

The selection and use of essential in vitro diagnostics

Report of the fourth meeting of the WHO Strategic Advisory Group of
Experts on In Vitro Diagnostics, 2022
(including the fourth WHO model list of essential in vitro diagnostics)



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**World Health
Organization**

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Abbreviations and acronyms

ACS	acute coronary syndrome
AKI	acute kidney injury
AMI	acute myocardial infarction
AMR	antimicrobial resistance
BG	blood glucose
BMD	bone mineral density
BUN	blood urea nitrogen
CAH	congenital adrenal hyperplasia
CDC	United States Centers for Disease Control and Prevention
CI	confidence interval
CKD	chronic kidney disease
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
cTn	cardiac troponin
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DTA	diagnostic test accuracy
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
EDL	WHO model list of essential in vitro diagnostics
eEDL	electronic EDL
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EML	WHO essential medicines list
ESC	European Society of Cardiology
EU	European Union

EV	enterovirus
FDA	U.S. Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FMH	fetomaternal haemorrhage
G6PD	glucose-6-phosphate dehydrogenase
GBD	Global Burden of Disease Study
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GTB	WHO Global Tuberculosis Programme
HbA1c	glycated haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HHV-6	human herpes virus-6
hs-cTnI	high-sensitivity troponin I
HSV	herpes simplex virus
ICER	incremental cost-effectiveness ratios
ICM	International Confederation of Midwives
ICU	intensive care unit
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon-gamma release assay
IQR	interquartile range
IVD	in vitro diagnostics
KB test	Kleihauer-Betke acid-elution test
LAMP	loop-mediated isothermal amplification
LF-LAM	lateral flow lipoarabinomannan
LMICs	low- and middle-income countries
LOS	length of stay
MD	mean difference

ME	meningitis and encephalitis
mPCR	multiplex polymerase chain reaction
NAAT	nucleic acid amplification test
NAT	nucleic acid test
NEDL	national essential in vitro diagnostics list
NGO	nongovernmental organization
NICE	National Institute for Health and Care Excellence, United Kingdom
NPV	negative predictive value
NSTEMI	non-ST-segment elevation myocardial infarction
PCR	polymerase chain reaction
PHPT	primary hyperparathyroidism
POC	point-of-care
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTH	parathyroid hormone
QALY	quality-adjusted life-year
qPCR	quantitative polymerase chain reaction
RDT	rapid diagnostic test
Rh	Rhesus factor
Rh(D)	Rhesus-D protein
RT-PCR	reverse transcriptase-polymerase chain reaction
SAGE IVD	Strategic Advisory Group of Experts on In Vitro Diagnostics
17-OHP	17-hydroxyprogesterone
SMBG	self-monitoring of blood glucose
SOC	standard of care
sPVS	selective parathyroid venous sampling
T1D	type 1 diabetes
TAT	turnaround time

TB	tuberculosis
TBST	<i>Mycobacterium tuberculosis</i> antigen-based skin test
TST	tuberculin skin test
URL	upper reference limit
VZV	varicella-zoster virus
WHO	World Health Organization
YLL	years of life lost

Management of conflicts of interest

Management of conflicts of interest is a priority in preparing the WHO model list of essential in vitro diagnostics (WHO EDL) and in establishing the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD).

Before participating in activities related to the fourth meeting of the WHO SAGE IVD (4th SAGE IVD meeting), all 2021 SAGE IVD members and consultants completed a declaration of interest form. After analysing each declaration, the WHO EDL Secretariat assisted by the WHO Office of Compliance, Risk Management and Ethics concluded that there were no significant conflicts of interest that would exclude any member from fully participating in the expert meeting.

More information about the declaration of interest for experts serving in an advisory role for WHO can be found on the WHO Office of Compliance, Risk Management and Ethics website: <https://www.who.int/about/ethics/#declarations> (accessed 8 April 2023).

Introduction

The 4th SAGE IVD meeting was held 14–18 November 2022 in a virtual format. On the first day of the meeting the WHO EDL Secretariat organized an open webinar session with the participation of worldwide laboratory medicine professionals and nongovernmental organizations (NGOs), and representatives of WHO regional offices, country offices and headquarters. In the subsequent days SAGE IVD members held closed discussions on the applications received for the fourth WHO model list of essential in vitro diagnostics (EDL 4) as well as on the way forward for the EDL and its role in increasing availability, access and proper use of IVDs. Dario Trapani (SAGE IVD member) chaired the closed sessions of the meeting.

This report includes the EDL 4 applications and provides a summary of SAGE IVD's deliberations, decisions and recommendations. EDL 4 is provided in section 5 of this report.

1. The EDL structure and review process

The EDL is a health policy document, based on scientific evidence, consisting of a list of categories of IVD tests and recommendations for using those tests in relation to the assay format, test purpose, specimen type and health care setting.

EDL 4 lists IVD tests that are recommended by WHO for use in countries to improve access to IVD testing. The list is not intended to be prescriptive with respect to the specific tests nor the level of the health care system at which IVDs can or should be used. Rather, the list aims to serve as a reference to guide development of or to update a national EDL (NEDL) at the country level within the framework of universal health coverage. In all cases, countries are expected to decide for themselves which IVD tests to select and where to use them depending on their local context, needs and priorities.

1.1 Objective

The EDL was developed to provide evidence-based guidance to countries for creating or updating their NEDLs and to guide policy on access to clinical laboratory services and IVD testing (1). It can be used by countries to prioritize the IVDs that should be available at different levels of the health care system and to support them in allocating often scarce resources to essential IVDs for ensuring a healthier population.

The EDL can also be informative for United Nations agencies and NGOs that support the selection, procurement, supply, donation and provision of IVDs as well as for the private health technology and manufacturing sectors, so that they focus on the IVDs necessary to address global health issues (2).

1.2 Scope

The EDL includes general and disease-specific IVDs for noncommunicable diseases and infectious diseases. The EDL does not list branded products but rather categories of IVD tests.

1.3 Structure

EDL 4 is organized in two tiers based on levels of care within the health system:

- I. Community settings and health facilities without laboratories
- II. Health care facilities with clinical laboratories

Each tier includes a section for general IVD tests that can be used for routine patient care as well as for detection and diagnosis of various diseases and conditions, and a section for disease-specific IVDs. In addition, tier II includes

a section for disease-specific IVD tests recommended to screen blood for transfusion purposes.

EDL 4 also includes a special section titled Do Not Do recommendations, which lists IVD tests recommended for discontinuation based either on evidence of harm or lack of benefit.

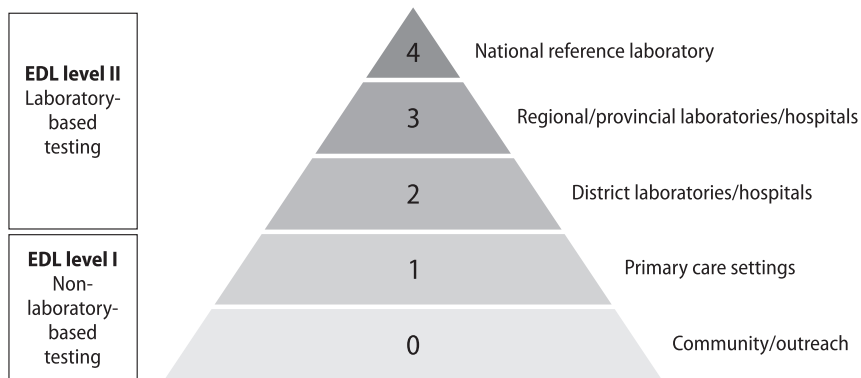
1.4 Recommended use

To use the EDL effectively and to adapt it for national requirements, Member States should consider factors such as local demographics, burden of disease, disease elimination priorities, availability of treatments (i.e. the NEDL should complement the national EML if available), training and experience of personnel, local unmet testing needs and gaps, supply chain, cost of IVDs, and of reagents and supplies, quality assurance capacity, financial resources, information technology capability and environmental factors.

EDL 4 should not be used in isolation but within the scope of integrated clinical laboratory testing services that meet the clinical needs and expectations of each country through its laboratory networks. Fig. 1 shows an example of a tiered health care delivery and laboratory network in a resource-limited country (1). The two first levels of the pyramid reflect testing at the community level and at primary care facilities, which serve most patients directly. Next, a smaller number of centralized facilities serve fewer patients directly. National reference laboratories and some provincial laboratories may not serve patients directly or may offer broad specialist consultation and serve as referral centres for quality assurance and training or for complex testing of samples sent either by facilities lower down the system and transported or from patients referred from other facilities. Other factors that determine use of IVDs are access to electricity, reagent-grade water and specialized human resources (3).

The two tiers of the EDL (I. Community settings and health facilities without laboratories and II. Health care facilities with clinical laboratories) are shown in levels 0 and 1 and levels 2, 3 and 4 in Fig. 1, respectively.

Fig. 1
Illustrative example of tiered testing services for use of IVDs



EDL: WHO model list of essential in vitro diagnostics; IVDs: in vitro diagnostics.
 Source: adapted from (1).

1.5 Methods used to develop EDL 4

From a review of several WHO publications (4, 5, 6, 7), past SAGE IVD recommendations (8, 9), published work on IVDs for the medicines listed in the WHO EML (10) and requests from WHO technical experts, the WHO EDL Secretariat identified 71 candidate tests to inform the EDL 4 call for applications. Additional discussions took place, and SAGE IVD reached consensus on the following 23 tests, which were identified as high priority:

- therapeutic drug monitoring, amikacin
- therapeutic drug monitoring, gentamicin
- therapeutic drug monitoring, phenytoin
- therapeutic drug monitoring, lithium
- therapeutic drug monitoring, methotrexate
- nucleic acid testing, *Neisseria meningitidis*
- antigen test, *Entamoeba*
- total testosterone
- protein electrophoresis (in serum and urine)
- immunofixation electrophoresis
- free light-chain test (in serum)
- immunoglobulin M (IgM) antibodies against scrub typhus
- IgM antibodies against *Leptospira*

- serology, yellow fever
- nucleic acid testing, diphtheria
- IVDs for *Bordetella pertussis*
- IVDs for poliovirus
- IVDs for rotavirus
- lead
- hepatitis delta (rapid diagnostic tests (RDTs), enzyme immunoassays (EIA) and RNA polymerase chain reaction (PCR))
- hepatitis E (RDTs, EIA and RNA PCR)
- 17-hydroxyprogesterone
- parathyroid hormone.

The call for applications was opened from January to July 2022. Although the WHO EDL Secretariat especially invited applications for the 23 high-priority tests, the Secretariat also welcomed applications for tests not mentioned in the high-priority list.

Applications to the EDL can be submitted by any stakeholder, including Member States, academics, professional organizations, NGOs, companies in the IVD industry and WHO personnel from headquarters, and regional or country offices.

There are five types of applications:

- addition of new IVDs
- Do Not Do recommendations
- edits
- additional evidence in support of IVDs conditionally listed
- delisting.

For the addition of new IVD tests and for the Do Not Do recommendations, the application process proceeded in two phases. The first phase consisted of a presubmission in which applicants were required to submit information to allow the WHO EDL Secretariat, in collaboration with WHO technical experts, to determine the suitability of the application. Accepted presubmissions then moved towards the second phase, which consisted of submitting a full application form and the relevant supporting evidence, such as systematic reviews, peer-reviewed publications or clinical guidelines from expert bodies.

Other types of applications involved a single-phase submission process that also required applicants to provide relevant supporting evidence.

All the applications were reviewed by the WHO EDL Secretariat and WHO technical experts (when appropriate) for completeness of information before being shared with the 2021 SAGE IVD members and the methodologists. The review process by SAGE IVD started in August 2022 and was finalized in October 2022. Each application was reviewed by two experts from SAGE IVD and by one expert methodologist. All applications as well as the reviews carried out by SAGE IVD members and the methodologists were published online on 28 September 2022 for 3 weeks for public review and comment.

Due to some restrictions associated with the coronavirus disease 2019 (COVID-19) pandemic still in place in 2022 at WHO headquarters, the 4th SAGE IVD meeting was planned as a virtual meeting. The remote process developed for the 3rd SAGE IVD meeting in 2020 was updated and used to allow the experts to deliberate on EDL 4 applications before and during the 4th SAGE IVD meeting, which was held from 14 to 18 November 2022. Further details on the 2022 remote process for deliberations are provided in section 1.5.3.

To find out more about the EDL process, please consult *Selection of essential in vitro diagnostics at country level: using the WHO Model List of Essential In Vitro Diagnostics to develop and update a national list of essential in vitro diagnostics* (11).

1.5.1 SAGE IVD

SAGE IVD is the advisory body on matters of global policy and strategy related to IVDs, including advising WHO on the tests to be included in the EDL (1, 12). SAGE IVD members serve in their personal capacities and represent the broad range of disciplines required to advise on the many aspects of IVDs and other clinical laboratory-related activities. WHO organizes periodic calls for applications to become a SAGE IVD member and maintains a roster of experts on IVDs to support the selection of SAGE IVD members. The names and profiles of 2021–2023 SAGE IVD members involved in reviewing EDL 4 applications are available here: <https://www.who.int/groups/who-strategic-advisory-group-of-experts-on-in-vitro-diagnostics> (accessed 14 April 2023).

1.5.2 EDL 4 electronic application portal

Applications for EDL 4 were managed through a web-based application portal. Applicants received an individual access key and secret code to log in to the electronic portal to prepare and submit their applications. When technical issues prevented applicants from completing their applications in the electronic portal, the applications were submitted through the WHO EDL Secretariat email account using a word processor-based application form. The content of the electronic application form and the word processor-based application form was the same.

1.5.3 Remote process to support the selection of IVDs

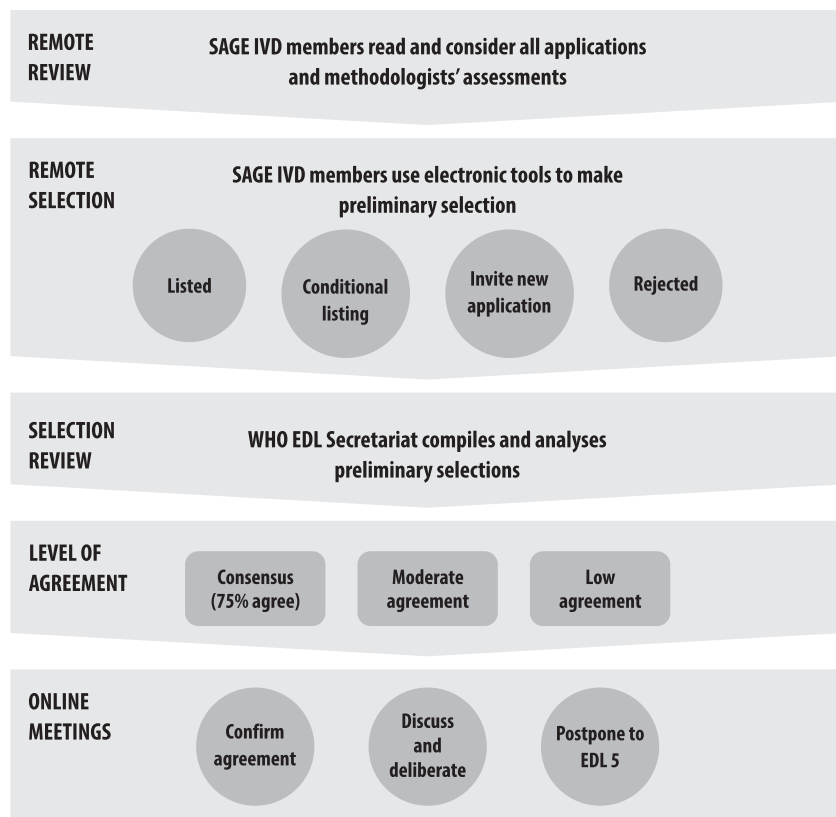
The 2022 remote process is based on the 2020 remote process (8) for deliberations. The aim of the remote process is to provide continuity to the EDL and the work of SAGE IVD without compromising the quality of the decision-making process by having a defined methodology to support the review of EDL 4 applications and the selection of IVDs to be included in the list.

SAGE IVD members received working documents through the EDL application portal, a cloud-based file-sharing application and email. Dedicated electronic tools were developed to support the remote selection process. The process used a combination of remote individual selection and online group deliberations to reach consensus on all applications (Fig. 2).

SAGE IVD members were first asked to review all the information that would have been presented during the face-to-face meeting and used a standard electronic selection table to make their preliminary individual selection. Each IVD test considered in the EDL 4 applications was classified as follows:

1. Listed in EDL 4 because the application contains convincing evidence that the submitted IVD test is accurate, clinically useful and accessible.
2. Conditionally listed in EDL 4 because the evidence around certain aspects or uses of the tests is lacking in the application but available; hence, listing the IVD test is contingent on the provision of this additional evidence.
3. Not listed in EDL 4 because while the IVD test is acknowledged to be useful, the evidence in the application is insufficient to recommend its inclusion in the list; a new submission could be relevant for EDL 5.
4. Not considered further because there is not enough evidence on the test's performance or utility or because there is evidence of lack of utility, poor performance or harm.

Fig. 2
Remote process for SAGE IVD decision-making



EDL: WHO model list of essential in vitro diagnostics; SAGE IVD: Strategic Advisory Group of Experts on In Vitro Diagnostics.

In each case, SAGE IVD members were asked to provide a rationale for their selection, including any recommended changes to the proposed wording for the IVD test name, test purpose, assay format and specimen type. Once all individual selection tables were received, the WHO EDL Secretariat analysed them to establish which applications had consensus (75% of agreement among SAGE IVD members on selection).

For all IVD tests that achieved consensus for listing, the discussion during the online meetings was limited to agreeing on the specific wording for the test name, test purpose, assay format, specimen type and health care facility level. The remaining tests were fully discussed by SAGE IVD members during the online meetings, with input from the methodologists and WHO technical experts (when relevant or appropriate).

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2. EDL 4 applications

In total, the WHO EDL Secretariat received 12 applications: nine applications were to add new IVD test categories, two proposed edits of IVDs listed in EDL 3, and one application involved including a Do Not Do recommendation.

2.1 Applications for adding new IVD tests

2.1.1 17-Hydroxyprogesterone

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

The application proposed adding a 17-hydroxyprogesterone immunoassay (17-OHP) test to the EDL as an IVD to diagnose and monitor congenital adrenal hyperplasia (CAH).

B. Applicant

International Federation of Biomedical Laboratory Science

C. WHO technical department

None

D. Background (from application)

Disease condition and impact on patients

CAH due to 21-hydroxylase deficiency is a potentially life-threatening congenital disorder with significant mortality/morbidity if not promptly diagnosed, with treatment initiated at birth. Presentations vary from neonatal salt wasting (with atypical genitalia in girls) to failure to thrive. The disease is characterized by impaired cortisol and aldosterone production and by androgen excess. The disorder is challenging to diagnose and treat due to the complex direct and indirect effects of steroids on physiology. CAH is an autosomal recessive disorder. There is a nonclassical form of the disease which is milder and may form part of the etiology of the hirsutism polycystic ovary spectrum of disorders. While 17-OHP estimation can be diagnostic in the classical form, it is part of the investigative pathway for the nonclassical form. This application is confined to the classical form of CAH.

Does the test meet a medical need?

Determining blood levels of 17-OHP is required to diagnose and to monitor treatment of CAH. 17-OHP is also useful for newborn screening for CAH. However, because of the high false-positive rate of immunoassay methods in the neonatal period, a second-tier test by liquid chromatography-tandem mass spectrometry is recommended (1).

How the test is used

Blood spot testing can be used as part of a newborn screening programme. Ideally, neonates should not be tested before 48 hours of age due to cross-reacting substances. The test is also used to monitor CAH treatment and for follow-up.

E. Public health relevance (from application)***Prevalence***

For the classical form of CAH, analysis of data from almost 6.5 million newborns screened in different populations worldwide has demonstrated an overall incidence of 1:15 000 live births. The prevalence in specific populations has been reported to be 1:300 in the Yupik Eskimos of Alaska, 1:5000 in Saudi Arabia, 1:10 000–1:16 000 in Europe and North America, 1:21 000 in Japan and 1:23 000 in New Zealand (1).

Socioeconomic impact

Not provided

F. WHO or other clinical guidelines relevant to the test (from application)

Readers may refer to the Endocrine Society's clinical practice guideline (2) for full details on recommendations.

G. Basic test characteristics (from application)

Test formats available	Immunoassay
Specimen types	Serum, plasma
Equipment required	Automated analyser
Regulatory status	CE-marked and FDA-approved
Availability	Global
Price per test range	None provided
Instrument price range	None provided

H. Evidence for diagnostic accuracy (from application)

Not provided.

I. Evidence for clinical utility/impact (from application)

Not provided.

J. Evidence for economic impact and/or cost-effectiveness (from application)

Not provided.

K. Ethics, equity and human rights issues (from application)

The prevalence of CAH varies, being particularly high in certain Jewish populations in North America. Interpreting 17-OHP test results requires expertise. This is an inherent inequity where that expertise is not readily available. Lack of early diagnosis leads to increased morbidity and mortality of affected individuals.

No specific ethical issues were identified.

L. Summary of evidence evaluation

CAH is a rare health problem, but it can be life-threatening if not diagnosed in a timely manner. The 17-OHP immunoassay has been developed for diagnosing this condition. In a clinical guideline, the assay is recommended for screening in newborns, and several countries have implemented this as part of their screening programme. However, the originator of this application provided no evidence (i.e. no systematic reviews, no primary studies) relating to diagnostic accuracy or clinical utility. Furthermore, the costs are unclear, and it is also unclear how this assay relates to other diagnostic tests.

M. Summary of SAGE IVD deliberations

The 17-OHP assay is intended to diagnose CAH.

SAGE IVD members noted that the evidence for the use of the test in different settings was not well defined in this application. For example, 17-OHP is appropriate for diagnosing CAH outside of the neonatal period as well as other adrenal and ovarian issues in older persons. Moreover, some experts questioned whether the test was intended for screening or for diagnosis.

One expert explained that this test is used to support the diagnosis of CAH outside of the neonatal period, to monitor CAH therapy, and to assess and manage hirsutism and infertility.

The group noted that WHO and the United Nations Children's Fund have referred to the unreliability of the test for screening for a range of pregnancy conditions. One member highlighted that using 17-OHP to screen in a neonatal

setup generates 1–2% false positives in the best case, making it unfeasible. And for neonatal screening, spectroscopy or high-performance chromatography are the preferred modalities in any event.

SAGE IVD acknowledged the limited evidence for the test within this application. However, the group saw value in this test.

The experts acknowledged that using 17-OHP to diagnose CAH is appropriate and important for patients. Consequently, SAGE IVD decided to list the 17-OHP assay specifically to diagnose CAH outside of the neonatal period, but not to screen for it.

N. SAGE IVD recommendations

SAGE IVD recommended listing the 17-hydroxyprogesterone (17-OHP) test category in EDL 4

- as a disease-specific IVD for use in clinical laboratories (EDL 4, Section II.b);
- using an immunoassay format;
- using serum and plasma as specimen types;
- to diagnose and monitor congenital adrenal hyperplasia (CAH) outside of the neonatal period.

SAGE IVD also recommended including a note to the EDL table stating that the test is not appropriate for screening.

O. References (from application)

1. Nimkarn S, Gangishetti PK, Yau M, New MI. 21-Hydroxylase-deficient congenital adrenal hyperplasia. 2002 Feb 26 [Updated 2016 Feb 4]. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW et al., editors. GeneReviews [website]. Seattle (WA): University of Washington; 1993–2023 (<https://www.ncbi.nlm.nih.gov/books/NBK1171/>, accessed 5 April 2023).
2. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2018;103(11):4043–88 (<https://doi.org/10.1210/jc.2018-01865>, accessed 1 August 2023).

2.1.2 ABO blood groups and Rhesus factor typing point-of-care test

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

The application proposed adding an ABO blood grouping and Rhesus (Rh) factor typing point-of-care (POC) dry format card test to the EDL as an IVD to determine ABO groups and Rh factor.

B. Applicant

ELDON Biologicals A/S

C. WHO technical department

None

D. Background (from application)

Disease condition and impact on patients

The proposed test intends to reduce the burden of Rh haemolytic disease of the fetus and newborn and complications of the disease, and expand access to blood products in settings with limited access to laboratory services.

Rh isoimmunization of fetus or newborn (also referred as Rh haemolytic disease or erythroblastosis fetalis) is caused by the passage of anti-Rh (anti-D) antibodies from an Rh-negative mother to her Rh-positive fetus, and results in stillbirths, neonatal deaths and brain damage due to severe hyperbilirubinaemia. At birth infants may have anaemia, hydrops fetalis, jaundice and hepatosplenomegaly.

Anti-Rh antibody development is caused by the entry of fetal Rh-positive red blood cells into the maternal circulation. It occurs in about 15% of pregnancies in which the fetus is Rh positive and the mother is Rh negative (1). Anti-Rh antibodies usually develop in the mother after birth, meaning that her first baby is typically not affected by Rh disease. However, in subsequent pregnancies, if the fetus is Rh-positive, the baby could be affected.

A series reported in the 1970s, when adequate prevention and management were not available, indicates that without treatment these pregnancies result in stillbirths (13%), neonatal deaths (25%) or severe hyperbilirubinaemia (25%), which can develop into irreversible brain damage (kernicterus) in 25% of cases but requires treatment in 33% of cases (2). Even

after therapy, which includes exchange transfusion, many surviving infants are at risk of permanent hearing loss.

Usually identified on antenatal screening tests, Rh disease is now uncommon in high-income countries (3). Administration of Rh immunoglobulin to the Rh-negative mother postpartum and during pregnancy is very effective in disease prevention (4).

When studying the gap between annual doses of anti-Rh(D) given and the annual doses required, it has been concluded that the highest priority is met only in high-income countries and countries such as Brazil, Czechia, Croatia, Greece, Hungary, the Islamic Republic of Iran, Lithuania, Malaysia, Saudi Arabia, Sri Lanka, the Republic of Korea, Thailand, Türkiye and Uruguay (4).

Treatment of a baby with Rh disease includes exchange blood transfusions, phototherapy and fetal transfusion. Prevention is preferable to avoid severe morbidity and mortality, as well as the cost and complications of therapy (3).

ABO haemolytic disease occurs when the mother's blood type is O and the infant's blood type is A or B. Maternal anti-A or anti-B immunoglobulins can cross the placenta and cause haemolysis in the infant. ABO is more frequent than Rh haemolytic disease; however, when promptly identified, ABO haemolytic disease is less likely to require exchange transfusion, or to cause brain damage or death than is Rh disease. Haemolysis with anaemia may progress during the first few weeks of life, and therefore careful monitoring of the newborn is necessary. There are no studies on the global burden of this condition.

Bilirubin-induced brain injury (kernicterus) is caused by severe jaundice and may result in death or long-term neurodevelopmental impairment. Jaundice within the first 24 hours of life is more likely to be haemolytic; total bilirubin levels may rise rapidly to very high levels. The main causes are Rh disease, ABO incompatibility, minor antigen incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency, hereditary spherocytosis and congenital infections. Extremely severe jaundice (bilirubin > 25 mg/dL) is estimated to affect 481 000 late-preterm and term newborns annually; 114 000 die and more than 63 000 survive with moderate or severe long-term neurological impairment (5).

Currently, standard practice in most countries during prenatal and antenatal care includes screening for ABO and Rh blood types in the mother. This test therefore identifies women with a blood group that is Rh-negative to administer postpartum anti-Rh immunoglobulin to avoid severe disease in future pregnancies. In the case of G6PD deficiency, neonatal screening using a blood spot has been shown to be effective and is cost-effective in regions with prevalence greater than 5%. Pre-discharge examination of women and their newborns will help identify early jaundice requiring more investigations, including blood typing and Coombs testing, and treatment.

Does the test meet a medical need?

The POC dry format card provides a reliable blood typing result that supports a final diagnosis of Rh incompatibility in pregnant women. The test is innovative and has the potential to address a need that is not met by current technologies. Existing strategies require venous blood samples, shipping the sample to specialized laboratory services and relocating Rh-negative women to deliver treatment. Compared with slide blood typing tests, the dry format card requires no electricity, no cold chain, no laboratory and no daily control of reagents, and therefore can be used as a POC test (6, 7).

The dry format card is currently being used in clinical practice in high-income countries and low- and middle-income countries (LMICs). In the United Kingdom the test is used to rule out Rh-negative women during pregnancy; and in LMICs the test has been used by Doctors Without Borders/Médecins Sans Frontières in emergency situations. Preliminary studies on feasibility and acceptability in LMICs show that the POC dry format card is accurate, user-friendly and acceptable for use by health professionals, lay workers and tested users (7, 8, 9).

While there are no studies on the cost-effectiveness of the POC test, prevention of Rh disease has been included among high-impact interventions to reduce stillbirths and neonatal deaths (10).

How the test is used

This POC test represents the first step in prevention of Rh disease by identifying Rh-negative women who can then receive preventive treatment with anti-D immunoglobulins (11). Additionally, the test will aid in the diagnosis of ABO incompatibility as the cause for haemolysis in newborns. Once a newborn is diagnosed, appropriate management of jaundice, anaemia and other complications can be initiated to prevent long-term disability and death.

E. Public health relevance (from application)

Prevalence

In LMICs access to laboratory facilities, prophylaxis and treatment for this condition is limited. Therefore, Rh disease continues to be a public health problem affecting more than 150 000 children annually (12). The prevalence of Rh negativity is not known in many LMICs. In Nigeria and India, it has been estimated at around 5% and in China at about 1%, whereas in Europe and North America prevalence is around 15% (3). Recent studies in Pakistan and Nigeria have found a prevalence comparable with that of industrialized countries (8, 9). However, due to the size of LMIC populations, millions of pregnant women are at risk. High fertility rates in some countries may also play a role as Rh disease becomes more severe with subsequent pregnancies. It is estimated that

50% of women around the world who require this type of immunoprophylaxis do not receive it (4). Globally, untreated Rh disease causes 52 000 stillbirths, 98 000 neonatal deaths, 67 000 cases of hyperbilirubinaemia and 17 000 cases of kernicterus each year (12).

Socioeconomic impact

Not provided.

F. WHO or other clinical guidelines relevant to the test (from application)

Guidelines for preventing Rh disease published by the International Federation of Gynecology and Obstetrics/International Confederation of Midwives (FIGO/ICM) in 2021 (11) provide recommendations to address the global burden of Rh disease, to be implemented according to a country's health system capacity (see box 1 on page 146 of the FIGO/ICM guideline).

Measures to prevent sensitization to Rh(D):

High priority

- Determine the maternal Rh factor, preferably in early pregnancy.
- For Rh(D)-negative women, determine the Rh factor of the newborn from umbilical cord blood.
- Administer anti-Rh(D) immunoglobulin within 72 hours of delivery to women with an Rh(D)-positive newborn, unless already sensitized.
- Use a dose of 500 IU (100 µg) of anti-Rh(D) immunoglobulin; if affordable and with sufficient supply, 1500 IU (300 µg) may be given, as is common in high-income countries. The intramuscular route is as effective as the intravenous route.

Middle priority

- Routine anti-Rh(D) prophylaxis during pregnancy: 1500 IU (300 µg) at 28–34 weeks.
- Anti-Rh(D) immunoglobulin prophylaxis (500 IU; 100 µg) after a surgical abortion or ectopic pregnancy (all gestational ages), or after spontaneous or medical abortion/miscarriage after 10 weeks.
- Anti-Rh(D) prophylaxis after bleeding, abdominal trauma in pregnancy and/or fetal death (500 or 1500 IU; 100 or 300 µg) during the second or third trimester. The Kleihauer-Betke test can be used to estimate the optimal dose.

Low priority

- Anti-Rh(D) prophylaxis after amniocentesis, chorionic villus sampling or external cephalic version (500 IU; 100 µg).

The FIGO/ICM guidelines specify that a prerequisite for prevention of Rh(D) sensitization is a priori knowledge of maternal Rh status and that the Rh(D) factor can be determined by collecting venous or capillary blood samples at local health care facilities and using classical or POC serologic methods. The guidelines also state that Rh(D) type should preferably be determined in the first trimester, because indications for anti-Rh(D) immunoprophylaxis may arise early in pregnancy, for example after miscarriage or ectopic pregnancy.

As reported in the FIGO/ICM guidelines, evidence shows that postpartum administration of anti-Rh(D) immunoglobulin reduces this risk to approximately 1.5% and is the most effective intervention in preventing Rh disease in subsequent pregnancies. Therefore, this approach should have the highest priority in countries and/or regions where no, or inadequate, prophylaxis is currently provided.

Prenatal administration seems to reduce sensitization further, from approximately 1.5% (achieved by administration of postpartum anti-Rh(D) immunoglobulin) to approximately 0.5%.

G. Basic test characteristics (from application)

Test formats available	POC test
Specimen types	Capillary whole blood
Equipment required	None required
Regulatory status	CE-marked, FDA-approved
Availability	Global
Price per test range	US\$ 0.75–3
Instrument price range	Not applicable

H. Evidence for diagnostic accuracy (from application)

No systematic reviews of the test's clinical accuracy yet exist. However, four studies have been published on the clinical accuracy, stability and reliability of the dry format POC test under different conditions in high- and middle-income countries.

The multicentre performance study published by Eldon Biologicals in 2004 evaluated the diagnostic accuracy of the dry format card test by comparing

results obtained blindly using EldonCards with results from conventional blood typing techniques in four blood testing centres in Denmark, Germany, Italy and the United Kingdom (13).

Of 2990 non-special samples regarding ABO blood types, 2988 concordant results were found at the initial testing (> 99.9% concordance). Of the eight weak A samples, three were detected by the dry card test, four were doubtfully positive and one was not detected. Of the 2988 samples, 2373 were found to be strong Rhesus D's by conventional testing. Of these, 2372 were detected by the experimental EldonCard at initial testing (> 99.9% concordance). Of the 39 weak Rh(D) samples, seven were detected by the anti-D formulation already in use on commercial EldonCards. The two new, experimental anti-D formulations on the cards were able to detect 15 and 19 of the weak D samples. The study concluded that the results of the ABO typing as well as the Rh(D) typing (including the results of the typing of weak D samples) show that an EldonCard is a reliable blood typing device which can be used for blood typing of patients and for primary screening of blood donors.

Bienek et al. assessed the accuracy of two dry card blood typing kits (the Eldon Home Kit 2511 and the ABO-Rh Combination Blood Typing Experiment Kit), tested under simulated military field conditions (6) and after long-term storage at various temperatures and humidities (14). Rates of positive tests among control groups, experimental groups and industry standards were measured and analysed using the chi-square and Fisher's exact tests to identify significant differences ($P \leq 0.05$). When the Eldon Home Kit 2511 was used under various operational conditions, the results were comparable to those obtained with the control group and with the industry standard. However, performance of the ABO-Rh Combination Blood Typing Experiment Kit was adversely affected by prolonged storage at temperatures above 37°C, indicating that performance of available kits varies with products and environmental conditions (6).

Ravichandran et al. evaluated the accuracy and reliability of the EldonCard test compared with the standard conventional slide and tube method in 808 volunteers selected randomly from Vinayaka Missions University, Salem, India. Compared with the standard laboratory method, both the sensitivity and specificity of the EldonCard method, as well as the positive and negative predictive value (PPV and NPV), were found to be 100%. The percentage of false positives and false negatives was 0% (7).

I. Evidence for clinical utility/impact (from application)

Primary studies on the POC dry format card test for blood group typing utility and impact have been conducted in Nigeria and Pakistan. Preliminary results have been presented at scientific meetings, and peer-reviewed papers are expected by the end of this year.

A study in Pakistan of the willingness of pregnant women to receive the POC test and the ability of health professionals to administer it and interpret the results showed 100% acceptance of the test and of treatment among Rh-positive women. Interpretation of the results had 100% concordance between health professionals and supervisors. These findings indicate that it will be feasible to implement a community-based programme for Rh haemolytic disease elimination in rural Pakistan (8).

Studies in Nigeria assessed feasibility and acceptability of the POC test in community settings targeting pregnant women and schoolchildren. The POC test was easy to perform and acceptable. In addition, it was easier for women to report their blood group through the card provided with the test result (9).

Implementation studies in Ghana, Kenya, Kyrgyzstan, Madagascar and Mexico are underway to develop community-based programmes to identify women who are Rh negative and to provide them with prophylaxis.

J. Evidence for economic impact and/or cost-effectiveness (from application)

Not provided.

K. Ethics, equity and human rights issues (from application)

The likelihood of an Rh-negative woman to have her baby affected by Rh disease is determined by where she lives. In high-income countries, stillbirth, neonatal mortality and disability due to this condition are uncommon. In contrast, in LMICs newborns affected by Rh disease often die either through lack of care at the lower level or inability to afford tertiary-level care. Inequities exist between and within countries, with women from the poorest communities facing the greatest barriers to access. In LMICs a large proportion of women do not have access to laboratory or preventive services.

The use of this ABO blood grouping and Rh factor typing POC dry format card will expand coverage of essential interventions for maternal and newborn health and reduce inequity. Women without access to laboratory facilities would know their Rh(D) antigen status and blood group and receive advice on accessing preventive care for Rh disease. Midwives could screen pregnant women in primary care facilities and at the home and immediately provide prophylactic treatment with anti-D immunoglobulin.

Diagnosis of haemolytic disease of the newborn will proceed more rapidly, and treatment could start to reduce the risk of kernicterus. Access to the screening test for Rh-negative and/or ABO status combined with access to the recommended treatment for preventing disease in pregnant women and for managing affected fetuses and newborns will lead to rapid elimination of the burden of Rh and ABO disease in less-developed countries (3, 4).

In addition, the POC dry format card could contribute to reducing maternal deaths due to obstetric haemorrhage by increasing access to blood

products in hard-to-reach settings through better access to blood typing for the pregnant women and in the general population.

No ethical issues were identified.

L. Summary of evidence evaluation

POC dry cards are a simple-to-use, cheap and easy-to-implement test. They aim to diagnose a severe condition which can have a significant impact on the lives of a large group of unborn children and their parents. Treatment for this condition appears to be effective.

The test requires limited infrastructure, facilities and training. The stability of samples is described in detail in technical documents (from the EldonCard producer). Documentation provided on diagnostic accuracy (e.g. sensitivity, specificity) in a real-world setting by untrained personnel is limited and of low quality. Nonetheless, given the clear effect (100% sensitivity and specificity) and the link with indirect evidence on concordance with laboratory tests (in a research setting), there is little reason to doubt the accuracy of this test. This is underpinned by the recommendation of several international guidelines.

Although the impact on clinical outcomes was not demonstrated using empirical studies (as is the case with the majority of diagnostic tests), the alternative of not providing this test would have severe consequences for a large group of unborn children and their parents. Given the anticipated costs of US\$ 1, minimal investment in supporting infrastructure and training, and the severity of the condition if left undetected and untreated, POC cards are expected to have a net positive cost-effectiveness. The availability of treatment, however, is a prerequisite for the IVD test to have any meaningful clinical impact. If availability is ensured, adopting the POC dry format card on the list would be recommended.

M. Summary of SAGE IVD deliberations

The ABO blood groups and Rh typing test is a straightforward, easy-to-use POC test for determining ABO groups and Rh. The test is very important in the context of maternal health care, in particular when laboratory-based tests are unavailable.

Several SAGE IVD members would have preferred a little more data on the impact of the test on clinical outcomes. The group noted that in the case of strong D antigen expression, concordance is reported to be 99.9%; performance in the case of weak D antigen expression is somewhat lower. One SAGE IVD member reported 100% concordance based on literature he consulted, although minor variants in ABO were not detected.

The experts proposed changing the title as submitted – “A, B and O blood groups and Rhesus (Rh) factor POC dry format card – to “ABO blood

groups and Rhesus factor typing point-of-care test” to be consistent with the way the test is reported in the literature. SAGE IVD made special note of the problem of weak D detection because it will have an impact on implementation.

Literature cited in the discussion:

Ravichandran S, Abraham P, Sugendran K, Hedegaard HO, Jones E. Trial and evaluation of dry format Eldon card for ABO & Rh blood grouping – “a new card concept”. *Natl J Basic Med Sci.* 2016;6(4):168–71.

N. SAGE IVD recommendations

SAGE IVD recommended including the ABO blood groups and Rh factor typing test category in EDL 4

- as a general IVD for use in community settings and health facilities without laboratories (EDL 4, Section I.a);
- using a POC test format;
- using capillary whole blood as specimen type;
- to determine ABO groups and Rh factor.

The group also noted that detection of the weak D antigen appears to be a limitation.

O. References (from application)

1. Ascari WQ, Levine P, Pollack W. Incidence of maternal Rh immunization by ABO compatible and incompatible pregnancies. *BMJ.* 1969;1:399–401.
2. Walker WC. Haemolytic disease of the newborn. In: Gairdner D, Hull D, editors. *Recent advances in paediatrics*, 4th edition. London: JA Churchill; 1971.
3. Zipursky A, Bhutani VK, Odame I. Rhesus disease: a global prevention strategy. *Lancet Child Adolesc Health.* 2018;2(7):536–42. doi:10.1016/S2352-4642(18)30071-3.
4. Pegoraro V, Urbinati D, Visser GHA, Di Renzo GC, Zipursky A, Stotler BA et al. Hemolytic disease of the foetus and newborn due to Rh(D) incompatibility: a preventable disease that still produces significant morbidity and mortality in children. *PLoS One.* 2020;15(7):e0235807. doi:10.1371/journal.pone.0235807.
5. Bhutani VK, Zipursky A, Blencowe H, Khanna R, Sgro M, Ebbesen F et al. Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. *Pediatr Res.* 2013 Dec;74 (Suppl 1):86–100. doi:10.1038/pr.2013.208.
6. Bienek DR, Charlton DG. Accuracy of user-friendly blood typing kits tested under simulated military field conditions. *Mil Med.* 2011;176(4):454.
7. Ravichandran S, Abraham P, Sugendran K, Hedegaard HO, Jones E. Trial and evaluation of dry format Eldon card for ABO & Rh blood grouping – “a new card concept”. *Natl J Basic Med Sci.* 2016;6(4):168–71.

8. Pell L. Models of implementation of Rh prophylaxis in rural settings: project update and panel discussion. In: Open Symposium on Global Eradication of Rh Disease: Victories and Pitfalls, Florence, Italy, 28 September 2019. (Preliminary results of a feasibility study in Pakistan; peer-reviewed publication in progress)
9. Okolo AA. Current issues on Rh disease: perspective from Nigeria. The 36th Conference of the International Society for Blood Transfusion, virtual meeting, 12–16 December 2020. (Feasibility and acceptability of POC test in community settings targeting pregnant women and school children in Nigeria; peer-reviewed publication in progress)
10. Bhutta ZA, Das JK, Bahl R, Lawn JE, Salam RA, Paul VK et al. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *Lancet*. 2014 Jul 26;384(9940):347–70. doi:10.1016/S0140-6736(14)60792-3.
11. Visser GH, Thommesen T, Di Renzo GC, Nassar AH, Spitalnik SL. FIGO/ICM guidelines for preventing Rhesus disease: a call to action. *Int J Gynecol Obstet*. 2021;152(2):144–47 (<http://doi.org/10.1002/ijgo.13459>, accessed 30 July 2023).
12. Zipursky A, Bhutani VK. Impact of Rhesus disease on the global problem of bilirubin-induced neurologic dysfunction. *Semin Fetal Neonatal Med*. 2015;20(1):2–5.
13. Testing blood types using Eldon Cards prepared with monoclonal antibodies anti-A, anti-B, and anti-D. Multi centre performance study on 3000 blood samples. Gentofte: Eldon Biologicals; 2004.
14. Bienek DR, Chang CK, Charlton DG. Stability of user-friendly blood typing kits stored under typical military field conditions. *Mil Med*. 2009;174(10):1075.

2.1.3 High-sensitivity troponin I point-of-care test

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

The application proposed adding a high-sensitivity troponin I (hs-cTnI) POC test to the EDL as an IVD to aid in the diagnosis of acute myocardial infarction.

B. Applicant

Siemens Healthineers

C. WHO technical department

None

D. Background (from application)

Disease condition and impact on patients

Cardiovascular disease (CVD) is the number one cause of death globally (1). Only 10% of patients who go to the emergency department with chest pain are actually experiencing a heart attack (2). Every year 17.7 million people die from

CVDs, an estimated 31% of all deaths worldwide (2). Over 75% of CVD deaths occur in LMICs (2). About 610 000 people die of heart disease in the United States every year, which amounts to one in every four deaths (3).

The hs-cTnI test at POC aims to relieve the burden of care in the emergency department. This is possible because the use of this test in the emergency department decreases turnaround time for diagnostic results (compared to sending samples to the laboratory or utilizing a contemporary POC troponin test), which in turn leads to faster patient throughput in the emergency department. If not utilized, greater emergency department overcrowding can occur, which is deleterious for patient outcomes.

For patients with non-ST-segment elevation myocardial infarction (NSTEMI), long emergency department stays were associated with decreased use of guideline-recommended therapies and a higher risk of recurrent myocardial infarction (4). In addition, hospital and emergency department overcrowding is associated with increased mortality. Reducing overcrowding may improve outcomes for patients requiring emergency hospital admission (5). Finally, emergency department crowding is associated with poor quality of care for patients with severe pain, namely, total lack of treatment or delay until treatment (6).

Does the test meet a medical need?

The new generation of highly sensitive troponin assays allows earlier detection of acute myocardial infarction, reducing the time window for serial measurement to 3 hours. Cardiac troponin (cTn) has become a continuous variable, with accurate measurement below the 99th percentile as well as absolute changes within 1 or 2 hours. This has enabled development of algorithms for reliable rule-out and rule-in of acute myocardial infarction within 2 hours. As a result, high-sensitivity cTn assays are an important aid to clinicians in optimizing management of acute coronary syndrome (ACS) in addition to clinical assessment and electrocardiogram (ECG), and enable definitive diagnosis of acute myocardial infarction. Serial measurements of high-sensitivity cTn are important in differentiating acute from chronic cardiac myocyte damage. Given that symptoms are not specific and ECG is not diagnostic 70% of the time, clinicians need cardiac biomarkers (7).

How the test is used

Using capillary blood from a finger stick, hs-cTnI results are achievable to aid in the diagnosis of myocardial infarction. This streamlined patient-testing workflow advances care delivery and accelerates clinical decision-making, as recommended by the European Society of Cardiology's rapid algorithm. This algorithm recommends that clinical decision-making be taken with a

high-sensitivity troponin test, signs and symptoms, a 12-lead ECG and a patient history.

E. Public health relevance (from application)

Prevalence

Not provided.

Socioeconomic impact

Not provided.

F. WHO or other clinical guidelines relevant to the test (from application)

- ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (8): pages 1299–1304 (3.3.2–3.3.4) for recommendation on the use of hs-cTn. Page 1306 (second table on the page) provides the level of evidence, including references to studies.
- National Institute for Health and Care Excellence: High-sensitivity troponin tests for the early rule-out of NSTEMI. Diagnostic guidance (9): pages 4–5 for recommendations on the use of hs-cTn; pages 14–24 for evidence.
- 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR¹ guideline for the evaluation and diagnosis of chest pain (10).

G. Basic test characteristics (from application)

Test formats available	Immunoassay, POC
Specimen types	Whole blood, plasma, capillary blood
Equipment required	None required
Regulatory status	CE-IVD, FDA-approved, TGA
Availability	Narrow
Price per test range	US\$ 12–20 per test in EU
Instrument price range	US\$ 5000–8000 in EU

¹ AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR: American Heart Association/American College of Cardiology/ American Society of Echocardiography/American College of Chest Physicians/Society for Academic Emergency Medicine/Society of Cardiovascular Computed Tomography/Society for Cardiovascular Magnetic Resonance.

H. Evidence for diagnostic accuracy (from application)

A systematic review and meta-analysis of diagnostic test accuracy studies were conducted to compare the diagnostic performance of various accelerated diagnostic algorithms of hs-cTn assays for patients with symptoms of acute myocardial infarction. A random-effects bivariate meta-analysis was conducted to estimate the summary sensitivity, specificity, likelihood ratios and area under the receiver operating characteristic curve.

Both hs-cTnI- and hs-cTnT-based accelerated diagnostic algorithms were shown to have high sensitivities but moderate specificities for early diagnosis of acute myocardial infarction. Overall, hs-cTnI-based algorithms have slightly higher specificities in early diagnosis of acute myocardial infarction. For patients presenting to the emergency department with typical symptoms, the use of hs-cTnT or hs-cTnI assays at the 99th percentile may help identify patients at low risk for myocardial infarction and promote early discharge from the emergency department (11).

Using serial sampling at 0 and 2 hours relative to the 99th percentile upper reference limit (URL), the whole blood POC Atellica VTLi assay showed comparable diagnostic performance for myocardial infarction to the central laboratory Abbott ARCHITECT and Siemens Atellica hs-cTnI assays. Specifically, the POC assay showed clinical sensitivities and NPVs demonstrating comparable diagnostic accuracy for ruling out myocardial infarction using both an overall 99th percentile URL, as well male and female sex-specific URLs. Similarly, the VTLi POC assay showed clinical specificities and PPVs demonstrating comparable rule-in performance to the central laboratory assays. The POC diagnostic data are novel and very timely. The Atellica VTLi POC hs-cTnI assay addresses the need for both busy, urban, medical centre emergency departments and rural hospital and clinic settings to be able to have the alternative of utilizing a rapid, whole blood POC hs-cTnI assay 24/7 for patient triage and management (12).

I. Evidence for clinical utility/impact (from application)

The primary clinical utility impact is the decreased length of stay (LOS) and more patients discharged from emergency departments, due to implementation of high-sensitivity troponin testing. Implementation of an early rule-out pathway for myocardial infarction reduced LOS and hospital admissions. Although noninferiority for the safety outcome was not demonstrated at 30 days, there was no increase in cardiac events at 1 year. Adoption of this pathway would have major benefits for patients and health care providers (13). For patients with NSTEMI, long emergency department stays were associated with decreased use of guideline-recommended therapies and a higher risk of recurrent myocardial infarction (4).

J. Evidence for economic impact and/or cost-effectiveness (from application)

The analysis shows that the use of a 1-hour algorithm is associated with reduction in overall acute myocardial infarction diagnostic costs, provided it is carefully implemented in clinical practice. These results need to be prospectively validated in the future (14).

Section 4.13 of the NICE guidelines states: “All early rule-out test strategies in the model are cost effective compared with standard troponin testing at 0 hours and 12 hours. ... Compared with standard troponin testing, high-sensitivity troponin test strategies resulted in incremental cost-effectiveness ratios (ICERs) of less than £7,000 per quality-adjusted life-year (QALY) gained. These ICERs are below £20,000 per QALY gained, which NICE would typically consider to be cost effective” (9).

Section 3.35 of the NICE guidelines also states: “The most recent study (Ambavane et al. 2017) reported that a 1-hour strategy using high-sensitivity troponin testing had higher sensitivity (87% compared with 69%) but lower specificity (96% compared with 97%) than standard care. The reference standard used to calculate diagnostic accuracy was determination of final diagnosis based on a comprehensive review of medical records. Total costs were less for the 1-hour strategy compared with standard care (£2,480 compared with £4,561). This was mainly because of a shorter length of stay in the emergency department” (9).

K. Ethics, equity and human rights issues (from application)

In areas where patients may not be able to access an established laboratory, POC high-sensitivity troponin improves access and reduces inequities due to cost, mobility/portability, size/weight, etc. Prior to this, these communities may have had no access or extremely delayed access due to long distances or commute times to medical centres (especially relevant for rural areas or areas that lack medical funding).

Delayed diagnosis can lead to poor quality of care or nonadherence to guideline-recommended care. Emergency department crowding is associated with poor quality of care for patients with severe pain, namely, total lack of treatment and delay until treatment (6). For patients with NSTEMI, long emergency department stays were associated with decreased use of guideline-recommended therapies and a higher risk of recurrent myocardial infarction (4).

L. Summary of evidence evaluation

Although the evidence provided in this application is incomplete and/or nonspecific, the existence of very well established guidelines in the European Union (EU), the United Kingdom and the United States with clear underpinnings and recommendations on hs-cTnI makes it clear that there is high value in the hs-cTnI test.

International guidelines endorse hs-cTnI. As such, no further evidence is warranted from the applicant. However, to make the application more complete, the following should have been considered:

- Specify condition(s) of interest. In this application CVD and myocardial infarction are used back and forth. The applicant used multiple interchangeable terms throughout the application (myocardial infarction, acute coronary syndrome, CVD).
- Provide more insight into the quality-of-life impact of the disease/condition of interest.
- Provide more insight into the costs and impact on costs of a potential intervention.
- The systematic review submitted does not mention POC test(s), so performance may differ significantly.
- Only one commercially available test has been reported in the scientific literature, and the domain of that publication is not the same (healthy vs symptomatic individuals).

M. Summary of SAGE IVD deliberations

Both hs-cTnT and hs-cTnI assays are essential tools in the management of coronary artery disease and the differential diagnosis of acute myocardial infarction.

SAGE IVD raised several concerns related to the confusing nature of this application. The application was ostensibly for a POC test, but the data supporting the POC were limited and referred only to diagnostic performance. Evidence on how to frame the diagnostic algorithm and on the clinical utility of the assay was all based on laboratory testing.

The experts know of no studies of POC capillary finger-stick tests outside of the hospital setting. Moreover, in 2020 the European Society of Cardiology (ESC) recommended against POC tests for the management of acute coronary syndromes. The FDA has also not approved any POC troponin test. One SAGE IVD member pointed out that this POC is intended for use in primary health care in remote areas; but if angioplasty or fibrinolysis are not available within 90 minutes, the proposition makes little sense. The experts also raised a methodological question about the predictive value of the test in low-prevalence settings.

SAGE IVD noted that Médecins Sans Frontières have made POC tests a priority in general in the interest of faster, more affordable results. Nonetheless, the SAGE IVD group maintained that more data are needed on the clinical validity of the tests and to ensure adequate performance, particularly with regard to false positives and negatives.

For these reasons, SAGE IVD agreed to list the submission as a laboratory-based test only but emphasized that the group fully supports further research into the POC version of the test and eventual application to EDL 5 with better evidence.

Literature cited in the discussion:

HEARTS: technical package for cardiovascular disease management in primary health care: risk-based CVD management. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/333221>, accessed 30 July 2023).

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N. SAGE IVD recommendations

SAGE IVD recommended including the high-sensitivity troponin I (hs-cTnl) test category in EDL 4

- in Section II.b Cardiovascular health;
- using the immunoassay format;
- using serum and plasma as specimen types;
- to aid in the diagnosis of acute myocardial infarction.

The group also recommended adding hs-cTnT to EDL 4 for consistency with the existing entry for a troponin test in EDL 3 and because the markers are similarly used.

The experts further recommended introducing a new section in the EDL to be called II.b: Cardiovascular health.

SAGE IVD also recommended linking the EDL entry to the WHO HEARTS technical package for cardiovascular disease management in primary health care.

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2.1.4 Hepatitis E virus nucleic acid test

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

The application proposed adding a hepatitis E virus (HEV) nucleic acid test (NAT) to the EDL as an IVD to diagnose acute hepatitis E infection.

B. Applicant

Department of Public Health, Syracuse University

C. WHO technical department

None

D. Background (from application)

Disease condition and impact on patients

HEV is an RNA virus and a leading cause of acute viral hepatitis worldwide (1). Hepatitis E disease presents as acute, viral hepatitis. During the first week of illness, many symptoms are nonspecific, including fever, malaise, nausea and vomiting. After the prodromal phase, patients experience a period of acute, icteric hepatitis, including jaundice, dark urine, pale stools and prolonged cholestasis with elevated liver enzymes. Symptoms can last 4–6 weeks (2). Most cases occur in older adolescents and adults. In general, these cases are mild and self-limiting, yet approximately 1–2% of cases die. However, some populations are more prone to severe disease. Women infected during pregnancy are at increased risk of fulminant hepatic failure and its associated complications, including hepatic encephalopathy, cerebral oedema and disseminated intravascular coagulation. HEV infection during pregnancy also has poor outcomes for the fetus, including low birth weight, small for gestational age, preterm birth and intrauterine death (3). A recent meta-analysis found the case fatality rate of hepatitis E during pregnancy to be 26% (IQR: 17–41%) for the mother, 33% (IQR: 19–37%) for the fetus and 8% (IQR 3–20%) for the neonate (4).

HEV is a pathogen of global concern (5). However, the burden of disease is not distributed evenly; HEV is very common in low-income countries, where it causes substantial burden of disease, while relatively few cases are reported from high-income countries (5). There are four genotypes of HEV that infect humans. Genotypes 1 and 2 only infect humans and are thought to be transmitted primarily via contaminated drinking water. These genotypes are most common in South-East Asia and Africa (6). They are responsible for large outbreaks, with cases numbering in the tens of thousands. Outbreaks have been reported from East and South-East Asia, and protracted outbreaks have occurred in Africa, often affecting displaced populations (7). However, genotypes 1 and 2 also cause substantial disease outside of outbreaks (6). In India, between 25% and 50% of clinical hepatitis cases are caused by HEV, even in the absence of an outbreak (6). Genotypes 3 and 4 infect humans and a wide range of mammals, notably wild and domestic swine. These genotypes are usually transmitted zoonotically from eating infected meat and are largely reported from Europe, East Asia and the Americas. Here, HEV is responsible for sporadic cases and small foodborne outbreaks (8).

Does the test meet a medical need?

The availability of HEV diagnostic tests will improve differential diagnosis capability in the case of acute jaundice syndrome. Early diagnosis will alert authorities to the possibility of an outbreak, which can mobilize mitigation efforts. Due to the lack of diagnostic testing in areas where HEV is most common, the burden of HEV disease is underestimated and often poorly understood at the country level. This lack of awareness and understanding by country officials has prevented the use of a vaccine during or in endemic areas, to prevent outbreaks.

How the test is used

NATs are considered the gold standard for diagnosing HEV infection. However, due to the laboratory requirements, NATs are not always available. When a suspect HEV case presents at the community level, defined as any person presenting with an acute (recent, new or abrupt) onset of jaundice (yellowing of whites of eyes or skin) or dark urine and pale clay stools, an anti-HEV IgM RDT should be performed, if available, to determine the diagnosis (9, 10). If the rapid IgM test is positive, this can be considered case confirmation. If the RDT is positive early in the clinical course of infection, samples may still be sent to a reference laboratory for PCR, or IgM enzyme-linked immunosorbent assay (ELISA) confirmation. If the patient tested negative on the RDT and no other cause for the acute jaundice has been found, an NAT such as a PCR test to detect HEV RNA or an ELISA to detect anti-HEV IgM should be performed to confirm the negative diagnosis (see link to diagnostic algorithm below).

In the case of immunocompromised individuals, antibody assays are less sensitive, and those with clinical suspicion should be confirmed via PCR (11). Patients who are immunocompromised should be tested for HEV RNA in three clinical settings: when the anti-HEV IgM is negative and alanine aminotransferase activity is elevated, when the HEV RNA in blood and stool persists for 3–6 months (to identify a chronic infection) and when a recent reduction in immunosuppression has been made or antiviral therapy has been started (to monitor chronic infection) (12).

HEV RNA testing can also be useful in immunocompetent individuals to confirm ongoing infection in the absence of anti-HEV IgM when suspicion for infection is high or to perform viral genotyping.

Note: the following algorithm was provided by the applicant as part of this application and is not a WHO algorithm.

Diagnostic algorithm for HEV infection: <https://docs.google.com/presentation/d/10Yd0I67LoepbYSHxIIZwrMEKUJttU9OA/edit#slide=id.p1> (accessed 1 August 2023).

E. Public health relevance (from application)

Prevalence

A commonly cited meta-analysis estimated that HEV causes 20.1 million infections, 3.4 million clinical cases, 70 000 deaths and 3000 stillbirths annually due to the epidemic-prone genotypes 1 and 2 (13). While there is increasing recognition of HEV in genotype 3 and 4 endemic areas, the burden of disease has not been well classified. However, the burden of disease of HEV is vastly underestimated due to the lack of diagnostic capabilities in areas where HEV is most common. Poor understanding of the global burden of disease has hindered efforts to implement control and prevention strategies.

Socioeconomic impact

Few studies have looked at the economic impact of hepatitis E. In Nepal, acute HEV infection led to an average of 10 bedridden days and 22 sick days; wage earners lost nearly 20% of their yearly income (14). An estimated 108 years of life lost (YLL) per 1000 individuals, 144 years lived with disability per 1000 individuals and 252 disability-adjusted life-years (DALYs) per 1000 individuals were attributed to an HEV outbreak in Uganda (15). However, this estimate used disability weights for untreated diarrhoeal disease and did not account for differential severity among pregnant women and neonates, therefore underestimating the true economic impact.

F. WHO or other clinical guidelines relevant to the test (from application)

The use of PCR to diagnose acute hepatitis E in suspected cases is supported by WHO guidance on recognition, investigation and control of waterborne outbreaks of hepatitis E (9, 10). NATs are an alternative test that can be used in serum, plasma or stool.

G. Basic test characteristics (from application)

Test formats available	NAT
Specimen types	Whole blood, plasma, serum, stool
Equipment required	PCR plates, calibrated pipettes, plate sealer, vortex, centrifuges, quantitative PCR (qPCR) machine
Regulatory status	CE-IVD
Availability	Likely global, but mostly in high- and middle-income countries
Price per test range	US\$ 16–30
Instrument price range	US\$ 10 000–250 000

H. Evidence for diagnostic accuracy (from application)

There are currently no systematic reviews that detail the clinical accuracy of HEV PCR tests. The applicant performed a systematic review to identify primary studies on the clinical accuracy of HEV PCR tests. A systematic search was conducted in PubMed using the search terms: ((HEV) OR (Hepatitis E Virus)) AND ((PCR) OR (polymerase chain reaction test) OR (Polymerase Chain Reaction) [Mesh]) AND ((clinical accuracy) OR (clinical precision) OR (Sensitivity and Specificity) [Mesh]) and ended up with a result of 330 studies. Results were limited to the English language. Thirty articles were found eligible for full-text review after the screening. Five primary studies were found relevant to report the clinical accuracy of PCR tests.

This review identified several primary studies that examined the clinical accuracy of different commercially available NATs. All studies used PCR products, including multiplex reverse transcriptase (RT)-PCR for simultaneous amplification of HBV, HCV and HEV (16), one-step real-time RT-PCR for rapid and sensitive detection (17), analytical sensitivity and performance of three HEV RT-PCR assays (18), and comparison between real-time RT-PCR and conventional RT-PCR (19) and RT-PCR-ELISA (20). Given the costs associated with establishing conventional single-target PCR, a study was designed to develop a reliable and cost-effective multiplex PCR assay (Bangalore Genei, India).

The multiplex PCR was compared to in-house single-virus PCR assays in serum samples from acute hepatitis patients from India. The clinical accuracy of the multiplex compared to single-virus detection was reported as follows: sensitivity for HEV was 74%, with 100% specificity. The PPV was found to be 100%, whereas NPV was $83.8 \pm 12\%$ (16).

Another study used the QuantiTect Probe RT-PCR Master Mix (Qiagen, Valencia, CA, United States). This assay was found to correctly detect 13 of 13 HEV isolates of four different HEV genotypes with 100% sensitivity. This *in vitro* study added HEV RNA to samples to evaluate the PCR assay (17).

A separate study examined the analytical sensitivity and performance of three HEV RT-PCR assays in asymptomatic blood donors from Europe: RealStar HEV RT-PCR, hepatitisE@ceeramTools HEV RT-PCR and ampliCube HEV RT-PCR. For individual sample screening, the RealStar HEV RT-PCR assay consistently had the highest sensitivity of 37.8 IU/mL (95% CI: 22.2–671.2), followed by the hepatitisE@ceeramTools kit with 86.8 IU/mL (95% CI: 68.9–124.7) and the ampliCube HEV RT-PCR kit with 180.4 IU/mL (95% CI: 128.5–355.2). Intra-assay and inter-assay variations were in acceptable ranges, with variation coefficients $< 5\%$ (18).

Ahn et al. compared real-time RT-PCR and nested RT-PCR in Asian serum samples. They found a significant difference in the limit of detection from 1.68×10^1 copies of RNA in real-time RT-PCR to 1.68×10^4 copies of RNA in nested RT-PCR (19).

In a study that used the MJ Mini thermal cycler (Bio-Rad, CA, United States), RT-PCR-ELISA was found to be 10–100 times more sensitive than nested RT-PCR with a 0.01 ng/ μ L limit of detection and did not falsely detect HEV in terms of specificity. This study used swine stool samples to detect HEV genotype 3, a genotype that infects both humans and swine (20).

I. Evidence for clinical utility/impact (from application)

A systematic search across several databases at the time of submission of this application found no systematic reviews that examined the direct clinical utility of HEV PCR tests on patient care and management. There is, however, one recent systematic review which examined data on the epidemiology of HEV in LMICs of Africa and Asia based on seroprevalence, outbreaks and risk factors for infection (21). The lack of routine testing is a major limiting factor to understanding the burden of HEV disease in LMICs. Ninety-one studies from 29 countries examined seroprevalence, which generally increased by age. Forty-nine completed or ongoing HEV outbreaks from 18 countries were reported from 1988 to 2017. However, most outbreaks are not reported in the published literature, and alternative sources were not used for this systematic review. Risk factors for HEV infection included increased exposure to contaminated water

sources and poor hygiene (although not all studies found this association). Risk factor data suggested an increased likelihood of current or recent HEV infection and disease associated with faecal-oral transmission of HEV, as well as exposures to blood and animals. However, the authors emphasized that most data on HEV prevalence and risk factors come from specialized studies or outbreak reports.

There are no primary studies specific to the clinical utility of HEV PCR tests on patient management and care. However, there are several preventative strategies that could reduce the number of future HEV cases and deaths, especially if these preventative measures are introduced early in an outbreak. The applicant identified 12 studies that point to the clinical utility of an HEV diagnosis and greater understanding of the epidemiology and burden of HEV disease in the local context. A better understanding of the local epidemiology and disease burden caused by HEV will allow country officials to make evidence-based decisions on intervention implementation both prior to and during outbreaks.

J. Evidence for economic impact and/or cost-effectiveness (from application)

No data available.

K. Ethics, equity and human rights issues (from application)

HEV PCR tests are needed to diagnose immunocompromised patients, who may not form sufficient antibodies. PCR tests require advanced laboratory infrastructure and trained personnel and therefore may be inaccessible to some populations. Increased availability of diagnostic testing would allow country officials to better understand the local burden of HEV, and therefore to make evidence-based decisions regarding use of vaccines both routinely and during outbreaks.

No ethical issues were identified.

L. Summary of evidence evaluation

This test addresses a significant global health problem. Nucleic acid detection tests for diagnosing HEV infection are included in the WHO guidance (9, 10). The 2018 European Association for the Study of the Liver (EASL) guidelines also recommend a combination of serology and nucleic acid testing for HEV infection (10.1016/j.jhep.2018.03.005). The test allows detection of acute infection, thereby possibly contributing to early warning of an outbreak. There is insufficient evidence to assess clinical diagnostic accuracy and clinical utility/effectiveness. Given that this test is the gold standard in the diagnosis of HEV, evaluating its clinical accuracy may not be the best way to judge the merits of this test. If studies of clinical effectiveness (on patient outcomes) are absent,

other factors may weigh more heavily in eventually deciding to use this test, such as resources required, acceptability and equity.

M. Summary of SAGE IVD deliberations

Hepatitis E is an acute viral hepatitis caused by HEV infection. Most affected people recover. However, a small proportion – generally less than 5% but much higher in pregnant women – develop acute liver failure. Hepatitis E should always be considered in outbreaks of acute jaundice syndrome, which have occurred more recently across sub-Saharan Africa, and particularly in the context of internally displaced person camps.

Definitive diagnosis of hepatitis E is challenging, as causes of acute jaundice are many and include yellow fever, hepatitis A and leptospirosis. For countries experiencing outbreaks, the problem of differential diagnosis is exacerbated by lack of access to hepatitis E assays.

The NAT is the gold standard test for diagnosing acute HEV infection. The assay is particularly important for people with immune suppression, including co-endemic HIV and HEV in outbreak situations. Nonetheless, SAGE IVD members expressed concern about the cost of the assay and the level of technology, human skill and workforce capacity needed for broad implementation in LMICs.

SAGE IVD members questioned the complexity of the test, its feasibility in a given setting and where it would fit in a referral algorithm linked to the HEV IgM RDT as a screening test. The group noted that NAT provides differential diagnosis when IgM is insufficient, but it is of lesser value than getting good serology for clinical management and is not indicated for surveillance.

SAGE IVD further discussed the need to clarify the language of the EDL with reference to the test's purpose (i.e. "to diagnose" vs "to confirm") but noted that this issue should resolve once a consolidated algorithm is available under the hepatitis E updated guidance from WHO currently in preparation.

Literature cited in the discussion:

European Association for the Study of the Liver. EASL clinical practice guidelines on hepatitis E virus infection. *J Hepatol.* 2018;68:1256–71 ([https://www.journal-of-hepatology.eu/article/S0168-8278\(18\)30155-7/fulltext](https://www.journal-of-hepatology.eu/article/S0168-8278(18)30155-7/fulltext), accessed 14 December 2022).

N. SAGE IVD recommendations

SAGE IVD recommended including the hepatitis E virus nucleic acid test (NAT) category in EDL 4

- as a disease-specific IVD for use in clinical laboratories (EDL 4, Section II.b);

- using an NAT format;
- using whole blood, plasma, serum and stool as specimen types;
- to diagnose acute hepatitis E virus infection.

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2.1.5 Immunoglobulin M antibodies to hepatitis E virus

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

The application proposed adding a hepatitis E IgM antibody test to the EDL as an IVD to diagnose acute hepatitis E infection.

B. Applicant

Department of Public Health, Syracuse University

C. WHO technical department

None

D. Background (from application)

Disease condition and impact on patients

HEV is an RNA virus and a leading cause of acute viral hepatitis worldwide (1). Hepatitis E disease presents as acute, viral hepatitis. During the first week

of illness, many symptoms are nonspecific, including fever, malaise, nausea and vomiting. After the prodromal phase, patients experience a period of acute, icteric hepatitis, including jaundice, dark urine, pale stools and prolonged cholestasis with elevated liver enzymes. Symptoms can last 4–6 weeks (2). Most cases occur in older adolescents and adults. In general, these cases are mild and self-limiting, yet approximately 1–2% of cases die. However, some populations are more prone to severe disease. Women infected during pregnancy are at increased risk of fulminant hepatic failure and its associated complications, including hepatic encephalopathy, cerebral oedema and disseminated intravascular coagulation. HEV infection during pregnancy also has poor outcomes for the fetus, including low birth weight, small for gestational age, preterm birth and intrauterine death (3). A recent meta-analysis found the case fatality rate of hepatitis E during pregnancy to be 26% (IQR: 17–41%) for the mother, 33% (IQR: 19–37%) for the fetus and 8% (IQR 3–20%) for the neonate (4).

HEV is a pathogen of global concern (5). However, the burden of disease is not distributed evenly; HEV is very common in low-income countries, where it causes substantial burden of disease, while relatively few cases are reported from high-income countries (5). There are four genotypes of HEV that infect humans. Genotypes 1 and 2 only infect humans and are thought to be transmitted primarily via contaminated drinking water. These genotypes are most common in South-East Asia and Africa (6). They are responsible for large outbreaks, with cases numbering in the tens of thousands. Outbreaks have been reported from East and South-East Asia, and protracted outbreaks have occurred in Africa, often affecting displaced populations (7). However, genotypes 1 and 2 also cause substantial disease outside of outbreaks (6). In India, between 25% and 50% of clinical hepatitis cases are caused by HEV, even in the absence of an outbreak (6). Genotypes 3 and 4 infect humans and a wide range of mammals, notably wild and domestic swine. These genotypes are usually transmitted zoonotically from eating infected meat and are largely reported from Europe, East Asia and the Americas. Here, HEV is responsible for sporadic cases and small foodborne outbreaks (8).

Does the test meet a medical need?

The availability of HEV diagnostic tests will improve differential diagnosis capability in the case of acute jaundice syndrome. Early diagnosis will alert authorities to the possibility of an outbreak, which can mobilize mitigation efforts. Due to the lack of diagnostic testing in areas where HEV is most common, the burden of HEV disease is underestimated and often poorly understood at the country level. This lack of awareness and understanding by country officials has prevented the use of a vaccine during outbreaks.

How the test is used

When a suspect HEV case presents at the community level, defined as any person presenting with an acute (recent, new or abrupt) onset of jaundice (yellowing of whites of eyes or skin) or dark urine and pale clay stools, a rapid IgM test should be performed, if available, to confirm the diagnosis (9). If the rapid IgM test is positive, this can be considered case confirmation. If the rapid test is positive early in an outbreak, samples may still be sent to a reference laboratory for IgM ELISA or PCR confirmation. If the patient tested negative on the rapid IgM test and no other cause for the acute jaundice has been found, an IgM ELISA or PCR should be performed to confirm the negative diagnosis.

Note: the following algorithm was provided by the applicant as part of this application and is not a WHO algorithm.

Diagnostic algorithm for HEV infection: <https://docs.google.com/presentation/d/10Yd0I67LoepbYSHxIIZwrMEKUJttU9OA/edit#slide=id.p1> (accessed 1 August 2023).

Anti-HEV IgM antibodies appear early during infection and indicate a current or recent infection. They are detectable in blood about 3–7 days after symptom onset (after approx. 1 month incubation period) and persist for several months (10). IgM EIAs that use an antibody capture technique are more specific than indirect antibody assays. IgM assays use recombinant antigens from the ORF2 or ORF3 region of HEV. ORF2-specific assays can detect antibodies in serum earlier in the course of infection and are more useful for diagnosis during the acute phase of the illness (11). Anti-HEV IgM antibody assays have high sensitivity (up to 98%) and specificity (up to 96%) and high PPV in patients with acute hepatitis in highly endemic areas (9). Additionally, where POC testing is not an option (dependent on setting and available lab infrastructure), specimens can be preserved so that ELISAs can be performed retrospectively.

E. Public health relevance (from application)**Prevalence**

A commonly cited meta-analysis estimated that HEV causes 20.1 million infections, 3.4 million clinical cases, 70 000 deaths and 3000 stillbirths annually due to the epidemic-prone genotypes 1 and 2 (12). While there is increasing recognition of HEV in genotype 3 and 4 endemic areas, the burden of disease has not been well classified. However, the burden of disease of HEV is vastly underestimated due to the lack of diagnostic capabilities in areas where HEV is most common.

Socioeconomic impact

Poor understanding of the global burden of disease has hindered efforts to implement control and prevention strategies. Few studies have looked at the economic impact of hepatitis E. In Nepal, acute HEV infection led to an average of 10 bedridden days and 22 sick days; wage earners lost nearly 20% of their yearly income (13). An estimated 108 YLL per 1000 individuals, 144 years lived with disability per 1000 individuals and 252 DALYs per 1000 individuals were attributed to an HEV outbreak in Uganda (14). However, this estimate used disability weights for untreated diarrhoeal disease and did not account for differential severity among pregnant women and neonates, therefore underestimating the true economic impact.

F. WHO or other clinical guidelines relevant to the test (from application)

The use of ELISA to diagnose acute hepatitis E in suspected cases is supported by the WHO guidance document *Waterborne outbreaks of hepatitis E: recognition, investigation and control* (9, 15). The ELISA is one of the first-line laboratory tests recommended for this purpose.

G. Basic test characteristics (from application)

Test formats available	ELISA
Specimen types	Serum, plasma
Equipment required	Multichannel pipettor capable of delivering 50 µL and 100 µL. Pipettor capable of delivering 1–1000 µL. ELISA microplate washer. Incubator 37 ± 1°C. Dual- or single-wavelength microassay plate reader. Computer compatible with the microassay plate reader.
Regulatory status	CE-IVD, FDA-approved
Availability	Global
Price per test range	US\$ 1.4–11.25 depending on the geographic region
Instrument price range	None provided

H. Evidence for diagnostic accuracy (from application)

There are currently no systematic reviews that detail the clinical accuracy of HEV IgM ELISAs. For the purposes of this application, it was therefore necessary to conduct a systematic review. To do so, a search was conducted through PubMed using the search terms ((HeV) OR (Hepatitis E Virus)) AND (ELISA) AND (specificity), which yielded 205 results. Results were limited to English language.

Initial searching made it necessary to narrow search results by filtering out articles with (latex) or (Hendra), limiting results to those published after 2000 and only using human sera, resulting in 178 hits. After review, 15 publications were found to be relevant to HEV IgM ELISAs specifically. Three further articles were found through snowballing.

Clinical accuracy was examined in these 18 studies, including 12 commercial ELISAs and three in-house tests.

Twelve articles discussed the Wantai HEV IgM ELISA (10, 11, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25).

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed using patients with acute infections from other viruses or healthy, HEV RNA-negative blood donors. Four studies involved Asian populations, two studies were of European populations, one involved an African population, and the rest did not specify the geographic location of their participants. The test was evaluated in patients infected with genotypes 1, 3 and 4, although many of the studies did not specify the infecting genotype.

Two studies had study designs that were likely to give low sensitivity values. One study included a mix of immunocompromised and immunocompetent participants but did not separately report test performance by immune status. Antibody assays are less sensitive in immunocompromised populations. The other study tested the ELISA using serial dilutions from a few patients but did not separately report sensitivity for the undiluted samples. The undiluted samples would most accurately reflect clinical sensitivity.

When these two studies are eliminated, the range of sensitivity is 82–98%.

One study had a study design that was likely to give a low specificity. The ELISA was evaluated in acute hepatitis patients within 4 weeks of symptom onset. The specificity was evaluated in the acute hepatitis patients who were HEV RNA negative. HEV RNA may not persist in the blood for 4 weeks, whereas IgM lasts for several months.

When this study is eliminated, the range of specificity is 97–100%.

Range of sensitivity: 65–100%

Range of specificity: 28–100%

Range of PPV: 41–100%

Range of NPV: 83–98%

Seven articles discussed MP Biomedical's Assure HEV IgM ELISA (11, 19, 23, 25, 26, 27, 28):

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed using patients with acute infections from other viruses or healthy, HEV RNA-

negative blood donors. Two studies involved Asian populations, two studies were in European populations, one study included participants from six countries, and two studies did not specify the geographic location of their participants. The test was evaluated in patients infected with all four genotypes.

Two studies had study designs that were likely to give low sensitivity values. One study included a mix of immunocompromised and immunocompetent participants but did not separately report test performance by immune status. Antibody assays are less sensitive in immunocompromised populations. The other study tested the ELISA using serial dilutions from a few patients but did not report the sensitivity for the undiluted samples. The undiluted samples would most accurately reflect clinical sensitivity.

When these two studies are eliminated, the range of sensitivity is 72–96%.

Range of sensitivity: 60–96%

Range of specificity: 84–99%

Range of PPV: 17–96%

Range of NPV: 98–99%

Five articles discussed Mikrogen's recomWell HEV IgM ELISA (11, 23, 27, 28, 29):

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed using patients with acute infections from other viruses or healthy, HEV RNA-negative blood donors. Two studies involved Asian populations, one study was in a European population, and two studies did not specify the geographic location of their participants. One study included only genotype 3 patients, one study included genotype 1 and 2 patients, one study included genotype 1 and 3 infections as well as a few patients with an unknown infecting genotype, one study included genotype 1, 2 and 3 infections, and the fifth included genotype 1, 3 and 4 infections.

Two studies had study designs that were likely to give low sensitivity values. One study included a mix of immunocompromised and immunocompetent participants but did not separately report test performance by immune status. Antibody assays are less sensitive in immunocompromised populations. The other study tested the ELISA using serial dilutions from a few patients but did not separately report sensitivity for the undiluted samples. The undiluted samples would most accurately reflect clinical sensitivity.

When excluding these two studies, the range of sensitivity is 92–100%.

Range of sensitivity: 74–100%

Range of specificity: 88–99%

PPV: 24%

NPV: 100%

Three articles discussed the DSI HEV IgM ELISA (11, 23, 29):²

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed using patients with acute infections from other viruses or healthy, HEV RNA-negative blood donors. One study included participants from six countries, and two studies did not specify the geographic location of their participants. One study included genotype 1, 2 and 3 patients, one study included only genotype 3 patients, and the third study included genotype 1 and 3 infections as well as a few patients with an unknown infecting genotype.

Two studies had study designs that were likely to give low sensitivity values. One study included a mix of immunocompromised and immunocompetent participants but did not separately report test performance by immune status. Antibody assays are less sensitive in immunocompromised populations. The other study tested the ELISA using serial dilutions from a few patients but did not separately report sensitivity for the undiluted samples. The undiluted samples would most accurately reflect clinical sensitivity.

The third study, without these study design issues, reported a clinical sensitivity of 98%.

Range of sensitivity: 71–98%

Range of specificity: 90–95%

Range of PPV: not given

Range of NPV: not given

Two articles discussed the Adaltis EIAGEN HEV IgM ELISA (26, 27):

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed using patients with acute infections from other viruses. One study included participants from Europe, and the other from Asia. One study included genotype 1, 3 and 4 patients; the other study included genotype 1 and 3 patients.

Range of sensitivity: 80–90%

Range of specificity: 87–100%

Range of PPV: 18–100%

Range of NPV: 98–99%

Two articles discussed Dia.Pro's HEV IgM ELISA (11, 21):

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed

² The commercial information for these ELISAs could not be obtained for inclusion in the commercially available IVD products table either because the ELISA was discontinued or because the company did not respond after repeated inquiries.

using patients with acute infections from other viruses or healthy, HEV RNA-negative blood donors. Neither study specified the geographic location of their participants. One study included only genotype 3 patients; the other study included genotype 1 and 3 infections as well as a few patients with an unknown infecting genotype.

The low sensitivity values reflect the study designs. One study included a mix of immunocompromised and immunocompetent participants but did not separately report test performance by immune status. Antibody assays are less sensitive in immunocompromised populations. The other study tested the ELISA using serial dilutions from a few patients but did not separately report sensitivity for the undiluted samples. The undiluted samples would most accurately reflect clinical sensitivity.

Range of sensitivity: 60–81%

Specificity: 98%

Range of PPV: not given

Range of NPV: not given

Two articles discussed Genelabs HEV IgM ELISA (17, 30):²

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed using patients with acute infections from other viruses or healthy, HEV RNA-negative blood donors. One study used a European population, and the other an Asian population. One study included genotype 1 and 3 patients; the other study did not specify the infecting genotype.

Range of sensitivity: 79–83%

Range of specificity: 94–99%

PPV: 97%

NPV: 94%

Two articles discussed the Kehua anti-HEV IgM ELISA (17, 25):²

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed using patients with acute infections from other viruses or healthy, HEV RNA-negative blood donors. Both studies were completed in an Asian population and did not specify the infecting genotype.

Range of sensitivity: 86–98%

Range of specificity: 89–100%

PPV: 100%

NPV: 95.9%

One article discussed the Bioelisa Biokit HEV IgM ELISA (19):²

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. This study was completed in a European population with mostly genotype 3 infections and a few genotype 1 infections.

Sensitivity: 92%

Specificity: not given

PPV: not given

NPV: not given

One article discussed the Euroimmun HEV IgM ELISA (11):

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. The geographic location of the participants was not specified, and only genotype 3 infections were included.

The low sensitivity value reflects the study design. This study tested the ELISA using serial dilutions from a few patients but did not report sensitivity for the undiluted samples. The undiluted samples would most accurately reflect clinical sensitivity.

Sensitivity: 62%

Specificity: not given

PPV: not given

NPV: not given

One article discussed International Immuno-Diagnostics' Anti-HEV IgM ELISA (28):²

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed using patients with acute infections from other viruses or healthy, HEV RNA-negative blood donors. This study was completed in participants from six countries, and included genotype 1, 2 and 3 infections.

Sensitivity: 82%

Specificity: 91%

PPV: not given

NPV: not given

One article discussed the Lizhu HEV ELISA kit (17):²

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed using patients with acute infections from other viruses or healthy, HEV RNA-negative blood donors. The study was performed in an Asian population and did not specify the infecting genotype.

Sensitivity: 84%
Specificity: 100%
PPV: 100%
NPV: 95.2%

Three articles developed and examined in-house immunoassays (27, 29, 31):

Sensitivity was assessed by comparing the ELISA to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed using patients with acute infections from other viruses or healthy, HEV RNA-negative blood donors. Two studies were in Asian populations; one was completed in participants from six countries. One study included genotype 1, 3 and 4 patients, one study included genotype 1, 2 and 3 patients, and the third did not specify the infecting genotype.

Range of sensitivity: 67–98%
Range of specificity: 78–96%
PPV: 40%
NPV: 98.9%

Note: the table of commercially available IVD products is required as part of all applications to add new IVDs to the EDL.

I. Evidence for clinical utility/impact (from application)

A systematic search across several databases at the time of submission of this application found no systematic reviews that examined the direct clinical utility of anti-HEV IgM ELISAs on patient care and management. However, one recent systematic review examined data on the epidemiology of HEV in LMICs of Africa and Asia based on seroprevalence, outbreaks and risk factors for infection (32). The lack of routine testing is a major limiting factor to understand the burden of HEV disease in LMICs. Ninety-one studies from 29 countries examined seroprevalence, with seroprevalence generally increasing by age. Forty-nine completed or ongoing HEV outbreaks from 18 countries were reported from 1988 to 2017. However, most outbreaks are not reported in the published literature, and alternative sources were not used for this systematic review. Risk factors for HEV infection included increased exposure to contaminated water sources and poor hygiene (although not all studies found this association). Risk factor data suggested an increased likelihood of current or recent HEV infection and disease associated with faecal-oral transmission of HEV, as well as exposure to blood and animals. However, the authors emphasized that most data on HEV prevalence and risk factors come from specialized studies or outbreak reports.

There are no primary studies specific to the clinical utility of the HEV IgM ELISA on patient management and care. However, several preventative strategies could reduce the number of future HEV cases and deaths, especially if these preventative measures are introduced early in an outbreak. The applicant identified 12 studies that point to the clinical utility of an HEV diagnosis and greater understanding of the epidemiology and burden of HEV disease in the local context. Better understanding of the local epidemiology and disease burden caused by HEV will allow country officials to make evidence-based decisions on intervention implementation both prior to and during outbreaks.

J. Evidence for economic impact and/or cost-effectiveness (from application)

No data available.

K. Ethics, equity and human rights issues (from application)

HEV IgM ELISAs have been demonstrated to have reduced sensitivity in transplant recipients, an immunocompromised population. In areas where HEV is endemic, HIV is likely to be the most common immunocompromising cause. ELISAs have not been evaluated in HIV-positive populations except for one study that included six HIV-positive patients. That study did not report lower sensitivity in these six patients; however, a systematic evaluation in HIV-positive patients is needed. The IgM ELISAs require a continuous power supply and basic laboratory infrastructure. These facilities may not be available in all areas and may be inaccessible to some populations. Increased availability of diagnostic testing would allow country officials to better understand the local burden of HEV, and therefore to make evidence-based decisions, for example regarding the routine use of HEV vaccine and its use during outbreaks.

No ethical issues were identified.

L. Summary of evidence evaluation

Hepatitis E infection is a significant global health problem. IgM EIAs for diagnosing HEV infection are included in the WHO guidance (11, 15). The 2018 EASL guidelines also recommend a combination of anti-HEV-IgM and nucleic acid testing for HEV infection (10.1186/S12884-020-03116-2). Evidence to assess clinical utility/effectiveness is insufficient. The diagnostic accuracy estimates presented for this application are probably too optimistic, as case-control designs were used in the studies. If diagnostic accuracy were suboptimal, the value of the test would depend on how it would be used in conjunction with other tests in the diagnostic pathway. More studies are needed that evaluate the test in the intended use population. In the absence of such evidence, other factors may weigh more heavily in eventually deciding to use this test, such as resources required, acceptability and equity.

M. Summary of SAGE IVD deliberations

Hepatitis E is an acute viral hepatitis caused by HEV infection. Most affected people recover. However, a small proportion – generally less than 5% but much higher in pregnant women – develop acute liver failure. Hepatitis E should always be considered in outbreaks of acute jaundice syndrome, which have occurred more recently across sub-Saharan Africa, and particularly in the context of internally displaced person camps.

Definitive diagnosis of hepatitis E is challenging, as causes of acute jaundice are many and include yellow fever, hepatitis A and leptospirosis. For countries experiencing outbreaks, the problem of differential diagnosis is exacerbated by lack of access to hepatitis E assays.

The HEV IgM ELISA is one of three hepatitis E assays submitted as new additions to EDL 4. ELISA is well established in many laboratories and settings. SAGE IVD members questioned whether all three assays are needed and noted uncertainties about how best to use the laboratory-based and RDT tests for diagnosing HEV infection. One SAGE IVD member noted that RDT and NAT and ELISA are all essential for a laboratory network and how individual countries choose to implement the tests will be decided on the ground. Moreover, WHO is currently updating its guidance, which includes generating a consolidated algorithm for HEV assays.

One SAGE IVD member also raised a concern that the evidence submitted is at higher risk of bias owing to the nature of the populations studied. However, it was pointed out that better studies are unlikely to be done in the near future.

Literature cited in the discussion:

European Association for the Study of the Liver. EASL clinical practice guidelines on hepatitis E virus infection. *J Hepatol.* 2018;68:1256–71 ([https://www.journal-of-hepatology.eu/article/S0168-8278\(18\)30155-7/fulltext](https://www.journal-of-hepatology.eu/article/S0168-8278(18)30155-7/fulltext), accessed 14 December 2022).

N. SAGE IVD recommendations

SAGE IVD recommended including the hepatitis E virus IgM ELISA antibody test category in EDL 4

- as a disease-specific IVD for use in clinical laboratories (EDL 4, Section II.b);
- using an immunoassay format;
- using serum and plasma as specimen types;
- to diagnose acute hepatitis E virus infection.

O. References (from application)

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2.1.6 Immunoglobulin M antibodies to hepatitis E virus rapid diagnostic test

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

The application proposed adding a hepatitis E IgM antibody rapid test to the EDL as an IVD to diagnose acute hepatitis E infection.

B. Applicant

Department of Public Health, Syracuse University

C. WHO technical department

None

D. Background (from application)

Disease condition and impact on patients

HEV is an RNA virus and a leading cause of acute viral hepatitis worldwide (1). Hepatitis E disease presents as acute, viral hepatitis. During the first week of illness, many symptoms are nonspecific, including fever, malaise, nausea and vomiting. After the prodromal phase, patients experience a period of acute, icteric hepatitis, including jaundice, dark urine, pale stools and prolonged cholestasis with elevated liver enzymes. Symptoms can last 4–6 weeks (2). Most cases occur in older adolescents and adults. In general, these cases are mild and self-limiting, yet approximately 1–2% of cases die. However, some populations are more prone to severe disease. Women infected during pregnancy are at increased risk of fulminant hepatic failure and its associated complications, including hepatic encephalopathy, cerebral oedema and disseminated intravascular coagulation. HEV infection during pregnancy also has poor outcomes for the fetus, including low birth weight, small for gestational age, preterm birth and intrauterine death (3). A recent meta-analysis found the case fatality rate of hepatitis E during pregnancy to be 26% (IQR: 17–41%) for the mother, 33% (IQR: 19–37%) for the fetus and 8% (IQR 3–20%) for the neonate (4).

HEV is a pathogen of global concern (5). However, the burden of disease is not distributed evenly; HEV is very common in low-income countries, where

it causes substantial burden of disease, while relatively few cases are reported from high-income countries (5). There are four genotypes of HEV that infect humans. Genotypes 1 and 2 only infect humans and are thought to be transmitted primarily via contaminated drinking water. These genotypes are most common in South-East Asia and Africa (6). They are responsible for large outbreaks, with cases numbering in the tens of thousands. Outbreaks have been reported from East and South-East Asia, and protracted outbreaks have occurred in Africa, often affecting displaced populations (7). However, genotypes 1 and 2 also cause substantial disease outside of outbreaks (6). In India, between 25% and 50% of clinical hepatitis cases are caused by HEV, even in the absence of an outbreak (6). Genotypes 3 and 4 infect humans and a wide range of mammals, notably wild and domestic swine. These genotypes are usually transmitted zoonotically from eating infected meat and are largely reported from Europe, East Asia and the Americas. Here, HEV is responsible for sporadic cases and small foodborne outbreaks (8).

Does the test meet a medical need?

Rapid testing has become common practice throughout the world since the development and wide application of COVID rapid test kits. Similar rapid diagnostics exist for influenza, HIV, HCV, malaria and many other infections. Several RDTs for the detection of anti-HEV IgM are available commercially. These tests can be used as a first-line tests, particularly in low-resource settings where HEV diagnostics are not usually performed (9). Anti-HEV IgM antibodies appear early during infection and indicate a current or recent infection. They are detectable in blood about 3–7 days after symptom onset (after approx. 1 month incubation period) and persist for several months (10). Availability of HEV diagnostic tests will improve the differential diagnosis capability in the case of acute jaundice syndrome. Early diagnosis can alert authorities to the possibility of an outbreak, giving critical time to plan mitigation efforts. Due to the lack of diagnostic testing in areas where HEV is most common, the burden of HEV disease is underestimated and often poorly understood at the country level. This lack of awareness and understanding by country officials is thought to be one reason why vaccines have not been used in outbreaks for a decade after the vaccine became licensed, leading to unnecessary mortality and morbidity.

There are several benefits of these rapid tests, including that they are simple to perform and therefore can be completed by health and care workers and non-skilled laboratory technicians; they are low cost, facilitating their distribution to health facilities that do not usually have such diagnostic capability; and the tests can be performed in a basic health facility space, as they do not require laboratory equipment. The good performance of anti-HEV IgM RDTs indicates that they can be used as effective tools for routine diagnosis (9, 11, 12, 13, 14).

How the test is used

Rapid tests are administered at POC and can give results in less than 1 hour, allowing health care providers to make real-time decisions about the future care of the patient. When a suspect HEV case presents at the community level, defined as any person presenting with an acute (recent, new or abrupt) onset of jaundice (yellowing of whites of eyes or skin) or dark urine and pale clay stools, a rapid IgM test should be performed, if available, to determine the diagnosis (15). If the rapid IgM test is positive, this can be considered case confirmation. If the rapid test is positive early in the clinical course of infection, samples may still be sent to a reference lab for PCR or IgM ELISA confirmation, but this is not necessary. If the patient tested negative on the rapid IgM test and no other cause for the acute jaundice has been found, a PCR test to detect HEV RNA or an ELISA to detect anti-HEV IgM should be performed to confirm the negative diagnosis.

Note: the following algorithm was provided by the applicant as part of this application and is not a WHO algorithm.

Diagnostic algorithm for HEV infection: <https://docs.google.com/presentation/d/10Yd0I67LoepbYSHxIIZwrMEKUJttU9OA/edit#slide=id.p1> (accessed 1 August 2023).

E. Public health relevance (from application)***Prevalence***

A commonly cited meta-analysis estimated that HEV causes 20.1 million infections, 3.4 million clinical cases, 70 000 deaths and 3000 stillbirths annually due to the epidemic-prone genotypes 1 and 2 (16). While there is increasing recognition of HEV in genotype 3 and 4 endemic areas, the burden of disease has not been well classified. However, the burden of disease of HEV is vastly underestimated due to the lack of diagnostic capabilities in areas where HEV is most common.

Socioeconomic impact

Poor understanding of the global burden of disease has hindered efforts to implement control and prevention strategies. Few studies have looked at the economic impact of hepatitis E. In Nepal, acute HEV infection led to an average of 10 bedridden days and 22 sick days; wage earners lost nearly 20% of their yearly income (17). An estimated 108 YLL per 1000 individuals, 144 years lived with disability per 1000 individuals and 252 DALYs per 1000 individuals were attributed to an HEV outbreak in Uganda (18). However, this estimate used disability weights for untreated diarrhoeal disease and did not account for differential severity among pregnant women and neonates, therefore underestimating the true economic impact.

F. WHO or other clinical guidelines relevant to the test (from application)

Use of the RDT to diagnose acute hepatitis E in suspected cases is supported by WHO guidance on recognition, investigation and control of waterborne outbreaks of hepatitis E (15, 19). The RDT is one of the first-line tests recommended for this purpose.

G. Basic test characteristics (from application)

Test formats available	Lateral flow RDT
Specimen types	Whole blood
Equipment required	No additional equipment required
Regulatory status	CE-IVD, Australia TGA, China NMPA
Availability	Global
Price per test range	US\$ 4–11.25
Instrument price range	NA

H. Evidence for diagnostic accuracy (from application)

There are currently no systematic reviews that detail the clinical accuracy of HEV RDTs. For the purposes of this application, it was therefore necessary to conduct a systematic review. To do so, a search was conducted through PubMed using the search terms ((HeV) OR (Hepatitis E Virus)) AND ((RDT) OR (rapid diagnostic test) OR (dipstick) OR (rapid antigen test) OR (antigen test)), calling up 209 results. Results were limited to the English language. Initial searching found it necessary to narrow search results by filtering out articles with (latex) or (Hendra), yielding 147 results. These articles were reviewed by hand, and five were found to be relevant to HEV RDTs specifically.

Clinical accuracy was examined in these five studies, with two of three commercially available RDTs: the MP Diagnostics Assure HEV IgM rapid test and the Wantai HEV IgM rapid test.

Four studies examined the Assure test (9, 10, 11, 12, 13, 14). Sensitivity was assessed by comparing the rapid test to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed using patients with acute infections from other viruses or healthy, HEV RNA-negative blood donors. One of the four studies used only genotype 3 samples, one used only genotype 1, and two used a mix of both genotypes 1 and 3. Three studies were performed in European populations, and one in South-East Asian populations.

Range of sensitivity: 82–93%

Range of specificity: 99–100%

Range of PPV: 99.5–100%

Range of NPV: 95.8–98%

Two of the five studies examined the Wantai test (9, 11). Sensitivity was assessed by comparing the rapid test to PCR-positive, acute hepatitis E patients early in the course of symptoms. Specificity was assessed using patients with acute infections from other viruses or healthy, HEV RNA-negative blood donors. Both studies primarily used genotype 3 samples, although one of the studies also included several genotype 1 samples. Both studies were performed in European populations.

One study compared the sensitivity, specificity, PPV and NPV of immunocompetent individuals with transplant recipients, an immunocompromised population. Although these values were similar, the values for immunocompromised individuals did tend to be lower and were not included in the following ranges.

Range of sensitivity: 90–96%

Range of specificity: 99–100%

Range of PPV: 99.5–100%

Range of NPV: 95.8–98%

I. Evidence for clinical utility/impact (from application)

A systematic search across several databases at the time of submission of this application found no systematic reviews that examined the direct clinical utility of HEV RDTs on patient care and management. However, one recent systematic review examined data on the epidemiology of HEV in LMICs of Africa and Asia based on seroprevalence, outbreaks and risk factors for infection (20). The lack of routine testing is a major limiting factor to understanding the burden of HEV disease in LMICs. Ninety-one studies from 29 countries examined seroprevalence, with seroprevalence generally increasing by age. Forty-nine completed or ongoing HEV outbreaks from 18 countries were reported from 1988 to 2017. However, most outbreaks are not reported in the published literature, and alternative sources were not used for this systematic review. Risk factors for HEV infection included increased exposure to contaminated water sources and poor hygiene (although not all studies found this association). Risk factor data suggested an increased likelihood of current or recent HEV infection and disease associated with faecal-oral transmission of HEV, as well as exposures to blood and animals. However, the authors emphasized that most data on HEV prevalence and risk factors come from specialized studies or outbreak reports.

There are no studies specific to the clinical utility of HEV RDT on patient management and care. However, several preventative strategies could reduce the number of future HEV cases and deaths, especially if these preventative

measures are introduced early in an outbreak. The applicant identified 12 studies that point to the clinical utility of an HEV diagnosis and greater understanding of the epidemiology and burden of HEV disease in the local context. Better understanding of the local epidemiology and disease burden caused by HEV will allow country officials to make evidence-based decisions on intervention implementation both prior to and during outbreaks.

J. Evidence for economic impact and/or cost-effectiveness (from application)

No data available.

K. Ethics, equity and human rights issues (from application)

HEV RDTs have been demonstrated to have lower sensitivity in transplant recipients, an immunocompromised population. In areas where HEV is endemic, HIV is likely to be the most common immunocompromising cause. HEV RDTs have not been evaluated in HIV-positive populations. Increased availability of diagnostic testing would allow country officials to better understand the local burden of HEV, and therefore to make evidence-based decisions regarding the use of vaccines both routinely and during outbreaks.

No ethical issues were identified.

L. Summary of evidence evaluation

HEV poses a significant clinical challenge, with a medium-high burden of disease. The diagnostic accuracy of commercially available RDTs was evaluated based on the five studies provided. Study sample sizes are often limited (< 100), and methodological quality is variable (no blinding, selection of cases and controls as opposed to cohort). The diagnostic accuracy of the RDTs, however, is high in general. There are no studies assessing the impact of the test on clinical utility or cost-effectiveness (which is not uncommon for diagnostic tests). Based on the body and quality of evidence available, it is necessary to request more high-quality studies on (indirect) effectiveness of this diagnostic test.

M. Summary of SAGE IVD deliberations

Hepatitis E is an acute viral hepatitis caused by HEV infection. Most affected people recover. However, a small proportion – generally less than 5% but much higher in pregnant women – develop acute liver failure. Hepatitis E should always be considered in outbreaks of acute jaundice syndrome, which have occurred more recently across sub-Saharan Africa, and particularly in the context of internally displaced person camps.

Definitive diagnosis of hepatitis E is challenging, as causes of acute jaundice are many and include yellow fever, hepatitis A and leptospirosis. For

countries experiencing outbreaks, the problem of differential diagnoses is exacerbated by lack of access to hepatitis E assays.

SAGE IVD noted the utility of the HEV IgM RDT both for surveillance and outbreaks. But the group noted that performance for RDTs for hepatitis E are generally poor. One SAGE member stressed that RDTs need to be done in combination with a system where referral-level ELISAs and NATs are available to confirm outbreaks.

The HEV IgM RDT is one of three hepatitis E assays submitted as new additions to EDL 4. The assays are all part of the clinical guidelines beyond WHO and are also mentioned in the EASL guidelines. WHO is currently updating its guidance on hepatitis E, including a performance review of hepatitis E RDTs.

Because the RDT has the advantage of solving an access issue, SAGE IVD agreed to list the test conditionally, pending additional information on performance, and guidance and consolidated algorithms from WHO.

Literature cited in the discussion:

European Association for the Study of the Liver. EASL clinical practice guidelines on hepatitis E virus infection. *J Hepatol.* 2018;68:1256–71 ([https://www.journal-of-hepatology.eu/article/S0168-8278\(18\)30155-7/fulltext](https://www.journal-of-hepatology.eu/article/S0168-8278(18)30155-7/fulltext), accessed 14 December 2022).

N. SAGE IVD recommendations

SAGE IVD recommended conditionally including the hepatitis E virus IgM antibody RDT category in EDL 4

- as a disease-specific IVD for use in community settings and health facilities without laboratories (EDL 4, Section I.b);
- using an RDT format;
- using capillary whole blood specimen type;
- to aid in the diagnosis and surveillance of hepatitis E virus infection;

pending the submission of more comprehensive data on performance and a clearer clinical algorithm.

SAGE IVD recommended adding a note to the listing table specifying serum and plasma for laboratory settings.

SAGE IVD also recommended linking the EDL entry to the WHO consolidated algorithm when it is published.

SAGE IVD further recommended adding hepatitis A to EDL 5.

SAGE IVD recommended clarifying in general what conditions need to be satisfied in conditional listings.

O. References (from application)

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2.1.7 Kleihauer-Betke acid-elution test

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eTIKGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

The application proposed adding the Kleihauer-Betke acid-elution test (KB test) to the EDL as an IVD to estimate fetomaternal haemorrhage (FMH), to aid in the prognosis of pregnancy and to guide anti-D immunoglobulin prophylaxis.

B. Applicant

International Federation of Biomedical Laboratory Science

C. WHO technical department

None

D. Background (from application)

Disease condition and impact on patients

Haemolytic disease of the fetus and newborn can be life-threatening if not diagnosed or prevented. The disease affects an Rh-positive fetus of a sensitized Rh-negative mother. Sensitization, which can occur following childbirth, fetal loss or blunt trauma to the abdomen, can be prevented via the use of prophylactic anti-D immunoglobulin.

When FMH occurs, fetal haemoglobin is mixed with maternal blood. In response to this exposure the maternal immune system is activated, and isoimmunization (formation of anti-Rh(D) antibodies) may occur if the mother is Rh(D) negative and the blood type of the fetus is Rh(D) positive. It takes only 0.01–0.03 mL of FMH for isoimmunization of the mother. Future pregnancies

may be at risk for Rh(D) disease if the fetus is Rh(D) positive. The maternal antibodies bind to fetal Rh(D)-positive erythrocytes, leading to haemolysis, anaemia, hydrops fetalis and possibly fetal death. Identification and quantification of a fetomaternal bleed can be used to direct prophylactic therapy with anti-D immunoglobulin (also known as Rho(D) immune globulin).

While quantification of the bleed can be undertaken using sophisticated methods such as flow cytometry, this is not readily available in all health care settings where maternity care is offered. The KB test is a simple examination requiring minimal equipment. It is, however, dependent on the skill of the laboratory scientist performing the analysis. The test remains useful for demonstrating haemoglobin of fetal origin in maternal circulation, and it is also recommended as part of the investigation of stillbirth.

Does the test meet a medical need?

The KB test is utilized to determine the presence of fetal blood in maternal circulation and to better estimate the amount of FMH with a threshold of 5 mL. KB testing has obstetrical implications in the diagnosis and prognosis of preterm labour, fetal demise and other conditions. The test can be used to guide anti-D immunoglobulin prophylaxis.

How the test is used

This test remains the gold standard for detecting FMH. For bleeds estimated to be less than 10 mL, the standard dose of anti-D prophylaxis can be used to prevent sensitization. Where the estimated bleed is > 5 mL, samples can be sent for confirmative flow cytometry where available.

E. Public health relevance (from application)

Prevalence

Not provided.

Socioeconomic impact

Not provided.

F. WHO or other clinical guidelines relevant to the test (from application)

Not provided.

G. Basic test characteristics (from application)

Test formats available	Reagents ready to use within a kit
Specimen types	Whole blood

Table *continued*

Equipment required	Microscope, stopwatch
Regulatory status	CE-IVD
Availability	No information provided
Price per test range	€0.4–3.1
Instrument price range	NA

H. Evidence for diagnostic accuracy (from application)

The KB test is not as precise or accurate as flow cytometry and tends to overestimate the volume of fetal blood in maternal circulation.

I. Evidence for clinical utility/impact (from application)

Alloimmunization from FMH remains an ongoing cause of haemolytic disease of the fetus and newborn. Though failure rates of postnatal prophylaxis have decreased to less than 1–2%, it is critical to minimize laboratory errors when calculating the Rh immunoglobulin dose to prevent maternal alloimmunization. Flow cytometry and the KB method are two means of calculating the necessary Rh immunoglobulin dose.

The advantages of using the KB test include its ease of access, inexpensive cost and lack of special equipment needed. Inherent limitations to using the test include a lack of standardization, associated labour to perform it and its relative imprecision, with a coefficient of variation of 30–80%.

Although flow cytometry can analyse a larger batch of samples (resulting in greater quantitative accuracy and reproducibility; is more precise, with a coefficient of variation less than 20%; and can distinguish between adult F-cells and fetal cells), it is relatively more expensive, time-consuming and inaccessible.

The KB test can also be used as a test to explain fetal anaemia.

J. Evidence for economic impact and/or cost-effectiveness (from application)

Not provided.

K. Ethics, equity and human rights issues (from application)

There is a 72-hour window from the sensitizing event within which to administer prophylactic anti-D immunoglobulin to prevent alloimmunization. Women may not present until 48 hours have elapsed. Where flow cytometry cannot be made available, a KB test is an acceptable alternative and its absence could lead to ethical issues in addition to inequal access to affordable health care.

L. Summary of evidence evaluation

Considering the fact that flow cytometry is not always available, this very easy, less accurate test can save lives. While flow cytometry may be more accurate, it is not readily available in all clinical situations and treatment may be delayed or inadequate without access to the KB test. The test kit is not too expensive.

M. Summary of SAGE IVD deliberations

The KB acid-elution test measures the presence of fetal blood in the maternal circulation. The test is extremely valuable in LMICs where FMH is suspected and the gold standard (flow cytometry) is scarcely available. The KB test is also used to determine the appropriate dose of anti-D immunoglobulin to give a mother to prevent problems related to blood incompatibility when there has been mixing of fetal and maternal blood.

The KB test is easy to use. But it is microscopy based, which means that it requires a high standard of laboratory training. The test also only picks up more than 5 mL of bleed. Flow cytometry provides a more accurate quantification of the amount of haemorrhage, but it is expensive and is usually done in a tertiary institution. SAGE IVD members emphasized that this characteristic is true for high-income countries as well as LMICs. One SAGE IVD member noted that a colleague in Australia reports doing 14 000 KB tests per year for FMH vs 30 flow cytometry tests.

One expert raised a concern about availability of anti-D immunoglobulin in LMICs and whether it makes sense to include the KB test in the EDL if the therapy is actually difficult to get. Experts working in India and Mexico reported that supplies of immunoglobulins in their countries could be unreliable. But it was pointed out that anti-D immunoglobulin has consistently appeared on essential medicine lists across the globe for years and is likely to be generally available.

SAGE IVD noted that the submission did lack a clear algorithm. Group members also questioned the quality of the evidence provided in the application, and specifically the lack of a direct comparison with flow cytometry. However, these concerns were not judged substantial enough to affect the decision to list.

Ultimately, SAGE IVD members agreed that the KB test is critical to have, especially to save the lives of babies and mothers in LMICs where access to flow cytometry is uncertain or nonexistent.

In the statement of test purpose, SAGE IVD recommended replacing “prognosis” with “treatment” to avoid giving the impression that the test predicts outcome.

Literature cited in the discussion:

Thorpe SJ, Sands D, Fox B, Behr-Gross ME, Schaffner G, Yu MW. 2nd WHO international standard for anti-D immunoglobulin. Geneva: World Health Organization; 2003 (WHO/Bs03.1962; <https://apps.who.int/iris/handle/10665/67735>, accessed 14 December 2022).

WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016 (<https://apps.who.int/iris/handle/10665/250796>, accessed 14 December 2022).

N. SAGE IVD recommendations

SAGE IVD recommended including the Kleihauer-Betke acid-elution test category in EDL 4

- as a general IVD for use in clinical laboratories (EDL 4, Section II.a);
- using microscopic examination of slides which may use different types of microscopes and stains;
- using whole blood as specimen type;
- to aid in the diagnosis and treatment of fetomaternal haemorrhage (FMH).

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2.1.8 Meningitis/encephalitis multiplex polymerase chain reaction panel

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

The application proposed adding a meningitis/encephalitis multiplex PCR panel to the EDL as an IVD to aid in the diagnosis of specific agents of meningitis and/or encephalitis.

B. Applicant

bioMérieux

C. WHO technical department

None

D. Background (from application)

Disease condition and impact on patients

Meningitis, a devastating disease with significant risk of mortality and long-term sequelae in survivors, remains a major global public health challenge (1). Meningitis, an inflammation of the membranes that surround the brain and spinal cord, is predominantly caused by infection of the central nervous system (CNS) by bacteria or viruses (2). Yeast and parasites are also causes of meningitis, with cryptococcal meningitis having a disproportionate impact among adults living with HIV (3). Cases and outbreaks are a threat in all countries around the globe. Meningitis and encephalitis (ME) are widespread and potentially life-threatening diseases.

These infections are associated with high morbidity and mortality, particularly in cases of bacterial meningitis, in which the disease can be fatal in healthy people in 24–48 hours and, if not diagnosed quickly, can lead to permanent sequelae such as loss of limbs, visual and auditory complications, seizures and cognitive deficits.

It is important to differentiate between bacterial meningitis (which is more lethal), and aseptic or viral meningitis (which is more common and sometimes less severe) (4). The pathogens most commonly associated with acute bacterial infections are *Streptococcus pneumoniae*, *S. agalactiae*, *Neisseria meningitidis* and *Haemophilus influenzae*, which together account for more than 80% of infections (4). Mortality related to bacterial meningitis varies significantly by infectious organism and patient age, as well as regional socioeconomic factors (1). Viral meningitis is more common than bacterial meningitis, with

enterovirus (EV) being the leading cause, and is usually associated with milder, self-limiting manifestations of the disease (5).

The pathogens that cause infectious encephalitis are primarily viral agents, with herpes simplex virus 1 (HSV-1) being the most common and most severe form of the illness. Varicella-zoster virus (VZV) is the second leading cause of infectious encephalitis in developed countries, and like HSV can be treated with antiviral agents. Rapid identification of cytomegalovirus (CMV) and human herpes virus 6 (HHV-6) associated encephalitis is critical for immunocompromised patients (6). Additionally, approximately 40% of encephalitis etiologies remain unknown (7).

ME pose a significant burden to populations everywhere, but especially in tropical zones, where the range of pathogens differs compared with that in more temperate climates (8, 9). Epidemics of meningitis occur worldwide. Western sub-Saharan Africa is at the heart of the “meningitis belt”, a strip of land composed of 26 countries and home to 400 million people with a historically high prevalence of meningitis outbreaks (10). The meningitis belt possesses an increased incidence of meningitis cases due to a combination of ambient temperature, animal and insect vectors, low vaccination rates, shortcomings in hygiene, migration and displacement, and other modifiable and non-modifiable factors (6, 11). Since changing ambient temperature and vaccination rates are major contributors to the host environment globally, the detection of pathogens in the meningitis belt is of relevance beyond the populations that reside there.

Does the test meet a medical need?

Commercially available multiplex PCR (mPCR) panels have been available since 2016 and have several distinct advantages over standard-of-care (SOC) diagnostics, primarily related to the rapid turnaround time (TAT) and relative ease of use of commercial mPCR. Table 1 summarizes the standard diagnostic methods used for pathogen identification in CSF.

Table 1

Standard diagnostic methodologies for pathogen identification in CSF

Diagnostic method	Purpose	Key limitations
CSF analysis	Cell count and biochemical analyses help to evaluate infectious etiologies	Poor sensitivity and specificity
CSF/blood culture	Gold standard for identifying the causative agent in cases of suspected bacterial ME	Long TAT Labour intensive Prior antibiotics reduce sensitivity

Table 1 *continued*

Diagnostic method	Purpose	Key limitations
Gram stain	Identifies and differentiates Gram-positive and -negative bacterial infections	Utility limited to bacterial pathogens Poor to moderate sensitivity
Antigen testing	Rapid and targeted detection of specific bacterial/fungal infections	Variable sensitivity and specificity
Singleplex PCR	Gold standard for identifying the causative agent in cases of suspected viral ME	Requires specialized facilities/equipment Long TAT due to send-out tests Limited to one/few target(s)
Low-plex PCR	Identifies more than one causative agent in cases of suspected viral ME	
Multiplex PCR	Identifies the causative agent of suspected ME infections using a small volume of CSF	Rapid TAT High sensitivity and specificity Easy to use, does not require specialized expertise Tests for multiple pathogens in a single assay

CSF: cerebral spinal fluid; ME: meningitis and encephalitis; PCR: polymerase chain reaction; TAT: turnaround time.

Most common pathogens for bacterial meningitis are covered by empiric therapy. Rapid identification of infective organisms allows for upstream antimicrobial triage, including discontinuing antibiotics when a viral etiology is confirmed, narrowing or expanding antibiotic coverage when appropriate, or adding antivirals and antifungals when indicated. Not only is reduction of unnecessary antibiotics a vital factor in combating antimicrobial resistance (AMR), but it also conserves antibiotics for those who need them most. Recent supply chain disruptions related to the COVID-19 pandemic have demonstrated the importance of resource conservation, especially in regions where antibiotic availability is limited at baseline.

The bacterial targets included in commercially available mPCR panels account for > 80% of bacterial meningitis cases (4). Additionally, *Haemophilus influenzae*, *N. meningitidis* and *S. pneumoniae* are vaccine-preventable causes of bacterial meningitis. These pathogens, along with *S. agalactiae* (also available in commercial mPCR panels), have been identified as key pathogens in WHO's

Defeating meningitis by 2030 roadmap (2). Rapid identification and vigilant surveillance of these pathogens can help detect regional disease outbreaks and assist in developing mitigation strategies and triaging resource allocation.

Viral meningitis can in many cases be managed with supportive care outside of the hospital setting, reducing the need for antibiotics, lengthy hospital stays and additional diagnostic tests. This is important to note, as viral meningitis is much more common than bacterial meningitis. The most common cause of meningitis is EV, which accounts for over 50% of known etiologies in both children and adults (12, 13). Using PCR to confirm EV meningitis during seasonal increases (which are proportionally higher in LMICs), may further enhance conservation of health care resources, by appropriately triaging antibiotics and other health care resources (e.g. hospital beds, labour) during times of increased EV disease circulation. The importance of reducing antibiotic exposure to combat AMR cannot be overstated and bears repeating here, as the rapid diagnosis of viral meningitis is a key factor in reducing unnecessary antibiotics.

Improving identification of patients infected with *N. meningitidis* has been shown to aid in timely contact tracing and antibiotic chemoprophylaxis of close contacts of infected individuals. Chemoprophylaxis of these contacts has been shown to aid in preventing meningococcal disease (14). In a retrospective cohort study in Israel, implementation of an mPCR panel for ME contributed to an increase in administration of antibiotic chemoprophylaxis in close contacts of *N. meningitidis*-infected individuals (50% vs 4%; $P = 0.01$) (15).

Lastly, the comprehensive nature of mPCR technology enhances the diagnostic yield of on-panel pathogens, as they might otherwise not be tested. The enhanced detection afforded by the mPCR panels aids in increasing our understanding of the regional epidemiology of ME.

How the test is used

When a patient is suspected of meningitis/encephalitis, traditional CSF culture methods can take up to 3 days to produce pathogen-specific results. Meningitis PCR syndromic testing is capable of simultaneously detecting and identifying multiple bacterial, viral and yeast nucleic acids directly from CSF specimens obtained via lumbar puncture from individuals with signs and/or symptoms of meningitis and/or encephalitis. The following organisms are the most commonly identified:

- bacteria: *Escherichia coli* K1, *H. influenzae*, *Listeria monocytogenes*, *N. meningitidis* (encapsulated), *S. agalactiae*, *S. pneumoniae*;
- viruses: CMV, EV, HSV-1/2, HHV-6, human parechovirus, VZV; and
- yeast: *Cryptococcus neoformans/gattii*.

Meningitis syndromic panel testing is indicated as an aid in the diagnosis of specific agents of meningitis and/or encephalitis, and results are meant to be used in conjunction with other clinical, epidemiological and laboratory data. Results from such tests are not intended to be used as the sole basis for diagnosis, treatment or other patient management decisions.

E. Public health relevance (from application)

Prevalence

There were an estimated 5.05 million cases of meningitis and 2.22 million cases of encephalitis globally in 2017 despite the introduction of preventative vaccines for several infectious causes of ME, with the vast majority of meningitis cases (approx. 53%) occurring in Africa and the majority of encephalitis cases (approx. 70%) occurring in Asia (2, 8, 16, 17). Globally in 2017, meningitis and encephalitis contributed to 288 000 and 92 400 deaths, respectively (17). The major risk factors for the two conditions are similar and include lack of immunization, a weakened immune system, travel to regions of high disease prevalence and young or elderly age (8, 18, 19, 20, 21).

Socioeconomic impact

The direct costs associated with ME are high and primarily driven by hospitalization and costs of diagnosis/treatment. It was estimated that the average hospitalization cost per ME patient in the United States between 2011 and 2014 was US\$ 15 572 for adults, US\$ 12 259 for infants and US\$ 11 119 for children, with the exact cost depending on etiology, time to diagnosis and the need for intensive care unit (ICU) stays (12, 22). In 2006, the total cost of hospitalization amounted to US\$ 1.2 billion across community hospitals (US\$ 17 100 per case) from 72 000 meningitis-related hospitalizations (23). The requirement for ICU stays was a key driver of costs associated with hospitalization, accounting for US\$ 23 660, US\$ 30 631 and US\$ 23 344 per case for adults, children and infants, respectively. Differences were seen between age groups in terms of the effect of etiology, with fungal ME having the highest costs in adults (US\$ 41 459 per case) but disease of unspecified viral and herpes virus etiology being associated with greater economic burden in infants and children, respectively (US\$ 41 397 and US\$ 30 906 per case) (22, 24).

The mean antimicrobial cost associated with ME was estimated at US\$ 1144 per adult patient, representing 42% of the total medication cost (21). Where there is a delay in the patient receiving targeted treatment, the duration of empirical treatment increases, with cost implications likely; this may be a particular problem in cases of viral and fungal meningitis initially treated with antibiotics (22). In cases of viral encephalitis, the same issues are potentially

associated with prolonged use of antivirals such as acyclovir, which can increase both hospital costs and LOS through its propensity to result in acute kidney injury (AKI) (25, 26). This highlights the need for patients to be given the most appropriate treatment as soon as possible.

Diagnostic tests and procedures also contribute to the high economic burden of ME, with mean diagnostic laboratory testing costs of US\$ 1222 for adults, US\$ 855 for children and US\$ 825 for infants (6, 24). These costs may be due in part to the labour involved in performing such tests, as well as the fact that many pathogens are not considered in the primary diagnosis, necessitating further etiology-specific testing (6). Outside of the United States, costs are also high. In Chile, mean laboratory costs associated with bacterial meningitis (in international dollars, I\$) have been estimated at I\$ 1604, and medication costs as high as I\$ 1284 in Russia (27).

The long-term consequences of ME can add to this economic burden, mostly due to the need for post-discharge care and the potential for readmission to the hospital. Other long-term consequences of ME can result in costs associated with rehabilitation and permanent disability, along with reduced work productivity for both patients and caregivers.

F. WHO or other clinical guidelines relevant to the test (from application)

It is important to note that no major guidelines have been updated since the widespread use and availability of commercially available mPCR technologies. In fact, several guidelines were revised near the time mPCR platforms came onto the market in 2016. These guidelines noted that new rapid mPCR technology was available, but that limited published data did not allow for clear recommendations for its use (28, 29). As such, the guidelines listed here concern general factors related to the diagnosis of ME and the use of generic PCR (often evaluating data on single- or low-plex PCR technology).

Bacterial meningitis:

- Broad-based PCR may be useful for excluding the diagnosis of bacterial meningitis, with the potential for influencing decisions to initiate or discontinue antimicrobial therapy (strength of recommendation – B, quality of evidence – II, pp. 1271–2) (30).
- Strongly recommended to start antibiotic therapy as soon as possible in acute bacterial meningitis, not to exceed 1 hour (grade A recommendation, p. S48) (28).
- CSF culture is positive in only 60–90% of bacterial meningitis patients, and pretreatment with antibiotics decreases the yield of CSF culture by 10–20% (level 2 conclusion, p. S47) (28).

- In patients with a negative CSF culture and CSF Gram stain, PCR has additive value in the identification of the pathogen (level 2 conclusion, p. S47) (28).
- In patients with negative CSF cultures, the causative microorganisms can be identified by PCR (grade A recommendation, p. S47) (28).

Viral meningitis:

- Rapid detection of EVs by PCR has emerged as a valuable technique that may be helpful in establishing the diagnosis of enteroviral meningitis (strength of recommendation – B, quality of evidence – II, p. 1273). Reduced time to identify EV may lead to shortened patient hospitalization, decreased use of antimicrobial therapy for treatment of presumed bacterial meningitis and reduced need for ancillary diagnostic tests (p. 1273) (30).

Encephalitis:

- Nucleic acid amplification tests (NAATs) (such as PCR) should be performed on CSF specimens to identify HSV-1/2, VZV, EVs and select etiologic agents in patients with encephalitis. Although a positive test result is helpful in diagnosing infection caused by a specific pathogen, a negative result cannot be used as definitive evidence against the diagnosis (strength of recommendation – A, quality of evidence – III, p. 305) (21).
- Herpes simplex PCR should be performed on all CSF specimens in patients with encephalitis (strength of recommendation – A, quality of evidence – III, p. 305) (21).
- In patients with encephalitis who have a negative herpes simplex PCR result, consideration should be given to repeating the test 3–7 days later in those with a compatible clinical syndrome or temporal lobe localization on neuroimaging (strength of recommendation – B, quality of evidence – III, p. 305) (21).
- HSV, VZV and EV PCR are imperative, and results must be available within 48 hours (grade A recommendation, pp. 180, 181) (31).
- The previous gold standard for viral detection (virus culture) has been replaced by the detection of specific nucleic acid from CSF (class Ia, p. 1004) (32).
- PCR of CSF is a major aid in diagnosis (level of recommendation – A, class of evidence I, p. 1009) (32).

G. Basic test characteristics (from application)

Test formats available	Qualitative multiplexed NAT
Specimen types	CSF
Equipment required	Proprietary loading station, system module(s) and software
Regulatory status	CE-IVD, FDA-approved, TGA, JMHLW, Health Canada
Availability	Global
Price per test range	Not provided
Instrument price range	Not provided

H. Evidence for diagnostic accuracy (from application)

At this time, there is only one commercially available mPCR panel with published data available (BioFire ME Panel, bioMérieux, Marcy-l'Étoile, France – hereafter referred to as ME Panel), with only two systematic reviews on test performance.

The ME Panel claims an overall sensitivity of 94.2% and specificity of 99.8%. To date, there are two systematic reviews on the clinical accuracy of the ME Panel, authored by Tansarli and Chapin (33) and Trujillo-Gómez et al. (34).

These two reviews analysed the clinical accuracy of the ME Panel in studies comprising 14 410 patients with CNS infections. The results reported by Trujillo-Gómez et al. provided the diagnostic accuracy measures discriminating bacteria and viruses included in the ME Panel, showing respective sensitivity/specificity for each microorganism. A brief description and conclusion of these two reviews is outlined below. For ease of reference for each of the reviews, in-text citations are consistent with the original manuscripts.

Note: readers can refer directly to the application to see the list of these citations submitted as part of this application. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

Tansarli and Chapin (33). An initial search returned 656 articles retrieved from the PubMed and Embase databases, as well as from manually searching the bibliographies of relevant articles. Of these, eight studies comprising 3059 patients met the inclusion criteria for diagnostic accuracy review of the ME Panel.^{3, 4, 15–20} Six studies evaluated the ME Panel retrospectively,^{4, 16, 18, 20–22} while six studies used the ME Panel on prospectively collected samples from patients with suspected ME.^{3, 15, 17, 23–25} One study included both retrospective and prospectively collected samples.¹⁹ Also, one study tested with the ME Panel used only frozen specimens that were previously positive with routine

testing methods.²² In total, eight studies reported on a mixed population (adult and paediatric patients) or did not determine the age of the study population,^{3, 16, 17, 19–22, 25} and five studies reported exclusively on paediatric patients.^{4, 15, 18, 23, 24} Sensitivity across the eight included studies varied between 60% and 100%, with most of the studies being between 88% and 94%. It is noteworthy that in the single study with low sensitivity (60%),¹⁷ two out of four false negative results were specimens positive for *C. neoformans/gattii* from patients already receiving antifungal treatment. Estimates of overall sensitivity and specificity with 95% confidence intervals were 90% (95% CI: 86–93%) and 97% (95% CI: 94–99%), respectively.

In this diagnostic accuracy review, the authors searched available evidence to assess the ME Panel in terms of sensitivity and specificity in patients with suspected CNS infections. Pooling of eight studies (3059 patients) revealed that both sensitivity and specificity were > 90%. The high accuracy estimates point out that this new RDT can be a very useful tool for the diagnosis of ME.

Trujillo-Gómez et al. (34). The authors performed a systematic review and meta-analysis of diagnostic test accuracy (DTA) studies. This manuscript follows the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for DTA studies. The authors retrieved 2018 references, and after removing duplicates, 1474 titles and abstracts were screened, of which 64 were selected for full-text review. Finally, they excluded 45 studies for multiple reasons and included 19 studies in the review. The 19 studies included 11 351 patients.^{10, 17–34} Four studies enrolled only children,^{18, 19, 27, 28} two included only adults, and the rest included both. They performed two analyses, using a reference test 1 (positive CSF/blood culture and viral PCR for bacteria and viruses, respectively) and a reference test 2 (final diagnosis was adjudicated following an additional test or a clinical analyses of the cases).

In the meta-analysis of reference test 1 (16 studies/6183 patients),^{10, 17–22, 24–27, 29–33} the authors reported a combined sensitivity and specificity of 89.5% (95% CI: 81.1–94.4) and 97.4% (95% CI: 94–98.9), respectively. For reference test 2 (15 studies/5524 patients),^{10, 17, 29–33, 18–22, 24, 26, 27} the authors reported a combined sensitivity and specificity of 92.1% (95% CI: 86.8–95.3) and 99.2% (95% CI: 98.3–99.6), respectively. They also performed meta-analyses for the detection of EV, HSV-1/2 and VZV. A combined sensitivity and specificity of greater than 90% was reported for EV, HSV-2 and VZV, for both reference test 1 and reference test 2. Combined sensitivity and specificity for HSV-1 was 75.5% and 99.9% for reference test 1, and 78.2% and 99.9% for reference test 2.

To summarize, the authors showed that the ME Panel is a valid diagnostic tool for identifying different microorganisms in CNS infections. The ME Panel has acceptable to high sensitivity, and high specificity for identifying bacteria and viruses in CNS infections, in immunocompetent patients. Moreover, the ME

Panel consistently demonstrates high diagnostic accuracy when compared with traditional diagnostic tests and other mPCR technologies.

I. Evidence for clinical utility/impact (from application)

Two published systematic reviews synthesize the results of multiple primary studies on the clinical utility/impact of the only commercially available mPCR product with published data.

Goodlet et al. (35). The systematic review from Goodlet et al. gathered publications from November 2010 through October 2020 using the following search terms: rapid diagnostics, stewardship, filmarray, PCR Panel, polymerase chain reaction, meningitis, central nervous system, encephalitis. They also included in their search assessment of antimicrobial duration (antibiotic and/or acyclovir). The TAT and hospital LOS were also recorded when available.

In this systematic review, Goodlet et al. described 10 controlled retrospective ME studies which evaluated antimicrobial use (Broadhurst et al., 2020; Dack et al., 2019; Evans et al., 2020; Hagen et al., 2020; Messacar et al., 2020; Mina et al., 2019; Moffa et al., 2020; Nabower et al., 2019; Posnakoglou et al., 2020; Walker et al., 2020). Most of the primary studies included in this systematic review utilized a control group except the primary study by Posnakoglou et al. (2020), which is a prospective randomized study. Four studies were conducted exclusively in paediatric populations, three were conducted exclusively in adult patients, and three included both. Four studies restricted inclusion to patients with CSF pleocytosis. No studies excluded polymicrobial CNS infections.

In this systematic review, the authors presented a description of each primary study due to the differences in patient population, study inclusion criteria and CSF positivity rates. These were cited as limitations to the systematic review.

The ME Panel TAT ranged from 2.2 to 6.2 hours vs 24 hours or longer in the control groups, and ME Panel cohorts generally had higher rates of organism positivity. Eight of 10 studies reported statistically significant reductions in either antibiotic or acyclovir duration after ME Panel implementation. Four of the eight studies reporting on antibiotic duration had significantly reduced antibiotic days of therapy. Three of the eight studies (Mina, 2019; Moffa, 2020; Posnakoglou, 2020) that measured LOS as one of their end-points reported reduction in LOS greater than 24 hours in the ME Panel cohort, with a fourth study very close to 24-hour reduction (5.2 days vs 6.1 days) (Evans, 2019).

With respect to guidance for providers, an educational intervention was distributed in Moffa et al. prior to ME Panel roll-out and Broadhurst et al. developed a testing algorithm to direct appropriate use of the ME Panel, with > 40% of ordered ME Panels rejected due to lack of CSF pleocytosis (Broadhurst et al., 2020; Moffa et al., 2020). Both studies had favourable outcomes with ME Panel implementation.

Hueth et al. (36). The systematic review from Hueth et al. (2022) reviewed publications on or after 2015 in the Embase and MEDLINE databases. After screening publications, 11 were retained for meta-analysis and 13 were retained for systematic review, which included a range of study designs including: retrospective cohort ($n = 4$), case-control ($n = 3$), pre-/post-interventions ($n = 3$), cross-sectional studies ($n = 1$), combination designs ($n = 1$) and randomized control trials ($n = 1$). Five publications reported exclusively on paediatric patients, with one study reporting no age and the remaining seven studies reporting on either adults or both children and adults.

The primary outcomes of interest for this review and meta-analysis were hospital LOS, duration of acyclovir use and duration of antimicrobial use. Of these, both LOS and acyclovir use demonstrated a statistically significant reduction across 11 studies, with the duration of antibiotics showing a reduction that did not reach statistical significance.

Likewise, seven studies reported information on duration of acyclovir therapy. Meta-analysis of these studies demonstrated a statistically significant reduction in mean duration of acyclovir therapy by 1.14 days (95% CI: -1.78, -0.50), with the strongest effect observed in studies that exclusively included paediatric patients.

Lastly, among the six studies which reported on duration of antibiotic therapy, three studies demonstrated a statistically significant reduction in mean duration of antibiotic therapy (all of which exclusively evaluated paediatric patients) of 1.85 days (95% CI: -2.50, -1.21). The overall reduction in mean duration of antibiotic therapy across the six studies was not statistically significant but showed a reduction of 1.01 days (95% CI: -2.39, 0.37).

Hueth et al. note that the overall number of publications, as well as the limited number of large-scale randomized studies, limits the generalizability of their findings. The authors also note that the heterogeneity of study sites and practice variation contribute to the variability of the outcomes of interest described in this meta-analysis.

To summarize, utilization of the ME Panel was associated with faster TAT of CSF testing and increased yield of viral organisms, supporting the potential of this panel to decrease unnecessary antimicrobial use and optimize utilization of antiviral therapies among patients with suspected CNS infection. The implementation of the ME Panel was shown to be cost-effective, particularly if reductions in length of hospitalization are realized.

J. Evidence for economic impact and/or cost-effectiveness (from application)

Although the cost of mPCR panels is higher than any single conventional test, the health economic outcomes of using an mPCR panel have been well documented in the literature and are documented below. Studies have demonstrated that

mPCR panels do not only result in downstream savings. Even compared just to SOC testing, the direct cost of testing is comparable at minimum, but with the significant benefits described previously.

In a retrospective study, Soucek et al. performed a cost justification for mPCR technology (37). In their evaluation they retrospectively identified costs for conventional microbiology testing, which averaged US\$ 239.63 per patient. They determined that the cost of each mPCR panel (including instrumentation) was US\$ 239.14. This evaluation demonstrates that testing costs are a net neutral; however, it is likely that the mPCR panel would result in several downstream savings that should also be quantified. Similarly, Cailleaux et al. demonstrated a 15% reduction in cost of care for ME cases, which considered the total cost of testing for the mPCR panel and savings from reduced LOS (38). Again, several other downstream savings need to be quantified to evaluate the full value of the panel.

One such downstream savings could be achieved through the reduction of incidence of AKI. According to the National Kidney Foundation, AKI occurs in 8–16% of hospital admissions and is associated with a fourfold increase in hospital mortality. AKI has a significant impact on the cost of care, with > 1% of the total health care expenditure in the United Kingdom being attributed to AKI. Silver et al. evaluated several studies to estimate the economic consequences of AKI. They conclude AKI increases hospital costs by US\$ 7933 and increases LOS by 3.2 days on average. Additionally, inpatient costs can increase to US\$ 42 077 on average if haemodialysis is required (39). Several medications can cause AKI, including vancomycin (given empirically if ceftriaxone-resistant *S. pneumoniae* is suspected) and acyclovir. The ME Panel has been shown to reduce the duration of acyclovir therapy duration simply as a result of the rapid TAT of the test. In an evaluation of the impact of implementing an mPCR panel on acyclovir therapy duration compared to using an SOC test, Evans et al. concluded that the cost avoidance of reducing AKI cases by discontinuing acyclovir sooner would ultimately be cost neutral or would result in cost savings by routinely using an mPCR panel (40).

An economic model has been published that aimed to evaluate the economic impact of RDTs for community-acquired ME in a paediatric population (41). The analysis estimated a cost savings of US\$ 2157/case when only abnormal CSF is tested on an mPCR panel and US\$ 3481 when all suspected ME cases are tested. The economic model used estimated the mean cost/case ranging from US\$ 17 599 to US\$ 22 025. Using a weighted mean of the estimated cost per case, the estimated cost reduction is 10.9% and 17.6% for testing with abnormal CSF only and testing all suspected ME cases, respectively. A similar modelling study by Duff was also conducted in adults (42). Their analysis estimated a cost savings of US\$ 812/case when only abnormal CSF

is tested on an mPCR panel and US\$ 2213 when all suspected ME cases are tested. The economic model used estimated the mean cost/case ranging from US\$ 17 076 to US\$ 19 651. Using a weighted mean of the estimated cost/case, the estimated cost reduction is 4.23% and 11.52% for testing with abnormal CSF only and testing all suspected ME cases, respectively.

K. Ethics, equity and human rights issues (from application)

mPCR offers rapid testing to expedite time to diagnosis and provision of optimal treatment, potentially accelerating recovery and reducing morbidity and mortality associated with CNS infections. Indeed, the mPCR assay is highly sensitive and specific, and can avoid misidentification of patients with ME. Likewise, the mPCR panel offers comprehensive testing for many of the common pathogens that can cause ME in a single run. It is easy to use and does not require specialized infrastructure or expertise. The test is accessible worldwide.

No ethical issues were identified.

L. Summary of evidence evaluation

Two reviews on diagnostic test accuracy were included. The most recent review includes overlapping studies. For that reason, this review was used as state-of-the-art evidence. The review was of high quality and considered the overall certainty of the evidence as “low” (GRADE).

Regarding GRADE by clinical experts, some additional considerations are relevant. Although all items scored low risk of bias for almost all domains, the authors downgraded due to reference standard criteria. (Note that mPCR should be compared here with single PCR tests, because that is the current practice at the moment.) Also, the authors downgraded for the relatively wide confidence interval for sensitivity. Results from the individual studies were heterogenous. (Note that here, too, the results for sensitivity vary; specificity is rather stable.) Overall, although the review authors consider the certainty of the evidence as low, moderate is also defensible, especially with regard to specificity.

The review included 19 studies (11 351 participants). For all bacteria with reference test 1 (16 studies/6183 patients), sensitivity was estimated at 89.5% (95% CI: 81.1–94.4), and specificity at 97.4% (95% CI: 94–98.9). With reference test 2 (15 studies/5524 patients), sensitivity was estimated at 92.1% (95% CI: 86.8–95.3) and specificity at 99.2 (95% CI: 98.3–99.6). For HSV-2, EVs and VZV, sensitivities were between 75.5% and 93.8%, and specificities above 99% (reference test 1).

Regarding utility, there was one review of high quality on the effect of patients tested with the multiplex ME Panel on LOS. The multiplex ME Panel had a reduction on average LOS (mean difference (MD) (95% CI): –1.20 days

(-1.96, -0.44), $n = 11$ studies). Use of the multiplex ME Panel was also associated with a reduction in the length of acyclovir therapy (MD [95% CI]: -1.14 days [-1.78, -0.50], $n = 7$ studies) and a nonsignificant reduction in the average number of days with antibiotics (MD [95% CI]: -1.01 days [-2.39, 0.37], $n = 6$). Whether this is clinically relevant was not stated. However, one can consider that every reduction is relevant.

One primary study on utility showed that multiplex panels were associated with faster TAT of CSF testing and increased yield of viral organisms, supporting the potential of this panel to decrease unnecessary antimicrobial use among patients with suspected CNS infection. However, reductions in antibiotic duration were not consistently observed, suggesting that diagnostics combined with antimicrobial stewardship efforts are likely needed to optimize panels' impact.

M. Summary of SAGE IVD deliberations

PCR plays an integral role in diagnosing ME. As such, it constitutes an essential diagnostic.

SAGE IVD members agreed that multiplex PCR in general is a promising approach. Nonetheless, concerns were raised about the clinical relevance of the application, which offers a single combination of pathogens that may not be suitable for all settings. The group highlighted that pathogen selection should be based on the epidemiology of a country.

Meningitis can be caused by many different pathogens, including bacteria, fungi and viruses. The causative pathogen can be difficult to identify; consequently, a useful multiplex platform should have an option for country-specific pathogens, such as meningococcus, pneumococcus, *H. influenzae*, HSV-1/2 and EV. The group noted that a country-specific multiplex diagnostic is one of the goals of WHO's *Defeating meningitis by 2030* global road map. Moreover, shorter panels which are not restricted by equipment and biosafety requirements will increase access to and uptake of ME diagnostics in remote settings which incur the highest burden from meningoencephalitis.

SAGE IVD also questioned the high cost of the test. A loop-mediated isothermal amplification (LAMP) assay for detecting ME exists and might be a more cost-effective alternative for LMICs, although wider evaluations are needed and supply chain issues may hinder wider availability of this test. The LAMP tests need further evaluation.

The experts emphasized that molecular-based multiplexed assays are increasingly required to enhance pathogen detection and pathogen-specific meningitis diagnosis, and developments in this area are required towards developing a flexible, multiplex assay that is also affordable, robust and can be scaled up to low-resource and preferably remote settings. Precision medicine, for

example, will only be possible with tests like this one. But listing an individual PCR is problematic; the multiplex needs to be more flexible. Currently, no commercial PCR tests are available for WHO priority pathogens.

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N. SAGE IVD recommendations

SAGE IVD recommended excluding the meningitis/encephalitis multiplex PCR panel to aid in the diagnosis of specific agents of meningitis and/or encephalitis from the fourth EDL. However, the experts also recommended:

- that manufacturers (applicants) collect wider data from LMICs to identify region-specific priority pathogen targets for their PCR panel, develop smaller panels (with fewer targets) consisting of priority pathogens and consider cost adjustments without compromising panel performance in order to make meningitis/encephalitis diagnosis more accessible to populations;
- that the WHO meningitis programme lead the determination of priority pathogens to inform manufacturers;
- encouraging multiplex panel test submissions for EDL 5 to allow more manufacturers to develop multiplex assays that can be scaled up for equitable, reliable meningitis/encephalitis diagnosis.

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2.1.9 Parathyroid hormone

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

The application proposed adding a parathyroid hormone (PTH) immunoassay test to the EDL as an IVD to aid in the evaluation of the causes of calcium homeostasis disorders and monitor the effects of treatment.

B. Applicant

Queensland Children's Hospital

C. WHO technical department

None

D. Background (from application)

Disease condition and impact on patients

PTH is an essential hormone which is central to maintaining the integrity and physiological function of the skeletal system. The skeletal system is one of the largest organs in the body responsible for providing structural integrity across the lifespan; facilitating movement through the network of joints, connective tissue and muscles; protecting and supporting vital organs, including the brain, heart, lungs, liver and kidneys; and storage of essential minerals such as calcium and phosphate. The skeleton also contains bone marrow, which is responsible

for haematopoiesis. The normal physiological functioning of the various organ systems is dependent on a healthy skeleton; conversely, skeletal health is a barometer of overall health.

The PTH assay is used to diagnose and monitor disorders of PTH secretion, including hyperparathyroidism (primary, secondary and tertiary), pseudohypoparathyroidism and hypoparathyroidism. These disorders are associated with a significant health and economic burden worldwide such as chronic kidney disease (CKD) and osteoporosis.

Bone mineral density (BMD) is predominantly determined by genetics, but adequate physical activity and nutrition both play vital role in attaining optimal peak BMD by young adulthood. Malnutrition is a significant problem affecting children in developing countries which affects growth and survival. In 2020, for children under 5 years of age, WHO estimated that 149 million had stunted growth (short for age), 45 million were underweight, and 45% of deaths were related to undernutrition. CKD is a significant cause of metabolic bone disease too.

Causes of primary hyperparathyroidism include solitary adenomas, hyperplasia of the parathyroid glands and parathyroid cancer. The rates of primary hyperparathyroidism have been shown to be increased in populations characterized by social deprivation. Unlike developed countries, where identification and optimal management of predominantly asymptomatic cases of primary hyperparathyroidism are the focus, in developing countries over 70% are symptomatic at presentation with worse clinical outcomes. The widespread availability of PTH assays is important to narrow the gap caused by social disadvantage.

Anterior neck surgery is the most common cause of acquired hypoparathyroidism, accounting for 75% of cases, with autoimmune and infiltrative disease also contributing to disease burden in adults. Genetic conditions such as 22q11 deletions are commonly responsible for hypoparathyroidism in the paediatric population. Hypoparathyroidism has been associated with a twofold increase in rates of fractures.

Severe vitamin D deficiency with or without hypocalcaemia is characterized by hyperparathyroidism as a homeostatic response. The rates of nutritional rickets in children from developing countries has been estimated to be over 50% and represents a significant disease burden.

Does the test meet a medical need?

Measurement of PTH will facilitate the diagnosis and assist in the management of conditions which are prevalent and have significant economic costs in both developed and developing countries. These include CKD and osteoporosis, and other causes of abnormal PTH secretion leading to disorders of bone and mineral metabolism.

How the test is used

Determination of PTH level is useful in the differential diagnosis of both hypercalcaemia and hypocalcaemia, for assessing parathyroid function in CKD and for evaluating parathyroid function in bone and mineral disorders. Readers can refer directly to the application to review diagnostic algorithms on hypercalcaemia, hypocalcaemia, nonsurgical hypoparathyroidism, secondary osteoporosis and hyperparathyroidism.

Note: the algorithms mentioned above were provided by the applicant as part of this application and are not WHO algorithms. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

- CKD – use of PTH in guiding management of CKD

In CKD, PTH measurement is utilized to assess parathyroid function, estimating bone turnover and guiding management. Established clinical practice guidelines are available (KDIGO – Kidney Disease Improving Global Outcomes) for the management of CKD mineral and bone disorder. Intact PTH levels are used to guide treatment in CKD, with current recommendations for evaluating modifiable factors (including hyperphosphataemia, hypocalcaemia, high phosphate intake and vitamin D deficiency) if levels are progressively rising or persistently above the upper range of normal in patients with CKD G1–G5, suggesting secondary hyperparathyroidism. Patients with high bone turnover caused by secondary hyperparathyroidism (advanced osteitis fibrosa) have the highest concentrations of PTH, whereas those with low-turnover, adynamic bone disease, including osteomalacia, have the lowest concentrations whether measured by whole or intact PTH assays.

- Hypoparathyroidism – assessing completeness of parathyroidectomy

In parathyroid surgery, intraoperative PTH is used to assess the effectiveness of removal as well as the risk of hypocalcaemia. Because of the short half-life of PTH (< 5 minutes), intraoperative intact PTH is often measured (just before incision and again 20 minutes after resection of hyperfunctioning parathyroid) to assess the completeness of parathyroidectomy. A decline of $\geq 50\%$ or more suggests adequate removal.

E. Public health relevance (from application)**Prevalence**

In a comprehensive systematic review and meta-analysis, the global prevalence of osteoporosis in adults, defined by WHO criteria as BMD that lies 2.5 standard deviations or more below average for age and gender, was estimated to be 18.3%

(95% CI: 16.2–20.7) with an age range of 15–105 years and a sample size of 103 334 579 people.

In 2017, the GBD Chronic Kidney Disease Collaboration estimated 697.5 million (95% CI: 649.2–752.0) cases of all-stage CKD for a global prevalence of 9.1%. CKD resulted in 35.8 million (95% CI: 33.7–38) DALYs. The burden of CKD was predominantly concentrated in the three lowest quintiles of the sociodemographic index.

Socioeconomic impact

Not provided.

F. WHO or other clinical guidelines relevant to the test (from application)

Primary hyperparathyroidism

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Secondary hyperparathyroidism in CKD

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Perioperative use of PTH measurement

AES Guidelines 06/01 Group. Australian Endocrine Surgeons Guidelines AES06/01. Postoperative parathyroid hormone measurement and early discharge after total thyroidectomy: analysis of Australian data and management recommendations. *ANZ J Surg.* 2007;77(4):199–202.

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Pseudohypoparathyroidism

Mantovani G, Bastepe M, Monk D, de Sanctis L, Thiele S, Usardi A et al. Diagnosis and management of pseudohypoparathyroidism and related disorders: first international Consensus Statement. *Nat Rev Endocrinol.* 2018;14(8):476–500.

G. Basic test characteristics (from application)

Test formats available	Immunoassay
Specimen types	Plasma, serum

Table *continued*

Equipment required	Automated analyser platform
Regulatory status	Not provided
Availability	Not provided
Price per test range	Not provided
Instrument price range	Not provided

H. Evidence for diagnostic accuracy (from application)

PTH is currently measured by immunoassays, with liquid chromatography-tandem mass spectrometry methods only available in a research capacity. The circulating PTH forms detected by immunoassays include both intact hormone and “inactive” fragments. These fragments, which are devoid of N-terminal regions, are conventionally thought not to possess classic PTH activity. However, more recently, separate receptors for C-terminal PTH have been identified in bone cells and the actions of these fragments may affect the maturation and biological activity of these cells.

C-terminal fragments have a very short half-life (< 1 hour) owing to rapid renal clearance via glomerular filtration. In individuals with normal renal function, 5–25% of total circulating PTH is intact hormone and 75–95% is C-terminal fragments. The half-life and circulating concentrations of fragments are increased in individuals with impaired renal function.

Three generations of PTH assays have been developed (Henrich et al., 2006), necessitated by the heterogeneity of the PTH molecule in both the physiological state and various pathophysiological conditions (especially CKD). Antibodies used in immunoassays may be monoclonal or polyclonal antibodies purified by affinity chromatography to produce sequence-specific antibodies.

For the quantitation of intact PTH (1–84), the carboxyl or middle region of the molecule (e.g. amino acid sequences 39–84, 44–84) are the usual targets of the capture antibody, while signal antibody is directed at the N-terminal amino acid sequence (1–34). However, the detection strategy is reversed in a number of methods, using capture antibodies against the N-terminal amino acid sequence (e.g. amino acids 26–32) and signal antibodies against the middle or C-terminal amino acid sequence (e.g. 55–64). A summary of the main characteristics of each generation of PTH assays follows.

First generation (radioimmunoassays; no longer in clinical use):

- First used in the 1960s.
- Competitive immunoassay.

- Used single polyclonal antibodies directed against the mid-, C-terminal portion of PTH.
- Had issues with clinical sensitivity and specificity due to cross-reactivity with inactive PTH fragments.

Second generation:

- Developed with aim to measure only the intact molecule of PTH (1–84), collectively known as intact assays.
- Noncompetitive (sandwich) immunometric assays with the capture and signal antibodies directed at different regions, either against the C-terminus or N-terminus (amino acids 1–34).
- Use in diagnosis of primary hyperparathyroidism and in monitoring secondary hyperparathyroidism is well-established.
- Overestimates the severity of PTH-related bone disease due to cross-reactivity with N-terminal-truncated fragments (PTH 7–84), which increases with worsening CKD.

Third generation:

- The epitope of N-terminally binding antibody consists of the first four to six amino acids of the PTH molecule.
- Collectively known as true intact PTH assays, whole PTH assays, bioactive PTH assays or cyclase-activating PTH assays.
- Currently no clear clinical advantage over second-generation assays.
- Thought to also detect amino PTH (D'Amour et al., 2003), which has its amino-terminal serine residue in a phosphorylated form.

Because early (first-generation) intact PTH assays measured N-terminal-truncated PTH, they overestimated the concentration of biologically intact hormone. The degree of overestimation is method dependent, with intact PTH 50% higher on average than PTH (1–8) measured by third-generation assays in patients with primary hyperparathyroidism or stage 5 CKD (Gao et al., 2001).

There is a lack of harmonization between commercial PTH assays (Reichel et al., 2003), especially when measuring samples from patients with CKD or receiving haemodialysis. This has highlighted the importance of the production and implementation of a commutable international standard material (IS 95/646), an endeavour which has been adopted by a committee of the International Federation of Clinical Chemistry and Laboratory Medicine.

Optimal sampling conditions: sample tube with EDTA is preferred, though some assays require serum (due to interference from EDTA of assay

signal by chelation of divalent cations required for enzymatic action of alkaline phosphatase label).

Storage: analysis within 72 hours if stored at 4°C. There is no consensus on the effects of storing samples at –20°C or –80°C.

Reference intervals: reference intervals vary significantly with the method used. Typical intervals are:

- intact PTH: 10–65 pg/mL or 1.1–68 pmol/L; and
- PTH (1–84): 6–40 pg/mL or 0.6–42 pmol/L.

I. Evidence for clinical utility/impact (from application)

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Van Ballegooijen AJ, Reinders I, Visser M, Brouwer IA. Parathyroid hormone and cardiovascular disease events: a systematic review and meta-analysis of prospective studies. *Am Heart J.* 2013 May;165(5):655–64, 664.e1–5.

J. Evidence for economic impact and/or cost-effectiveness (from application)

No cost-effectiveness data are available.

K. Ethics, equity and human rights issues (from application)

Diagnosis and management of disorders of PTH secretion and action, including hyperparathyroidism, hypoparathyroidism, CKD and osteoporosis are significantly compromised in developing countries compared to developed countries, resulting in much worse outcomes. The availability of PTH measurement will go a long way to addressing some of these inequities. There are no ethical considerations.

L. Summary of evidence evaluation

The role between PTH assays differs, and for that reason the needed accuracy and clinical impact will differ. Therefore, it is difficult to know which test is being appraised in the context of this application (second generation or third generation). Clinical guidelines agreed upon testing for PTH for several indications, so for that reason PTH assays will have a positive impact on health in LMICs. Systematic review of the role of PTH for several indications and the potential clinical impact are given. However, systematic reviews on the accuracy of PTH testing are not given for each of the indications.

In general:

- First-generation assays are no longer in clinical use because of issues with clinical sensitivity and specificity due to cross-reactivity with inactive PTH fragments.
- Challenges in determining the diagnostic accuracy include: (i) the lack of a reference method, (ii) the lack of standardization of the

assays, (iii) on some occasions the lack of consistent reference range and (iv) stability problems/large intra-individual variation.

How accurately can we assess the levels of PTH (with second- or third-generation assays) and for which indication does it matter the most?

- For classic primary hyperparathyroidism (PHPT), the type of PTH assay used will not affect diagnosis or management because the precise concentration of PTH is less relevant.
- In CKD, the guideline recommends treating secondary hyperparathyroidism above a twofold to ninefold PTH increase, which will result in different clinical decisions depending on the assay used.
- For patients after bariatric surgery, guidelines state absolute cutoff values for PTH, but the impact of different-generation assays is unknown because direct comparison of PTH assays has never been performed.
- During parathyroid surgery, PTH measurements with a third-generation assay reflect treatment success more rapidly than second-generation assays. Increased awareness among clinicians regarding the complexity of PTH measurements is warranted because it can affect clinical decisions.

Diagnostic accuracy measures:

- Regarding the utility of PTH levels in predicting temporary post-thyroidectomy hypocalcaemia for an absolute PTH threshold, the median accuracy, sensitivity and specificity were 86%, 85% and 86%, respectively. For a percentage change over time, the median accuracy, sensitivity and specificity were 89%, 88% and 90%, respectively (QUADAS-2: moderate to high quality). However, there was considerable selection bias among the studies. The studies included diverse populations.
- Pooled sensitivity and specificity of selective parathyroid venous sampling (sPVS) in PHPT patients was 0.74 (95% CI: 0.70–0.77) and 0.41 (95% CI: 0.33–0.48), respectively. Summary performance estimates of positive likelihood ratio for sPVS was 1.55 (95% CI: 1.33–1.82) and for negative likelihood ratio was 0.47 (95% CI: 0.39–0.58). The area under the receiver operating characteristic curve was 0.684, indicating an average discriminatory ability of sPVS (QUADAS-2: moderate to high quality).

Sensitivity issues:

- Assay less sensitive at lower concentrations.
- Percutaneous blood sampling for parathyroid gland localization showed poor sensitivity.

M. Summary of SAGE IVD deliberations

SAGE IVD agreed that PTH is an important test that needs to be available. However, it is expensive (a single test may cost US\$ 20 to US\$ 25) and as such should only be included in reference laboratories for second-level evaluation of changes in calcium or phosphorus, including kidney failure. The group also noted that there are different generations of tests, but that the application did not provide a good sense for how to use the second- and third-generation tests.

Members of the group noted that generation (active, bioactive and so forth) probably matters more for procurement decisions made at the country or laboratory manager level. One SAGE IVD member pointed out that earlier-generation diagnostics are generally offered to countries in low-income settings, and that clarifying the generational differences enables countries to make better decisions. After discussion, the experts agreed to add a footnote specifying that the test is approved for both the second-generation (intact) and third-generation (bioactive or bio-intact) forms of the assay.

Literature cited in the discussion:

Smit MA, van Kinschot CM, van der Linden J, van Noord C, Kos S. Clinical guidelines and PTH measurement: does assay generation matter: *Endocrine Rev.* 2019;40(6):1468–80 (<https://academic.oup.com/edrv/article/40/6/1468/5487988>, accessed 14 December 2022).

N. SAGE IVD recommendations

SAGE IVD recommended listing the parathyroid hormone (PTH) test category in EDL 4

- as a disease-specific IVD for use in clinical laboratories (EDL 4, Section II.b);
- using an immunoassay format;
- using plasma and serum as specimen types;
- to aid in the evaluation of the causes of calcium homeostasis disorders and monitor the effects of treatment.

SAGE IVD also recommended adding a footnote to the test category stating that the test is approved for both the second-generation (intact) and third-generation (bioactive or bio-intact) forms of PTH.

O. References (from application)

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2.2 Applications for edits

2.2.1 Glucose

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

Life for a Child and FIND jointly submitted this edits application with the goal of extending the list of test purposes of the Glucose IVD test category, Assay format: Glucose meter, listed in Section I.b of EDL 3 under Diabetes mellitus, to include specific mention of “self-monitoring” for people living with diabetes.

B. Applicant

Joint application from Life for a Child and FIND

C. WHO technical department

Not applicable.

D. Background and public health relevance (from application)

For young people living with type 1 diabetes, daily insulin replacement is required for survival. Self-monitoring of blood glucose (SMBG) is universally recognized as the most important part of insulin therapy. Regular, daily SMBG outside of the health facility ensures that people using insulin are able to use it safely and efficaciously and helps them maintain target-range daily glucose levels, thus reducing glycated haemoglobin (HbA1c) levels and early and devastating complications, including blindness and renal failure.

Life for a Child has done extensive research, with international colleagues, documenting the provision of blood glucose meters and test strips for SMBG purposes (1, 2, 3, 4) and has consistently found that access to this crucial component of care for people living with type 1 diabetes is extremely deficient in LMICs. Low rates of access to SMBG are largely due to lack of health system provision. The consequences of this include poorly controlled diabetes, high prevalence of complications and catastrophic financial impacts on patients and their families.

In a 2018 paper (2) published in *Lancet Diabetes & Endocrinology*, Life for a Child first expressed support on seeing that glucose testing was included as a diagnostic for diabetes in the first WHO model list of essential in vitro diagnostics but argued that this ought to include SMBG supplies for long-term use in future versions.

FIND together with partners has published a market report on diabetes self-monitoring devices in LMICs (5) that analyses the blood glucose test strip market and access barriers to testing supplies. Further to this work, FIND has engaged with blood glucose test strip manufacturers to improve the affordability of these products for LMICs (6), resulting in some of the lowest access pricing available to LMIC buyers today (7).

The addition of “Diabetes mellitus” to the disease-specific section of the third EDL and the associated listing of blood glucose meters as IVDs recommended for use in community settings and health facilities without laboratories was welcome to raise the priority of these IVDs for availability at low levels of care, where blood glucose meters are frequently absent (8).

This application is submitted with the goal of extending the list of test purposes to include specific mention of self-monitoring for people living with diabetes. The applicants believe this would further strengthen the important role these IVDs play in diabetes management and heighten awareness among stakeholders who consult the EDL to define diagnostics needs in their country. While the EDL includes terminology such as “home-based” and “self-testing”, the applicants deem the extension of the test purpose to include “self-monitoring” as critical to ensure the neglected use case of blood glucose meters and test strips for self-monitoring gets the attention that people living with diabetes need at the country level.

E. WHO or other clinical guidelines relevant to the test (from application)

American Diabetes Association. Standards of medical care in diabetes – 2022. *J Clin Appl Res Educ.* 2022;45 Suppl 1.

- “All children and adolescents with type 1 diabetes should monitor glucose levels multiple times daily (up to 6–10 times/day by blood glucose meter or continuous glucose monitoring), including prior to meals and snacks, at bedtime, and as needed for safety in specific situations such as exercise, driving, or the presence of symptoms of hypoglycemia.”

Basit A, Khan A, Khan RA. BRIGHT guidelines on self-monitoring of blood glucose. *Pak J Med Sci.* 2014;30(5):1150–5.

- The high costs of test strips may render recommended guidelines unattainable for some people in low-resource settings; monitoring blood glucose at a reduced frequency and rotating daily test times can often be used productively.

International Society for Pediatric and Adolescent Diabetes guidelines – Chapter 8: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. Berlin: ISPAD; 2018.

- “Regular self-monitoring of glucose (using accurate fingerstick blood glucose [BG] measurements ... is essential for diabetes management for all children and adolescents with diabetes. Each child should have access to technology and materials for self-monitoring of glucose measurements to test enough to optimize diabetes care.”
- “When fingerstick BGs are used, testing may need to be performed 6 to 10 times per day to optimize intensive control.”
- “Chronic hyperglycemia has adverse effects on neurocognitive function and brain structure and development in children and adolescents with diabetes. Chronic hyperglycemia and wide glucose fluctuations during the years of rapid brain development affect brain structure and development, including impairment of the growth of the hippocampus.”
- “Hypoglycemia is also a significant risk for children and adolescents with diabetes. Severe hypoglycemia, particularly in young children, is associated with adverse neurocognitive effects.”

New WHO report maps barriers to insulin availability and suggests actions to promote universal access. In: WHO/News [website]. Geneva: World Health Organization; 2021.

- Since 2021, there have been commitments from WHO to include blood glucose test strips in the prequalification programme.
- “The expansion of WHO’s prequalification programme to include glucose monitoring devices, test strips and diagnostic tools, and the inclusion of additional forms of insulin and other diabetes medicines in the latest update of the WHO Model Lists of Essential Medicines are expected to lead to improved access in countries where demand is currently unmet.”

Ogle GD, von Oettingen JE, Middlehurst AC, Hanas R, Orchard TJ. Levels of type 1 diabetes care in children and adolescents for countries at varying resource levels. *Pediatr Diabetes*. 2019;20(1):93–8.

- “All people with type 1 diabetes (T1D) deserve quality care. In countries that can afford it, comprehensive, guidelines-based care should be provided through the respective government health service. Currently, however, many less-resourced countries are only providing what we have defined as ‘minimal care,’ which has a high morbidity and mortality. We therefore encourage and recommend that less-resourced countries support ‘intermediate care,’ an approach that is substantially less expensive than comprehensive care but can still achieve markedly improved outcomes. The key components of intermediate care are human insulin in a basal bolus regimen, SMBG, point-of-care HbA1c testing, diabetes education, basic complications screening, and access to a doctor and nurse experienced in T1D care in young people.”
- “Access to SMBG is a profound issue for improving T1D care in less-resourced settings, and national and international advocacy and innovative approaches are needed to address this issue.”

Silver B, Ramaiya K, Andrew SB, Fredrick O, Bajaj S, Kalra S. East African diabetes study guidelines: insulin therapy in diabetes. *Diabetes Ther*. 2018;9(2):449–92.

- “Blood glucose monitoring is an integral part of effective insulin therapy and should not be omitted in the patient’s care plan.”

WHO global coverage targets for diabetes. 2022.

- In April 2022, Member States of the World Health Assembly voted for the adoption of the WHO diabetes recommendations and

coverage targets. These targets in particular include that “100% of people with Type 1 diabetes have access to affordable insulin treatment and blood glucose self-monitoring.”

F. Other evidence supporting this application (from application)

Gomes MB, Tannus LRM, Cobas RA, Matheus ASM, Dualib P, Zucatti AT et al. Determinants of self-monitoring of blood glucose in patients with type 1 diabetes: a multi-centre study in Brazil. *Diabet Med* 2013;30:1255–62.

- “HbA1c levels were similarly associated with SMBG frequency, although with no additional benefit beyond four tests per day.”

Klatman EL, Jenkins AJ, Ahmedani MY, Ogle GD. Blood glucose meters and test strips: global market and challenges to access in low-resource settings. *Lancet Diabetes Endocrinol.* 2019;7(2):150–60.

- “Diabetes is a unique medical condition with respect to the frequency of home measurements required.”
- “Hypoglycaemia and hyperglycaemia occur acutely and frequently in people with diabetes, particularly in those who are treated with insulin. Long-term glycaemia is also a major determinant of chronic complications. Therefore, home monitoring of blood glucose with meters and test strips (self-monitoring of blood glucose [SMBG]) is widely used.”
- “Home glucose monitoring began in the 1940–50s with urine testing, first using Benedict’s solution heated over a Bunsen burner, then effervescent tablets, and then urine test strips. SMBG was first used at home by Richard Bernstein in 1969. Since then, reflectance meters have been replaced by biosensor meters, with subsequent improvements in speed, miniaturisation, accuracy, and connectivity.”
- The majority of blood glucose test strips used in LMICs today are utilized in health care facilities, and government procurement largely focuses on glucose testing needs in facilities.
- The cost of test strips for people living with diabetes in LMICs is often prohibitive. This often limits SMBG to the absolute minimum for this group of people, sometimes leading them to forgo usage altogether, leading to dangerous extremes of glycaemia, highly impaired quality of life, and increased risk of developing serious and preventable metabolic complications.

Klatman EL, McKee M, Ogle GD. Documenting and visualising progress towards universal health coverage of insulin and blood glucose test strips for people with diabetes. *Diabetes Res Clin Pract.* 2019;157:107859.

- Provision of test strips through the health system is, for many people with diabetes, the only option to perform critically important SMBG, yet the large majority of LMIC health care systems do not provide test strips for self-monitoring.
- In LMICs, provision of test strips is rarely covered within public health system benefit packages.
- This study looking at provision of test strips found this number to be 14% of countries surveyed ($n = 37$). This is still the case in health insurance schemes, where a small percentage of the population can afford enrolment. This leaves people living with insulin-treated diabetes with no choice but to purchase test strips for SMBG out of pocket at private retail pharmacies (at a cost that can range from US\$ 0.25 to US\$ 1.65 (median US\$ 0.49, mean US\$ 0.56) for one test strip).
- Given this lack of provision and high out-of-pocket costs for SMBG supplies, global commitments made towards Goal 3 of the United Nations' Sustainable Development, Goals which calls on governments to ensure healthy lives and promote well-being for all at all ages, are leaving those with insulin-treated diabetes behind.

Miller KM, Beck RW, Bergenstal RM, Golland RS, Haller MJ, McGill JB et al. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. *Diabetes Care.* 2013;36(7)2009–14:

- “The advent in the 1980s of meters for self-monitoring of blood glucose (SMBG) has had a substantial impact on the management of type 1 diabetes.”
- “SMBG is the cornerstone of modern-day therapy for people with type 1 diabetes.”
- “Several studies have demonstrated a strong correlation between frequency of SMBG and glycemic control.”
- “A higher number of SMBG measurements per day was strongly associated with a lower HbA1c in all age-groups.”
- “There was no significant interaction between SMBG and household income on HbA1c levels for any age-group.”

- “The association between SMBG and HbA1c levels appeared to level-off at approximately 10 SMBG measurements per day, with adjusted mean HbA1c being similar in participants testing 10–12 times as in those testing more than 13 times per day, 7.8 and 7.7%, respectively.”

Noorani M, Ramaiya K, Manji K. Glycaemic control in type 1 diabetes mellitus among children and adolescents in a resource limited setting in Dar es Salaam – Tanzania. *BMC Endocr Disord.* 2016;16:29.

- “Adherence to BGM regimen was associated with lower mean HbA1c in those with average adherence as compared to those with poor adherence.”

Ogle GD, Kim H, Middlehurst AC, Silink M, Jenkins AJ. Financial costs for families of children with Type 1 diabetes in lower-income countries. *Diabet Med.* 2016;33(6):820–6.

- “For people living with diabetes in LMICs, even two test strips per day for SMBG over the course of a year often outweigh the annual cost of human insulin. The cost of two strips per day for one year as a percentage of per capita gross national income (GNI) ranged from 4% in Saint Lucia to 129% in Burkina Faso. The mean cost of two strips per day was 41% of the per capita GNI, and the median cost was 24%.”

Pastakia SD, Cheng SY, Kirui NK, Kamano JH. Dynamics, impact, and feasibility of self-monitoring of blood glucose in the rural, resource constrained setting of western Kenya. *Clin Diabetes.* 2015;33:136–43.

- “This study shows that, despite resource challenges that can impede the performance of frequent SMBG, patients in a semi-urban and rural setting in western Kenya achieved a 4-point reduction in median A1C after 6 months of participation in an intensive SMBG and insulin adjustment program.”

Ziegler R, Heidtmann B, Hilgard D, Hofer S, Rosenbauer J, Holl R et al. Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. *Pediatr Diabetes.* 2011;12(1):11–7.

- “There is an association between increasing SMBG use up to five times per day and reductions in HbA1c and acute complications in children and adolescents with type 1 diabetes.”
- “Knowing the accurate blood glucose level is the only way to adjust the patient’s insulin dose, eating behavior, and physical exercise.”

G. Summary of evidence evaluation

Evidence of the effectiveness of self-monitoring, relative to no self-monitoring or other alternatives, is scarce and of questionable validity (one case series) and applicability (association between monitoring frequency and outcomes). Available evidence, while of very low certainty, suggests that higher frequencies of self-monitoring might improve HbA1c control. Despite this lack of good quality evidence, self-monitoring appears to be widely recommended as part of routine care in diabetic patients using insulin therapy.

H. Summary of SAGE IVD deliberations

This edit would add a new test purpose for self-monitoring diabetes at home to the already existing glucose meter non-laboratory-based assay in the EDL.

SAGE IVD considered the submission to be generally good and aligned with WHO guidelines, in particular for diabetes, for primary health care interventions and for self-health care. One expert observed that promoting self-monitoring of glucose at home with test strips will result in better control of diabetes and will also help to make support for the technology a priority at the government level. In this regard, including the test in the EDL constitutes a step towards reducing inequities.

It was also noted that this application was the only one to receive considerable attention during the call for public comments phase, including two comments from people living with diabetes who provided evidence. SAGE IVD also commented on the role of the EDL in highlighting what is available and useful in the field even when it is not yet in the guidelines, especially in settings where access to clinical laboratories is limited.

One point of confusion concerned a footnote included in the proposed edit to the test purpose provided by the applicant appearing to say that the test was for self-monitoring type 2 diabetes when indicated or recommended but not for type 1. SAGE IVD suggested removing the footnote to avoid misunderstanding, as the test is clearly meant for self-monitoring of both type 1 and type 2 diabetes.

Literature cited in the discussion:

Diabetes. In: WHO/Health topics [website]. Geneva: World Health Organization; 2022 (https://www.who.int/health-topics/diabetes#tab=tab_1 accessed 14 December 2022).

HEARTS D: diagnosis and management of type 2 diabetes. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/331710>, accessed 14 December 2022).

I. SAGE IVD recommendations

SAGE IVD recommended including the proposed edits to the test purpose of the glucose IVD test, for the glucose meter assay format in EDL 4

- as a disease-specific IVD for use in community settings and health facilities without laboratories (EDL 4, Section I.b);
- using a glucose meter format;
- using capillary whole blood as specimen type;
- to self-monitor type 1 and type 2 diabetes mellitus at home.

J. References (from application)

1. Klatman EL, McKee M, Ogle GD. Documenting and visualising progress towards universal health coverage of insulin and blood glucose test strips for people with diabetes. *Diabetes Res Clin Pract.* 2019 Nov;157:107859. doi:10.1016/j.diabres.2019.107859.
2. Klatman EL, Jenkins AJ, Ahmedani MY, Ogle GD. Blood glucose meters and test strips: global market and challenges to access in low-resource settings. *Lancet Diabetes Endocrinol.* 2019 Feb;7(2):150–60. doi:10.1016/S2213-8587(18)30074-3. Erratum in: *Lancet Diabetes Endocrinol.* 2018 Aug 30.
3. Ogle GD, Kim H, Middlehurst AC, Silink M, Jenkins AJ. Financial costs for families of children with type 1 diabetes in lower-income countries. *Diabet Med.* 2016 Jun;33(6):820–6. doi:10.1111/dme.12997.
4. Ogle GD, Middlehurst AC, Silink M. The IDF Life for a Child Program Index of diabetes care for children and youth. *Pediatr Diabetes.* 2016 Aug;17(5):374–84. doi:10.1111/pedi.12296.
5. Market report: diabetes self-monitoring devices in low-and middle-income countries. October 2021. In: HAI [website]. Amsterdam: Health Action International; 2021 (https://haiweb.org/wp-content/uploads/2021/09/Market-Report_Self-monitoring-Devices-in-LMICs.pdf, accessed 4 April 2023).
6. FIND partners with glucose test strip manufacturers to improve affordability of blood glucose self-monitoring in low- and middle-income countries. In: FIND/Publications and statements [website]. Geneva: FIND; 2022 (https://www.finddx.org/wp-content/uploads/2022/12/2021_0818_prr_glucose_test_strips_FV_EN.pdf, accessed 4 April 2023).
7. Towards insulin for all: operationalising the WHA74 resolution on diabetes. Technical Brief May 2022. Grenoble: Santé Diabète; 2022 (https://santediabete.org/wp-content/uploads/2022/05/SD-MSF-Diabetes_NCDs_TechBrief_AC-SD_Diabetes-resolution_ENG_May2022.pdf, accessed 4 April 2023).
8. Diabetes supplies: are they there when needed? Seattle (WA): PATH; 2015 (<https://www.ghtcoalition.org/resources/diabetes-supplies-are-they-there-when-needed.pdf>, accessed 4 April 2023).

2.2.2 *Mycobacterium tuberculosis* DNA

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

The applicant proposed to include the IVD category *M. tuberculosis* DNA in Section I.b of the EDL, under Tuberculosis (TB), with the assay format of POC NAT.

B. Applicant

Stop TB Partnership with support from the United States Agency for International Development, TBpeople Global and FIND

C. WHO technical department

Not applicable

D. Background and public health relevance (from application)

Not provided as this IVD category is already listed in the EDL.

E. WHO or other clinical guidelines relevant to the test (from application)

Since the time of publication of the third edition of the WHO model list of essential in vitro diagnostics, the WHO Global Tuberculosis Programme (GTB) has issued recommendations on the use of the Truenat MTB, MTB Plus and MTB Rif-Dx assays as initial diagnostic tests for people undergoing evaluation for TB and for the detection of rifampicin resistance (1). Furthermore, the GTB has introduced a classification system for the evaluation of diagnostic tests which includes the complexity of the test for implementation (low, moderate and high – considering requirements of infrastructure, equipment and technical skills) (2). The class of low-complexity automated NAATs now comprises the Xpert and Truenat assays, as they can be used at POC in community settings and health facilities without laboratories (3). Lastly, the 2021 WHO consolidated HIV guidelines (4) call for integrated TB and HIV screening for people with advanced disease to include lateral flow lipoarabinomannan (LF-LAM) antigen and molecular (NAT) TB testing at POC: “to increase access to the package [of care for people with advanced HIV disease], improving access at peripheral sites through mobile outreach or decentralization should be encouraged and may be enabled by providing point-of-care diagnostic tests at all levels where feasible (CD4 cell count, cryptococcal antigen testing, LF-LAM testing, and molecular TB testing)”.

F. Other evidence supporting this application (from application)

For the test category *M. tuberculosis* DNA, listed in Section II.b of the EDL, under Tuberculosis (TB), test purpose: to diagnose active TB and simultaneously or sequentially detect rifampicin resistance, the applicants propose the POC NAT assay format for community and health settings without laboratories, in addition to the NAT assay format for clinical laboratories.

An analysis of early programme implementation of Xpert testing in nine countries under the TB REACH (5) programme showed that with adequate procurement support, infrastructure and supervision, Xpert could be placed at or very close to POC in many settings. Clinical trials in South Africa (6) and Zimbabwe (TB-NEAT) (7) showed that POC Xpert testing was feasible and could be accurately performed by non-laboratory staff in primary care clinics leading to same-day diagnosis and treatment initiation. Further evaluations of Xpert using one-module instruments placed in rural facilities with no access to laboratory testing (8), and coupled with HIV testing in mobile units (9), increased the proportion of patients receiving a bacteriological confirmation of TB, reduced time to treatment initiation and improved treatment completion rates. Similar evaluations of Truenat MTB in India also showed that the deployment of Truenat instruments at the POC was cost-effective (10) and improved TB case detection by 30% (11).

In conclusion, the applicants recommend adding the TB POC NAT to Section I.b: Disease-specific IVDs for use in community settings and health facilities without laboratories, when sufficient training and monitoring can be provided, to align with evidence from multiple studies that have shown that use of low-complexity automated NAATs (low-complexity TB NAATs) in community settings or at lower-level health facilities not only is feasible but also leads to reductions in pretreatment loss to follow-up and time to TB treatment initiation, and improves treatment completion rates. The addition of this category in EDL 4 would also facilitate access to integrated TB and HIV testing.

G. Summary of evidence evaluation

Limited randomized trial evidence suggests that use of POC Xpert MTB/RIF testing, relative to laboratory Xpert MTB/RIF, leads to shorter time to treatment initiation and higher treatment completion rates while having similar diagnostic accuracy for TB and proportion of patients receiving appropriate treatment.

One randomized trial showed that nurse-performed Xpert MTB/RIF at the clinic has a higher rate of same-day diagnosis and same-day treatment initiation but does not impact TB-related morbidity in culture-positive patients, relative to sputum smear microscopy.

WHO guidelines conditionally recommend the use of Truenat MTB or MTB Plus as an initial diagnostic test for TB and rifampicin resistance.

This body of evidence is not aggregated by means of a systematic literature search, and no formal assessment of study quality was performed.

H. Summary of SAGE IVD deliberations

The requested edit would move the TB DNA test, which was already listed in EDL 3 as a laboratory-based test, to the first level of the table – Community settings and health facilities without laboratories. This move is tantamount to listing the test as a POC test. However, WHO does not currently endorse POC testing for TB; indeed, WHO's GTB Programme did not support the application on the grounds that it misinterprets WHO guidelines.

SAGE IVD members agreed that the test category under consideration is not truly a POC test. It is a near-patient test that still requires laboratory capacity. Moreover, the test is relatively expensive. It is not clear how to frame the test within the health system, and without specifications and approval, availability may be poor.

SAGE IVD appreciates that POC testing is important to achieve end-TB targets. But the test is not yet ready for wide implementation. The experts do support the need to move to the level where smears can be replaced with approved tests like molecular WHO-recommended rapid diagnostics for screening (mWRDs) at the lowest tier to improve results and to prevent patients with presumptive TB from being turned back.

SAGE members noted that while the application provides some evidence of POC use, further evidence of POC and near-patient use in other high-burden settings and their impact on current national TB programme efficiencies in these settings is critical to endorsing widespread POC use of existing technologies.

SAGE IVD rejected the requested edit and requested that wider evidence be generated to ensure that POC use of the existing tests listed in the EDL is appropriate, cost-effective and does not disrupt the existing TB programmes in LMICs with a high TB burden. The test is already listed as a laboratory-based test (Section II: Health care facilities with clinical laboratories), and any near-patient use by programmes needs to be guided by the WHO strategy for TB control, which currently reserves technology use to laboratory settings.

Literature cited in the discussion:

The End TB strategy. In: WHO/Global Tuberculosis Programme [website]. Geneva: World Health Organization; 2022 (<https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy>, accessed 14 December 2022).

Land KJ, Boeras DI, Chan XS, Ramsay AR, Peeling RW. REASSURED diagnostics to inform disease control strategies, strengthen health systems and improve patient outcomes. *Nat Microbiol.* 2019;4:46–54 (<https://www.nature.com/articles/s41564-018-0295-3>, accessed 14 December 2022).

Niemz A, Ferguson TM, Boyle DS. Point-of-care nucleic acid testing for infectious diseases. *Trends Biotechnol.* 2013;29(5):240–50 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3746968/>, accessed 14 December 2022).

I. SAGE IVD recommendations

SAGE IVD rejected the requested edit to include the IVD category *M. tuberculosis* DNA in Section I of the EDL: Community settings and health facilities without laboratories as a POC NAT.

J. References (from application)

1. WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/332862>, accessed 29 July 2023).
2. WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection (2021 update). Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/342331>, accessed 29 July 2023).
3. Manual for selection of molecular WHO-recommended rapid diagnostic tests for detection of tuberculosis and drug-resistant tuberculosis. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/handle/10665/353596>, accessed 29 July 2023).
4. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/342899>, accessed 29 July 2023).
5. Creswell J, Codlin AJ, Andre E, Micek MA, Bedru A, Carter EJ et al. Results from early programmatic implementation of Xpert MTB/RIF testing in nine countries. *BMC Infect Dis.* 2014;14:2. doi:10.1186/1471-2334-14-2.
6. Lessells RJ, Cooke GS, McGrath N, Nicol MP, Newell ML, Faussett PG. Impact of point-of-care Xpert MTB/RIF on tuberculosis treatment initiation: a cluster-randomized trial. *Am J Respir Crit Care Med.* 2017;196(7):901–10. doi:10.1164/rccm.201702-0278OC.
7. Theron G, Zijenah L, Chanda D, Clowes P, Rachow A, Lesosky M et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. *Lancet.* 2014;383(9915):424–35. doi:10.1016/S0140-6736(13)62073-5.
8. Van Den Handel T, Hampton KH, Sanne I, Stevens W, Crous R, Van Rie A. The impact of Xpert® MTB/RIF in sparsely populated rural settings. *Int J Tuberc Lung Dis.* 2015;19(4):392–8. doi:10.5588/ijtld.14.0653.
9. Bassett IV, Forman LS, Govere S, Thulare H, Frank SC, Mhlongo B et al. Test and treat TB: a pilot trial of GeneXpert MTB/RIF screening on a mobile HIV testing unit in South Africa. *BMC Infect Dis.* 2019;19(1):110. doi:10.1186/s12879-019-3738-4.
10. Lee DJ, Kumarasamy N, Resch SC, Sivaramakrishnan GN, Mayer KH, Tripathy S. et al. Rapid, point-of-care diagnosis of tuberculosis with novel Truenat assay: cost-effectiveness analysis for India's public sector. *Plos One.* 2019;14(7):e0218890. doi:10.1371/journal.pone.0218890.
11. Jeyashree K, Shanmugasundaram D, Rade K, Gangakhedkar RR, Murhekar. Impact and operation feasibility of TrueNat™ MTB/Rif under India's RNTCP. *Public Health Action.* 2020;10(3):87–91. doi:10.5588/pha.20.0004.

2.3 Applications for Do Not Do recommendations

2.3.1 Serological tests for detection of typhoid antigen and immunoglobulin M/immunoglobulin G antibodies

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

The application proposed adding serological tests for detection of typhoid antigen and IgM/IgG antibodies such as the Widal test and other RDTs to the Do Not Do recommendations section of the EDL.

B. Applicant

FIND

C. WHO technical department

None

D. Background and public health relevance (from application)

Typhoid fever is an enteric bacterial infection caused by the bacterium *Salmonella* Typhi (*S. Typhi*), which is primarily transmitted through contaminated food or water (1). Symptoms include prolonged fever, fatigue, headache, nausea, abdominal pain, constipation or diarrhoea, with severe cases leading to serious complications and even death (2). In 2018, it was reported that 11–20 million people worldwide contract typhoid each year, resulting in 128 000–161 000 deaths (2).

Because of the primary mode of transmission, typhoid cases are most prevalent in places with poor sanitation and a lack of safe drinking water, most commonly LMICs (2, 3). Of these, endemic regions with the highest incidence of typhoid are sub-Saharan Africa (accounting for 40% of all cases), South Asia, North Africa and the Middle East (3). While the disease can be effectively treated with antibiotics, escalating global AMR, including the emergence of extensively drug-resistant *S. Typhi* in Pakistan and the prevalence of azithromycin-resistant *S. Typhi* in many countries mainly in LMICs, indicates that short- to medium-term control of typhoid through vaccination may be the best strategy for reducing disease burden in endemic populations (2, 4, 5). However, with no reliable POC diagnostic, accurately measuring disease burden in order to effectively target areas where routine vaccination would provide the greatest benefit remains a challenge (5).

An accurate diagnosis of typhoid can prove difficult, as the characteristic symptoms are similar to other undifferentiated febrile illnesses such as malaria or dengue fever. Typhoid can also be mistaken for vector-borne febrile illnesses such as scrub typhus (6). As such, microbiological testing is usually required to confirm a diagnosis of *S. Typhi*, with blood and bone marrow cultures currently considered the gold-standard tests (7, 8). However, blood culture testing can be expensive, has low sensitivity, and requires infrastructure and skilled staff that are not always available in LMICs and are not adequate for rapid patient management (7, 8). Tests using bone marrow cultures may have a higher sensitivity than blood culture tests, but they are not routinely performed, as obtaining bone marrow aspirates involves skilled, invasive techniques (7, 8).

As a result, alternative tests have been widely adopted, especially in LMICs. These tests can be performed within half an hour and at a lower cost compared with culture (9). The most widely used RDT is the Widal test, despite numerous reports of poor sensitivity and specificity, leading in some cases to multiple misdiagnoses in disease outbreaks, treatment delays and even deaths (7, 10, 11, 12). Limitations have also been reported for other typhoid RDTs, such as Typhidot (IDL Biotech), TUBEX (Reszon Diagnostics) and Test-it Typhoid IgM (LifeAssay Diagnostics) (7). While these show improvements over the Widal test, they still only exhibit moderate sensitivity and specificity (7). However, many accuracy studies into the effectiveness of typhoid RDTs have variations in methodology and reference standards, making it difficult for health care providers and policymakers to make robust decisions or recommendations for the utility of commercial tests in different settings.

E. WHO or other clinical guidelines relevant to the test (from application)

The United States Centers for Disease Control and Prevention (CDC) states: “The Widal test is unreliable but is widely used in developing countries because of its low cost. It measures elevated antibody titers in patients with recent typhoid or paratyphoid fever but may not accurately distinguish acute from past infection and lacks specificity, resulting in false-positive results. Serologic assays are not an adequate substitute for blood, stool, or bone marrow culture.”

- Typhoid and paratyphoid fever: CDC Yellow Book 2024. In: CDC/Traveler’s health [website]. Atlanta (GA): Centers for Disease Control and Prevention; 2023 (<https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/typhoid-and-paratyphoid-fever>, accessed 19 May 2023).

F. Other evidence supporting this application (from application)

Many studies on typhoid RDTs, including the Widal test, have documented the poor sensitivity and specificity of the entire class of tests. The poor performance of these RDTs not only results in misdiagnosis of typhoid but also overdiagnosis due to circulating antibodies in endemic regions, leading to misclassification of other febrile illnesses and skewed surveillance data. FIND recently conducted a standardized head-to-head comparison of commercially available typhoid RDTs which confirmed the existing evidence regarding the poor sensitivity and specificity of the existing tests.

The material that follows details studies on typhoid RDTs with data.

- Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008892.pub2/full> (accessed 19 May 2023).

This Cochrane review evaluated 37 studies on the diagnostic accuracy of enteric fever RDTs and concluded that three main RDTs and variants (TUBEX, Typhidot and Test-It) had moderately diagnostic accuracy.

Results:

- i. TUBEX: 78% sensitivity; 87% specificity
 - ii. Typhidot (Typhidot, Typhidot-M and TyphiRapid-Tr02): 84% sensitivity; 79% specificity
 - iii. Test-It Typhoid and prototype tests (KIT): 69% sensitivity; 90% specificity
- Comparative analysis of commercially available typhoid point-of-care tests: results of a prospective and hybrid retrospective multicenter diagnostic accuracy study in Kenya and Pakistan: <https://journals.asm.org/doi/10.1128/jcm.01000-22> (accessed 21 August 2023).

This study was conducted in two typhoid endemic geographical regions, Kenya and Pakistan. Nine RDTs currently available on the market, including the Widal test, were evaluated. Overall, all typhoid RDTs evaluated in this study had sensitivity and specificity values that were lower than recommended for an accurate diagnosis.

Results:

- i. Widal test: 47.7% sensitivity; 79.4% specificity
- ii. SD Bioline Salmonella typhi IgM: 21.6% sensitivity; 100% specificity

- iii. SD Bioline Salmonella typhi IgG: 9.1% sensitivity; 99.6% specificity
 - iv. Typhidot Rapid IgM combo test: 46.2% sensitivity; 82.8% specificity
 - v. Typhidot Rapid IgG combo test: 11.4% sensitivity; 98.9% specificity
 - vi. Enterocheck WB: 72.7% sensitivity; 86.5% specificity
 - vii. Test-It Typhoid IgM: 63.6% sensitivity; 95.1% specificity
 - viii. CTK Typhoid IgM Combo Rapid Test CE (CTK): 1.5% sensitivity; 100% specificity
 - ix. CTK Typhoid IgG Combo Rapid Test CE (CTK): 78.8% sensitivity; 59.2% specificity
 - x. Typhoid IgM Rapid Test Cassette (Spectrum): 49.6% sensitivity; 78.7% specificity
 - xi. Typhoid IgG Rapid Test Cassette (Spectrum): 31.8% sensitivity; 91.8% specificity
 - xii. Diaquick S. typhi/paratyphi Ag cassette: 0% sensitivity; 100% specificity
 - xiii. TUBEX TF: 60.6% sensitivity; 94.0% specificity
- Clinical value of Tubex™ and Typhidot® rapid diagnostic tests for typhoid fever in an urban community clinic in Bangladesh: <https://www.sciencedirect.com/science/article/abs/pii/S0732889308001958?via%3Dihub>, accessed 19 May 2023).

This study, conducted in community clinics in Bangladesh, evaluated two typhoid RDTs, TUBEX and Typhidot. Overall, this evaluation demonstrates that TUBEX and Typhidot were not useful for the diagnosis of typhoid fever in a community clinic in urban Bangladesh, where typhoid fever is endemic.

Results:

- i. TUBEX: 60% sensitivity; 58% specificity
 - ii. Typhidot: 67% sensitivity; 54% specificity
- Sensitivity and specificity of typhoid fever rapid antibody tests for laboratory diagnosis at two sub-Saharan African sites: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165980/> (accessed 19 May 2023).

This study was conducted in Mpumalanga, South Africa, and Moshi, United Republic of Tanzania, and evaluated three commercial

typhoid RDTs: the Widal test, TUBEX and Typhidot. The Widal test performed poorly. TUBEX and Typhidot sensitivity and specificity were also suboptimal for deployment in routine care settings in sub-Saharan Africa.

Results:

- i. Widal (semi-quantitative slide agglutination): 25% PPV
 - ii. Widal (semi-quantitative tube agglutination): 20% PPV
 - iii. TUBEX: 73% sensitivity; 69% specificity
 - iv. Typhidot IgM: 75% sensitivity; 60.7% specificity
 - v. Typhidot IgG: 69.2% sensitivity; 70.4% specificity
- Typhoid fever among febrile Nigerian patients: prevalence, diagnostic performance of the Widal test and antibiotic multi-drug resistance: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6895380/> (accessed 19 May 2023).

This study showed poor performance of the Widal test.

Results:

- i. Widal test: 49.1% sensitivity; 90.7% specificity
- Diagnostic value of Widal test in the diagnosis of typhoid fever: a systematic review: <https://www.hilarispublisher.com/open-access/diagnostic-value-of-widal-test-in-the-diagnosis-of-typhoid-fever-a-systematic-review-2161-0703-1000248.pdf> (accessed 19 May 2023).

This systematic review included 16 articles from 1994 to 2015 and concluded that the reliability of the Widal test is comparatively poor. The mean sensitivity is $73.5 \pm 12.6\%$. The lowest sensitivity of the Widal test was 45.6%.

- Evaluation of sensitivity and specificity of ELISA against Widal test for typhoid diagnosis in endemic population of Kathmandu: <https://bmcinfctdis.biomedcentral.com/articles/10.1186/s12879-015-1248-6> (accessed 19 May 2023).

This study compared the diagnostic accuracy of the Widal test to ELISA using blood culture as the gold standard and concluded the Widal test is not suitable enough for an endemic setting like Nepal.

G. Summary of evidence evaluation

Points for consideration include the following:

- No minimal performance criteria have been specified for these tests, so the qualification of “poor sensitivity and specificity” is not yet well substantiated. Especially given the high heterogeneity in accuracy estimates described under section 12 of the submission form (peer-reviewed studies and systematic reviews supporting the application), it seems premature to conclude that this category of tests has accuracy that is not fit for purpose.
- Other potential roles of these RDTs have not been described by this applicant, for example RDT as a triage test for culturing.
- Reasonable alternatives for RDTs at the same position in the clinical pathway in the intended setting (perhaps one in which culturing may not be readily available) have not been proposed.

It would be desirable to know what the reasonable alternative is for RDTs if culture is not readily available, and why absence of RDT testing would be more beneficial in these scenarios.

H. Summary of SAGE IVD deliberations

This application was submitted by FIND to add serological tests for detection of typhoid antigen and IgM/IgG antibodies as a Do Not Do recommendation to the EDL, based on evidence of poor performance according to several publications, including a systematic review conducted by Cochrane. A comparative study of commercially available typhoid POC tests performed by FIND was also included in the application. Médecins Sans Frontières also endorsed the Do Not Do recommendation in the call for public comments because the test does not appear to be used effectively or to help improve diagnosis.

SAGE IVD acknowledged that the performance of the tests is low and there are no guidelines or algorithms for them. The experts noted that post-test probability increases appreciably for some typhoid tests but that examining just one aspect of the tests is not enough. According to one SAGE IVD member, because the tests generally have lower sensitivity than blood culture and require less blood, they are easy to do and tend to be misused. False negatives lead to high costs of illness; false positives miss other febrile illnesses, mostly dengue and malaria. By the same token, mortality is low because antibiotics are available over the counter.

Many in the group emphasized that a Do Not Do recommendation means that countries will essentially have nothing. The gold standard for typhoid testing is blood culture. But it is positive only on specific timing of the disease,

and not feasible in many LMICs. Others argued that continuing to use the test would result in overprescription of antibiotics and increase typhoid resistance, in particular to macrolides such as azithromycin and cephalosporin.

SAGE IVD agreed that better diagnostic tests for typhoid are needed and that the test should be used in the context of an algorithm. The WHO EDL Secretariat suggested that some professional organization might be willing to take on the problem of typhoid tests and put in the time to create policy.

The consensus of SAGE IVD was that typhoid testing is a priority area and that a Do Not Do recommendation would be too strong a step at this point. The group recommended outlining next steps from a global health perspective as well as endorsing FIND's position that the area of typhoid testing requires better data and clarification.

Literature cited in the discussion:

Frempong SN, Sutton AJ, Davenport C, Barton P. Early economic evaluation to identify the necessary test characteristics of a new typhoid test to be cost effective in Ghana. *Pharmacoecon Open*. 2020;4(1):143–57 (<https://pubmed.ncbi.nlm.nih.gov/31377968/>, accessed 14 December 2022).

LILACS, scientific health information from Latin America and the Caribbean countries. In: LILACS [website]. Washington DC: Pan American Health Organization; 2022 (<https://lilacs.bvsalud.org/en/>, accessed 14 December 2022).

Lipecs. In: Virtual Health Library [database]. Washington DC: Pan American Health Organization; 2022 (<http://repebis.upch.edu.pe/cgi-bin/wxis.exe/iah/scripts/?IsisScript=iah.xis&base=lipecs&lang=en&form=A>, accessed 14 December 2022).

Mather RG, Hopkins H, Parry CM, Dittrich S. Redefining typhoid diagnosis: what would an improved test need to look like? *BMJ Glob Health*. 2019;4:e001831 (<https://gh.bmj.com/content/4/5/e001831>, accessed 14 December 2022).

Pokharel S, White LJ, Aguas R, Celhay O, Pellé KG, Dittrich S. Algorithm in the diagnosis of febrile illness using pathogen-specific rapid diagnostic tests. *Clin Infect Dis*. 2020;70(11):2262–9 (<https://pubmed.ncbi.nlm.nih.gov/31313805/>, accessed 14 December 2022).

Sapkota J, Hasan R, Onsare R, Arafah S, Kariuki S, Shakoor S. Comparative analysis of commercially available typhoid point of care tests: results of a prospective and hybrid retrospective multicenter diagnostic accuracy study in Kenya and Pakistan. *J Clin Microbiol*. 2022;60(12) (<https://journals.asm.org/doi/10.1128/jcm.01000-22>, accessed 14 December 2022).

Wijedoru L, Mallett S, Parry C. Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever. *Cochrane Database Syst Rev.* 2017;5:CD008892 (<https://archive.lstmed.ac.uk/7226/>, accessed 14 December 2022).

I. SAGE IVD recommendations

SAGE IVD rejected the recommendation that serological tests for diagnosis of typhoid fever should not be used in endemic regions and do not constitute an adequate substitute for blood, stool or bone marrow culture.

The experts recommended that better assays for diagnosing typhoid fever be developed.

The group also recommended outlining next steps towards improved tests from a global health perspective.

SAGE IVD further recommended reviewing the Latin American literature (in Spanish) on typhoid fever from the 1980s as a way of informing diagnostic algorithms.

J. References (from application)

1. Crump JA. Progress in typhoid fever epidemiology. *Clin Infect Dis.* 2019;68(Suppl 1):S4–S9.
2. Typhoid. In: WHO/Newsroom/Fact sheets [website]. Geneva: World Health Organization; 2023 (<https://www.who.int/news-room/fact-sheets/detail/typhoid>, accessed 31 July 2023).
3. Amicizia D, Micale RT, Pennati BM, Zangrillo F, Iovine M, Lecini E et al. Burden of typhoid fever and cholera: similarities and differences. Prevention strategies for European travelers to endemic/epidemic areas. *J Prev Med Hyg.* 2019;60(4):E271–E285.
4. Ayuкеkbong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: causes and control strategies. *Antimicrob Resist Infect Control.* 2017;6:47.
5. Meiring JE, Giubilini A, Savulescu J, Pitzer VE, Pollard AJ. Generating the evidence for typhoid vaccine introduction: considerations for global disease burden estimates and vaccine testing through human challenge. *Clin Infect Dis.* 2019;69(Suppl 5):S402–S407.
6. Hamaguchi S, Cuong NC, Tra DT, Doan YH, Shimizu K, Tuan NQ et al. Clinical and epidemiological characteristics of scrub typhus and murine typhus among hospitalized patients with acute undifferentiated fever in Northern Vietnam. *Am J Trop Med Hyg.* 2015;92(5):972–8.
7. Mather RG, Hopkins H, Parry CM, Dittrich S. Redefining typhoid diagnosis: what would an improved test need to look like? *BMJ Glob Health.* 2019;4(5):e001831.
8. Moore CE, Pan-Ngum W, Wijedoru LPM, Sona S, Nga TVT, Duy PT et al. Evaluation of the diagnostic accuracy of a typhoid IgM flow assay for the diagnosis of typhoid fever in Cambodian children using a Bayesian latent class model assuming an imperfect gold standard. *Am J Trop Med Hyg.* 2014;90(1):114–20.
9. Wijedoru L, Mallett S, Parry CM. Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever. *Cochrane Database Syst Rev.* 2017;5(5):CD008892.
10. Khanam F, Sheikh A, Sayeed MA, Bhuiyan MS, Choudhury FK, Salma U et al. Evaluation of a typhoid/paratyphoid diagnostic assay (TPTest) detecting anti-Salmonella IgA in secretions of peripheral blood lymphocytes in patients in Dhaka, Bangladesh. *PLoS Negl Trop Dis.* 2013;7(7):e2316.

11. Siba V, Horwood PF, Vanuga K, Wapling J, Sehuko R, Siba PM et al. Evaluation of serological diagnostic tests for typhoid fever in Papua New Guinea using a composite reference standard. *Clin Vaccine Immunol.* 2012;19(11):1833–7.
12. Basnyat B. Typhoid versus typhus fever in post-earthquake Nepal. *Lancet Glob Health.* 2016;4(8):e516–7.

3. Revisions to EDL 3

3.1 Changes requested by the WHO Global Tuberculosis Programme

The GTB proposed changes for the TB disease-specific sections of EDL 3 based on updates to its guidelines in September 2022 (1, 2). Following a review by the WHO EDL Secretariat and the GTB, the following changes were implemented:

- Tuberculin skin test (TST) (Mantoux test) was renamed “Skin test for TB infection”; its test purpose was edited with the word “latent” removed to become “to diagnose TB infection”; two assay formats were added. The new assay formats are: tuberculin skin test (TST) and *Mycobacterium tuberculosis* antigen-based skin test (TBST); the columns WHO prequalified products and WHO supporting documents for this IVD were also updated. To review the new links, please refer to the EDL 4 table in section 5.
- Lipoarabinomannan (LAM) antigen: the columns WHO prequalified products and WHO supporting documents were updated. To review the new links, please refer to the EDL 4 table in section 5.
- *M. tuberculosis* DNA assay format Loop-mediated isothermal amplification (LAMP) was deleted.
- *M. tuberculosis* DNA mutations associated with resistance assay format molecular line probe assay (LPA) was deleted.
- *M. tuberculosis* DNA assay format NAT test purpose was updated with the addition of “+/- isoniazid”. Now it reads: “to diagnose active TB and simultaneously or sequentially detect rifampicin +/- isoniazid resistance”. Two more test purposes were added to this IVD test: “to diagnose active TB” and “to detect resistance to other anti-TB medicines”. The assay format was edited. Now it reads: “NAT-isothermal, NAT-automated, NAT-automated-reverse hybridization”. The specimen type was edited: Bronchoalveolar lavage (BAL) was removed to include “other respiratory specimens”, and gastric aspirate and stool were added. The columns WHO prequalified products and WHO supporting documents for this IVD were also updated. To review the new links, please refer to the EDL 4 table in section 5.
- *Mycobacterium tuberculosis* bacteria: the assay formats “microscopy and bacterial culture” were changed to “fluorescent microscopy, light microscopy and mycobacterial culture”; “automated liquid medium and solid medium” were also added to the assay formats.

- Drug susceptibility testing of *M. tuberculosis*: the culture assay format was edited. Now it reads: “mycobacterial culture drug susceptibility testing: -automated liquid medium and -solid medium”; the columns WHO prequalified products and WHO supporting documents for this IVD were updated too. To review the new links, please refer to the EDL 4 table in section 5.
- Immune response by interferon-gamma release assay (IGRA) test purpose was edited. The word “latent” was deleted. Now it reads: “to diagnose TB infection”. The columns WHO prequalified products and WHO supporting documents for this IVD were also updated. To review the new links, please refer to the EDL 4 table in section 5.
- *Mycobacterium tuberculosis* serology was renamed “Immune response by *Mycobacterium tuberculosis* antibody detection test”.

3.2 Changes requested by the WHO HIV and Hepatitis Department

The WHO HIV and Hepatitis Department proposed changes for the HIV disease-specific sections of the EDL based on the 2021 updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (3). Following a review by the WHO EDL Secretariat and the WHO technical department on HIV infection, the following changes were implemented:

- Quantitative HIV nucleic acid test (NAT) was added to Section I.b as a point-of-care NAT (conditionally listed) using plasma and serum as specimen type to monitor response to antiretroviral treatment for priority populations and to diagnose HIV infection in infants < 18 months of age (only if validated by the manufacturer).
- Lipoarabinomannan (LAM) antigen was added to Sections I.b and II.b as a rapid diagnostic test (RDT) using urine as specimen type to aid in the diagnosis of TB in seriously ill HIV-positive inpatients and in HIV-positive adult outpatients with signs and symptoms of TB.

The WHO HIV and Hepatitis Department also proposed changes to the wording for the Hepatitis B and Hepatitis C disease-specific sections in the EDL. Following a review by the WHO EDL Secretariat and the WHO technical department on hepatitis infection, the following changes were implemented:

- The Hepatitis B surface antigen (HBsAg) test purpose was updated by adding “for acute infection, IgM-specific antibodies to hepatitis B core antigen (IgM anti-HBc) are needed in addition to HBsAg”. Now it reads: “to screen for HBV infection and to aid in the diagnosis of chronic and acute HBV infection: infants > 12 months

of age, children, adolescents and adults. (For acute infection, IgM-specific antibodies to hepatitis B core antigen (IgM anti-HBc) are needed in addition to HBsAg).”

- The Hepatitis B e antigen (HBeAg) RDT test purpose was updated with the addition of “together with ALT measurement”. Now it reads: “staging to assess the need for HBV treatment in chronic HBV infection together with ALT measurement, and as a criterion for use of antivirals in the mother to prevent mother-to-child transmission. (This test is used only when an HBV DNA test is not available).”
- Qualitative or quantitative HCV nucleic acid test: the test purpose was updated by removing “and to monitor response to treatment”. Now it reads: “to diagnose viraemic HCV and as a test of cure”.

3.3 Changes proposed by external partners

In addition to the updates requested by WHO technical departments, SAGE IVD received seven comments proposing changes, additions and delisting to six general IVD tests in Sections I.a and II.a of the EDL, within the clinical chemistry discipline, and for one disease-specific test in Section I.b Diabetes mellitus:

I.a: Glucose and bilirubin;

II.a: Albumin, blood urea nitrogen (BUN), total protein, uric acid;

I.b: Haemoglobin A1c (HbA1c).

All comments were considered by SAGE IVD and the WHO EDL Secretariat, resulting in the update of applicable tests’ purpose or assay format according to the evidence (4, 5, 6, 7, 8, 9, 10, 11, 12) available to the experts. The following changes were implemented:

- Glucose test purpose was updated by removing “to diagnose” and adding “to detect”. Now it reads: “to detect hypoglycaemia”; this change applies only for the clinical chemistry section in I.a.
- Albumin assay format was edited: “optical methods” was removed and “quantitative immunochemical methods” was added. Now it reads: “quantitative immunochemical methods on semi-automated or automated chemistry analysers”; this change applies only for Section II.a.
- Blood urea nitrogen (BUN) test purpose was changed. Now it reads: “to correlate with uremic symptoms in advanced chronic kidney disease and to track adherence to low protein diet where dialysis isn’t available”.

One expert suggested inviting an application to add a fructosamine test in a future edition of the EDL for situations when HbA1c is not a suitable measure of diabetes control, for example in cases of anaemia, haemoglobinopathies or malaria.

The WHO EDL Secretariat noted that proposals for additions, revisions/changes or removal of an IVD category need to be formally requested by using the applicable application form (i.e. addition of a new IVD test, edits, delisting) and including the most recent observational data, primary studies, systematic reviews or guideline recommendations as part of the application.

4. Summary of recommendations

In total, SAGE IVD considered:

- 9 applications for the addition of new IVDs;
- 2 applications for edits;
- 1 application for Do Not Do recommendations; and
- 7 comments on the IVDs listed in EDL 3.

Following the review and deliberation of each application and all comments, SAGE IVD made the following recommendations for EDL 4:

4.1 Additions

Section I.a: General IVDs recommended for use in community settings and health facilities without laboratories

- ABO blood groups and Rhesus (Rh) factor typing POC test

Section I.b: Disease-specific IVDs recommended for use in community settings and health facilities without laboratories

- IgM antibodies to hepatitis E virus, RDT (*conditionally listed*)

Section II.a: General IVDs recommended for use in health facilities with clinical laboratories

- Kleihauer-Betke acid-elution test

Section II.b: Disease-specific IVDs recommended for use in health facilities with clinical laboratories

- IgM antibodies to hepatitis E virus, immunoassay
- Hepatitis E virus nucleic acid test (NAT)
- High-sensitivity troponin I test (hs-cTnI), immunoassay
- 17-Hydroxyprogesterone (17-OHP), immunoassay
- Parathyroid hormone (PTH), immunoassay

4.2 Edits and revisions

Section I.a: General IVDs recommended for use in community settings and health facilities without laboratories

- Glucose (within Clinical chemistry, assay format: glucose meter)

Section I.b: Disease-specific IVDs recommended for use in community settings and health facilities without laboratories

- Glucose (within Diabetes mellitus, assay format: glucose meter)

Section II.a: General IVDs recommended for use in health facilities with clinical laboratories

- Albumin
- Blood urea nitrogen (BUN)

Note: all changes requested by WHO technical departments described in 3.1 and 3.2 were accepted as per the SAGE IVD Terms of Reference (13), which states that where policy and technical recommendations on IVDs are provided through WHO established advisory mechanisms, SAGE IVD would accept such recommendations without further review and incorporate such advice in its consideration of organization-wide policies.

4.3 Rejections

After careful review, SAGE IVD rejected three applications:

- Meningitis/encephalitis multiplex PCR panel, as an addition to the EDL to aid in the diagnosis of specific agents of meningitis and/or encephalitis;
- Serological tests for the detection of typhoid antigen and IgM/IgG antibodies as a Do Not Do recommendation; and
- *M. tuberculosis* DNA, POC NAT as an IVD to diagnose active TB and simultaneously or sequentially detect rifampicin resistance in community settings and health facilities without laboratories.

4.4 General recommendations

Sage IVD made a series of general recommendations related to EDL products, processes and strategy, as listed below. Progress on the suggested actions will be reported to SAGE IVD at its fifth meeting.

4.4.1 EDL format

- Consider clarifying what is meant by testing in a “non-laboratory” setting (in other words, clarify if Section I lists tests that could potentially be placed outside of laboratory settings or tests that should be available in every facility without laboratories). A related matter concerns whether the EDL should make specific references to

infrastructure (currently, it does not) and whether it should stick to two levels or add a third.

- Consider clarifying what is needed to reverse a conditional listing to a full listing and within what time frame.
- Together with WHO, clarify and consolidate definitions of “point-of-care (POC)” (e.g. POC and RDT are often interpreted as being synonymous, but they are not).
- Consider whether the distinction between “to aid in diagnosing” and “to diagnose” is clear enough and whether it is consistently applied in the test purpose in the EDL.
- Consider adding a new category to be called Cardiovascular health in Section II.b.
- Consider adding hepatitis A to EDL 5.
- Set up an ad hoc call to have a discussion on the structure of the list.

4.4.2 EDL processes

- Ensure a participatory approach to developing the EDL that provides partners and countries with the information they need to make a contribution and engages more stakeholders in disseminating the EDL and encouraging its use.
- Streamline the EDL application to make it less intimidating.
- Request more specific information in the application to improve applicants’ chance of success.
- Increase outreach to associations to understand their needs for IVDs and to encourage submissions of applications.

4.4.3 EDL-related products

- Consider producing at least one commentary or PR publication that would come out with the EDL to increase awareness.

4.4.4 EDL strategy

- Prioritize NEDL advocacy to move forward and gain visibility.
- Develop a plan for penetrating the academic network to attract academic efforts.
- Work with Non-State actors (NSA) in official relationships, collaborating centres and manufacturers to promote the EDL.
- Focus on implementation and NEDLs.

4.5 IVD tests recommended for EDL 5

As part of its deliberations, SAGE IVD issued the following requests for full submissions for consideration as additions to EDL 5:

- antibodies to hepatitis A virus;
- fructosamine; and
- all the tests deemed as high-priority tests for the EDL mentioned in section 1.5 of this report, and for which no applications were submitted for EDL 4.

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13. 2023 terms of reference for the Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD). Geneva: World Health Organization; 2023 ([https://www.who.int/publications/m/item/2023-terms-of-reference-for-strategic-advisory-group-of-experts-on-in-vitro-diagnostics-\(sage-ivd\)](https://www.who.int/publications/m/item/2023-terms-of-reference-for-strategic-advisory-group-of-experts-on-in-vitro-diagnostics-(sage-ivd))), accessed 9 April 2023).

5. The fourth WHO model list of essential in vitro diagnostics (EDL 4)

The EDL is presented by health care facility level in two tiers:

- I. Community settings and health facilities without laboratories, with two sections:
 - a. General IVDs recommended for use in community settings and health facilities without laboratories
 - b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories
- II. Health care facilities with clinical laboratories, with three sections:
 - a. General IVDs recommended for use in clinical laboratories
 - b. Disease-specific IVDs recommended for use in clinical laboratories
 - c. Disease-specific IVDs recommended for use in blood screening laboratories

and a section on Do Not Do recommendations.

Note: The specimen types listed for each IVD test category comprise possible specimens for that category; however, not all test brands within each category will be validated for all the specimen types listed. It is assumed that products within each category will be used strictly in accordance with the manufacturer's instructions for use.

Assay formats listed are generic and may be based on different methodologies, e.g. immunoassays are available in various forms – manual microplate assays and automated platforms – with various types of chemical detection (e.g. turbidimetry, chemiluminescence and electrochemiluminescence assays). Selection of products and assay formats should be based on local processes.

I. Community settings and health facilities without laboratories

These lists contain IVD tests recommended for use in community settings and health facilities that include health posts and centres, doctors' offices, outreach clinics, ambulatory care and home-based and self-testing. The tests in this level of the EDL are also assumed to be available, in combination with the extended list in Section II, at health care facilities with laboratories, though assay formats may vary. The list comprises sections for:

- a. General IVDs recommended for use in community settings and health facilities without laboratories
- b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories

I.a. General IVDs recommended for use in community settings and health facilities without laboratories

Discipline	IVD test	Test purpose	Assay format	Specimen type
Blood typing	ABO blood groups and Rhesus (Rh) factor typing	To determine ABO groups and Rh factor	Point-of-care test	Capillary whole blood
			Slide agglutination test	Capillary whole blood Venous whole blood ¹
Clinical chemistry	Albumin	To detect or monitor kidney disease	Dipstick	Urine
	Bilirubin	To detect or monitor liver disease and bile duct disorders	Dipstick	Urine
	Glucose	To detect hypoglycaemia	Glucose meter	Capillary whole blood
	Ketones	To aid in the diagnosis of ketosis, e.g. in uncontrolled diabetes, starvation, pregnancy or in diabetic ketoacidosis	Dipstick	Urine
	Urinalysis test strips	To aid in the diagnosis of urinary tract infections (UTIs) by detection of leukocyte esterase derived from white blood cells or nitrites as a result of bacteria in urine	Dipstick	Urine

¹ If a phlebotomist is available.

I.a. General IVDs recommended for use in community settings and health facilities without laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type
Haematology	Erythrocyte sedimentation rate (ESR)	To detect inflammation as an indicator of various conditions when C-reactive protein (CRP) is not available	Westergren	Venous whole blood ²
	Haemoglobin (Hb)	To diagnose and monitor anaemia To monitor the safety of certain drugs (e.g. zidovudine for HIV infection) To screen potential blood donors	Haemoglobinometer	Capillary whole blood Venous whole blood ²
		Clinical marker for certain severe infections (e.g. malaria, viral haemorrhagic fevers) To aid in the diagnosis of intravascular haemolysis, renal conditions, rhabdomyolysis (myoglobinuria) ³	Dipstick	Urine
Pregnancy testing	Human chorionic gonadotropin (hCG)	To aid in the early detection of pregnancy	RDT (dipstick and cassette), latex agglutination	Urine (early morning)

² If a phlebotomist is available.

³ This test does not differentiate between myoglobin and haemoglobin.

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Chagas disease	<i>Trypanosoma cruzi</i> IgG antibody	<p>For surveillance of <i>T. cruzi</i> infection</p> <p>To screen girls, women of childbearing age and pregnant women without previous treatment for <i>T. cruzi</i> infection</p> <p>To screen children and other at-risk populations</p> <p>To aid in the diagnosis of chronic <i>T. cruzi</i> infection (Chagas disease)</p> <p>(Only in settings where laboratory-based methods are not available)</p>	RDT ⁴	<p>Capillary whole blood</p> <p>Venous whole blood⁵</p> <p>Serum</p>	N/A	<p>Guidelines for the diagnosis and treatment of Chagas disease (2018)</p> <p>https://www.who.int/publications/i/item/9789275120439</p> <p>https://www.who.int/health-topics/chagas-disease#tab=tab_1</p>

⁴ A negative result does not exclude infection.

⁵ If a phlebotomist is available.

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cholera	<i>Vibrio cholerae</i> antigen	For initial detection or exclusion of a cholera outbreak (Not for use in case management)	RDT	Stool Rectal swab	N/A	Health topics - Cholera https://www.who.int/health-topics/cholera#tab=tab_1

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Coronavirus disease (COVID-19)	SARS-CoV-2 antigen ⁶	To diagnose COVID-19 in settings where NAT is unavailable or where prolonged turnaround times preclude clinical utility ⁷ To aid in the diagnosis of COVID-19 in the early symptomatic phases of illness, or in asymptomatic individuals with known contact with a confirmed case ⁷	RDT Handheld or small benchtop instrument for POC use	Upper respiratory specimens (e.g. nasopharyngeal or nasal swab)	Emergency Use Listing (EUL) https://extranet.who.int/pqweb/vitro-diagnostics/coronavirus-disease-covid-19-pandemic-%E2%80%94-emergency-use-listing-procedure-eul-open	Antigen-detection in the diagnosis of SARS-CoV-2 infection: interim guidance (6 October 2021) https://apps.who.int/iris/handle/10665/345948 Guidance on SARS-CoV-2 testing is reviewed regularly based on available evidence. For up-to-date guidance, see: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications

⁶ Listing was based on available evidence and interim WHO guidelines, which are subject to change. Regulatory oversight of most commercially available tests was limited to emergency use authorizations at the time of listing.

⁷ A negative test does not rule out infection and should not determine clinical care.

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Diabetes mellitus	Glucose	To aid in the diagnosis of diabetes mellitus (if blood glucose testing is not available)	Dipstick	Urine	N/A	HEARTS-D: diagnosis and management of type 2 diabetes (2020) https://apps.who.int/iris/handle/10665/331710 https://www.who.int/health-topics/diabetes#tab=tab_1
		To screen for type 2 diabetes mellitus ⁸				
		To diagnose and monitor ⁹ type 1 and type 2 diabetes mellitus	Glucose meter	Capillary whole blood		
		To diagnose impaired fasting glucose/ impaired glucose tolerance				
		To screen for type 2 diabetes mellitus and impaired fasting glucose/impaired glucose tolerance				
		To self-monitor type 1 and type 2 diabetes mellitus at home				

⁸ Screening for diabetes is possible with various methods, both biochemical and non-biochemical, of varying sensitivity and specificity. Urine glucose testing can be used if the aim of screening is to identify people who have more severe hyperglycaemia within the diabetes spectrum.

⁹ If HbA1c testing is not available.

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Diabetes mellitus <i>continued</i>	Haemoglobin A1c (HbA1c)	To diagnose and monitor diabetes mellitus	Handheld and small analysers	Capillary whole blood	N/A	HEARTS-D: diagnosis and management of type 2 diabetes (2020) https://apps.who.int/iris/handle/10665/331710 https://www.who.int/health-topics/diabetes#tab=tab_1
Hepatitis B virus (HBV) infection	Hepatitis B surface antigen (HBsAg)	To screen for HBV infection, and to aid in the diagnosis of chronic and acute HBV infection: infants > 12 months of age, children, adolescents and adults. (For acute infection, IgM-specific antibodies to hepatitis B core antigen (IgM anti-HBc) are needed in addition to HBsAg)	RDT	Capillary whole blood Venous whole blood ¹⁰	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=63	Guidelines on hepatitis B and C testing (2017) https://apps.who.int/iris/handle/10665/254621 https://www.who.int/news-room/fact-sheets/detail/hepatitis-b

¹⁰ If a phlebotomist is available.

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Hepatitis B virus (HBV) infection <i>continued</i>	Hepatitis B e antigen (HBeAg)	Staging to assess the need for HBV treatment in chronic HBV infection together with ALT measurement, and as a criterion for use of antivirals in the mother to prevent mother-to-child transmission (This test is used only when an HBV DNA test is not available)	RDT	Capillary whole blood Venous whole blood ¹¹	N/A	Guidelines on hepatitis B and C testing (2017) https://apps.who.int/iris/handle/10665/254621 https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
Hepatitis C virus (HCV) infection	Antibodies to hepatitis C virus (anti-HCV)	To screen for and to aid in the diagnosis of viraemic HCV infection: infants > 18 months of age, children, adolescents and adults	RDT	Oral fluid Capillary whole blood Venous whole blood ¹¹	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=59	Guidelines on hepatitis B and C testing (2017) https://apps.who.int/iris/handle/10665/254621 https://www.who.int/news-room/fact-sheets/detail/hepatitis-c
Hepatitis E virus (HEV) infection	IgM antibodies to hepatitis E virus (anti-HEV IgM)	To aid in the diagnosis and surveillance of hepatitis E virus infection	RDT	Capillary whole blood	N/A	Waterborne outbreaks of hepatitis E: recognition, investigation and control: technical report (2014) https://apps.who.int/iris/handle/10665/129448

¹¹ If a phlebotomist is available.

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV infection	Antibodies to HIV 1/2 (anti-HIV Ab)	HIV self-testing to aid in the diagnosis of HIV infection	RDT	Oral fluid Capillary whole blood	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=60	Guidelines on HIV self-testing and partner notification: supplement to consolidated guidelines on HIV testing services (2016) https://apps.who.int/iris/handle/10665/251655 Consolidated guidelines on HIV testing services (2019) https://apps.who.int/iris/handle/10665/336323 WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection: module 10: testing providers (2017) https://apps.who.int/iris/handle/10665/258516 HIV molecular diagnostics toolkit to improve access to viral load testing and infant diagnosis: HIV treatment and care (2019) https://apps.who.int/iris/handle/10665/325961/
		To screen for or to aid in the diagnosis of HIV infection: adults, adolescents, children and infants > 18 months of age	RDT	Oral fluid Capillary whole blood Venous whole blood ¹²		
	Combined HIV antibody/p24 antigen (anti-HIV/p24 Ag)	To screen for or to aid in the diagnosis of HIV infection: adults, adolescents, children and infants > 18 months of age	RDT	Capillary whole blood Venous whole blood ¹²		
	Qualitative HIV nucleic acid test (NAT)	To diagnose HIV infection in infants < 18 months of age	Point-of-care NAT	Capillary whole blood Venous whole blood ¹² Dried blood spots (DBS)		

¹² If a phlebotomist is available.

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV infection <i>continued</i>	Quantitative HIV nucleic acid test (NAT)	To monitor response to antiretroviral treatment for priority populations To diagnose HIV infection in infants < 18 months of age (only if validated by the manufacturer)	Point-of-care NAT	Plasma ¹³ Serum ¹³		Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (2021) https://apps.who.int/iris/handle/10665/340190 https://www.who.int/health-topics/hiv-aids/#tab=tab_1
	CD4 cell enumeration	To stage advanced HIV disease To monitor response to antiretroviral therapy (in settings where quantifying viral load is not available)	Point-of-care flow cytometry platform	Capillary whole blood Venous whole blood ¹³	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=66	Consolidated guidelines on HIV testing services (2019) https://apps.who.int/iris/handle/10665/336323 Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy (2017) https://apps.who.int/iris/handle/10665/255884 https://www.who.int/health-topics/hiv-aids/#tab=tab_1

¹³ If a phlebotomist is available.

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV infection <i>continued</i>	Cryptococcal antigen	To screen for and diagnose cryptococcal meningitis in people with advanced HIV disease	RDT	Capillary whole blood Venous whole blood ¹⁴	N/A	Guidelines for the diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents and children (2018) https://apps.who.int/iris/handle/10665/260399 Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy (2017) https://apps.who.int/iris/handle/10665/255884

¹⁴ If a phlebotomist is available.

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV infection <i>continued</i>	Lipoarabinomannan (LAM) antigen	To aid in the diagnosis of TB in seriously ill HIV-positive inpatients and in HIV-positive adult outpatients with signs and symptoms of TB	RDT	Urine	N/A	<p>Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (March 2021) https://apps.who.int/iris/handle/10665/340190</p> <p>WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021 update https://apps.who.int/iris/handle/10665/342331</p> <p>WHO operational handbook on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021 update https://apps.who.int/iris/handle/10665/332864</p>

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Influenza	Influenza A and B antigen	To aid in the diagnosis of seasonal influenza infection (Not recommended for surveillance testing)	RDT Instrument-based point-of-care immunoassay	Nasal swab Nasopharyngeal swab Nasopharyngeal aspirate or wash	N/A	Use of influenza rapid diagnostic tests (2010) https://apps.who.int/iris/handle/10665/44304 Manual for the laboratory diagnosis and virological surveillance of influenza (2011) https://apps.who.int/iris/handle/10665/44518
	Influenza A and B nucleic acid test	To diagnose seasonal influenza infection	Point-of-care NAT	Nasal swab Nasopharyngeal swab Nasopharyngeal aspirate or wash	N/A	Global epidemiological surveillance standards for influenza (2013) https://apps.who.int/iris/handle/10665/311268 https://www.who.int/health-topics/influenza-seasonal#tab=tab_1

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Malaria	<i>Plasmodium</i> spp. antigens; species-specific (e.g. HRP2) and/or pan-species-specific (e.g. pan-pLDH)	To diagnose one or more human malaria parasite species (<i>P. falciparum</i> , <i>P. vivax</i> , <i>P. malariae</i> , <i>P. ovale</i>)	RDT	Capillary whole blood Venous whole blood ¹⁵	Public reports of WHO prequalified IVDs https://extranet.who.int/pgweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=64	Guidelines for the treatment of malaria, 3rd edition (2015) https://apps.who.int/iris/handle/10665/162441 Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: round 8 (2016–2018) https://apps.who.int/iris/handle/10665/276190 Good practices for selecting and procuring rapid diagnostic tests for malaria (2011) https://apps.who.int/iris/handle/10665/44530 Recommended selection criteria for procurement of malaria rapid diagnostic tests (2018) https://apps.who.int/iris/handle/10665/259870 WHO guidelines for malaria (2022) https://apps.who.int/iris/handle/10665/351995 https://www.who.int/health-topics/malaria#tab=tab_1

¹⁵ If a phlebotomist is available.

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Streptococcal pharyngitis	Group A <i>Streptococcus</i> antigen	To aid in the diagnosis of Group A streptococcal pharyngitis	RDT	Throat swab	N/A	N/A
Sickling disorders	Sickle cell testing	To screen for or to aid in the diagnosis of sickle cell disease, C trait (SCT) and other variant sickling disorders	RDT	Capillary whole blood Venous whole blood ¹⁶	N/A	N/A

¹⁶ If a phlebotomist is available.

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Syphilis	Antibodies to <i>Treponema pallidum</i>	To diagnose or to aid in the diagnosis of <i>T. pallidum</i>	RDT	Capillary whole blood Venous whole blood ¹⁷	N/A	Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus (2013) https://apps.who.int/iris/handle/10665/85343 https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis)
	Combined antibodies to <i>T. pallidum</i> and HIV 1/2	To diagnose or to aid in the diagnosis of HIV 1/2 and/or <i>T. pallidum</i>	RDT	Capillary whole blood Venous whole blood ¹⁷	Public reports of WHO prequalified IVDs https://extranet.who.int/pgweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=57	WHO information note on the use of dual HIV/syphilis rapid diagnostic tests (RDT) (2017) http://apps.who.int/iris/handle/10665/252849 Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations (2016 update) https://apps.who.int/iris/handle/10665/246200

¹⁷ If a phlebotomist is available.

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Tuberculosis (TB)	Skin test for TB infection	To diagnose TB infection	Tuberculin skin test (TST) <i>Mycobacterium tuberculosis</i> antigen-based skin tests (TBSTs)	N/A	All TB tests are evaluated and guidelines developed by the WHO TB Programme https://www.who.int/teams/global-tuberculosis-programme/overview	WHO consolidated guidelines on tuberculosis: module 3: diagnosis: tests for TB infection (2022) https://apps.who.int/iris/handle/10665/362936 WHO operational handbook on tuberculosis: module 3: diagnosis: tests for tuberculosis infection (2022) https://apps.who.int/iris/handle/10665/363335 https://www.who.int/health-topics/tuberculosis#tab=tab_1

I.b. Disease-specific IVDs recommended for use in community settings and health facilities without laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Tuberculosis (TB) <i>continued</i>	Lipoarabino-mannan (LAM) antigen	To aid in the diagnosis of TB in seriously ill HIV-positive inpatients and in HIV-positive adult outpatients with signs and symptoms of TB	RDT	Urine		<p>Lateral flow urine lipoarabino-mannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV: policy update 2019 https://apps.who.int/iris/handle/10665/329479</p> <p>The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV: policy update (2015) http://apps.who.int/iris/handle/10665/193633 https://www.who.int/health-topics/tuberculosis#tab=tab_1</p>
Visceral leishmaniasis (kala-azar)	Recombinant K39 (rK39) antigen	To aid in the diagnosis of clinically suspected visceral leishmaniasis	RDT	Capillary whole blood Serum ¹⁸ Venous whole blood ¹⁸	N/A	<p>Control of the leishmaniasis: report of a meeting of the WHO Expert Committee on the Control of Leishmaniasis, Geneva, 22–26 March 2010. https://apps.who.int/iris/handle/10665/44412 https://www.who.int/teams/control-of-neglected-tropical-diseases</p>

¹⁸ If a phlebotomist is available.

II. Health care facilities with clinical laboratories

These lists contain additional IVD tests recommended for use in district, regional, provincial or specialized hospitals or laboratories, and national reference laboratories. It is assumed that trained laboratory technologists, specialist expertise, and laboratory infrastructure and equipment are available at the appropriate level. All tests available in community settings and health facilities as described in Section I are assumed to be available at higher levels, as appropriate. The list comprises sections for:

- a. General IVDs recommended for use in clinical laboratories
- b. Disease-specific IVDs recommended for use in clinical laboratories
- c. Disease-specific IVDs recommended for use in blood screening laboratories

II.a. General IVDs recommended for use in clinical laboratories

Discipline	IVD test	Test purpose	Assay format	Specimen type	WHO supporting documents
Anatomical pathology ¹⁹	Histopathology	To assess tissue for infection, neoplasia, inflammatory and degenerative disorders	<p>Macroscopic assessment of tissue and selection of areas for microscopic examination</p> <p>Microscopy of tissue sections mounted on slides and stained most commonly with haematoxylin and eosin in the first instance, then treated with a variety of special stains, selected case by case to identify pathogens and other abnormal features</p>	<p>Surgical resection</p> <p>Biopsy</p> <p>Core biopsy</p> <p>Cell block</p>	<p>WHO list of priority medical devices for cancer management (2017)</p> <p>https://apps.who.int/iris/handle/10665/255262</p> <p>Basic histopathology and anatomical pathology services for developing countries with variable services (2003)</p> <p>https://apps.who.int/iris/handle/10665/119675</p>
	Cytology (cytopathology)	To assess cells for infection, neoplasia, inflammatory and degenerative disorders	Microscopy of stained cells on slides	<p>Cervical specimen for Papanicolaou (Pap) smear</p> <p>Body fluids (e.g. cerebrospinal fluid, pleural fluid, peritoneal fluid, urine)</p> <p>Lymph nodes, spleen and other tissues (obtained through fine-needle aspiration)</p> <p>Bone marrow aspirate</p> <p>Respiratory specimens (e.g. sputum, bronchial brushings, bronchoalveolar lavage [BAL])</p> <p>Skin samples</p>	<p>Guide for establishing a pathology laboratory in the context of cancer control (2019)</p> <p>https://apps.who.int/iris/handle/10665/330664</p>

¹⁹ Note: The tests described in this section require specialized anatomical pathology laboratories and trained anatomical pathologists.

II.a. General IVDs recommended for use in clinical laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type	WHO supporting documents
Anatomical pathology ²⁰ <i>continued</i>	Immunohistochemistry (IHC)	To assess cells for specific markers to identify infection, neoplasia, inflammatory and degenerative disorders	Microscopy of histopathology tissue sections mounted on slides and stained with antibodies to specific markers (Refer to EDL sections on disease-specific tests for individual assays)	Surgical resection Biopsy Core biopsy Cell block	
	Post-mortem examination	To determine the cause of death and correlation with pre-mortem clinical features and investigations	Macroscopic assessment and microscopy of tissue sections (Procedures selected case by case)	Tissue from cadaver	

²⁰ Note: The tests described in this section require specialized anatomical pathology laboratories and trained anatomical pathologists.

II.a. General IVDs recommended for use in clinical laboratories <i>continued</i>				
Discipline	IVD test	Test purpose	Assay format	Specimen type
Blood typing	ABO blood groups and Rhesus (Rh) factor typing	To determine ABO groups and Rh factor	Slide agglutination test	Venous whole blood
Clinical microbiology	Staining procedures	For the presumptive identification of pathogens and for determination of microbial morphology	Microscopic examination of slides which may use different types of microscopes and stains	Disease-appropriate specimens (e.g. sputum, venous whole blood, urine, stool, body fluids, cerebrospinal fluid or cultures)
	Culture	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Culture on growth media plates or broth in an incubator followed by recovery of isolates and species identification (traditional manual techniques or automated equipment)	Disease-appropriate specimens (e.g. urine, stool, sputum, body fluids, e.g. cerebrospinal fluid, etc.)
	Blood culture	To detect bacterial and fungal bloodstream infections (sepsis)	Blood culture bottle in an incubator followed by recovery of isolates (traditional manual techniques or automated equipment)	Venous whole blood
	Genus and species identification of bacteria and fungi	To identify the genus or species of bacteria or fungi from microbial isolates	A range of biochemical tests that may be performed manually or on automated equipment	Bacteria or fungal isolates

II.a. General IVDs recommended for use in clinical laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type
Clinical microbiology <i>continued</i>	Antimicrobial susceptibility testing (AST)	Final step in selection of appropriate antibiotics after species identification and interpretation by EUCAST ²¹ and CLSI guidelines ²² Note: WHO regards the development of antimicrobial resistance (AMR) as a high-priority global health issue. See WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS): https://www.who.int/activities/facilitating-global-surveillance-of-antimicrobial-resistance	Antimicrobial susceptibility testing of isolates may be done manually (by disc diffusion, gradient tests and broth microdilution), or by automated platforms	Bacteria isolates

²¹ EUCAST, European Committee on Antimicrobial Susceptibility Testing: Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0.

²² CLSI, Clinical and Laboratory Standards Institute: CLSI M100 performance standards for antimicrobial susceptibility testing, 29th edition.

II.a. General IVDs recommended for use in clinical laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type
Clinical chemistry ²³	Tests under this subsection may be requested together as part of a liver profile²⁴			
	Alanine aminotransferase (ALT)	To aid in the diagnosis of liver disease as a marker of liver injury	Optical methods on semi-automated or automated chemistry analysers	Serum Plasma
	Aspartate aminotransferase (AST)	To aid in the diagnosis of liver disease as a marker of liver injury	Optical methods on semi-automated or automated chemistry analysers	Serum Plasma
	Albumin	To aid in the diagnosis and monitoring of diseases affecting protein metabolism (synthesis, loss, intake, absorption), e.g. liver disease, kidney disease, severe malnutrition, malabsorption, burns, etc. ²⁵	Quantitative immunochemical methods on semi-automated or automated chemistry analysers	Serum Plasma
	Alkaline phosphatase (ALP)	To aid in the diagnosis of hepatobiliary and bone disorders	Optical methods on semi-automated or automated chemistry analysers	Serum Plasma
	Gamma-glutamyl transferase (GGT)	To assess hepatobiliary function To distinguish between bone and hepatobiliary causes of raised ALP	Optical methods on semi-automated or automated chemistry analysers	Serum Plasma

²³ Combinations of tests of clinical chemistry are often referred to as basic and comprehensive metabolic panels. However, the content of these may vary according to laboratory and health care system resources, disease profiles and patient needs.

²⁴ Often termed in common usage as "liver function tests", which may include other tests such as tests of coagulation, like prothrombin time. These individual tests, however, reflect different disease processes in the liver and do not all assess liver synthetic, metabolic or excretory function.

²⁵ Serum albumin levels may also decrease acutely in systemic inflammation, e.g. sepsis.

II.a. General IVDs recommended for use in clinical laboratories <i>continued</i>				
Discipline	IVD test	Test purpose	Assay format	Specimen type
Clinical chemistry <i>continued</i>	Globulin	To determine the globulin fraction levels which may indicate underlying infections, chronic inflammatory diseases or haematologic malignancies ²⁶	N/A (Calculation)	N/A
	Total protein	To measure total protein in blood and body fluids	Optical methods on semi-automated or automated chemistry analysers	Serum Plasma Body fluids
	Total bilirubin	To detect hyperbilirubinaemia as an aid in diagnosis and monitoring of diseases of the liver, biliary duct or pancreas, haemolysis and other causes like neonatal hyperbilirubinaemia	Optical methods on semi-automated or automated chemistry analysers	Serum Plasma
	Direct bilirubin and indirect bilirubin	To measure direct (conjugated) bilirubin and to estimate indirect (unconjugated) bilirubin as an aid in the differential diagnosis of hyperbilirubinaemia	Optical methods on semi-automated or automated chemistry analysers	Serum Plasma
	Tests under this subsection may be requested as part of a renal panel that will vary depending on the context			
	Albumin	To monitor kidney function	Quantitative immunochemical methods on semi-automated or automated chemistry analysers	Urine
	Blood urea nitrogen (BUN)	To correlate with uraemic symptoms in advanced chronic kidney disease and to track adherence to low protein diet where dialysis isn't available	Optical methods on semi-automated or automated chemistry analysers	Serum Plasma

²⁶ Calculated as total protein minus albumin. As such, many proteins are included in this calculation and include the sum of alpha 1, alpha 2, beta and gamma globulin (primarily immunoglobulin) fractions.

II.a. General IVDs recommended for use in clinical laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type
Clinical chemistry <i>continued</i>	Total calcium	To identify hypercalcaemia or hypocalcaemia, to assess calcium metabolism, to monitor total calcium levels in patients with underlying disease such as certain kinds of cancer (e.g. multiple myeloma, breast cancer and lung cancer), kidney disease, parathyroid disorder or malabsorption	Semi-automated or automated chemistry analyser	Serum Plasma
	Ionized calcium	To measure free (ionized) calcium in situations in which there are changes in the concentrations of certain proteins (such as albumin) and/or changes in physiological status such as acid–base disorders. To diagnose and monitor hypercalcaemia or hypocalcaemia	Blood gas analysers, including portable analysers for emergency and critical care	Arterial whole blood Venous whole blood Capillary whole blood
	Creatinine	To assess kidney function through estimated glomerular filtration rate (eGFR), urine albumin : creatinine ratio (ACR) and urine protein : creatinine ratio <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Electrochemical or optical methods on semi-automated or automated chemistry analysers	Serum Urine
	Electrolytes (sodium, potassium, chloride and bicarbonate ²⁷)	To monitor fluid, electrolyte and acid–base balance <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Electrochemical or optical methods on semi-automated or automated chemistry analyser	Serum Plasma

²⁷ Bicarbonate is sometimes measured as total carbon dioxide.

II.a. General IVDs recommended for use in clinical laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type
Clinical chemistry <i>continued</i>	Magnesium	To detect hypomagnesaemia in patients with underlying conditions (i.e. malabsorption, malnutrition), to detect hypermagnesaemia, to aid in the monitoring of kidney function	Semi-automated or automated chemistry analyser	Serum Plasma
	Phosphate	To monitor phosphorus levels in diseases of the kidney, parathyroid, vitamin D metabolism and in tumour lysis syndrome	Optical methods on semi-automated or automated chemistry analysers	Serum Plasma
	Blood pH and gases	To assess lung function, metabolic or kidney disorders and monitor oxygen therapy (includes blood pH, partial pressure of O ₂ and carbon dioxide, electrolytes and calculated anion gap) <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Blood gas analysers, including portable analysers for emergency and critical care	Arterial whole blood
	C-reactive protein (CRP)	To detect inflammation as an indicator of various conditions To monitor response to treatment <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	RDT	Venous whole blood Serum Plasma
			Latex agglutination assay Immunoassay	
Whole blood lactate	To assess metabolic acidosis, diabetic ketoacidosis, sepsis and dehydration <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Chemistry analyser, blood gas analyser and handheld analyser	Venous whole blood	

II.a. General IVDs recommended for use in clinical laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type
Clinical chemistry <i>continued</i>	Glucose	To diagnose hypoglycaemia <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Optical and electrochemical methods on semi-automated or automated chemistry analysers	Serum Plasma
	Glucose-6-phosphate dehydrogenase (G6PD)	To screen newborns for G6PD deficiency To determine G6PD activity (normal, intermediate, deficient) for a decision to administer oxidant drugs, e.g. 8-aminoquinoline drugs for radical cure of <i>P. vivax</i> malaria ²⁸	Semi-quantitative fluorescent spot test	Venous whole blood
	Lipase	To assess acute pancreatitis and other pancreatic disorders <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Optical methods, automated chemistry analyser if available	Serum Plasma
	Amylase	To assess acute pancreatitis and other pancreatic disorders	Optical methods, automated chemistry analyser if available	Serum Plasma Peritoneal fluid
	Procalcitonin	To guide antibiotic therapy or its discontinuation in sepsis and lower respiratory tract infections	RDT Point-of-care immunoassay Immunoassay	Serum Plasma Venous whole blood Capillary whole blood Plasma Serum Plasma

²⁸ Guidelines for the treatment of malaria, 3rd edition (2015), <https://apps.who.int/iris/handle/10665/162441>.

II.a. General IVDs recommended for use in clinical laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type
Clinical chemistry <i>continued</i>	Uric acid	To aid in the diagnosis and to monitor treatment of gout To aid in the diagnosis of tumour lysis syndrome associated with acute kidney injury by renal urate deposition during chemotherapy administration	Optical methods, automated chemistry analyser if available	Serum Plasma
	Urine chemistry	To detect and quantify substances in urine associated with metabolic disorders, renal dysfunction or UTIs <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Automated chemical analyser	Urine

II.a. General IVDs recommended for use in clinical laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type
Haematology	Blood cross-matching	To determine blood compatibility for blood transfusions <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Slide and/or tube agglutination tests	Capillary whole blood Venous whole blood
	Complete blood count (CBC), automated	To evaluate overall health and to detect a wide range of disorders, including anaemia, infections, leukaemias, and red blood cell (RBC), white blood cell (WBC) and platelet abnormalities, and primary immune disorders To diagnose and monitor chemotherapy-associated myelotoxicity <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Automated haematology analyser, total and differential counts of WBCs, RBCs, platelets, Hb and haematocrit (Hct)	Capillary whole blood Venous whole blood
	Basic cerebrospinal fluid (CSF) profile (CSF leukocyte count, CSF differential leukocyte count and CSF protein and glucose)	CSF leukocyte count: To aid in the diagnosis of bacterial, mycobacterial, fungal and viral meningitis ²⁹		Haemocytometer/automated haematology analysers with body fluid mode
CSF leukocyte differential count: To aid in the diagnosis of bacterial, mycobacterial, fungal and viral meningitis ²⁹			Wright–Giemsa-stained smears/automated haematology analysers with body fluid mode	Cerebrospinal fluid
CSF protein and glucose: To aid in the diagnosis of bacterial, mycobacterial, fungal and viral meningitis ²⁹			Automated/semi-automated chemistry analyser	

²⁹ Definitive diagnosis requires microbiological confirmation – Gram staining, culture, antigen testing, nucleic acid testing.

II.a. General IVDs recommended for use in clinical laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type
Haematology <i>continued</i>	D-Dimer	To diagnose disseminated intravascular coagulation To aid in the diagnosis of deep vein thrombosis, pulmonary embolism	Immunoassay	Citrate plasma
	Direct antiglobulin test (DAT)/direct Coombs test	To aid in the diagnosis of the cause of immune haemolytic anaemias To investigate a blood transfusion reaction To diagnose haemolytic disease of the newborn (HDNB)	Haemagglutination	Venous whole blood
	Fibrinogen	To diagnose disseminated intravascular coagulation	Handheld or automated coagulation analyser (fibrinogen activity) Immunoassay (fibrinogen antigen)	Citrate plasma
	Haematocrit (Hct)	To diagnose and monitor anaemia <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Micro-haematocrit method (if automated haematology analyser not available) Haematology analyser (preferred)	Capillary whole blood Venous whole blood

II.a. General IVDs recommended for use in clinical laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type
Haematology <i>continued</i>	Haemoglobin (Hb)	To diagnose and monitor anaemia and polycythaemia To monitor the safety of certain drugs (e.g. zidovudine for HIV infection) To screen potential blood donors Clinical marker for certain severe infections (e.g. malaria, viral haemorrhagic fevers) To aid in the diagnosis of intravascular haemolysis, renal conditions, rhabdomyolysis (myoglobinuria) <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Optical methods, haemoglobinometer (if automated haematology analyser not available) Haematology analyser (preferred)	Capillary whole blood Venous whole blood
	Indirect antiglobulin test (IAT)/indirect Coombs test/ red blood cell antibody screen	To screen for antibodies to red blood cells before a blood transfusion or during pregnancy To aid in the diagnosis of haemolytic anaemia and blood transfusion reactions	Haemagglutination	Serum
	Iron studies: Iron Ferritin Transferrin Calculated total iron-binding capacity (TIBC) or transferrin saturation	To diagnose iron deficiency and overload	Optical methods (iron and TIBC) Immunoassay (ferritin and transferrin)	Serum Plasma

II.a. General IVDs recommended for use in clinical laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type
Haematology <i>continued</i>	Kleihauer-Betke acid-elution test	To aid in the diagnosis and treatment of fetomaternal haemorrhage (FMH)	Microscopic examination of slides which may use different types of microscopes and stains	Whole blood
	Partial thromboplastin time (PTT)/ activated partial thromboplastin time (APTT)	To diagnose bleeding or thrombotic disorders To monitor anticoagulant therapy	Handheld or automated coagulation analyser	Citrate plasma
	Peripheral blood film examination	To detect red blood cell, white blood cell and platelet abnormalities, malignancies and parasites, and for white blood cell differential count	Microscopic examination of Romanowsky-stained blood films	Capillary whole blood Venous whole blood
	Platelet count	To diagnose thrombocytopenia or thrombocytosis Marker to manage severe infections associated with bleeding or sepsis (e.g. viral haemorrhagic fever, meningococcaemia) and certain haematological disorders <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Haemocytometer (if automated haematology analyser is not available) Haematology analyser (preferred)	Capillary whole blood Venous whole blood
	Prothrombin time and international normalized ratio (PT/INR)	To detect or diagnose bleeding or thrombotic disorders (PT) To monitor performance of anticoagulant medications (INR) <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Handheld or automated coagulation analyser	Citrate plasma

II.a. General IVDs recommended for use in clinical laboratories *continued*

Discipline	IVD test	Test purpose	Assay format	Specimen type
Haematology <i>continued</i>	White blood cell count, total	To aid in the diagnosis of infections and leukaemias	Haemocytometer (if automated haematology analyser not available)	Capillary whole blood Venous whole blood
	Sickle cell testing	To aid in the diagnosis of sickle cell anaemia, sickle cell trait and other sickling disorders	Sodium metabisulfite slide test Haemoglobin solubility	Venous whole blood
		To diagnose sickle cell anaemia, sickle cell trait and other sickling disorders	Haemoglobin electrophoresis	Venous whole blood
Clinical Pathology	Urine microscopy	To aid in the diagnosis of kidney and urologic diseases by detecting the presence of cells (white blood cells, red blood cells, epithelial cells), casts and crystals in urine sediment To detect the presence of pathogens	Microscopic examination May require staining procedures for microbial pathogens (e.g. Gram stain, modified Ziehl–Neelsen stain)	Urine
	Body fluid microscopy	To aid in the diagnosis of inflammatory, infectious and neoplastic diseases involving body fluids (e.g. pleural, peritoneal, synovial, pericardial) by detecting the presence or absence of cells (white blood cells, red blood cells, mesothelial cells) along with cell count and differential count	Microscopic examination May require staining procedures for pathogens and cytological examination for neoplastic cells	Body fluids
Pregnancy testing	Human chorionic gonadotropin (hCG)	To detect and/or confirm pregnancy	Optical method Immunoassay	Serum

II.b. Disease-specific IVDs recommended for use in clinical laboratories

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Aspergillosis	<i>Aspergillus</i> IgG antibody	To aid in the diagnosis of chronic pulmonary aspergillosis	RDT Immunoassay	Serum Plasma	N/A	N/A
	<i>Aspergillus</i> antigen test	To aid in the diagnosis of invasive aspergillosis in immunocompromised patients	RDT Immunoassay	Bronchoalveolar lavage (BAL) Serum bronchoalveolar lavage (BAL)	N/A	

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer	Alpha-fetoprotein (AFP)	To screen for hepatocellular carcinoma (HCC) in high-risk individuals with liver cirrhosis or with a family history, in conjunction with ultrasound For staging and monitoring of germ cell tumours To aid in the diagnosis and staging of hepatoblastoma	Immunoassay	Serum Plasma	N/A	Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection (2018) https://apps.who.int/iris/handle/10665/273174 Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (2015) https://apps.who.int/iris/handle/10665/154590 WHO classification of tumours of the urinary system and male genital organs. WHO classification of tumours, 4th edition, volume 8 https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Urinary-System-And-Male-Genital-Organs-2016

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer <i>continued</i>						WHO classification of tumours of female reproductive organs. WHO classification of tumours, 4th edition, volume 6 https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Female-Reproductive-Organs-2014
	Basic panel for immunohistochemical (IHC) testing for diagnosis of lymphoma	To aid in the diagnosis, sub-classification, prognosis and treatment of lymphoma (including HIV-associated conditions)	IHC testing (ki-67, CD45, BCL6, IRF4/MUM1, MYC, CD20, CD5, CD10, BCL2, CD23, CD79a, cyclinD1, CD3, CD15, CD30, TdT, CD138/syndecan-1, kappa and lambda chains, PAX5)	Formalin-fixed paraffin-embedded tissue (FFPE) ³⁰	N/A	WHO classification of tumours of haematopoietic and lymphoid tissues. WHO classification of tumours, revised 4th edition, volume 2 https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017 Guide for establishing a pathology laboratory in the context of cancer control (2019) https://apps.who.int/iris/handle/10665/330664

³⁰ Only for use in specialized anatomical pathology laboratories – see Anatomical Pathology under II.a. General IVDs recommended for use in clinical laboratories.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer <i>continued</i>	Basic panel of immunohistochemical (IHC) markers for diagnosis of solid tumours	To aid in diagnosis, prognosis and treatment of solid tumours, especially childhood cancer	IHC testing markers include desmin, cytokeratin, AE1/AE3, S100, synaptophysin, myogenin, hCG, PLAP, Oct3/4, NANOG, CD30, CD117/c-kit, WT1, SALL4	Formalin-fixed paraffin-embedded tissue (FFPE) ³¹	N/A	WHO classification of tumours https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours WHO list of priority medical devices for cancer management (2017) https://apps.who.int/iris/bitstream/handle/10665/255262/9789241565462-eng.pdf Guide for establishing a pathology laboratory in the context of cancer control (2019) https://apps.who.int/iris/handle/10665/330664

³¹ Only for use in specialized anatomical pathology laboratories – see Anatomical Pathology section under II.a. General IVDs recommended for use in clinical laboratories.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer <i>continued</i>	BCR-ABL1 and ABL1 transcripts	To diagnose and monitor therapy of chronic myelocytic leukaemia (CML) and CML variants (e.g. neutrophilic CML) and prognosis of acute lymphoblastic leukaemia (ALL)	NAT	Venous whole blood Bone marrow	N/A	WHO classification of tumours of haematopoietic and lymphoid tissues. WHO classification of tumours, revised 4th edition, volume 2 https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017 WHO model list of essential medicines: 22nd list (2021) https://apps.who.int/iris/handle/10665/345533
	Epidermal growth factor receptor (EGFR) gene mutation	To aid in the diagnosis and treatment of non-squamous non-small cell lung carcinoma	NAT	Formalin-fixed paraffin-embedded tissue (FFPE) and buffered lung tumour specimen ³²	N/A	

³² Only for use in specialized anatomical pathology laboratories – see Anatomical Pathology section under II.a. General IVDs recommended for use in clinical laboratories.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer <i>continued</i>	Basic flow cytometry panel of antibodies for leukaemia ³³	To aid in the diagnosis of acute leukaemias	Flow cytometry (CD10, CD19, CD45, CD34, CD7, CD33, CD117, myeloperoxidase, CD79a, cytoplasmic CD3, HLA-DR, CD5, CD23, CD43)	Bone marrow Peripheral blood Body fluids Tissue Lymph node aspirate	N/A	WHO classification of tumours of haematopoietic and lymphoid tissues. WHO classification of tumours, revised 4th edition, volume 2 https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017 WHO list of priority medical devices for cancer management (2017) https://apps.who.int/iris/handle/10665/255262 Guide for establishing a pathology laboratory in the context of cancer control (2019) https://apps.who.int/iris/handle/10665/330664

³³ Detection of 10 unique items among 12 components for four-colour fluorochrome cytometry.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer <i>continued</i>	Faecal immuno-chemical test (FIT)	To screen for colorectal cancer	Latex agglutination immune-turbidimetry	Stool	N/A	WHO list of priority medical devices for cancer management (2017) https://apps.who.int/iris/handle/10665/255262 Colorectal cancer screening. IARC handbooks of cancer prevention, volume 17 https://publications.iarc.fr/Book-And-Report-Series/larc-Handbooks-Of-Cancer-Prevention/Colorectal-Cancer-Screening-2019

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer <i>continued</i>	Human chorionic gonadotrophin (hCG) (measured as total beta-hCG ³⁴)	To aid in the diagnosis of and monitoring of germ cell tumours and gestational trophoblastic disease	Immunoassay	Plasma	N/A	<p>WHO classification of tumours of the urinary system and male genital organs. WHO classification of tumours, 4th edition, volume 8 https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Urinary-System-And-Male-Genital-Organs-2016</p> <p>WHO classification of tumours of female reproductive organs. WHO classification of tumours, 4th edition, volume 6 https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Female-Reproductive-Organs-2014</p>

³⁴ To include both free and intact beta-hCG.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer <i>continued</i>	Lactate dehydrogenase (LDH)	To aid in the prognosis and monitoring of haematological malignancies (e.g. lymphoma) and germ cell tumours Note: Also used as a marker for liver disease, <i>Pneumocystis</i> infection, thrombotic thrombocytopenic purpura (TTP) and other malignancies	Optical methods, automated chemistry analyser if available	Serum Plasma	N/A	WHO classification of tumours of haematopoietic and lymphoid tissues. WHO classification of tumours, revised 4th edition, volume 2. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017 WHO classification of tumours of the urinary system and male genital organs. WHO classification of tumours, 4th edition, volume 8. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Urinary-System-And-Male-Genital-Organs-2016

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer <i>continued</i>						WHO classification of tumours of female reproductive organs. WHO classification of tumours, 4th edition, volume 6. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Female-Reproductive-Organs-2014
	Estrogen (ER) and progesterone (PgR) receptors	To aid in diagnosis, prognosis and treatment of breast cancer	IHC testing	Formalin-fixed paraffin embedded tissue (FFPE) ³⁵	N/A	WHO classification of tumours of the breast. WHO classification of tumours, 4th edition, volume 4. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Breast-2012 WHO list of priority medical devices for cancer management (2017) https://apps.who.int/iris/handle/10665/255262/

³⁵ Only for use in specialized anatomical pathology laboratories – see Anatomical Pathology section under II.a. General IVDs recommended for use in clinical laboratories.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer <i>continued</i>						<p>WHO model list of essential medicines: 22nd list (2021) https://apps.who.int/iris/handle/10665/345533</p> <p>Guidelines for management of breast cancer. WHO Regional Office for the Eastern Mediterranean (2006) https://apps.who.int/iris/handle/10665/119806</p> <p>Guide for establishing a pathology laboratory in the context of cancer control (2019) https://apps.who.int/iris/handle/10665/330664</p>

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer <i>continued</i>	Papanicolaou (Pap) smear test	To screen for and to aid in early diagnosis of cervical cancer	Microscopic examination of cervical cells on slides	Cervical smear from liquid cytology specimen	N/A	<p>WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention (2013) https://apps.who.int/iris/handle/10665/94830</p> <p>Guide for establishing a pathology laboratory in the context of cancer control (2019) https://apps.who.int/iris/handle/10665/330664</p> <p>Comprehensive cervical cancer control: a guide to essential practice, 2nd edition (2014) https://apps.who.int/iris/handle/10665/144785</p> <p>Global strategy to accelerate the elimination of cervical cancer as a public health problem (2020) https://apps.who.int/iris/handle/10665/336583</p> <p>Guide to cancer early diagnosis (2017) https://apps.who.int/iris/handle/10665/254500</p>

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer <i>continued</i>						WHO technical guidance and specifications of medical devices for screening and treatment of precancerous lesions in the prevention of cervical cancer (2020) https://apps.who.int/iris/handle/10665/331698
	Prostate-specific antigen (PSA)	To aid in diagnosis, prognosis and monitoring of prostate cancer	Immunoassay	Peripheral blood	N/A	WHO classification of tumours of the urinary system and male genital organs. WHO classification of tumours, 4th edition, volume 8 https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours-Of-The-Urinary-System-And-Male-Genital-Organs-2016

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer <i>continued</i>	Tyrosine-protein kinase receptor (erbB-2) or human epidermal growth factor receptor 2 (HER-2) overexpression	To aid in treatment and prognosis of breast cancer	IHC testing	Formalin-fixed paraffin-embedded tissue (FFPE) ³⁶ (Referred specimens must be fixed correctly before transport)	N/A	WHO classification of tumours of the breast. WHO classification of tumours, 4th edition, volume 4 https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Breast-2012 WHO list of priority medical devices for cancer management (2017) https://apps.who.int/iris/handle/10665/255262 WHO model list of essential medicines: 22nd list (2021) https://apps.who.int/iris/handle/10665/345533 Guide for establishing a pathology laboratory in the context of cancer control (2019) https://apps.who.int/iris/handle/10665/330664

³⁶ Only for use in specialized anatomical pathology laboratories – see Anatomical Pathology section under II.a. General IVDs recommended for use in clinical laboratories.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cardio-vascular health	High-sensitivity troponin I (hs-cTnI)/ High-sensitivity troponin T (hs-cTnT)	To aid in the diagnosis of acute myocardial infarction <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Immunoassay	Plasma Serum	N/A	HEARTS: technical package for cardiovascular disease management in primary health care: risk-based CVD management (2020) https://apps.who.int/iris/handle/10665/333221
	Lipid profile	To assess risk of cardiovascular disease (CVD) by measuring cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) ³⁷	Optical methods, automated chemistry analyser if available	Plasma Serum		
	Troponin T/I	To diagnose myocardial infarction <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Immunoassay (handheld or large automated instrument)	Venous whole blood Serum Plasma		

³⁷ While low-density lipoprotein (LDL) can be measured, it is routinely calculated.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Coronavirus disease (COVID-19)	SARS-CoV-2 nucleic acid test	To diagnose infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in symptomatic and asymptomatic individuals suspected of having been exposed For surveillance and confirmation of outbreaks	NAT ³⁸	Upper respiratory specimens (e.g. nasopharyngeal and oropharyngeal) and lower respiratory specimens (e.g. BAL)	Emergency Use Listing (EUL) https://extranet.who.int/pqweb/vitro-diagnostics/coronavirus-disease-covid-19-pandemic-%E2%80%94-emergency-use-listing-procedure-eul-open	Diagnostic testing for SARS-CoV-2: interim guidance (11 September 2020) https://apps.who.int/iris/handle/10665/334254 Guidance on SARS-CoV-2 testing is reviewed regularly based on available evidence. For up-to-date guidance, see: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications

³⁸ Listing was based on evidence for RT-PCR tests. Other types of nucleic acid amplification require more evidence and will be subject to further review.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Diabetes mellitus	Glucose	To diagnose and monitor ³⁹ type 1 and type 2 diabetes mellitus To diagnose impaired fasting glucose/ impaired glucose tolerance To screen for type 2 diabetes mellitus and impaired fasting glucose/impaired glucose tolerance <i>Note: When used for emergency or critical care, results are time-sensitive.</i>	Optical methods, automated chemistry analyser if available	Serum Plasma	N/A	HEARTS-D: diagnosis and management of type 2 diabetes (2020) https://apps.who.int/iris/handle/10665/331710
	Haemoglobin A1c (HbA1c)	To diagnose and monitor diabetes mellitus	Immunoassay	Venous whole blood	N/A	HEART-D: diagnosis and management of type 2 diabetes (2020) https://apps.who.int/iris/handle/10665/331710

³⁹ If HbA1c is not available.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Endocrine disorders	Cortisol (total) ⁴⁰	To diagnose central (pituitary) or primary (adrenal, Addison's disease) cortisol deficiency ⁴¹ To diagnose central (pituitary) or primary (adrenal) hypercortisolism (Cushing's syndrome) ⁴²	Immunoassay	Serum Plasma	N/A	N/A
	Estradiol ⁴⁰	To aid in the diagnosis of anovulation, gonadal dysfunction, precocious puberty, and primary and secondary amenorrhoea To aid in the evaluation and management of infertility ⁴⁰	Immunoassay	Serum Plasma	N/A	N/A

⁴⁰ For use in specialized health care settings.⁴¹ Often used with timed collection and stimulation with cosyntropin.⁴² Often used with timed collection and suppression with dexamethasone.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Endocrine disorders <i>continued</i>	Follicle-stimulating hormone (FSH)	To aid in the diagnosis of anovulation, gonadal dysfunction, precocious puberty, and primary and secondary amenorrhea To aid in the evaluation and management of infertility ⁴³	Immunoassay	Serum Plasma	N/A	N/A
	Luteinizing hormone (LH)	To aid in the diagnosis of anovulation, gonadal dysfunction, precocious puberty, and primary and secondary amenorrhoea To aid in the evaluation and management of infertility ⁴³	Immunoassay	Serum Plasma	N/A	N/A

⁴³ For use in specialized health care settings.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Endocrine disorders <i>continued</i>	Parathyroid hormone (PTH) ⁴⁴	To aid in the evaluation of the causes of calcium homeostasis disorders and monitor the effects of treatment	Immunoassay	Serum Plasma	N/A	N/A
	Progesterone ⁴⁵	To confirm ovulation during infertility evaluation and treatment	Immunoassay	Serum Plasma	N/A	N/A
	Prolactin ⁴⁵	To diagnose and monitor hyperprolactinaemia (including prolactinoma)	Immunoassay	Serum Plasma	N/A	N/A
	Thyroid-stimulating hormone (TSH)	To screen ⁴⁶ for and to diagnose hypothyroidism and hyperthyroidism	Immunoassay	Serum Plasma Capillary whole blood (newborns)	N/A	N/A

⁴⁴ The test is approved for both the second-generation (intact) and third-generation (bioactive or bio-intact) forms of the assay.

⁴⁵ For use in specialized health care settings.

⁴⁶ Only in the context of neonatal screening for congenital hypothyroidism and of screening of patients with medical conditions such as type 1 diabetes mellitus where the incidence of hypothyroidism is higher than in the general population.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Endocrine disorders <i>continued</i>	17-Hydroxy-progesterone (17-OHP) ⁴⁷	To diagnose and monitor congenital adrenal hyperplasia (CAH) outside of the neonatal period (Not appropriate for screening)	Immunoassay	Serum Plasma	N/A	N/A

⁴⁷ For use in specialized health care settings.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Hepatitis B virus (HBV) infection	Hepatitis B surface antigen (HBsAg)	To screen for HBV infection, and to aid in the diagnosis of chronic and acute HBV infection: infants > 12 months of age, children, adolescents and adults (For acute infection, IgM-specific antibodies to hepatitis B core antigen (IgM anti-HBc) are needed in addition to HBsAg)	RDT	Venous whole blood Capillary whole blood Plasma Serum	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=63	Guidelines on hepatitis B and C testing (2017) http://apps.who.int/iris/handle/10665/254621 https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
	Quantitative HBV nucleic acid test	To stage chronic HBV infection, to determine the need for treatment (including use of antivirals in the mother to prevent mother-to-child transmission) and to monitor response to treatment	NAT	Serum Plasma	N/A	

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Hepatitis B virus (HBV) infection <i>continued</i>	Hepatitis B e antigen (HBeAg)	Staging to assess the need for HBV treatment in chronic HBV infection together with ALT measurement, and as a criterion for use of antivirals in the mother to prevent mother-to-child transmission (This test is used only when HBV DNA test is not available)	Immunoassay	Serum Plasma	N/A	
	IgM-specific antibodies to hepatitis B core antigen (IgM anti-HBc)	To aid in the diagnosis of acute HBV infection in the context of outbreak investigation	Immunoassay	Serum Plasma	N/A	
	Antibodies to hepatitis B surface antigen (anti-HBs)	To determine immune status due to HBV immunization	Immunoassay	Serum Plasma	N/A	

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Hepatitis C virus (HCV) infection	Antibodies to hepatitis C virus (anti-HCV)	To screen for and to aid in the diagnosis of viraemic HCV infection: infants > 18 months of age, children, adolescents and adults	RDT	Capillary whole blood Venous whole blood Plasma Serum	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=59	Guidelines on hepatitis B and C testing (February 2017) http://apps.who.int/iris/handle/10665/254621 https://www.who.int/news-room/fact-sheets/detail/hepatitis-c
			Immunoassay	Serum Plasma		
	Combined antibodies to HCV (anti-HCV) and HCV core antigen (HCVcAg)	To screen for HCV infection, and to aid in the diagnosis of viraemic HCV infection: infants > 18 months of age, children, adolescents and adults	Immunoassay	Serum Plasma		
	HCV core antigen (HCVcAg)	To aid in the diagnosis of viraemic HCV infection	Immunoassay	Serum Plasma		
	Qualitative or quantitative HCV nucleic acid test	To diagnose viraemic HCV and as a test of cure	NAT	Capillary whole blood Venous whole blood Serum Plasma Dried blood spots		

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Hepatitis E virus (HEV) infection	IgM antibodies to hepatitis E virus (anti-HEV IgM)	To aid in the diagnosis and surveillance of hepatitis E virus infection	RDT	Capillary whole blood Plasma Serum	N/A	Waterborne outbreaks of hepatitis E: recognition, investigation and control: technical report (2014) https://apps.who.int/iris/handle/10665/129448
		To diagnose acute hepatitis E virus infection	Immunoassay	Plasma Serum	N/A	
	Hepatitis E virus nucleic acid test (NAT)	To diagnose acute hepatitis E virus infection	NAT	Plasma Serum Stool Whole blood	N/A	

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV infection	Antibodies to HIV 1/2 (anti-HIV Ab)	To screen for or to aid in the diagnosis of HIV infection: adults, adolescents, children and infants > 18 months of age	RDT	Venous whole blood Plasma Serum	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=58	Consolidated guidelines on HIV testing services (2019) https://apps.who.int/iris/handle/10665/336323 Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (2021) https://apps.who.int/iris/handle/10665/340190 WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection: module 10: testing providers (2017) https://apps.who.int/iris/handle/10665/258516 https://www.who.int/health-topics/hiv-aids/#tab=tab_1
			Immunoassay	Serum Plasma		
	Combined HIV antibody/p24 antigen (anti-HIV/p24 Ag)		RDT	Venous whole blood Plasma Serum		
			Immunoassay	Serum Plasma		

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV infection <i>continued</i>	Qualitative HIV nucleic acid test (NAT)	To diagnose HIV infection in infants < 18 months of age	NAT	Capillary whole blood Venous whole blood Dried blood spots Plasma	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=61	Consolidated guidelines on HIV testing services (2019) https://apps.who.int/iris/handle/10665/336323 Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (2021) https://apps.who.int/iris/handle/10665/340190
	Quantitative HIV nucleic acid test (NAT)	To monitor response to antiretroviral treatment To diagnose HIV infection in infants < 18 months of age (only if validated by the manufacturer)	NAT	Dried blood spots Serum Plasma		WHO HIV molecular diagnostics toolkit to improve access to viral load testing and infant diagnosis: HIV treatment and care (2019) https://apps.who.int/iris/handle/10665/325961

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV infection <i>continued</i>	CD4 cell enumeration	To stage advanced HIV disease To monitor response to antiretroviral therapy (in settings where quantifying viral load is not available)	Flow cytometry	Capillary whole blood Venous whole blood	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=66	Consolidated guidelines on HIV testing services (2019) https://apps.who.int/iris/handle/10665/336323 Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy (2017) https://apps.who.int/iris/handle/10665/255884 https://www.who.int/health-topics/hiv-aids/#tab=tab_1
	Cryptococcal antigen	To screen for and diagnose cryptococcal meningitis in people with advanced HIV disease	RDT	Cerebrospinal fluid Capillary whole blood Venous whole blood Serum Plasma	N/A	Guidelines for the diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents and children (2018) http://apps.who.int/iris/handle/10665/260399 Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy (2017) https://apps.who.int/iris/handle/10665/255884
			Immunoassay	Cerebrospinal fluid Serum Plasma		

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV infection <i>continued</i>	<i>Histoplasma capsulatum</i> antigen	To aid in the diagnosis of disseminated histoplasmosis	Immunoassay	Urine	N/A	Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy (2017) https://apps.who.int/iris/handle/10665/255884
	Lipoarabinomannan (LAM) antigen	To aid in the diagnosis of TB in seriously ill HIV-positive inpatients and in HIV-positive adult outpatients with signs and symptoms of TB	RDT	Urine	N/A	Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (March 2021) https://apps.who.int/iris/handle/10665/340190 WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021 update https://apps.who.int/iris/handle/10665/342331 WHO operational handbook on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021 update https://apps.who.int/iris/handle/10665/342369

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Human papilloma-virus (HPV) infection	HPV nucleic acid test (NAT)	For cervical cancer screening	NAT	Cervical cells collected in test-specific transport fluid/ vessel	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=65	Introducing and scaling up testing for human papillomavirus as part of a comprehensive programme for prevention and control of cervical cancer: a step-by-step guide (2020) https://apps.who.int/iris/handle/10665/336668 WHO human papillomavirus laboratory manual, 1st edition (2009) http://apps.who.int/iris/handle/10665/70505 Comprehensive cervical cancer control: a guide to essential practice, 2nd edition (2014) https://apps.who.int/iris/handle/10665/144785 Global strategy to accelerate the elimination of cervical cancer as a public health problem (2020) https://apps.who.int/iris/handle/10665/336583

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Human papilloma-virus (HPV) infection <i>continued</i>						WHO technical guidance and specifications of medical devices for screening and treatment of precancerous lesions in the prevention of cervical cancer (2020) https://apps.who.int/iris/handle/10665/331698
Influenza	Influenza A and B nucleic acid test (NAT)	To diagnose seasonal influenza	NAT	Nasal swab Nasopharyngeal swab Nasopharyngeal aspirate or wash	N/A	Manual for the laboratory diagnosis and virological surveillance of influenza (2011) https://apps.who.int/iris/handle/10665/44518 Global epidemiological surveillance standards for influenza (2013) https://apps.who.int/iris/handle/10665/311268

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Malaria	<i>Plasmodium</i> spp. antigens; species-specific (e.g. HRP2) and/or pan-species-specific (e.g. pan-pLDH)	To diagnose infection by one or more human malaria parasite species (<i>P. falciparum</i> , <i>P. vivax</i> , <i>P. malariae</i> , <i>P. ovale</i>)	RDT	Capillary whole blood Venous whole blood	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=64	Guidelines for the treatment of malaria, 3rd edition (2015) https://apps.who.int/iris/handle/10665/162441 Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: round 8 (2016–2018) https://apps.who.int/iris/handle/10665/276190 Good practices for selecting and procuring rapid diagnostic tests for malaria (2011) https://apps.who.int/iris/handle/10665/44530 Recommended selection criteria for procurement of malaria rapid diagnostic tests (2018) https://apps.who.int/iris/handle/10665/259870 WHO guidelines for malaria (2022) https://apps.who.int/iris/handle/10665/351995 https://www.who.int/health-topics/malaria#tab=tab_1

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Malaria <i>continued</i>	<i>Plasmodium</i> spp.	To diagnose infection by one or more human malaria parasite species (<i>P. falciparum</i> , <i>P. vivax</i> , <i>P. malariae</i> , <i>P. ovale</i>) and monitoring response to treatment	Light microscopy	Capillary whole blood Venous whole blood	N/A	Guidelines for the treatment of malaria, 3rd edition (2015) https://apps.who.int/iris/handle/10665/162441 Basic malaria microscopy, 2nd edition (2010) http://apps.who.int/iris/handle/10665/44208 General safety procedures in the malaria microscopy laboratory. Malaria microscopy standard operating procedures (2016) https://apps.who.int/iris/handle/10665/340471

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Neglected tropical diseases	Qualitative dengue virus nucleic acid test	For surveillance (serotype differentiation) and confirmation of outbreaks	NAT	Serum Plasma Dried blood spots	N/A	Dengue guidelines for diagnosis, treatment, prevention and control: new edition (2009) https://apps.who.int/iris/handle/10665/44188
	Dengue virus IgM antibody	To aid in the diagnosis of dengue fever (always in combination with NS1) and for population surveys	RDT	Serum Venous whole blood	N/A	
			Immunoassay	Venous whole blood Dried blood spots Saliva		
Dengue virus antigen (NS1)	To aid in the diagnosis of dengue fever (always in combination with dengue virus IgM antibody) and for population surveys	RDT	Serum Venous whole blood	N/A		
		Immunoassay	Serum Plasma			

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Neglected tropical diseases <i>continued</i>	Kato-Katz faecal smear	For surveillance and diagnosis of soil-transmitted helminthiasis and schistosomiasis caused by <i>Schistosoma mansoni</i> , <i>S. intercalatum</i> , <i>S. japonicum</i> , <i>S. mekongi</i>	Microscopic slide examination	Fresh stool	N/A	N/A
	<i>Trypanosoma cruzi</i> IgG antibody	For surveillance of <i>T. cruzi</i> infection To screen girls, women of childbearing age and pregnant women without previous treatment for <i>T. cruzi</i> infection To screen children and other at-risk populations To diagnose chronic <i>T. cruzi</i> infection (Chagas disease) To monitor treatment of <i>T. cruzi</i> infection	Immunoassay	Serum Plasma	N/A	Guidelines for the diagnosis and treatment of Chagas disease (2019) https://iris.paho.org/handle/10665.2/49653

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Neglected tropical diseases <i>continued</i>	Visceral leishmaniasis direct agglutination test	To aid in the diagnosis of clinically suspected visceral leishmaniasis (kala-azar)	Agglutination assay	Serum Dried blood spots	N/A	Control of the leishmaniases: report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22–26 March 2010. https://apps.who.int/iris/handle/10665/44412 https://www.who.int/teams/control-of-neglected-tropical-diseases
<i>Pneumocystis</i> pneumonia	<i>Pneumocystis jirovecii</i> nucleic acid test	To aid in the diagnosis of <i>Pneumocystis</i> pneumonia ⁴⁸	NAT	Respiratory specimens (sputum, bronchoalveolar lavage fluid)	N/A	

⁴⁸ Particularly relevant in immunocompromised patients.

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Primary immunodeficiencies	HIV 1/2 antibody (anti-HIV Ab)	For differential diagnosis of primary immunodeficiencies	RDT	Oral fluid Capillary whole blood Venous whole blood	N/A	N/A
	Plasma immunoglobulin levels (IgG, IgA, IgM)	To identify patients with low plasma immunoglobulin levels and to monitor replacement	Radial immunodiffusion (RID)	Serum	N/A	N/A
			Immunoassay	Serum Plasma		
Lymphocyte subtype enumeration: CD3, CD4, CD8, B cells CD19 and/or CD20, CD16/56 T cells and NK cells (Refer to HIV infection for enumeration of CD4 cells only)	To aid in the diagnosis of primary and secondary immunodeficiencies	Flow cytometry	Venous whole blood	N/A		

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Sexually transmitted infections	Qualitative nucleic acid test (NAT) for <i>Chlamydia trachomatis</i> (CT) and <i>Neisseria gonorrhoeae</i> (NG) infections	To diagnose chlamydial and/or gonorrhoeal urogenital disease and extragenital infection	NAT	Urine	N/A	Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus (2013) https://apps.who.int/iris/handle/10665/85343 Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations (2016 update) https://apps.who.int/iris/handle/10665/246200
				Urethral swabs Endocervical swabs Vaginal swabs Rectal swabs Oropharyngeal swabs Liquid cytology		
	Antibodies to <i>Treponema pallidum</i>	To diagnose or to aid in the diagnosis of <i>T. pallidum</i>	RDT	Venous whole blood Plasma Serum	N/A	Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus (2013) http://apps.who.int/iris/handle/10665/85343
			Immunoassay	Serum Plasma		

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Sexually transmitted infections <i>continued</i>	Combined antibodies to <i>T. pallidum</i> and HIV 1/2	To diagnose or to aid in the diagnosis of HIV 1/2 and/or <i>T. pallidum</i>	RDT	Venous whole blood Plasma Serum	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=57	WHO information note on the use of dual HIV/syphilis rapid diagnostic tests (RDT) (2017) http://apps.who.int/iris/handle/10665/252849/ Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations (2016 update) https://apps.who.int/iris/handle/10665/246200
	Non-treponemal rapid plasma reagin (RPR)	To screen for syphilis and monitor treatment effectiveness	Particle/Charcoal agglutination assay	Serum Plasma	N/A	Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus (2013) http://apps.who.int/iris/handle/10665/85343
	Non-treponemal venereal disease research laboratory (VDRL) test	To screen for, diagnose and confirm neurosyphilis	Flocculation test	Serum Plasma Cerebrospinal fluid	N/A	

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Sexually transmitted infections <i>continued</i>	<i>T. pallidum</i> haemagglutination (TPHA) test	To confirm syphilis infection and diagnose early and late syphilis	Haemagglutination assay	Serum (preferred) Plasma	N/A	Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus (2013) https://apps.who.int/iris/handle/10665/85343
	<i>T. pallidum</i> particle agglutination (TPPA) test	infection	Particle agglutination assay		N/A	
Streptococcal pharyngitis	Group A <i>Streptococcus</i> antigen	To aid in the diagnosis of Group A streptococcal pharyngitis	RDT Immunoassay	Throat swab	N/A	N/A

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Tuberculosis (TB)	<i>Mycobacterium tuberculosis</i> bacteria	To diagnose and monitor treatment of active TB	Fluorescent microscopy Light microscopy	Sputum or other specimen types	All TB tests are evaluated and guidelines developed by the WHO Global TB Programme https://www.who.int/teams/global-tuberculosis-programme/overview	Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis, 2nd edition (2018) https://apps.who.int/iris/handle/10665/272644 Implementing tuberculosis diagnostics: policy framework (2015) https://apps.who.int/iris/handle/10665/162712
		To diagnose and monitor treatment of active TB, including drug-resistant TB	Mycobacterial culture: - Automated liquid medium - Solid medium	Sputum or other specimen types		
	<i>M. tuberculosis</i> DNA	To diagnose active TB	NAT - isothermal	Sputum Other respiratory specimens		
		To diagnose active TB and simultaneously or sequentially detect rifampicin +/- isoniazid resistance	NAT - automated	Gastric aspirate Stool Other extra-pulmonary TB specimen types	WHO consolidated guidelines on tuberculosis: module 3: diagnosis: tests for TB infection (2022) https://apps.who.int/iris/handle/10665/362936	
		To detect resistance to other anti-TB medicines	NAT - automated - reverse hybridization		WHO operational handbook on tuberculosis: module 3: diagnosis: tests for tuberculosis infection (2022) https://apps.who.int/iris/handle/10665/363335	

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Tuberculosis (TB) <i>continued</i>	Drug susceptibility testing of <i>M. tuberculosis</i> culture	To detect resistance to first-line and/or second-line anti-TB medicines	Mycobacterial culture drug susceptibility testing: - Automated liquid medium - Solid medium	Bacterial culture of <i>M. tuberculosis</i>	All TB tests are evaluated and guidelines developed by the WHO Global TB Programme https://www.who.int/teams/global-tuberculosis-programme/overview	Implementing tuberculosis diagnostics: policy framework (2015) https://apps.who.int/iris/handle/10665/162712 Technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis (2018) https://apps.who.int/iris/handle/10665/275469 Technical report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis (2018) https://apps.who.int/iris/handle/10665/260470 Technical report on critical concentrations for drug susceptibility testing of isoniazid and the rifamycins (rifampicin, rifabutin and rifapentine) (2021) https://apps.who.int/iris/handle/10665/339275

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Tuberculosis (TB) <i>continued</i>	Immune response by interferon-gamma release assay (IGRA)	To diagnose TB infection	Immuno-assay or enzyme-linked immune absorbent spot (ELISpot) assay	Venous whole blood		WHO consolidated guidelines on tuberculosis: module 3: diagnosis: tests for TB infection (2022) https://apps.who.int/iris/handle/10665/362936 WHO operational handbook on tuberculosis: module 3: diagnosis: tests for tuberculosis infection (2022) https://apps.who.int/iris/handle/10665/363335

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Vaccine-preventable diseases	Measles nucleic acid test	To diagnose clinically suspected measles infection	NAT	Oral fluid Throat swab Nasopharyngeal aspirates or swabs Urine	N/A	Manual for the laboratory diagnosis of measles and rubella virus infection, 2nd edition (2007) https://apps.who.int/iris/handle/10665/70211
	Measles IgM antibody	To diagnose clinically suspected measles infection	Immunoassay	Serum Plasma Dried Blood Spots Oral fluid	N/A	Manual for the laboratory-based surveillance of measles, rubella, and congenital rubella syndrome, 3rd edition (2018) https://www.who.int/teams/immunization-vaccines-and-biologicals/immunization-analysis-and-insights/surveillance-surveillance-for-vpds/laboratory-networks/measles-and-rubella-laboratory-network/manual-for-the-laboratory-based-surveillance-of-measles-rubella-and-congenital-rubella-syndrome
	Measles IgG antibody	To aid in the diagnosis of clinically suspected measles infection	Immunoassay	Serum Plasma Dried blood spots Oral fluid	N/A	https://apps.who.int/iris/handle/10665/275754
	Rubella IgM antibody	To diagnose active rubella infection or recent exposure	Immunoassay	Serum Plasma Dried blood spots Oral fluid	N/A	Surveillance standards for vaccine-preventable diseases, 2nd edition (2018) https://apps.who.int/iris/handle/10665/275754
	Rubella IgG antibody	To screen for prior exposure to rubella infection or vaccination, particularly in pregnant women	Immunoassay	Serum Plasma Dried blood spots Oral fluid	N/A	Immunological basis for immunization: rubella (2008) https://apps.who.int/iris/handle/10665/43922

II.b. Disease-specific IVDs recommended for use in clinical laboratories *continued*

Disease	IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Zika virus infection	IgM antibodies to Zika virus	To aid in the diagnosis of suspected Zika virus infection ⁴⁹	Immunoassay	Serum (Not to be used with CSF)	N/A	Laboratory testing for Zika virus infection: interim guidance (2016) https://apps.who.int/iris/handle/10665/204671
	Zika virus nucleic acid test (NAT)	To diagnose acute Zika virus infection ^{50, 51}	NAT	CSF Plasma Serum Urine Venous whole blood	WHO Emergency Use Listing (EUL) https://extranet.who.int/pqweb/vitro-diagnostics/zika-virus-disease	

⁴⁹ Because of potential cross-reactivity with dengue and other flaviviruses, and persistence of Zika IgM antibody that may reflect infection prior to pregnancy, currently available Zika virus IgM test results should not be used alone for clinical decision-making in pregnancy.

⁵⁰ Zika virus RNA is typically detectable in serum by NAT assays only within the first week of infection. A negative result does not rule out infection.

⁵¹ To reduce risk of false-positive results in pregnant women, a positive NAT test should be confirmed by re-extraction and repeat NAT testing of the same specimen.

II.c. Disease-specific IVDs recommended for use in blood screening laboratories

Disease	Screening IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Hepatitis B virus (HBV)	Hepatitis B surface antigen (HBsAg)	To screen blood donations for HBV	RDT ^{52, 53}	Capillary whole blood Venous whole blood Plasma Serum	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=63	Screening donated blood for transfusion-transmissible infections: recommendations (2009) http://apps.who.int/iris/handle/10665/44202
			Particle agglutination assay ^{52, 53}	Plasma Serum		
			Immuno-assay ⁵²	Plasma Serum		

⁵² The only assays recommended for blood screening are those that have been validated for this purpose by the manufacturer.

⁵³ May be performed in laboratories with small throughput, in remote areas or emergency situations.

Note: Please refer to the Haematology section for information on General IVDs for blood transfusion.

II.c. Disease-specific IVDs recommended for use in blood screening laboratories *continued*

Disease	Screening IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Hepatitis C virus (HCV)	Antibodies to HCV (anti-HCV)	To screen blood donations for HCV	RDT ^{54, 55}	Capillary whole blood Venous whole blood Plasma Serum	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=63	Screening donated blood for transfusion-transmissible infections: recommendations (2009) http://apps.who.int/iris/handle/10665/44202
			Immuno-assay ⁵⁴	Serum Plasma		
	Combined antibodies to HCV (anti-HCV) and HCV core antigen (HCVcAg)	To screen blood donations for HCV	Immuno-assay ⁵⁴	Serum Plasma		

⁵⁴ The only assays recommended for blood screening are those that have been validated for this purpose by the manufacturer.

⁵⁵ May be performed in laboratories with small throughput, in remote areas or emergency situations.

II.c. Disease-specific IVDs recommended for use in blood screening laboratories <i>continued</i>						
Disease	Screening IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV	Antibodies to HIV 1/2 (anti-HIV Ab)	To screen blood donations for HIV	RDT ^{56, 57}	Capillary whole blood Venous whole blood Serum Plasma	Public reports of WHO prequalified IVDs https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=58	Screening donated blood for transfusion-transmissible infections: recommendations (2009) http://apps.who.int/iris/handle/10665/44202
			Particle agglutination assay ^{56, 57}	Serum Plasma		
			Immuno-assay ⁵⁶	Serum Plasma		
	Combined HIV antibody/p24 antigen (anti-HIV/p24 Ag) test	To screen blood donations for HIV	Immuno-assay ⁵⁶	Serum Plasma		

⁵⁶ The only assays recommended for blood screening are those that have been validated for this purpose by the manufacturer.

⁵⁷ May be performed in laboratories with small throughput, in remote areas or emergency situations.

II.c. Disease-specific IVDs recommended for use in blood screening laboratories *continued*

Disease	Screening IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Malaria ⁵⁸	Antibodies to <i>Plasmodium</i> spp.	To screen blood donations for one or more human malaria species (<i>P. falciparum</i> , <i>P. vivax</i> , <i>P. malariae</i> , <i>P. ovale</i>) in non-endemic areas	Immunoassay	Serum Plasma	N/A	Screening donated blood for transfusion-transmissible infections: recommendations (2009) http://apps.who.int/iris/handle/10665/44202
	<i>Plasmodium</i> spp. antigens	To screen blood donations for one or more human malaria species (<i>P. falciparum</i> , <i>P. vivax</i> , <i>P. malariae</i> , <i>P. ovale</i>) in endemic areas	Immunoassay	Serum Plasma		
	<i>Plasmodium</i> spp.	To screen blood donations for one or more human malaria species (<i>P. falciparum</i> , <i>P. vivax</i> , <i>P. malariae</i> , <i>P. ovale</i>) in endemic areas ⁵⁹	Light microscopy	Capillary whole blood Venous whole blood		

⁵⁸ Testing should be implemented in combination with the donor selection and deferral strategies.

⁵⁹ To selectively screen blood donations from individuals identified to be at risk of transmitting malaria, travellers or previous residents of endemic countries to detect antibodies to the *Plasmodium* species prevalent in their donor population.

II.c. Disease-specific IVDs recommended for use in blood screening laboratories <i>continued</i>						
Disease	Screening IVD test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
<i>Treponema pallidum</i>	Antibodies to <i>T. pallidum</i>	To screen blood donations for syphilis	Immuno-assay ^{60,61}	Serum Plasma	N/A	Screening donated blood for transfusion-transmissible infections: recommendations (2009) http://apps.who.int/iris/handle/10665/44202
Other transfusion-transmitted organisms		To screen for other blood-transmitted microorganisms (e.g. <i>T. cruzi</i> , human T-lymphotropic virus (HTLV I/II), Zika virus, <i>Babesia</i> species and West Nile virus) in blood donations, depending on local risks of contamination	Immuno-assay ⁶⁰	Serum Plasma	N/A	

⁶⁰ The only assays recommended for blood screening are those that have been validated for this purpose by the manufacturer

⁶¹ In populations with a high incidence of syphilis, screening should be performed with a non-treponemal assay: venereal disease research laboratory (VDRL) or rapid plasma reagin (RPR).

Do Not Do recommendations

The following test categories have been listed for discontinuation. These recommendations are based on either evidence of harm or a lack of benefit. Listings are supported by current WHO policies.

Disease	IVD test	Recommendation	Assay format	WHO supporting documents
HIV	HIV western blot	Western blotting and line immunoassays should not be used in national HIV testing strategies and algorithms (Strong recommendation, low-quality evidence)	Western blot assay Line immunoassay	Consolidated guidelines on HIV testing services (2019) https://apps.who.int/iris/handle/10665/336323 WHO recommends countries move away from western blot and line immunoassays in HIV testing strategies and algorithms: policy brief (2019) https://apps.who.int/iris/handle/10665/329915
Tuberculosis	Immune response by <i>Mycobacterium tuberculosis</i> antibody detection test	Serodiagnostic tests for diagnosis of tuberculosis should not be used in individuals suspected of active pulmonary or extra-pulmonary TB, irrespective of their HIV status	RDT Immunoassay	Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement (2011) https://apps.who.int/iris/handle/10665/44652

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List of participants 4th SAGE IVD meeting

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The following experts conducted the evidence review for all applications received to support the addition of a test category to the list:

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Bada Yang, Assistant Professor, Julius Center, University Medical Center Utrecht, Netherlands

Giselle Weiss, Technical Editor, Allschwil, Switzerland

WHO EDL Secretariat

Francis Gabriel Moussy, Team Lead

Ana Aceves Capri, Technical Officer

Naofumi Hashimoto, Technical Officer

WHO invited experts

The following experts participated in the 4th SAGE IVD meeting open session day:

Stephen Himley, Technical Officer, Health Technologies, WHO Regional Office for South-East Asia

Benedikt Huttner, Team Lead, Essential Medicines, WHO headquarters

Alexandre Lemgruber, Regional Advisor, Health Technologies, Pan-American Health Organization

Adriana Velazquez Berumen, Team Lead, Medical Devices and In Vitro Diagnostics, WHO headquarters

Wei Zhang, Technical Officer, Access to Assistive Technology, WHO headquarters

Annex 1

4th SAGE IVD meeting – open session day

SAGE IVD held its fourth meeting from 14 to 18 November 2022 in a virtual format. On the first day of the meeting, the WHO EDL Secretariat planned for an open session in the format of a webinar. Participants had the opportunity to submit questions and comments through Zoom’s Q&A feature during the Q&A session.

All materials related to the open session day, including the recording, slides and the Q&A, are available here: <https://www.who.int/news-room/events/detail/2022/11/14/default-calendar/webinar-open-session-day-4th-sage-ivd-meeting> (accessed 14 April 2023).

Annex 2

EDL-related products

Electronic EDL

The electronic EDL (eEDL) is a user-friendly web-based application of the WHO EDL and was launched in a beta version on 29 January 2021. The eEDL allows the user to search for tests using various filters, such as disease/health condition, setting, assay format, IVD purpose and specimen type. Individual IVD webpages are printable; and the user selections, as well the whole list, can be exported as a Microsoft Excel worksheet or a pdf.

As of June 2023, the eEDL contains technical specifications for IVDs listed in the EDL for syphilis, for cryptococcal antigen, for Group A *Streptococcus*, for influenza A and B, for HBV and for HCV.

The beta eEDL version is not fully tested, and it may therefore contain bugs and not fully implemented features. This version will continue to be enhanced by input from multiple stakeholders during the beta phase. Users should be aware that historical records of EDL listings are not complete in the eEDL.

It is also important to highlight that nowadays the eEDL does not substitute for the paper-based version of the EDL.

The eEDL is offered to the public as a freely available resource; its contents are available under the Creative Commons Attribution CC BY 3.0 IGO.

The eEDL is available here: <https://edl.who-healthtechnologies.org/> (accessed 13 April 2023).

EDL technical specifications

EDL technical specifications are developed to support the selection and procurement of specific IVD products in line with test categories listed in the EDL. Made up of a range of predefined criteria, they provide information on the minimum requirements to ensure good quality, safety and efficacy of the products. EDL technical specifications are not absolute and must be tailored to meet individual country needs.

The process to develop these specifications includes: horizon scanning of existing tests and platforms; analysis of existing products in the market based on approval from stringent regulatory authorities; review of WHO guidance and guidelines (when available); review of peer-reviewed publications, textbooks, and published qualitative and quantitative comparative studies of existing tests and platforms; comparative study of test specifications (i.e. accuracy, precision,

positive and negative predictive value, likelihood ratios); comparison and review of the package inserts and user manuals of products which were approved by stringent regulatory authorities; comparison and review of documents and data on the safety and performance of approved products which were uploaded to the websites of stringent regulatory authorities; external quality assessment data and technical expert opinion. All technical specification drafts were available for public comments through the WHO website.

As of June 2023, the WHO EDL Secretariat has developed:

- 16 technical specifications for hepatitis B virus;
- 15 technical specifications for syphilis;
- 13 technical specifications for hepatitis C virus;
- 3 technical specifications for influenza A and B;
- 1 technical specification for Group A *Streptococcus* antigen; and
- 1 technical specification for cryptococcal antigen.

These technical specifications are available to download through the eEDL.

For more information on recommended procurement practices for IVDs and laboratory equipment, see: Guidance for procurement of in vitro diagnostics and related laboratory items and equipment. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/handle/10665/255577>, accessed 7 April 2023).

Guidance for countries

Since the first edition of the EDL, WHO has encouraged countries to develop NEDLs based on the model of the WHO EDL and has published a guidance document to support countries in this endeavour. So far, the guidance document is available in English, Portuguese and Spanish, with translations to Arabic and French in progress. You can download the guidance document in English, Portuguese and Spanish here: <https://apps.who.int/iris/handle/10665/343385> (accessed 7 April 2023).

The guidance document describes the best practices for selecting categories of IVD tests for an NEDL, consistent with the evidence-based methods used to update the WHO EDL. The document helps countries to identify the most relevant categories of IVD tests listed in the WHO EDL for inclusion in the NEDL according to countries' context and needs, national health plan, national laboratory strategic plan, priority health interventions, national programmes, insurance packages, universal health coverage packages and other related initiatives. The document also includes an overview of use of an NEDL for enabling and improving access to clinical laboratory services.

In addition to the guidance document, the WHO EDL Secretariat supports countries in their plans to develop NEDLs through webinars and country-based projects in coordination with WHO regional offices and country offices. Currently, the WHO EDL Secretariat is working with the Regional Office for South-East Asia and the regional Office for the Western Pacific on a gap analysis on the availability of IVDs in relation to recommendations in the WHO EDL covering eight countries. This project, funded by the Economic Research Institute for ASEAN and East Asia, includes the organization of technical workshops, webinars and development of advocacy materials to support targeted countries in developing their NEDLs.

Annex 3

The EDL and its relationship with other WHO essential/priority lists

The WHO EDL is one of several evidence-based lists published by WHO for Member States, donor agencies and policymakers to support them in the selection of health products. The lists are complementary, and the listed products cover the entire continuum of care – prevention, diagnosis, treatment, rehabilitation and palliation.

Publications that complement the WHO EDL are described below.

- WHO published its first EML in 1977 to improve access to medicines. More than 100 countries have used the WHO EML to formulate their national EMLs and to use them to control medicine prices, prioritize procurement, streamline the supply chain, develop guidelines and ensure access. This list is updated every 2 years (1).
- Since 2015, WHO has prepared lists of priority medical devices for prevention, protection, diagnosis and treatment in areas including reproductive, maternal, newborn and child health; cancer management; Ebola virus disease; and COVID-19 (2).
- Since 2017, the WHO Priority Assistive Products List has provided guidance on 50 assistive devices (3).

References

1. The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2021 (including the 22nd WHO model list of essential medicines and the 8th WHO model list of essential medicines for children). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1035; <https://apps.who.int/iris/handle/10665/351172>, accessed 9 April 2023).
2. Prioritizing medical devices. In: WHO/Activities [website]. Geneva: World Health Organization; 2023 (<https://www.who.int/activities/prioritizing-medical-devices>, accessed 9 April 2023).
3. Priority assistive products list. Geneva: World Health Organization; 2016 (<https://apps.who.int/iris/handle/10665/207694>, accessed 9 April 2023).

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The selection and use of essential in vitro diagnostics: report of the third meeting of the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics, 2020 (including the third WHO model list of essential in vitro diagnostics). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1031). Licence: CC BY-NC-SA 3.0 IGO.

<https://iris.who.int/handle/10665/339064>

Selection of essential in vitro diagnostics at country level using the WHO Model List of Essential In Vitro Diagnostics to develop and update a national list of essential in vitro diagnostics. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

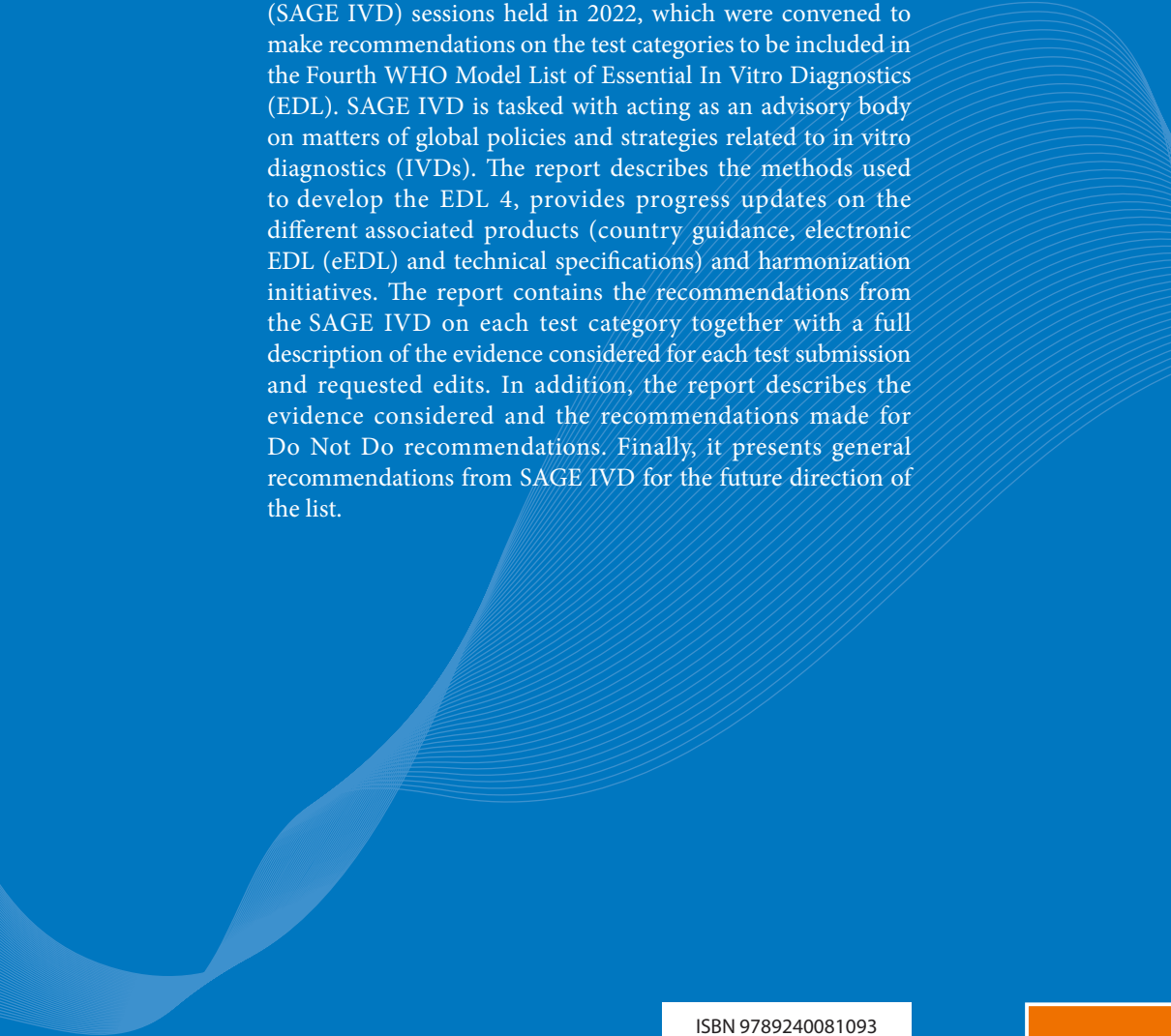



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The selection and use of essential in vitro diagnostics: report of the second meeting of the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics, 2019 (including the second WHO model list of essential in vitro diagnostics). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1022). Licence: CC BY-NC-SA 3.0 IGO.


<https://iris.who.int/handle/10665/329527>

First WHO Model List of Essential In Vitro Diagnostics. Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1017). Licence: CC BY-NC-SA 3.0 IGO.

<https://iris.who.int/handle/10665/311567>



This report presents the deliberations and findings of the Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD) sessions held in 2022, which were convened to make recommendations on the test categories to be included in the Fourth WHO Model List of Essential In Vitro Diagnostics (EDL). SAGE IVD is tasked with acting as an advisory body on matters of global policies and strategies related to in vitro diagnostics (IVDs). The report describes the methods used to develop the EDL 4, provides progress updates on the different associated products (country guidance, electronic EDL (eEDL) and technical specifications) and harmonization initiatives. The report contains the recommendations from the SAGE IVD on each test category together with a full description of the evidence considered for each test submission and requested edits. In addition, the report describes the evidence considered and the recommendations made for Do Not Do recommendations. Finally, it presents general recommendations from SAGE IVD for the future direction of the list.



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