

AANBEVELINGEN BETREFFENDE ZELF-TESTS EN ADEMTESTS

RAG subgroep Testing – 3 maart 2021

Opmerking: De huidige aanbevelingen zijn onderhevig aan veranderingen afhankelijk van nieuwe wetenschappelijke gegevens en/of de evolutie van de epidemie.

Aanbevelingen:

Zelf-testen

- Er bestaan potentieel nuttige indicaties voor zelftesten, en de RAG raadt daarom aan om het verbod op zelftesten en zelf-afname van een wissel op te heffen.
- De precieze context waarin zelf-afname en zelftesten nuttig kunnen zijn/aanbevolen worden, zal worden bepaald terwijl het legaliseringsproces gaande is. Mogelijke toepassingen zijn die welke momenteel in andere landen worden getest/ uitgevoerd, zoals zelftesten thuis voor zelfcontrole of herhaald zelftesten in collectiviteiten voor het voorkomen van clusteruitbraken.
- Ook de operationele modaliteiten (te gebruiken staal en test, leeftijdsdrempel...) zullen in een later stadium worden bepaald.
- Zelftesten moet altijd worden ingebed in een bredere strategie die een goede communicatie omvat over hoe de testresultaten te interpreteren. Een negatieve test mag nooit een vrijbrief zijn om de voorzorgsmaatregelen niet langer te respecteren.
- Alvorens zelftesten op grote schaal in te voeren, moeten de haalbaarheid, de aanvaardbaarheid en het effect op het gedrag op kleine schaal worden getest.
- Alternatieve benaderingen, zoals het verbreden van de testindicaties voor de algemene bevolking of het testen in apotheken, moeten ook verder worden onderzocht.

Ademtests

- Ademtests zijn een veelbelovende methode om met een grote gevoeligheid COVID-19 infecties snel op te sporen.
- Het Leuvens onderzoeksinstituut IMEC ontwikkeld momenteel een ademtest. Eens de definitieve resultaten van het validatieonderzoek gekend zijn, zal bekeken worden of en hoe de test aanbevolen kan worden.
- Er zijn momenteel geen andere ademtests beschikbaar voor gebruik in België en het is derhalve nog te vroeg om indicaties voor het gebruik ervan te bepalen.

De volgende personen hebben deelgenomen aan dit advies:

Emmanuel André (KU Leuven); Emmanuel Bottieau (ITG/IMT) ; Bénédicte Delaere (CHU-UCL Namur); Olivier Denis (CHU-UCL Namur); Herman Goossens (UAntwerpen); Yves Lafont (Sciensano); Barbara Legiest (ZG); Pieter Libin (UHasselt); Romain Mahieu (COCOM); Elizaveta Padalko (UZGent); Ann Van den Bruel (KU Leuven); Steven Van Gucht (Sciensano); Pieter Vermeersch (UZ-Leuven)

CONTEXT

The increased availability of rapid Ag tests and the current RT-PCR capacity offer opportunities to expand test indications for SARS-CoV-2. Possible strategies to enhance accessibility to testing are self-collection of respiratory samples and/or self-testing. Self-swabbing and self-testing are legally not allowed in Belgium, and the RAG testing was requested to review the current evidence with regard to these topics and assess their possible usefulness.

In addition, an update was requested with regards to the use of alternative samples, such as breath tests.

SELF-COLLECTION AND SELF-TESTING

Previous recommendations

The current recommendation for sample collection is that a nasopharyngeal swab administered by a health care provider (HCP) is the “gold standard”. Saliva samples are a valid alternative in repetitive testing or when a naso-pharyngeal swab is difficult or impossible to administer. A combined nose throat swab, collected by a HCP, is also a valid alternative.

In the *August testing update*, self-swabbing/self-collecting was evaluated as a potential alternative for saliva sampling in screening settings. Based on the very limited available evidence on the performance of self-swabbing at the time, it was not recommended to be used. More studies were said to be urgently needed to assess acceptability and performance in order to determine if self-swabbing of nasal and/or throat samples could be used as an alternative to saliva testing in screening settings (compare saliva results with results of self-collected nasal/throat swabs; comparing self-swabbing with saliva and/or swabbing performed by healthcare workers). Self-swabbing could be an interesting option in e.g. test villages (under medical supervision), but further studies were urgently needed before implementing it.

In the *September testing update*, self-sampling of saliva was recommended only in the context of repeated testing, as part of a preventive screening. For self-sampling with swabs, it was recommended to be done under medical supervision.

Background literature

Self-Collection

Numerous studies have been conducted comparing the performance of self-collected respiratory samples with health care provider (HCP)-collected specimens. The type of samples studied included spitted saliva, gargled or mouth-rinsed oral fluids, oral swabs, nasal swabs (anterior

nasal or mid-turbinate nasal) and combined swabs (oral/nasal or oropharyngeal/nasal). A summary of the results of some of these studies is presented in Annex. A more extensive literature review, specifically on saliva samples, is available in previous RAG advices.

Overall is the conclusion that levels of agreement with HCP-collected specimens is sufficiently high to justify the use of self-collected samples, particularly considering that it is more acceptable to the client and that missed positive cases are mostly cases with a low viral load (1). An important limitation of home collection is the turnaround time, which can be several days (2).

Performance by type of self-collected sample varies from study to study. Overall, gargled samples appear to perform very well. (Spitted) saliva and combined samples generally perform better than simple nasal samples. and simple oral samples perform worse.

However, almost all of these studies were conducted in people with a high risk of infection (people with symptoms suggestive of COVID-19, or high-risk contacts) and no study was identified in a context of screening low-risk asymptomatic people. Most studies assessed self-collection at the PoC, mostly under supervision of a health care provider.

Only few studies assessed the performance of samples self-collected at home. Braz-Silva et al. compared at-home collected saliva with at-home collected combined nasal-oropharyngeal swabs, and found that saliva performed slightly better (3). They did, however, not compare with a health care provider-collected sample. McCulloch et al. assessed an at-home collected mid-nasal swab, which performed rather poorly (sensitivity=76%) although that the viral load in the missed cases was on average low (4). Kojima et al. compared at-home collected oral fluid swabs with oral fluid swabs collected under supervision of a health care provider, and found that under supervision the results were much better (90% detection vs. 66% at-home) (5). The number of participants (29) was however low. Guest et al. evaluated the quality of returned kits of home-collected oropharyngeal swabs and saliva, and found that 96% of the saliva samples and 97% of the oropharyngeal samples were of sufficient quality for laboratory testing (6).

Cooch et al. assessed the feasibility of self-collection of anterior nasal samples in indoor summer camps to inform school reopening (7). They concluded that it was feasible to implement, including staff participation supervising camper test collection, and the observed adherence to stated camp mitigation policies for masking, physical distancing, and stable cohorting was generally high.

Self-testing

Self-testing has been suggested by some as a potential useful strategy. The benefits include wider availability with lower costs, mitigated risk of exposure to the virus, decentralized care and promotion of social distancing (8). It could also alleviate overburdened health services, minimize nosocomial risks and promote health equity and patient-centeredness. Providing access to such testing could reduce language, cultural, or logistical barriers to seeking care. Many individuals, particularly hourly workers and those without reliable childcare or ready access to transportation, may be better able to obtain testing if necessary.

Studies assessing the performance of self-testing for the presence of SARS-CoV-2 (using rapid Ag tests) are still scarce.

Lindner et al compared the results of a self-administered rapid Ag test (SD Biosensor) on a self-collected nasal mid-turbinate sample in 146 symptomatic patients consulting a hospital out-patient department with a HCP-administered rapid Ag test on a HCP-collected naso-pharyngeal sample

and a RT-PCR on a HCP-collected naso-pharyngeal sample (9). Of the 40 participants who tested positive with the RT-PCR, 33 (82.5%) had tested positive with the self-testing and 34 (85.0%) with the HCP-administered rapid Ag test on a NPS. All negative RT-PCR results had been negative with the self-administered rapid Ag tests, and there was one false positive among the HCP-administered rapid Ag tests (specificity=100% and 99.1%, respectively). In patients with high viral load ($\geq 7.0 \log_{10}$ copies/ml) the sensitivity was 96.6% (28/29; 95% CI 82.8-99.8) for both self-testing and professional testing. One patient with a positive self-test had falsely interpreted his result as negative. 80.9% of participants stated that the test was rather easy to perform, 16.3% medium easy/difficult, and 2.8% rather difficult.

Hoehl et al. piloted at-home self-testing of teachers with a rapid Ag test on a self-collected anterior nasal swab (10). On a total of 10,836 tests among 602 teachers, 21 tested positive, but only 5 of these were confirmed by the RT-PCR performed on the same sample (resulting in a positive predictive value of only 23.8%). Negative results were not verified with RT-PCR and a calculation of the sensitivity was therefore not possible. However, for four teachers, a false negative result in the antigen test was assumed, as they reported to have received a positive PCR test result, in another context, during the period of self-testing.

Stohr et al. assessed the performance of at-home self-testing with a rapid Ag test (BD Veritor and Roche) of HCP-collected oro- and nasopharyngeal swabs among visitors of a testing center (11). Specificity was 99.7% and 99.9% for the BD Veritor and Roche test, respectively. Sensitivity was 48.9% for the BD Veritor and 61.5% for the Roche test. Sensitivity among samples with a high viral load (Ct value by LDA \leq 23; Ct value by AA \leq 24.5) was 75.5% and 80.1%, respectively. Determinants independently associated with a false-negative self-testing result were: higher age, low viral load and finding self-testing difficult.

Although not assessing self-testing as such, another study of interest is by Peto et al. As part of a national systematic evaluation of rapid Ag tests in the UK, they evaluated performance of the Innova test by type of operator. Performance was optimal when used by laboratory scientists (sensitivity: 78.8%, 95% CI: 72.4-84.3%) relative to trained healthcare workers (70.0%, 95% CI: 63.5-75.9%) and self-trained members of the public given a protocol (57.5%, 95% CI: 52.3-62.6%; $p < 0.0001$).

International and national guidelines

The latest WHO and ECDC guidance on testing (dated September 2020) do not provide any recommendations with regard to self-collection of samples or self-testing. Also at national level, there are only a few countries that authorize self-collection/ self-testing and/or provide guidance. For example, no guidelines were identified from The Netherlands or France. A summary of indications for self-testing from a number of selected countries is presented in Annex.

United States

The CDC updated its advice on home testing on 16 February 2021 (12). It states that patients and their healthcare provider might consider either an at-home collection kit or an at-home test if they have signs and symptoms of COVID-19 and they can't get tested by a healthcare provider. At-home collection kits and tests are available either by prescription or over the counter in a pharmacy or retail store without a prescription.

Some tests require a nasal specimen that can be collected using an anterior nasal swab or a nasal mid-turbinate swab. Other tests require a saliva specimen. Once collected, the specimen is to be sent to a testing facility or tested at home, as described in the manufacturer's instructions. The result is communicated to their healthcare provider, who is responsible for reporting the test results to the state health department. Some at-home tests have an app that allows to report the results to the state health department directly.

By February 25, 2021, the FDA has approved two rapid Ag tests for home testing: the Ellume COVID-19 Home Test for over the counter Home Testing and the BinaxNOW COVID-19 Ag Card Home Test from Abbott for prescription home testing (13).

United Kingdom

In the UK, the Medicines and Healthcare products Regulatory Agency has granted NHS Test & Trace an exceptional use authorization to use certain rapid Ag tests on combined nasal-throat swabs as self-tests to detect infection in people who do not have any COVID-19 symptoms and who may not otherwise have been tested (14). The tests can be used by a member of the public with no previous experience of testing, in their own home or another community setting such as a place of work. Positive results must be reported to the NHS. If testing negative national and local rules and guidelines including regular handwashing, social distancing and wearing face coverings, need to be followed.

Austria

The Austrian Ministry of Health considers self-testing an important addition to the test strategy (15). Negative self-test results, however, cannot be recognized as proof and need to be confirmed with another test. They can be used by asymptomatic persons for self-information, for example before family visits. Since self-application tests are less sensitive than PCR tests, it is important that the protective measures (minimum distance, FFP2 mask, etc.) are consistently adhered to even with a negative test result. This applies in particular to meetings with members of the risk group. When positive, all social contacts need to be restricted and the health services be called.

The list of tests that can currently be used in Austria without medical personnel is published on The Federal Office for Health Safety (BASG) website (16).

Austria has also started to make self-tests available in schools (17). Two rapid Ag tests are used (LEPU-Medical and Flowflex from Acon) on a self-collected nasal anterior swab. Testing is obligatory for pupils and voluntary for staff. At elementary and special schools up to the 4th grade and in boarding schools self-tests will be carried out twice a week at the start of classes. At all other schools, all pupils are tested immediately after the semester breaks in two groups: one on the first day of school (Monday), and a second group on the Wednesday of that week. The tests must be supervised, and in elementary, special and lower secondary schools, students or their teachers are assisted by school physicians. People testing negative still have to respect all protective measures.

According to popular media, the Austrian government will enhance access to free self-tests for use at home from 1 March 2021 onwards (18,19). Test kits will be available at pharmacies. Five pieces per person should be available per month. The target is up to 3.5 million tests per week. The tests are intended solely for self-control.

Germany

Also the German Ministry of Health has announced that free rapid Ag tests will become available for home testing in the near future, mainly based on the results of the above mentioned Lindner study (20). Approval has been requested. Possible samples to collect include saliva or nasal samples. Each state (Bundesland) will decide if they want to use it as part of their test strategy or not. They can, for example, be used as part of test strategy for daycare centers and schools. Positive test results must, however, always be confirmed with an RT-PCR test.

Conclusions

Evidence on the performance of self-collected respiratory samples is now substantial. Overall, the conclusions are:

- Self-collected specimens generally have a lower sensitivity than HCP-collected naso-pharyngeal swabs
- Nevertheless, levels of agreement are sufficiently high to justify their use, in particular because of greater client-acceptability and missing mostly cases with a low viral load
- Gargled or spit saliva samples and combined nasal-pharyngeal samples appear to give better results than simple nasal samples, and certainly than simple oral samples
- Most studies on self-collection have been done in a medical environment, under supervision of a health care provider, and there is less evidence with regards to at-home self-collection
- There is some evidence that unsupervised self-collection performs less well than supervised self-collection
- An important disadvantage of at-home self-collection, without self-testing, is the delay in getting the results
- Self-collection is allowed and possible in some countries, such as the US

On the other hand, scientific evidence on at-home self-testing with rapid Ag tests is still scarce.

- Only a few studies assessing self-testing have been published so far, often in a specific context (in a hospital environment, on HCP-collected naso-pharyngeal samples) and sometimes with disappointing results (PPV of 24%)
- Nevertheless, several countries have allowed or plan to allow at-home testing (US, UK, Austria, Germany) mostly in a context of self-information/ self-control, or self-testing in the context of preventing cluster outbreaks, for example in schools (Austria, Germany)
- The self-collected sample is either saliva (Germany), combined nasal-throat swabs (UK) or nasal swabs (US, Austria, Germany)
- Because of the higher risk of false-negative results, protective measures generally need to be maintained after a negative result
- In some countries (Germany), positive results need to be confirmed by a RT-PCR on a HCP-collected naso-pharyngeal swab
- All of these self-testing initiatives have only recently been initiated and there is still no proof of their effectiveness in reducing SARS-CoV-2 transmission.

Discussion

- There exist potentially useful indications for self-testing, and the ban on self-swabbing and self-testing is therefore best lifted. This is already the case for some other diseases, such as HIV.

- Little is yet known about the effect of self-testing on reducing transmission. There is always the risk that a negative result leads to neglecting protective measures, although that there is no evidence that this is effectively so. Self-testing must therefore always be in a context of good communication about a correct interpretation of the results. Piloting is needed before implementing on a large scale.
- An issue to address is the reporting of the results. There is a great risk of underreporting with consequences for surveillance.
- While the process of lifting the legal ban on self-testing is taken place, it can be explored in what context self-swabbing/ self-testing can be useful, and be defined what other operational criteria need to be defined (age threshold, type of sample...). Self-testing as a screening method before participation in a mass event was said not to be a good indication.
- The EC has approved the use of a molecular self-test (PCR). Self-tests must therefore not necessarily be done on rapid Ag Tests.
- The tests to use have to fulfill certain criteria, but these do not necessarily have to be based on a new validation study.
- Equally, or even more, important than initiating self-testing is to reevaluate the current test indications and see if they can be expanded, as is currently already in place for students of KU Leuven.
- Another strategy worth exploring is testing at pharmacies, as currently done in France and being piloted in Brussels.

Recommendations

- The RAG testing recommends that self-swabbing and self-testing for COVID-19 be made legal, as is already the case for some other diseases (for example HIV).
- The exact context in which self-swabbing/ self-testing will be useful/ recommended will be defined while awaiting the legalization process. Possible uses are those as currently piloted/ implemented in other countries, such as at-home self-testing for self-control or repetitive self-testing in collectivities for cluster outbreak prevention.
- Also the operational modalities (sample and test to use, age threshold...) can be defined at a later stage.
- Self-testing should always be embedded in a broader strategy that encompasses good communication about how to interpret the test results. A negative test should never be a free pass to stop respecting the protective measures in place.
- Before implementing self-testing on a broad scale, the feasibility, acceptability and effect on behavior need to be assessed on a small scale.
- Alternative approaches, such as broadening test indications for the general population or testing at pharmacies, should also be further explored.

BREATH TESTS

Background literature

The potential use of breath tests for the diagnosis of COVID-19, examining exhaled breath for signatures of the host-response to infection, has been explored by several research institutions. Most tests detect endogenously produced volatile organic compounds (VOCs) present in exhaled breath. Even if not used as a final confirmatory measure, the rapid nature of this reagent-free, logistically simple test may be useful for high throughput screening of asymptomatic cases in large or unique populations (for example, prior to boarding an airplane, or entering a sports stadium) (21).

Tests have been developed or are under development in several countries. The performance of different VOC analysis techniques and of some developed devices has been evaluated. Overall, the tests have a high sensitivity, detecting all or most of the COVID-19 infections, but a low specificity (see table below).

	Test	N positive	N negative	Sensitivity	NPV	Specificity
De Vries et al.	SpiroNose	35	869	98% to 100%	99.9% to 100%	78% to 80%
Wintjens et al.	Aeonose	57	162	86%	96%	54%
Berna et al.	VOC analysis	11	15	100%	100%	66.6%
Ruszkiewicz et al.	VOC analysis	31	67	82.4% to 90%		75% to 80%
Shan et al.	VOC analysis	49	58	100%		61%
Steppert et al.	VOC analysis	16	44	100%		97.7%
Grassin-Delyle et al.	VOC analysis	28	12	90%		94%

De Vries et al. tested an eNose device (SpiroNose) in three different study sets in testing centers, two with a mixture of symptomatic and asymptomatic people, one with only asymptomatic (22). Sensitivity compared to RT-PCR was very high (100%, 99.6% and 98% in the three study sets, respectively), but specificity rather low (78%, 79.8% and 78.4%, respectively).

Wintjens et al. tested another eNose device (Aeonose) and found a sensitivity of 86% and a specificity of 54% (23). The negative predictive value was 92%, but could be increased to 96% by adding clinical variables to the machine-learning classifier via multivariate logistic regression analysis.

Ruszkiewicz et al. studied the feasibility of using breath-analysis to distinguish between different respiratory infections, using VOC analysis by near-patient gas chromatography-ion mobility spectrometry (GC-IMS) (24). Ninety-eight patients were recruited in two study sites (Edinburgh and Dortmund), of whom 31 had COVID-19. Differentiation of patients with definite diagnosis of COVID-19 from non-COVID-19 was possible with 80% accuracy in Edinburgh (sensitivity/specificity 82.4%/75%) and 81.5% in Dortmund (sensitivity / specificity 90%/80%).

Berna et al. analyzed the breath volatile composition of 11 SARS-CoV-2-infected and 15 - uninfected children admitted to a major pediatric academic medical center (25). The analysis

revealed that six volatile organic compounds increased significantly in SARS-CoV-2-infected children. Together, these biomarkers demonstrated 100% sensitivity and 66.6% specificity. The work will form the basis for developing a future “breathalyzer” test for SARS-CoV-2 infection in children.

Shan et al. assessed a developed breath device composed of a nanomaterial-based hybrid sensor array with multiplexed detection capabilities that can detect disease-specific biomarkers from exhaled breath (26). The device exhibited an accuracy of 76% accuracy in differentiating patients from controls (100% sensitivity and 61% specificity) as well as 95% accuracy in differentiating between patients with COVID-19 and patients with other lung infections.

Steppert et al. did a VOC analysis using multicapillary-column-coupled ion mobility spectrometry (MCC-IMS) in 16 patients with COVID-19 and 44 controls, and found both a high sensitivity (100%) and specificity (98%) (27).

Grassin-Delyle et al. used real-time, online, proton transfer reaction time-offlight mass spectrometry to perform a metabolomic analysis of expired air from adults undergoing invasive mechanical ventilation in the intensive care unit due to severe COVID-19 or non-COVID-19 acute respiratory distress syndrome (ARDS) (28). Sensitivity among 28 patients who had proven COVID-19 was 90% and specificity among 12 patients without proven COVID-19 94%, resulting in an accuracy of 93%.

Belgium

The Leuven research institute IMEC is working since October 2020 on a breathalyzer that detects COVID-19 viral particles that are contained in aerosols and droplets (29). It will consist of a sample collector that will contain the chip that captures the aerosol particles and an analysis unit that will measure the amount of viral material through real-time quantitative PCR. After no more than five minutes, the test results are provided through the cloud. The institute is currently in the process of conducting clinical studies assessing the performance of the device. According to the coordinators (personal communication), the first results are promising.

International and national guidelines

No international guidance on the use of breath tests was located. Popular media in some countries report that breath tests are planned to be introduced (30–33), but only one country was identified that effectively initiated the use of breath tests.

The Netherlands

The Dutch institute for public health (RIVM) states on its website that breath tests can properly rule out an infection, but not properly demonstrate it (34). A 'positive' breath test should therefore always be confirmed with another test, such as PCR, LAMP or an antigen test.

The SpiroNose test, developed by a Dutch company, is being piloted in four testing centers in Amsterdam among people 18 years or older (35). Preliminary results showed that two-thirds of visitors who get tested do not need an additional test. The objective is to roll out the breath tests in the whole of The Netherlands, and to achieve 40,000 tests a day by the end of March. During February the pilot was temporarily put on hold because of some misinterpreted results (36). According to the test centrum, these problems have been resolved.

Conclusion

- Several breath analyzing systems have been tested showing a very high sensitivity in detecting COVID-19 infections, including among children, but with a rather low specificity.
- Some of these systems have resulted in the development of commercial devices.
- One of these devices is currently piloted in the Netherlands, as a first screening tool in testing centers.
- A device is being developed by IMEC, but using a different technique.

Discussion

- The breathalyzer under development at IMEC is indeed showing positive first results, and this device is definitely worth considering once finalized. It will, however, still take time to finalize it.
- The SpiroNose device, developed by the university of Amsterdam and currently used in The Netherlands, is not commercially available and in insufficient quantity to allow export.
- It is therefore too early to decide on possible uses of a breath test. Once there is more clarity about availability and about the performance of the available tests, it can be re-discussed.
- Breath tests detecting VOCs are based on a similar principal as the detection of COVID-19 by search dogs. Indications for their use will therefore be similar and need to be coordinated. An update is needed with regard to the training of search dogs by the Faculty of Veterinary Medicine of UGent. Apparently, six dogs have been trained so far and the faculty is currently validating their performance.

Recommendations

- The RAG testing agreed to await the final results of the validation study of the IMEC breathalyzer, before recommending on its use.
- No other breath test device is currently available and there is therefore no need to define at this moment indications for the use of breath tests.

REFERENCES

1. Cockerill FR, Wohlgemuth JG, Radcliff J, Sabol CE, Kapoor H, Dlott JS, et al. Evolution of Specimen Self-Collection in the COVID-19 Era: Implications for Population Health Management of Infectious Disease. *Popul Health Manag.* 2021 Feb;24(S1):S26–34.
2. Catania JA, Martin J, Dolcini MM, Orellana ER, Henne J. Shifting Coronavirus Disease 2019 Testing Policy and Research to Include the Full Translation Pipeline. *Open Forum Infectious Diseases* [Internet]. 2021 Feb 1 [cited 2021 Feb 25];8(ofaa649). Available from: <https://doi.org/10.1093/ofid/ofaa649>
3. Braz-Silva PH, Mamana AC, Romano CM, Felix AC, Paula AV de, Ferreira NE, et al. Performance of At-Home Self-Collected Saliva and Nasal-Oropharyngeal Swabs in the Surveillance of COVID-19. *medRxiv.* 2020 Oct 27;2020.10.23.20218487.
4. McCulloch DJ, Kim AE, Wilcox NC, Logue JK, Greninger AL, Englund JA, et al. Comparison of Unsupervised Home Self-collected Midnasal Swabs With Clinician-Collected Nasopharyngeal Swabs for Detection of SARS-CoV-2 Infection. *JAMA Netw Open.* 2020 Jul 1;3(7):e2016382.
5. Kojima N, Turner F, Slepnev V, Bacelar A, Deming L, Kodeboyina S, et al. Self-Collected Oral Fluid and Nasal Swabs Demonstrate Comparable Sensitivity to Clinician Collected Nasopharyngeal Swabs for Covid-19 Detection. *medRxiv.* 2020 Apr 15;2020.04.11.20062372.
6. Guest JL, Sullivan PS, Valentine-Graves M, Valencia R, Adam E, Luisi N, et al. Suitability and Sufficiency of Telehealth Clinician-Observed, Participant-Collected Samples for SARS-CoV-2 Testing: The iCollect Cohort Pilot Study. *JMIR Public Health Surveill.* 2020 Jun 25;6(2):e19731.
7. Cooch P, Watson A, Olarte A, Crawford E, Consortium Clia, DeRisi J, et al. Supervised self-collected SARS-CoV-2 testing in indoor summer camps to inform school reopening. *medRxiv.* 2020 Oct 23;2020.10.21.20214338.
8. Nundy S, Patel KK. Self-Service Diagnosis of COVID-19—Ready for Prime Time? *JAMA Health Forum.* 2020 Mar 16;1(3):e200333.
9. SARS-CoV-2 patient self-testing with an antigen-detecting rapid test: a head-to-head comparison with professional testing | *medRxiv* [Internet]. [cited 2021 Feb 19]. Available from: <https://www.medrxiv.org/content/10.1101/2021.01.06.20249009v1>
10. Hoehl S, Schenk B, Rudych O, Göttig S, Foppa I, Kohmer N, et al. At-home self-testing of teachers with a SARS-CoV-2 rapid antigen test to reduce potential transmissions in schools: Results of the SAFE School Hesse Study. *medRxiv.* 2020 Dec 7;2020.12.04.20243410.
11. Stohr JJM, Zwart VF, Goderski G, Meijer A, Nagel-Imming CRS, Bergh MFQK den, et al. Self-testing for the detection of SARS-CoV-2 infection with rapid antigen tests. *medRxiv.* 2021 Feb 23;2021.02.21.21252153.
12. CDC. COVID-19 and Your Health [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2021 Feb 25]. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/testing/at-home-testing.html>

13. Health C for D and R. In Vitro Diagnostics EUAs. FDA [Internet]. 2021 Feb 23 [cited 2021 Feb 25]; Available from: <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas>
14. For patients, the public and professional users: a guide to COVID-19 tests and testing kits [Internet]. GOV.UK. [cited 2021 Feb 25]. Available from: <https://www.gov.uk/government/publications/how-tests-and-testing-kits-for-coronavirus-covid-19-work-for-patients-the-public-and-professional-users-a-guide-to-covid-19-tests-and-testing-kits>
15. FAQ: Testungen und Quarantäne [Internet]. [cited 2021 Feb 25]. Available from: <https://www.sozialministerium.at/Informationen-zum-Coronavirus/Coronavirus---Haeufig-gestellte-Fragen/FAQ--Testungen-und-Quarantaene.html>
16. COVID-19 [Internet]. BASG. [cited 2021 Feb 25]. Available from: <https://www.basg.gv.at/fuer-unternehmen/medizinprodukte/covid-19>
17. Antigen-Selbsttests für alle Schülerinnen und Schüler – Ergebnis in nur 15 Minuten [Internet]. [cited 2021 Feb 25]. Available from: <https://www.bmbwf.gv.at/Themen/schule/beratung/corona/selbsttest.html>
18. Austria to roll out free home coronavirus testing from March [Internet]. 2021 [cited 2021 Feb 23]. Available from: <https://www.thelocal.at/20210215/free-coronavirus-home-tests-to-be-rolled-out>
19. red austria O at/Agencies. Apotheken geben Selbsttests gratis ab [Internet]. oesterreich.ORF.at. 2021 [cited 2021 Feb 25]. Available from: <https://oesterreich.orf.at/stories/3090312/>
20. Besserer Schutz in Pflegeheimen und Krankenhäusern [Internet]. Bundesgesundheitsministerium. [cited 2021 Feb 26]. Available from: <https://www.bundesgesundheitsministerium.de/coronatest/faq-schnelltests.html>
21. Davis CE, Schivo M, Kenyon NJ. A breath of fresh air – the potential for COVID-19 breath diagnostics. EBioMedicine [Internet]. 2021 Jan 1 [cited 2021 Feb 26];63. Available from: [https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964\(20\)30559-4/abstract](https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30559-4/abstract)
22. Vries R de, Vigeveno RM, Mulder S, Farzan N, Vintges DR, Goeman JJ, et al. Ruling out SARS-CoV-2 infection using exhaled breath analysis by electronic nose in a public health setting. medRxiv. 2021 Feb 16;2021.02.14.21251712.
23. Wintjens AGWE, Hintzen KFH, Engelen SME, Lubbers T, Savelkoul PHM, Wesseling G, et al. Applying the electronic nose for pre-operative SARS-CoV-2 screening. Surg Endosc. 2020 Dec 2;
24. Ruszkiewicz DM, Sanders D, O'Brien R, Hempel F, Reed MJ, Riepe AC, et al. Diagnosis of COVID-19 by analysis of breath with gas chromatography-ion mobility spectrometry - a feasibility study. EClinicalMedicine [Internet]. 2020 Dec 1 [cited 2021 Feb 26];29. Available from: [https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370\(20\)30353-9/abstract](https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30353-9/abstract)
25. Berna AZ, Akaho EH, Harris RM, Congdon M, Korn E, Neher S, et al. Breath biomarkers of pediatric SARS-CoV-2 infection: a pilot study. medRxiv. 2020 Dec 7;

26. Shan B, Broza YY, Li W, Wang Y, Wu S, Liu Z, et al. Multiplexed Nanomaterial-Based Sensor Array for Detection of COVID-19 in Exhaled Breath. *ACS Nano*. 2020 Sep 22;14(9):12125–32.
27. Steppert C, Steppert I, Sterlacci W, Bollinger T. Rapid detection of SARS-CoV-2 infection by multicapillary column coupled ion mobility spectrometry (MCC-IMS) of breath. A proof of concept study. *medRxiv*. 2020 Sep 10;2020.06.30.20143347.
28. Grassin-Delyle S, Roquencourt C, Moine P, Saffroy G, Carn S, Heming N, et al. Metabolomics of exhaled breath in critically ill COVID-19 patients: A pilot study. *EBioMedicine*. 2021 Jan;63:103154.
29. Coronavirus breathalyzer | imec [Internet]. [cited 2021 Mar 1]. Available from: <https://www.imec-int.com/en/expertise/life-sciences/coronavirus-breathalyzer>
30. Coronavirus Breath Testing System Developed in Japan [Internet]. *nippon.com*. 2020 [cited 2021 Feb 26]. Available from: <https://www.nippon.com/en/news/yjj2020101601096/>
31. Coronavirus : un dépistage par l’haleine à l’étude [Internet]. *France Bleu*. 2020 [cited 2021 Feb 26]. Available from: <https://www.francebleu.fr/infos/sante-sciences/covid-19-un-depistage-par-l-haleine-a-l-etude-1607499397>
32. Breath analysis to detect COVID-19 [Internet]. *Imspex Diagnostics Ltd*. 2021 [cited 2021 Feb 26]. Available from: <http://www.imspe.com/breath-analysis-to-detect-covid-19/>
33. Breath Test Detecting COVID-19 | IONICON [Internet]. [cited 2021 Feb 26]. Available from: <https://www.ionicon.com/blog/2020/breath-test-detecting-covid-19?s=08&cHash=757b5f710901813aeb6c49b233cc44d1>
34. Testen | RIVM [Internet]. [cited 2021 Feb 26]. Available from: <https://www.rivm.nl/coronavirus-covid-19/testen>
35. Amsterdam. Ademtest geeft razendsnel uitslag [Internet]. *GGD Amsterdam. Gemeente Amsterdam*; [cited 2021 Feb 26]. Available from: <https://www.ggd.amsterdam.nl/nieuwsoverzicht/ademtest-geeft-razendsnel-uitslag/>
36. Amsterdam. Ademtest betrouwbaar: GGD Amsterdam en Breathomix werken samen aan hervatting [Internet]. *GGD Amsterdam. Gemeente Amsterdam*; [cited 2021 Feb 26]. Available from: <https://www.ggd.amsterdam.nl/nieuwsoverzicht/ademtest-betrouwbaar/>
37. Goldfarb DM, Tilley P, Al-Rawahi GN, Srigley JA, Ford G, Pedersen H, et al. Self-collected Saline Gargle Samples as an Alternative to Healthcare Worker Collected Nasopharyngeal Swabs for COVID-19 Diagnosis in Outpatients. *J Clin Microbiol*. 2021 Jan 29;
38. Kandel CE, Young M, Serbanescu MA, Powis JE, Bulir D, Callahan J, et al. Detection of severe acute respiratory coronavirus virus 2 (SARS-CoV-2) in outpatients: A multicenter comparison of self-collected saline gargle, oral swab, and combined oral-anterior nasal swab to a provider collected nasopharyngeal swab. *Infect Control Hosp Epidemiol*. 2021 Jan 13;1–5.

39. Shakir SM, Barker AP, Hillyard DR, Gilmore N, Barrett JW, Orlandi RR, et al. Combined Self-Collected Anterior Nasal and Oropharyngeal Specimens versus Provider-Collected Nasopharyngeal Swabs for the Detection of SARS-CoV-2. *J Clin Microbiol.* 2020 Dec 17;59(1).
40. Ku CW, Shivani D, Kwan JQT, Loy SL, Erwin C, Ko KKK, et al. Validation of self-collected buccal swab and saliva as a diagnostic tool for COVID-19. *medRxiv.* 2020 Oct 5;2020.10.03.20205278.
41. Tan SY, Tey HL, Lim ETH, Toh ST, Chan YH, Tan PT, et al. The Accuracy of Healthcare Worker versus Self Collected (2-in-1) Oropharyngeal and Bilateral Mid-Turbinate (OPMT) Swabs and Saliva Samples for SARS-CoV-2. *medRxiv.* 2020 Sep 18;2020.09.17.20197004.
42. Therchilsen JH, von Buchwald C, Koch A, Dam Nielsen S, Rasmussen DB, Thudium RF, et al. Self-Collected versus Healthcare Worker-Collected Swabs in the Diagnosis of Severe Acute Respiratory Syndrome Coronavirus 2. *Diagnostics (Basel).* 2020 Sep 9;10(9).
43. Teo AKJ, Choudhury Y, Tan IB, Cher CY, Chew SH, Wan ZY, et al. Validation of Saliva and Self-Administered Nasal Swabs for COVID-19 Testing. *medRxiv.* 2020 Aug 14;2020.08.13.20173807.
44. Tu Y-P, Jennings R, Hart B, Cangelosi GA, Wood RC, Wehber K, et al. Swabs Collected by Patients or Health Care Workers for SARS-CoV-2 Testing. *N Engl J Med.* 2020 Jul 30;383(5):494–6.
45. Hanson KE, Barker AP, Hillyard DR, Gilmore N, Barrett JW, Orlandi RR, et al. Self-Collected Anterior Nasal and Saliva Specimens versus Healthcare Worker-Collected Nasopharyngeal Swabs for the Molecular Detection of SARS-CoV-2. *medRxiv.* 2020 Jul 19;2020.07.17.20155754.
46. Wehrhahn MC, Robson J, Brown S, Bursle E, Byrne S, New D, et al. Self-collection: An appropriate alternative during the SARS-CoV-2 pandemic. *J Clin Virol.* 2020 Jul;128:104417.

ANNEX: RESULTS OF SELECTED STUDIES ASSESSING SENSITIVITY FOR DETECTING SARS-COV-2 WITH SELF-COLLECTED SAMPLES

Author	Sample*	Population	N	Sensitivity	
Goldfarb et al. (37)	saliva	symptomatic out-patients	40	78.8%	
	saline mouth rinse/ gargle			97.5%	
Kandel et al. (38)	saline gargle	testing center attendees	65	89.2%	
	oral swab			80.4%	
	combined oral–anterior nasal			42	85.7%
	HCP-collected NPS			163	97.5%
Shakir et al. (39)	combined anterior nasal- oropharyngeal	testing center attendees	118	96.6%	
	HCP-collected NPS			99.2%	
Braz-Silva et al. (3)	at-home collected saliva	symptomatic out-patients	70	78.6%	
	at-home collected combined nasal-oropharyngeal			74.3%	
Ku et al. (40)	saliva	hospitalized patients	42	67.7%	
	buccal swab			56.7%	
	HCP-collected NPS			96.8%	
Tan et al. (41)	saliva	hospitalized patients	373	79.6%	
	combined oropharynx - mid-turbinate nasal			80.7%	
	saliva + combined oropharynx - mid-turbinate nasal			93.0%	
	HCP-collected combined oropharynx - mid-turbinate nasal			90.1%	
Therchilsen et al. (42)	combined oropharynx - mid-turbinate nasal	symptomatic out-patients	19	84.2%	
	HCP-collected combined oropharynx - mid-turbinate nasal			89.5%	
Teo et al. (43)	saliva	symptomatic cases	155	93.5%	
	nasal			61.9%	
	HCP-collected NPS			79.4%	
	saliva	asymptomatic cases	75	85.3%	
	nasal			41.3%	
	HCP-collected NPS			36.0%	
	saliva	Ct value<30	63	98.4%	
	nasal			90.5%	
Tu et al. (44)	tongue	symptomatic out-patients	51	90.2%	
	nasal			94.1%	
	mid-turbinate nasal			52	96.2%
	HCP-collected NPS			154	98.1%
Hanson et al. (45)	saliva	testing center attendees	86	94.2%	
	anterior nasal swabs			81.4%	
	HCP-collected NPS			93.0%	

Author	Sample*	Population	N	Sensitivity
McCulloch et al. (4)	at-home collected mid-nasal	symptomatic out-patients	41	75.6%
	HCP-collected NPS			92.7%
Wehrhahn et al. ** (46)	combined throat-nasal	symptomatic out-patients	25	100%
Kojima et al. (5)	at-home collected oral fluid swab	testing center attendees	29	65.5%
	supervised oral fluid swab			89.7%
	supervised mid-turbinate nasal			79.3%
	HCP-collected NPS			79.3%

*Self-collected at the PoC unless otherwise indicated

**Compared to HCP-collected combined throat-nasal

ANNEX 2: SELF-TESTING INDICATIONS IN A SELECTED NUMBER OF COUNTRIES

Country	Indications (according the national guidelines)	References
The Netherlands	No indications for self-testing	
France	No indications for self-testing	
Germany	Still to be defined, at state level	Fragen und Antworten zu Schnelltests zum Nachweis von SARS-CoV-2 - Bundesgesundheitsministerium
United Kingdom	‘to detect infection in people who do not have any COVID-19 symptoms and who may not otherwise have been tested’ ‘to help them stay safe and stop the spread of the virus’	For patients, the public and professional users: a guide to COVID-19 tests and testing kits - GOV.UK (www.gov.uk) COVID-19 self-test help - GOV.UK (www.gov.uk)
United States	‘if you have signs and symptoms of COVID-19 and if you can’t get tested by a healthcare provider’	At-Home Testing CDC
Austria	‘by asymptomatic persons for self-information, e.g. before family visits’ At schools, obligatory for pupils and voluntary for staff. In elementary and special schools up to the 4th grade and in boarding schools: twice a week at the start of classes. At all other schools, immediately after the semester breaks in two groups: one on the first day of school (Monday), and a second group on the Wednesday of that week.	FAQ: Testungen und Quarantäne (sozialministerium.at) Antigen-Selbsttests für alle Schülerinnen und Schüler – Ergebnis in nur 15 Minuten (bmbwf.gv.at)
Canada	Has approved self-testing kits, but not yet defined indications	FDA authorizes first over-the-counter, non-prescription COVID-19 test system for home use CTV News
Ireland	No indications for self-testing	
Denmark	No indications for self-testing	
Sweden	No indications for self-testing	