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Swissnoso decision aid on diagnostic methods for detecting Covid-19 infection in acute care setting (v.2, 18 May 2021)

Introduction

After more than one year into the pandemic, several diagnostic methods are available for the detection of SARS-CoV-2 in symptomatic or asymptomatic individuals.[1] Detection of viral nucleic acid (via Polymerase Chain Reaction, PCR), viral antigen (Rapid Antigen Detection Test, RADT) or antibodies (blood serology) can be used to confirm infection, and chest computed tomography (CT) to identify Covid-19 disease manifestation. However, interpretation of test results is challenging and determining infectiousness is still a matter of debate. Several factors play a role, e.g. type, quality and timing of samples and diagnostic method, in relation to the disease course. Combining different diagnostic methods may help to improve diagnostic yield and guide further management.

PCR

Nucleic acid amplification testing via PCR (molecular testing) remains the gold standard for detecting or excluding SARS-CoV-2 infection in adequate respiratory tract samples or saliva. **Quantitative PCR tests** are increasingly available and very useful to determine CT value (indirect measure of viral load: lower CT values correspond to higher viral load). In general, CT values of >35 (very low viral load) indicate extremely low risk of infectiousness[2].

For confirmed positive samples, **further molecular testing** might be indicated (e.g. for the detection of significant SARS-CoV-2 variants, if suspected, via mutation-specific targeted PCR or via genome sequencing[3]). **Flow chart 1** provides an example[4] of a *decision aid on interpreting positive SARS-CoV-2 PCR results* in symptomatic vs. asymptomatic individuals that can be adjusted to the local setting.

Rapid antigen detection test (RADT)

Where rapid access to PCR testing is limited, RADTs may support swift decision-making on management and isolation of patients and healthcare workers (HCWs). The highest yield for RADTs is in symptomatic individuals/during the early infection phase. Whereas overall sensitivity and specificity of RADTs are lower compared to PCR tests, RADTs are more specific regarding infectiousness (i.e. a positive RADT usually detecting infectious individuals).

Clinicians need to be aware how pretest probability influences interpretation of results [1,5]: The risk of a false-negative RADT result is higher when population disease rates are high (due to the lower negative predictive value). Vice-versa, the risk of false-positive RADT results is higher when disease rates are low (lower positive predictive value).[6] Confirmatory PCR testing is recommended in case of doubtful results (already when taking a sample for the RADT, a second sample can be taken and sent off for routine PCR (SARS-CoV-2 confirmation) or further testing as required (e.g. respiratory pathogen panel for other pathogens or, testing for SARS-CoV-2 variants, if indicated). **Flow chart 2** ***Decision aid on the use of RADTs in acute care setting where rapid access to PCR testing is limited.***

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[1] Peeling RW, et al. Scaling up COVID-19 rapid antigen tests: promises and challenges. The Lancet Infectious Diseases. 2021 Feb 23. https://doi.org/10.1016/S1473-3099(21)00048-7

[2] Singanayagam et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. 2) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7427302/

[3] Upon decision by the cantonal physician (on case-by-case basis) https://www.bag.admin.ch/bag/de/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/information-fuer-die-aerzteschaft/covid-testung.html

[4] Adapted from HUG, Interprétation d'une RT-PCR SARS-CoV-2 positive, v1 26.2.21 https://www.hug.ch/sites/interhug/files/structures/coronavirus/documents/interpretation-rt-pcr-plus-35-milieu-hospitalier.pdf

[5] Estimated probability of disease before test is performed, based on a local prevalence, clinical likelihood, see also https://asm.org/Articles/2020/June/Why-Pretest-and-Posttest-Probability-Matter-in-the

[6] ECDC guidelines suggest high disease rates >10% vs. low <=2%. ECDC, 17 Nov 2020 https://www.ecdc.europa.eu/sites/default/files/documents/Options-use-of-rapid-antigen-tests-for-COVID-19_0.pdf

Antibody testing (serology)

Blood serology on its own cannot be safely used for diagnosing acute infection and interpretation is part of ongoing research[7]. However, in settings where SARS-CoV-2 serology is available, after an inconclusive PCR result the detection of antibodies may provide further evidence for recent or past infection. **Flow chart 1**

New approach to sample collection and larger group testing

Lately, several easier sampling techniques (e.g. nose swabs, saliva[8]), in addition to nasopharyngeal swabs have been validated for PCR and RADT to achieve broader testing for the fast detection and control of viral transmission in community[9] and hospitals. **Individual testing** is most common in patients with suspected Covid-19 infection on admission or, for routine admission screening. However, **mass testing** for larger groups of patients and HCWs is increasingly used, whether as part of outbreak investigations or repetitive screening (e.g. long-term stayers, ward staff when population case numbers are high), similar to community mass testing.

Sample **pooling** is mass testing, where specimens collected from several individuals are joined into one sample that will undergo PCR testing (provided that this method is validated at the local laboratory). It can be useful for testing larger groups of people, although only in low-prevalence setting, since after a positive signal, members of this group need subsequently be retested individually, to identify and manage the positive person(s).

Patients, HCWs, visitors

Testing may be carried out in ambulatory vs. acute care patients (symptomatic or asymptomatic), in HCWs following exposure to Covid-19 cases or as part of repetitive screening, and even be considered for visitors- although benefit and feasibility might be limited. An *overview of COVID-19 testing in acute healthcare setting - symptomatic individuals* is provided for different groups and settings in **Table 1** (**symptomatic** individuals) and **Table 2** (**asymptomatic** individuals).

Fully vaccinated persons (or temporary immunity following infection)

Definitions[10] for *fully vaccinated/temporary immunity* change over time, as more data on duration of immunity after either vaccination or infection become available. **Individuals with symptoms compatible with Covid-19 infection** who are fully vaccinated and/or recovered from a confirmed Covid-19 infection should continue to be clinically evaluated and tested accordingly. Protection following vaccination or disease appears to last in most cases for at least six months,[11] but might be undermined by newer variants potentially escaping the immune response (SARS-CoV-2 with gene mutations classified as variants of concern, VOCs).

Asymptomatic, fully vaccinated HCWs following exposure to a confirmed Covid-19 case may continue working under strict adherence to hygiene measures (→see Swissnoso recommendations[12]). Until more robust data will be available it might be cautions to consider **asymptomatic, fully vaccinated patients** for quarantine and testing following an exposure, and routine screening (e.g. admission or repetitive screening) where in place and depending on local guidelines. All individuals even with a negative test result should strictly adhere to general hygiene and distancing measures.

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[7] Antibody tests to diagnose acute Covid-19 infection not yet fully validated for routine clinical use; a variety of methods are under development (e.g. capillary blood test).
[8] Evaluation in Switzerland: CHUV https://www.medrxiv.org/content/10.1101/2020.12.01.20241778v1; and Zurich, https://www.medrxiv.org/content/10.1101/2020.11.23.20237057v1
[9] FOPH Covid-19 testing strategy, see https://www.bag.admin.ch/bag/de/home/medizin-und-forschung/heilmittel/covid-testung.html#-1047800939
[10] According to FOPH definition: Side effects questions, last updated on 22.04.2021, accessible under https://foph-coronavirus.ch/vaccination/side-effects-questions/#contents3
[11] See ECDC statement from 29 Mar 2021 https://www.ecdc.europa.eu/en/news-events/ecdc-report-examines-sars-cov-2-transmission-risk-vaccinated-previously-infected-individuals
[12] Swissnoso Recommendations for healthcare workers, having had unprotected close contact with COVID-19 cases, under https://www.swissnoso.ch/forschung-entwicklung/aktuelle-ereignisse

Table 1 ***Overview of COVID-19 testing in acute healthcare setting - symptomatic individuals (see above notes on fully vaccinated persons)***

Purpose of testing • rapid triage (COVID 19 cohort, non-Covid wards) • rapid decision about maintaining or abandoning isolation precaution measures		
Group to test	**Setting**	**Symptomatic individuals = high likelihood**
Patients	Ambulatory, outpatient	**Testing imperative** **Preferred diagnostic method:** • PCR testing (nasopharyngeal, oropharyngeal or saliva) **Alternative diagnostic method** • Rapid antigen test (RADT) if PCR unavailable or results are markedly delayed, and if onset of symptoms was within the last 5 days (Note: in order to rule out false-negative RADT result confirm all negatives via routine PCR) **Flow chart 2** **Additional diagnostic method** • More severe cases and indeterminate laboratory results: thoracic Computed Tomography scanning to detect Covid-19 disease manifestation
	On admission	
	hospitalized	
Health-care worker	Covid ward/ "high-risk-exposure" (known Covid-19 contact)	**Testing imperative** **Preferred diagnostic method:** • PCR testing (nasopharyngeal or oropharyngeal swab or saliva) **Alternative diagnostic method** • Antigen test from nasopharyngeal swab (or nasal swab) if PCR unavailable or results are markedly delayed, and if onset of symptoms was within the last 5 days. (Note: in order to rule out false-negative RADT result confirm all negatives via routine PCR) **Flow chart 2**
	Non-covid ward or "low-risk exposure"	
Visitors	Any setting	Advised not to visit the hospital if symptomatic (follow FOPH rules for quarantine and isolation)

Table 2 ***Overview of COVID-19 testing in acute healthcare setting - asymptomatic individuals (see above notes on fully vaccinated persons)***

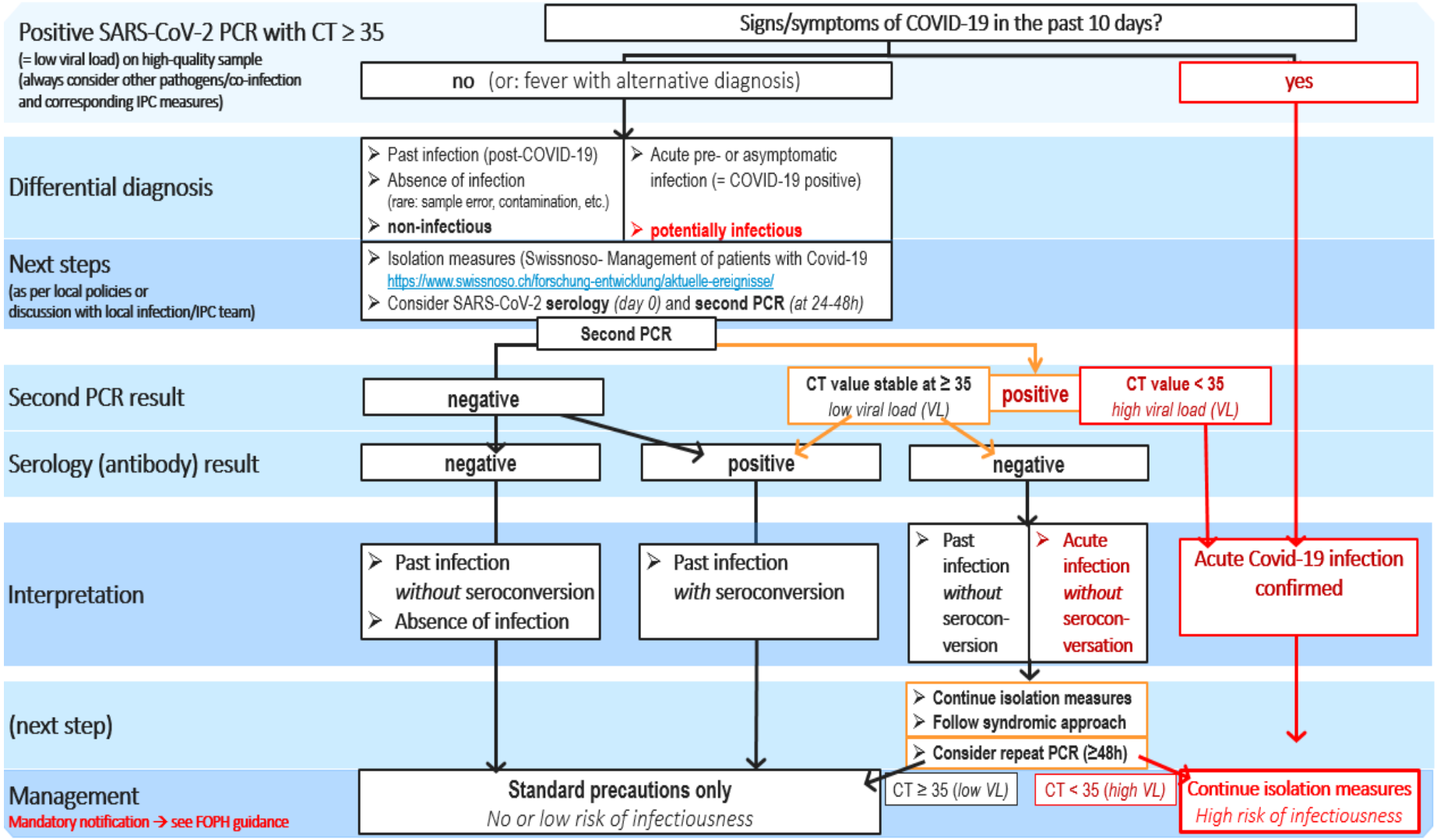
Purpose of testing • Complementary to excellent adherence to standard and transmission-based precaution measures, to reduce risk of hospital-based transmission • Potentially detecting/preventing silent transmission among patients and HCW on general wards		
Group to test	**Setting**	**Asymptomatic = low to moderate likelihood**
Patients	Ambulatory/outpatient	• Not recommended
	On admission	• Local epidemiology: Not recommended in low prevalence settings; consider in medium or high prevalence settings • Recommended if known unprotected exposure to positive case(s) https://www.bag.admin.ch/bag/de/home/medizin-und-forschung/heilmittel/covid-testung.html#-1047800939

	Hospitalized	• Local epidemiology: consider in medium or high prevalence settings
		• Consider in specific populations (without significant exposure; hospitalized for other reasons)
		• Investigation of a healthcare-associated COVID-19 outbreak
		• Consider repetitive testing for the following situations, e.g.:
		  ○ Expected long-term stay patients
		  ○ for volunteers (at least 1x/week) by pooled PCR or RADT according to the federal strategy https://www.bag.admin.ch/bag/de/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/testen.html#-1395414004
		  Could avoid staff quarantines if ≥ 80% of participation https://www.bag.admin.ch/dam/bag/de/dokumente/mt/k-und-i/aktuelle-ausbrueche-pandemien/2019-nCoV/faktenblatt-kostenuebernahme-dez-2020.pdf.download.pdf/faktenblatt-kostenuebernahme-dez-2020.pdf
		Preferred diagnostic method:
		• **Rapid PCR** (nasopharyngeal, oropharyngeal or saliva)
		Alternative diagnostic method
		• Antigen test if PCR unavailable (**Flow chart 2)**

Health-care worker	Covid ward/ "high-risk-exposure" (known Covid-19 contact)	• Local epidemiology: consider in medium or high prevalence settings
		• Consider repetitive testing (at least once a week) for:
		  ○ Volunteers by (pooled) PCR ideally from saliva or RADT (ideally a nasal swab) according to the federal strategy
		  Remark: Could avoid staff quarantine if ≥ 80% of participation (see above)
		Preferred diagnostic method:
		• PCR on nose or saliva samples preferred because of discomfort of repetitive nasopharyngeal swabs and possibility of pooling (saliva).
		• Beware of HCWs with positive PCR due to viral RNA remnants with absence of infectiousness
		Alternative diagnostic method
		• Antigen test if PCR unavailable or results are markedly delayed **(Flow chart 2)**

	Non-covid ward or "low-risk exposure"	
Visitors		Consider in medium or high prevalence settings (disease rates > 2 %)[5] • In the 24 hours before visit by PCR or RADT. • Naso-pharyngeal swab for RADT, saliva or naso-pharyngeal swab for PCR. • See Swissnoso algorithm for the interpretation of RADT according to pre-test probability

Flow chart 1 *Decision aid on interpreting positive SARS-CoV-2 PCR with CT ≥ 35 (low viral load) in acute care [adapted from HUG[4]]*



Flow chart 2 *Decision aid on indication, use and interpretation of RADTs in acute care setting where rapid access to PCR testing is limited.*

	low clinical risk			medium clinical risk		high clinical risk	
Patients *Examples:*	No Covid-19 compatible signs/symptoms; Routine admission screening or, repetitive screening (long-term stay)			Signs/symptoms *might* suggest Covid-19 **but** alternative diagnosis likely; Investigation of healthcare-assoc.outbreak		**Covid-compatible signs/symptoms ≤5d; Known unprotected exposure to positive Covid-19 case(s)**	
HCWs *Examples:*	Routine / repetitive staff screening			As part of outbreak screening (lower exposure risk)		**Close contact/household exposure; monitoring during 'work-quarantine'**	
Local positivity rate* < 2%	unlikely			possible		possible	
Local positivity rate 2-10%	possible	*likelihood matrix*		possible	*likelihood matrix*	**probable**	
Local positivity rate >10%	possible			**probable**		**probable**	
Likelihood SARS-CoV-2 (from *likelihood matrix* above)	unlikely			possible		**probable**	
SARS-CoV-2 RADT test result (nasal/NP swab)	**negative**	**indet.**	**positive**	**negative** (or indeterminate)	**positive**	**negative** (or indeterminate)	**positive**
Interpretation Positive or negative predictive values	**Covid-19 infection excluded** High NPV: false-neg result unlikely	Covid-19 infection not excluded low PPV (false-positive result) or, low NPV (false-negativ result possible), respectively					**Covid-19 infection confirmed** High PPV: false-pos. result unlikely
Further testing...consider other pathogens/co-infection & corresponding IPC measures	**Consider PCR-testing (if doubtful result)**	SARS-CoV-2 PCR Testing					**If indicated: consider targeted PCR/genome sequencing to test for virus mutations ****
Management	**Mandatory notification**	**Await PCR results**					**Mandatory notification**
	Isolate patient until asymptomatic for >24h	**If symptomatic: follow isolation precautions (local guidelines) until further results available**					**Continue isolation measures**
	HCW may go to work						**HCW to stay home**

FOPH links to a) list of compatible symptoms https://bag-coronavirus.ch/check/ and b) RADTs meeting FOPH recommendations, see under also https://www.bag.admin.ch/dam/bag/de/dokumente/mt/msys/covid-19-verdachts-meldekriterien.pdf.download.pdf/Verdachts_Beprobungs_und_Meldekriterien.pdf and under https://www.bag.admin.ch/bag/de/home/medizin-und-forschung/heilmittel/covid-testung.html#-1047800939
RADT sensitivity highest if symptom onset ≤ 5 days, as per ECDC, 17 Nov 2020 https://www.ecdc.europa.eu/sites/default/files/documents/Options-use-of-rapid-antigen-tests-for-COVID-19_0.pdf
*** Estimate for local Covid-19 population prevalence rates, see FOPH dashboard, share of positive tests (%), per canton, under https://www.covid19.admin.ch/en/epidemiologic/test**
**Upon decision by the cantonal physician (on case-by-case basis): https://www.bag.admin.ch/bag/de/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/information-fuer-die-aerzteschaft/covid-testung.html
Already when sampling for RADT: Consider taking second sample to send for routine PCR (SARS-CoV-2 ± respiratory pathogen panel ± sequencing) for confirmation or, if other cause/new variant suspected