ARCHIVED VERSION (Status: 15 March 2022) Minimum Criteria for Rapid SARS-CoV-2 Antigen Tests Pursuant to Section 1 para 1 Sentence 1 TestVO (Statutory Test Regulation): Rapid Antigen Tests

Rapid antigen tests (also called point-of-care tests (POCTs) can be conducted outside a laboratory with a minimum of inconvenience for the patient and more rapidly than PCR (polymerase chain reaction) in 15-30 minutes. Thus, suitable SARS-CoV-2 POC antigen tests can play a role in situations, where results need to be available quickly, and in which the contagiousness of a person must be assessed rapidly on site.

Since the sensitivity of the current POC antigen tests is lower than that of the PCR/NAT by several orders of magnitude, they appear to be suitable for persons with a high viral load (range 10^6 virus genomes/mL of respiratory sample). This is the case in the pre-symptomatic phase (1-3 days before the beginning of the symptoms) and in the early symptomatic phase of the disease within the first 5-7 days, before the beginning of antibody development. POCTs can therefore contribute to the interruption of transmission by targeted isolation of infected persons and their close contacts. In persons who became infected longer than 7 days ago, a lower viral load and false negative results due to this are more likely in antigen tests[1].

Beside POCTs, antigen lab tests are available which require a laboratory infrastructure and the appropriate equipment. In general, based on their technology, they are more sensitive in detecting SARS-CoV-2 than POSTs and require less laboratory time than many PCR methods. Suitable antigen lab tests can thus also be considered as an alternative to PCR, particularly if there is a shortage of molecular biology test reagents.

Rapid antigen tests must fulfil the requirements (minimum requirements) set forth below:

The following minimum criteria apply to the areas of application intended within the TestVO:

(a) Performance indicators

The performance requirements for rapid antigen tests, for which a claim exists pursuant to Section 1 (1) sentence 1 TestVO, reflect the current “state of art and technology” (March 2022); the requirements will be adapted to any future changes in the state of art and technology. The adaptations will be announced in a timely manner.

At present, the minimum criteria for sensitivity and specificity (see below) are fulfilled by the SARS-CoV-2 antigen tests.

[1] http://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Vorl_Testung_nCoV.html

Prerequisites for estimating sensitivity

Limitations

(1) For the determination of analytical sensitivity there is a WHO International Standard for SARS-CoV-RNA avaible (20/146, NIBSC, UK). A respective international reference preparation for SARS-CoV-2 antigen is in preparation, but has yet not been established by WHO.

(2) Even though Ct values of PCR systems provide points of orientation for the underlying virus concentration, they are onlycomparable to a limited extent between different PCR methods, since the sample volume used in the extraction, the proportion of elution volume in the PCR assay, and the extraction, elution, and amplification efficiency may differ between various PCR protocols. The WHO International Standard as common reference preparation across tests enables the reporting of results in IU/ml.

Determination of the diagnostic sensitivity

Method: Parallel examination of diagnostic PCR tests and antigen tests in at least 100 persons with COVID-19 symptoms within seven days after onset of symptoms

Criterion antigen test: >80% of at least 100 unselected PCR-positive samples, positive in the SARS-CoV-2-rapid antigen test

For comparative PCR always from a throat swab (nasopharyngeal or oropharyngeal), the sample for the antigen test is taken according the respective instructions for use. An analysis should be performed of the correlation between the antigen-positive/PCR-positive and the antigen-negative/PCR-negative samples with the Ct values or IU/ml of the PCR. In addition, the PCR protocol should be described. The mean Ct value or IU/ml should be determined for the antigen- positive samples. In another evaluation, the detection rate of the antigen test (e.g. detection rate >90%) should be observed in relation to the ct value or IU/ml. However, it should again be noted that the Ct values vary between PCR tests in the case of a given concentration of the target RNA.

Specificity

Determination of the diagnostic specificity

Method: Examinations of at least 100 asymptomatic persons without a concrete risk of exposure in the rapid SARS-CoV2 antigen test; clarification of any reactive samples by means of PCR.

Criterion rapid antigen test: Specificity >97%

Cross-reactivity

Method: Examination of samples including those with a high concentration of related human coronaviruses (e.g. human coronavirus 229E, human coronavirus OC43, human coronavirus NL63, MERS coronavirus).

Mention of markers tested and indication of any cross-reactivities determined to be included in the package leaflet.

Interference

Method: Examinations should also be performed on pathogen-positive samples in which the pathogen can cause analogous symptoms (e.g. influenza A, B; RSV), or could interfere with the test principle (e.g. protein A-positive *Staphylococcus aureus* in the case of nasal swabs as sample matrix).

Mention of markers tested and indication of determined interferences to be included in the package leaflet.

(b) Details on the test design

The applicant must provide details on the specific SARS-CoV-2 proteins (antigens), which will be identified by the respective test. The appropriate data on the modes of action of the tests shall also be included in the package leaflet conforming to the specifications contained in the IVD Directive or the IVD Regulation.

When the respective antigen test detects the SARS-CoV-2 surface protein (“spike”), evidence must be provided that mutations of SARS-CoV-2, which lead to a variation in the spike antigen (e.g. the “UK variant”, “Omicron”) are reliably detected. Furthermore, for tests detecting the viral nucleoprotein details of the antibodies used within the test are to be provided (antibody type (e.g. monoclonal (number, clone no.) or polyclonal; antibody class; target epitope on the nucleoprotein; immunogens used; manufacturer of the antibodies, order no. or item no.).

(c) Availability of tests in Germany

The applicant must confirm that he will provide users in Germany with a number of POCTs appropriate in view of the infection situation. In addition, on request, 120 tests must be provided within two weeks for any comparative evaluations (see Section d).

(d) Results of comparative evaluations, if applicable

The performance data may be checked in a comparative evaluation by different institutions in Germany (e.g. Robert Koch-Institut; Paul-Ehrlich-Institut; reference lab for coronaviruses; Institute for Microbiology of the German Army (Bundeswehr)) using a common sample panel
.
If, on the basis of such a comparative evaluation, the RKI/Paul-Ehrlich-Institut concludes that a rapid SARS-CoV-2 antigen test does not meet the state of technology, the minimum criteria are not fulfilled.

There is no claim for inclusion into the comparative evaluation.

Sources
https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays

Scheiblauer H et al. Comparative sensitivity evaluation for 122 CE-marked rapid diagnostic tests for SARS-CoV-2 antigen, Germany, September 2020 to April 2021. Euro Surveill. 2021;26(44):pii=2100441.
https://doi.org/10.2807/1560-7917.ES.2021.26.44.2100441