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
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EVIDENCE SUMMARY

RESEARCH QUESTION: **Among patients suspected to have COVID-19, how accurate are self-administered rapid antigen tests alone compared to RT-PCR for the diagnosis of COVID-19?**

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We recommend the use of self-administered rapid antigen test for the diagnosis of SARS-CoV-2 in symptomatic individuals, provided that ALL OF THE FOLLOWING conditions are met: 1. Ease of collecting samples is ensured; 2. Ease of interpretation is ensured; 3. Test kits have passed flex studies (Studies that challenge the robustness of a diagnostic kit under various conditions of stress); AND 4. Individuals present with symptoms for less than 7 days.	Moderate	Strong
We recommend against the use of self-administered rapid antigen test for asymptomatic individuals.	Moderate	Strong

Consensus Issues

1) The previous recommendation on “routine screening” was removed since the evidence base presented are among asymptomatic individuals. To be consistent with the results of the evidence base, the Panel decided to vote on changing the recommendation to “recommend against diagnosis among asymptomatic individuals”. Further review of evidence solely focused on routine screening should be done.
2) The Panel noted that there is the are not enough evidence presented on the use of self-administered rapid antigen tests among special populations such as healthcare workers and immunocompromised individuals.

WHAT’S NEW IN THIS VERSION?

This update contains eight additional observational studies that assessed the diagnostic accuracy of self-administered rapid antigen tests. Five among these were published in 2022, three of which specifically involved the Omicron SARS-CoV-2 variant, the most prevalent variant in our country based on the latest COVID-19 biosurveillance report [1]. The studies included varied test brands, specimen types, and symptom status.

Relative to the previous review, pooled sensitivity obtained from a total of 15 studies is 0.74 (95% CI 0.63-0.82) from 0.77 (95% CI 0.62-0.87). A pooled specificity of 0.991 (95% CI 0.99-0.99) also does not deviate from the previously obtained 0.996 (95% CI 0.99-1.00). Heterogeneity among studies had an I^2 value of 54% (from I^2=97%) as the studies yielded more similar results. Three studies which included children and

adolescents as test subjects provided a sensitivity of 0.66 (95% CI 0.64-0.68). This version also discussed updates on the guidelines set by other groups.

KEY FINDINGS

- Fifteen observational studies (eight new studies added to the 7 studies previously reviewed) assessed the diagnostic accuracy of self-administered rapid antigen tests against RT-PCR as the reference standard. The studies included varied test brands (n=13), specimen types, and symptom status.
- The pooled sensitivity of self-administered rapid antigen test was 0.74 (95% CI 0.63-0.82) while the pooled specificity was high at 0.991 (95% CI 0.99-0.99). Heterogeneity among studies had an I^2 value of 54% (from I^2=97%) as the studies yielded more similar results.
- On subgroup analysis, self-administered rapid antigen test showed the following sensitivity results when used in the following conditions:
    - Symptomatic individuals (Sn 0.78, 95% CI 0.70-0.85; n=5,761) with a heterogeneity of I^2 =0.48 across studies;
    - Asymptomatic individuals (Sn 0.57, 95% CI 0.27-0.83; n=9,639) with a heterogeneity of I^2 =0.24 across studies;
    - Specimens of symptomatic individuals taken from exhaled breath condensate (Sn 0.92, 95% CI 0.64-1.00; n=105), nasal mid-turbinate (Sn 0.86, 95% CI 0.80-0.91; n=696), or anterior nares (Sn 0.76, 95% CI 0.75-0.78; n=7,915);
    - Specimens of asymptomatic individuals taken from nasal mid-turbinate (Sn 0.75, 95% CI 0.35-0.97; n=157), anterior nares (Sn 0.26, 95% CI 0.23-0.31; n=3,978), or combined oropharyngeal and nasopharyngeal areas (Sn 0.40, 95% CI 0.28-0.52; n=5,504)
    - Specimens of symptomatic individuals with high viral loads at RT-PCR cycle threshold <25 (Sn 0.95, 95% CI 0.89-0.98; n=140);
      Specimens of asymptomatic individuals with high viral loads at RT-PCR cycle threshold <25 (Sn 0.76, 95% CI 0.64-0.76; n=187);
    - Specific brands of rapid antigen test, namely LumiraxDx (Sn 0.97, 95% CI 0.92-0.99; n=5,535), Inflammacheck device (Sn 0.92, 95% CI 0.64-1.0; n=105), COVID-VIRO ALL IN (Sn 0.91, 95% CI 0.83-0.96; n=593), Drager antigen test (Sn 0.89, 95% CI 0.79-0.95; n=379), and Abbott Panbio (Sn 0.84, 95% CI 0.71-0.94; n=290);
    - Seven studies with high methodological quality or low risk of bias on symptomatic individuals (Sn 0.75, 95% CI 0.73-0.77; n=5,061); and
    - Two studies with high methodological quality or low risk of bias on asymptomatic individuals (Sn 0.26, 95% CI 0.22-0.30; n=3,872).
- The overall certainty of evidence for test sensitivity was tagged as moderate for both symptomatic and asymptomatic individuals due the presence of risk of bias issues (patient selection, conduct of index test, and reference standard) despite having similar results across studies.

PREVIOUS RECOMMENDATIONS
As of 11 November 2021

We suggest the use of self-administered rapid antigen test for the diagnosis of COVID-19 in symptomatic individuals, provided that ALL OF THE FOLLOWING conditions are met: *(Low certainty of evidence; Weak recommendation)*

1. Ease of collecting samples is ensured;
2. Ease of interpretation is ensured;
3. Test kits have passed flex studies; AND
4. Individuals present with symptoms for less than 7 days.

We suggest against the use of self-administered rapid antigen test for routine screening of COVID-19. *(Low certainty of evidence; Weak recommendation)*

Consensus Issues
The Panel unanimously agreed that all the following four conditions should be met when using self-administered antigen tests for the diagnosis of COVID-19:

1. Ease of sample collection, because incorrect performance of self-administered tests largely affects diagnostic accuracy;
2. Ease of interpretation, because proper interpretation is important for the accurate clinical management of patients;
3. The test kits should have passed the flex studies, because the quality of the self-administered test kit should be ensured; and
4. Individuals present with symptoms for less than 7 days, because antigen tests perform best during this period; and beyond this, the use of the test is not cost-effective, thereby incurring costs without added benefit.

The panel decided on a weak recommendation based on evidence including seven observational studies where performance of self-testing by participants was supervised by trained personnel either onsite or via telehealth. None were conducted in a home setting. Additionally, the studies did not specify if the participants were close contacts of COVID-19 patients or if they have a high- or low-risk of contracting COVID-19.

Other issues raised include (1) the lack of locally FDA-approved self-administered antigen test kits, (2) differentiating antigen tests manufactured for self-administration versus those that are not (i.e., for trained personnel), (3) the method of reporting the test results, and (4) the subsequent management and/or protocols after a positive test result (e.g., contact tracing).

INTRODUCTION

Much of the development and research efforts in the pandemic comes from the diagnostics and treatment arms including mass vaccination, effective quarantine measures, novel approaches to management, and faster detection of infection. Restrictions have changed across the globe and some countries have lifted using masks in public places; despite this, new challenges arise, keeping the healthcare sector vigilant and better prepared for the next COVID-19 wave.

Reverse-transcriptase polymerase chain reaction (RT-PCR) still remains as the gold standard in detecting SARS-CoV-2. However, the presence of strains with high infectivity that demand rapid detection in the most cost-effective way requires the use of a more practical approach to diagnosis. RT-PCR-based assay is not entirely ideal for all testing scenarios due to its need for specialized equipment in a laboratory setting, trained health personnel, and overall cost.

Immunoassays, such as rapid antigen tests (RAgTs), have been proven to be effective in detecting specific strains with faster results as these are performed at the point of care, and come at more affordable prices

compared to RT-PCR tests [2]. An early review by Burog et al. in March 2021 showed that the pooled sensitivity and specificity of RAgTs across 30 studies and 10 evaluation reports were 72% (95% CI 64-78%, I^2=95.77) and 99% (95% CI 99-100%, I^2=93.16) respectively [3]. Although this and several initial studies used healthcare personnel-collected samples, this gave rise to the possibility of conducting self-administered RAgTs for faster identification of COVID-19 infection as quarantine measures change.

As defined by the World Health Organization (WHO), self-testing involves either self-sampling, self-performance of testing, self-reading of test results, or all three. Self-administered RAgTs may potentially cut costs on personnel and equipment, with an added option of being done at the home setting [2]. Although local data on cost-effectiveness are needed, a recent study from Germany attests to the benefits of self-administered RAgTs [3]. Albeit minor, the effect of self-testing done in a population with a high incidence rate is nonetheless acceptable in the presence of higher-risk contacts given its low cost. An Australia-based study was conducted via a decision-tree model to determine the feasibility of government subsidy of self-administered RAgTs. This revealed that projected reductions in COVID-19 transmission rates due to early isolation would justify additional costs should this become government policy [5].

Collecting samples for nasopharyngeal swabs induce discomfort and results take time which is why a majority of people would favor RAgTs. With the advent of self-testing, preference over the latter are expected to rise. The accuracy of self-performed RAgTs may be similar to that of professionally administered RAgTs but their precision relative to RT-PCR is still dependent on several factors. These include ease of use, cycle threshold, even age of the patient as some studies in self-administered RAgTs have also included children [6-8].

The previous clinical practice guideline on the diagnostic accuracy of RAgTs was done last November 2021, reporting a pooled sensitivity of 0.77 (95% CI 0.62-0.87) and low certainty of evidence for test sensitivity because of high heterogeneity and risk of bias. This current review serves as an update and includes new studies since then.

REVIEW METHODS

A literature search for published studies was done using MEDLINE. Medical subject headings (MESH) combined with free text terms related to COVID-19 or SARS-CoV-2 and rapid antigen tests/testing were used, with no language limits or method filters.

Preprint studies were identified using the COVID-19 Living Evidence Database (https://zika.ispm.unibe.ch/assets/data/pub/search_beta/) with "antigen" as the search term. This database is updated daily and includes preprints from medRxiv and bioRxiv, as well as published articles from EMBASE and PubMed. The Cochrane COVID-19 Study Register (covid-19.cochrane.org/) was also searched using "antigen" as a search term. Search for related links and journals was also carried out. Bibliography sections of the included studies were reviewed for relevant articles that might be missed by database search. The final search was done on October 20, 2022.

To supplement the initial search yield, available data on RAgT from FIND SARS-CoV-2 Diagnostic pipeline (https://www.finddx.org/covid-19/dx-data/) was retrieved. Relevant clinical trials were searched on clinicaltrials.gov. Local publications such as health technology assessments on the use of RAgTs were also sought. Finally, a cold search was performed on google.com to check for studies not included in any of the databases. The methodological quality of the diagnostic accuracy studies were assessed by independent reviewers using the QUADAS-2 tool.

Summary estimates from the data of individual studies were computed externally through Review Manager 5 and a web-based app (https://ciberisciii.shinyapps.io/MetaDiSc2/).To determine heterogeneity, a random-effects bivariate binomial model of analysis was done using the same application. In anticipation of significant heterogeneity among the included studies, pooled sensitivity and specificity estimates were obtained by subgrouping studies according to test brand, type of specimen used, cycle threshold value used, and participant characteristics. Sensitivity analysis was performed by removing studies with low

methodologic quality or with risk of bias issues in certain QUADAS-2 domains, and subsequently assessing their impact on overall diagnostic accuracy estimates.

A total of 2,049 titles and abstracts were screened (adding 1574 to the 475 yielded in the first review). From this, 87 additional full-text articles (in addition to the previous 192) with correspondence to the key question were retrieved. Review of the retrieved articles yielded a total of 15 studies that specifically tackled the diagnostic accuracy of self-administered RAgTs.

RESULTS

Characteristics of included studies

Fifteen observational studies including a total sample of 18,084 were found on self-administered antigen testing. Thirteen different RAgT brands were evaluated using RT-PCR as the reference standard. All studies were done in a community setting. The studies used varied RAgT specimens: four used nasal mid-turbinate specimens [7-10], nine used anterior nares specimens [8-17, 21], three used combined nasal and oropharyngeal swabs [17-19], and one used exhaled breath condensates [20]. Ten studies involved symptomatic patients [7-11,14-16,18,19] while five included asymptomatic patients [7,11,12,15, 21]. Three studies included children as participants [13, 18, 21]. Two studies from the update were done in a home setting [14,18]. The rest were done at the point of care and involved personnel who supervised the participant at the study site. Four studies also assessed ease of use through scaled evaluation from the participants. [10,14,15,19]. Appendix 3 shows a summary of the characteristics of included studies.

Methodological quality of included studies

The overall methodological quality of the included studies was rated as moderate. Of the fifteen studies, eight were rated as high quality [8-10,13,15,18,19, 21] while the remaining seven were of moderate quality [7,11,12,14,16,17, 20] due to issues of unclear patient selection, index test, and reference standard. Appendix 4 shows a detailed assessment of the risk of bias of included studies.

Diagnostic accuracy of self-administered RAgT

A. Overall diagnostic accuracy

Pooled analysis of the fifteen studies included in this updated review showed that self-administered RAgT had a sensitivity of 0.74 (95% CI 0.63-0.82) from the previous 0.77 (95% CI 0.62-0.87) and a high specificity of 0.99 (95% CI 0.99-0.99) from the previous 0.996 (95% CI 0.99-1.00). Heterogeneity among studies had an I^2 value of 54% (from I^2=97%) as the studies yielded more similar results. Figure 1 shows the forest plots of the pooled sensitivity and pooled specificity of self-administered RAgTs.

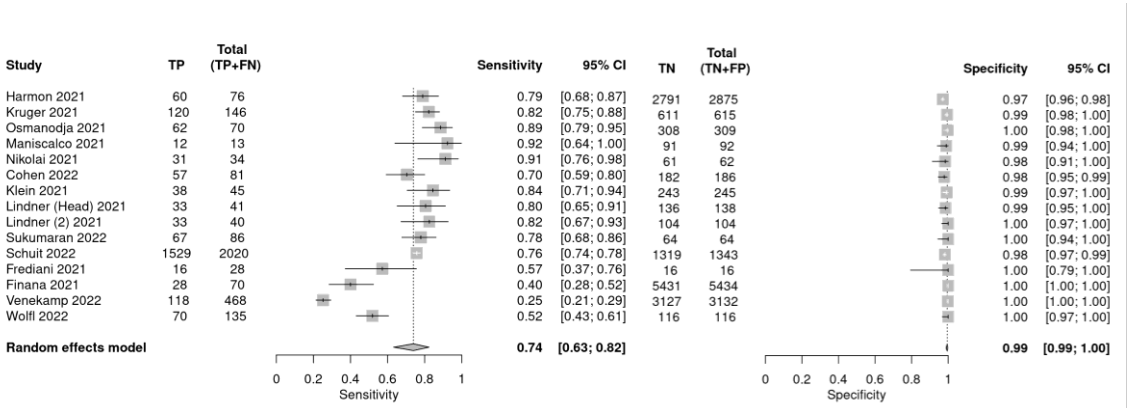

Figure 1. Forest plots of pooled sensitivity and specificity of self-administered RAgTs

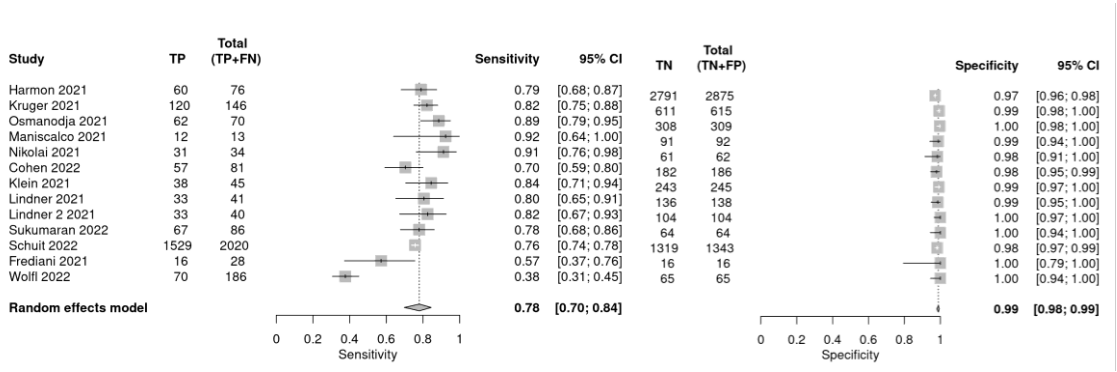

Figure 2. Forest plots of sensitivity and specificity of self-administered RAgTs in symptomatic individuals

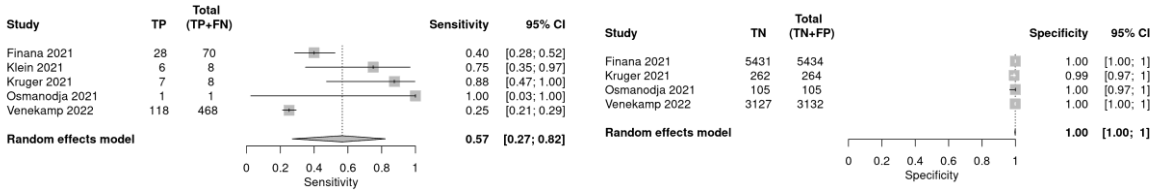

Figure 3. Forest plots of sensitivity and specificity of self-administered RAgTs in asymptomatic individuals

B. Subgroup Analysis

Table 1 shows the sensitivity of self-administered RAgTs per subgroup.

Table 1. Subgroup Analysis for Sensitivity of Self-administered RAgTs

Variable	References	No. of Studies (n= no. of participants)	Sensitivity	95% CI
Presence of symptoms				
Symptomatic	[7-11,14-16,18,19]	10 (n=5,761)	0.77	(0.75, 0.78)
Asymptomatic	[7,11,12,15]	5 (n=9,639)	0.57	(0.27, 0.82)
Timing of testing in relation to symptoms				
Mixed timing	[7,8]	2 (n=469)	0.83	(0.73, 0.90)
Early	[9-11,14-17]	7 (n=1,226)	0.87	(0.83, 0.90)
Late	[15]	1 (n=7)	0.53	(0.59, 0.77)
Test brand				

Inflammacheck® device (Exhalation technology LTD, Cambridge, UK)	[20]	1 (n=105)	0.92	(0.64, 1.00)
Dräger Antigen Test SARS-CoV-2 (Dräger Safety AG and Co. KGaA, Lübeck, Germany)	[11]	1 (n=379)	0.89	(0.79, 0.95)
Panbio™ Ag-RDT (Abbott)	[7]	1 (n=290)	0.84	(0.71, 0.94)
STANDARD Q COVID-19 Ag Test (SD Biosensor, Korea)	[8-10]	3 (n=414)	0.86	(0.79, 0.92)
BinaxNOW SARS-CoV-2 (Abbott)	[17]	1 (n=44)	0.57	(0.37, 0.76)
Innova LFT (Innova Medical Group Inc)	[12]	1 (n=5,504)	0.40	(0.28, 0.52)
COVID-VIRO ALL IN	[13]	1 (n=593)	0.91	(0.83, 0.96)
LumiraxDx	[15]	1 (n=5,535)	0.97	(0.92, 0.99)
AG-Q COVID-19 N-Ag self-test kit	[16]	1 (n=128)	0.78	(0.68, 0.86)
Medomics SARS-CoV-2 antigen test device	[19]	1 (n=204)	0.32	(0.24, 0.42)
Clinitest	[18, 21]	2 (n=1,849)	0.62	(0.58, 0.66)
Flowflex	[18, 21]	2 (n=2,391)	0.69	(0.66, 0.72)
MPBio	[18, 21]	2 (n=2,743)	0.66	(0.63, 0.69)
Specimen type (Symptomatic)				
Exhaled breath condensate	[20]	1 (n=105)	0.92	(0.64, 1.00)
Nasal mid-turbinate	[7-10]	4 (n=696)	0.86	(0.80, 0.91)
Anterior nares	[11,13-16,18, 21]	7 (n=7,915)	0.76	(0.75, 0.78)
Specimen type (Asymptomatic)				
Nasal mid-turbinate	[7]	1 (n=157)	0.75	(0.35, 0.97)

Anterior nares	[15, 11, 21]	3 (n=3,978)	0.26	(0.23, 0.31)
Nasal + oropharyngeal	[12]	1 (n=5,504)	0.40	(0.28, 0.52)
Cycle threshold (Ct) value (Symptomatic)				
Low (<25)[a]	[7,12]	2 (n=140)	0.95	(0.89, 0.98)
Mixed[b]	[8-11,14,18]	8 (n=7,361)	0.76	(0.75, 0.78)
High (>25)[c]	[7,12,13, 16]	4 (n=901)	0.76	(0.75, 0.78)
Cycle threshold (Ct) value (Asymptomatic)				
Low (<25)	[7, 12, 15]	3 (n=187)	0.76	(0.64, 0.86)
High (>25)	[7, 15]	2 (n=48)	0.24	(0.13, 0.40)
Studies involving children				
Studies involving children	[13, 18, 21]	3 (n=7,230)	0.66	(0.64, 0.68)
Methodological quality (Symptomatic)				
Studies with no serious risk of bias	[8-10,13,15,18,19]	7 (5,061)	0.75	(0.73, 0.77)
Studies with serious risk of bias				
Related to patient selection	[7,11,14,16, 20]	5 (3,875)	0.82	(0.78, 0.87)
Related to index test administration	[11,12,17]	3 (5,927)	0.63	(0.55, 0.70)
Related to reference standard administration	[7,18]	2 (334)	0.74	(0.62, 0.84)
Methodological quality (Asymptomatic)				
Studies with no serious risk of bias	[15, 21]	2 (3,872)	0.26	(0.22, 0.30)
Studies with serious risk of bias Related to patient selection	[7, 11]	2 (263)	0.78	(0.40, 0.97)

[a] One study [11] used CT values of 18.3-24.4, while another study [7] used 12.7-23.1.
[b] One study [9] used CT values of 17.3-35.5, while seven studies [8,10,11,14,17,18,20] did not report any CT value.
[c] One study [12] used CT values of 24.4-35.5, while another study [7] used 23.1-34.5.

By presence of symptoms
The pooled sensitivity of self- administered tests on symptomatic and asymptomatic individuals was 0.74 , (95% CI 0.63-0.82; n=18,084; 15 studies). This was lower compared to that of symptomatic cases alone (Sn 0.77, 95% CI 0.75-0.78; n=5,761; 10 studies), and much higher than that of asymptomatic individuals alone (Sn 0.29, 95% CI 0.25-0.33; n=9,639; 5 studies).

By time of testing in relation to symptom onset
Samples collected within 7 days (around day 3-4) from symptom onset (early phase of the disease) had a pooled sensitivity of 0.87 (95% CI 0.83-0.90; n=1,226; 7 studies). Two studies that used self-administered RAgTs in both the early (0-7 days) and late phase (>7 days) of the disease had a pooled sensitivity of 0.83 (95% CI 0.73-0.90; n=469; 2 studies), the same studies used in the previous review as data from other studies are not available for pooling under this subgroup. The study by Kruger also included samples obtained in the late phase (the longest time being 14 days from symptom onset) with a sensitivity of 0.53 (95% CI 0.59-0.77).

By test brand
The basis for certainty of sensitivity (low or high) in terms of test brand was based on the World Health Organization (WHO) standard for Ag-RDTs (≥ 80% sensitivity among symptomatic individuals). In this case, LumiraxDx had the highest sensitivity (Sn 0.97, 95% CI 0.92-0.99; n=5,535). Unlike lateral flow assays, this brand uses a microfluidic immunofluorescence assay read through a portable device. This was followed by Inflammacheck (Sn 0.92, 95% CI 0.64-1.00; n=105), then COVID-VIRO ALL IN (Sn 0.91, 95% CI 0.83-0.96). Three other brands showed a sensitivity of more than 0.80: Dräger Antigen Test SARS-CoV-2 (Sn 0.89, 95% CI 0.79-0.95; n=379) and Abbott Panbio (Sn 0.84, 95% CI 0.71-0.94, n=290). The pooled sensitivity for STANDARD Q COVID-19 Ag Test, from the results of three studies (adding the study of Nikolai et al. to two previous studies), was 0.86 (95% CI 0.79-0.92; n=414).

Relatively lower sensitivities were demonstrated by seven RAgT brands: Innova LFT (Sn 0.40, 95% CI 0.28-0.52; n=5504), BinaxNOW SARS-CoV-2 (Sn 0.57, 95% CI 0.37-0.76; n=44), AG-Q COVID-19 N-Ag self-test kit (Sn 0.78, 95% CI 0.68-0.86), Medomics (Sn 0.32, 95% CI 0.24-0.42), Flowflex (Sn 0.62, 95% CI 0.58-0.66; n=1,849), MP-Bio (0.69, 95% CI 0.66-0.72; n=2,391), and Clinitest (Sn 0.66, 95% CI 0.63-0.69; n=2,723).

By type of specimen used for the index test
In symptomatic individuals, the specimen types with the highest pooled sensitivities include those taken from the exhaled breath condensate (Sn 0.92, 95% CI 0.64-1.00). To obtain a sample, the subject breathes into a breath collection unit that is then mounted onto a cartridge with a single-use macromolecule-coated sensor. This is followed by samples from the nasal middle turbinate (Sn 0.86, 95% CI 0.75-0.91; n=704) and anterior nares (Sn 0.68, 95% CI 0.66-0.70; n=11,515). These specimen types entail using a cotton swab aimed at a 45-degree angle towards the collection site, as provided in the instructions in each test brand.

This is similarly seen in asymptomatic individuals. Samples from mid turbinate had a sensitivity of 0.75 (95% CI 0.35-0.97; n=157) while those taken from anterior nares had a sensitivity of 0.26 (95% CI 0.23-0.31; n=3978). The specimen type with the lowest sensitivity was the combined nasal and oropharyngeal specimens (Sn 0.40, 95% CI 0.28-0.52; n=5,504).

By cycle threshold (CT) value used for the RT-PCR
RAgTs in symptomatic individuals performed better when tested against RT-PCR assays that used lower Ct values of <25 (Sn 0.95, 95% CI 0.89-0.98; n=140) compared to those that used higher CT values of >25 (Sn 0.38, 95% CI 0.35-0.42; n=901) as the criterion for classifying positive COVID-19 cases. This may indicate that RAgT is most sensitive when applied to samples with high viral loads.

As for asymptomatic individuals, specimens with CT values <25 had a sensitivity of 0.76 (95% CI 0.64-0.86; n=187) while those with CT values >25 had a sensitivity of 0.24 (95% CI 0.13-0.40; n=48).

C. Sensitivity analysis
For studies that involved symptomatic individuals, self-administered tests showed a moderate sensitivity when only those with high methodological quality were included in the analysis (Sn 0.75, 95% CI 0.73-0.77; n=5,061; 7 studies). Studies with potential risk of bias issues related to conduct of the RAgT or reference standard reduced the test sensitivity of RAgTs. Those that presented with selection bias tended to overestimate sensitivity to 0.82 (95% CI 0.78-0.87; n=3,875).

In the studies that included asymptomatic individuals, sensitivity of those with high methodological quality was 0.25 (95% CI 0.22-0.30; n=3,872). Studies with potential risk of bias issues related to patient selection had an overestimated sensitivity of 0.78 (95% CI 0.40-0.97; n=263).

RECOMMENDATIONS FROM OTHER GROUPS

Table 3 summarizes the recommendations from different agencies, countries, and organizations regarding the use of self-administered RAgTs.

Table 3. Summary of Recommendations from Other Groups

Group or Agency	Recommendation	Date

DOH HTAC [36]	Self-administered rapid antigen tests are currently recommended by HTAC only for very specific purposes: ● For targeted screening and diagnosis of suspected and probable cases of COVID-19 (i.e., with a high index of suspicion) among individuals with high risk of developing severe COVID-19 and needing immediate provision of antiviral drugs (refer to list from CDC* or subject to discretion of a physician), and meeting the clinical and/or epidemiologic criteria in the hospital or community settings as defined below: ● Suspected cases of COVID-19 are individuals: with acute onset of the following signs and symptoms adopted on the WHO clinical criteria, (Fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status, anosmia (loss of smell) or ageusia (loss of taste) OR ● satisfying the following epidemiology criteria): ○ Residence or work in an area with high risk of transmission of virus (e.g. congregate settings) ○ Residence or travel to an area with community transmission ○ Work in any healthcare setting Probable cases of COVID-19 are: ● Individuals meeting the above clinical criteria AND is a contact of a probable or confirmed case or linked to a cluster of COVID-19 cases ● Suspect cases with chest imaging suggestive of COVID-19 ● Individuals with sudden onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause.	April 06, 2022
WHO [37]	COVID-19 self-testing, using SARS-CoV-2 Ag-RDTs, should be offered in addition to professionally administered testing services (Strong recommendation, low to moderate certainty evidence). COVID-19 self-test kits should meet the existing. World Health Organization (WHO) standards for Ag-RDTs (≥80% sensitivity and ≥97% specificity among symptomatic individuals).	March 9, 2022
UK NHS [38]	In the UK, the MHRA has granted NHS Test & Trace an exceptional use authorization to use certain lateral flow devices as self-tests to detect infection in people who do not have any COVID-19 symptoms. This means that the tests can be used by anyone without previous experience of testing, in their own home or another community setting such as a place of work.	October 7, 2022

Government of the Netherlands [39]	Rapid antigen self-testing can be done for individuals with symptoms of COVID-19 or those who have been exposed to somebody who has contracted the disease. If returning from abroad, a self-test is done on the day of arrival back in the Netherlands, before meeting others, and another test at day 5 (also applies even for vaccinated and recovered persons). Self testing is not encouraged in the following: - Healthcare workers - Immunocompromised patients (institutionalized, aged 70 years old and above, with severe immune system dysfunction) - People who go to a daytime activity group consisting of more than 70 persons - Unable to do a self-test, even with help - Need for proof of recovery.	October 2022
NSW, Australia [40]	Self performed rapid antigen tests are recommended for asymptomatic and symptomatic individuals unless advised otherwise by their general physician. For people with a higher risk of severe illness and those coming overseas who developed symptoms within 14 days are advised to do PCR testing instead.	October 16, 2022
Canada [41]	Individuals with or without symptoms can use self-testing kits to assess and monitor their own infection status. Health Canada has identified self-testing technologies as a high priority.	February 21, 2022
US CDC [42]	Self-tests may be performed by a person at home or anywhere, provided that all instructions for performing the test must be followed. Self-tests can be used by anyone who is symptomatic, asymptomatic persons exposed to a known positive case (must be done at least 5 days after exposure, if negative, must be repeated after 1-2 days), and individuals going to indoor gatherings (immediately before the event).	September 6, 2022

ONGOING STUDIES AND RESEARCH GAPS

As of October 2022, there are three ongoing studies registered in clinicaltrials.gov, that are evaluating different brands of self-administered RAgTs (SD Biosensor, Wong et al.; Abbott PanBio, Pai et al., and Binax NOW, Shriver, et al.) [21,22,23]. One study solely aims to evaluate the diagnostic accuracy of self-collected RAgTs against RT-PCR in an asymptomatic population [21]. Another study is a randomized controlled trial investigating the effectiveness of a COVID testing digital application which will include diagnostic accuracy of the RAgTs as a secondary outcome [22]. The final study by Shriver involves the feasibility of in-home self-testing or guardian-guided self testing on children with medical complexity (with chronic conditions and disabilities) [23]. Appendix 5 shows the details of the registered studies.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

In the United States of America, a study done by Paltiel et al showed the clinical and economic effects of widespread home-based antigen testing. A simple compartmental epidemic modeling was used. Compared to no testing at all, the use of home-based antigen testing yielded the following incremental cost-effectiveness ratio: $7,890 (₱450, 000.00) per infection averted and $1.43 million (₱60 million) per death

averted [16]. To support this evidence, an analysis by Gandjour in January 2022 determined the the cost-effectiveness of self-administered RAgTs–from the German consumer's perspective, the cost of testing for every clinical event avoided and every quality-adjusted life year (QALY) gained amounted to €5870 (₱300, 000.00) [4]. In another Australia-based study by Karnon et al, a decision tree model justified government subsidy of self-administered RAgTs due to proposed reduction in transmission rate [5]. In lieu of applicability concerns, this calls for establishment of local data on the economic evaluation of self-administered RAgT.

Results of flex or robustness studies are one of the considerations of WHO for the Emergency Use Listings (WHO EUL) of in vitro diagnostics (IVDs) for detecting SARS-Cov-2 [25]. The US Food and Drug Administration (US FDA) also takes into account flex studies prior to giving Emergency Use Authorization for molecular and antigen diagnostic COVID-10 tests for home use [26]. Flex studies are expected to challenge the kit or system under various conditions of stress. This is to identify potential device deficiencies and determine the robustness (i.e., ability of the test to be unaffected by slight variations) of the kit [17]. The test should still function properly on various conditions of improper use [27]. Examples of conditions that flex studies of RAgTs should consider are the following: multiple skill levels of users (includes reader and reagent problems), specimen and/or reagent volume, operating temperature, visual reading, specimen type, device orientation, and disturbances during analysis [25, 26].

Among the test kits included in this review, Standard Q Covid-19 Ag test (SD Biosensor), Innova LFT (Innova Medical Group), Panbio Ag-RDT (Abbott), BinaxNow SARS-CoV-2 (Abbott), COVID VIRO ALL-IN, and Medomics (Jiangsu Medical Technology Co., Ltd.) have approval from foreign agencies [27-31]. As of October 2022, the FDA has also approved Flowflex, Clinitest, LumiraxDx among the other tests used in the studies [33].

The Research Institute of Tropical Medicine (RITM) has currently approved 32 rapid antigen kits for self-testing including Panbio Ag-RDT (Abbott), Flowflex (ACON Biotech); while the Philippine Food and Drug Administration included Zybio SARS-COV-2 assay kit for self-testing [34]. Local studies on cost-effective analysis specific for self-administered RAgT are yet to be performed.

The price cap for RAgTs in the Philippines as issued in the Department of Health (DOH) memorandum dated January 28, 2022 is now at ₱350, costing 60% less than the first price cap released three months prior (₱960) [35]. Table 2 lists the local unit cost of the self-administered RAgT kits used by the studies included in this review.

Table 2. Unit Price of Self-Administered RAgT Kits

Brand	Unit Price of Self-administered RAgT Kits Available in the Philippines
Panbio™ Ag-RDT	₱520 or US $13
STANDARD Q COVID-19 Ag Test	₱550
BinaxNOW SARS-CoV-2 (Abbott)	₱250 or US $5
STANDARD Q	₱128 or US $2.0
Flowflex	₱350 or US $6.0
MPBio	₱340 or US $5.8

Clinitest	₱230 or €3.98

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

There are no studies found on patient values, preference, equity, acceptability, and feasibility regarding self-administered rapid antigen tests.

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APPENDICES

Appendix 1: Preliminary Evidence to Decision

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (N=1)	Yes (N=4)					
Benefits	Large (N=2)	Moderate (N=3)	Small	Uncertain			
Harms	Large	Moderate (N=2)	Small (N=3)	Uncertain			
Balance of Benefits and Harms	Favors the use of self-test (N=2)	Probably favors the use of self-test (N=3)	Varies				
Certainty of Evidence	High	Moderate (N=5)	Low	Very low			Overall, the studies included are of moderate methodological quality. Eight studies are of high quality while seven others are of moderate quality due to unclear issues on patient selection, index test and reference standard.
Accuracy	Very Accurate	Accurate (N=4)	Inaccurate	Very Inaccurate	Varies (N=1)	Don't Know	Across 15 studies, self-administered RAgT had a sensitivity of 0.74 (95% CI 0.63-0.82) with heterogeneity of I2=54%, and a consistently high specificity at 0.99 from 0.996 (95% CI 0.99-0.99).

Values	Important uncertainty or variability (N=1)	Possibly important uncertainty or variability (N=3)	Possibly NO important uncertainty or variability (N=1)	No important uncertainty or variability			
Resources Required	Varies (N=1)	Large cost (N=1)	Moderate Cost (N=2)	Negligible cost	Moderate savings (N=1)	Large savings	
Certainty of evidence of required resources	No included studies (N=2)	Very low (N=1)	Low	Moderate (N=1)	High (N=1)		In the United States of America, a study done by Paltiel et al showed the clinical and economic effects of widespread home-based antigen testing. A simple compartmental epidemic modeling was used. Compared to no testing at all, the use of home-based antigen testing yielded the following incremental cost-effectiveness ratio: $7,890 (₱450, 000.00) per infection averted and $1.43 million (₱60 million) per death averted.[16] To support this evidence, an analysis by Gandjour in January 2022 determined the the cost-effectiveness of self-administered RAgTs–from the German consumer's perspective, the cost of testing for every clinical event avoided and every quality-adjusted life year (QALY) gained amounted to €5870 (₱300, 000.00)[4] In the Philippines, the Department of Health issued a memorandum dated January 28, 2022 strictly placing a price cap of Php 350 for rapid antigen testing in all testing and clinical laboratories.The cost per unit of each rapid antigen test ranges from ₱ 130 to ₱500. No local cost-effectiveness studies are available as of press time on comparing self-administered rapid antigen tests and RT-PCR.
Cost effectiveness	No included studies (N=3)	Favors the comparator (N=1)	Does not favor either self-test or the comparator	Probably favors the self-test (N=1)	Favors self-test		
Equity	Don't Know	Reduced	Probably no impact	Probably	Increased	Varies	

		(N=1)		Increased (N=2)		(N=2)	
Acceptability	Don't Know	No	Probably No	Yes (N=1)	Probably yes (N=4)	Varies	
Feasibility	Don't Know	No	Probably No	Yes (N=4)	Probably yes (N=1)	Varies	

Appendix 2: Search Yield and Results

Search	Query	Results	Time
#13	Search **#11 and #12**	12	08:31:11
#12	Search **#9 and #10**	87	08:25:12
#11	Search: **"self test" OR "self-test" OR "self administration" OR "self-administration" OR "self" OR "self done" OR "self performed" OR "self-performed"**	196109	08:24:53
#10	Search: **"diagnostic accuracy" and "sensitivity" and "specificity"**	6835	08:24:32
#9	Search **#1 and #8**	1574	08:24:08
#8	Search **#7 OR #2**	3825	08:23:52
#7	Search **#5 OR #6**	3810	08:23:35
#6	Search: **rapid antigen test* OR "rapid antigen detection test" OR radt OR radts OR rdt OR rdts OR (antigen* n3 detect*)**	3803	08:23:11
#5	Search **#3 and #4**	32	08:22:59
#4	Search: **(test OR tests OR detect* OR diagnos* OR kit OR kits OR assay*)**	1,733,941	08:22:38
#3	Search: **((rapid OR point-of-care OR "point of care" OR poc OR poct) n3 antigen)**	34	08:22:18
#2	Search: **"COVID-19 Ag Respi-Strip" OR "BIOCREDIT COVID-19 Ag" OR "STANDARD F COVID-19 Ag" OR "STANDARD Q COVID-19 Ag" OR "Bioeasy"**	54	08:21:57
#1	Search: **("Coronavirus Infections"[Mesh] OR novel coronavirus OR NCOV OR "COVID-19"[Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2)**	300,711	08:21:34

Appendix 3: Characteristics of Included Studies

Study ID	Setting	Index Test	Index Test Specimen	Population	Sample Size	Reference Standard	
						Test	Specimen
Lindner 2021 [8]	Germany	STANDARD Q COVID-19 Ag Test (SD Biosensor, Korea)	NMT for self-administered, NP for staff-collected	Symptomatic patients at ambulatory testing facility (community setting)	146	RT-PCR (not specified)	NP/OP
Lindner 2021 [9]	Germany	STANDARD Q COVID-19 Ag Test (SD Biosensor, Korea)	NMT for self-administered, NP for staff-collected	Symptomatic patients at ambulatory testing facility (community setting)	287	Roche Cobas and Tib Molbiol®	NP/OP
Maniscalco 2021 [20]	Italy	Inflammacheck® device (Exhalation technology LTD, Cambridge, UK)	Exhaled breath condensate	≥ 18 y/o with or without symptoms in a community setting	105	NeumoDx	NP
Osmanodja 2021 [11]	Germany	Dräger Antigen Test SARS-CoV-2 by Dräger Safety AG and Co. KGaA (Lübeck, Germany)	Anterior Nares	≥ 18 y/o with or without symptoms in a community setting	379	Roche Cobas SARS-CoV-2 assay (Pleasanton, CA, USA)	NP and OP

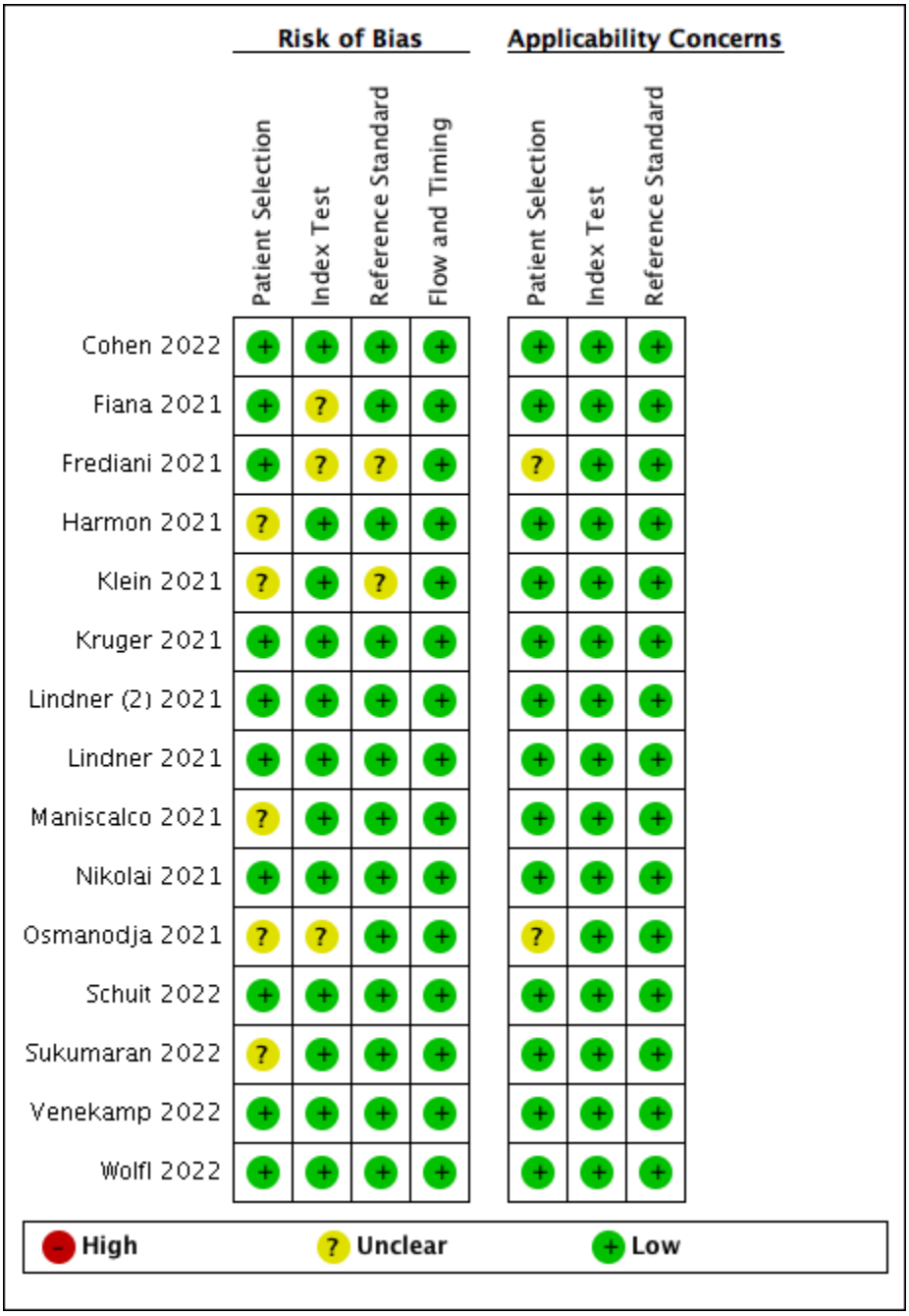
Fiñana 2021 [12]	UK	Innova LFT	Combined throat and nose	> 18 y/o with or without symptoms in a community setting	5504	TaqPath; ThermoFisher Scientific	Combined throat and nose (also collected by participant)
Klein 2021 [7]	Germany	Panbio™ Ag-RDT	NMT for self-administered, NP for staff-collected	Symptomatic adults and high-risk contacts of confirmed SARS-Cov-2 in an in-drive in testing center (community setting)	290	Tib Molbiol®	NP
Frediani 2021 [17]	USA	BinaxNOW SARS-CoV-2 (Abbott)	Anterior nares	> 7 y/o (adults and pedia) symptomatic within 7 days from onset in community-based and hospital-based testing center (community setting)	44 self-collected; 297 staff-collected	Cobas 6800 (Roche Diagnostics), Abbott Alinity (Abbott Labs), Panther Fusion (Hologic)	NP
Cohen 2022 [13]	France	COVID-VIRO ALL IN	Anterior nares	Children ≥6 months to 15 years old with suggestive symptoms of COVID-19 or children in contact with a COVID-19–positive patient in ambulatory care and emergency units (community setting)	907	RT-PCR (not specified)	NP

Harmon 2021 [14]	USA	Unknown	Anterior nares	Symptomatic affiliates (adults) of coworking laboratories in Cambridge and Massachusetts (community setting)	685	RT-PCR (not specified)	Nasal
Kruger 2021 [15]	Germany, India	LumiraxDx	Anterior nares	Symptomatic and asymptomatic adults at a point-of-care center (community setting)	5535	All-plexTM SARS-CoV-2 assay	NP and OP
Nikolai 2021 [10]	Germany	STANDARD Q COVID-19 Ag Test	NMT	Symptomatic adults at a point-of-care center (community setting)	162	RT-PCR (not specified)	NP
Schuit 2022 [18]	Netherlands	Flowflex, MPBio, Clinitest	Anterior nares and OP	Symptomatic individuals aged ≥16 years presenting and a point-of-care center (community setting)	430	Cobas 6800 or 8800 platform (Roche Diagnostics International)	NP, OP, and Nasal
Sukumaran 2022 [16]	India	AG-Q COVID-19 N-Ag self-test kit	Anterior nares and OP	Symptomatic adults at a point-of-care center (community setting)	128	COVIPATH COVID-19 RT–PCR kit from Thermo Fisher Scientific.	NP and OP
Wolfl 2022 [19]	Austria	Medomics SARS-CoV-2 antigen test de-vice	Anterior nares and OP	Symptomatic adults at a point-of-care center (community setting)	204	CE/IVD-certified Roche Cobas 6800 RT-PCR system	NP

Venekamp 2022 [21]	Netherlands	Flowflex, MPBio, Clinitest	Anterior nares	Asymptomatic individuals aged ≥16 years presenting and a point-of-care center (community setting)	3600	RT-PCR (not specified)	Nasopharyngeal

NMT: Nasal midturbinate; NP: Nasopharyngeal; OP: Oropharyngeal.

Appendix 4: Risk of Bias and Applicability Concerns of Included Studies



Title / Study Design / NCT	Population	Intervention	Comparator	Outcomes	Status
COVID-19 Rapid Testing for Self-Administration Among an Asymptomatic Sample[20] ● Open-label, single-center study ● University of British Columbia ● NCT04896710	● **Inclusion Criteria:** ○ Male or female aged 16 years and over ○ Living or working at University of British Columbia ○ Self identified as asymptomatic for COVID-19 ○ Participants able to give written informed consent ● **Exclusion Criteria:** ○ Anyone who is self identified as having COVID-19 symptoms ○ Those diagnosed with COVID-19 in last 30 days	SD Biosensor Nasal swab SD biosensor to be self administered	Health care professional administered SD Biosensor	**Primary** ● Concordance (calculated using Cohen's Kappa) between self administered and health care professional administered SD Biosensor rapid antigen test results. ● Ability of rapid antigen test to detect COVID-19 positive	**Enrolling by invitation** **Study start**: May 26, 2021 **Primary completion**: August 31, 2021 **Study completion**: August 31, 2021

A Randomized Controlled Trial of a Digital, Self-testing Strategy for COVID-19 Infection in South Africa [21] ● Randomized single-blind controlled trial ● McGill University Health Centre/Research Institute of the McGill University Health Centre ● NCT05436795	● Inclusion Criteria: ○ Aged 18 years and above ○ All sexes and genders ○ Suspecting COVID-19 exposure ○ Symptomatic or asymptomatic for COVID-19 ○ Mental capacity to provide informed consent ○ Access to internet connectivity and digitally literate ○ Access to a smart device that can download and run the COVIDSmart CARE! App (e.g., Android tablet version 6 or higher). ● Exclusion Criteria: ○ Participants with serious mental health or clinical condition which limits their capacity to provide informed consent. ○ Those with apparent severe COVID-19 symptoms requiring urgent hospitalization (e.g., severe shortness of breath, impaired level of consciousness, etc.).	Device: Abbott Panbio rapid antigen self-tests COVID-19 self-testing will be performed using investigational Abbott Panbio rapid antigen self-test kits that require self-sampled nasal swabs. Other: COVIDSmart CARE! app Guided by the application that connects, educates, and communicates a digital, contactless open access strategy, participants will have the opportunity to self-test and assess their risk level of COVID-19 infection, as well as the option to refer their close contacts to testing for those who are COVID-19 positive, through the study platform.	Polymerase chain reaction (PCR) test	**Primary** ● Estimating the impact on turnaround time (TAT) from the point of taking a test to initiating a clinical action plan. Secondary ● The impact of the COVIDSmart CARE! self-testing strategy on the proportion of participants taking an appropriate COVID-19 related action compared to conventional COVID-19 testing strategies at 24 hours post randomization. ● Impact on detection of new COVID-19 infections in each arm.	**Active, not recruiting** **Study start**: July 2022 **Primary completion**: April 2023 **Study completion**: April 2023

ReSET Aim 1a: Restarting Safe Education and Testing for Children With Medical Complexity - Feasibility of In-home Cohort COVID-19 Testing Strategies, and Associations With CMC Parent Perceptions About In-person School Attendance [22] ● Open-label, single-center study ● University of Wisconsin, Madison ● NCT04895085	● Inclusion Criteria: ○ The caregiver is willing to comply with all study procedures and expects to be available for the duration of the study. ○ The caregiver is at least 18 years of age. ○ The caregiver is proficient in English. ○ The caregiver is self-identified as the primary caregiver (parent, foster parent, legal guardian) of a CMC who is aged 5-16 years at the start of the study and who is enrolled in the Pediatric Complex Care Program (PCCP) at the University of WI-Madison. ○ The caregiver is currently providing care on an ongoing basis to their CMC. The child may not be housed in a skilled nursing facility, an acute care or transitional facility, a rehabilitative hospital, a medical group home or in a foster home (unless the primary caregiver for the study is the foster parent). ○ The caregiver has access to a web-enabled device (phone, tablet, or computer). ○ Caregiver and child are residents of Wisconsin. ○ The child attended in-person school pre-pandemic. (Child can currently be attending school in-person, remotely or a hybrid combination). ○ The caregiver provides a written informed consent form. ● Exclusion Criteria: ○ Failure to meet all inclusion criteria. ○ The child is hospitalized at the time of enrollment (visit may be rescheduled) ○ Children not currently enrolled in public or private school and whose caregiver has no plan to enroll them in the Fall of 2021 (e.g., children currently homeschooling with plans to homeschool in the Fall of 2021 are ineligible).	BinaxNOW Rapid Antigen System	Polymerase chain reaction (PCR) test	●Change in Positive rate: Number of positive COVID-19 tests compared to total number of tests performed ●Change in False-positive rate: number of negative confirmatory Polymerase chain reaction (PCR) as compared to total PCR run for COVID-19 testing	**Enrolling by invitation** **Study start**: April 27, 2021 **Primary completion**: March 31, 2023 **Study completion**: March 31, 2023

Appendix 5: GRADE Evidence Profile

Should self-administered rapid antigen test be used to diagnose COVID-19 in symptomatic individuals?

Patient or population: Symptomatic individuals
Setting: Community
New test: Self-administered rapid antigen tests
Cut-off value: Not applicable
Pooled sensitivity: 0.77 (95% CI: 0.75 to 0.78)
Pooled specificity: -- (95% CI: -- to --)

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 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	10 studies (5,761 patients)	Cross-sectional (cohort type accuracy study)	serious a	not serious	not serious	not serious	none	39 (38 to 39)	77 (75 to 78)	154 (150 to 156)	⊕⊕⊕◯ Moderate
False negatives (patients incorrectly classified as not having COVID-19)											
True negatives (patients without COVID-19)	8 studies (5,761	Cross-sectional (coho	serious a	not serious	not serious	not serious	none	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	⊕⊕⊕◯ Moderate

False positives (patients incorrectly classified as having COVID-19)	patients)	rt type accuracy study)									

CI: confidence interval

Explanations

[a]Unclear issues in patient selection and conduct of index test and reference standard

Should self-administered rapid antigen test be used to diagnose COVID-19 in asymptomatic individuals?

Patient or population: asymptomatic individuals
Setting: Community
New test: Self-administered rapid antigen tests
Cut-off value: Not applicable
Pooled sensitivity: 0.56 (95% CI: 0.27 to 0.83)
Pooled specificity: -- (95% CI: -- to --)

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 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	5 studies (9,639	Cross-sectional (cohort type	seriousa	not serious	not serious	not serious	none	28 (14 to 42)	56 (27 to 83)	112 (54 to 166)	⊕⊕⊕◯ Moderate

False negatives (patients incorrectly classified as not having COVID-19)	patients)	accuracy study)						22 (8 to 36)	44 (17 to 33)	88 (34 to 146)	
True negatives (patients without COVID-19)	5 studies (9,639 patients)	Cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	⊕⊕⊕◯ Moderate
False positives (patients incorrectly classified as having COVID-19)								950 (950 to 950)	900 (900 to 900)	800 (800 to 800)	

CI: confidence interval

Explanations

[a]Unclear issues in patient selection and conduct of index test and reference standard