breath tests in diagnosing COVID-19. A systematic literature search from 04 October 2021 until 15 October 2022 was performed in online

databases (MEDLINE and Cochrane CENTRAL Database), trial registries (ClinicalTrials.gov) and pre-print servers (MedRxiv, BioRxiv, and chinaRxiv).

The search terms “COVID-19”, “SARS-COV2”, “Breath Test”, “Volatile Organic Compounds”, “Sensitivity” and “Specificity” were used. No language restrictions were applied. Narratives, commentaries, case report, case series articles, and case-control studies were excluded in the analysis. Preprints were also excluded. Eligible studies from pre-print servers were subsequently checked through google, and only those with final published papers were included. Existing meta-analyses related to the topic of interest were looked into to check for additional possible eligible studies. All new eligible studies along with the previously included eligible studies were appraised.

Pooled sensitivity and specificity were calculated with univariate meta-analyses with random-effects models using the 'meta' package in R. Subgroup analysis was performed according to the mechanism of breath testing (spectrometry or spectroscopy, olfactory technology (electronic nose) and rapid-antigen using Inflammacheck® technology) and symptomatology of participants.

RESULTS

Characteristics of included studies

A total of 11 studies were included in this review: six prospective studies [10-15] and five cross-sectional studies [3-5,16, 17,]. Five new studies were added from the previous version of this review. Patient selection, index test, and reference standards were applicable to this review. The population included in the studies were all adults ranging from asymptomatic, symptomatic, to severely ill individuals. Diagnosis was confirmed using RT-PCR as the reference standard. All of the studies utilized a breath test as the index test. However, the devices, the component of breath (VOCs, antigen, and a combination of VOCs, non-volatile, and semi-volatile compounds) tested for analysis, and the mechanism of how those components were detected differed across the included studies. VOCs were the most commonly analyzed among the studies.

Methodological quality

The overall methodological quality of the studies were moderate to high. Five studies presented with low risk of bias [4, 5,12,15,17]. Most of the studies rated as moderate methodological quality were unclear on how they prevented their index test results from being affected by the reference standard results and vice versa.

Diagnostic accuracy of breath tests

A. Overall diagnostic accuracy

Breath testing showed an overall pooled sensitivity of 95% (95% CI 0.90-0.97) with individual sensitivity values ranging from 67-100% based on 11 studies. Overall pooled specificity of the 11 included studies was 93% (95% CI 0.85-0.97), with individual specificity values ranging from 54-100%. Although diagnostic accuracy appeared moderate to high, certainty of evidence was downgraded due to issues of risk of bias among the included studies (patient selection, index test, reference standard, and flow and timing). Aside from this, substantial heterogeneity was noted for both the pooled sensitivity (I^2=67.1) and pooled specificity (I^2=90.7) estimates, downgrading certainty of evidence to low for sensitivity and very low for specificity. The component used for analysis (VOCs, antigen, non-volatile compounds) and the device used were identified as possible sources of heterogeneity.

Table 1. Subgroup analysis for sensitivity and specificity of breath testing

Variable	SENSITIVITY			SPECIFICITY		
	Studies (Samples)	Pooled estimate (95%CI)	I^2	Studies (Samples)	Pooled estimate (95%CI)	I^2

OVERALL	**11 (760)**	**0.95 (0.89-0.98)**	**67.1%**	**11 (4726)**	**0.93 (0.85, 0.97)**	**90.7%**
Method of Breath Testing						
Spectrometry/ Spectroscopy	8 (377)	0.91 (0.83-0.96)	62.7%	8 (1179)	0.96 (0.89-0.98)	70.1%
Olfactory Technology	2 (370)	0.98 (0.90-1.00)	78.1%	2 (3455)	0.74 (0.64-0.82)	94.4%
Rapid-antigen using exhaled breath condensate	1 (13)	0.92 (0.64-1.00)		1 (92)	0.99 (0.94-1.00)	
Symptomatology						
Asymptomatic	3 (88)	0.98 (0.92-1.00)	0%	3 (932)	0.95 (0.78-0.99)	92.7%
Symptomatic	6 (517)	0.94 (0.85-0.97)	53.2%	6 (3188)	0.83 (0.72-0.90)	93.2%
Unknown	4 (155)	0.92 (0.73-0.98)	80.2%	4 (606)	0.98 (0.90-1.00)	54.6%

B. Subgroup analysis

By method of breath testing

Subgroup analysis by method of breath testing showed that VOCs using olfactory technology had the highest sensitivity (Sn 0.98, 95% CI 0.90-1.00), followed by rapid antigen test through exhaled breath condensate (Sn 0.92, 95% CI 0.64-1.00), and VOCs using spectrometry or spectroscopy (Sn 0.91, 95% CI 0.83-0.96). The highest specificity was demonstrated by rapid antigen using exhaled breath condensate (Sp 0.99, 95% CI 0.94-1.00), followed by VOCs using spectrometry or spectroscopy (Sp 0.96, 95% CI 0.89-0.98), and VOCs using olfactory technology (Sp 0.74, 95% CI 0.64-0.82).

While breath tests that use spectrometry or spectroscopy demonstrate high sensitivity, the diagnostic accuracy of these methods for SARS-CoV-2 detection cannot be fully established due to substantial heterogeneity in the sensitivities (I^2=62.7%) and specificities (I^2=70.1%) among the included studies. Certainty of evidence was also downgraded to low due to issues of risk of bias (patient selection, index test, reference standard).

Similar results were found among breath tests that analyzed VOCs through olfactory technology. Despite having the highest sensitivity among other subgroups, studies that utilized olfactory technology had serious risks of bias (patient selection, reference standard). There were also issues of inconsistency on pooled sensitivity (I^2=78.1%), and very serious inconsistency on pooled specificity (I^2=94.4%). Certainty of evidence for the sensitivity and specificity of breath tests by olfactory technology were then downgraded to low and very low, respectively.

Sources of substantial or significant heterogeneity within these subgroups may be attributed to differences in the devices used per study (e.g. brand, material) despite having common mechanisms of detecting COVID-19-associated components of breath.

Breath test through Inflammacheck® Rapid antigen testing on exhaled breath condensate maintains to have only one study as noted in the previous evidence summary, with 92% sensitivity and 99% specificity.

Certainty of evidence for sensitivity and specificity was low for this test due to very serious issues of imprecision (low sample sizes).

B. By symptomatology
For asymptomatic patients, pooled sensitivity was 98% (95% CI 0.92-1.00). Certainty of evidence was rated low due to very serious issues of imprecision attributed to low sample size. Pooled specificity of breath tests in asymptomatic patients was 95% (95% CI 0.78-0.99). Certainty of evidence was rated low due to very serious issues of inconsistency with an I^2 of 92.7%

When used for testing symptomatic individuals, six studies showed that breath tests had pooled sensitivity of 94% (95% CI 0.85-0.97). Certainty of evidence was rated low due to serious issues of risk of bias (patient selection, index test, reference standard, flow and timing) and inconsistency with I^2 of 53.2%. Pooled specificity of these breath tests in symptomatic individuals, on the other hand, was 83% (95% CI 0.72-0.90). Certainty of evidence was rated very low due to serious issues of risk of bias (patient selection, index test, reference standard), and very serious issues of inconsistency with I^2 of 93.2 %

When tested on individuals with unknown presence of symptoms, 4 breath test studies had an overall pooled sensitivity of 92% (95% CI 0.73-0.98). Certainty of evidence was rated low due to issues of risk of bias (patient selection, index test, reference standard, flow and timing), and inconsistency with I^2 of 80.2%. Pooled specificity in individuals with unknown symptomatology was 98% (95% CI 0.90-1.00). Certainty of evidence was low due to serious risk of bias and heterogeneity with I^2 of 54.6%

RECOMMENDATIONS FROM OTHER GROUPS

Currently, there are no published recommendations on the use of breath tests in the diagnosis of COVID-19 infection from the World Health Organization and the US National Institutes of Health.

The updated interim guidelines of the Centers for Disease Control and Prevention for collecting and handling of clinical specimens for COVID-19 testing included the use of InspectIR COVID-19 Breathalyzer, a portable GC-MS tool that detects COVID-associated VOCs. Use of this breathalyzer is only authorized by the US Food and Drug Administration through Emergency Use Authorization [18].

The Malaysian Health Technology Assessment Section (MaHTAS) of the Ministry of Health Malaysia recognized the good sensitivity and specificity of breath test analysis to discriminate and screen for COVID-19 infection among COVID-19 confirmed patient and healthy controls [7]. However, it recommended further evaluation and validation studies with larger sample size are required to ascertain its effectiveness and safety.

In May 2021, two breathalyzer tests (BreFence Go COVID-19 Breath Test System, TracieX Breathalyzer) were given provisional authorization by the Singapore Health Sciences Authority to be tested on incoming travelers from Malaysia. Individuals who tested positive in the breath test underwent confirmatory PCR swab [6]. Results of these large-scale trials have not yet been published.

EVIDENCE TO DECISION

Information about the cost of breath testing, its resource requirements, and its cost-effectiveness in the local and international setting are limited.

The price of Singapore BreFence Go COVID-19 Breath Test were listed as S$5 (₱190) to S$20 (₱735) [6]. One recently developed commercial breath test called TERABioStation offers rapid testing for US$4.44 (₱243) [17,19].

ONGOING STUDIES AND RESEARCH GAPS

There are no ongoing studies on breath test in the Philippines. Studies on the accuracy of breath tests in children have not yet been done.

One non-randomized clinical trial on breath test in Israel (n=4,000) was estimated to be done by July 2021 but was extended to May 2023 still on actively recruiting status. In addition to this, there are three more ongoing non-randomized open-label clinical trials for breath tests in COVID, one of which is from the United Kingdom which is still actively recruiting patients despite the estimated date of completion to be last July 2022.

Three observational studies from the US, Canada, and Turkey are still currently investigating the diagnostic accuracy of breath test in COVID-19 infection. Their estimated completion is at the end of Oct 2022 for the study from the US, and March to June 2022 for the remaining two studies. Another observational study from Canada is looking into the application of a breath test on patients during and after COVID-infection. Its estimated date of completion was May 2021, but enrolment of patients is still ongoing.

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=5/9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	Varies (N=1)	Yes (N=4)					RT-PCR currently being used as gold standard requires time-consuming and invasive specimen collection which is also hazardous to health personnel acquiring the sample.
Benefits	Large	Moderate (N=4)	Small (N=1)	Varies	Uncertain		Breath testing will decrease the need for significant health personnel contact during specimen collection and time needed for analysis will be greatly reduced. Breath testing does not require invasive nasopharyngeal and/oropharyngeal collection.
Harms	Large	Moderate (N=2)	Small (N=3)	Uncertain			
Accuracy	Very Accurate	Accurate (N=4)	Inaccurate	Very Inaccurate	Varies (N=1)		Overall sensitivity of 11 studies on breath testing is 95% (95%CI 0.89-0.98, I^2=62.7%), and overall specificity of testing is 93% (95%CI 0.85-0.97, I^2=90.7%).
Balance of Benefits and Harms	Favors the use of Breath tests	Probably favors the use of breath tests (N=3)	Does not favor diagnostic or no diagnostic (N=1)	Favors no intervention	Don't Know (N=1)		Certainty of evidence is low due to issues of risk of bias among the included studies, significant and substantial heterogeneity (I^2=67.1for sensitivity, I^2=90.7 for specificity across the included studies). The component used for analysis (VOCs, antigen, non-volatile compounds) and the device used were identified as possible sources of heterogeneity.
Certainty of Evidence	High	Moderate	Low (N=5)	Very Low			
Values	Important uncertainty or variability (N=1)	Possibly important uncertainty or variability (N=4)	Possibly NO important uncertainty or variability (N=1)	No important uncertainty or variability			The price of Singapore BreFefnce Go COVID-19 Breath Test were listed as S$5 (₱190) to S$20 (₱735).

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Resources Required	Don't Know (N=3)	Large cost (N=1)	Moderate Cost	Negligible cost or savings (N=1)	Varies	Large Savings	One recently developed commercial breath test called TeraBioStation offers rapid testing for US$4.44 (₱243)
Certainty of evidence of required resources	No included studies (N=3)	Very low	Low (N=1)	Moderate (N=1)	High		
Cost effectiveness	No included studies	Favors the comparator (N=3)	Does not favor either criteria or the comparator	Probably favors the intervention	Favors criteria	Varies (N=2)	
Equity	Don't Know (N=1)	Probably Reduced (N=1)	Reduced (N=1)	Probably Increased (N=1)	Increased	Varies (N=1)	
Acceptability	Don't Know	No	Probably No	Yes (N=1)	Probably yes (N=3)	Varies (N=1)	
Feasibility	Uncertain	No	Probably No	Yes (N=1)	Probably yes (N=3)	Varies (N=1)	

Appendix 2: Search Yield and Results

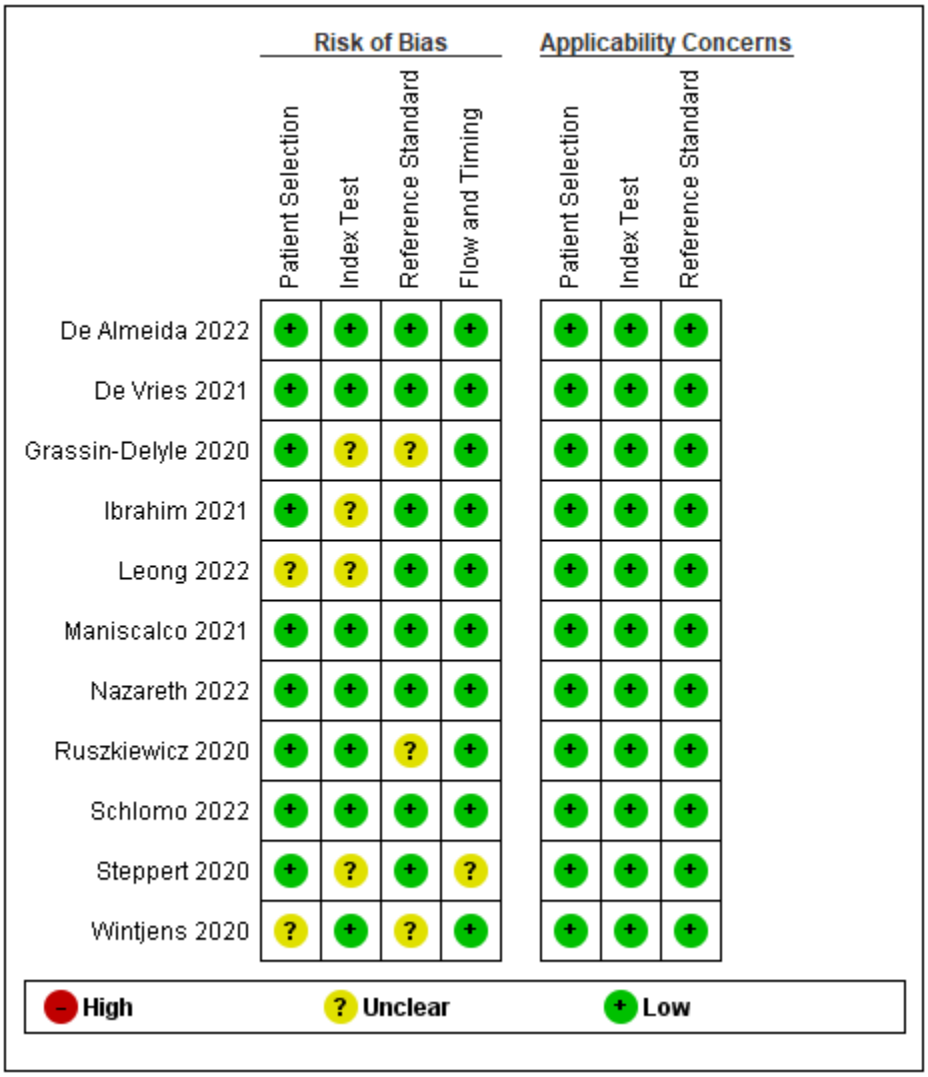
Database	Search Strategy	Results	Eligible Studies
PubMed	((("Sensitivity") OR ("Specificity")) AND ((COVID-19) OR (SARS-COV-2)) AND ((Breath Test) OR (Volatile Organic Compounds))) AND (("2021/10/04"[Date - Publication] : "3000"[Date - Publication]))	50	4
Cochrane	((("Sensitivity") OR ("Specificity")) AND ((COVID-19) OR (SARS-COV-2)) AND ((Breath Test) OR (Volatile Organic Compounds))) in All Text - with Cochrane Library publication date Between Oct 2021 and Oct 2022 (Word variations have been searched)	66	0
medRxiv	((“Sensitivity”) OR (“Specificity”)) AND ((COVID-19) OR (SARS-COV-2)) AND ((Breath Test) OR (Volatile Organic Compounds))" and posted between "04 Oct, 2021 and 15 Oct, 2022”	354	1
bioRxiv	((“Sensitivity”) OR (“Specificity”)) AND ((COVID-19) OR (SARS-COV-2)) AND ((Breath Test) OR (Volatile Organic Compounds))" and posted between "04 Oct, 2021 and 15 Oct, 2022	104	0
chinaRxiv	All Fields:(Breath Test) AND All Fields:(COVID-19) AND The years from:[2021-10-04T00:00:00Z TO 2022-10-15T23:59:59Z](1)	1	0
Clinicaltrials.gov	Condition or Disease: COVID-19 | Other Terms: Breath Test	55	8 ongoing research of interest
ChiCTR	Target Disease: COVID-19 | Intervention: Breath Test	0	0
HERDIN Plus	All Fields: COVID-19 AND All Fields: Breath Test	1	0

Appendix 3: Table of Included Studies

Study (Sample)	Study Design	Population	Index Test	Gold Standard	Outcome
De Almeida 2022 [17] (n=1140)	Cross-sectional	Symptomatic and asymptomatic individuals aged 18 years old and above	Breath Testing for VOCs (TERA.Bio)	RT-PCR	*Symptomatic Set:* (n=404) Sn: 0.92 (0.83,0.97) Sp: 0.96 (0.93,0.98) Asymptomatic Set: (n=166) Sn:1.00 (0.40,1.00) Sp:0.96 (0.92,0.99) Mixed Set: (n=570) Sn: 0.93 (0.84,0.98) Sp: 0.96 (0.94,0.98)
De Vries 2021 [12] (n=3,606)	Cross-sectional	Individuals 18 years old and above with symptoms suggestive of COVID-19 and/or who had been in contact to a known case	Breath testing for VOCs (eNose)	RT-PCR	*Validation Set:* (n=904) Sn: 1.00(0.89, 1.00) Sp: 0.78(0.75, 0.81) *Replication Set:* (n=1,948) Sn: 1.00(0.98, 1.00) Sp: 0.80(0.78, 0.82) *Asymptomatic Set:* (n=754) Sn: 0.98(0.89, 1.00) Sp: 0.78(0.75, 0.81)
Grassin-Delyle 2020 [11] (n=40)	Cross-sectional	Adult patients above 18 years old in the intensive care unit requiring mechanical ventilation	Breath testing for VOCs (mass spectrometry [Ionicon Analytic GmBH])	RT-PCR	Sn: 0.89(0.72, 0.98) Sp: 0.92(0.62, 1.00)
Ibrahim 2021 [13] (n=81)	Cross-sectional	Patients admitted to the hospital with suspected COVID-19 infection	Breath testing for VOCs (thermal desorption gas chromatography mass spectrometry [Agilent 7820A with 5977B MS])	RT-PCR	Sn: 0.67(0.53, 0.80) Sp: 0.86(0.68, 0.96)

Leong 2022 [14] (n=501)	Cross-sectional	Adult patients aged 18-99 from different testing centers	Breath testing for VOCs (spectroscopy [Surface Enhanced Raman Scattering (SERS)-Based Breathalyzer])	RT-PCR	Sn: 0.96(0.89, 0.99) Sp: 1.00(0.99, 1.00)
Maniscalco 2021 [5] (n=105)	Cross-sectional	Adult patients above 18 years old with clinical suspicion of COVID-19	Breath testing utilizing rapid-antigen on exhaled breath condensate (Inflammacheck®)	RT-PCR	Sn: 0.92(0.64, 1.00) Sp: 0.99(0.94, 1.00)
Nazareth 2022 [15] (n=105)	Cross-sectional	Hospitalized patients aged 16 years old and above	Breath testing for VOCs (gas chromatography-ion mobility spectrometry [BreathSpec])	RT-PCR	Sn: 0.85(0.74, 0.92) Sp: 0.90(0.68, 0.99)
Ruszkiewicz 2020 [3] (n=98)	Cross-sectional	Patients presenting with respiratory symptoms at the emergency room	Breath testing for VOCs (gas chromatography-ion mobility spectrometry [BreathSpec])	RT-PCR	*Dortmund Set:* (n=65) Sn: 0.90(0.55, 1.00) Sp: 0.80(0.67, 0.90) *Edinburgh Set:* (n=33) Sn: 0.81(0.58, 0.95) Sp: 0.75(0.43, 0.95)
Schlomo 2022 [4] (n=100)	Cross-sectional	Patients seen in the emergency department with previous exposure to COVID-19-infected persons	Breath testing for volatile, non-volatile, and semi-volatile organic compounds in breath (Fourier-transform infrared (FTIR) spectroscopy [Breath of Health Ltd. (BOH) Merkava I.I device])	RT-PCR	Sn: 1.00(0.90, 1.00) Sp: 1.00(0.95, 1.00)
Steppert 2020 [16] (n=74)	Cross-sectional	Adults with suspected COVID-19	Breath testing for VOCs (multi-capillary-coupled ion mobility spectrometry [STEP IMS NOO])	RT-PCR	Sn: 1.00(0.79, 1.00) Sp: 0.97(0.88, 1.00)
Wintjens 2020 [10] (n=219)	Cross-sectional	Employees with COVID-19 symptoms	Breath testing for VOCs (Aenose)	RT-PCR	Sn: 0.86(0.74, 0.94) Sp: 0.54(0.46, 0.62)

Appendix 4: Detailed Study Appraisal



Appendix 5: GRADE Evidence Profile

Should breath tests be used to diagnose COVID-19?

Pooled sensitivity: 0.95 (95% CI: 0.89 to 0.97)
Pooled specificity: 0.93 (95% CI: 0.85 to 0.97)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 14%	
True positives (patients with COVID-19)	11 studies (760 patients)	Cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	133 (126 to 136)	⊕⊕◯◯ Low[a,b]
False negatives (patients incorrectly classified as not having COVID-19)								7 (4 to 14)	
True negatives (patients without COVID-19)	11 studies (4,726 patients)	Cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[c]	not serious	none	802 (738 to 834)	⊕◯◯◯ Very Low[a,c]
False positives (patients incorrectly classified as having COVID-19)								58 (26 to 122)	

Explanations
a. unclear issues in patient selection, index test, reference standard, flow and timing
b. substantial heterogeneity among included studies
c. significant heterogeneity among included studies

Should breath tests by spectrometry/spectroscopy be used to diagnose COVID-19?

Pooled sensitivity: 0.91 (95% CI: 0.83 to 0.96)
Pooled specificity: 0.96 (95% CI: 0.89 to 0.98)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 24%	
True positives (patients with COVID-19)	8 studies (377 patients)	Cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	218 (199 to 230)	⊕⊕◯◯ Low[a,b]
False negatives (patients incorrectly classified as not having COVID-19)								22 (10 to 41)	
True negatives (patients without COVID-19)	8 studies (1,179 patients)	Cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	730 (676 to 745)	⊕⊕◯◯ Low[a,b]
False positives (patients incorrectly classified as having COVID-19)								30 (15 to 84)	

Explanations
a. unclear issues in patient selection, index test, reference test
b. substantial heterogeneity among included studies

Should breath tests for VOCs by olfactory technology be used to diagnose COVID-19?

Pooled sensitivity: 0.98 (95% CI: 0.90 to 1.00)
Pooled specificity: 0.74 (95% CI: 0.64 to 0.82)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 9.7%	
True positives (patients with COVID-19)	2 studies (370 patients)	Cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	95 (87 to 97)	⊕⊕◯◯ Low[a,b]
False negatives (patients incorrectly classified as not having COVID-19)								2 (0 to 10)	
True negatives (patients without COVID-19)	2 studies (3,455 patients)	Cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[c]	not serious	none	668 (578 to 740)	⊕◯◯◯ Very Low[a,c]
False positives (patients incorrectly classified as having COVID-19)								235 (163 to 325)	

Explanations
a. unclear issues in patient selection, reference test
b. substantial heterogeneity among included studies
c. significant heterogeneity among included studies

Should breath tests utilizing rapid-antigen on exhaled breath condensate be used to diagnose COVID-19?

Sensitivity: 0.92 (95% CI: 0.61 to 0.99)
Specificity: 0.99 (95% CI: 0.93 to 1.00)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 12%	
True positives (patients with COVID-19)	1 studies (13 patients)	Cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	none	110 (73 to 119)	⊕⊕◯◯ Low[a]
False negatives (patients incorrectly classified as not having COVID-19)								10 (1 to 47)	
True negatives (patients without COVID-19)	1 studies (92 patients)	Cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	none	871 (818 to 880)	⊕⊕◯◯ Low[a]
False positives (patients incorrectly classified as having COVID-19)								9 (0 to 62)	

Explanations
a. low sample size

Should breath tests be used to diagnose COVID-19 in asymptomatic individuals?

Pooled sensitivity: 0.99 (95% CI: 0.92 to 1.00)
Pooled specificity: 0.96 (95% CI: 0.73 to 1.00)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 8.6%	
True positives (patients with COVID-19)	3 studies (88 patients)	Cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	None	85 (79 to 86)	⊕⊕◯◯ Low[a]
False negatives (patients incorrectly classified as not having COVID-19)								1 (0 to 7)	
True negatives (patients without COVID-19)	3 studies (932 patients)	Cross-sectional (cohort type accuracy study)	not serious	not serious	very serious[b]	not serious	None	877 (667 to 914)	⊕⊕◯◯ Low[b]
False positives (patients incorrectly classified as having COVID-19)								37 (0 to 247)	

Explanations
a. small sample size
b. significant heterogeneity among included studies

Should breath tests be used to diagnose COVID-19 in symptomatic individuals?

Pooled sensitivity: 0.94 (95% CI: 0.85 to 0.97)
Pooled specificity: 0.83 (95% CI: 0.72 to 0.90)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 14%	
True positives (patients with COVID-19)	6 studies (517 patients)	Cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	132 (119 to 136)	⊕⊕◯◯ Low[a,b]
False negatives (patients incorrectly classified as not having COVID-19)								8 (4 to 21)	
True negatives (patients without COVID-19)	6 studies (3,188 patients)	Cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[c]	not serious	none	714 (619 to 774)	⊕◯◯◯ Very Low[a,c]
False positives (patients incorrectly classified as having COVID-19)								146 (86 to 241)	

Explanations
a. unclear issues in patient selection, index test, reference standard, flow and timing
b. substantial heterogeneity among included studies
c. significant heterogeneity among included studies

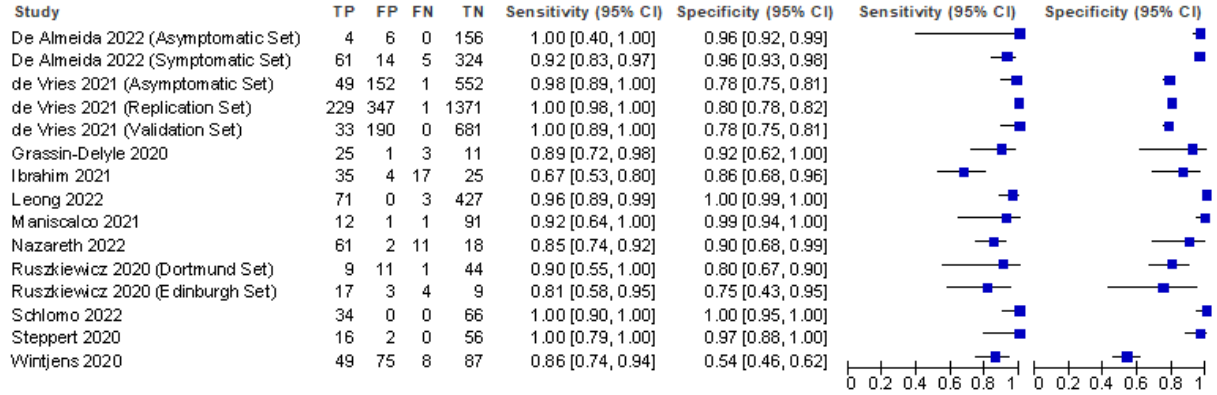
Should breath tests be used to diagnose COVID-19 in individuals with unknown symptomatology?

Pooled sensitivity: 0.92 (95% CI: 0.73 to 0.98)
Pooled specificity: 0.98 (95% CI: 0.90 to 1.00)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 20%	
True positives (patients with COVID-19)	5 studies (225 patients)	Cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	184 (158 to 196)	⊕⊕◯◯ Low[a,b]
False negatives (patients incorrectly classified as not having COVID-19)								16 (4 to 42)	
True negatives (patients without COVID-19)	5 studies (1106 patients)	Cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	784 (736 to 800)	⊕⊕◯◯ Low[a,b]
False positives (patients incorrectly classified as having COVID-19)								16 (0 to 64)	

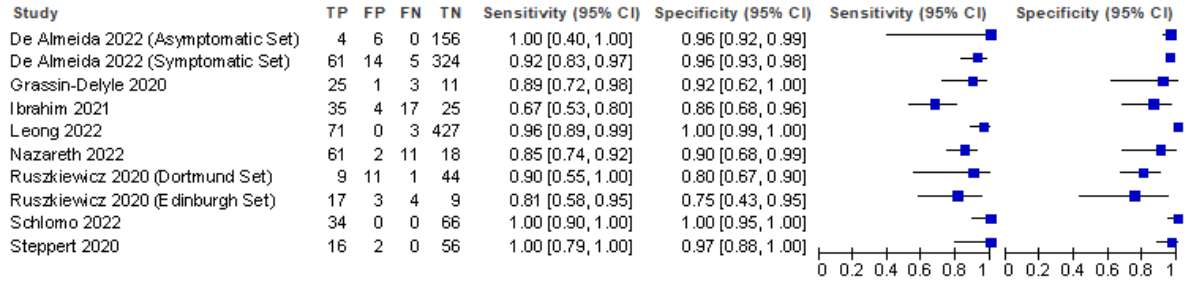
Explanations
a. unclear issues in patient selection, index test, reference standard, flow and timing
b. substantial heterogeneity among included studies

Appendix 6: Forest plots



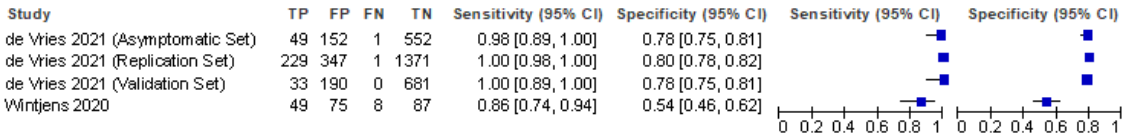
Pooled Sn: 0.95 (0.89,0.98) with I2=62.7%; Pooled Sp: 0.93 (0.85, 0.97); I^2=90.7%

Figure 1. Overall sensitivity and specificity of breath test



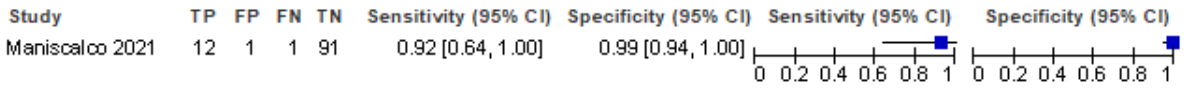
Pooled Sn: 0.91 (0.83,0.96) with I2=62.7%; Pooled Sp: 0.96 (0.89,0.98) with I^2=70.1%

Figure 2. Sensitivity and specificity of breath test using spectrometry or spectroscopy



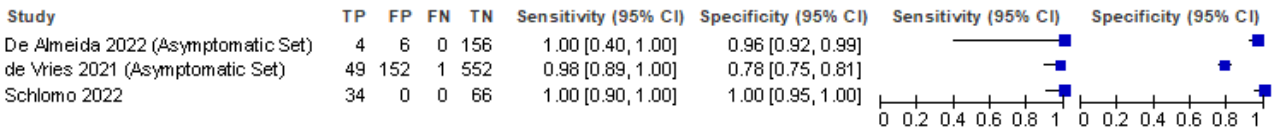
Pooled Sn: 0.98 (0.90,1.00) with I2=78.1%; Pooled Sp: 0.74 (0.64,0.82) with I2=94.4%

Figure 3. Sensitivity and specificity of breath test using olfactory technology



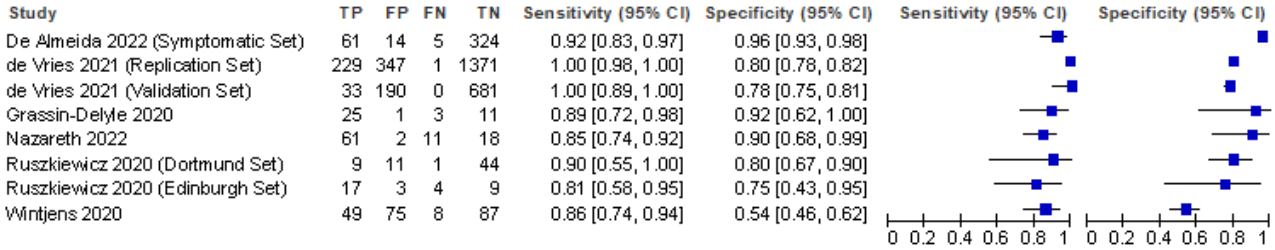
Sn: 0.92 (0.61,0.99); Sp: 0.99 (0.93,1.00)

Figure 4. Sensitivity and specificity of breath test for rapid-antigen on exhaled breath condensate



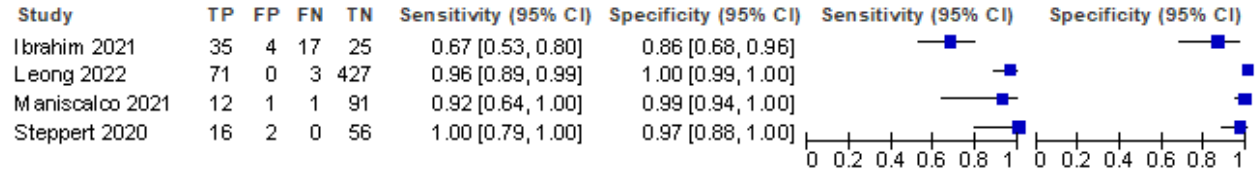
Sn: 0.98 (0.92, 1.00) with I^2=0%; Sp: 0.95 (0.78, 0.99) with I^2=92.7%

Figure 5. Sensitivity and specificity of breath test in asymptomatic individuals



Pooled Sn: 0.94 (0.85,0.97) with I^2=53.2%; Pooled Sp: 0.83 (0.72, 0.90) with I^2=93.2%

Figure 6. Sensitivity and specificity of breath test in symptomatic individuals



Pooled Sn: 0.92 (0.73, 0.98) with I^2=80.2%; Pooled Sp: 0.98 (0.90, 1.00) with I^2=54.6%

Figure 7. Sensitivity and specificity of breath test in individuals with unknown symptomatology

Appendix 7: Table of Ongoing Studies

Study ID Design	Design	Sample Size	Population / Setting	Intervention/s	Gold Standard
NCT04602949 (Israel)	Non-randomized open-label clinical trial	4000	COVID-19	Breath Test Analysis	RT-PCR
NCT04867213 (Canada)	Prospective Cohort (Observational)	200	COVID-19	Breath Test Analysis	RT-PCR
NCT04760639 (United States of America)	Feasibility study (Observational)	100	COVID-19	Breath Test Analysis	RT-PCR
NCT05224622 (Israel)	Non-randomized open-label clinical trial	500	COVID-19	Breath Test Analysis	RT-PCR
NCT05088902 (Turkey)	Prospective Cohort (Observational)	1000	COVID-19	Breath Test Analysis	RT-PCR
NCT05094674 (United Kingdom)	Non-randomized Open-label clinical trial	500	COVID-19	Breath Test Analysis	RT-PCR
NCT05162495	Non-randomized Open-label Clinical Trial	500	COVID-19	Breath Test Analysis	RT-PCR
NCT04714333 (Canada)	Prospective Cohort (Observational)	1000	COVID-19	Breath Test Analysis	RT-PCR