EVIDENCE SUMMARY

Should breath test be used to detect COVID-19 infection?

Evidence Reviewers: Christopher G. Manalo, MD, Cary Amiel G. Villanueva, MD, & Howell Henrian G. Bayona, MSc

RECOMMENDATION

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

Consensus Issues

No recommendation was made as there was only one study found that used a technology that is not accessible at the moment.

Key Findings

Based on one prospective population-based diagnostic accuracy study with high methodological quality, breath test analysis showed high sensitivity and specificity in detecting COVID-19 infection among symptomatic and asymptomatic individuals in the Netherlands. Further studies are needed to validate the findings and to recommend the use of breath test analysis as a real-time diagnostic modality to detect COVID-19 infection in the general population.

Introduction

A novel technology utilizing human exhaled breath analysis is currently being investigated as a possible alternative to RT-PCR for detecting COVID-19 infection [1]. Metabolic changes from respiratory viral infection leads to changes in breath profiles, suggesting that infection-associated volatile organic compounds (VOCs) may be used to develop non-invasive diagnostic modalities through breath analyzers using sensor arrays or electronic noses. Breath metabolic profiling is particularly attractive for SARS-CoV-2 biomarker as a number of viral infections like influenza are known to alter VOCs present in breath exhalate [2].

Recent exploratory clinical and observational case-control studies on breath test analysis [2-5] (n=1002) reported a pooled sensitivity 0.88 (95% CI 0.81-0.93) and specificity 0.67 (95% CI 0.55-0.77) in detecting COVID-19 infection compared to SARS-CoV-2 RT-PCR as gold standard. These studies, however, had limited sample size, utilized different test principles (gas chromatography and metal oxide sensors), and had imprecise specificity estimates which ranged from poor to acceptable. At present, the US, Finland, Singapore, India, and Israel are testing whether this technology can also be used as a mass screening tool for COVID-19 [6-7]. This review aims to present current evidence on the accuracy of breath tests in detecting COVID-19 infections.

Review Methods

We searched for articles that investigated the utility of breath test in detecting COVID-19 infection among asymptomatic and symptomatic individuals. A systematic literature search up to 01 May 2021 was performed in online databases (MEDLINE, Cochrane CENTRAL Database), trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform), pre-print servers (MedRxiv, BioRxiv), and existing COVID-19 repositories (COVID-19 Open Living Evidence Synthesis [https://covid-nma.com/), Living Evidence on COVID-19 [https://zika.ispm.unibe.ch/ assets/data/pub/search_beta]).

Search terms related to “COVID-19”, “SARS-COV-2”, “breath test”, and “volatile organic compounds” were used. No language restrictions were applied. Narratives, commentaries, case report and case series articles, and case-control studies were excluded in the analysis. Sensitivity, specificity, and area under the receiver-operator-characteristic (AUROC) curve were extracted, analyzed, and reported.

Results

Characteristics of the Included Study

One prospective population-based study [8] with a total sample population of 2,702 participants investigated exhaled human breath test in detecting COVID-19 infection in the Netherlands. Among these participants, 1,948 (72%) were symptomatic while 754 (28%) were asymptomatic close contacts of COVID-confirmed patients. Upon presentation at the test facility, all study participants underwent a combined throat and nasopharyngeal swab followed by assessment of exhaled breath using eNose (SpiroNose, Breathomix, Leiden, The Netherlands) technology. The SpiroNose consists of seven different cross-reactive metal oxide semiconductor (MOS) sensors integrated with an online server and analytical platform for real-time automated analysis. The combination of sensor signals generated an individual breath profile to characterize the VOC composition in exhaled breath. SARS-CoV-2 RT-PCR was used as gold standard for diagnostic classification. Test-based diagnostic classification using SARS-CoV-2 RT-PCR was done ≤7 days after inclusion. Prevalence of COVID-19 infection was found to be 12% and 7% in the symptomatic and asymptomatic groups, respectively.

Diagnostic accuracy

Pooled results showed that exhaled breath analysis was highly sensitive 0.99 (95% CI 0.97-1.00) and moderately specific 0.79 (95% CI 0.78-0.81) in detecting COVID-19 infection among symptomatic and asymptomatic individuals. In the subgroup analysis, the symptomatic group showed a sensitivity of 1.00 (95% CI 0.98-1.00) and a specificity of 0.80 (95% CI 0.78-0.82) with an AUROC of 0.94 (95% CI 0.93-0.95). The asymptomatic set, however, showed a slightly lower sensitivity of 0.98 (CI 0.90-0.99) and specificity of 0.78 (95% CI 0.75-0.81) with AUROC of 0.91 (0.88-0.94). While results showed high sensitivity and modest specificity, significant false positive results from the breath test system were noted. In the study, false positive results were attributed to concerns about false negative RT-PCR results. RT-PCR was used as reference standard for detecting SARS-CoV-2 in the study. No further investigations were done to determine cross-reaction among the participants with false positive result or to identify alternative diagnosis among symptomatic participants with false positive result. Nevertheless, as a highly sensitive test, the use of breath test analysis presents as a potential screening modality in rapidly detecting COVID-

19 infection in symptomatic and asymptomatic individuals. However, these encouraging results require further validation in larger population-based studies or clinical trials.

Overall quality of evidence

Despite the good methodologic quality of the study, the overall quality of evidence was downgraded to low as inconsistency and publication bias could not be ascertained with only one study (See Appendix 4).

Recommendations from Other Groups

Currently, there are no published recommendations on the use of breath test in detecting COVID-19 infection from the World Health Organization, US National Institutes of Health, and the Centers for Disease Control. The Malaysian Health Technology Assessment Section (MaHTAS) [7] 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. However, further evaluation and validation studies with larger sample size are required to ascertain its effectiveness and safety.

Research Gaps

One non-randomized clinical trial (n=4000) from Israel and three observational studies (n=500) from the US and Canada are currently investigating the diagnostic accuracy of breath test in COVID-19 infection among asymptomatic and symptomatic individuals.

References

[1] Giovannini G, Haick H, Garoli D. Detecting COVID-19 from Breath: A Game Changer for a Big Challenge. ACS Sens. 2021 Apr 23;6(4):1408-1417. doi: 10.1021/acssensors.1c00312. Epub 2021 Apr 7. PMID: 33825440; PMCID: PMC8043202.

[2] Berna AZ, Akaho EH, Harris RM, Congdon M, Korn E, Neher S, M'Farrej M, Burns J, John ARO. Breath biomarkers of pediatric SARS-CoV-2 infection: a pilot study. medRxiv [Preprint]. 2020 Dec 7:2020.12.04.20230755. doi: 10.1101/2020.12.04.20230755. PMID: 33330891; PMCID: PMC7743102.

[3] Ruszkiewicz DM, Sanders D, O'Brien R, Hempel F, Reed MJ, Riepe AC, Bailie K, Brodrick E, Darnley K, Ellerkmann R, Mueller O, Skarysz A, Truss M, Wortelmann T, Yordanov S, Thomas CLP, Schaaf B, Eddleston M. Diagnosis of COVID-19 by analysis of breath with gas chromatography-ion mobility spectrometry - a feasibility study. EClinicalMedicine. 2020 Dec;29:100609. doi: 10.1016/j.eclinm.2020.100609. Epub 2020 Oct 24. PMID: 33134902; PMCID: PMC7585499.

[4] Shan B, Broza YY, Li W, Wang Y, Wu S, Liu Z, Wang J, Gui S, Wang L, Zhang Z, Liu W, Zhou S, Jin W, Zhang Q, Hu D, Lin L, Zhang Q, Li W, Wang J, Liu H, Pan Y, Haick H. Multiplexed Nanomaterial-Based Sensor Array for Detection of COVID-19 in Exhaled Breath. ACS Nano. 2020 Sep 22;14(9):12125-12132. doi: 10.1021/acsnano.0c05657. Epub 2020 Aug 27. PMID: 32808759; PMCID: PMC7457376.

[5] Wintjens AGWE, Hintzen KFH, Engelen SME, Lubbers T, Savelkoul PHM, Wesseling G, van der Palen JAM, Bouvy ND. Applying the electronic nose for pre-operative SARS-CoV-2 screening. Surg Endosc. 2020 Dec 2:1–8. doi: 10.1007/s00464-020-08169-0. Epub ahead of print. PMID: 33269428; PMCID: PMC7709806.

[6] National University of Singapore. 60-second breath test to detect COVID-19. National University of Singapore; 2020 October 20 [cited 2021 May 01]. Available from https://news.nus.edu.sg/60-second-breath-test-to-detect-covid-19_20201026094346785/

[7] Malaysian Health Technology Assessment Section. COVID-19 Breathanalyser Screening Tools. [Internet]. Ministry of Health Malaysia; 2020 November 26 [cited 2021 May 01]. Available from http://covid-19.moh.gov.my/kajian-dan-penyelidikan/mahtas-covid-19-rapid-evidence-updates/10_COVID-19_Breathanalyser_screening_tools.pdf.

[8] de Vries R, Vigeveno RM, Mulder S, Farzan N, Vintges DR, Goeman JJ, Bruisten S, van den Corput B, Geelhoed JJM, Visser LG, van der Lubben M, Sterk PJ, Veen JCCM, Groeneveld GH. Ruling out SARS-CoV-2 infection using exhaled breath analysis by electronic nose in a public health setting [cited 15 May 2021] from https://www.medrxiv.org/content/10.1101/2021.02.14.21251712v1#:~:text=In%20three%20independent%20validation%20cohorts,specificity%20between%2078%2D84%25.

Appendix 1: Characteristics of Included Study

Study	Study Design	Population	Index Test	Gold Standard	Outcome
De Vries 2021 (n=2,702)	Prospective, real-world data	General (unselected population) who presented to a test facility Symptomatic Set (n=1,948) Asymptomatic Set (n=754)	eNose (SpiroNose, Breathomix, Leiden, The Netherlands)	SARS-CoV-2 RT-PCR	Replication Set (n=1948) Sn 100% (98-100) Sp 80% (78-82) PPV 40% (36-44) NPV 100% (99-100) AUROC 0.937 (0.926-0.947) Asymptomatic Set (n=754) Sn 98% (90-99) Sp 78% (75-81) PPV 25% (19-31) NPV 100% (99-100) AUROC 0.909 (0.88-0.94)

Sn=sensitivity; Sp=specificity; NPV=negative predictive value; PPV=positive predictive value; AUROC=area under the receiver operator characteristic curve

Appendix 2: Results

De Vries et al., 2021	TRUE POSITIVE	FALSE POSITIVE	FALSE NEGATIVE	TRUE NEGATIVE	Sensitivity	Specificity
Symptomatic (Replication) Set (n=1948)	229	347	1	1371	1.0 (0.98 to 1.00)	0.80 (0.78 to 0.82)
Asymptomatic Set (n=754)	49	152	1	552	0.98 (0.90 to 0.99)	0.78 (0.75 to 0.81)
Pooled Estimate					0.99 (0.97 to 1.00)	0.79 (0.78 to 0.81)

Appendix 3A: GRADE Evidence Profile for Symptomatic and Asymptomatic Patients

Question: Should breath test be used to detect COVID-19 infection in symptomatic and asymptomatic individuals?

Sensitivity	0.99 (95% CI: 0.97 to 1.00)
Specificity	0.79 (95% CI: 0.78 to 0.80)

Prevalences	10%		

Outcome	№ of studies (№ of patients)	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 10%	
True positives (patients with COVID-19 infection)	1 studies 280 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	not serious	serious [b]	99 (97 to 100)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having COVID-19 infection)								1 (0 to 3)	
True negatives (patients without COVID-19 infection)	1 studies 2422 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	not serious	serious [b]	711 (702 to 720)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having COVID-19 infection)								189 (180 to 198)	

Explanations

a. Inconsistency cannot be ascertained with only one study
b. Publication bias cannot be ascertained with only one study

Appendix 3B: GRADE Evidence Profile for Symptomatic Patients

Question: Should breath test be used to detect COVID-19 infection in symptomatic individuals?

Sensitivity	1.00 (95% CI: 0.98 to 1.00)
Specificity	0.80 (95% CI: 0.78 to 0.82)

Prevalences	12%		

Outcome	№ of studies (№ of patients)	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 infection)	1 studies 230 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	not serious	serious [b]	120 (118 to 120)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having COVID-19 infection)								0 (0 to 2)	
True negatives (patients without COVID-19 infection)	1 studies 1718 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	not serious	serious [b]	704 (686 to 722)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having COVID-19 infection)								176 (158 to 194)	

Explanations

a. Inconsistency cannot be ascertained with only one study
b. Publication bias cannot be ascertained with only one study

Appendix 3C: GRADE Evidence Profile for Asymptomatic Patients

Question: Should breath test be used to detect COVID-19 infection in asymptomatic?

Sensitivity	0.98 (95% CI: 0.90 to 0.99)
Specificity	0.78 (95% CI: 0.75 to 0.81)

Prevalences	7%		

Outcome	№ of studies (№ of patients)	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 7%	
True positives (patients with COVID-19 infection)	1 studies 50 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	not serious	serious [b]	69 (63 to 69)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having COVID-19 infection)								1 (1 to 7)	
True negatives (patients without COVID-19 infection)	1 studies 704 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	not serious	serious [b]	725 (698 to 753)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having COVID-19 infection)								205 (177 to 232)	

Explanations

a. Inconsistency cannot be ascertained with only one study
b. Publication bias cannot be ascertained with only one study

Appendix 4: QUADAS-2 Risk of Bias and Applicability Evaluation

Patient Selection

A. Risk of Bias	
Was a consecutive or random sample of patients enrolled?	YES
Was a case-control design avoided?	YES
Did the study avoid inappropriate exclusions?	YES
Could the selection of patients have introduced bias?	LOW RISK
B. Concerns Regarding Applicability	
Are there concerns that the included patients and setting do not match the review question?	LOW CONCERN

Index Test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the reference standard?	YES
If a threshold was used, was it pre-specified?	YES
Could the conduct or interpretation of the index test have introduced bias?	LOW RISK
B. Concerns Regarding Applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	LOW CONCERN

Reference Standard

A. Risk of Bias	
Is the reference standard likely to correctly classify the target condition?	YES
Were reference standard results interpreted without knowledge of the results of the index test?	YES
Could the reference standard, its conduct, or its interpretation have introduced bias?	LOW RISK
B. Concerns Regarding Applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	LOW CONCERN

Flow and Timing

A. Risk of Bias	
Was there an appropriate interval between index test and reference standard	YES
Did all patients receive the same reference standard	YES
Were all patients included in the analysis	YES
Could the patient flow have introduced bias?	LOW CONCERN

Appendix 5: Characteristics of Ongoing Studies

Study ID Design	Sample Size	Population / Setting	Intervention/s	Gold Standard
NCT04602949 Non-randomized open-label clinical trial Israel	4000	COVID-19	Breath Test Analysis	RT-PCR
NCT04867213 Prospective Cohort (Observational) Canada	200	COVID-19	Breath Test Analysis	RT-PCR
NCT04341012 Prospective Cohort (Observational) United States of America	200	COVID-19 & Liver Disease	Breath Test Analysis	RT-PCR
NCT04760639 Feasibility study (Observational) United States of America	100	COVID-19	Breath Test Analysis	RT-PCR