

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)



1022

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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)



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Abbreviations and acronyms

AFP	alpha-fetoprotein
ALL	acute lymphoblastic leukaemia
CML	chronic myelogenous leukaemia
DALY	disability-adjusted life-year
DENV	dengue virus
ECLIA	electrochemiluminescence immunoassay
EDL	Essential In Vitro Diagnostics List
eEDL	electronic EDL
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EML	Essential Medicines List
ER	oestrogen receptor
FDA	Food and Drug Administration (USA)
FIT	faecal immunochemical test
gFOBT	guaiac faecal occult blood test
hCG	human chorionic gonadotrophin
HER2	human epidermal growth factor receptor 2
HPV	human papillomavirus
IARC	International Agency for Research on Cancer
Ig	immunoglobulin
IHC	immunohistochemistry
IHR	International Health Regulations (2005)
IPOPI	International Patient Organisation for Primary Immunodeficiencies
IU	international units
IVD	in vitro diagnostic
LDH	lactate dehydrogenase
LMICs	low- and middle-income countries

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nucleic acid amplification test
nucleic acid test
nongovernmental organization
polymerase chain reaction
progesterone receptor
primary health care
public health emergency of international concern
prostate-specific antigen
quality-adjusted life-year
rapid diagnostic test
reverse transcriptase PCR
Strategic Advisory Group of Experts
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Treponema pallidum particle agglutination
universal health coverage
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Declarations of interests of the Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD), observers, reviewers and consultants

Management of conflicts of interest is a priority in preparing the Essential In Vitro Diagnostics List (EDL) and in establishment of the Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD).

Before the meeting, all temporary advisers, consultants, reviewers and observers submitted written disclosures of relevant competing interests for consideration before being confirmed as participants in the said meeting. Possible conflicting interests include employment by a commercial entity, consultancy, board or advisory board membership, lecture fees, expert witness income, industry-sponsored grants including for contracted research, patents received or pending, royalties, stock ownership or options, other personal financial interests and any financial relation between the institution or employer and a commercial entity that has an interest in the field of the IVDs evaluated by the SAGE IVD.

Participants were also asked to disclose academic or scientific activities, including leadership of research or grant applications, in either primary clinical studies or reviews directly bearing on a decision about IVDs. In addition, all members were asked at the start of the meeting to update their declarations if any new conflicts had arisen in the meantime.

After analysing each declaration, the Secretariat of the EDL, assisted by the Office of Compliance, Risk Management and Ethics, concluded that there were no significant conflicts of interest that would exclude any member from participating fully in the Expert Committee. Any conflicts of interests declared were considered minor.

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WHO thanks the more than 150 external stakeholders, including Member States' representatives, industry associations, civil society and other non-State actors in official relations with WHO, who participated in the open session of the SAGE IVD meeting (in person and remotely) and those who submitted new test categories for the EDL.

WHO thanks the United Kingdom Department for International Development (DfID) for financial support for establishment of the expert group and creation of the WHO List of Essential In Vitro Diagnostics.

Executive summary

The second meeting of the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD) was held on 18–22 March 2019 at WHO headquarters in Geneva, Switzerland.

An open session was held on the first day, attended by interested partners and representatives of nongovernmental organizations (NGOs), WHO Member States and the diagnostics industry. Participants discussed, the proposal for the second WHO Model List of In Vitro Diagnostics (EDL), revisions to the first EDL, the relation between the List and other WHO initiatives and country implementation. The outcomes of a consultation on eligibility criteria for WHO prequalification of IVDs was reported and discussed. The participants welcomed the positive impact of the first EDL and discussed challenges for drawing up the second List and for country uptake.

The second SAGE IVD subsequently met in closed session to discuss their methods of work, review submissions for test categories to be added to the second EDL, review proposals for changes to the first EDL and discuss a review on therapeutic drug monitoring and submissions for WHO prequalification. The Secretariat presented the lessons learnt from the first round of submissions and review and indicated changes had been proposed to entries in the first EDL by SAGE IVD members, WHO staff and external partners.

Submissions of new product categories for the second EDL was opened in July 2018, and 31 full submissions were received for the priority disease areas identified by the first SAGE IVD: for use in public health emergencies, to diagnose and monitor noncommunicable diseases and neglected tropical diseases, to support global efforts to tackle antimicrobial resistance (AMR) and for the diagnosis of fungal diseases. All submissions were reviewed by members of the SAGE IVD and external experts and published for public comment, which was considered by the second SAGE IVD.

A discussion on the definitions of health care tiers for the List resulted in revision of the titles of the two sections: IVDs for use in community settings and health facilities without laboratories and IVDs for use in clinical laboratories, with indications for those that require specialized laboratories and those for blood screening laboratories. In accordance with the recommendation of the first SAGE IVD, proposals for general and anatomical pathology tests were reviewed by the General Laboratory Working Group of SAGE IVD, endorsed by the SAGE IVD and published on the WHO website for comment.

The EDL Secretariat described means for supporting countries in implementing their national EDLs, including the laboratory and IVDs website, prioritization and nomenclature. Integration of the List with other WHO initiatives towards universal health coverage was also presented.

The second SAGE IVD made general recommendations on the second EDL, on country implementation, on prequalification and on submission and review. They formed four working groups to follow-up implementation of the recommendations and made further recommendations on the work of the EDL Secretariat.

1. Introduction

The second meeting of the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD) was held on 18–22 March 2019 at WHO headquarters in Geneva, Switzerland.

Dr Emer Cooke, Director, Regulation of Medicines and other Health Technologies, WHO, welcomed Group members and temporary advisers, representatives from NGOs and other participants on behalf of the Director-General. She described the work of her programme, including prequalification, which is relevant to the work of the Group.

The SAGE IVD agreed and recommended the Second Model List of Essential In Vitro Diagnostics. The List is provided in Annex 1 to this report.

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2. Open session²

An open session was held on the first day of the meeting, which was attended by interested partners, representatives of NGOs, WHO Member States and representatives of the diagnostics industry. The session comprised a 2-h open consultation on prioritization of in vitro diagnostics (IVDs) for prequalification and a 4-h discussion of the second WHO Model List of In Vitro Diagnostics (EDL) and related topics, which included revisions to the first EDL, the relations between the List and other WHO initiatives and country implementation. The objective was to hear stakeholders' comments, both live and via the Internet, and to address all the comments made in the public consultations.

First part. Prioritization of IVDs for prequalification

Deus Mubangizi described the background to prequalification of IVDs. The process comprises dossier review, site inspection and performance evaluation in the setting in which the test is intended to be used. Tests are selected according to requests from WHO disease programmes. The eligibility criteria include their provenance only from the original manufacturer, commercial availability and appropriateness. A strategic approach is required to define priorities and ensure the greatest access. As the first SAGE IVD had agreed that a consultation with a wider range of stakeholders was required to define priority products for prequalification, a web-based consultation was organized, and the Julius Center, Netherlands, was requested to analyse the results and present them to the SAGE IVD.

Kevin Jenniskens, consultant, Julius Center, reported the outcomes of the consultation on eligibility criteria for WHO prequalification of IVDs. They had analysed 27 responses from 10 organizations and proposed prioritization by burden of disease, IVD test performance and whether patient management and treatment were available. Burden of disease was suggested to be measured as disability-adjusted life-years (DALYs) to account for differences in prevalence and incidence. He noted that priorities for prequalification depend on the outcome chosen, evidence for the performance of IVDs and the availability and effectiveness of patient management and treatment to follow diagnosis.

In the ensuing discussion, participants noted that IVDs should be selected as part of an essential diagnostic package for universal health coverage (UHC); that the survey did not follow the advice of the first SAGE IVD, which was to consult existing WHO guidelines and independent WHO reviews of evidence; that many IVDs are not specific for a disease but for determining how a patient

² Presentations made at this session and the webcast are available at https://www.who.int/medical_ devices/diagnostics/selection_in-vitro/selection_in-vitro-meetings/sage-ivd-second-meeting/en/.

should be treated; that use of burden of disease as a criterion for prioritization for prequalification might restrict selection to those with highest rank, and other criteria should be considered, such as for early detection of outbreaks; that neglected tropical diseases would probably never be included on the List if the criterion of burden of disease was retained; and that the burden of diseases such as cholera is unknown because of poor diagnostics and rapid treatment. The consultants commented that pneumonia is the disease with the highest burden, as the term includes pneumonia due to bacteria, viruses and fungi.

Deus Mubangizi commented that tests have been added for prequalification in response to ad hoc requests and also for emergencies. As prequalification of IVDs began before the EDL, it has been an interim process until products are added to the EDL.

The EDL Secretariat suggested that the survey be sent to other stakeholders. A package of essential IVDs for primary health care (PHC) is being discussed with the health financing department. It was suggested that only EDL products that are priorities for WHO and that have no other support should be proposed for prequalification.

Second part: Model List of Essential In Vitro Diagnostics³

Dr Mariângela Batista Galvão Simão, Assistant Director-General for Medicines, Vaccines and Health Products, noted the enormous interest and the success of the first EDL shown by the media, industry, ministries of health and NGOs. Essential IVDs must be accessible and affordable in order to have an impact in Member States, and rapid implementation of the List must be ensured to support the functions of other WHO departments and UHC. The methods for submission and for reviews and publication should be reviewed, as they are not yet systematic. The List must respond to Member States' needs. Point-of-care diagnostics for both infectious and chronic diseases and outbreaks in primary care settings are essential. She thanked SAGE members for having conducted monthly meetings and thanked the DfID for financial support.

The participants first discussed the impact and challenges of the first List and then reviewed the process for drawing up the second List and country implementation. Comments from the public consultation were addressed.

The EDL Secretariat presented the objectives, context and inclusion criteria for the first EDL and explained the difference between the EDL and the list of WHO prequalified IVDs. The former is intended to guide policy on the implementation of access to IVD testing and the WHO prequalification list is intended to support product assessment for procurement.

³ All discussions and presentations at the open session on the EDL are available at https://www.who. int/medical_devices/diagnostics/selection_in-vitro/selection_in-vitro-meetings/sage-ivd-secondmeeting/en/.

Media and advocacy coverage of the first List had been extensive, and various stakeholders had made statements. The first SAGE made seven recommendations for consideration in the second edition of the EDL:

- include a list of high-priority tests recommended for the next edition of the EDL.
- prepare a detailed preface to the EDL,
- emphasize the infrastructure and processes required to support use of IVDs,
- set up an EDL website,
- update the WHO laboratory manual and
- implement the EDL globally.

The IVDs recommended by SAGE IVD for the next EDL are for AMR, neglected tropical diseases, noncommunicable diseases, public health emergencies, influenza, reproductive health and fungal diseases. The submissions received included tests for the neglected tropical diseases dengue fever, visceral leishmaniasis and soil transmitted helminths/schistosomiasis and for cancer. The first EDL was reviewed by relevant departments in WHO for tests for cardiac diseases and diabetes and found to be sufficient. In addition, all general IVDs for emergency medicine were identified and will be flagged in the second EDL. Submissions were also received for public health emergencies (Zika virus infection and cholera), for influenza, reproductive health (chlamydia, gonorrhoea and additional tests for syphilis) and fungal disease (histoplasmosis). A paragraph was added to the Microbiology section of the EDL to highlight the importance of testing for AMR.

A detailed preface to the first EDL includes a paragraph on the importance of ensuring the infrastructure, processes and skills necessary to ensure reliable IVD test results. The EDL website⁴ was launched in November 2018, and work was begun on updating the laboratory manual on diagnostics. The EDL Secretariat asked participants for assistance in updating the WHO laboratory manual, which dates from 2003. The first EDL was also issued in the WHO Technical Report Series. The EDL Secretariat presented a plan for supporting country implementation of the EDL.

The EDL Secretariat also made a presentation on the impact of the first EDL. A WHO consultation had been held in January 2019 on the use and impact of the WHO lists of essential medicines, IVDs, priority medical devices and priority assistive products. The group had concluded that the four lists should be integrated, made easier to use, made available in electronic format, disseminated

https://www.who.int/in-vitro-diagnostic/en/

and implemented in countries.⁵ It was proposed that IVDs be included in the WHO-UNICEF Package of Health Products for Primary Health Care, which is in preparation. Furthermore, work on WHO facility assessment tools includes tests that are on the first EDL to ensure their availability in health facilities, and it is planned to include the first EDL and eventually the second in WHO packages of health interventions for UHC.

Participants welcomed the positive impact of the first EDL and made several proposals. The EDL could be used in advocacy for diagnostics, and they expressed their willingness to ensure access and sustainability. A measure of the success of the List is its adoption by countries, its adaptation to national EDLs and its use in health facilities; however, there is limited awareness of the EDL, even in WHO country and regional offices. They said that dissemination of the WHO global atlas of medical devices and country profiles of regulatory systems would facilitate country implementation of the EDL. It was suggested that joint external evaluations of capacity for implementing the International Health Regulations (2005) (IHR) could be used to identify countries that are ready to implement the EDL. Participants acknowledged that different regions in large countries might have different disease patterns, and hospitals might choose different supplies. Another proposal was to collaborate with academies of pathology and specific diseases such as cardiology, which had developed evidence-based guidelines.

In the session on the second EDL, the EDL Secretariat made a presentation on its development. WHO had received 31 new submissions and 117 proposals for changes to the first EDL. They had added a new anatomical pathology section, expanded the sections on general IVDs and were proposing a section on therapeutic drug monitoring. The process for review of applications and the information to be included for new product categories was described. A consultant clarified the selection of additional general laboratory tests, which were approved by the General Laboratory Working Group of SAGE IVD, and the process for selecting therapeutic drug monitoring tests. Comments received from seven external organizations were also considered.⁶

The EDL Secretariat made a presentation on country implementation of the EDL. An IVD and laboratory web portal⁷ grouped all the available information and resources on IVDs and laboratories, which had been scattered across THE WHO website. The information on the website on procurement, installation and maintenance could be complemented by input from external partners.

⁵ The full report is available at https://www.who.int/health-technology-assessment/tech-consultation-selhealth-products/en/.

⁶ Presentations on these proposals can be found at https://www.who.int/medical_devices/diagnostics/ selection_in-vitro/selection_in-vitro-meetings/sage-ivd-second-meeting/en/.

⁷ https://www.who.int/in-vitro-diagnostic/en/

The representative of the Islamic Republic of Iran proposed inclusion of relevant tests for infectious and non-infectious diseases covered by the IHR and a list of tests required for syndromic care. He called for active collaboration between WHO country offices and ministries of health to ensure that the EDL corresponds to country needs and priorities. Obstacles to the acquisition of laboratory equipment and provision of services by countries should be removed. Other participants noted that countries should be encouraged to accelerate uptake of the EDL, perhaps with case "stories" on the website, an event at the World Health Assembly or tax exemption for products on the EDL. Products on the EDL should be listed by priority. One participant said that the EDL is particularly welcome in view of diminishing global funding, especially if the products could be obtained tax-free. Participants also welcomed a proposal to standardize the nomenclature of IVDs, which will be done with the International Classification of Disease (11th revision) software and support from the European Commission and other stakeholders. The creation of an electronic version of the EDL will allow searches by all types of categories, including disease, section of the List and assay format. As it has been agreed not to use brand names, one participant suggested that broad categories be listed and not specific products relevant to one technology. The EDL Secretariat acknowledged that some assay formats under test categories might have been missed and encouraged manufacturers to point out such oversights.

One participant suggested that white papers be issued, written by scientists and clinicians, on the EDL and the impact of its adoption on patient outcomes, including self-testing and testing by nonspecialized health care workers.

The open session ended at 16:00. The agenda, material, presentations and the webcast can be seen at: https://www.who.int/medical_devices/diagnostics/ selection_in-vitro/selection_in-vitro-meetings/sage-ivd-2nd-meeting/en/.

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3. General items

The second SAGE IVD met in closed session to discuss their methods of work, to review proposals for changes to the first EDL, proposals for addition of general laboratory and anatomical pathology tests for the second EDL, and to discuss the review on therapeutic drug monitoring and submissions for WHO prequalification.

3.1 Methods used to establish the second EDL

The working draft of the second EDL was based on changes proposed to the first EDL, submissions for new product categories, a study on general laboratory and anatomical pathology tests and a report on therapeutic drug monitoring tests. All the procedures were transparent and based on input from internal and external stakeholders, SAGE IVD members and members of the public interested in policy or implementation of the EDL. All the suggested changes, submissions, reviews and responses to the reviews were published on the WHO website for comment, and all public comments received were acknowledged.⁸

The EDL Secretariat presented the lessons learnt from the first round of submissions and review. With regard to the submission process, the "datacol" output forms were found to be difficult to read, as the name of test did not appear at the top and the output from tables was not in tabular form; it was proposed to redesign the input for a neater output. In response to the comment that presubmission of more than one test resulted in loss of some tests, the proposed solution was to require a separate pre-submission for each test and simplify the pre-submission form. Submitters found that the requirement for a written review of the literature on evidence was too onerous, and it was proposed that publications be described briefly, and their abstracts be simply cut and pasted. Another comment was that many of the details requested, on e.g. performance characteristics, stability and time to result, were specific to one product or brand and could therefore not be compared; it was proposed that the need for performance data be clarified and the way in which the questions are asked be improved. To the comment that many submitters do not have a background in diagnostics and might not know the difference between, for example, screening and diagnosis or the role and purpose of the EDL, it was proposed that the meaning of each question be clarified on the basis of experience. Repetitive questions would be deleted.

With regard to the review process, several reviewers had expressed concern that some products on the market in a given test category were of poor

⁸ https://www.who.int/medical_devices/diagnostics/selection_in-vitro/selection_in-vitro-meetings/sageivd-2nd-meeting/en/

quality and performance; it was proposed that a paragraph be added to the preamble emphasizing that the EDL supports policy formulation as a first step to increase access to IVDs but that countries should ensure that the IVDs procured are of appropriate quality and were selected on the basis of well-formulated technical specifications. Questions about the extent to which details of test performance are required for inclusion of products on the EDL would be discussed by SAGE, and the EDL Secretariat would decide when and if the names of reviewers would be revealed to submitters. To the comment that some reviewers completed the reviewer questionnaire themselves, the Secretariat proposed that the title be changed to "reviewer guide" or "submission assessment tool".

General comments included one about lack of transparency on how tests were selected for the EDL; the response will be to clarify the process of inclusion of different types of tests, which includes "grandfathering" of general laboratory tests but a requirement for full submissions for disease-specific tests, extending application of laboratory-based tests to PHC and changing existing tests. To the question of whether the EDL lists "test purposes" that are off-label, the Secretariat suggested that submitters be required to verify the intended use of the test categories they proposed. As it is not clear whether industry could make submissions, the situation would be clarified in an appropriate forum, publication or website.

3.1.1 Changes to entries in the first EDL

After publication of the first EDL in May 2018, 117 suggestions were made, primarily by SAGE IVD members, WHO staff and by external partners, to improve the entries. Typographical and factual errors were corrected in November 2018, resulting in a second version of the first EDL. Additional suggested changes were reviewed by SAGE IVD members and the EDL Secretariat and published for public comment on 19 February 2019. All comments and suggested changes received over 3 weeks were considered one by one by SAGE IVD members during the meeting and incorporated when relevant. Details of the suggested changes are available on the website of the second SAGE IVD meeting.⁹

3.1.2 Submissions for new product categories

A call for pre-submissions for new product categories for the second EDL was opened from 20 July to 15 September 2018. Those who had submitted relevant product categories, and which were considered by the EDL Secretariat to

⁹ https://www.who.int/medical_devices/diagnostics/selection_in-vitro/selection_in-vitro-meetings/sageivd-second-meeting/en/.

comply with the requested information and aligned with WHO policies were invited to make full submissions between 15 September and 15 November 2018. Applications were invited from relevant WHO departments, regional offices and country offices and from external stakeholders, including Member States, academia, NGOs, IVD industry and trade associations. The criteria for selection of products for the second EDL were:

- the usefulness for public health of the category of tests, as determined, for example, from the disease burden, and whether the proposed category could fill a gap in diagnostics in primary care facilities;
- the validity of commercial IVDs, as confirmed by sound, adequate data on quality, safety, performance and regulatory status;
- their clinical effectiveness, as confirmed by published, peer-reviewed data on safety and cost-effectiveness;
- the appropriateness of the IVD category for use at specified levels of the laboratory or health care system; and
- the infrastructure required, target user(s), sample type and volume, sample handling, time to results, storage conditions, operating conditions, shipping requirements, training and skill requirements, associated equipment, throughput, need for maintenance, disposal and connectivity, as appropriate.

Applications for specific branded products or for IVDs that were not commercially available at the time of submission were rejected.

WHO encouraged applications in all IVD categories; however, preference was given to those for the priority disease areas identified by the first SAGE IVD: IVDs for use in public health emergencies, to diagnose and monitor noncommunicable diseases and neglected tropical diseases, to support global efforts to tackle AMR and for the diagnosis of fungal diseases.

The 31 submissions received were all relevant to the priority disease categories; 13 were for the diagnosis, prognosis, treatment or monitoring of cancer. All submissions were reviewed by at least two reviewers who were either members of the SAGE IVD or external experts for special applications. All the reviewers used the same standardized assessment tool to review the applications. Queries arising from the reviews were sent to the submitters for response. All submissions, supporting documentation, reviews and responses to reviews were published for public comment, and the comments received were published on the WHO website and considered by the SAGE IVD during the meeting.

Details of the submissions are provided in Section 5.

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3.1.3 **Proposals for general and anatomical pathology tests**

General and anatomical pathology IVDs are used to detect several conditions and to decide on a defined intervention (including treatment), surgery or other options. The first EDL included 35 general IVDs – 12 for use in primary care and 23 for use in clinical laboratories. After publication of the first EDL in May 2018, WHO commissioned a study to identify high-priority tests for prescribing medicines on the Essential Medicines List (EML). The tests identified as high priority were reviewed for the EDL and compared with other WHO lists, such as that of priority medical devices for cancer management.¹⁰ Proposals were also collected from SAGE IVD members and WHO disease programmes. The list of general IVDs and a list of anatomical pathology tests were reviewed by the General Laboratory Working Group of SAGE IVD and endorsed by the SAGE IVD before publication on the WHO website for comment. Five new categories were suggested in the clinical chemistry section and five in the haematology section. All the comments received were reviewed by the SAGE IVD during the meeting.

3.1.4 Proposal for inclusion of therapeutic drug monitoring tests

The EML was reviewed for medicines for which monitoring is required, and two independent reviews provided a list of 11 medicines. The list was subsequently evaluated, and the evidence on use of monitoring tests was reviewed. A report¹¹ with evidence was submitted for review by two SAGE IVD members, and their reviews were published for public comment and considered by the SAGE IVD during the meeting. The list was prioritized as follows:

- high priority: most authors considered that monitoring would be useful, even for use in non-critically ill patients, of amikacin, gentamicin, phenytoin, lithium;
- moderate priority: monitoring would be useful in patients treated concomitantly with other drugs or with clinical complications, such as impaired renal function, of vancomycin, methotrexate and cyclosporin; and
- low priority: careful clinical assessment is enough in most cases, or there is evidence of no difference between patients in whom the drug was monitored, of digoxin, phenobarbital, carbamazepine and valproate.

¹⁰ https://apps.who.int/iris/bitstream/handle/10665/255262/9789241565462-eng.pdf

¹¹ The full report is available at https://www.who.int/medical_devices/diagnostics/selection_in-vitro/ selection_in-vitro-meetings/sage-ivd-2nd-meeting/en/.

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3.1.5 **Public consultation**

Seven external NGOs, industry and civil society sent 51 comments, which were of six types:

- general comments on the process and the List and its implementation;
- a change in the tier of the health care system in which tests should be used, with several requests to move IVDs in the laboratory section of the List to the primary care section;
- a change in the purpose of a test, such as addition of intended populations and uses;
- changes in the assay formats listed;
- addition or deletion of some specimen types; and
- comments on full submissions.

3.1.6 **Process for decision-making**

In order to ensure systematic decisions on the inclusion or exclusion of additional product categories to the EDL, the SAGE IVD reviewed each suggested change and comment, every additional general and anatomical pathology IVD suggested and every submission received. Before they made a recommendation, they were asked to vote for:

- inclusion with no reservation;
- conditional inclusion, pending submission of additional evidence;
- rejection because of insufficient evidence but resubmission encouraged for a future EDL; or
- rejection.

A decision was accepted when 75% of the SAGE IVD members present agreed.

3.2 Changes to the structure of the List

The first EDL was divided into two main sections: one for IVDs for PHC settings and one for IVDs for health care facilities with clinical laboratories. The definition of IVDs for use in PHC was:

typically, self-testing and rapid diagnostics tests are available, but there are either no laboratories or only *small laboratories* with trained health care personnel but no trained laboratory technicians.

This definition was reviewed by SAGE IVD members and then discussed with the EDL secretariat. It was agreed that, in order to remove any ambiguity about the meaning of "small laboratories", the new definition should be:

IVDs for use in community settings and health facilities without laboratories, including health posts and centres, doctors' offices, outreach clinics, ambulatory care and home-based and self-testing. If laboratory facilities are available in a primary care facility, the IVD should be moved to the second tier. If laboratory facilities are not available, samples may be collected, transported to and processed at a higher tier of the health system.

As a result, certain IVDs listed in the section on PHC in the first EDL were moved to the section on IVDs for clinical laboratories. The new definition does not exclude use of these IVDs in primary care settings that have access to a laboratory or can refer specimens to a laboratory at a higher tier of the health care system.

The change in the definition resulted in changes to the titles of the two main sections of the EDL, which are presented by health care facility level in two tiers:

- I. Community settings and health facilities without laboratories, with the following sections:
 - a. General IVDs
 - b. Disease-specific IVDs
- II. Health care facilities with clinical laboratories, with the following sections:
 - a. General IVDs
 - b. Disease-specific IVDs
 - c. Disease-specific IVDs for blood screening laboratories

3.3 **Country implementation plans**

The EDL Secretariat described the process for supporting countries in implementation of their national EDLs. To this end, the laboratory and IVDs website has been useful, and it will continue to be updated. In addition, countries will be supported in prioritizing their needs, and a working group will be established for that purpose, based on the second EDL, once it is published. A further working group will discuss technical specifications for procurement, with a common template. Further work is being done to link the EDL to the UHC menu. This year, two countries will participate in a pilot programme as a basis for guidance for implementation from the EDL Secretariat.

A list of products on the first and second EDLs for use in primary care settings is being drafted and will be issued jointly with UNICEF.

Input from the second EDL will be added to the UHC menu, which lists interventions by health problem, setting, guidelines, health workforce required, health products required (EDL, EML, priority medical devices), cost, time required and context, such as use in emergencies. The first draft UHC menu will be ready before the United Nations meeting on UHC in September 2019 and will be continually updated by all sectors.

WHO reviewed the status of nomenclature systems for medical devices in Member States and found that, while many such systems exist, 70% of countries in the African Region have no official nomenclature, which poses a problem for procurement and regulation.¹² An International Classification and Nomenclature of Medical Devices is being prepared that includes IVDs, to provide common codes for procurement, hospitals and regulation. Future EDLs and e-EDL will include the WHO codes and definitions.

3.4 Integration of the List within other WHO initiatives

3.4.1 Integration with the Essential Medicines List

Dr Nicola Magrini, Secretary, WHO Expert Committee on the Selection and Use of Essential Medicines, described how the EML had evolved over the years, with changes in the definition of the word "essential". It took the Committee several years to set criteria for prioritizing entries; the final criteria are disease burden, public health relevance and sound, adequate data on efficacy, safety and cost–effectiveness. They also consider feasibility studies in different populations, regulatory status and guidelines. The 2017 EML introduced a standard format that includes efficacy and harm. Many applications require support from the Committee to present complete submissions. They have also introduced the concept of "magnitude of benefit", such as length of survival. The main aim is to support WHO programmes. As they consider that rejections should be visible, they are listed separately. The clear link with the EDL is the diagnostic tests required before prescribing. The EML will soon be available in electronic form and will be searchable for comparison with the EDL.

The EDL Secretariat collaborated with the EML Secretariat in considering tests that should be included for therapeutic drug monitoring (see section 3.1.4).

¹² https://www.who.int/medical_devices/priority/mde_nomenclature/en/.

3.4.2 Integration with the WHO Expert Committee on Biological Standardization

Clare Morris described the structure of the WHO Expert Committee on Biological Standardization, which includes blood products, IVDs, vaccines and biotherapeutic medicines. It issues written measurement standards and physical standards, which consist of reference material in vials for calibrating tests. She urged the EDL to insist on the use of international units (IU), which would facilitate collaboration and standardization of technologies, as the uptake of some has been low. The aim of the Committee is to reduce variation among laboratories, which can affect patient treatment.

Ivana Knezevic, Secretariat of the WHO Expert Committee on Biological Standardization, proposed regular consultations with EDL to share information. Public consultations are held during the development of standards, and collaborative studies are carried out with "custodian laboratories", which need more participants. The studies are good opportunities to see how standards can improve the interpretation of results. New companies with no experience often considered standards as their enemies; however, the larger ones understand the importance of standardization with these products.

SAGE IVD members agreed on the importance of WHO standards.

3.5 Eligibility for prequalification

Following the SAGE IVD recommendation in 2018 to extend the scope of prequalification, an online consultation was organized to collect information on the most immediate needs of WHO disease programmes, partner organizations and other stakeholders in terms of prequalified IVDs. The survey on prequalification for eligibility was sent to selected stakeholders (51 contacts in 26 organizations) on 23 November 2018, with an initial deadline of 31 December, which was extended to 1 February 2019. The survey resulted in 23 responses, including three from WHO, three from FIND and nine from MSF (39% of responses originating from the same submitter). Additional responses received after the close of the survey were also considered.

During the open session of the second SAGE IVD meeting, the prequalification team presented the importance of and challenges to prequalification. The external consultants presented the results of the survey analysis and suggested ranking diseases according to several criteria, including disease burden and DALYs saved. The floor was then opened for input from stakeholders, who suggested that the priority of a disease carries greater weight than the burden of disease, while others considered that the burden of disease should have greater weight. Furthermore, priority diseases are different in high-income and low- and middle-income countries (LMICs). Re-emerging diseases

like cholera should also be considered. A systematic approach is needed in order to make valid decisions.

The purpose of prequalification is to assist the United Nations in deciding on procurement. If a manufacturer wishes a test to be considered, it can apply for prequalification of products for WHO priority diseases. A suggestion was made to limit the number of tests accepted for assessment for a particular test category in order to save WHO resources; however, the EDL Secretariat pointed out that placing a limit on the number of tests would unfairly prevent some companies from entering the market.

The prequalification team and the external consultants took into consideration all the comments received from stakeholders during the open session and presented a new multi-criteria decision-making tool for evaluation of IVD categories during the closed session. As not all members of SAGE IVD were present on the last day of the meeting when the new model was presented, it was decided to defer a final decision on the scoring and weighting of criteria for prequalification. SAGE IVD members and the EDL Secretariat considered that they require further input from Member States, WHO departments on specific disease areas and external stakeholders and validation by the prequalification team.

The EDL Secretariat and some SAGE IVD members commented that the importance attached to the burden of disease would essentially disqualify the inclusion of neglected tropical diseases. This could be avoided by stating that the criteria are to be applied only to LMICs.

4. Summary of recommendations

4.1 General recommendations

In reference to the second EDL:

- Change the definitions of health care tiers for the List. This resulted in two sections: IVDs for use in community settings and health facilities without laboratories and IVDs for use in clinical laboratories, with indications for those that require specialized laboratories and those for blood screening laboratories.
- In the preface to the second EDL, explain the changes made to the headings of the sections.
- In a glossary, define the functions of tests: screening, diagnosis, aid in diagnosis, monitoring, prognosis, prediction, companion diagnostics, surveillance.
- Provide links to WHO guidance and recommendations for each product, when available.
- Identify the general laboratory and the disease-specific sections and subsections with appropriate guiding text.
- For the next EDL, consider:
 - a. additional tests for the diagnosis and management of noncommunicable diseases;
 - a section on endocrinology, including fertility profile tests (follicle-stimulating hormone, luteinizing hormone, prolactin, oestradiol, progesterone, testosterone, triiodothyronine and thyroxine);
 - c. additional general IVDs, including for coagulation, platelet aggregation, bleeding time, whole blood clotting time and clot retraction time;
 - d. tests for AMR (with a link to stewardship);
 - e. additional tests for the diagnosis and management of neglected tropical diseases;
 - f. additional tests for emergencies and outbreaks;
 - g. additional IVDs for vaccine-preventable diseases; and
 - h. recent Cochrane systematic reviews for IVDs that could be used as full submissions for:
 - i. typhoid fever;
 - ii. aspergillosis (immunoassay and polymerase chain reaction (PCR));

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iii. pneumococcal pneumonia, urinary antigen test;

- iv. Down syndrome;
- v. streptococcus A in children with pharyngitis;
- vi. thromboelastogram test and rotational thromboelastometry;
- vii. rapid leishmaniasis test; and
- viii. neonatal sepsis, molecular assays.

The following recommendations were made during the discussion on suggested new additions to the List and on certain full submissions:

- i. for D-dimer: a full submission to support the use of the test for deep vein thrombosis;
- direct agglutination test for leishmaniasis: a full submission, especially to support diagnosis in geographical regions where the rk39 antigen test has been shown to be less accurate;
- iii. commission a systematic review of evidence on rk28 antigen test for possible submission as a new entry for the third EDL to support diagnosis in geographical regions where the rk39 antigen test has been shown to be less accurate;
- iv. erythrocyte sedimentation rate: a full submission to support inclusion in the third EDL; and
- v. a full submission to review point-of-care diagnostics for sickle cell disease.
- 2. Link EDL entries to PHC interventions and to disease commodity packages for emergencies and outbreaks.
- 3. Include "negative" recommendations: a full submission for a negative recommendation will be required except when a WHO negative recommendation exists.
- 4. Present the report on therapeutic drug monitoring tests to the Expert Committee on the Selection and Use of Essential Medicines for endorsement or modification of the prioritized list of medicines. Full submissions will be requested according to the List recommended by that Committee.

Country implementation:

1. Countries should increase the availability of laboratory infrastructure and trained personnel in primary care settings to ensure early diagnosis and adopt an integrated approach to testing in order to minimize duplication of resources for different disease areas and to support UHC.

- 2. Define a "prioritization tool" to support country implementation of the EDL (e.g. define a core list and a complementary list, as is done for the EML).
- 3. Continue to prepare guidance for country implementation, pilot-test the draft guidance in at least three countries and present the results to the next SAGE IVD. The findings will be incorporated into the final guidance.
- 4. Instead of updating the WHO laboratory manual of basic techniques for a health laboratory,¹³ organize all the information available worldwide to facilitate online training and liaise with other organizations to include as much information as possible.

Prequalification:

WHO Prequalification should finalize the multi-criteria decision model to prioritize IVDs for prequalification and finalize the criteria and the weight assigned to them. The criteria discussed were:

- EDL listing (critical, 10)
- existing WHO guidance (critical, 5)
- priority disease (critical, 5)
- burden of disease (important, 5)
- associated health interventions (2)
- priority for diagnostic supply: for example, reported issues with quality, transformational diagnostic category, regulatory approval by an organization that is not a founding member of the Global Harmonization Task Force (weight to be further defined) and to consider burden of disease specifically for LMICs to address neglected tropical diseases
- available or expected donor funding (not in weighting criteria).

The SAGE IVD members present during the discussion requested that all SAGE IVD members review the criteria before a final recommendation is made. The SAGE IVD members also noted, during discussion of submissions to the EDL, that the following tests should be prequalified, as they have highly variable quality and performance:

- influenza rapid diagnostic tests (RDTs)
- dengue immunoglobulin (Ig) M tests
- dengue NS1 tests

¹³ Manual of basic techniques for a health laboratory, second edition. Geneva: World Health Organization; 2003 (https://apps.who.int/iris/handle/10665/42295).

Submission and review:

- 1. Pre-submission and full submission forms:
 - Maintain a pre-submission mechanism and integrate all the necessary information from the pre-submission form into the full submission.
 - Identify compulsory sections (to be defined over the next few months).
 - Insist that all submissions include WHO references, guidelines or guidance, and identify the relevant passages in documents in which reference is made to recommendations on the IVD category.
 - Include evidence of use of the IVD category in LMICs, when available. Use updated evidence or justify citation of old publications.
 - Request submitters to classify the purpose of the test as per the definitions in the second EDL.
- 2. Review the process for submission, and prepare guidance for submitters, stressing that submissions must include relevant content from the guidelines cited and other references (They should not just refer the reviewer to the documents.) and complete references to published reviews.
- 3. Ask a methodologist to triage submissions before accepting them for review.
- 4. Review the questionnaire and the pre-submission and full submission forms used by reviewers to assess submissions.

Follow-up of recommendations:

Four working groups were proposed to follow up the recommendations on:

- implementation by countries,
- prioritization of IVDs on the EDL for implementation by countries,
- submission and review forms and
- training in laboratory techniques (collect information and create a training portal).

To the EDL Secretariat:

 Encourage manufacturers to use WHO international standards for technologies, when available, and encourage use of international units (IU) to improve harmonization of standards (to be discussed at future SAGE IVD meetings).

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- Liaise with the Immunization, Vaccines and Biologicals department for submission of IVDs relevant to vaccine-preventable diseases.
- Continue to liaise with WHO teams for the EML, the Expert Committee on Biological Standardization, Prequalification, various disease areas, emergencies and outbreaks, UHC and PHC.
- Work towards e-EDL and standardization of nomenclature.
- Support the recommendation on laboratory strengthening to ensure access to and use of IVDs, which is a strategic priority for the achievement of UHC.

4.2 Additions to the List

Section I: Community settings and health facilities without laboratories

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

Clinical chemistry: a test for ketones for the diagnosis of diabetic ketoacidosis

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

Cholera: a rapid test for antigens to *Vibrio cholerae* for use in screening patients with acute watery diarrhoea who present with the clinical case definition of cholera for the early, initial detection of a cholera outbreak (not for use in case management).

HIV infection: a point-of-care CD4 cell enumeration test for staging advanced HIV disease and, in settings where data on viral load are not available, for monitoring response to antiretroviral therapy.

A cryptococcal antigen RDT was added for screening and diagnosis of cryptococcal meningitis in people living with advanced HIV disease.

Influenza

Influenza A and B antigen detection RDT and instrument-based point of care immunoassay were added conditionally to the List to aid in the diagnosis of seasonal influenza infection (not recommended for surveillance) pending publication of updated WHO guidelines.

Influenza A and B point-of-care nucleic acid test (NAT) for diagnosis of seasonal influenza infection.

Neglected tropical diseases: rK39 antigen RDT for use in the diagnosis of visceral leishmaniasis.

Section II.a. General in vitro diagnostics for clinical laboratories

Anatomical pathology

Cytology (cytopathology): Microscopic assessment of cells for infection, neoplasia and inflammatory and degenerative disorders.

Histopathology: Microscopic assessment of tissue for infection, neoplasia, inflammatory and degenerative disorders.

Immunohistochemistry: Microscopic assessment of cells for specific markers to identify infection, neoplasia, inflammatory and degenerative disorders.

Post-mortem examination: Macroscopic tissue assessment and microscopic examination of tissue sections for the determination of cause of death and correlation with pre-mortem clinical features and investigations.

Bacteriology

Genus and species identification of bacteria and fungi for identification in cultured isolates.

Clinical chemistry:

Direct and indirect bilirubin tests to detect or monitor liver disease, bile duct disorders and haemolytic anaemia and to differentiate between these causes of jaundice.

 γ -Glutamyl transferase test to assess hepatobiliary function and to distinguish between bone and hepatobiliary causes of raised alkaline phosphatase.

Human chorionic gonadotropin (hCG): addition of a test purpose for detection of germ-cell neoplasms.

Phosphate test to monitor chronic kidney disease and to prevent and manage tumour lysis syndrome.

Procalcitonin immunoassay and RDT to guide antibiotic therapy or discontinuation in sepsis and lower respiratory tract infection (for use only in tertiary and more advanced care facilities).

Thyroid-stimulating hormone test for screening for hypothyroidism and hyperthyroidism.

Uric acid test for diagnosis and monitoring of gout and prevention and management of tumour lysis syndrome.

Haematology:

D-dimer immunoassay for diagnosis of disseminated intravascular coagulation.

Direct antiglobulin test (Coombs test) as an aid in the diagnosis of the cause of haemolytic anaemia, to investigate blood transfusion reactions and to diagnose haemolytic disease of the newborn.

Fibrinogen test for diagnosis of disseminated intravascular coagulation.

Indirect antiglobulin test (indirect Coombs test or red blood cell antibody screen) to screen for antibodies to red blood cells before a blood transfusion and in pregnancy and to aid in the diagnosis of haemolytic anaemia and blood transfusion reaction.

Iron tests, including iron, ferritin, total iron-binding capacity or calculated transferrin saturation for the diagnosis of iron deficiency and iron overload.

Partial thromboplastin time (activated partial thromboplastin time) to diagnose bleeding disorders and thrombotic disorders and to monitor anticoagulant therapy.

Peripheral blood film examination for the detection of red blood cell, white blood cell and platelet abnormalities, malignancies and parasites.

Sickle cell testing to aid in the diagnosis of sickle cell anaemia, sickle cell trait and other sickling disorders. SAGE IVD recommended that a full submission for a point-of-care test be sent for consideration for the next EDL.

Section II.b. General in vitro diagnostics for clinical laboratories

Cancer:

Alpha-fetoprotein (AFP) immunoassay for diagnosis, prognosis and monitoring of liver and germ-cell cancers. SAGE IVD requested additional evidence for germ-cell tumours.

Basic panel of immunohistochemical (IHC) testing to aid in the diagnosis, subclassification, prognosis and treatment of lymphoma, including HIV-associated conditions.

Basic panel of IHC markers to aid in diagnosis, prognosis and treatment of solid tumours, especially childhood cancer.

BCR-ABL1 (Philadelphia chromosome) and *ABL1* transcripts: reverse transcriptase (RT), quantitative PCR-based nucleic acid amplification test (NAT) for diagnosis and therapeutic monitoring of chronic myelogenous leukaemia (CML) and CML variants (neutrophilic) and prognosis of acute lymphoblastic leukaemia (ALL).

Essential flow cytometry panel of antibodies for leukaemia: added conditionally to the List for use as an aid in the diagnosis of leukaemia and definition of

prognostic and predictive features. SAGE IVD encouraged the requesters to submit additional evidence for use in LMICs, as highly skilled laboratory technicians are required to conduct flow cytometry.

Faecal immunochemical test (FIT) for screening for colorectal cancer.

hCG plus beta-hCG: immunoassay to aid in the diagnosis of and surveillance for germ-cell tumours and gestational trophoblastic disease. SAGE IVD encouraged the requesters to submit additional evidence for gestational trophoblastic disease.

Lactate dehydrogenase (LDH) assay was added to the List as an aid in the prognosis and monitoring of haematological malignancies (lymphoma) and germ-cell tumours.

Oestrogen (ER) and progesterone (PgR) receptors IHC test to aid in the diagnosis, prognosis and treatment of breast cancer.

Papanicolau (Pap) smear test for screening and as an aid in early diagnosis of cervical cancer.

Prostate-specific antigen (PSA) immunoassay was added to the List as an aid in the diagnosis, prognosis and monitoring of prostate cancer. SAGE IVD encouraged the requesters to submit additional evidence to support use of a point-of-care application.

Tyrosine–protein kinase erbB-2 receptor or human epidermal growth factor receptor 2 (HER2) overexpression IHC test to aid in the diagnosis, prognosis and treatment of breast cancer.

HIV infection:

Histoplasma antigen immunoassay was added conditionally to the List as an aid in the diagnosis of histoplasmosis. SAGE IVD requested WHO to consider this test in the next revision of their HIV guidelines. A full submission for an RDT was also requested for a future edition of the EDL.

Neglected tropical diseases:

Dengue virus (DENV) IgM antibody and NS1 antigen immunoassays and RDTs for use as an aid in the diagnosis of dengue fever (always in combination with NS1 antigen test) and for population surveys. Although the two types of test were submitted separately, SAGE IVD considered that they should always be used together.

DENV nucleic acid: a qualitative test was added conditionally to the List for surveillance (serotype differentiation) and confirmation of outbreaks. SAGE IVD

requested further evidence to support its use for diagnosis and confirmation and pending publication of new WHO recommendations.

Kato-Katz test for surveillance and diagnosis of soil-transmitted helminthiasis and schistosomiasis caused by *Schistosoma mansoni*, *S. intercalatum*, *S. japonicum* and *S. mekongi*. SAGE IVD noted the low sensitivity of the test and proposed that newer tests be evaluated further. The need for this test should be reviewed within the next 2 years.

Primary immunodeficiency disorders:

Enumeration of lymphocyte subtypes (CD8, CD20 and CD16/56 cells, B cells and NK cells) by flow cytometry was added conditionally to the List to aid in the diagnosis of primary and secondary immunodeficiencies. SAGE IVD requested additional evidence for use in LMICs.

Plasma levels of IgG, IgA and IgM measurement by radial immunodiffusion or immunoassay was added conditionally to the List to identify patients with low levels of immunoglobulins and to monitor replacement. SAGE IVD requested additional evidence of diagnostic accuracy.

HIV1/2 antibody for differential diagnosis of primary immunodeficiencies was added to both this section and that on HIV infection.

Sexually transmitted infections:

Chlamydia trachomatis and *Neisseria gonorrhoeae*: qualitative NAT as an aid in the diagnosis of chlamydial and gonorrhoeal urogenital disease and extragenital infection.

Syphilis:

Non-treponemal rapid plasma reagin test for screening for syphilis and monitoring treatment effectiveness

A Venereal Disease Research Laboratory (VDRL) test for screening, diagnosis and confirmation of neurosyphilis

A *T. pallidum* particle agglutination (TPPA) test and a *Treponema pallidum* haemagglutination assay (TPHA) for confirmation of syphilis infection and diagnosis of early and late syphilis infection.

Zika virus infection:

An immunoassay for Zika virus (ZIKV) IgM antibodies was added conditionally to the List as an aid in the diagnosis of suspected ZIKV infection. SAGE IVD requested additional evidence for the specificity of the test and clear guidelines.

A test for ZIKV nucleic acid to diagnose acute ZIKV infection.

4.3 **Deletions from the List**

Section I.a. General IVDs for use in community settings and health facilities without laboratories: Loop-mediated isothermal amplification (LAMP) for diagnosis of active tuberculosis (TB), white blood cell count, manual complete blood count, peripheral blood film examination and microscopy were deleted from section I.a in accordance with the new definition of the first section and added to section II.a, as these tests cannot be performed without minimal laboratory infrastructure.

4.4 Changes to listings

The SAGE IVD reviewed and considered each one of the 117 submitted changes suggested to the first edition of the EDL. Most of the changes were accepted. Nine changes – described in the following section – were rejected. Details of the suggested changes are available on the website of the second SAGE IVD meeting.¹⁴

4.5 **Rejected proposed changes**

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

Point-of-care testing for sickle cell disease at primary care level.

Requester: WHO

Recommendation: Rejected. SAGE IVD requested a full submission to support inclusion of point-of-care tests in the third EDL.

Section II.a. General IVDs for use in clinical laboratories:

Erythrocyte sedimentation rate

Requester: WHO

Recommendation: Rejected. More information required on the role of the erythrocyte sedimentation rate in inflammatory disorders, including its added value over C-reactive protein and in diagnosis, especially for temporal arteritis and polymyalgia rheumatica. SAGE IVD requested a full submission for possible inclusion in the third EDL.

Cartridge-based TB NAT for use at primary care level Requester: CHAI, Treatment Action Group Recommendation: Rejected. Inadequate evidence to support use of a TB NAT at primary care tier. Relevant WHO endorsement and guidelines required.

¹⁴ https://www.who.int/medical_devices/diagnostics/selection_in-vitro/selection_in-vitro-meetings/sageivd-second-meeting/en/.

Lipoarabinomannan antigen for use at primary care level Requester: Treatment Action Group, MSF

Recommendation: Rejected. SAGE IVD requested to wait until revision of the WHO guidelines.

Lipase or amylase test: Proposal to indicate that lipase is unnecessary if amylase can be requested.

Requester: IFCC

Recommendation: Rejected. Lipase is more sensitive and more specific. Lipase would be the preferred analyte, with amylase as a backup. Both analytes have been included.

Blood urea nitrogen: Proposal to indicate that this test is unnecessary if creatinine can be requested.

Requester: IFCC

Recommendation: Rejected. Both analytes are required in certain clinical algorithms. The EDL is not intended to provide guidance on the use of the tests. Clinical guidelines should be followed to decide when to use which test.

Haemoglobin A1c: Request for addition of "homogeneous immunoassay" or "turbidimetric inhibition immunoassay", enzyme-linked immunosorbent assay (ELISA).

Requester: Roche Diagnostics International (CH) / Roche Tissue Diagnostics (USA)

Recommendation: Rejected. All immunoassays on the List will henceforth be referred to simply as "immunoassays" to avoid omission of specific assay formats.

Papanicolaou (Pap) smear test: Proposal to add use of p16/ki-67 dual-stained cytology as a triage test for high-risk human papillomavirus (HPV)-positive women.

Requester: Roche Diagnostics International (CH) / Roche Tissue Diagnostics (USA)

Recommendation: The requesters are encouraged to submit an application for inclusion in the third EDL.

M. tuberculosis DNA mutations associated with resistance: Proposal to change assay format from "molecular line probe assay" to a generic term such as "nucleic acid test" (NAT).

Requester: Roche Diagnostics International (CH) / Roche Tissue Diagnostics (USA)

Recommendation: Rejected. The entry does not refer to a specific brand of assay format. Only IVDs recommended by WHO for detection of resistance to second-line anti-TB medicines are listed. Removal of "line probe assay" might imply that any NAT could also be used for this purpose.

Lipoarabinomannan antigen: Proposed change to include lipoarabinomannan in the primary care setting and to the test purpose, as follows "As an aid in the diagnosis of TB in all people living with HIV admitted to hospital, regardless of CD4 count or symptoms, and for all people living with HIV presenting to ambulatory care with advanced disease or CD4 < 200 cells/mm³ if CD4 testing is available."

Requester: Treatment Action Group

Recommendation: Rejected. SAGE IVD recommended waiting for the revision of the current WHO guidelines.

Troponin T/I: Proposed addition to the test purpose of diagnosis of peri-operative myocardial injury associated with non-cardiac surgery.

Requester: Roche Diagnostics International (CH)

Recommendation: Rejected. SAGE IVD requested a full submission to support this particular test purpose.

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

Cartridge-based TB NAT: Proposal for use at primary care tier.

Requesters: Treatment Action Group and CHAI

Recommendation: Rejected. SAGE IVD recommended waiting for revision of the current WHO guidelines.

Cartridge-based TB NAT: Proposal to extend the population in the test purpose to all people living with HIV admitted to hospital, regardless of CD4 count or symptoms, and for all people living with HIV presenting for ambulatory care with advanced disease or CD4 < 200 cells/mm³, if CD4 testing is available. Requester: Treatment Action Group

Recommendation: Rejected. SAGE IVD recommended waiting for revision of the current WHO guidelines.

Lactate dehydrogenase (LDH): Proposed that the submission include a specific brand of dry chemistry product, although it is not named. The current practice in LDH diagnosis globally is wet chemistry, i.e. ultraviolet test on a clinical chemistry analyser, which should be mentioned in the submission.

Requester: Roche Diagnostics International (CH) / Roche Tissue Diagnostics (USA)

Recommendation: Not applicable. The entry will not refer to any particular test.

Tyrosine-protein kinase receptor (erbB-2) or HER2: Proposal to use the latest American Society of Clinical Oncology and College of American Pathologists guidelines for HER2 testing.

Requester: Roche Diagnostics International (CH) / Roche Tissue Diagnostics (USA)

Recommendation: Not applicable. EDL is intended to list only tests and not to provide guidance on use of any test.

Tyrosine-protein kinase receptor (erbB-2) or HER2: Proposal for inclusion of in-situ hybridization as a confirmatory test.

Requester: Roche Diagnostics International (CH) / Roche Tissue Diagnostics (USA)

Recommendation: Rejected. The complexity and therefore the requirement for highly skilled workers as well as the cost of in-situ hybridization are the main reasons for omitting it from the List. The test will be considered for the next List upon receipt of a submission.

4.6 **Rejected applications**

High-sensitivity guaiac faecal occult blood (gFOBT) test for screening for colorectal cancer

Requester: WHO

Recommendation: Rejected. SAGE IVD requested evidence for the usefulness of this test in screening programmes when a FIT is not available.

Vaccine response test (tetanus and pneumococcal pneumonia) in the diagnosis of antibody immunodeficiency

Requester: International Patient Organisation for Primary Immunodeficiencies (IPOPI)

Recommendation: Rejected. SAGE IVD requested additional information and evidence of differential patient management based on test results and on the diagnostic accuracy of the test for this purpose.

Plasma and urine protein electrophoresis and immunofixation in the diagnosis of primary and secondary immunodeficiency and of monoclonal plasma cell disorders (e.g. multiple myeloma)

Requester: IPOPI

Recommendation: Rejected. Application incomplete, with insufficient evidence to support its use. SAGE IVD requested a new, complete full submission, including evidence for diagnosis of multiple myeloma.

5. Accepted applications for the second Model List of Essential In Vitro Diagnostics

This section provides summaries of the complete submissions received by the EDL Secretariat, the reviewers' comments and the SAGE recommendations for applications that were accepted for inclusion on the second EDL. The information presented below for each test, except the SAGE IVD recommendation, was edited from the full application submission forms. The complete submissions provided by each applicant are posted on the WHO website and can be found at: https://www.who.int/medical_devices/diagnostics/selection_in-vitro/selection_in-vitro-meetings/new-prod-categories/en/.

When evidence was not provided in the full submission form, the SAGE members or reviewers may have consulted additional references to those provided in the applications.

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

Leishmania rk39 antigen: rapid diagnostic test

Test category RDT for visceral leishmaniasis

Addition, change or deletion Addition

Proposed test purpose

Rapid diagnosis of clinically suspected visceral leishmaniasis due to *L. donovani* in South-East Asia and East Africa. Indicated for individual case management of visceral leishmaniasis and as a diagnostic tool in the field, in elimination programmes and for population surveys after elimination.

Applicant(s) Jose Antonio Ruiz Postigo, WHO

WHO technical department Control of Neglected Tropical Diseases

Background

Disease condition and impact on patients: Visceral leishmaniasis, also known as kala-azar, is fatal in over 95% of cases if untreated. It is characterized by irregular episodes of fever, weight loss, enlargement of the spleen and liver and anaemia.

Does the test meet a medical need? The test is used for serological confirmation of primary visceral leishmaniasis. As the signs and symptoms are non-specific, the diagnosis is confirmed from standard clinical criteria and a positive rK39 test. The rK39 test detects antibodies against a recombinant antigen, rK39, derived from *L. chagasi* that is present in serum and blood of patients. The target antibodies bind to the recombinant antigen on the test strip, yielding a visual positive result. The test can be used in the field, and results are available within 20–30 min. The rK39 test is highly sensitive and specific in endemic countries in South-East Asia but has shown less sensitivity and specificity in East African countries, where a negative test does not totally rule out visceral leishmaniasis if clinical suspicion is strong. As antibodies remain in the body for many years, even after the patient is cured, this test cannot differentiate between present and past infection.

How the test is used: Patients with probable visceral leishmaniasis (> 2 weeks of fever, splenomegaly and/or weight loss) in endemic areas or with a history of travel to an endemic area are tested. Each test is for single use (1, 2).

Public health relevance

Prevalence: The leishmaniases are caused by protozoan *Leishmania* parasites of more than 20 species, which are transmitted by the bite of infected female phlebotomine sand flies. The three main forms of leishmaniasis are visceral (the most serious form of the disease), cutaneous (the most common) and mucocutaneous (the most destructive). An estimated 700 000 to 1 million new cases and 20 000–30 000 deaths occur annually.

Visceral leishmaniasis is endemic in all six WHO regions. Most cases occur in Brazil, East Africa and South-East Asia. An estimated 50 000–90 000 new cases occur worldwide each year. In 2015, more than 90% of new cases reported to WHO occurred in seven countries: Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan. The disease affects some of the poorest people and is associated with malnutrition, population displacement, poor housing, a weak immune system and lack of financial resources. Leishmaniasis is also linked to environmental changes such as deforestation, building of dams, irrigation schemes, urbanization and climate change.

Socioeconomic impact: The economic impact of the disease on affected populations and communities is huge. For example, in Bihar, India, 83% of households in communities with high rates of the disease were in the poorest 40% of wealth distribution. The evidence is most complete for visceral leishmaniasis, as studies in many countries show that, even when diagnosis and medicines are provided free of charge, 25–75% of households of victims experience some form of financial catastrophe.

WHO or other clinical guidelines relevant to the test

The WHO document on use of visceral leishmaniasis RDTs (1) is intended for training but serves as guidance.

Basic test ch	aracteristics
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Test purpose	For detection of primary visceral leishmaniasis
Test format	rK39 immunochromatographic RDT
Specimen types	Most RDTs have been validated and approved for use with serum but are always performed with whole blood in field conditions, with good results. In a comparison of test results with serum and with whole blood, the Cohen kappa index was 0.88, indicating excellent concordance (<i>3</i>).
Equipment required	None
Regulatory status	Some assays are FDA-approved or CE-marked
Availability	Broad, in all endemic countries in South-East Asia and East Africa Available from many manufacturers Easy to use and inexpensive. No cold chain or equipment is required.
Price per test range	A box of 24 tests of one brand costs 42.44 € (US\$ 47.73). In a box of 25 tests of another brand, each test cost US\$ 1.75–2.02 for WHO.
Instrument price range	Not available

Evidence for clinical usefulness and impact

The WHO document on use of visceral leishmaniasis RDTs (1) states that, when used according to the manufacturer's instructions, the rK39 RDT is highly effective in detecting visceral leishmaniasis. In a comprehensive scientific review of published studies, its sensitivity was estimated to be 93.9% (87.7–97.1%). Its sensitivity was higher and more consistent in studies in South Asia, with a specificity of 90.6% (66.8–97.9%) in a clinical setting with febrile patients as negative controls.

Evidence for economic impact and/or cost-effectiveness

The rK39 RDT does not require a specialized set-up or specialized laboratory technicians. It is mainly for field use in primary care settings; a health care worker can use it after a proper demonstration and training. It is highly cost–effective for diagnosing primary visceral leishmaniasis in endemic areas, with high sensitivity and specificity.

Ethics, equity and human rights issues

Consent is required to obtain a serum sample. The availability of rK39 RDT in primary care settings and the field has greatly improved access to diagnosis and treatment of fatal visceral leishmaniasis, significantly reducing inequity.

SAGE IVD evidence review

Key supporting evidence is given in a Cochrane review of diagnostic test accuracy of the rK39 immunochromatographic test (ICT) that comprised 18 studies with a total of 3622 participants (4). The results were heterogeneous, but the overall sensitivity was 91.9% (95% confidence interval (95% CI) 84.8 ; 96.5), and the specificity was 92.4% (95% CI 85.6 ; 96.8). The sensitivity was lower in East Africa (85.3%; 95% CI 74.5 ; 93.2) than on the Indian subcontinent (97.0%; 95% CI 90.0 ; 99.5).

SAGE IVD considerations for recommendation

Visceral leishmaniasis is fatal in over 95% of cases if untreated. As the clinical features lack specificity, a confirmatory test is essential, to avoid unnecessary, costly treatment with toxic medications in uninfected people. Field studies show high diagnostic accuracy of the rK39 test in practice in various settings, although the performance on the Indian subcontinent is better than that in East Africa, where the sensitivity and negative predictive values are lower. The test can be performed by trained non-laboratory health staff, does not require a cold chain or specific instruments and is relatively inexpensive. Treatment for the disease is available and is included in the EML.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion on the EDL of the RDT for antibodies against *Leishmania* rK39 antigen for use in settings with no clinical laboratory facilities, noting the good accuracy and simplicity of the test when used according to WHO leishmaniasis control guidelines.

The Group recommended, however, that regulatory approval of the available tests be included, with a statement on whether any of the tests has been prequalified and a summary of any studies of cost–effectiveness. The Group requested WHO to accelerate a submission for inclusion of a direct agglutination test for leishmaniasis and to commission a systematic review of rK28 assays that may show greater accuracy in East African countries. The group further recommended that the test purpose not be limited to detection of *L. donovani* so that its use could be broadened to include *L. infantum*.

Recommended test purpose

As an aid in the diagnosis of clinically suspected visceral leishmaniasis.

References

- 1. The use of visceral leishmaniasis rapid diagnostic tests. Geneva: World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases; 2008 (http://apps.who.int/iris/bitstream/handle/10665/44012/9789241597357_eng.pdf?sequence=1&is Allowed=y, accessed April 2019).
- 2. Visceral leishmaniasis rapid diagnostic test performance (Diagnostics Evaluation Series No.4). Geneva: World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases; 2011 (http://www.who.int/tdr/publications/documents/vl-rdt-evaluation.pdf, accessed April 2019).
- 3. Matlashewski G, Ravi Das VN, Pandey K, Singh D, Das S, Ghosh AK, et al. Diagnosis of visceral leishmaniasis in Bihar India: comparison of the rK39 rapid diagnostic test on whole blood versus serum. PLoS Negl Trop Dis. 2013;7(5):e2233.
- 4. Boelaert M, Verdonck K, Menten J, Sunyoto T, van Griensven J, Chappuis F, et al. Rapid tests for the diagnosis of visceral leishmaniasis in patients with suspected disease. Cochrane Database Syst Rev. 2014;(6):CD009135.

Vibrio cholerae antigen: rapid diagnostic test

Test description RDT for detecting antigen to *Vibrio cholerae*

Addition, change or deletion Addition

Proposed test purpose

To screen patients with acute watery diarrhoea who present with the clinical case definition of cholera. A positive test should raise an alert while selected samples are sent for culture to confirm toxigenic *V. cholerae*.

Applicant(s) World Health Organization

WHO technical department

Health Emergencies, Infectious Hazards Management

Background

Disease condition and impact on patients: Cholera is an acute diarrhoeal disease caused by infection of the intestine with the bacterium *V. cholerae*, type O1 or O139, at any age. About 20% of people infected with *V. cholerae* have acute, watery diarrhoea, and approximately 20% have severe watery diarrhoea, many with vomiting. If these patients are not promptly and adequately treated, loss of fluid and salts can lead to severe dehydration and death within hours, with

a case-fatality rate of 30–50%. Treatment (rehydration) is straightforward, and, if it is provided rapidly and appropriately, the case-fatality rate should remain < 1%. Cholera is transmitted by ingestion of faecally contaminated water or food and remains an ever-present risk in many countries. New outbreaks can occur in any part of the world where the water supply, sanitation, food safety and hygiene are inadequate. The risk is considerably increased in humanitarian emergencies, when there is significant population movement and crowding and frequent disruption of or inadequate access to health care services, clean water, sanitation and hygiene. The malnutrition status and health conditions of displaced populations can also lead to higher mortality. As the incubation period of cholera is short (2 h to 5 days), the numbers of cases and deaths can rise quickly, thus leading to an acute public health problem (1–3).

Does this test meet a medical need? The test is used to screen stool samples for detection of toxigenic *V. cholerae* O1 or O139 from patients presenting with the clinical symptoms of cholera. It is used at primary care level for early detection of new cases and establishment of a cholera outbreak alert.

How the test is used: Current cholera RDTs are lateral flow devices to detect the lipopolysaccharide of V. cholerae O1 and O139 in ICTs. They are intended for use in primary care settings for surveillance purposes. The RDTs increase the specificity of the clinical diagnosis of cholera and improve its positive predictive value by permitting triage of specimens for laboratory confirmation. Cholera RDTs may be used for early outbreak detection, for an initial alert and for monitoring outbreaks and seasonal peaks in highly endemic areas. In all situations, the tests should be used only for clinically suspected cholera cases. In areas in which confirmed cholera cases have not recently been reported, positive RDT results for one or more patients with clinically suspected cholera are sufficient to launch a cholera alert, send stool specimens to a reference laboratory for confirmation by culture and initiate response measures (e.g. inform authorities and mobilize resources and material). In areas with ongoing outbreaks, positive RDTs can be used to select stool specimens from suspected cases for culture. If all the results are negative, cholera should be ruled out. RDTs are not a substitute for stool culture: any positive RDT result must be confirmed by culture or PCR as soon as possible before the alert is confirmed and a cholera outbreak declared. Culture or molecular testing allows not only identification but also characterization and genotyping of circulating strains, which is useful for epidemiological purposes.

Public health relevance

Prevalence: In 2016, 38 countries reported a total of 132 121 cases of cholera and 2420 deaths to WHO. The global burden of cholera is, however, largely

unknown, because most cases are not reported owing to limited capacity for epidemiological surveillance and laboratory testing and also social, political and economic disincentives for reporting. Epidemiological reporting and spatial regression modelling indicate that there are 2.86 million cases of cholera annually and 95 000 deaths in 69 endemic countries.

Socioeconomic impact: Cholera often occurs in large explosive outbreaks that spread rapidly. From a public health perspective, the management of cholera outbreaks requires immediate identification, because of the pathogen's potential for spread and the devastating consequences of epidemics. The economic impact of outbreaks has been estimated to be a loss of 1–2% of GDP in each outbreak year. WHO has estimated that US\$ 26 billion will be lost each year in the next 10 years if the global cholera burden is not addressed.

WHO or other clinical guidelines relevant to the test

Global Task Force on Cholera Control. Interim technical note. The use of cholera RDTs. November 2016 (4); and Global Task Force on Cholera Control. Interim guidance document on cholera surveillance. June 2017 (5).

Test purpose	Screening for cholera infection in outbreak settings
Test format	Lateral flow dipstick assay
Specimen types	Fresh stool, rectal swab
Equipment required	Dipstick cartridge, vial, buffer, dropper
Regulatory status	No information
Global availability	Broad
Price per test range	US\$ 2 per test
Instrument price range	Not available

Basic test characteristics

Evidence for clinical usefulness and impact

No direct studies of the impact of use of cholera RDTs have been reported. According to expert opinion, use of a point-of-care test for cholera can provide an initial indication of toxigenic *V. cholerae* transmission and thus reduce the danger of a nascent cholera epidemic. In the contexts in which cholera is most common, laboratory capacity and availability tend to be limited, and standard methods for cholera detection (culture and biochemical tests) are either unavailable or are available only after several days. As cholera outbreaks are explosive, the only

realistic means of extinguishing an outbreak before it spreads is to raise an alert and begin a rapid response as soon as an RDT shows a positive result in an area known to be endemic for cholera.

Evidence for economic impact and/or cost-effectiveness

As is the case for other RDTs, the costs include that of the test (US\$ 2) and of the supply chain system for monitoring and replacing stocks. In addition, although laboratory personnel are not required to perform the test, front-line health care workers should have a session of training and job aids for use, interpretation and follow-up of results.

Cholera RDTs are not meant for individual diagnosis but rather to detect possible toxigenic cholera transmission in an endemic community and monitoring of the outbreak during its course. Thus, annual use in terms of the number of tests per year in an identified cholera hotspot (per 200 000 population) has been estimated at 50–100 tests. The cost per person living in an area at risk of cholera is estimated to be less than US\$ 0.01 per year. Quality control and assurance and surveillance of proper RDT use must be included to ensure the most effective use of the test in a cholera surveillance system.

Ethics, equity and human rights issues

Consent is required to obtain a faecal sample. As the test is intended for points of care in peripheral health centres and even for community health workers, the wide availability of cholera RDTs would improve equity in communities by providing evidence of an impending cholera outbreak for rapid protective measures. At present, the benefit is at community rather than individual level.

SAGE IVD evidence review

A review of the development and evaluation of cholera diagnostics since 1990 (6) included a systematic search for studies, an analysis of methodological challenges in the studies and limited details of evaluation studies; however, the quality of the studies was not assessed, and a meta-analysis was not undertaken. Many methodological limitations and variations in accuracy among test kits were identified. Five tests were considered promising, with a sensitivity that may exceed 90% and a specificity of about 80%, although there is considerable variation among tests.

SAGE IVD considerations for recommendation

Cholera outbreaks must be detected and monitored for rapid control. As they often occur in low-resource settings or in emergency situations, diagnostic tests that are simple to use at primary care level must be available. RDTs for cholera have been evaluated in many studies. Current cholera RDTs are intended for use in

primary care settings for surveillance. They increase the specificity of the clinical diagnosis of cholera and permit triage of specimens for laboratory confirmation. Cholera RDTs may be used for early outbreak detection, for an initial alert and for monitoring outbreaks and seasonal peaks in highly endemic areas. In areas in which confirmed cholera cases have not recently been reported, positive RDT results for one or more patients with clinically suspected cholera are sufficient to launch a cholera alert, send stool specimens to a reference laboratory for confirmation by culture and initiate response measures (e.g. inform authorities and mobilize resources and material). In areas with ongoing outbreaks, positive RDTs can be used to select stool specimens from suspected cases for culture. Any positive RDT result must be confirmed by culture or PCR as soon as possible before the alert is confirmed and a cholera outbreak declared.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion on the EDL of the rapid antigen test for *V. cholerae* in the detection and monitoring of cholera epidemics at primary care level and for ruling out outbreaks.

The Group noted that the test is rapid and easy to use, with acceptable diagnostic accuracy for the purpose. SAGE IVD noted, however, that, in view of its high cost and the variation among studies, studies of its impact would be useful to demonstrate its utility.

Recommended test purpose

For early, initial detection or exclusion of a cholera outbreak (not for use in case management).

References

- 1. Clemens JD, Nair GB, Ahmed T, Qadri F, Holmgren J. Cholera. Lancet 2017;390:1539–49.
- 2. Ali M, Nelson AR, Lopez AL, Sack DA. Updated global burden of cholera in endemic countries. PLoS Negl Trop Dis. 2015;9(6):e0003832.
- 3. Keddy KH, Sooka A, Parsons MB, Njanpop-Lafourcade BM, Fitchet K, Smith AM. Diagnosis of Vibrio cholerae O1 infection in Africa. J. Infect Dis. 2013;208(Suppl.1):S23–31.
- Interim technical note. The use of cholera rapid diagnostic tests. Geneva: World Health Organization, Surveillance Laboratory Working Group, Global Task Force on Cholera Control; 2016 (https://www.who.int/cholera/task_force/Interim-guidance-cholera-RDT.pdf?ua=1, accessed April 2019).
- Interim guidance document on cholera surveillance. Geneva: World Health Organization, GTFCC Surveillance Laboratory Working Group, Global Task Force on Cholera Control; 2017 (https:// www.who.int/cholera/task_force/GTFCC-Guidance-cholera-surveillance.pdf?ua=1, accessed May 2019).
- 6. Dick MH, Guillerm M, Moussy F, Chaignat CL. Review of two decades of cholera diagnostics how far have we really come? PLoS Negl Trop Dis. 2012;6(10):e1845.

Section II.a General in vitro diagnostics for clinical laboratories *Clinical chemistry*

Procalcitonin in serum and plasma: immunoassay

Test category Procalcitonin immunoassay

Addition, change or deletion Addition

Proposed test purpose Early identification of sepsis in patients with bacterial infections

Applicant organization(s) Global Sepsis Alliance

Background

Disease condition and impact on patients: According to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis is a life-threatening organ dysfunction caused by dysregulated host-response to systemic infection. Mortality due to severe sepsis is 28–50% or more, even in developed countries, despite significant investments in critical care resources.

Does the test meet a medical need? The procalcitonin test has several potential uses in sepsis, and the results are useful, with other factors, for deciding when to start and when to discontinue antibiotic treatment.

How the test is used: The currently approved intended uses are to:

- a. assess the risk of critically ill patients with infections on admission to an intensive care unit for progression to severe sepsis and septic shock;
- b. decide to discontinue antibiotic therapy as early as possible; and
- c. assess the cumulative 28-day risk for all-cause mortality of patients with severe sepsis or septic shock in an intensive care unit or in emergency or other medical wards.

Other proposed intended uses are in deciding on antibiotic therapy for inpatients or outpatients with suspected or confirmed lower respiratory tract infections, community-acquired pneumonia, acute bronchitis or acute exacerbation of chronic obstructive pulmonary disease and in deciding to discontinue antibiotic therapy in these patients (1).

Public health relevance

Prevalence: Sepsis arises when the body's response to an infection injures its own tissues and organs, potentially leading to death or significant morbidity. The burden of sepsis is probably highest in LMICs; however, the available data are from studies in high-income countries. An estimated 30 million people are affected worldwide every year, potentially leading to 6 million deaths; 3 million newborns and 1.2 million children globally per year have sepsis. One in ten deaths associated with pregnancy and childbirth is due to maternal sepsis, and over 95% of deaths due to maternal sepsis occur in LMICs.

Socioeconomic impact: In an analysis of billings in the US health care system in 2013, sepsis cost nearly US\$ 24 billion annually and is thus the most expensive condition treated in the entire system. The mean expense per hospital stay was > US\$ 18 000, which was 70% more expensive than the average stay. The cost of care for sepsis rose by 19% between 2011 and 2013 (*2*).

WHO or other clinical guidelines relevant to the test

Report by the WHO Secretariat for the Seventieth World Health Assembly in 2017 (3) and resolution WHA70.7 on improving the prevention, diagnosis and clinical management of sepsis.

Acknowledged in a WHO meeting on sepsis in 2018 and recommended for discontinuation of antibiotics for lower respiratory tract infections by the Infectious Diseases Society of America, the Agency for Healthcare Research and Quality and the United Kingdom National Institute for health and Care Excellence. Recommended for discontinuation of antibiotics in sepsis only by the first two organizations.

Test purpose	For detection of bacterial sepsis
Test format	RDT, immunoassay
Specimen types	For RDT: serum or plasma immunoassay at points of care For instruments: venous or capillary whole blood, EDTA whole blood and plasma For manual assay: serum or plasma For bench-top instruments: serum, plasma (heparin, EDTA) For large automated instruments: serum or plasma
Equipment required	lmmunoassay analyser RDT enzyme immunoassay (EIA) analyser High-throughput chemiluminescent immunoassay
Regulatory status	CE, FDA and other

Basic test characteristics

Table continued

Global availability	Broad
Price per test range	About US\$ 20
Instrument price range	Small analysers: about US\$ 10 000 Large, fully automated analysers: about US\$ 100 000

Evidence for clinical usefulness and impact

Treatment of sepsis, "a life-threatening organ dysfunction caused by dysregulated host-response to systemic infection" (4), is based on treatment of the underlying infection. It involves a difficult balance between administration of antibiotics as soon as possible, as any delay increases the mortality rate by 2% per hour and stopping broad-spectrum antibiotics to prevent the emergence of AMR as soon as they are no longer required. Patients with sepsis are often treated with antimicrobials for 10–14 days, although evidence suggests that treatment could be reduced to 5–7 days without harm. As the clinical signs and symptoms are not specific to sepsis and sepsis may be caused by bacterial but also by viral infections, antibiotics are not always indicated. Furthermore, the results of blood cultures for bacterial infection and of antibiotic susceptibility testing can take at least 24 h and sometimes up to 72 h. Blood culture positivity rates are typically low. Early identification of sepsis cases due to bacterial infections is therefore critical.

During the past decade, procalcitonin testing has become widely used to identify bacterial sepsis. The sensitivity and specificity of the test to differentiate infectious from non-infectious causes of systemic inflammation are higher than those of other markers of inflammation and infection, such as C-reactive protein and cytokines such as IL-6. Furthermore, procalcitonin is not strongly increased in viral infections without bacterial superinfections. Elevated procalcitonin levels appear to be correlated with increasing bacterial load, and low procalcitonin levels tend to be associated with a low likelihood of a positive blood culture. Although it has limitations, a significant advantage of procalcitonin as a marker of bacterial sepsis is its early response to increased infection and to resolution of infection. It is therefore a useful aid, with clinical judgement and recognition that a number of non-infectious causes increase procalcitonin, in deciding when to start and when to discontinue antibiotic treatment.

Evidence for economic impact and/or cost-effectiveness

Balk et al. (5) concluded from a study on the effect of procalcitonin testing on health care use and costs in the USA that testing on admission to an intensive care unit significantly decreased the length of stay in hospital and in intensive care and the total cost of care. Steuten & Mantjes (6) concluded from a study by Assink-de Jong et al. (7) that hundreds of euros per patient were saved by use of procalcitonin testing and also reduced mortality, suggested in some countries to have a monetary value of US\$ 50 000–150 000 per life-year saved.

Ethics, equity and human rights issues

Consent is required to obtain a serum or plasma sample. If the test becomes available at a low price on modern point-of-care testing platforms, it should reduce inequity, especially in resource-limited settings, where inappropriate use of antibiotics is often more common than in high-income countries, by providing antibiotics in a timely manner to those who need them and to prevent their misuse.

SAGE IVD evidence review

Key supporting evidence was contained in a Cochrane review of randomized clinical trials (RCTs) of procalcitonin test strategies used to initiate or discontinue antibiotics in acute respiratory infections (8). The review comprised 32 RCTs with analysis of data on individual participants in 26 and a total of 6708 participants. The main benefits were a 2.4-day reduction in exposure to antibiotics (5.7 versus 8.1 days, 95% CI -2.71; -2.15, P < 0.001) and a lower risk for antibiotic-related side-effects (16.3% versus 22.1%, adjusted odds ratio 0.68, 95% CI 0.57; 0.82, P < 0.001). No difference in mortality was noted in 11 trials in emergency departments (76/1892 versus 79/1913) (RR=0.97 (0.70, 1.36), no heterogeneity), but a reduction in mortality was evident in 16 trials in intensive care units (530/2617 versus 586/2616) (RR=0.88 (0.77, 1.00), no heterogeneity). No significant difference was found in treatment failure (procalcitonin test 23.0%, control group 24.9%). The length of stay in hospital and in intensive care units was similar. Data were presented only for mortality and treatment failure; however, additional data to support the conclusion on antibiotic use and sideeffects were provided to the SAGE IVD by the authors of the review.

A second Cochrane review of RCTs of procalcitonin test strategies used in adults with sepsis, severe sepsis or septic shock (9) comprised 10 RCTs published up to 2015, with a total of 1215 participants. The mean time to receiving antimicrobial therapy in the intervention groups was reduced by 1.28 days with procalcitonin testing (95% CI: -1.95; -0.61). The mortality rate was reduced at the longest follow-up (RR=0.81 (0.65–1.01)) and at 28 days (RR 0.89, (0.61–1.31)) but not at discharge from intensive care (RR 1.03 (0.5– 2.11)) or hospital (RR 0.98 (0.75–1.27)). None of the primary studies had included an analysis of a change in antimicrobial regimen from a broad to a narrower spectrum. The authors considered that the inevitable lack of blinding in test-treatment trials incurred a risk of bias, which was not considered a concern by SAGE IVD.

SAGE IVD considerations for recommendation

The evidence that the procalcitonin test could reduce the use of antibiotics appears to be strong and justifies its use in diagnosis and during treatment to contribute to a decision on starting and discontinuing antibiotics. While data on reductions in mortality rates varied by setting and condition, showing either a reduction or no effect, there was no evidence that reducing antibiotic use put patients at risk of harm. Although the accuracy of diagnosis of sepsis was not high and while a single measurement could predict progression to severe sepsis but not mortality, the test-treatment trials provide convincing evidence that use of the test benefits patients and reduces antibiotic use.

No comparison has been reported of procalcitonin with other, cheaper biomarkers, such as C-reactive protein, which can be used for the same purpose.

SAGE IVD recommendation, with rationale

SAGE IVD recommended inclusion on the EDL of the test for procalcitonin levels in serum and plasma, noting the strong evidence for its quality and performance and the flexible assay formats and levels.

SAGE IVD considered that guidelines or an algorithm are required for its use, although the complexity and variability of sepsis might make this difficult. The test should therefore be used only in tertiary care facilities where physicians are available to modify or override decision thresholds where required in view of clinical presentation and patient characteristics.

Recommended test purpose

To guide antibiotic therapy initiation or discontinuation in sepsis and lower respiratory tract infection (for use only in tertiary care facilities).

References

- Goldberg B. Clinical considerations for procalcitonin-guided evaluation and management of lower respiratory tract infections and sepsis. Silver Spring (MD): Food and Drug Administration; 2017 (https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/UCM529262. pdf).
- 2. Introduction to the HCUP national inpatient sample. Rockville (MD): Healthcare Cost and Utilization Project (HCUP) and the Agency for Healthcare Research and Quality; 2014 (https://www.hcup-us.ahrq.gov/db/nation/nis/NISIntroduction2014.pdf, accessed April 2019).
- 3. Improving the prevention, diagnosis and clinical management of sepsis (A70/13). Geneva: World Health Organization; 2017 (https://www.who.int/servicedeliverysafety/areas/sepsis/en/, accessed April 2019).
- 4. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–10.

 Balk RA, Kadri SS, Cao Z, Robinson SB, Lipkin C, Bozzette SA. Effect of procalcitonin testing on health-care utilization and costs in critically ill patients in the United States. Chest. 2017;151(1):23–33.

- 6. Steuten L, Mantjes G. Economic value of procalcitonin guidance. Lancet Infect Dis. 2016;16(9):1000.
- 7. Assink-de Jong E, de Lange DW, van Oers JA, Nijsten MW, Twisk JW, Beishuizen A. Stop Antibiotics on guidance of Procalcitonin Study (SAPS): a randomised prospective multicenter investigatorinitiated trial to analyse whether daily measurements of procalcitonin versus a standard-of-care approach can safely shorten antibiotic duration in intensive care unit patients – calculated sample size: 1816 patients. BMC Infect Dis. 2013;13:178–84.
- Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev. 2017;(10):CD007498.
- 9. Andriolo BNG, Andriolo RB, Salomão R, Atallah ÁN. Effectiveness and safety of procalcitonin evaluation for reducing mortality in adults with sepsis, severe sepsis or septic shock. Cochrane Database Syste Rev. 2017;(1): CD010959.

Section II.b Disease-specific in vitro diagnostics for clinical laboratories

Cancer

Alpha fetoprotein immunoassay for diagnosis of liver and germ-cell tumours

Test description

AFP immunoassay

Addition, change or deletion Addition

Proposed test purpose For the diagnosis, prognosis and monitoring of liver and germ-cell cancers

Applicant organization(s) World Health Organization

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Disease condition and impact on patients: Monitoring of patients at high risk of hepatocellular carcinoma (HCC) (with chronic hepatitis B or cirrhosis) with AFP combined with ultrasound is effective in detecting these tumours.

Some guidelines recommend AFP testing as one of several tests for staging and treatment decisions for germ-cell cancer.

Does this test meet a medical need? The AFP immunoassay is used to screen for HCC in patients with cirrhosis, as noted in the WHO guidelines for the management of viral hepatitis, including monitoring high-risk patients (1).

How this test is used: The AFP immunoassay is used for diagnosis, prognosis and monitoring of liver and germ-cell cancers.

Public health relevance

Prevalence: Testicular cancer is diagnosed in approximately 9600 men each year in the USA, but only approximately 400 men die of their disease (4.2%). According to data from the International Agency for Research on Cancer (IARC) for 2018, 11 290 new cases of testicular cancer were reported in LMICs, with 3984 related deaths, accounting for 35.3% of the cases. Testicular cancer is the most frequently diagnosed tumour in young men. Globally, the prevalence is 284 073.

According to IARC, liver cancer was predicted to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death in 2018, with 841 000 new cases and more than 780 000 related deaths.

Socioeconomic impact: Germ-cell tumours arise mainly in young men; timely access to treatment, surgery, chemotherapy and radiotherapy with curative intention can increase their survival substantially at all stages of disease. According to IARC, testicular cancer is most frequently diagnosed between the ages of 20 and 34 years. Disparities in survival from testicular cancer have been described, with a large gap between high-income (mortality to incidence ratio: 0.03) and LMICs (0.17).

For liver cancer, the highest rates are observed mainly in lower-income settings: liver cancer is the most common cancer diagnosed in 13 countries in northern and western Africa and east and south-east Asia. This is related to suboptimal control of the risk factors, including vaccination coverage against hepatitis B virus. For instance, liver cancer incidence rates in Mongolia exceeded those of any other country in the same region as a result of a high prevalence of uncontrolled hepatitis B and C, affecting more than 20% of the population.

WHO or other clinical guidelines relevant to the test

WHO has not issued treatment guidelines but has issued lists of priority medical devices for cancer management (2, 3). WHO guidelines for hepatitis B and C include a recommendation to monitor patients with AFP and ultrasound to detect HCC.

Test purpose	Diagnosis and monitoring of liver cancer, germ-cell tumours
Test format	Immunoassay
Specimen types	Serum, plasma
Equipment required	Basic, automated
Global availability	Broad
Price per test range	US\$ 5–100
Instrument price range	US\$ 1000

Basic test characteristics

Evidence for clinical usefulness and impact

A meta-analysis showed that the test increased detection of early HCC in patients with cirrhosis, with a sensitivity of 63% (4). Use of AFP for tumour monitoring and prognosis is recommended on the basis of evidence-based national and regional guidelines for germ-cell tumours (testicular, ovarian, non-genital midline and unknown primary germ-cell tumours) (5–7). AFP has been used in indicating the prognosis of germ-cell tumours for classifying the risk of advanced tumours (8) and monitoring the response of non-seminomatous germ-cell tumours to anticipate platinum resistance and intensify treatment (9, 10). AFP can predict the prognosis of patients with HCC (11).

Evidence for economic impact and/or cost-effectiveness

AFP is a generally low-cost, feasible test. AFP with liver ultrasound as a screening strategy for patients at high risk for liver cancer has been used only in highincome countries, where cost–effectiveness has been assessed, with varying results. For example, a comparison of AFP and liver ultrasound with ultrasound only in the USA showed that the combination would yield an additional 27.8 lifeyears gained (US\$ 13 000 per life-year gained), while ultrasound alone would result in 38.9 life-years gained (US\$ 21 000 per life-year gained) (*12*).

Use of AFP on blood samples does not require highly specialized laboratory personnel, and it is considered a standard laboratory biochemical test.

Ethics, equity and human rights issues

Consent is required to obtain a serum or plasma sample. When AFP is used in patients with cirrhosis to monitor the disease and screen for liver cancer, timely access to care must be ensured. Early recognition of HCC ensures successful treatment of small, localized tumours, including multi-nodular liver presentations amenable to local and locoregional approaches (13).

Use of AFP to monitor germ-cell tumours, which are generally diagnosed in young patients, allows early detection of relapse of cancers that are amenable to curative treatment in a high percentage of cases. Furthermore, early, accurate diagnosis allows adaptation of treatment to reduce toxicity and avoid overtreatment. Moreover, the kinetics of AFP levels after initiation of treatment predict resistance to treatment, so that a timely change can be made to the cytotoxic regimen.

SAGE IVD evidence review

Monitoring patients at high risk of HCC with AFP combined with ultrasound is effective in detecting HCC (WHO guidelines).

AFP testing is recommended by WHO for screening for HCC in patients with cirrhosis in the guidelines for the management of viral hepatitis B and C, including monitoring high- risk patients. Use of AFP increased the sensitivity of detection of early HCC in patients with cirrhosis in a metanalysis (RR 0.81; 95% CI 0.71; 0.93), with a sensitivity of 63% (95% CI: 48; 75), demonstrating its effectiveness for detecting more diseases at an earlier stage, when it is eligible for curative treatment (4). AFP has also been suggested as a prognostic marker for HCC, with an HR for survival of 4.35 when AFP is > 1000 ng/mL (11).

AFP testing is recognized as an aid in diagnosis, prognosis, staging and disease monitoring for germ-cell tumours in international guidelines (6-8). AFP testing plays a critical role in prognostication of germ-cell tumours, in risk classification of advanced tumours and in risk- adapted intensity of treatments for patients, according to the International Germ Cell Cancer Collaborative Group (8), as well as in early monitoring of the response of non-seminomatous germ-cell tumours, to anticipate platinum resistance and intensify treatment in a personalized approach (10).

SAGE IVD considerations for recommendation

The test is recommended for screening people at high risk for HCC (with chronic hepatitis B or C, a family history or cirrhosis), in conjunction with ultrasound, consistent with WHO guidelines, although testing by ultrasound should have precedence over AFP testing. The test is also used for staging and disease monitoring of germ-cell tumours for deciding the intensity of treatment, although there are few data on this use. Consensus documents on staging and management of adolescent tumours include AFP, as ultrasound is not sufficient for paediatric tumours, and testing for AFP and hCG are necessary. The advantage of AFP testing is that it is done on blood samples, which can be sent elsewhere, whereas ultrasound requires the person to be present. Expert opinion and systematic reviews on AFP thresholds should be provided.

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SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion on the EDL of AFP testing. Updated international guidelines on its use in the staging, determining the intensity of treatment and monitoring of germ-cell tumours, especially in adolescents would be useful. The Group called for a systematic review of thresholds for AFP that indicate the presence of malignancy.

Recommended test purpose

Screening for HCC in high-risk individuals with chronic hepatitis B or C, a family history or cirrhosis, in conjunction with ultrasound and for staging and disease monitoring of germ-cell tumours.

References

- 1. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/handle/10665/254621/9789241549981-eng.pdf;jsessionid=31 A015 94E5FB11FCA57D141A0FBEC796?sequence=1, accessed April 2019)
- WHO list of priority medical devices for cancer management. Geneva: World Health Organization; 2017 (http://www.who.int/medical_devices/publications/priority_med_dev_cancer_management/ en/, accessed May 2019).
- 3. Hepatocellular carcinoma: hepatitis B and C guidelines (in preparation).
- Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a metaanalysis. Gastroenterology. 2018;154(6):1706–18.
- Honecker F, Aparicio J, Berney D, Beyer J, Bokemeyer R, Cathomas R, et al. ESMO 2018 consensus conference guidelines on testicular germ-cell cancer: diagnosis, treatment and follow-up. Ann Oncol. 2018;29:1658–86.
- 6. NCCN Clinical Practice Guidelines in Oncology. Fort Washington (PA): National Comprehensive Cancer Network; 2018
- Clinical guidelines for the management of testicular cancer. Arnhem: European Association of Urology; 2018 (https://uroweb.org/guideline/testicular-cancer/, accessed August 2019).
- International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ-cell cancers. J Clin Oncol. 1997;15(2):594–603.
- 9. Fizazi K, Pagliaro L, Laplanche A, Fléchon A, Mardiak J, Geoffrois L, et al. Personalised chemotherapy based on tumour marker decline in poor prognosis germ-cell tumours (GETUG 13): a phase 3, multicentre, randomised trial. Lancet Oncol. 2014;15(13): 1442–50.
- 10. Fizazi K, Flechon A, Le Teuff G, Mardiak J, Pagliaro LC, Geoffrois L, et al. Mature results of the GETUG 13 phase III trial in poor-prognosis germ-cell tumors (GCT). J Clin Oncol. 2016;34 (Suppl):abstract 4504.
- 11. Tyson GL, Duan Z, Kramer JR, Davila JA, Richardson PA, El-Serag HB. Level of alpha-fetoprotein predicts mortality among patients with hepatitis C-related hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2011;9(11):989–94.

- 12. Gounder PP, Bulkow LR, Meltzer MI, Bruce MG, Hennessy TW, Snowball M, et al. Cost-effectiveness analysis of hepatocellular carcinoma screening by combinations of ultrasound and alpha-fetoprotein among Alaska Native people, 1983–2012. Int J Circumpolar Health. 2016;75:31115.
- 13. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 2016;334(11):693–9.

Basic panel of immunohistochemical tests for diagnosis of lymphoma

Test category Panel of immunohistochemical tests for diagnosis of lymphoma

Addition, change or deletion Addition

Proposed test purpose

In the diagnosis, sub-classification, prognosis and treatment of lymphoma, including HIV-associated subtypes

Applicant organization(s) World Health Organization

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Disease condition and impact on patients: According to IARC, lymphoma accounts for 2.6– 2.8% of global cancer incidence and mortality. More than 500 000 new cases were diagnosed in 2018, with 250 000 deaths. There are two main groups of lymphomas, Hodgkin and non-Hodgkin lymphoma (NHL). New cases of NHL occurred at equal rates in high- and middle- to lower-income regions; however, deaths occurred more frequently in the latter (62%) (1). Some NHL subtypes are more prevalent in LMICs, especially south of the Sahara, as a result of the HIV endemic, as some lymphomas are on an etio- pathogenetic continuum to HIVinduced immunosuppression, including opportunistic infections. Treatments for lymphoma are highly active and can result in high curative rates, if they are provided in a timely way to eligible patients.

Does this test meet a medical need? The basic panel of immunohistochemical tests can be used for the diagnosis of lymphoma, definition of lineage (B or T cells) and clinically useful sub-classifications for prognosis and treatment,

including HIV-associated and defining conditions and for paediatric and adult haematological malignancies.

How the test is used: The panel is intended for laboratory use in qualitative identification of the antigens by IHC in formalin-fixed, paraffin-embedded human tissues. The basic panel should be considered in the clinical and pathological diagnosis of haematological malignancies arising from lymph nodes. It is applicable in a resource- sparing algorithm according to the morphology of the specimen.

Public health relevance

Prevalence: According to IARC, more than 1.6 million cases are diagnosed, treated or survive. In high-income countries, more patients survive, as a result of timely access to effective, good-quality diagnosis, safe treatment and care during survival.

Socioeconomic impact: Lymphoma can arise as an AIDS-defining condition in 3% of cases and is the cause of death in up to 16% of patients with HIV infection, especially in countries where coverage of antiretroviral medicines is suboptimal (2). As prognosis depends on timely access to curative treatment, the prognosis of lymphoma may be conditioned by socioeconomic status; a lower life expectancy of lymphoma patients with lower socioeconomic status has been reported (3), indicating inequality for the poorest populations.

WHO or other clinical guidelines relevant to the test

WHO has set the international diagnostic criteria for classification and stratification of lymphomas (4). The WHO classification is based on a combination of morphology and immune histochemistry, refined by molecular diagnostics as appropriate.

Basic test characteristics

Basic panel for the diagnosis and classification of lymphoma: ki-67, CD45, BCL6, IRF4/MUM1, MYC, CD20, CD5, CD10, BCL2, CD23, CD79a, cyclinD1, CD3, CD15, CD30, TdT.

Test purpose	In the diagnosis, classification, prognosis and treatment of lymphoma, including HIV-associated conditions
Test format	Immunohistochemistry
Specimen types	Tissue, formalin-fixed, paraffin-embedded
Equipment required	Machine for IHC

Table continued

Regulatory status	Recognized as a diagnostic aid by regulatory bodies
Global availability	Not provided
Price per test range	Not provided
Instrument price range	Installing machines and training personnel require a large initial investment. Subsequently, the cost is for reagents and maintenance.

Evidence for clinical usefulness and impact

Haematological malignancies must be identified and classified so that appropriate lineage- and subtype-oriented protocols adapted to the aggressiveness of the lymphoma can be used. Some low-grade lymphomas can be adequately managed by close surveillance or de-escalated regimens, and some are difficult to detect, requiring timely curative treatment (diffuse B-cell lymphoma, Hodgkin lymphoma, Burkitt lymphoma). Some subtypes (cerebral primitive lymphoma, primary effusion lymphoma) are specific to HIV-infected patients and are managed as HIV-related, AIDS-defining conditions. WHO recognizes the importance of identifying subtypes of lymphomas, and IARC has published a classification of tumours of haematopoietic and lymphoid tissues (4) to guide diagnosis with IHC panels to support morphology findings for accurate diagnosis and treatment. Limited-panel IHC is recognized as a basic requirement for the diagnosis and prognosis of lymphoma by leading haematology and oncology societies such as the College of American Pathologists. Rituximab is on the WHO EML for CD20-positive lymphoid malignancies, and WHO prequalification of similar biotherapeutic products has been initiated, highlighting the importance of a basic panel that includes CD20.

The panel has been proposed by international oncology and haematology societies and working groups for use in LMICs to provide optimal care for adult and child patients with haematological malignancies. Its use reduces the requirement for external referral and migration for health, enhancing patients' financial protection. A basic panel that covers more than two thirds of a diagnosis is aligned with the principles of UHC. The current clinical guidelines require correct identification of subtypes of lymphoma to reduce the risk of overtreatment of indolent disease, treat CD20-positive lymphoma with targeted agents and adapt the intensity for more aggressive types (5-14).

Evidence for economic impact and/or cost-effectiveness

The cost of reading a panel of three to five antibodies and five slices in LMICs would be about US\$ 15 for consumables, reagents and antibodies (*15*).

Use of the CD status kit requires a laboratory technician for incubation and staining on an automatic strainer and a trained pathologist to read the slides and interpret the results.

Ethics, equity and human rights issues

Consent is required to obtain a tissue sample. The availability of lymphocyte differentiation antigens is an essential requirement for personalizing the treatment of lymphomas. Knowledge of a patient's CD20 status permits the choice of targeted agents, including rituximab. For low-grade disease with an indolent course, less invasive management can be used, including close surveillance, which reduces the risk of overtreatment.

SAGE IVD evidence review

Evidence was provided that the proposed panel of markers is adequate to subtype the majority of lymphomas efficiently. As immunohistopathology is considered the reference standard, no estimate of accuracy was reported. The benefits of using this panel of markers for subtyping is presumed to be based on evidence of the benefits of different treatment approaches for different lymphoma types.

SAGE IVD considerations for recommendations

The widely different types of lymphoma require different treatment approaches, and the sub-groups can often be differentiated only by IHC. Diagnosis of lymphoma and other haematological malignancies by immunophenotyping and IHC is established in high-income countries and is essential for individualized care for response and long-term survival. This panel of monoclonal antibodies aids in appropriate diagnosis and sub-classification of lymphomas and allows faster triaging of patients for adapted treatment. Once a diagnosis is suspected, a trained laboratory technologist can use an appropriate algorithm to produce additional stains to aid the pathologist who is assessing the case. This will shorten the turn-around time for diagnosis, which will improve the timeliness of treatment decisions. The test can be used in laboratories with limited skills and is cost–effective.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion of the basic panel of IHC tests for diagnosis of lymphoma, noting that identification of lymphoma subtypes can indicate the appropriate treatment. They also noted the requirement for qualified laboratory staff.

Recommended test purpose

As an aid in the diagnosis, sub-classification, prognosis and treatment of lymphoma (including HIV-associated conditions)

References

- 1. Phillips AA, Smith DA. Health disparities and the global landscape of lymphoma care today. Am Soc Clin Oncol Educ Book.2018;37:526–34.
- 2. Bower M, Fisher M, Hill T, Reeves I, Walsh J, Orkin C, et al. CD4 counts and the risk of systemic non-Hodgkin's lymphoma in individuals with HIV in the UK. Haematologica. 2009;94(6):875–80.
- 3. Tao L, Foran JM, Clarke CA, Gomez SL, Keegan TH. Socioeconomic disparities in mortality after diffuse large B-cell lymphoma in the modern treatment era. Blood 2014;123(23):3553–62.
- 4. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO classification of tumours, revised 4th edition, Vol. 2, WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: international Agency for Research on Cancer; 2017 (http://publications. iarc.fr/Book-And-Report-Series/Who-larc-Classification-Of-Tumours/Who-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017, accessed May 2019).
- Di Santo MG, Ambrosio MR, Rocca BJ, Ibrahim HA, Leoncini L, Naresh KN. Optimal minimal panels of immunohistochemistry for diagnosis of B-cell lymphoma for application in countries with limited resources and for triaging cases before referral to specialist centers. Am J Clin Pathol. 2016;145(5):687–95.
- Naresh KN, Raphael M, Ayers L, Hurwitz N, Calbi V, Rogena E, et al. Lymphomas in sub-Saharan Africa – what can we learn and how can we help in improving diagnosis, managing patients and fostering translational research? Br J Haematol. 2011;154(6):696–703.
- 7. NCCN resource stratified guidelines for B-cell non-Hodgkin lymphoma, basic resource. V5. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2018
- ESMO clinical practice guidelines: haematological malignancies. Lugano: European Society for Medical Oncology; 2019 (https://www.esmo.org/Guidelines/Haematological-Malignancies, accessed May 2019).
- 9. Spinner MA, Advani RH, Connors JM, Azzi J, Diefenbach C. New treatment algorithms in Hodgkin lymphoma: too much or too little? Am Soc Clin Oncol Educ Book. 2018;38:626–36.
- Laboratory workup of lymphoma. In: ASH clinical practice guidelines. Washington DC: American Society of Hematology; 2019 (http://www.hematology.org/Clinicians/Guidelines-Quality/Guidelines.aspx#lymphoma, accessed May 2019).
- 11. Tan D. Management of B cell non-Hodgkin lymphoma in Asia: resource-stratified guidelines. Lancet Oncol. 2013;14(12):e548–61.
- 12. Yeoh AE, Tan D, Li CK, Hori H, Tse E, Pui CH. Management of adult and paediatric acute lymphoblastic leukaemia in Asia: resource-stratified guidelines from the Asian Oncology Summit 2013. Lancet Oncol. 2013;14(12):e508–23.
- Nadiminti K, Nasr M, Mott SC, Syrbu S, Rosenstein LJ. A novel immunohistochemistry (IHC) algorithm for assigning cell of origin status in diffuse large B-cell lymphoma (DLBCL) that better predicts survival as compared to the Hans algorithm (Abstract). In: Abstracts for the 2019 ASCO annual meeting. Alexandria (VA): American Society of Clinical Oncology; 2019 (https:// meetinglibrary.asco.org/record/96127/abstract, accessed May 2019).

 Hussong JW, Arber DA, Bradley KT, Brown MS, Chang CC, de Baca MR, et al. Protocol for the examination of specimens from patients with non-Hodgkin lymphoma/lymphoid neoplasms. Northfield (IL): College of American Pathologists; 2013 (https://cap.objects.frb.io/protocols/ nonhodgkinlymph-17protocol-3201.pdf, accessed May 2019).

15. Ch'ng ES, Khiro FI. Letter to Editor. Low cost immunohistochemistry bench for developing countries. Malaysian J Pathol. 2018;40(2):209–11.

Basic panel of immunohistochemical tests for diagnosis of solid tumours

Test category

Basic panel of IHC markers for paediatric and adult solid tumours

Addition, change or deletion Addition

Proposed test purpose

In the diagnosis, sub-classification, prognosis and treatment of solid tumours, especially in children

Applicant organization(s) World Health Organization

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Disease condition and impact on patients: The global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths in 2018. One in five men and one in six women worldwide develop cancer during their lifetime, and one in eight men and one in 11 women die from the disease.

Does this test meet a medical need? The test is for diagnosis of paediatric and adult solid tumours and for clinically useful sub-classification for prognosis and treatment, including HIV-associated and defining conditions. The panel is a minimum panel for diagnosis of solid tumours. The work incorporates and builds on that of the Global Initiative for Childhood Cancer and should be considered a starting-point for the diagnosis of solid tumours, upon which to build future applications.

How the test is used: The panel is intended for laboratory use in qualitative identification of the antigens by IHC in formalin-fixed paraffin-embedded human tissues.

Public health relevance

Prevalence: Worldwide, the total number of people who are alive within 5 years of a cancer diagnosis is estimated to be 43.8 million.

Socioeconomic impact: The economic impact of cancer is significant; in 2010, the total annual economic cost of cancer was estimated at approximately US\$ 1.16 trillion, threatening economies at all income levels as well as causing financial catastrophe for individuals and families.

WHO or other clinical guidelines relevant to use of the test

WHO classification of tumours (1) and WHO list of priority medical devices for cancer management (2).

Basic test characteristics

Basic panel of IHC markers comprising desmin, cytokeratin AE1/AE3, S100, synaptophysin, myogenin.

Test purpose	Diagnosis of solid tumours, especially paediatric tumours
Test format	IHC
Specimen types	Tissue, formalin-fixed paraffin-embedded
Equipment required	Not stated
Regulatory status	Single IHC tests are widely used and are approved by regulatory agencies and authorized. This panel has been customized for the submission to suggest an entry-level IHC as an aid in diagnosis of solid tumours
Global availability	Not stated
Price per test range	Average cost per slide, US\$ 10–20
Instrument price range	Not stated

Evidence for clinical usefulness and impact

These tests are used routinely worldwide for detailed typing of malignant tumour tissue for classification and further management. The basic panel is intended as a resource-sparing strategy for making a definitive diagnosis (e.g. epithelial or non-epithelial) and orienting treatment (e.g. Ewing sarcoma or osteosarcoma). The IHC may be affected by procedural inefficiency, some of which is expected and can be controlled (*3*). The most common causes of false-negative immunostaining are poor tissue fixation, over-diluted or improperly optimized antibodies and epitope retrieval methods not optimized for individual antibodies.

The clinical value of the panel of five antibodies has not been evaluated in a published paper, although it has been identified as a basic requirement in LMICs by expert pathologists working in global oncology, including the stakeholders of the WHO Global Initiative on Childhood Cancer. Studies of the clinical accuracy of single antibodies and evidence of the impact of the tests in clinical practice indicate that the basic panel allows diagnostic evaluation of soft tissue sarcomas such as rhabdomyosarcoma, leiomyosarcoma, Ewing sarcoma, other primitive neuroectodermal tumours, desmoplastic small round cell tumours, sarcomatoid carcinoma (and other cytokeratin-positive malignancies), melanoma, nerve sheath tumours, Wilms tumour, neuroblastoma, neuroendocrine carcinoma and other carcinomas (4-6). The treatment of these epithelial and non-epithelial cancers is distinct.

The panel allows more accurate tumour tissue typing and therefore better tumour management and longer survival.

Evidence for economic impact and/or cost-effectiveness

The estimated average cost of an IHC test with five antibodies in LMICs is US\$ 10–20 per slide (7).

Use of the kit requires a laboratory technician for incubation and staining on an automatic stainer and a trained pathologist to read the slides and interpret the results.

Ethics, equity and human rights issues

Consent is required to obtain a tissue sample. The availability of a marker to define the nature and origin of paediatric solid tumours makes it possible to tailor treatment. Knowledge of the exact histology of cancers is recommended in the principal clinical guidelines for treatment, including multimodal approaches, sensitivity to chemotherapeutic agents and targeted agents. Microscopic histology cannot precisely identify the cancer type in some cases or its epithelial or non-epithelial origin, reducing the possibility of multimodal, integrated, tailored histology-driven therapy for children who have no access to or cannot afford IHC tests.

SAGE IVD evidence review

IHC is the reference standard for classification thus no studies of the accuracy of the approach are available. Evidence provided supported stepwise testing using a restricted batch of antibodies as an efficient testing process.

SAGE IVD considerations for recommendation

The basic panel of IHC stains is applicable in the clinical and pathological diagnosis of solid malignancies in a resource-sparing algorithm for settings with

limited diagnostic tools or molecular testing. The panel is clinically useful for classification of solid tumours for prognosis and treatment of paediatric and adult solid malignancies. The panel should be considered a starting-point for the diagnosis of solid tumours, to which other antigens will be added, as appropriate.

SAGE IVD recommendations, with rationale

The SAGE IVD recommended inclusion on the EDL of the basic panel of IHC tests for the diagnosis of solid tumours (to be used only in tertiary level). The Group noted that the panel is to be extended in future submissions.

Recommended test purpose

To aid in diagnosis, prognosis and treatment of solid tumours especially in childhood cancer.

References

- Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO classification of tumours, revised 4th edition, Vol. 2, WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: international Agency for Research on Cancer; 2017 (http://publications. iarc.fr/Book-And-Report-Series/Who-larc-Classification-Of-Tumours/Who-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017, accessed May 2019).
- WHO list of priority medical devices for cancer management. Geneva: World Health Organization; 2017 (http://www.who.int/medical_devices/publications/priority_med_dev_cancer_ management/en/, accessed May 2019).
- 3. Gown AM. Diagnostic immunohistochemistry: What can go wrong and how to prevent it. Arch Pathol Lab Med. 2016;140(9):893–8.
- Fanburg-Smith JC, Miettinen M. Angiomatoid "malignant" fibrous histiocytoma: a clinicopathologic study of 158 cases and further exploration of the myoid phenotype. Hum Pathol. 1999;30(11): 1336–43.
- 5. Folpe AL, McKenney JK, Bridge JA, Weiss SW. Sclerosing rhabdomyosarcoma in adults: report of four cases of a hyalinizing, matrix-rich variant of rhabdomyosarcoma that may be confused with osteosarcoma, chondrosarcoma, or angiosarcoma. Am J Surg Pathol. 2002;26(9):1175–83.
- 6. Oliva E, Young RH, Amin MB, Clement PB. An immunohistochemical analysis of endometrial stromal and smooth muscle tumors of the uterus: a study of 54 cases emphasizing the importance of using a panel because of overlap in immunoreactivity for individual antibodies. Am J Surg Pathol. 2002;26(4):403–12.
- 7. Ch'ng ES, Khiro FI. Letter to Editor. Low cost immunohistochemistry bench for developing countries. Malaysian J Pathol. 2018;40(2):209–11.

BCR-ABL1 and *ABL1* transcripts for diagnosis of chronic myelogenous leukaemia (CML) and CML variants and prognosis of acute lymphoblastic leukaemia (ALL)

Test category

Detection of BCR-ABL1 and ABL1 transcripts by nucleic acid testing and PCR for BCR-ABL

Addition, change or deletion Addition

Proposed test purpose

Reverse transcription, quantitative PCR-based NAT for the detection of BCR-ABL1 (Philadelphia chromosome) and ABL1 transcripts in the diagnosis and therapeutic monitoring of CML and CML variants (neutrophilic), and prognosis of ALL. It could also be used to propose treatment discontinuation in patients with long-lasting remission of CML under treatment.

Applicant organization(s) World Health Organization

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Disease condition and impact on patients: Reports from several European registries of CML show an annual incidence of 0.7–1.0/100 000, a median age at diagnosis of 57–60 years and a male:female ratio of 1.2–1.7 (1). The estimated median prevalence is 10/100 000, which is projected to increase because of the dramatic improvement in survival of these patients due to introduction of a life-saving medicine, imatinib. Acute leukaemia is the most common childhood cancer, accounting for up to 25% of all childhood malignancies. ALL is the most common variant of leukaemia in children; Philadelphia chromosome dictates the prognosis of ALL, requiring an intensified cure.

The prognosis of leukaemia is related to the health system capacity and directly to access to care. Childhood leukaemia is curable with inexpensive essential antineoplastic medicines. In certain LMICs, the prognosis of ALL can be as poor as 20% at 5 years, far behind the prognosis in higher-income settings, where > 95% survive (2, 3). For CML, access to imatinib is one of the most critical determinants of the outcome; traditional treatments, including cytotoxic agents and hydroxyurea, did not increase survival. Disparities have been described

among patients covered by different insurance schemes, mirroring the effect of disparities in access to molecular diagnostics and targeted treatments (4).

Does the test meet a medical need? CML and ALL are highly curable diseases. The prognosis of leukaemia reflects the efficiency of health systems in providing timely access to high-quality, safe treatment, including supportive care. Access to molecular diagnosis is essential for the entire management of CML: *BCR-ABL* translocation is both pathognomonic and predictive of the benefit of imatinib and other tyrosine kinase inhibitors and defines the disease and treatment response.

How the test is used: IVDs are used in diagnosis, treatment and monitoring.

Public health relevance

Prevalence: The median prevalence of CML is estimated to be 10/100 000 inhabitants, which is projected to increase because of the dramatic improvement in survival of these patients due to introduction of a life-saving medicine, imatinib, and other tyrosine kinase inhibitors.

Socioeconomic impact: The economic impact of cancer is significant; in 2010, the total annual economic cost of cancer was estimated at approximately US\$ 1.16 trillion, threatening economies at all income levels as well as causing financial catastrophe for individuals and families.

WHO or other clinical guidelines relevant to the test

A basic panel of IHC markers is on the list of Priority medical devices for cancer management (5).

The role of detection of BCR- ABL1 transcripts in a diagnosis of CML and the prognostic value in ALL are acknowledged in the revised WHO classification of tumours of haematopoietic and lymphoid tissues (*6*).

Test purpose	Diagnosis and therapeutic monitoring of CML and CML variants (neutrophilic) and prognosis of ALL
Test format	PCR
Specimen types	Blood or bone marrow (review of application)
Equipment required	Basic, automated
Global availability	50–100 countries
Price per test range	US\$ 300
Instrument price range	US\$ 2000–5000

Basic test characteristics

Evidence for clinical usefulness and impact

PCR is the standard technique for the diagnosis and monitoring of minimal residual disease in order to predict response and emerging resistance to treatment with imatinib and other tyrosine kinase inhibitors. Detection of the t(9;22) BCR-ABL1 translocation is recommended in guidelines for the diagnosis and management of CML, including ESMO (7) and NCCN (8). The BCR-ABL onco-protein can be targeted with the specific tyrosine kinase inhibitors on the WHO EML (imatinib, dasatinib and nilotinib) and other approved treatments. Demonstration of pathogenetic translocation is the essential diagnostic finding for targeted treatment, with a significant impact on the natural history of the disease and longer overall survival (9). Other classes of drug (hydroxyurea, interferon) resulted in significantly smaller increases in survival. In a sample Spanish population, it was estimated that a diagnosis of CML in 1990 in a 55-yearold woman would on average have reduced her life expectancy by 24.9 years, whereas a diagnosis in 2010 with tyrosine kinase inhibitors for the same woman would reduce her life expectancy by only 2.9 years (10). Monitoring of CML and early recognition of resistant clones that would require a change in treatment are based on molecular criteria or failure of response, suggesting no further benefit of therapy with a tyrosine kinase inhibitor and a switch to another, noncross-resistant tyrosine kinase inhibitor (11-13). The WHO EML committee recognized the requirement for monitoring CML treatment and transition to second-line therapy and included second-line tyrosine kinase inhibitors in the List in 2017.

Evidence for economic impact and/or cost-effectiveness

The cost of a PCR per patient is generally US\$ 100–300 in high-income settings (*14*). In comparative cost–effectiveness studies, imatinib appeared to be more effective than previous standard drug treatments in terms of cytogenetic response and progression-free survival, with fewer side-effects. Imatinib, which is available as a generic drug (US\$ 277 401; 3.87 quality-adjusted life years (QALYs)) offered patients a 0.10 decrement in QALYs at a saving of US\$ 88 343 over 5 years as compared with other tyrosine kinase inhibitors (US\$ 365 744; 3.97 QALYs). The incremental cost–effectiveness ratio was US\$ 883 730 per QALY (*15–17*).

Assessment and interpretation of molecular tests require skilled, trained pathologists or molecular biologists and a thermocycler for PCR testing.

Ethics, equity and human rights issues

Consent is required to obtain a blood or bone marrow sample. CML is a rare but highly curable disease, with targeted treatments that significantly affect the natural history of the disease when it is diagnosed and treated early, in the

so-called chronic phase of CML. The availability of a diagnostic test is an ethical imperative to protect vulnerable patients affected with rare curable diseases.

SAGE IVD evidence review

As PCR is the reference standard test, there are no studies of test accuracy or standard assessments of test performance. Strong evidence is available, however, of the importance of assessing *BCR-ABL1* and *ABL1* transcripts for diagnosis and treatment monitoring. For example, evidence of the effectiveness of treatments for acute myeloid leukaemia as documented in the EML indicates its importance for identifying who will benefit from treatment. Many studies indicate that rising levels of these transcripts after treatment predict a poor clinical outcome.

SAGE IVD considerations for recommendation

PCR for detecting *BCR-ABL1* fusion transcript is the recognized reference method for assessing response to treatment and disease monitoring. Detection of the t(9;22) *BCR-ABL1* translocation is recommended in the principal guidelines for the diagnosis and management of CML. The BCR-ABL onco-protein can be targeted with specific inhibitors that are on the WHO EML.

SAGE IVD recommendation, with rationale

SAGE IVD recommended inclusion of nucleic acid testing for *BCR-ABL1* translocation in patients with CML, noting that the test is highly cost–effective and increases the efficacy of CML therapy.

Recommended test purpose

For diagnosis and therapeutic monitoring of CML and CML variants (neutrophilic CML) and prognosis of ALL.

- 1. Hoglund M, Sandin F, Simonsson B. Epidemiology of chronic myelocytic leukaemia: an update. Ann Hematol. 2015;94(Suppl):S241–7.
- 2. Howard SC, Zaidi A, Cao X, Weil O, Bey P, Patte C, et al. The My Child Matters programme: effect of public-private partnerships on paediatric cancer care in low-income and middle-income countries. Lancet Oncol. 2018;19(5):e252–61.
- 3. Lam CG, Howard SC, Bouffet E, Pritchard-Jones K. Science and health for all children with cancer. Science 2019.
- 4. Master SR, Koshy N, Mills G, Shi RR. Disparities in survival outcomes based on insurance status in CML: a national cancer database analysis (abstract). In: Proceedings of the Ninth AACR Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved; 2016 Sep 25-28; Fort Lauderdale, FL. Cancer Epidemiol Biomarkers Prev. 2017;26(2 Suppl):abstract C16.

- Priority medical devices for cancer management (WHO medical device technical series). Geneva: World Health Organization; 2017 (http://www.who.int/medical_devices/publications/priority_ med_dev_cancer_management/en/).
- Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition (WHO Classification of Tumours, Volume 2; IARC WHO Classification of Tumours, No. 2). Lyon: International Agency for Research on Cancer; 2008 (http://publications.iarc.fr/Book-And-Report-Series/Who-larc-Classification-Of-Tumours/Who-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017, accessed May 2019).
- 7. Hochhaus A, Saussele S, Rosti G, Mahon FX, Janssen JJWM, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO clinical practice guidelines. Ann Oncol. 2017;28(Suppl 4):iv41–51.
- Radich JP, Deininger M, Abboud CN, Altman JK, Berman E, Bhatia R, et al. Chronic myeloid leukemia, version 1.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16(9):1108–135.
- Kantarjian H, O'Brien S, Jabbour E, Garcia-Manero G, Quintas-Cardama A, Shan J, et al. Improved survival in chronic myeloid leukemia since the introduction of imatinib therapy: a singleinstitution historical experience. Blood 2012;119(9):1981–7.
- 10. Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer. 2012;118:3123–7.
- 11. Saussele S, Hehlmann R, Fabarius A, Jeromin S, Proetel U, Rinaldetti S, et al. Defining therapy goals for major molecular remission in chronic myeloid leukemia: results of the randomized CML Study IV. Leukemia. 2018;32:1222–8.
- 12. Thompson PA, Kantarjian H, Cortes JE. Diagnosis and treatment of chronic myeloid leukemia (CML) in 2015. Mayo Clin Proc. 2015;90(10):1440–54.
- Fava C, Rege-Cambrin G, Dogliotti I, Gottardi E, Berchialla P, di Gioacchino B, et al. Early BCR-ABL1 reduction is predictive of better event-free survival in patients with newly diagnosed chronic myeloid leukemia treated with any tyrosine kinase inhibitor. Clin Lymphoma Myeloma Leuk. 2016;16(Suppl):S96–100.
- Hughes T. New and advanced monitoring techniques and their costs. In: CML advocacy: learn, share, grow. 3–5 May 2013, Prague, Czech Republic. Bern: CML Advocates Network for Chronic Myeloid Leukemia Patient Group Advocates; 2013 (https://www.cm ladvocates.net/download/ cml-horizons-conferences/cml-horizons-2013/presentations/343-hughes-new-and-advancedcmlmonitoring-techniques-and-their-costs/file).
- Li N, Zheng B, Cai HF, Yang J, Luo XF, Weng LZ, et al. Cost effectiveness of imatinib, dasatinib, and nilotinib as first-line treatment for chronic-phase chronic myeloid leukemia in China. Clin Drug Investig. 2018;38(1):79–86.
- Dalziel K, Round A, Stein K, Garside R, Price A. Effectiveness and cost–effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. Health Technol Assess. 2004;8(28):iii.
- 17. Padula WV, Larson RA, Dusetzina SB, Apperley JF, Hehlmann R, Baccarani M, et al. Cost-effectiveness of tyrosine kinase inhibitor treatment strategies for chronic myeloid leukemia in chronic phase after generic entry of imatinib in the United States. J Natl Cancer Inst. 2016;108(7):djw003.

Essential panel of antibodies for flow cytometry for leukaemia

Test description Essential panel of antibodies for flow cytometry in the diagnosis of leukaemia

Addition, change or deletion Addition

Proposed test purpose

In the diagnosis of acute leukaemias and definition of prognostic and predictive features

Applicant organization(s) World Health Organization

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Disease condition and impact on patients: Acute leukaemia is fatal if not diagnosed and treated rapidly. It represents a heterogeneous group of malignancies, with different clinical, morphological, immunophenotypic and genetic features.

Does the test meet a medical need? Differentiation of acute and chronic leukaemia, the myeloid and lymphoid lineages and specific subtypes is essential for choosing the correct treatment, as is exclusion of non-neoplastic haematological disease (e.g. leukaemoid reaction in systemic inflammatory processes). In ALL, classification of aggressiveness allows risk-adapted curative treatment. Immunophenotyping by flow cytometry is a rapid, reliable method for diagnosing, assessing prognosis and deciding on targeted therapy and follow-up for leukaemia (1-4). According to the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (5), diagnosis of leukaemia requires a precise morphological evaluation, with appropriate flow cytometry immunophenotyping and cytogenetic and molecular genetic testing (6). Another application of cytometry in the management of patients with leukaemia is in follow-up and monitoring of minimal residual disease, i.e. the leukaemic population that is undetectable morphologically.

How the test is used: The panel is intended for laboratory use in qualitative identification of antigens by flow cytometry. It contains the minimum number of markers necessary to classify leukaemia at diagnosis and for follow-up, as

reviewed by experts (5, 6). The markers should be considered a starting-point for diagnosis of leukaemia, upon which future applications could be built to monitor the response to therapy and diagnosis of haematological cancers other than acute leukaemias.

Public health relevance

According to IARC, about 440 000 new cases of leukaemia were diagnosed in 2018, with a mortality of more than 300 000. The prevalence of leukaemia was 1 174 433 globally, suggesting that many patients survive this disease.

Socioeconomic impact: Childhood leukaemia accounts for 25% of all childhood malignancies. It is curable with inexpensive essential antineoplastic medicines. In certain LMICs, the prognosis of leukaemia may be as poor as 20% at 5 years, far lower than that in higher-income settings, where > 95% of affected children survive (*7*, *8*).

WHO or other clinical guidelines relevant to the test

IARC guidelines on diagnostic criteria for myeloproliferative neoplasms (9) and the WHO priority list of medical devices for cancer management (10).

Basic test characteristics

Essential panel of antibodies, including the following markers: (10 unique items among 12 components for four-colour fluorochrome cytometry) CD10, CD19, CD45, CD34; CD7, CD33, CD45, CD117; myeloperoxidase, CD79a, CD45, cytoplasmic CD3.

Test purpose	In the diagnosis of acute leukaemias and definition of prognostic and predictive features
Test format	Flow cytometry
Specimen types	Bone marrow, peripheral blood, body fluid, tissue or lymph node cytology
Equipment required	Flow cytometer
Regulatory status	Diagnosis with monoclonal antibodies is recognized by regulatory bodies.
Global availability	Not stated
Price per test range	Not stated
Instrument price range	Not stated

Evidence for clinical usefulness and impact

Flow cytometry is widely used for immunophenotyping blood and leukaemia cells, as it allows quantification of antigen expression, rapid analysis of large numbers of cells and determination of DNA content (7, 8). Flow cytometry can be used to detect one leukaemic cell among 10 000 normal cells and to differentiate between neoplastic and non-neoplastic regenerating blasts (for example as an effect of antineoplastic chemotherapy or other toxic myelosuppression) in assessment of the risk of relapse (11, 12). Use of flow cytometry for characterizing the immunophenotype of leukaemia cells is recommended by the principal scientific societies for adult and paediatric haematological malignancies (the European Society for Medical Oncology, the European Leukaemia Net, the International Society of Paediatric Oncology, the American Society of Hematology and the US National Comprehensive Cancer Network). According to the WHO Classification of tumours of haematopoietic and lymphoid tissues (9), diagnosis of leukaemia requires a precise morphological evaluation, with appropriate use of flow cytometry immunophenotyping and cytogenetic and molecular genetic testing (13).

Evidence for economic impact and/or cost-effectiveness

Stratification of patients by risk according to characterization of the leukaemia subtype and prognostic class ensures cost–effective treatment (*14*). In particular, patients with ALL who have a favourable prognosis might be spared treatment intensification or bone-marrow transplantation. Flow cytometry with a simplified panel as proposed in this application is also cost–effective when used locally or in a centralized site in resource-limited settings (*9*).

Flow cytometry requires laboratory technicians trained in incubation and staining and a pathologist and/or a laboratory scientist trained to interpret the results.

Ethics, equity and human rights issues

Consent is required to obtain a sample. Flow cytometry is often not available in countries with limited resources, although it is commonly available for diagnosis of HIV infection. Cancers are therefore not diagnosed, or patients are not stratified according to risk of relapse, which ensures safe, cost–effective use of treatment (2, 5).

Since chemotherapy became available, about 98% of children with ALL go into remission within weeks of starting treatment, and 90% are in remission after 10 years. In LMICs, however, survival may be only 20–50% at 10 years because of late referral to care and lack of diagnostics, cytotoxic treatment and supportive care.

SAGE IVD evidence review

Evidence was provided on the accuracy of flow cytometry for the purposes listed, was limited. The disease classes that they cause are the basis for choosing therapy, and it is anticipated that there are RCTs that show the benefits of various treatments for different subtypes of disease, thus providing evidence for the usefulness of this test.

SAGE IVD considerations for recommendations

A diagnosis of acute leukaemia requires immunophenotyping, and this panel will simplify diagnosis in countries with minimal skilled staff and pathologists. For the diagnosis and management of acute leukaemia in LMICs, where limited treatment is available, it is essential to make the basic distinction between acute myeloid leukaemia and ALL, and ALL must be further classified into B or T cell, as the management differs. Although this is a basic panel, it will be invaluable for LMICs.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended conditional inclusion on the EDL of the proposed essential panel of antibodies for flow cytometry for differentiation of leukaemia subtypes, pending submission of additional evidence of use in LMICs that lack highly skilled laboratory staff.

The Group requested submission of more evidence on clinical use of the test and use of the panel in a wider range of countries and regions.

Recommended test purpose

As an aid in the diagnosis of acute leukaemias.

- 1. Gajendra S. Flow cytometry in acute leukemia. Clinics Oncol. 2016;1:1166.
- 2. Webber BA, Cushing MM, Li S. Prognostic significance of flow cytometric immunophenotyping in acute myeloid leukemia. Int J Clin Exp Pathol. 2008;1(2):124–33.
- 3. Lee EJ, Yang J, Leavitt RD, Testa JR, Civin CI, Forrest A, et al. The significance of CD34 and TdT determinations in patients with untreated de novo acute myeloid leukemia. Leukemia. 1992;6(11):1203–9.
- Kita K, Miwa H, Nakase K, Kawakami K, Kobayashi T, Shirakawa S, et al. Clinical importance of CD7 expression in acute myelocytic leukemia. The Japan Cooperative Group of Leukemia/Lymphoma. Blood. 1993;81(9):2399–405.
- Howard SC, Campana D, Coustan-Smith E, Antillon FG, Bonilla M, Fu L, Pui CH, Ribeiro RC, Wilimas JA, Lorenzana R. Development of a regional flow cytometry center for diagnosis of childhood leukemia in Central America. Leukemia. 2005;19:323–5.

- 6. Campana D, Behm FG. Immunophenotyping of leukemia. J Immunol Meth. 2000;243(1–2):59–75.
- Howard SC, Zaidi A, Cao X, Weil O, Bey P, Patte C, et al. The My Child Matters programme: effect of public-private partnerships on paediatric cancer care in low-income and middle-income countries. Lancet Oncol. 2018;19(5):e252–61.
- 8. Lam CG, Howard SC, Bouffet E, Pritchard-Jones K. Science and health for all children with cancer. Science 2019.
- Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, editors. WHO classification of tumours of haematopoietic and lymphoid tissues, fourth edition (WHO classification of tumours, Volume 2; IARC WHO classification of tumours, No. 2). Lyon: International Agency for Research on Cancer; 2008 (http://publications.iarc.fr/Book-And-Report-Series/Who-larc-Classification-Of-Tumours/Who-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017, accessed May 2019).
- Priority medical devices for cancer management (WHO medical device technical series). Geneva: World Health Organization; 2017 (http://www.who.int/medical_devices/publications/priority_ med_dev_cancer_management/en/, accessed May 2019).
- 11. Basso G, Buldini B, De Zen L, Orfao A. New methodologic approaches for immunophenotyping acute leukemias. Haematologica. 2001;86(7):675–92.
- 12. Behm FG. Diagnosis of childhood acute myeloid leukemia. Clin Lab Med. 1999;19:187–237.
- van Dongen JJ, van der Velden VH, Brüggemann M, Orfao A. Minimal residual disease diagnostics in acute lymphoblastic leukemia: need for sensitive, fast, and standardized technologies. Blood. 2015;125(26):3996–4009.
- 14. Chatterjee T, Somasundaram V. Flow cytometric detection of minimal residual disease in B-lineage acute lymphoblastic leukemia by using "MRD lite" panel. Med J Armed Forces India. 2017;73(1):54–7.
- 15. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.
- 16. Bonilla M, Moreno N, Marina N, deReyes G, Shurtleff SA, Downing JR, et al. Acute lymphoblastic leukemia in a developing country: preliminary results of a nonrandomized clinical trial in El Salvador. J Pediatr Hematol Oncol. 2000;22(6):495–501.

Faecal immunochemical test (FIT) for screening for colorectal cancer

Test category

FIT

Addition, change or deletion Addition

Proposed test purpose Screening and diagnosis of colorectal cancer

Applicant organization(s) World Health Organization

66

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Disease condition and impact on patients: Colorectal cancer is the fourth most common cancer worldwide and the third most common cause of death, with 1.8 million and 880 000 new cases, in 2018 (1, 2).

Does the test meet a medical need? About one in three middle-income countries and two of three low-income countries do not have basic diagnostic capacity for cancer. It is estimated that 5–30% of cancer cases are not diagnosed because of lack of diagnostic capacity. These significant testing gaps have major public health consequences.

How this test is used: FIT is generally considered easy to use, and Cancer Care Ontario reported that the newly designed collection device reduces the contact people have with their stool when collecting it, increasing the acceptability (3).

Public health relevance

Prevalence: Colorectal cancer is the fourth most common cancer worldwide and the third most common cause of death, with 1.8 million and 880 000 new cases, in 2018 (1, 2).

Socioeconomic impact: A "mandate of acceptability" has been launched to acknowledge the importance of easy-to-use, wordless instructions for devices for rural, vulnerable and disadvantaged populations (4–6).

WHO or other clinical guidelines relevant to the test

WHO recommends use of FIT for early detection of colorectal cancer in screening programmes (7). IARC has endorsed the use of stool-based tests for population screening of colorectal cancer on the basis of systematic reviews of the literature (8).

Test purpose (brief)	Screening and diagnosis of colorectal cancer
Test format	immunoassay (including ELISA)
Specimen types	Stool
Equipment required	Simple, hand-held

Basic test characteristics

Regulatory status	Method WHO endorsed
Global availability	Broad
Price per test range	According to the manufacturer, the price of one kit to the US public is US\$ 25. The cost per person ranges from \pounds 25 to \pounds 62 (US\$ 33–81) in England. The test is sold at 1179 rands (US\$ 70) in South Africa and US\$ 60 in India.

Table continued

Evidence for clinical usefulness and impact

FIT is essential for early detection of colorectal cancer in screening programmes (7). Use of FIT for colorectal cancer screening is associated with a reduction in cancer-related mortality of 10-40% (2). In a large population-based study in Taiwan (China), 1 160 895 people aged 50–69 years were screened with one to three rounds of FIT and compared with an unscreened group. After a maximum follow-up of 6 years, a 10% decrease in colorectal cancer mortality was seen in the screened population (9). A study in Italy showed a 10% decrease in cumulative incidence and a 27% decrease in mortality (10). Extrapolation from a modelling analysis showed that the number of life-years gained with use of FIT was comparable to that with colonoscopy every 10 years (11).

Evidence for economic impact and/or cost-effectiveness

An IARC working group compared guaiac- and FIT-based screening programmes and found various levels of potential harm and benefit (8). All the tests for occult blood in stool increased QALYs as compared with no screening. The more sensitive tests are more expensive. Smith et al. (12) analysed the costeffectiveness of management of a screening programme, identifying patients, FIT kits and their processing and diagnostic colonoscopy after a positive FIT. The cost per person was US\$ 33–92, whereas the cost–effectiveness for an additional advanced neoplasia detected was US\$ 11 198–28 389. The number of cancers avoided per 1000 screens was estimated to be 1.46–4.86. In a microsimulation model, Lansdorp-Vogelaar et al. (13) showed that biennial FIT screening of people aged 55–75 years provided 84.9 life-years gained at a cost of US \$137 000 per 1000 participants, which was considered to be cost–effective as compared with no screening. Screening for colorectal cancer with FIT, gFOBT or colonoscopy resulted in a return on investment.

The FIT system is automated and does not require highly skilled laboratory operators or special training, and the samples can be collected by patients at home. Education for sample collection is the responsibility of general practitioners as part of awareness of early diagnosis of cancer. A FIT programme must, however, be part a wider programme of screening for colorectal cancer, including estimates of the workforce (gastroenterologists) and devices (colonoscopes) necessary for secondary and tertiary care and an appropriate oncology surgery service integrated into a multidisciplinary environment. FIT screening can be managed in primary care settings, the general practitioner informing and referring patients screened as positive for endoscopic assessment of the causes of occult bleeding, tracking the results and informing patients about subsequent diagnostic and therapeutic steps. Post-test counselling by a general practitioner is important to ensure adherence to the follow-up diagnosis and treatment.

Ethics, equity and human rights issues

Consent is required to obtain a faecal sample. FIT has been denoted by WHO as a priority medical device for cancer management (7) as a diagnostic and screening test for occult gastrointestinal causes of bleeding, including colorectal cancer and curable pre-cancerous conditions such as polyps. Ensuring access as part of UHC is an ethical issue. In a screening programme for colorectal cancer based on FIT, a referral pathway must be ensured for high-risk patients who screen positive to ascertain the nature of the disease, rapidly resect any cancer or pre-cancerous lesion and prevent malignant transformation of high-risk colorectal adenomas.

The acceptability of the test has been acknowledged to ensure comprehension by the entire population, including low-literacy and tribal groups, and acceptance of a colorectal cancer diagnosis. Easy-to-deliver screening methods generally reach a large proportion of the population at primary care level.

SAGE IVD evidence review

The evidence for the impact on mortality of FIT testing in colon cancer screening programmes is derived from observational studies (8) and not RCTs. Primary studies of the accuracy of FIT as compared to gFOBT, however, indicate equivalent or better accuracy, although no systematic review of these studies has been published.

SAGE IVD considerations for recommendation

Given the strong evidence from RCTs of the benefits of gFOBT in screening programmes and the emerging evidence of the benefits of FIT over gFOBT, the Group considered that the evidence is strong enough to include FIT on the EDL.

SAGE IVD recommendation, with rationale

SAGE IVD recommended addition of FIT to the EDL, noting the strong evidence that it clinically supports diagnosis, resulting in reduced mortality from colorectal

cancer. SAGE further recommended that a systematic review of studies comparing FIT with gFOBT be undertaken.

Recommended test purpose Screening of colorectal cancer

References

- 1. Cancer tomorrow. Lyon: International Agency for Research on Cancer; 2019 (http://gco.iarc.fr/ tomorrow/home, accessed May 2019).
- 2. Cancer key facts. Geneva: World Health organization; 2018 (http://www.who.int/news-room/fact-sheets/detail/cancer, accessed May 2019).
- Transition to fecal immunochemical testing (FIT). Frequently asked questions for primary care providers. Toronto: Cancer Care Ontario; 2017 (https://archive.cancercare.on.ca/common/pages/ UserFile.aspx?fileId=381441, accessed April 2019).
- Allison JE, Fraser CG, Halloran SP, Young GP. Population screening for colorectal cancer means getting FIT: the past, present, and future of colorectal cancer screening using the fecal immunochemical test for hemoglobin (FIT). Gut Liver. 2014;8(2):117–30.
- 5. Pham R, Cross S, Fernandez B, Corson K, Dillon K, Yackley C, et al. "Finding the right FIT": rural patient preferences for fecal immunochemical test (FIT) characteristics. J Am Board Fam Med. 2017;30(5):632–44.
- 6. Coronado GD Sanchez J, Petrik A, Kapka T, DeVoe J, Green B. Advantages of wordless instructions on how to complete a fecal immunochemical test: lessons from patient advisory council members of a federally qualified health center. J Canc Educ. 2013;29(1):86–90.
- WHO list of priority medical devices for cancer management (WHO medical device technical series). Geneva: World Health Organization; 2017 (http://www.who.int/medical_devices/ publications/priority_med_dev_cancer_management/en/, accessed April 2019).
- Lauby-Secretan B, Vilahur N, Bianchini F, Guha N, Straif K for the International Agency for Research on Cancer Handbook Working Group. The IARC perspective on colorectal cancer screening. N England J Med. 2018;378:1734–40.
- 9. Chiu HM, Chen SL, Yen AM, Chiu SY, Fann JC, Lee YC, et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. Cancer. 2015;121:3221–9.
- Giorgi Rossi P, Vicentini M, Sacchettini C, Di Felice E, Caroli S, Ferrari F, et al. Impact of screening program on incidence of colorectal cancer: a cohort study in Italy. Am J Gastroenterol. 2015;110(9):1359–66.
- 11. Zauber AG, Lansdorp-Vogelaar I, Knudsen L, Wilschut J, van Ballegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the US Preventive Services Task Force. Ann Intern Med. 2008;149:659–69.
- 12. Smith DH, O'Keeffe Rosetti M, Mosen DM, Rosales AG, Keast E, Perrin N, et al. Balancing adherence and expense: the cost–effectiveness of two-sample vs one-sample fecal immunochemical test. Popul Health Manag. 2019;22(1):83–9.
- 13. Lansdorp-Vogelaar I, Goede SL, Bosch LJW, Melotte V, Carvalho B, van Engeland M, et al. Costeffectiveness of high-performance biomarker tests vs fecal immunochemical test for noninvasive colorectal cancer screening. Clin Gastroenterol Hepatol. 2018;16(4):504–12.

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Guaiac faecal occult blood test

Test category Guaiac faecal occult blood test (gFOBT)

Addition, change or deletion Addition

Proposed test purpose Screening and diagnosis of colorectal cancer

Applicant organization(s) World Health Organization

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Disease condition and impact on patients: Colorectal cancer is the fourth most common cancer worldwide and the third most common cause of death, with 1.8 million new cases and 880 000 deaths, respectively, in 2018 (1, 2).

Does this test meet a medical need? About one in three middle-income countries and two in three low-income countries do not have basic diagnostic capacity for cancer. It is estimated that 5–30% of cancer cases are not diagnosed because of lack of diagnostic capacity. These significant testing gaps have major public health consequences. Delayed diagnosis and treatment of colorectal cancer are associated with more advanced stages at presentation, resulting in higher mortality and disability for patients and higher costs and use of health systems.

How the test is used: The test is intended to be used at home. It is generally considered easy to use and acceptable, as the sample of stool is collected with a plastic device.

Public health relevance

Prevalence: Colorectal cancer is the fourth most common cancer worldwide and the third most common cause of death, with 1.8 million and 880 000 new cases in 2018 (1, 2).

Socioeconomic impact: A "mandate of acceptability" has been launched to acknowledge the importance of easy-to-use, wordless instructions for devices for rural, vulnerable and disadvantaged populations (4-6).

WHO or other clinical guidelines relevant to the test

WHO has issued guidance on selecting priority medical devices for cancer management (3) and lists the test for screening for colorectal cancer. IARC has endorsed use of stool-based tests for population screening for colorectal cancer on the basis of reviews of the literature (7).

Test purpose	Screening and diagnosis of colorectal cancer
Test format	Hydrogen peroxide developer
Specimen types	Stool
Equipment required	Simple, hand-held
Regulatory status	Method endorsed by WHO
Global availability	Broad
Price per test range	US\$ 5–20
Instrument price range	Not available

Basic test characteristics

Evidence for clinical usefulness and impact

In a pooled estimate (4) of the reduction in mortality from colorectal cancer from data obtained in four studies (5, 6, 8, 9) with a combined sample of 313 180 people screened with the gFOBT, the reduction was 18% over a median follow-up of 18.25 years. The number of screens required to prevent one death from colorectal cancer was 377, and the relative reduction in mortality for biennial screening was 13%. The trials were conducted among asymptomatic patients at average risk for colorectal cancer. In the Minnesota Colon Cancer Control Study, > 46 000 participants were randomized to screening with gFOBT annually or biennially or no screening. Cumulative mortality from colorectal cancer per 1000 people evaluated up to 13 years was 5.88 in the group screened annually and 8.83 in the unscreened group, and the difference was statistically significant (10). gFOBT tests are recommended for screening for colorectal cancer by IARC (7), the American Cancer Society, the Multi-society Task Force on Colorectal Cancer in the USA, the American College of Radiology, the US Preventive Services Task Force, the American College of Physicians, the American College of Gastroenterology and the National Comprehensive Cancer Network in the

USA and acknowledged by the US Centers for Disease Control and Prevention. The recommendation of the US Preventive Services Task Force and the National Comprehensive Cancer Network is "grade A", and that of the American Cancer Society is "qualified". According to IARC, gFOBT is the only test that results in a reduction in mortality in RCTs; most of the findings for other tests are from observational studies of screening, with highly consistent results (*10*). Higher sensitivity is obtained with gFOBT screening every 1 or 2 years, as recommended by IARC on the basis of the results of two RCTs, two large cohort studies with up to 11 screening rounds and one case–control study (*10*).

Evidence for economic impact and/or cost-effectiveness

An IARC working group that compared guaiac- and FIT-based screening programmes found various levels of potential harm and benefit (10). All the tests for occult blood in stool increased the number of QALYs as compared with no screening. The more sensitive tests are more expensive. gFOBT was also compared with FIT in an analysis of the NHS Bowel Cancer Screening Programme in England (11), in which FIT was found to be more cost–effective, and in a metanalysis of studies of cost-effectiveness (12). Screening as compared with no screening resulted in 0.16 life-year gained in the population eligible for screening and 0.006 life-year gained in the general population. The cost saved per life-year gained with annual gFOBT testing was > US\$ 56 000. In comparison, for FIT, the per-person cost was US\$ 33–92, and the cost-effectiveness was US\$ 11 198-28 389 for an additional advanced neoplasm detected, with an estimated 1.46-4.86 cancers avoided per 1000 screens (13). In a microsimulation model, Lansdorp-Vogelaar et al. (14) showed that biennial FIT screening of people aged 55-75 years resulted in 84.9 life-years gained at a cost of US\$ 137 000 per 1000 participants, which was considered to be cost-effective.

Screening for colorectal cancer with gFOBT, FIT or colonoscopy also results in a return on investment in prevention. gFOBT does not required highly skilled laboratory operators, and samples are collected by patients, commonly at home. Education in sampling is the responsibility of general practitioners as part of awareness of early diagnosis of cancer. A gFOBT programme must, however, be part a wider programme of screening for colorectal cancer, including estimates of the workforce (gastroenterologists) and devices (colonoscopes) necessary for secondary and tertiary care and an appropriate oncology surgery service integrated into a multidisciplinary environment. gFOBT screening can be managed in primary care settings, the general practitioner informing and referring patients screened positive for endoscopic assessment of the causes of occult bleeding, tracking the results and timely informing patients about subsequent diagnostic and therapeutic steps.

Ethics, equity and human rights issues

Consent is required to obtain a faecal sample. Occult blood detection tests must be accompanied by a timely referral pathway for endoscopy for patients who screen positive. Patients must be well counselled and informed about the possibility that the reliability of the test might be altered by some food and medications (e.g. chronic use of anti-platelet drugs).

A test that can be used at home or in primary care settings for early diagnosis of cancer will more readily extend coverage, including populations in remote and underserved areas, for whom referral to specialized facilities for screening may be difficult. Introduction of any screening programme into a health system must, however, be in accordance with the priorities and the performance of the system at the time and the capacity and the impact on the population.

The acceptability of the test has been acknowledged to ensure comprehension by the entire population, including low-literacy and tribal groups, and acceptance of a colorectal cancer diagnosis. Easy-to-deliver screening methods generally reach a large proportion of the population at primary care level.

SAGE IVD evidence review

There is strong evidence from RCTs that screening with gFOBT, followed by colonoscopy if the test is positive, reduces mortality below the rate without screening. The evidence is summarized in a Cochrane review (last updated in 2010) of four RCTs. However, the accuracy of gFOBT, summarized in a systematic review in 2010, was moderate (*15*), as occult blood was detected in only about 50% of cases, with a specificity of 80%. FIT appears to be more accurate than gFOBT and is thus likely to be the preferred screening test.

SAGE IVD considerations for recommendation

There is evidence that screening for colorectal cancer with gFOBT, followed by colonoscopy if positive, reduces mortality. The SAGE expressed concern over the positive predictive value of gFOBT in these screening programmes (the number of individuals who required unnecessary colonoscopy) or the numbers of missed cases. The evidence suggests that the FIT is likely to be the better test.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended rejection of the submission for inclusion of the gFOBT on the EDL.

The Group noted that the gFOBT is not specific for human haemoglobin, resulting in false-positive results (avoidance of consumption of red meat for the days prior to testing is required). The test may be used in settings in which FIT is not available. Some concern was raised about the stability of FIT in settings

with high ambient temperatures, and more evidence from those areas should be obtained. SAGE IVD requested evidence for the usefulness of this test in screening programmes when a FIT is not available.

- 1. Cancer. Geneva: World Health Organization; 2019 (http://www.who.int/news-room/fact-sheets/ detail/cancer, accessed May 2019).
- 2. Cancer tomorrow. Lyon: International Agency for Research on Cancer; 2019 (http://gco.iarc.fr/ tomorrow/home, accessed May 2019).
- WHO list of priority medical devices for cancer management (WHO medical device technical series). Geneva: World Health Organization; 2017 (http://www.who.int/medical_devices/ publications/priority_med_dev_cancer_management/en/, accessed April 2019).
- 4. Fitzpatrick-Lewis D, Ali MU, Warren R, Kenny M, Sherifali D, Raina P. Screening for colorectal cancer: a systematic review and meta-analysis. Clin Colorectal Cancer. 2016;15(4):298–313.
- Kronborg O, Jørgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol. 2004;39(9):846–51.
- 6. Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. Br J Surg. 2008;95(8):1029–36.
- 7. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut. 2012;61(7):1036–40.
- Lauby-Secretan B, Vilahur N, Bianchini F, Guha N, Straif K for the International Agency for Research on Cancer Handbook Working Group. The IARC perspective on colorectal cancer screening. N Engl J Med. 2018;378:1734–40.
- 9. Shaukat A, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS, et al. Long-term mortality after screening for colorectal cancer. N Engl J Med. 2013;369(12):1106–14.
- Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993;328(19):1365–71.
- 11. Colorectal cancer screening. IARC Handbooks of Cancer Prevention, Vol. 17. Lyon: International Agency for Research on Cancer; 2018.
- Murphy J, Halloran S, Gray A. Cost-effectiveness of the faecal immunochemical test at a range of positivity thresholds compared with the guaiac faecal occult blood test in the NHS Bowel Cancer Screening Programme in England. BMJ Open. 2017;7(10):e017186.
- 13. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. Epidemiol Rev. 2011;33(1):88–100.
- 14. Smith DH, O'Keeffe Rosetti M, Mosen DM, Rosales AG, Keast E, Perrin N, et al. Balancing adherence and expense: the cost–effectiveness of two-sample vs one-sample fecal immunochemical test. Popul Health Manag. 2018;22(1):83–9.
- 15. Lansdorp-Vogelaar I, Goede SL, Bosch LJW, Melotte V, Carvalho B, van Engeland M, et al. Costeffectiveness of high-performance biomarker tests vs fecal immunochemical test for noninvasive colorectal cancer screening. Clin Gastroenterol Hepatol. 2018;16(4):504–12.
- Zhu MM, Xu XT, Nie F, Tong JL, Xiao SD, Ra ZH. Comparison of immunochemical and guaiac-based fecal occult blood test in screening and surveillance for advanced colorectal neoplasms: a metaanalysis. J Dig Dis. 2010;11:148–60.

Human chorionic gonadotrophin plus β -human chorionic gonadotrophin immunoassay to aid in the diagnosis of and surveillance for germ-cell tumours and gestational trophoblastic disease

Test description

Quantitative determination of the sum of hCG plus β -hCG in an ECLIA

Addition, change or deletion Addition

Proposed test purpose

For the diagnosis, prognostication and monitoring of germ-cell tumours and gestational trophoblastic disease

Applicant organization(s) World Health Organization

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Disease condition and impact on patients: Germ-cell malignancies (testicular, ovarian, non-genital midline and unknown primary germ-cell tumours) and trophoblastic disease are highly curable. They arise more commonly in younger patients, including during pregnancy (gestational trophoblastic disease), which is associated with high potential economic loss for countries. The use of hCG for monitoring and prognosis of germ-cell tumours and gestational trophoblastic disease is recommended by established, recognized professional society guidelines (1, 2). Some non-gestational malignancies express genes for the β subunit of hCG, resulting in activation and production of low levels of hyperglycosylated free β subunit, which may become a useful marker or prognostic factor for these tumours (3). Gestational trophoblastic neoplasia may have cytotrophoblasts that produce hyperhydroxylated hCG.

Does this test meet a medical need? Use of hCG for monitoring and prognosis is recommended by the guidelines of established professional societies for germ-cell tumours (testicular, ovarian, non-genital midline and unknow primary) and gestational trophoblastic disease (4–6). hCG has been used to determine the prognosis of germ-cell tumours to classify risk in advanced tumours (7) and in

monitoring the response of non-seminomatous germ-cell tumours to anticipate resistance to platinum-based regimens and to intensify treatment (8, 9).

How this test is used: For monitoring and prognosis of germ-cell tumours and diagnosis, prognosis and monitoring of gestational trophoblastic disease.

Public health relevance

Prevalence: Testicular cancer is diagnosed in approximately 9600 men each year in the USA, but only approximately 400 men die of their disease (4.2%). According to IARC (1), in 2018 in LMICs, 11 290 new cases of testicular cancer were reported, with 3984 deaths (35.3%). Testicular cancer is the diagnosed mainly young males. The global prevalence is 284 073 cases.

Socioeconomic impact: Germ-cell tumours arise mainly in young people; timely access to treatment, surgery, chemotherapy and radiotherapy can substantially increase survival when delivered with curative intention at all the stages of disease. According to IARC (1), testicular cancer is diagnosed mainly in men aged 20-34 years. Disparities in survival from testicular cancer have been described, with a large gap between high-income countries (mortality to incidence ratio: 0.03) and LMICs (0.17).

WHO or other clinical guidelines relevant to the test

WHO guidelines list β -hCG for prognosis and response to treatment (3, 4).

Test purpose	In diagnosis, prognostication and monitoring germ-cell tumours and trophoblastic disease.
Test format	Immunoassay
Specimen types	Plasma
Equipment required	Basic, automated
Global availability	Broad
Price per test range	Not available
Instrument price range	Not available

Basic test characteristics

Evidence for clinical usefulness and impact

The prognostic role of hCG in germ-cell tumours has been demonstrated for classifying the risk of advanced tumours (7) and for monitoring the response

of non-seminomatous germ-cell tumours to anticipate platinum resistance and intensify the treatment in a personalized approach (8, 9).

Evidence for economic impact and/or cost-effectiveness

No relevant comparative studies of cost or cost-effectiveness were identified. Assessment of hCG in blood samples does not require highly specialized laboratory personnel and is considered a standard laboratory biochemical analysis.

Ethics, equity and human rights issues

Consent is required to obtain a plasma sample. Use of hCG for monitoring germ-cell tumours, which are generally diagnosed in young patients, permits classification of risk for advanced disease that is still amenable to curative treatment in a high percentage of cases and adaptation of treatment according to risk. The availability of hCG testing allows accurate cancer treatment and prognostication of cancers and can also avoid over-treatment. hCG is also associated with better prediction of resistance to treatment, allowing a timely change of cytotoxic regimen.

SAGE IVD evidence summary

Guideline recommendations for using the sum of hCG and β -hCG for the diagnosis and surveillance of germ-cell tumours and gestational trophoblastic disease are clear. Evidence from trials was provided that showed that tailoring chemotherapy for the treatment of germ-cell tumours with an unfavourable decrease in tumour markers (based in part on hCG assessment) was beneficial and prognostic (8).

SAGE IVD considerations for recommendation

Use of hCG for monitoring germ-cell tumours, which are generally diagnosed in young patients, permits classification of risk for advanced disease while it is still amenable to curative treatment and to adapt the treatment according to the level of hCG detected. The availability of hCG testing allows accurate treatment and prognosis of cancers, prescription of treatments listed in the WHO EML and avoidance of over-treatment. Moreover, the kinetics of hCG is associated with better prediction of resistance to treatment, as a basis for a timely change of the cytotoxic regimen.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended conditional inclusion on the EDL of the test for the sum of hCG and β -hCG for the diagnosis and surveillance of germ-cell

tumours and gestational trophoblastic disease, and requested submission of more evidence of reference ranges for the general population of men and women in the countries and ethnic population in which the test will be used. The group proposed that proficiency testing or an external quality assurance programme be introduced to ensure local performance of the assay.

Recommended test purpose

As an aid in the diagnosis and surveillance for germ-cell tumours and gestational trophoblastic disease

- 1. Tavassoli FA, Devilee P, editors. Pathology and genetics of tumours of the breast and female genital organs (WHO classification of tumours, 3rd Edition), Vol. 4, Chapter 2. Germ cell tumours. Lyon: International Agency for Research on Cancer; 2003.
- Honecker F, Aparicio J, Berney D, Beyer J, Bokemeyer C, Cathomas R, et al. ESMO 2018 Consensus Conference guidelines on testicular germ-cell cancer: diagnosis, treatment and follow-up. Ann Oncol. 2018;29:1658–86.
- 3. Acevedo HF, Tong JY, Hartsock RJ. Human chorionic gonadotropin-beta subunit gene expression in cultured human fetal and cancer cells of different types and origins. Cancer 1995;76:1467.
- 4. Testicular cancer, version 2018. Fort Washington (PA): National Comprehensive Cancer Network; 2018.
- 5. Clinical guidelines for the management of testicular cancer. Arnhem: European Association of Urology; 2018 (https://uroweb.org/guideline/testicular-cancer/, accessed August 2019).
- 6. Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L, Sessa C. Gestational trophoblastic disease. ESMO clinical practice guidelines. Ann Oncol. 2013;24(Suppl 6):vi39–50.
- International Germ Cell Collaborative Group. International germ cell consensus classification: a prognostic factor-based staging system for metastatic germ-cell tumours. J Clin Oncol. 1997;15(2):594–603.
- Fizazi K, Pagliaro L, Laplanche A, Fléchon A, Mardiak J, Geoffrois L. et al. hCG has a relevant role in monitoring for treatment effectiveness and tailoring chemotherapy according to tumour marker decline in poor prognosis germ-cell tumours (GETUG 13): a phase 3, multicentre, randomised trial. Lancet Oncol. 2014;15(13):1442–50.
- Fizazi K, Flechon A, Le Teuff G, Mardiak J, Pagliaro LC, Geoffrois L, et al. Mature results of the GETUG 13 phase III trial in poor-prognosis germ-cell tumors (GCT). J Clin Oncol. 2016;34 (Suppl):abstract 4504.
- Ferraro S, Trevisol C, Gion M, Panteghini, M. Review: Human Chorionic Gonadotropin Assays for Testicular Tumors: Closing the Gap between Clinical and Laboratory Practice. J. Clin. Chem. 2018; 64(2): 270-278.

Human epidermal growth factor receptor 2 (HER2) or tyrosine-protein kinase receptor (erbB-2) or overexpression: immunohistochemical tests to aid in diagnosis, prognosis and treatment of breast cancer

Test category

Immunohistochemistry for evaluation of overexpression of human epidermal growth factor receptor 2 (HER2) or the tyrosine–protein kinase erbB-2 receptor

Addition, change or deletion Addition

Proposed test purpose

To define prognostic and predictive features of breast cancer and for breast cancer diagnosis, prognosis and treatment

Applicant organization(s) World Health Organization

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Disease condition and impact on patients: Breast cancer is the most prevalent cancer in women and the most frequent cause of death from cancer in women. According to IARC (1), worldwide, about 2.1 million cases of female breast cancer were newly diagnosed in 2018, accounting for almost one in four cancer cases among women. More than 50% of the deaths occur in LMICs.

Does this test meet a medical need? HER2/erbB-2 protein overexpression dictates a worse prognosis and predicts the benefit of trastuzumab, a monoclonal antibody that blocks HER2. Trastuzumab is a valuable medicine for the treatment of this type of breast cancer, particularly in early and locally advanced stages, and is on the WHO EML.

How this test is used: The kit is used to grade HER2 overexpression in neoplastic breast tissue that has been processed and paraffin-embedded routinely for histological evaluation. Testing for HER2 overexpression is required to prescribe trastuzumab.

Public health relevance

Prevalence: HER2 overexpression is found in 15–25% of cases of breast cancer.

Socioeconomic impact: Breast cancer incidence and mortality are major causes of productivity loss. In Europe, breast cancer-related premature mortality was responsible for US\$ 7 billion in losses (2). In a study of women in Brazil, China, India, the Russian Federation and South Africa, the total productivity loss was highest for breast cancer (US\$ 2.1 billion) and cervical cancer (US\$ 1.5 billion) (3). According to IARC (1), only 40% of new cases and 28% of mortality for breast cancer occur in high-income countries. Large disparities in breast cancer survival have also been reported, predominantly related to differences in time of presentation and different insurance schemes, resulting in diverse treatments and follow-up care (4). For instance, the mortality:incidence ratio for breast cancer in women in LMICs is 0.48, while that in high-income settings is 0.17.

WHO or other clinical guidelines relevant to the test

The test is on the WHO Priority list of medical devices for cancer management (5). The prognostic and predictive role of HER2 is described in WHO Classification of tumours of the breast (6).

Test purpose	To define prognostic and predictive features of breast cancer In diagnosis, prognosis and treatment of breast cancer
Test format	Immunohistochemistry
Specimen types	Breast tissue, formalin-fixed, paraffin-embedded
Equipment required	Basic, automated
Global availability	Broad
Price per test range	US\$ 50–100
Instrument price range	US\$ 2000

Basic test characteristics

Evidence for clinical usefulness and impact

Over-expression of HER2 in breast cancer is a recognized risk factor for an increased risk of relapse in resected primary tumours and overall mortality, as shown in both high-income and LMICs (7, 8). In current guidelines for the diagnosis of breast cancer, the HER2 immunochemistry test gives one of three possible scores: no over-expression (0 and 1+), over-expression (3+) or equivocal (2+). In the case of an equivocal score, which is found in 20–25% of cases tested, in-situ hybridization is recommended for confirmation of HER2 status (9); no benefit of trastuzumab has been reported in cases of equivocal tests (2+) with non-amplified HER2. Overexpression of HER2 defines appropriate treatment.

All women with radically resected breast cancer are eligible for adjuvant chemotherapy in combination with an anti-HER2 agent and/or trastuzumab if they have metastases. Trastuzumab is the first approved anti-HER2 agent and is on the 20th WHO EML for use in both early (adjuvant) treatment and for metastatic cancer (palliative use). Biosimilars are undergoing WHO prequalification. The indication is supported by clinical guidelines for breast cancer management (*10-14*). Use of trastuzumab is associated with a significant improvement in overall survival of women with HER2-positive breast cancer (*15, 16*). On the basis of data from the HERA trial (17), the European Society for Medical Oncology evaluated the absolute benefit and safety of trastuzumab as an adjuvant and concluded that it is a priority drug, scoring it "A" (priority medicine) for adjuvant use. The reviewers underlined the critical importance of a test for quality, including an assurance scheme or protocol; ASCO and CAP guidelines for high-quality HER2 testing and assurance were discussed (*18*).

Evidence for economic impact and/or cost-effectiveness

Use of trastuzumab as an adjuvant has been considered cost-effective by the principal health and technology assessment agencies. The cost of trastuzumab per QALY was £ 2387 (US\$ 3122) (19).

Use of the HER2 kit requires a laboratory technician for incubation and staining on an automatic stainer, and a trained pathologist for reading slides and interpreting the results. Immunohistochemistry for HER2 testing is appropriate for most health systems. In-situ hybridization tests require reagents that are significantly more expensive (US\$ 140 versus US\$ 10) and require a longer testing time (36 h versus 4 h) and a longer interpretation time (7 min versus 45 s) (20).

Ethics, equity and human rights issues

Consent is required to obtain a breast tissue sample. Disparities in the accessibility and affordability of trastuzumab have been reported in global surveys, partially related to issues in accessing HER2 testing. Access to HER2 testing should be ensured for patients likely to benefit from trastuzumab (*21*).

SAGE IVD evidence review

There is no reference standard against which to compare immunohistochemistry for evaluation of overexpression of HER2 or the tyrosine–protein kinase erbB-2 receptor. Data from comparisons with other panels show that IHC detects about 70% of samples that are positive by any other method and do not indicate samples as positive that are not positive by any other method. There is strong evidence from trials of the benefit of HER2 testing for stratifying treatments for breast cancer according to HER2 status, which are summarized in the EML.

SAGE IVD considerations for recommendation

HER2 testing is essential for identification of breast cancer that can be treated with trastuzumab, which is on the WHO EML. Use of trastuzumab is associated with significant improvement in overall survival of HER2-positive breast cancer patients.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion of IHC for detecting overexpression of HER2 in patients with breast cancer to ensure appropriate treatment. The Group noted that trastuzumab, an anti-HER2 drug, is on the WHO EML.

The SAGE IVD also recommended that WHO consider submissions for other endocrine diagnostics.

Recommended test purpose

As an aid in the diagnosis, prognosis and treatment of breast cancer.

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clinicians. 2018;68(6):394–424.
- Hanly P, Soerjomataram I, Sharp L. Measuring the societal burden of cancer: the cost of lost productivity due to premature cancer-related mortality in Europe. Int J Cancer. 2015; 136(4):136–45.
- 3. Pearce A, Sharp L, Hanly P, Barchuk A, Bray F, de Camargo Cancela M, et al. Productivity losses due to premature mortality from cancer in Brazil, Russia, India, China, and South Africa (BRICS): a population-based comparison. Cancer Epidemiol. 2018;53:27–34.
- Silber JH, Rosenbaum PR, Ross RN, Reiter JG, Niknam BA, Hill AS, et al. Disparities in breast cancer survival by socioeconomic status despite Medicare and Medicaid insurance. Milbank Q. 2018;96(4):706–54.
- Priority medical devices for cancer management (WHO Medical Device Technical Series). Geneva`: World Health Organization; 2017 (http://www.who.int/medical_devices/publications/priority_ med_dev_cancer_management/en/).
- 6. WHO classification of tumours of the breast. WHO Classification of Tumours, 4th Edition, Volume 4. Geneva: World Health Organization; 2012 (http://publications.iarc.fr/Book-And-Report-Series/ Who-larc-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Breast-2012).
- Mejri N, Boussen H, Labidi S, Benna F, Afrit M, Raha K. Relapse profile of early breast cancer according to immunohistochemical subtypes: guidance for patient's follow up? Ther Adv Med Oncol. 2015;7(3):144–52.
- 8. Katzorke N, Rack BK, Haeberle L, Neugebauer JK, Melcher CA, Hagenbeck C, et al. Prognostic value of HER2 on breast cancer survival. J Clin Oncol. 2013;31(15 Suppl):640.
- Stenehjem DD, Yoo M, Unni SK, Singhal M, Bauer H, Saverno K, et al. Assessment of singleinstitution HER2 testing patterns, rate of HER2+ disease, and utilization of trastuzumab in early breast cancer. J Clin Oncol. 2013;31(Suppl):124.

- Morigi G. Highlights from the 15th St Gallen International Breast Cancer Conference 15–18 March, 2017, Vienna: tailored treatments for patients with early breast cancer. ecancermedicalscience. 2017;11:732.
- 11. Curigliano G, Burstein HJ, Winer E, Gnant M, Dubsky P, Loibl S, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Ann Oncol. 2017;28(8):1700–12.
- 12. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol. 2018;29(8):1634–57.
- 13. Hu X, Li T, Wang B, Zhang J, Yu X, Shao Z. Comparison of 4th ESO-ESMO international consensus guidelines for advance breast cancer and Chinese anti-cancer association committee of Breast Cancer Society guideline. Breast. 2019;45:36–42.
- 14. Breast cancer. Guidelines for invasive breast cancer. Fort Washington (PA): National Comprehensive Cancer Network; 2018.
- Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195–205.
- 16. Daniels B, Kiely BE, Lord SJ, Houssami N, Lu CY, Ward RL, et al. Long-term survival in trastuzumabtreated patients with HER2-positive metastatic breast cancer: real-world outcomes and treatment patterns in a whole-of-population Australian cohort (2001–2016). Breast Cancer Res Treat. 2018;171(1):151–9.
- 17. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659–72.
- Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. Arch Pathol Lab Med. 2018;142(11):1364–82.
- 19. Mayor S. NICE approves trastuzumab for early stage breast cancer. BMJ. 2006;332(7555):1409.
- 20. Yaziji H, Goldstein LC, Barry TS, Werling R, Hwang H, Ellis GK, et al. HER-2 testing in breast cancer using parallel tissue-based methods. JAMA. 2004;291(16):1972–7.
- 21. Cherny NI, Sullivan R, Torode J, Saar M, Eniu A. ESMO International Consortium study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in countries outside of Europe. Ann Oncol. 2017;28(11):2633–47.

Lactate dehydrogenase activity to aid in the prognosis and monitoring of haematological malignancies and germ-cell tumours

Test category

Colorimetric chemical assay for LDH activity

Addition, change or deletion

Addition

Proposed test purpose

The use of lactate dehydrogenase (LDH) as an aid in the diagnosis of cancer, primarily non-Hodgkin lymphoma and germ-cell tumours.

Applicant organization(s) World Health Organization

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Does this test meet a medical need? In oncology, an increase in LDH levels in blood may be a sign of relapse or an indication for re-staging disease during follow-up. LDH testing is relevant because lymphoma and germ-cell tumours can be cured if a relapse is diagnosed rapidly.

How the test is used: To measure LDH levels in blood.

Public health relevance

Prevalence: According to IARC (1), lymphoma is diagnosed and treated in more than 1.6 million patients. It occurs mainly in high-income countries, where more patients survive as a result of timely access to effective, high-quality diagnosis, safe, effective treatment and care for survivors. More than 65% of lymphomas are non-Hodgkin lymphomas.

Testicular cancer is diagnosed in approximately 9600 men each year in the USA, but only approximately 400 men die of their disease (4.2%). In 2018 in LMICs, 11 290 new cases of testicular cancer were reported, with 3984 deaths (35.3%) (1). Testicular cancer is diagnosed mainly in young males.

Socioeconomic impact: Lymphoma arises as an AIDS-defining condition in 3% of cases and is the cause of death in \leq 16% of HIV-infected patients, especially in countries with suboptimal coverage of antiretroviral medicines (2). As prognosis is strongly affected by the time to access to curative treatment, the prognosis of lymphoma is conditioned by socioeconomic status: a lower life expectancy of lymphoma patients with lower socioeconomic status has been reported, indicating inequality (3). Germ-cell tumours arise mainly in young people, and timely access to surgery, chemotherapy and radiotherapy delivered with curative intention at all stages of disease can substantially increase their survival. According to IARC (1), testicular cancer is usually diagnosed in men aged 20–34 years.

WHO or other clinical guidelines relevant to the test

IARC guidelines on diagnostic criteria for myeloproliferative neoplasms (4) and the WHO Classification of tumours of the urinary system and male genital organs (5)

Basic test characteristics

Test purpose	In determining the prognosis of and in monitoring haematological malignancies (lymphoma) In diagnosis, prognostication and monitoring of germ-cell tumours (seminomatous) In the prognosis and monitoring of lymphoma
Test format	Chemical assay
Specimen types	Serum, plasma, whole blood sample
Equipment required	Basic, automated
Global availability	Broad
Price per test range	US\$ 5–50
Instrument price range	US\$ 1000

Evidence for clinical usefulness and impact

LDH is a prognostic parameter for lymphoma and seminomatous germ-cell tumours. The International Germ Cell Consensus Classification Group for metastatic germ-cell tumours included LDH as essential for determining the prognosis of these testicular, ovarian and midline germ-cell tumours (6). LDH is also included in the prognostic score for non-Hodgkin lymphoma (e.g. follicular lymphoma) and useful during follow-up (7). LDH is measured in metastatic germ-cells to establish the intensity of chemotherapy and avoid over-treatment of this rare class of tumours, which includes testicular and ovarian germ-cell cancer, and which affect young males and females; paediatric variants are also described. It is recommended by the principal oncology and urology societies (*8*, *9*).

Evidence for economic impact and/or cost-effectiveness

Assessment of LDH in blood samples does not require highly specialized laboratory personnel and is considered a standard biochemical analysis.

Ethics, equity and human rights issues

Consent is required to obtain a blood sample. LDH is part of the prognostic score for both lymphoma and germ-cell tumours for deciding on strategy (lymphomas) or the intensity of treatment (germ-cell tumours) and thus the appropriate therapy of patients at all income levels.

SAGE IVD evidence review

No evidence was provided to support the use of LDH for the prognosis and monitoring of haematological malignancies (lymphoma) and germ-cell tumours.

Although guidelines recommend its use, the evidence for these recommendations is not clear.

SAGE IVD considerations for recommendations

High LDH levels are associated with poor survival in patients with solid tumours, and LDH is a useful, inexpensive biomarker of metastatic disease. LDH levels are high in various conditions, however, including heart and liver disease, in addition to lymphoma and germ-cell tumours. Furthermore, the levels are spuriously high unless samples are analysed within a few hours. Many of the multichannel analysers available in larger laboratories can provide values for LDH that can be used in association with other clinical parameters in the diagnosis and monitoring of many malignant and non-malignant conditions.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion of measurement of LDH activity, as a biomarker of cancer and advised submission of evidence of other uses.

The Group noted that measurement of LDH requires an analyser, and purchase of this expensive equipment would not be justified for measuring LDH levels alone. The test also requires trained health care workers.

Recommended test purpose

As an aid in the prognosis and monitoring of haematological malignancies (lymphoma) and germ-cell tumours.

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clinicians. 2018;68(6):394–424.
- 2. Bower M, Fisher M, Hill T, Reeves I, Walsh J, Orkin C, et al. CD4 counts and the risk of systemic non-Hodgkin's lymphoma in individuals with HIV in the UK. Haematologica. 2009;94(6):875–80.
- 2. Tao L, Foran JM, Clarke CA, Gomez SL, Keegan TH. Socioeconomic disparities in mortality after diffuse large B-cell lymphoma in the modern treatment era. Blood 2014;123(23):3553–62.
- Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO classification of tumours, revised 4th edition, Vol. 2, WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: international Agency for Research on Cancer; 2017 (http://publications. iarc.fr/Book-And-Report-Series/Who-larc-Classification-Of-Tumours/Who-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017, accessed May 2019).
- 4. Moch H, Humphrey PA, Ulbright TM, Reuter VE, editors. WHO classification of tumours of the urinary system and male genital organs. WHO Classification of Tumours, 4th Edition, Volume 8. Lyon: international Agency for Research on Cancer; 2016 (http://publications.iarc.fr/Book-And-Report-Series/Who-larc-Classification-Of-Tumours/Who-Classification-Of-Tumours-Of-The-Urinary-System-And-Male-Genital-Organs-2016, accessed May 2019).

- 5. Barlow LJ, Badalato GM, McKiernan JM. Serum tumor markers in the evaluation of male germ cell tumors. Nature Rev Urol. 2010;7:610–7.
- 6. William BM, Bongu NR, Bast M, Bociek RG, Bierman PJ, Vose JM, et al. The utility of lactate dehydrogenase in the follow up of patients with diffuse large B-cell lymphoma. Rev Bras Hematol Hemoter.2013;35(3):189–91.
- 7. Honecker F, Aparicio J, Berney D, Beyer J, Bokemeyer C, Cathomas R, et al. ESMO Consensus Conference Guidelines on testicular germ-cell cancer: diagnosis, treatment and follow-up. Ann Oncol. 2018;29:1658–86.
- 8. Clinical guidelines for the management of testicular cancer. Arnhem: European Association of Urology; 2018 (https://uroweb.org/guideline/testicular-cancer/).

Oestrogen and progesterone receptors in breast cancer: immunohistochemical test

Test category

IHC for the detection of oestrogen (ER) and progesterone (PgR) receptors in breast cancer

Addition, change or deletion

Addition

Proposed test purpose

To evaluate breast cancer tumour cells in tissue for ER and PgR protein expression to identify the subset of breast tumours that may respond to anti-oestrogen therapy (e.g. tamoxifen or aromatase inhibitor)

Applicant organization(s) World Health Organization

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Disease condition and impact on patients: Breast cancer is the most prevalent cancer in women and the most frequent cause of death from cancer in women. More than 50% of the deaths occur in LMICs.

Does the test meet a medical need? ER and PgR protein expression in breast cancer tissue identifies the subset of breast tumours that may respond to antioestrogen therapy.

How the test is used: The IHC kit is used to identify ER and PgR expression in normal and neoplastic tissues that have been routinely processed and paraffinembedded for histological evaluation.

Public health relevance

Prevalence: Breast cancer is the most prevalent cancer in women and the most frequent cause of death from cancer in women, and more than 85% of breast cancers are ER-/PgR-positive.

Socioeconomic impact: In contrast to high-income countries, breast cancer occurs mainly in pre-menopausal women in LMICs, who are typically still raising families and contributing to the workforce. There is published evidence that for most families in lower-resource settings a diagnosis of breast cancer pushes the family into poverty.

WHO or other clinical guidelines relevant to use of the test

The prognostic and predictive role of ER and PgR is described in WHO Classification of tumours of the breast (1), as ER and PR define a specific subset of tumours and are required for diagnosis (luminal-like breast cancer). WHO Priority medical devices for cancer management (2) acknowledges that IHC for ER and PgR is an essential diagnostic test for breast cancer care.

Test purpose	In breast cancer diagnosis, prognosis and treatment; definition of prognostic and predictive features of breast cancer
Test format	IHC assay
Specimen types	Tissue, formalin-fixed paraffin-embedded
Equipment required	Basic, automated
Global availability	Broad
Price per test range	US\$ 50–100
Instrument price range	US\$ 2000

Basic test characteristics

Evidence for clinical usefulness and impact

Characterization of breast cancer as hormone receptor-positive or -negative is relevant for diagnosis, prognosis and management and for identifying candidates for hormone therapy, as recommended by the principal clinical guidelines for

breast cancer management (3–8). The expression of hormone receptors is also related to overall survival from both early and metastatic cancer (9, 10). Hormone therapy for ER-/PgR-positive breast cancer patients is critical for appropriate prescription of tamoxifen and aromatase inhibitors, which depends on the availability of a diagnostic test for ER/PgR.

Evidence for economic impact and/or cost-effectiveness

Appropriate diagnostic tests and medicines (endocrine therapy) are considered to be cost–effective. In the Republic of Korea and in a model used by the United Kingdom National Health Service, treatment of patients with surgical resection of primary tumours and adjuvant tamoxifen and/or aromatase inhibitors was found to be cost–effective (11, 12)

Use of an ER/PgR kit requires a laboratory technician for incubation, staining on an automatic stainer and a trained pathologist to read the slides and interpret the results.

Ethics, equity and human rights issues

Consent is required to obtain a breast tissue sample. The ER/PgR test is essential for personalizing the treatment of breast cancer. Knowledge of hormone receptor status permits the choice of more conservative surgery for some patients (no axillary lymph node dissection), less radiation therapy at locoregional level and treatment of metastatic tumours with hormone therapy only, thus reducing exposure to more toxic antineoplastic agents. The test can also indicate precautionary adjuvant therapy for patients with curable cancer and even support the decision of no chemotherapy for lower-risk patients, generally positive for hormone receptors, with a few exceptions (e.g. tumours < 5 mm). As more than 85% of breast cancers are ER-/PgR-positive, detection of receptor status is relevant for the large population of women with this cancer.

SAGE IVD evidence review

As immunohistopathology is the reference standard for assessment of ER and PgR status in breast cancer, there are no studies of test accuracy. Trials clearly indicate the benefit to patients of testing, including the benefits of tamoxifen and aromatase inhibitors according to ER and PgR status, as indicated in the EML. Strong evidence for differences in prognosis was also provided.

SAGE IVD considerations for recommendations

Expression of hormone receptors is an indicator of overall survival in both early and metastatic disease, and expression of ER and PgR indicates treatment with hormone therapy, as recommended by the principal clinical guidelines for breast

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cancer management. The IHC test for hormone receptors is therefore essential for appropriate treatment of all breast cancers; the test will affect treatment decisions for more than 75% of breast cancer cases, in both early and advanced stages.

SAGE IVD recommendation, with rationale

SAGE IVD recommended inclusion on the EDL of the IHC test for expression of ER and PgR receptors in breast tumour tissue.

The Group noted that tamoxifen and aromatase inhibitors are on the WHO EML.

Recommended test purpose

As an aid in the diagnosis, prognosis and treatment of breast cancer

- Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ, editors. WHO classification of tumours of the breast. WHO classification of tumours, 4th edition, Volume 4. Lyon: International Agency for Research on Cancer; 2012 (http://publications.iarc.fr/Book-And-Report-Series/Who-Iarc-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Breast-2012, accessed May 2019).
- WHO list of priority medical devices for cancer management. Geneva: World Health Organization; 2017 (http://www.who.int/medical_devices/publications/priority_med_dev_ cancer_management/en/, accessed May 2019).
- Curigliano G, Burstein HJ, Winer EP, Gnant M, Dubsky P, Loibl S, et al. De-escalating and escalating treatments for early-stage breast cancer: the St Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Ann Oncol. 2017;28(8):1700–12.
- 4. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO–ESMO international consensus guidelines for advanced breast cancer (ABC4). Ann Oncol. 2018;29:1634–57.
- 5. Breast cancer guidelines for invasive breast cancer. Fort Washington (PA): National Comprehensive Cancer Network; 2018.
- Krop I, Ismaila N, Andre F, Bast RC, Barlow W, Collyar DE, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J. Clin Oncol. 2017;35(24):2838–47.
- Yang L, Zhong X, Pu T, Qiu Y, Ye F, Bu H. Clinical significance and prognostic value of receptor conversion in hormone receptor positive breast cancers after neoadjuvant chemotherapy. World J Surg Oncol. 2018;16(1):51.
- Van Maaren MC, de Munck L, Strobbe LJA, Sonke GS, Westenend PJ, Smidt ML, et al. Ten-year recurrence rates for breast cancer subtypes in the Netherlands: A large population-based study. Int J Cancer. 2018;144(2):263–72.
- 9. Hennigs A, Riedel F, Gondos A, Sinn P, Schirmacher P, Marmé F, et al. Prognosis of breast cancer molecular subtypes in routine clinical care: a large prospective cohort study. BMC Cancer. 2016;16:734.

- Mansel R, Locker G, Fallowfield L, Benedict Á, Jones D, on behalf of the ATAC Trialists' Group. Cost-effectiveness analysis of anastrozole vs tamoxifen in adjuvant therapy for early stage breast cancer in the United Kingdom: the 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen alone or in combination) trial. Br J Cancer. 2007;97:152–61.
- 11. Yang JJ, Park SK, Cho LY, Han W, Park B, Kim H, et al. Cost-effectiveness analysis of 5 years of postoperative adjuvant tamoxifen therapy for Korean women with breast cancer: retrospective cohort study of the Korean Breast Cancer Society database. Clin Ther. 2010;32(6):1122–38.

Papanicolau smear test

Test category Papanicolau (Pap) smear test

Addition, change or deletion Addition

Proposed test purpose Indication for microscopic assessment of tissues of cervix uteri

Applicant organization(s) World Health Organization

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Disease condition and impact on patients: Cervical cancer is the fourth most common cancer among women globally, with an estimated 570 000 new cases and 311 000 deaths in 2018 (1). It is predicted that the burden of cervical cancer will increase, reaching 460 000 related deaths by 2040, an increase of almost 50%; 90% of the deaths will occur in LMICs. Currently, most cases in LMICs are diagnosed at a late stage, as a result of delayed clinical presentation due to untimely referral of symptomatic patients to appropriate diagnosis and treatment, often as a consequence of disconnection between the continuum of care at primary health care level and fragmentation of health services at secondary and tertiary levels. The WHO Director-General has called for global action towards the elimination of cervical cancer by addressing multiple dimensions, including the social and economic consequences. The WHO goal is to reduce drastically the number of incident cases per year (elimination) through prevention (HPV vaccination), early detection, treatment of pre-invasive cancer and treatment of invasive cancer (1, 2).

Does this test meet a medical need? The Pap smear is a conventional cytological test for detecting abnormal cervical cells. It has been in use in developed countries for many decades and has been responsible for reducing the number of cancer deaths due to cervical cancer by up to 80%.

How this test is used: The test is performed by skilled health providers, including mid-level health workers such as trained midwives, general practitioners and gynaecologists. Pap smears are used for primary screening for cervical cancer and for triage after a positive HPV result to avoid overtreatment of cervical lesions. It is also used for follow-up after treatment of cervical lesions (3, 4).

Public health relevance

Prevalence: Cervical cancer is the fourth most frequent cancer in women, with an estimated 570 000 new cases in 2018, representing 7.5% of all female cancers. The prevalence in 2018 was 1.5 million patients.

Socioeconomic impact: According to WHO, lower-income countries will have the greatest relative increase in the incidence of cervical cancer in the next 20 years, exacerbating the current disparity. Cervical cancer patients face financial constraints, particularly catastrophic health expenditure, for life-saving treatment. In a study in rural China, > 50% of patients had financial problems due to such expenditure, which was more pronounced among illiterate and rural populations (*3*). According to IARC, cervical cancer has a strong economic impact among women in Brazil, China, India, the Russian Federation and South Africa, amounting to US\$ 1.6 billion annually in productivity losses, particularly in South Africa (*4*).

WHO or other clinical guidelines relevant to the test

WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention (5).

Test purpose	Screening for cervical cancer and for triaging after a positive HPV result to avoid overtreatment of cervical lesions
Test format	95% ethanol or a spray fixative
Specimen types	Usually cervical exfoliated cells but can be adapted for cerebrospinal fluid, urine, pleural and peritoneal fluids, fine- needle aspirate, bone marrow aspirate, sputum, bronchial brushings, bronchoalveolar lavage. For this application, only cervical epithelium.

Basic test characteristics

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Equipment required	Simple
Global availability	Broad
Price per test range	US\$ 5–20
Instrument price range	US\$ 1 000

Table continued

Evidence for clinical usefulness and impact

An analysis was conducted of 24 studies (27 publications) found in a literature review and five studies in a review by the US Preventive Services Task Force on screening for cervical cancer (6). An RCT in India showed that even a single lifetime screening test significantly decreased the risk of mortality from and incidence of advanced cervical cancer. Cytological screening was shown in a cohort study to significantly reduce the risk of a diagnosis of invasive cervical cancer. Pooled evidence from 12 case-control studies also indicated a significant protective effect of cytological screening. No conclusive evidence was found for establishing optimal ages for starting and stopping cervical screening or for the frequency of screening; however, the studies suggested substantial protective effects of screening among women aged ≥ 30 years and for intervals of ≤ 5 years. Training and re-training, from collection to specimen preparation, has been shown to ensure good-quality Pap smears, and a "role delegation" model has been proposed for collection of specimens by community workers, specialized nurses, general practitioners in some settings and midwives, for reliable reproducibility and performance. The procedure is easy to learn and is considered to be a basic skill for gynaecologists and obstetricians.

Evidence for economic impact and/or cost-effectiveness

A microsimulation economic model was used to compare the cost–effectiveness of recommended screening policies for cervical cancer in high-income countries (7). The authors found that 15 of the policies were efficient from the point of view of life-years gained for lower costs. For 2–40 total scheduled examinations, the age range increased gradually from 40–52 years to 20–80 years as the screening interval decreased from 12 to 1.5 years. The predicted gain in life expectancy ranged from 11.6 to 32.4 days, with a gain of 46 days if cervical cancer mortality were eliminated entirely. The average cost–effectiveness increased from US\$ 6700 for the longest screening interval to US\$ 23 900 per life-year gained. In some countries, the recommended screening policies were close to efficient, but the cost–effectiveness could be improved by reducing the number of scheduled examinations, starting them at later ages or lengthening the screening interval.

Preparation of specimens requires physicians or trained non-physician mid-level health workers. Reading of Pap smear tests requires a pathologist or technical staff trained in cytopathology.

Ethics, equity and human rights issues

Consent is required to obtain a cervical tissue sample. Counselling should be provided to all women undergoing cervical cancer screening (1). Pap smears are widely used for cervical cancer screening, and increased participation rates in screening and early treatment of precancerous lesions have been proven to reduce cervical cancer incidence, which is generally higher in vulnerable populations, including lower socioeconomic groups and women who are HIV-positive.

SAGE IVD evidence review

The Group was aware of substantial evidence of reductions in cervical cancer mortality in countries in which Pap smear testing has been used. The Group also noted emerging evidence of the greater benefits of screening with HPV testing than with the Pap smear (8) but recognized that HPV testing may not be feasible in all settings.

SAGE IVD considerations for recommendation

There is strong evidence for the accuracy of Pap smear testing and the impact of screening programmes with this test on mortality and advanced cancer rates. It is unclear whether Pap smear testing can be used to triage women with HPV infection.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion of the Pap smear test on the EDL, noting that the test is already widely used and is an effective alternative to HPV screening.

Recommended test purpose

For screening and as an aid in early diagnosis of cervical cancer

References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clinicians. 2018;68(6):394–424.
- Cancer. Geneva: World Health Organization; 2019 (http://www.who.int/news-room/fact-sheets/ detail/cancer).
- 3. Thapa N, Maharjan M, Xiong Y, Jiang D, Nguyen TP, Petrini MA, et al. Impact of cervical cancer on quality of life of women in Hubei, China. Sci Rep. 2018;8(1):11993.

- 4. Pearce A, Sharp L, Hanly P, Barchuk A, Bray F, de Camargo Cancela M, et al. Productivity losses due to premature mortality from cancer in Brazil, Russia, India, China, and South Africa (BRICS): a population-based comparison. Cancer Epidemiol. 2018;53:27–34.
- 5. WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva: World Health Organization; 2013.
- 6. Peirson L, Fitzpatrick-Lewis D, Ciliska D, Warren R. Screening for cervical cancer: a systematic review and metaanalysis. Syst Rev. 2013;2:35.
- Van den Akker-van Marle ME, van Ballegooijen M, van Oortmarssen GJ, Boer R, Habbema JDF. Cost effectiveness of cervical cancer screening: comparison of screening policies. JNCI. 2002;94(3):193–204.
- 8. Koliopoulos G, Nyaga VN, Santesso N, Bryant A, Martin-Hirsch PPL, Mustafa RA, et al. Cytology versus HPV testing for cervical cancer screening in the general population. Cochrane Database Syst Rev. 2017;(8):CD008587.

Prostate-specific antigen

Test description Determination of total PSA

Addition, change or deletion Addition

Proposed test purpose

For the diagnosis, prognosis and surveillance of prostate cancer

Applicant organization(s) World Health Organization

WHO technical department

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

Background

Disease condition and impact on patients: Prostate cancer is the second most frequently diagnosed cancer in 105 countries, affecting 1.3 million men in 2018 (1). In low-income countries, prostate cancer is the most frequently diagnosed cancer in men and is associated with a poorer prognosis than in higher-income countries, with a mortality incidence ratio of 0.63, which is much higher than the average world ratio (0.27) and that in high-income countries (0.19). Prostate cancer is the leading cause of death from cancer in 46 countries, particularly in sub-Saharan Africa and the Caribbean (2).

Does this test meet a medical need? The role of PSA in the work-up and prognosis of prostate cancer has been evaluated in several studies, and PSA has been included in the prognostic risk score for localized prostate cancer for deciding whether to provide conservative (active surveillance) or interventional treatment, the intensity of interventions (surgery with or without radiation, hormone therapy or chemotherapy) and the type of intervention (surgery and/or radiation) (*3*, *4*).

The role of PSA in clinical diagnosis, staging, prognostication and monitoring of prostate cancer is recognized in all principal international, regional and national clinical guidelines. Use of a composite score for recurrence and clinical staging at presentation permits health care providers to discriminate between low- (87% recurrence-free) and high-risk patients (59% recurrence-free) as compared with patients treated by prostatectomy (5), with possible risk-adapted intensification of treatment with radiation therapy (4) or hormone therapy (6). PSA is also essential for following up patients.

How this test is used: Included in the prognostic risk score for localized prostate cancer for deciding whether to provide conservative (active surveillance) or interventional treatment, the intensity of interventions and the type of intervention (surgery and/or radiation) (3, 4).

Public health relevance

Prevalence: Globally, 3.7 million patients today live with prostate cancer (2), with 70% of the prevalence reported in high-income countries, where the probability of survival is much higher as a result of timely access to early diagnosis and high-quality curative treatment.

Socioeconomic impact: The age-standardized mortality from prostate cancer is highest in some African and Caribbean countries. For instance, sub-Saharan LMICs are most strongly affected, due to a combination of constraints in access to timely diagnosis and treatment and intrinsically more aggressive pathology.

WHO or other clinical guidelines relevant to the test

PSA is included in WHO guidance on Priority medical devices for cancer management (6).

Test purpose	In diagnosis, prognosis and surveillance of prostate cancer
Test format	ECLIA
Specimen types	Peripheral blood sample

Basic test characteristics

Table continued

Equipment required	Basic automated
Global availability	Broad
Price per test range	US\$ 5–100
Instrument price range	US\$ 500

Evidence for clinical usefulness and impact

Treatments for localized prostate cancer are chosen on the basis of clinical and pathological features, and PSA provides essential information. Use of a composite clinical-pathological score to estimate the risk of recurrence, including histological grading on the basis of PSA results and clinical stage at presentation, allows health care providers to categorize cases into prognostic groups and to provide risk-adapted therapy (3-5). PSA is also essential in follow-up for biochemical relapse in patients who have undergone resection and for progression of disease in patients with metastases, in whom PSA recurrence often precedes clinical recurrence or resistance to therapy (7, 8).

Evidence for economic impact and/or cost-effectiveness

No analysis of the cost-effectiveness of PSA in the management of prostate cancer has been reported, although there are studies of its cost-effectiveness in screening. In view of the use of PSA in defining risk for recurrence, a cost-effectiveness study was conducted of active surveillance versus treatment of low-risk prostate cancer, which showed that conservative management of low-risk disease optimizes health outcomes and significantly reduces costs (9). The cost of a PSA test in both Italy and the USA is US\$ 20–50. PSA testing requires a laboratory for diagnostics, with technicians; however, no additional training is required for following the instructions for testing provided by the manufacturers.

Ethics, equity and human rights issues

Consent is required to obtain a blood sample. PSA is not proposed for screening in asymptomatic populations in view of the lack of robust data that it reduces mortality from prostate cancer. A PSA programme for active surveillance of patients with low-risk, localized prostate cancer or with resection should be associated with a diagnostic facility for timely referral of those who are more likely to have progression or recurrence of disease.

PSA can be used with pathological (Gleason score) and clinical monitoring (for co-morbid conditions) to personalize the treatment of prostate cancer and

avoid overtreatment of indolent cancers. Thus, access and equity are assured by risk stratification, with more equitable treatment among population groups.

SAGE IVD evidence review

PSA has a stated role in prognostic models for recurrence, in the diagnostic workup of symptomatic patients and in post-treatment surveillance, as per the supporting evidence.

SAGE IVD considerations for recommendation

PSA is recommended for use in the diagnosis of prostate cancer and in risk stratification and surveillance. The levels of evidence for these recommendations are considered to be moderate to high.

SAGE IVD recommendation, with rationale

SAGE IVD recommended that the test for determination of total PSA be included on the EDL, based on the evidence for its use as an aid in the diagnosis of prostate cancer and for prognosis and monitoring. The Group noted that the test is not suitable for use in screening or for a definitive diagnosis.

The Group recommended that rapid, semi-quantitative point-of-care tests for use in primary care be evaluated at a future meeting.

Recommended test purpose

As an aid in the diagnosis, prognosis and monitoring of prostate cancer

References

- 1. Global Cancer Observatory. Lyon: International Agency for Research on Cancer; 2019 (https://gco. iarc.fr/).
- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clinicians. 2018;68(6):394–424.
- D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998;280(11):969–74.
- Antebi E, Eldefrawy A, Katkoori D, Soloway CT, Manoharan M, Soloway MS. Oncological and functional outcomes following open radical prostatectomy: how patients may achieve the "Trifecta"? Int Braz J Urol. 2011;37(3):320–7.
- Denham JW, Steigler A, Lamb DS, Joseph D, Turner S, Matthews J, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol. 2011;12(5):451–9.

- 6. Priority medical devices for cancer management (WHO Medical Device Technical Series). Geneva: World Health Organization; 2017 (http://www.who.int/medical_devices/publications/priority_ med_dev_cancer_management/en/).
- Horwitz EM, Thames HD, Kuban DA, Levy LB, Kupelian PA, Martinez AA, et al. Definitions of biochemical failure that best predict clinical failure in patients with prostate cancer treated with external beam radiation alone: a multi-institutional pooled analysis. J Urol 2005;173(3): 797–802.
- Stephenson AJ, Kattan MW, Eastham JA, Dotan ZA, Bianco FJ Jr, Lilja H, et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. J Clin Oncol. 2006;24(24):3973–8.
- 9. Prostate cancer guidelines. Arnhem: European Association of Urology; 2018 (https://uroweb.org/ guideline/prostate-cancer/).

HIV infection

Histoplasma antigen enzyme immunoassay

Test category Histoplasma antigen test

Addition, change or deletion Addition

Proposed test purpose For the diagnosis of histoplasmosis

Applicant organization(s) Global Action Fund for Fungal Infections

Background

Disease condition and impact on patients: Progressive disseminated histoplasmosis is an increasingly common recognized cause of infection in patients with advanced HIV infection in areas endemic for histoplasmosis (1, 2). Histoplasmosis is the most common endemic human mycosis (3). It is caused by the thermally dimorphic fungus *Histoplasma capsulatum*, which has worldwide distribution, and *Histoplasma duboisii*, which is endemic in Africa. Histoplasma is transmitted through the respiratory tract, but, once inhaled into the alveoli, the organism readily spreads throughout the body, causing a wide spectrum of manifestations that range from subclinical infections to progressive disseminated disease, affecting both immunocompetent and immunosuppressed individuals (4). Bat guano is the primary ecological niche of histoplasma, and the number of cases shows substantial seasonal variation. The clinical presentation of disseminated histoplasmosis in patients with AIDS is subtly different from that of TB, with more gastrointestinal and fewer respiratory features, pyrexia and usually some

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degree of pancytopenia. Most patients with disseminated histoplasmosis and AIDS are in their 30s, and in the absence of treatment, death usually occurs within 10–14 days. The fungus typically takes 2 weeks to grow on mycological media and does not grow on media for bacterial culture.

Does this test meet a medical need? Histoplasma antigen has been detected in the urine of 95–100% and in the serum of 80% of patients with disseminated AIDS (5–7). The availability of a simple, rapid method to detect *H. capsulatum* infection in LMICs would dramatically decrease the time to diagnosis and treatment and the number of deaths among patients with AIDS-related disseminated histoplasmosis.

Skin test reactivity in immunocompetent people indicates previous exposure and contributes to assessment of local risk of exposure; it could be used to focus diagnostic testing. In immunocompromised people, tests for detecting histoplasma polysaccharide antigen in urine, serum, bronchoalveolar lavage and cerebrospinal fluid samples allow rapid diagnosis of disseminated histoplasmosis before positive cultures can be identified (8). The concentration of antigen is highest in urine and can be used to monitor the response to antifungal therapy and to identify relapses (9).

How the test is used: Histoplasma antigen testing is used in patients with advanced HIV infection, similar to testing for cryptococcal antigen or lipoarabinomannan.

Public health relevance

Prevalence: The number of cases of disseminated histoplasmosis in people with AIDS has been estimated to be 100 000-300 000 (10, 11). Very high rates are confined to certain countries and localities. For example, in Fortaleza, Brazil, 164 (43%) of 378 consecutively hospitalized HIV-positive patients had disseminated histoplasmosis (12), and, in Venezuela, autopsies of 66 patients with AIDS revealed histoplasmosis in 44% (13). In a series in Brazil, overall mortality was 71% in 275 patients (14). Disseminated histoplasmosis also occurs in Africa (15), on the Indian subcontinent and in southern China and South East Asia. The estimated global burden in people with AIDS is 100 000 cases, with about 80 000 deaths, as most cases are not diagnosed (16). The estimates in AIDS patients in countries with suboptimal diagnostic methods were 300 cases in Indonesia, 175 cases in Malaysia, 158 cases in Mozambique, 32 cases in Thailand and 135 cases in the United Republic of Tanzania, which are probably significant underestimates. Large and small outbreaks have been attributed to histoplasmosis, but most infections are sporadic (3), and localized hot spots have been well described but poorly mapped. Focal hotspots confound global estimates of the burden of disease.

Socioeconomic impact: Not provided

WHO or other clinical guidelines relevant to the test The test is recommended in the WHO guidelines for advanced HIV infection (*17*).

Basic test characteristics

Test purpose	In the diagnosis of histoplasmosis
Test format	EIA
Specimen types	Urine
Equipment required	ELISA reader
Regulatory status	Products available approved by stringent regulatory authorities
Global availability	Narrow
Price per test range	US\$ 9–850
Instrument price range	US\$ 5000–10 000

Evidence for clinical usefulness and impact

The impact of accurate, fast diagnosis with antigen testing of disseminated histoplasmosis in people with AIDS has been modelled (*16*).

Evidence for economic impact and/or cost-effectiveness

The test has a small effect on budgets overall; however, it should be focused on areas of moderate and high prevalence.

Ethics, equity and human rights issues

Consent is required to obtain a urine sample. Lack of availability of the test is a major contributor to deaths from AIDS in endemic areas, especially in Brazil and French Guiana. Death from histoplasmosis in people with AIDS typically occurs in the prime of life, around 35 years. A reduction in the number of such deaths would be beneficial for the affected individuals, families and communities.

SAGE IVD evidence review

The evidence for the accuracy of the test presented in the systematic review raised some questions. Some studies show good diagnostic accuracy, but there appears to be unexplained variation in the accuracy of the test. Further detailed analysis of the evidence is needed to evaluate the quality of the studies and their findings.

SAGE IVD considerations for recommendation

Histoplasma antigen has been detected in the urine of 95–100% and in the serum of 80% of patients with disseminated AIDS. The availability of a simple, rapid method to detect *H. capsulatum* infection in LMICs would dramatically decrease the time to diagnosis and treatment and the number of deaths among patients with AIDS-related disseminated histoplasmosis. In immunocompromised people, tests for detecting histoplasma polysaccharide antigen in urine, serum, bronchoalveolar lavage and cerebrospinal fluid samples allow rapid diagnosis of disseminated histoplasmosis before positive cultures can be identified. The concentration of antigen is highest in urine, which can be used to monitor the response to antifungal therapy and to identify relapses. Lack of availability of the test is a major contributor to deaths from AIDS in endemic areas.

SAGE IVD recommendation, with rationale

SAGE IVD recommended conditional inclusion in the EDL of the histoplasma antigen EIA, and requested submission of more evidence on the performance of the test.

The Group requested the WHO technical department on HIV infection to include advice on use of the test in their guidelines.

Recommended test purpose

As an aid in the diagnosis of disseminated histoplasmosis

References

- Johnson PC, Sarosi GA, Septimus EJ, Satterwhite TK. Progressive disseminated histoplasmosis in patients with acquired immune deficiency syndrome: a report of 12 cases and a literature review. Semin Resp Infect. 1986;1(1):1–8.
- Adenis AA, Valdes A, Cropet C, McCotter OZ, Derado G, Couppie P, et al. Burden of HIV-associated histoplasmosis compared with tuberculosis in Latin America: a modelling study. Lancet Infect Dis. 2018;18(10):1150–9.
- 3. Kauffman CA. Histoplasmosis. Clin Chest Med. 2009;30(2):217.
- 4. Wheat LJ. Histoplasmosis: a review for clinicians from non-endemic areas. Mycoses. 2006;49(4): 274–82.
- 5. Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. Infect Dis Clin North Am. 2016;30(1):207–27.
- 6. Scheel CM, Samayoa B, Herrera A, Lindsley MD, Benjamin L, Reed Y, et al. Development and evaluation of an enzyme-linked immunosorbent assay to detect *Histoplasma capsulatum* antigenuria in immunocompromised patients. Clin Vaccine Immunol. 2009;16(6):852–8.
- Cáceres DH, Samayoa BE, Medina NG, Tobón AE, Guzmán BJ, Mercado D, et al. Multicenter validation of commercial antigenuria reagents to diagnose progressive disseminated histoplasmosis in people living with HIV/AIDS in two Latin American countries. J Clin Microbiol. 2018;56:e01959-17.
- Hage CA, Ribes JA, Wengenack NL, Baddour LM, Assi M, McKinsey DS, et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. Clin Infect Dis. 2011;53(5):448–54.

9. Richardson MD, Warnock DW. Fungal infection: diagnosis and management, 4th edition. New York City (NY): Wiley; 2012.

- 10. Armstrong-James D, Meintjes G, Brown GD. A neglected epidemic: fungal infections in HIV/AIDS. Trends Microbiol. 2014 ;22(3):120–7.
- Global fungal infection forum III. Essential diagnostics for advanced HIV disease and serious fungal infections. Kampala, Uganda, 10–12 April 2018. Geneva: Global Action Fund for Fungal Infections; 2018 (https://www.who.int/medical_devices/diagnostics/selection_in-vitro/selection_in-vitromeetings/00005_12_GFIF3Report_email.pdf?ua=1).
- 12. Daher EF, Silva GB Jr, Barros FA, Takeda CF, Mota RM, Ferreira MT, et al. Clinical and laboratory features of disseminated histoplasmosis in HIV patients from Brazil. Trop Med Int Health. 2007;12(9):1108–15.
- 13. Murillo J, Castro KG. HIV infection and AIDS in Latin America. Epidemiologic features and clinical manifestations. Infect Dis Clin North Am. 1994 ;8(1):1–11.
- 14. Silva TC, Treméa CM, Zara ALSA, Mendonça AF, Godoy CSM, Costa CR, et al. Prevalence and lethality among patients with histoplasmosis and AIDS in the midwest region of Brazil. Mycoses. 2017;60(1):59–65.
- 15. Oladele RO, Ayanlowo OO, Richardson MD, Denning DW. Histoplasmosis in Africa: an emerging or a neglected disease? PLoS Negl Trop Dis. 2018;12(1):e0006046.
- 16. Denning DW. Minimizing fungal disease deaths will allow the UNAIDS target of reducing annual AIDS deaths below 500 000 by 2020 to be realized. Phil Trans R Soc B. 2016;371:20150468
- 17. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. Geneva: World Health Organization; 2017 (http://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/).

Influenza

Influenza antigen: rapid immunoassay to aid in diagnosis of seasonal influenza

Test category

Rapid diagnostic test

Addition, change or deletion

Addition

Proposed test purpose

For rapid detection of influenza viral antigens in adults and children with suspected influenza

Applicant organization(s) World Health Organization

WHO technical department Pandemic and Epidemic Diseases

Background

Disease condition and its impact on patients: Seasonal influenza causes disease all year, globally. Illness ranges in severity: most people recover within 1 week without requiring medical attention, but influenza can lead to hospitalization and death.

Does this test meet a medical need? The RDT provides a result within 10–15 min, therefore allowing physicians and nurses to diagnose influenza and decide on treatment at a single patient visit.

How the test is used: Immunoassays for influenza are typically used at or close to points of care as a single test in patients with suspected influenza.

Public health relevance

Prevalence: Worldwide, seasonal influenza is estimated to result in 3–5 million cases of severe illness and about 290 000–650 000 deaths from respiratory conditions. The US Centers for Disease Control and Prevention estimated that influenza has caused 9.3–49.0 million cases of illness, 140 000–960 000 hospitalizations and 12 000–79 000 deaths annually in the USA since 2010. WHO states that the estimated national influenza burden determines influenza prevention and control programmes; however, reliable data are not available for LMICs.

Socioeconomic impact: The WHO project on the burden of influenza, in partnership with the Pandemic Influenza Preparedness framework, is improving understanding of the burden of influenza (1).

WHO or other clinical guidelines relevant to the test

WHO recommendations on the use of rapid testing for influenza diagnosis (2, 3). The latest guideline is from 2010 and is currently being updated. Laboratory confirmation of influenza virus from throat, nasal and nasopharyngeal secretions or tracheal aspirates or washings is commonly done by direct antigen detection, virus isolation or detection of influenza-specific RNA by RT-PCR.

Test purpose	For diagnosis of influenza
Test format	RDT
Specimen types	RDTs and instrument tests: nasal swabs, nasopharyngeal swabs, nasopharyngeal aspirates or washes
Equipment required	Hand-held lateral flow strip

Basic test characteristics

Table continued

Regulatory status	CE, FDA
Global availability	Yes
Price per test range	About US\$ 9–15
Instrument price range	RDTs do not require instruments. Digital immunoassay instruments cost US\$ 400–1000.

Evidence for clinical usefulness and impact

WHO Recommendations on the use of rapid testing for influenza diagnosis (2) indicate that a rapid diagnostic test performed within 48 h of the onset of symptoms can have important implications for case management, including the use of antiviral agents. Other benefits may include the isolation and cohorting of confirmed cases to prevent nosocomial outbreaks and a reduction in inappropriate use of antibiotics. Use of rapid tests that provide timely evidence of influenza virus infection should be considered; however, test performance depends on the prevalence of influenza in the community. A low prevalence outside the normal influenza season can lead to an increase in false-positive results.

Evidence for economic impact and/or cost-effectiveness

In 2010, computer simulations were used to evaluate the economic value of seven strategies for testing and managing seasonal and pandemic influenza: clinical judgement alone, PCR, an RDT at points of care, a combination of a point-of-care test and clinical judgement, clinical judgement with confirmation by PCR, treating everyone with antivirals and treating no one with antivirals (4). For healthy adults < 65 years presenting with influenza-like illness in a seasonal influenza scenario, strategies were cost-effective only from a societal perspective. Clinical judgement, followed by PCR and point-of-care testing, was found to be cost-effective in situations of a high influenza probability. Doubling the hospitalization risk and mortality (representing either individuals at higher risk or more virulent strains) made clinical judgement to decide on prescription of antiviral agents cost-effective, as did PCR testing, point-of-care testing and point-of-care testing in conjunction with clinical judgement. For healthy adults \geq 65 years, PCR was the most cost-effective option, the closest competitor being clinical judgement, with an accuracy \geq 50%. Point-of-care testing plus clinical judgement were cost-effective for higher probabilities of influenza. Treating all patients with influenza-like illness with antiviral agents was cost-effective only for older adults. This study showed the importance of accuracy, with PCR or highly sensitive clinical judgement.

Ethics, equity and human rights issues

Consent is required to obtain a sample. RDTs for influenza are readily accessible for use in outpatient settings. The typical price in the US of US\$ 9–15 per test may limit access in LMICs. However, pricing of the same products in LMIC's may not be the same as in the US and was not available at the time of submission.

SAGE IVD evidence review

There is strong evidence from systematic reviews (5) that older rapid tests for influenza are highly specific but vary in sensitivity, with a mean value of only 60%. Thus, these RDTs can only be used to confirm influenza and not to rule it out.

The newer digital immunoassays (antigen detection tests) with an automated reader are more sensitive (77–80% overall), especially for children (83–88%), but require the use of an instrument and are more expensive than older RDTs.

SAGE IVD considerations for recommendation

Clinical diagnosis of influenza is difficult because its manifestations are often nonspecific. Rapid, point-of-care diagnosis can help to ensure prompt initiation of antiviral therapy, fewer ancillary diagnostic tests, fewer hospitalizations and less unnecessary use of antibiotics. While traditional rapid ICTs have been used for several decades, their sensitivity remains suboptimal. The newer digital immunoassays are substantially more sensitive, with comparable specificity. These assays can be performed at primary care level by trained health workers and are likely to improve patient outcomes and surveillance. The cost–effectiveness of these tests in LMICs has not been demonstrated, and sample collection requires training.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended conditional inclusion on the EDL of the rapid immunoassay for influenza, only for patient management and pending issuance of updated WHO guidelines.

The Group noted that the older rapid ICTs are not sensitive enough and are likely to be phased out, while newer digital immunoassays are sensitive and rapid and could be used for diagnosis at points of care. The simpler lateral flow tests are useful for detection if no other tests are available but should not be used for surveillance and should meet international performance standards.

The Group recommended that rapid immunoassays for influenza be a priority for WHO prequalification and that influenza guidelines be updated.

The selection and use of essential in vitro diagnostics

Recommended test purpose

As an aid in the diagnosis of seasonal influenza (not recommended for surveillance).

References

- 1. Special issue: influenza disease burden. Influenza Other Resp Viruses. 2018;12(1):1–192 (https://onlinelibrary.wiley.com/toc/17502659/12/1, accessed April 2019).
- 2. WHO recommendations on the use of rapid testing for influenza diagnosis. Geneva: World Health Organization; 2005 (https://www.who.int/influenza/resources/documents/RapidTestInfluenza_WebVersion.pdf, accessed April 2019).
- Use of influenza rapid diagnostic tests. Geneva: World Health Organization; 2010 (https://apps. who.int/iris/bitstream/handle/10665/44304/9789241599283_eng.pdf;sequence=1, accessed April 2019).
- Lee BY, McGlone SM, Bailey RR, Wiringa AE, Zimmer SM, Smith KJ, et al. To test or to treat? An analysis of influenza testing and antiviral treatment strategies using economic computer modelling. PLoS One. 2010;5(6):e11284.
- 5. Bruning AHL, Leeflang MMG, Vos JMBW, Spijker R, de Jong MD, Wolthers KC, et al. Rapid tests for influenza, respiratory syncytial virus, and other respiratory viruses: a systematic review and meta-analysis. Clin Infect Dis. 2017;65(6):1026–32.
- 6. Merckx J, Wali R, Schiller I, Caya C, Gore GC, Chartrand C, et al. Diagnostic accuracy of novel and traditional rapid tests for influenza infection compared with reverse transcriptase polymerase chain reaction: a systematic review and meta-analysis. Ann Intern Med. 2017;167(6): 394–409.

Influenza A and B: nucleic acid test for diagnosis of seasonal influenza

Test category

PCR molecular test for influenza

Addition, change or deletion

Addition

Proposed test purpose

Detection of influenza-specific RNA in adults and children with suspected influenza

Applicant organization(s) World Health Organization

WHO technical department Pandemic and Epidemic Diseases

Background

Disease condition and impact on patients: Seasonal influenza causes disease all year, globally. Illness ranges in severity: most people recover within 1 week without requiring medical attention, but influenza can lead to hospitalization and death.

Does the test meet a medical need? Molecular tests for Influenza are rapid, automated IVD tests for qualitative detection of influenza A and B in nasal or nasopharyngeal swabs or washes eluted in viral transport medium. A molecular amplification technique, e.g. PCR or isothermal amplification, is used to target and detect conserved regions of the influenza virus in the nucleic acid hybridization reaction. A test result is obtained within 10–15 min, allowing physicians and nurses to diagnose influenza and decide on treatment at a single patient visit. The performance is far more reliable than that of RDTs, but the tests are more expensive. Although the best results are obtained from a nasopharyngeal swab, which is uncomfortable to obtain from patients, molecular tests also perform well with nasal swabs, which are much easier to obtain, especially from small children.

How the test is used: PCR-based influenza tests are typically used at or close to points of care as a single test in patients with suspected seasonal influenza. Some manufacturers provide multiplex PCR tests for both influenza A and B and respiratory syncytial virus A and B in the same reaction.

Public health relevance

Prevalence: Worldwide, influenza epidemics are estimated to result in 3–5 million cases of severe illness and about 290 000–650 000 deaths from respiratory conditions. The US Centers for Disease Control and Prevention estimated that influenza has caused 9.3–49.0 million cases of illness, 140 000–960 000 hospitalizations and 12 000–79 000 deaths annually in the USA since 2010. WHO states that the estimated national influenza burden determines influenza prevention and control programmes; however, reliable data are not available for LMICs.

Socioeconomic impact: The WHO project on the burden of influenza, in partnership with the Pandemic Influenza Preparedness framework, is improving understanding of the burden of influenza (1).

WHO or other clinical guidelines relevant to the test

The WHO guideline is from 2010 and is currently being updated. Laboratory confirmation of influenza virus from throat, nasal and nasopharyngeal secretions or tracheal aspirate or washings is commonly done by direct antigen detection, virus isolation or detection of influenza-specific RNA by RT-PCR.

Basic	test	charact	eristics
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Test purpose	Diagnosis of Influenza
Test format	PCR
Specimen types	Nasal swabs, nasopharyngeal swabs, aspirates or washes
Equipment required	Small, easy-to-use bench-top PCR instruments
Regulatory status	Commercially available products with CE-marked, FDA
Global availability	Yes
Price per test range	US\$ 25–40 per test The typical price for an influenza A or B test is about US\$ 25. If the test includes respiratory syncytial virus, the price may be up to US\$ 40 per test.
Instrument test range	US\$ 12 000–25 000

Evidence for clinical usefulness and impact

Several studies have shown that molecular tests are more accurate than RDTs; however, no recent studies were found that showed that molecular assays that give results within 15–20 min improve clinical outcomes or antimicrobial stewardship.

Evidence for economic impact and/or cost-effectiveness

Only one study was found of the cost-effectiveness of rapid molecular testing for influenza (2). A decision analytical model was used to simulate the outcomes of a hypothetical cohort of elderly patients presenting with influenza-like illness at outpatient clinics in Hong Kong (China) during the peak influenza season, with rapid PCR and with clinical judgement alone. The outcome measures included direct medical cost, hospitalization rate, mortality rate, QALY loss and incremental cost per QALY saved. PCR was cost-effective in 60.6% and 99.4% of 10 000 Monte Carlo simulations of willingness to pay threshold one and three times the gross domestic product per capita, respectively.

Whereas RDTs cost about US\$ 15 per test, rapid molecular influenza tests cost about US\$ 25 per test, and up to US\$ 45 per test if they include respiratory syncytial virus.

Ethics, equity and human rights issues

Consent is required to obtain a sample. Like RDTs, rapid molecular tests for influenza are accessible for use in any outpatient setting, owing to their ease of use. The typical price of US\$ 25 per test may limit access in LMICs.

SAGE IVD evidence review

There is strong evidence for the high accuracy of nucleic acid amplification tests (NAATs). In a meta-analysis of 13 studies of NAATs, the estimated sensitivity for detecting influenza A was 91.6% (84.9; 95.9), and that for detecting influenza B was 95.4% (87.3%; 98.7%). The pooled specificity was about 99% (*3*).

SAGE IVD considerations for recommendation

Clinical diagnosis of influenza is difficult because the manifestations are often nonspecific. PCR for influenza is the most sensitive rapid test and is widely held to be the reference standard for detection of influenza-specific RNA, with high sensitivity and high specificity. PCR is also necessary for surveillance in national hospitals and reference laboratories. Their uptake in LMICs is, however, limited by economic factors and lack of infrastructure and training.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion on the EDL of the PCR test for influenza, noting that it is the most sensitive rapid influenza test for both clinical management and surveillance. They further recommended that point-of-care tests could be used in the primary care settings as well as in district hospitals and in secondary and tertiary care facilities.

Recommended test purpose

For diagnosis of seasonal influenza

References

- Nicholson KG, Abrams KR, Batham S, Medina MJ, Warren FC, Barer M, et al. Randomised controlled trial and health economic evaluation of the impact of diagnostic testing for influenza, respiratory syncytial virus and *Streptococcus pneumoniae* infection on the management of acute admissions in the elderly and high-risk 18- to 64-year olds. Health Technol Assess. 2014;18(36): 1–274,vii–viii.
- 2. You JHS, Tam L, Lee NLS. Cost-effectiveness of molecular point-of-care testing for influenza viruses in elderly patients at ambulatory care setting. PLoS One. 2017;12(7):e0182091.
- 3. Merckx J, Wali R, Schiller I, Caya C, Gore GC, Chartrand C, et al. Diagnostic accuracy of novel and traditional rapid tests for influenza infection compared with reverse transcriptase polymerase chain reaction: a systematic review and meta-analysis. Ann Intern Med. 2017;167(6):394–409.

Neglected tropical diseases

Dengue virus antibody enzyme immunoassay or rapid diagnostic test

Test category

EIA or RDT for DENV antibody (IgM)

Addition, change or deletion Addition

Proposed test purpose Diagnosis of dengue fever

Applicant(s) World Health Organization

WHO technical department Control of Neglected Tropical Diseases

Background

Disease condition and impact on patients: Dengue fever occurs in a broad spectrum of clinical presentations, often with unpredictable clinical evolution and outcome. While most patients recover after a self-limiting, non-severe clinical course, a small proportion progress to severe disease, characterized mainly by plasma leakage with or without haemorrhage. Intravenous rehydration is the therapy of choice and can reduce the case fatality rate to < 1% of severe cases. The characteristics of patients with dengue that progresses from non-severe to severe are difficult to define. This is an important concern, as appropriate treatment may prevent more severe clinical illness.

Does the test address a medical need? Efficient, accurate diagnosis of dengue is of primary importance for clinical care (for early detection of severe cases, case confirmation and differential diagnosis from other infectious diseases), surveillance, outbreak control, pathogenesis, academic research, vaccine development and clinical trials. In relation to the EDL, antibody and antigen tests are essential for case management and surveillance. During the early stages of the disease, detection of antigens can be used to diagnose an infection, while, at the end of the acute phase of infection, serology is the method of choice. The choice of the assay for diagnosis depends on the time of sample collection and the purpose of testing (1). As for other Aedes-borne arboviruses, viraemia is present during the acute phase, and 90% of cases of primary and secondary dengue fever

can be identified accurately from a single serum specimen collected during the first 10 days of illness, with DENV-1-4 real-time RT-PCR plus IgM ELISA or NS1 antigen ELISA (*2*, *3*).

Purpose of testing: In surveillance, testing is used to alert health authorities to the possible emergence of an outbreak. Testing is usually done with highthroughput immunoassays for IgM antibodies. While they are not ideal markers of active infection (which can persist for 5-6 months), they can be used as the basis for an outbreak alert when an increase in IgM-positive cases is reported or unusually high IgM titres are observed. EIA can be used to identify the cause of an outbreak. The tests must be highly sensitive and specific for detecting DENV directly, by isolation of the virus or its nucleic acid or antigen in the acute phase of infection. Infection can also be diagnosed retrospectively from seroconversion of IgM or a fourfold rise in IgG between samples collected in the acute and convalescent stages > 14 days apart. A combination of IgM and either NAAT or antigen detection tests extends the window of detection of acute infection and was effective in a retrospective study of DENV infections. In surveys, EIA can be used to assess the extent of an outbreak, inform control strategies and identify hotspots. High-throughput, ideally highly specific, tests that can be used in various populations are required. In research, the tests are used to assess the impact of control interventions and increase understanding of the pathogen and its pathogenesis.

How the test is used: The DENV IVD can be used at three levels of a health system: primary care centres, district centres and reference centres. A single test is sufficient if a sample is taken within the defined time. As dengue fever is easily confused with other illnesses, particularly in non-epidemic situations, the DENV IVD can also be used for differential diagnosis.

Public health relevance

Prevalence: Dengue fever is the most rapidly spreading mosquito-borne viral disease in the world. Its incidence has increased by 30 times in the past 50 years, and it is spreading to other countries; during the current decade, it has spread from urban to rural settings. An estimated 50 million cases of dengue infection occur annually among the 2.5 billion people who live in countries endemic for the disease. World Health Assembly resolution WHA55.17 in 2002 urged WHO and its Member States to make a greater commitment to controlling dengue fever. World Health Assembly resolution WHA58.3 on revision of the IHR gives dengue fever as an example of a disease that may constitute a public health emergency of international concern (PHEIC), with implications for health security due to disruption and rapid epidemic spread beyond national borders.

The selection and use of essential in vitro diagnostics

Socioeconomic impact

The estimated global cost of the prevention and control of dengue fever is at almost US\$ 9 billion per year (4), and WHO has estimated that more than 3 billion DALYs are lost due to dengue fever.

WHO or other clinical guidelines relevant to use of the test

Guidelines for patient care in the Region of the Americas (5).

Test purpose	To confirm DENV infection during onset of the disease
Test format	ELISA: The IgM antibody-capture ELISA detects DENV- specific IgM in serum, usually 3–5 days after the onset of fever. The assay detects all IgM with human-specific IgM bound to a solid phase and can also be used with whole blood specimens on dried blood spots and with saliva, but not urine. RDT: The IgM RDT is based on lateral flow immunochromatography on a strip in a cassette.
Specimen types	Serum, plasma or stored blood filter-paper samples.
Equipment required	Basic, automated Hand-held for ELISA, simple hand-held for RDT For ELISA: Pipette, incubator, plate reader, Vortex tube mixer, tubes For RDT: Pipette, tubes
Regulatory status	Stringent regulatory authorities
Global availability	> 100 countries are estimated to have access to this IVD
Price per test range	Estimated US\$ 1–5 per test
Instrument price range	Not stated

Basic test characteristics

Evidence for clinical usefulness and impact None provided.

Evidence for economic impact and/or cost-effectiveness

If only a subset of patients is tested during an outbreak or for confirmation in endemic periods, the impact on overall budgets will be small.

Ethics, equity and human rights issues

Consent is required to obtain a serum sample. Dengue fever predominantly affects populations living in poverty, and access to high-quality diagnostics can reduce the burden and improve equity.

SAGE IVD evidence review

Several studies of use of IgM ELISA and RDTs have been conducted, but no systematic review has been done to determine any risk of bias or the applicability of the findings. The studies show that the sensitivity and specificity of these tests is variable and low, and they are not accurate enough to be used on their own. Several studies have evaluated the combination of NS1 and IgM, as separate tests or in a purpose-made dual RDT, which appears to increase sensitivity without compromising specificity, but no systematic review of studies of this test combination has been reported.

SAGE IVD considerations for recommendation

Dengue fever is the most rapidly spreading mosquito-borne viral disease in the world. Antibody and antigen tests are essential for detection, case management, surveillance and confirmation of outbreaks. Detection of antigens can be used to diagnose an early infection, while viraemia present during the acute phase requires use of DENV-1-4 real-time RT-PCR plus IgM ELISA or NS1 antigen ELISA.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion on the EDL of the EIA or RDT for DENV IgM only if used in combination with the EIA or RDT for DENV NS1 antigen (see below) in a specified algorithm.

The Group noted that the tests for DENV IgM cross-react with other flaviviruses, and seroconversion cannot be measured owing to the high rate of attrition in the countries in which dengue is endemic. They noted that guidelines for DENV testing would become available shortly. The Group recommended that the test be prequalified to ensure that the most appropriate tests are available.

Recommended test purpose

As an aid in the diagnosis of dengue fever (always in combination with NS1) and for population surveys.

References

1. Peeling R, Murtagh M, Olliaro P. Epidemic preparedness: why is there a need to accelerate the development of diagnostics? Lancet Infect Dis. 2019;19(5):e172–8.

- Hunsperger EA, Muñoz-Jordán J, Beltran M, Colón C, Carrión J, Vazquez J, et al. Performance of dengue diagnostic tests in a single-specimen diagnostic algorithm. J Infect Dis. 2016;214(6): 836–44.
- 3. Peeling RW, Olliaro P. Reimagining the future of the diagnosis of viral infections. J Infect Dis. 2016;214:828–9.
- 4. Shepard DS, Undurraga EA, Halasa YA, Stanaway JD. The global economic burden of dengue: a systematic analysis. Lancet Infect Dis. 2016;16(8):935–41.

Dengue virus antigen (NS1) enzyme immunoassay or rapid diagnostic test

Test category EIA or RDT for DENV antigen (NS1)

Addition, change or deletion Addition

Proposed test purpose of test For population surveys and in the diagnosis of DENV infection

Applicant organization(s) World Health Organization

WHO technical department Control of Neglected Tropical Diseases

Background

Disease condition and impact on patients: Dengue fever has a broad spectrum of clinical presentations, often with unpredictable clinical evolution and outcome. While most patients recover after a self-limiting, non-severe clinical course, a small proportion of cases progress to severe disease, characterized mainly by plasma leakage with or without haemorrhage. Intravenous rehydration is the therapy of choice, as it can reduce the fatality rate of severe cases to < 1%. Progression from non-severe to severe disease is difficult to define; however, appropriate treatment can prevent more severe clinical conditions.

Does this test meet a medical need? Efficient, accurate diagnosis of dengue is of primary importance for clinical care (for early detection of severe cases, case confirmation and differential diagnosis from other infectious diseases), surveillance, outbreak control, pathogenesis, academic research, vaccine development and clinical trials. In relation to the EDL, antibody and antigen tests are essential for case management and surveillance. During the early stages of the disease, detection of antigens can be used to diagnose an infection, while,

at the end of the acute phase of infection, serology is the method of choice. The choice of the assay for diagnosis depends on the time of sample collection and the purpose of testing (1). As for other Aedes-borne arboviruses, viraemia is present during the acute phase, and 90% of cases of primary and secondary dengue fever can be identified accurately from a single serum specimen collected during the first 10 days of illness, with DENV-1-4 real-time RT-PCR plus IgM ELISA or NS1 antigen ELISA (2, 3).

Purposes of testing: In surveillance, the test is used to alert health authorities to possible emergence of an outbreak. Tests to identify the cause of an outbreak must be highly sensitive and specific in detecting DENV directly by isolation of the virus, its nucleic acid or its antigen in the acute phase of infection. Infection can also be diagnosed retrospectively from seroconversion of IgM or a four-times increase in IgG between the acute and convalescent values in serum samples collected > 14 days apart. A combination of IgM and either NAATs or antigen detection tests extends the window of detection of acute infection. The tests can also be used to assess the extent of an outbreak, inform control strategies and identify hotspots. High-throughput, ideally highly specific tests that can be used in various populations are required. In research, they are used to assess the impact of control interventions and improve understanding of the pathogen and its pathogenesis.

DENV NS1 testing by ELISA or RDT is essential to confirm DENV infection directly, during onset of the disease. Both tests are straightforward EIA and RDT assays, and no significant difficulties have been reported by users. Disposal of the kits is routine and does not require special precautions.

How the test is used: Depending on the set-up, the assay can be used at three levels of health systems: primary care centres, district centres and reference centres. A single test is sufficient if the sample is taken within the predefined time. As dengue fever is easily confused with non-dengue illnesses, particularly in non-epidemic situations, the DENV IVD can also be used as a differential test.

The NS1 glycoprotein is produced by all flaviviruses and is secreted from mammalian cells. NS1 produces a very strong humoral response. Many studies have shown that detection of NS1 can be used to make an early diagnosis of DENV infection. Commercial kits for the detection of NS1 antigen are available, although they do not differentiate between DENV serotypes.

Public health relevance

Prevalence: Dengue fever is the most rapidly spreading mosquito-borne viral disease in the world. Its incidence has increased 30 times over the past 50 years, with increasing geographical spread to new countries and, in the current

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decade, from urban to rural settings. An estimated 50 million cases of DENV infection occur annually, and approximately 2.5 billion people live in dengueendemic countries. World Health Assembly resolution WHA55.17 in 2002 urged greater commitment to dengue by WHO and its Member States. Of particular significance is World Health Assembly resolution WHA58.3 on revision of the IHR in 2005, which included dengue fever as an example of a disease that may constitute a PHEIC, with implications for health security due to disruption and rapid epidemic spread beyond national borders.

Socioeconomic impact: The global cost of dengue fever is estimated to be almost US\$ 9 billion per year for prevention and control (4), and WHO estimated that more than 3 billion DALYs are lost annually from dengue illness.

WHO or other clinical guidelines relevant to the test

Guidelines for patient care in the Region of the Americas (5).

Test purpose	Population survey and as an aid in the diagnosis of DENV infection Population surveys, case management
Test format	RDT, ELISA
Specimen types	Serum, plasma
Equipment required	Basic automated hand-held ELISA, simple hand-held RDT
Regulatory status	Stringent regulatory authorities
Global availability	> 100
Price per test range	US\$ 1–5
Instrument price range	Not provided

Basic test characteristics

Evidence for clinical usefulness and impact

In a review of the performance of commercially available NS1 RDTs, Blacksell et al. (6) summarized the results of evaluations of each of the SD Bioline Dengue Duo (Alere, USA) (four studies), the Panbio[®] Early Rapid NS1 (Alere, USA) (three studies) and the Dengue NS1 Strip (Bio-Rad, France) (12 studies) in various countries. The sensitivity of the RDTs varied from 48.5% to 98.9%, but their specificity was reasonably consistent, all being > 92%. Blacksell et al. (6), however, noted that the comparator used in the studies, RT-PCR or NS1-ELISA, was "skewed", and the authors did not investigate the possibility of false-negative

results by testing paired sera to determine a dynamic rise in serological assays such as IgM- or IgG-capture ELISAs. In studies of the diagnostic accuracy of NS1 assays in primary and secondary infections, the RDTs were generally more sensitive in primary than in secondary infections (7-10).

Evidence for economic impact and/or cost-effectiveness

If only a subset of patients is tested during outbreaks or endemic periods for confirmation, the impact on overall budgets will be small.

Ethics, equity and human rights issues

Consent is required to obtain a serum sample. Dengue predominantly affects populations living in poverty, and access to high-quality diagnostics can reduce the burden and improve equity.

SAGE IVD evidence review

A systematic review and meta-analysis of 30 studies showed low sensitivity and high specificity for two different assays: sensitivity 66% (95% CI 61; 71) and 74% (95% CI 63; 82); specificity 99% (95% CI 96; 100) and 99% (95% CI 97; 100).

SAGE IVD considerations for recommendation

Dengue fever is the most rapidly spreading mosquito-borne viral disease in the world. Antibody and antigen tests are essential for case management, surveillance and confirmation of outbreaks. There is substantial evidence that NS1 ELISA and RDT tests have poor sensitivity when used alone, although their specificity is consistently high. Several studies have evaluated the combination of NS1 and IgM, as separate tests or in a purpose-made dual RDT, which appears to increase sensitivity without compromising specificity, but no systematic review of studies of this test combination has been reported.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion on the EDL of the EIA or RDT for dengue NS1 antigen only if used in combination with the EIA or RDT for DENV IgM (see above) in a specified algorithm.

The Group noted that guidelines for DENV testing would become available shortly and recommended that the test be prequalified to ensure that the most appropriate tests are available.

Recommended test purpose

As an aid in the diagnosis of dengue fever (always in combination with NS1) and for population surveys

The selection and use of essential in vitro diagnostics

References

- 1. Peeling R, Murtagh M, Olliaro P. Epidemic preparedness: why is there a need to accelerate the development of diagnostics? Lancet Infect Dis. 2019;19(5):e172–8.
- Hunsperger EA, Muñoz-Jordán J, Beltran M, Colón C, Carrión J, Vazquez J, et al. Performance of dengue diagnostic tests in a single-specimen diagnostic algorithm. J Infect Dis. 2016;214(6): 836–44.
- 3. Peeling RW, Olliaro P. Reimagining the future of the diagnosis of viral infections. J Infect Dis. 2016;214(6):828–9.
- 4. Shepard DS, Undurraga EA, Halasa YA, Stanaway JD. The global economic burden of dengue: a systematic analysis. Lancet Infect Dis. 2016;16(8):935–41.
- 5. Dengue: Guidelines for patient care in the Region of the Americas. Second edition. Washington DC: Pan American Health Organization; 2016.
- 6. Blacksell SD. Commercial dengue rapid diagnostic tests for point-of-care application: recent evaluations and future needs? J Biomed Biotechnol. 2012:151967.
- Guzman MG, Jaenisch T, Gaczkowski R, Ty Hang VT, Sekaran SD, Kroeger A, et al. Multi-country evaluation of sensitivity and specificity of two commercially-available NS1 ELISA assays for dengue diagnosis. PLoS Negl Trop Dis. 2010;4(8):e811.
- Shu PY, Yang CF, Kao JF, Su CL, Chang SF, Lin CC, et al. Application of the dengue virus NS1 antigen rapid test for on-site detection of imported dengue cases at airports. Clin Vac Immunol. 2009;16:589–91.
- Hang VT, Nguyet NM, Trung DT, Tricou V, Yoksan S, Dung NM, et al. Diagnostic accuracy of NS1 ELISA and lateral flow rapid tests for dengue sensitivity, specificity and relationship to viraemia and antibody responses. PLoS Negl Trop Dis. 2009;1:e360.
- 10. Chaiyaratana W, Chuansumrit A, Pongthanapisith V, Tangnararatchakit K, Lertwongrath S, Yoksan S. Evaluation of dengue nonstructural protein 1 antigen strip for the rapid diagnosis of patients with dengue infection. Diagn Microbiol Infect Dis. 2009;64:83–4.

Dengue virus nucleic acid test

Test category

Test for DENV nucleic acid

Addition, change or deletion

Addition

Proposed test purpose For population surveys and for confirmation of DENV infection

Applicant organization(s) World Health Organization

WHO technical department Control of Neglected Tropical Diseases

Background

Disease condition and impact on the patient: Dengue fever has a wide spectrum of clinical presentations, often with unpredictable clinical evolution and outcome. While most patients recover after a self-limiting, non-severe clinical course, a small proportion of cases progress to severe disease, characterized mainly by plasma leakage with or without haemorrhage. Intravenous rehydration is the therapy of choice, as it can reduce the fatality rate of severe cases to < 1%. Progression from non-severe to severe disease is difficult to define; however, appropriate treatment can prevent more severe clinical conditions.

Does the test meet a medical need? Efficient, accurate diagnosis of dengue is of primary importance for clinical care (for early detection of severe cases, case confirmation and differential diagnosis from other infectious diseases), surveillance, outbreak control, pathogenesis, academic research, vaccine development and clinical trials. During the early stages of the disease, detection of antigens can be used to diagnose an infection, while, at the end of the acute phase of infection, serology is the method of choice. The choice of the assay for diagnosis depends on the time of sample collection and the purpose of testing (1). As for other Aedes-borne arboviruses, viraemia is present during the acute phase, and 90% of cases of primary and secondary dengue fever can be identified accurately from a single serum specimen collected during the first 10 days of illness, with DENV-1-4 real-time RT-PCR plus IgM ELISA or NS1 antigen ELISA (2, 3).

Purposes of testing: In surveillance, the test is used to alert health authorities to possible emergence of an outbreak. Tests to identify the cause of an outbreak must be highly sensitive and specific in detecting DENV directly by isolation of the virus, its nucleic acid or its antigen in the acute phase of infection. Infection can also be diagnosed retrospectively from seroconversion of IgM or a four-times increase in IgG between the acute and convalescent values in serum samples collected > 14 days apart. A combination of IgM and either NAATs or antigen detection tests extends the window of detection of acute infection. The tests can also be used to assess the extent of an outbreak, inform control strategies and identify hotspots. High-throughput, ideally highly specific tests that can be used in various populations are required. In research, they are used to assess the impact of control interventions and improve understanding of the pathogen and its pathogenesis.

How the test is used: There are many NAATs for DENV, which can be used with whole blood, sera or tissue specimens taken from patients during the acute phase of infection. NAAT assays can provide results the same or the next day

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for DENV in serum or plasma taken from patients in the acute phase of the infection. Depending on the set-up, the assay can be used at three levels of health systems: primary care centres, district centres and reference centres. A single test is sufficient if the sample is taken within the predefined time. As dengue fever is easily confused with non-dengue illnesses, particularly in non-epidemic situations, the DENV IVD can also be used as a differential test.

Public health relevance

Prevalence: Dengue fever is the most rapidly spreading mosquito-borne viral disease in the world. Its incidence has increased 30 times over the past 50 years, with increasing geographical spread to new countries and, in the current decade, from urban to rural settings. An estimated 50 million cases of DENV infection occur annually, and approximately 2.5 billion people live in dengue-endemic countries. World Health Assembly resolution WHA55.17 in 2002 urged greater commitment to dengue fever by WHO and its Member States. Of particular significance is World Health Assembly resolution WHA58.3 on revision of the IHR in 2005, which included dengue fever as an example of a disease that may constitute a PHEIC, with implications for health security due to disruption and rapid epidemic spread beyond national borders.

Socioeconomic impact: The global cost of dengue fever is estimated to be almost US\$ 9 billion per year for prevention and control (*4*), and WHO estimated that more than 3 billion DALYs are lost annually from dengue illness.

WHO or other clinical guidelines relevant to the test

Guidelines for patient care in the Region of the Americas (5).

Test purpose	DENV surveillance, confirmation
Test format	PCR
Specimen types	Serum, plasma or stored filter-paper blood samples
Equipment required	Various basic instruments (PCR, centrifuge, pipettes)
Regulatory status	Stringent regulatory authorities
Global availability	> 100
Price per test range	US\$ 5–10
Instrument price range	Not stated

Basic test category characteristics

Evidence for clinical usefulness and impact

Najioullah et al. (6) evaluated four commercial real-time RT-PCR kits: Simplexa™ dengue RT-PCR assay (Focus Diagnostics, USA), RealStar Dengue RT-PCR kit 1.0 (Altona Diagnostics, Germany), DENV general type real-time RT-PCR kit Liferiver[™] (Shanghai ZJ Bio-Tech Co, China) and DENV 1-4 real-time RT-PCR kit (Genome Diagnostics Pvt, India). In three of the assays, amplification and detection were performed on the ABI Prism® 7500 (Applied Biosystems, France). For Simplexa, the 3M integrated cycler provided by Focus was used. The Liferiver[™] kit was poorly sensitive in the initial panel of 40 positive samples, detecting only 40%, and was not evaluated further. The sensitivity of the other three assays was 85.2% for Geno-sen', 83.3% for Realstar and 93.2% for Simplexa. Saengsawang et al. (7) evaluated two commercial real-time PCR assays for the detection of DENV infection, abTES DEN 5 quantitative PCR (abTES) (AITbiotech, Singapore) and the DETECT Two-step assay (innuDETECT; Analytik, Germany). Amplification and detection were done with the compact CFX96 realtime thermocycler (Bio-Rad Laboratories, Hercules, CA, USA). Positive results for DENV were found for 117 samples by nested RT-PCR and IgM/IgG ELISA. Serotypes were identified by nested RT-PCR. The abTES assay performed well, with an overall sensitivity of 97.4%, while the innuDETECT assay showed an overall sensitivity of only 44.4%. The eight control serum samples were negative in both assays, giving a specificity of 100%. The authors concluded that the abTES assay allows rapid diagnosis of DENV infection, which could be useful when urgent clinical care is needed.

Evidence for economic impact and/or cost-effectiveness

If only a subset of patients is tested during outbreaks or endemic periods, for confirmation, the impact on budgets will be small.

Ethics, equity and human rights issues

Consent is required to obtain a blood sample. Dengue fever predominantly affects populations living in poverty, and access to high-quality diagnostics could reduce the burden and improve equity.

SAGE IVD evidence review

Data were available from only two primary studies on banked sets of DENVpositive sera from the Caribbean and from Thailand for analysis in six tests of 279 positive samples and 78 negative samples. The results showed good sensitivity and specificity in four of the six tests. Their performance appears promising, but the small number of participants (particularly DENV-negative) and the availability of only two studies provide only weak evidence. The selection and use of essential in vitro diagnostics

SAGE IVD considerations for recommendation

Dengue fever is the most rapidly spreading mosquito-borne viral disease in the world. There are many NAATs for DENV, which can be used with whole blood, sera or tissue specimens taken from patients during the acute phase of DENV infection.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended conditional inclusion on the EDL of tests for DENV nucleic acid, pending submission of better-designed studies with commercially available tests and evaluation in clinical settings. The Group noted that it should be used in conjunction with EIA or RDT for DENV IgM and NS1 antigen (see above) in a specified algorithm.

The Group noted that the test should be used only for confirmation; a standardized assay would be required for its application in diagnosis. The test is suitable only for use in reference laboratories, where it would also be useful for tracking changes in the virus serotype.

Recommended test purpose

For surveillance (serotype differentiation) and for confirmation of outbreaks

References

- 1. Peeling R, Murtagh M, Olliaro P. Epidemic preparedness: why do we need to accelerate the development of diagnostics? Lancet Infect Dis. 2019;19(5):e172–8.
- Hunsperger EA, Muñoz-Jordán J, Beltran M, Colón C, Carrión J, Vazquez J, et al. Performance of dengue diagnostic tests in a single-specimen diagnostic algorithm. J Infect Dis. 2016;214(6): 836–44.
- 3. Peeling RW, Olliaro P. Reimagining the future of the diagnosis of viral infections. J Infect Dis. 2016;214(6):828–9.
- 4. Shepard DS, Undurraga EA, Halasa YA, Stanaway JD. The global economic burden of dengue: a systematic analysis. Lancet Infect Dis. 2016;16(8):935–41.
- 5. Dengue: Guidelines for patient care in the Region of the Americas. Second edition. Washington DC: Pan American Health Organization; 2016.
- 6. Najioullah F, Viron F, Césaire R. Evaluation of four commercial real-time RT-PCR kits for the detection of dengue viruses in clinical samples. Virol J. 2014; 11:164.
- Saengsawang J, Nathalang O, Kamonsil M, Watanaveeradej V. Comparison of two commercial real-time PCR assays for detection of dengue virus in patient serum samples. J Clin Microbiol 2014;52:3781–3.

Kato-Katz test for soil-transmitted helminths and intestinal schistosomes

Test category Kato-Katz test

Addition, change or deletion Addition

Proposed test purpose

Diagnosis of soil-transmitted helminthiasis and schistosomiasis for individual treatment or community diagnosis to determine whether preventive chemotherapy is necessary

Applicant organization(s) World Health Organization

WHO technical department Control of Neglected Tropical Diseases

Background

Disease condition and impact on patients: Soil-transmitted helminths are a group of parasites that are transmitted among humans from faecally contaminated soil. The group is composed of four species: Ascaris lumbricoides, Trichuris trichiura, Necator americanus and Ancylostoma duodenale. The morbidity caused by these organisms results from disturbance of normal nutritional processes, the mechanism of which varies by species but is proportional to the number of worms infecting the host. For this reason, it is important that the diagnostic method measure the intensity of infection.

Does the test meet a medical need? As many as 2 billion people are affected by soil-transmitted helminthiasis and intestinal schistosomiasis.

How the test is used: The Kato-Katz test is a low-cost, well-known laboratory method for diagnosing the presence and intensity of schistosome and soil-transmitted helminth infections; the two groups of helminths can be identified at the same time. The method involves measurement of a standard quantity of faeces (41 mg), clarification with formalin and observation under a microscope to identify and count the eggs of the different parasites separately. The number of parasite eggs on each microscope slide allows quantification of the number of eggs per gram of faeces as a measure of the intensity of infection. The eggs are much larger than those of other parasites, with a distinct morphology,

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so that the diagnosis is 100% specific; no tests for its validity have therefore been conducted.

Public health relevance

Prevalence: The public health importance of soil-transmitted helminthiasis is due to the large number of people infected – as many as two billion – and the direct and indirect morbidity resulting from infection.

Socioeconomic impact: WHO attributed a global loss in 2010 of 3.394 million DALYs due to soil-transmitted helminthiasis, for all ages.

WHO or other clinical guidelines relevant to the test

The methods for conducting tests have been described (1) but not evaluated. Regular surveys with the Kato-Katz technique are recommended to assess disease prevalence and determine whether a community intervention is necessary.

Test purpose	DENV surveillance, confirmation
Test format	PCR
Specimen types	Serum, plasma or stored filter-paper blood samples
Equipment required	Various basic instruments (PCR, centrifuge, pipettes)
Regulatory status	Stringent regulatory authorities
Global availability	> 100
Price per test range	US\$ 5–10
Instrument price range	Not stated
Global availability Price per test range	> 100 US\$ 5–10

Basic test characteristics

Evidence for clinical usefulness and impact

The Kato-Katz test was compared with alternatives (MINI Flotac, FecPACK and quantitative PCR) in one WHO collaborating centre, which found that the Kato-Katz thick smear method was equivalent or superior. The main constraint of the test is its poor sensitivity for infections of very low intensity, when only a few eggs are present in faeces, as only 41 mg of faeces are used. In helminthology, however, low-intensity infections are of limited clinical relevance, as helminths do not replicate in the host and low-intensity infections do not necessarily evolve into more severe cases.

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Evidence for economic impact and/or cost-effectiveness

A kit of 400 tests costs about US\$ 40, and the material is recyclable. Capacity to perform the test is well developed in all endemic countries.

Ethics, equity and human rights issues

Consent is required to obtain a faecal sample. The test is readily accessible because of its low cost.

SAGE IVD evidence review

Evidence of the accuracy of the test is not currently available. A study has been submitted for publication but was not made available to the SAGE IVD.

SAGE IVD considerations for recommendation

The Kato-Katz test has been used for more than 50 years. It is valuable for diagnosis and can be used anywhere, including in rural areas where the disease thrives but where there is limited infrastructure. The method is non-invasive, and the kit does not require a cold chain and can be stored for years in field conditions. Templates, spatulas and sample collection containers can be re-used if washed thoroughly. The sensitivity of the test depends on the intensity of infection, but the specificity is 100%.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended conditional inclusion on the EDL of the Kato-Katz test, pending submission of evidence of its performance.

The Group noted that, although the test is widely used, no evidence was submitted on its performance, applicability or precision. The poor sensitivity of the test precludes its use in elimination settings. A complete submission should also include comparisons with newer tests and evidence for their use.

Recommended test purpose

For surveillance and diagnosis of soil- transmitted helminthiasis and schistosomiasis caused by *Schistosoma mansoni*, *S. intercalatum*, *S. japonicum* and *S. mekongi*

Reference

1. Helminth control in school-age children: a guide for managers of control programmes, second edition. Geneva: World Health Organization; 2011.

Primary immunodeficiency disorders Lymphocyte subtypes (CD4, CD8, CD20 and CD16/56 cells, B cells and NK cells)

Test description

Enumeration of lymphocyte subtypes: CD4 (in HIV infection), CD8, CD20 and CD16/56 cells, B cells and NK cells

Addition, change or deletion Addition

Proposed test purpose In the diagnosis of primary and secondary immunodeficiency disorders

Applicant organization(s) IPOPI

WHO technical department Not available

Background

Disease condition and impact on patients: In a study of 32 patients with primary immunodeficiency, more than two thirds experienced diagnostic delay, which led to serious morbidity, including pneumonia, meningitis, osteomyelitis and septicaemia (1). In the USA, the proportion of hospital admissions for primary immunodeficiency increased each year between 2001 and 2005, and patients had significantly longer hospital stays. The most common comorbidities included nonspecific fever, splenomegaly and failure to thrive, respiratory infections, pathogenspecific infections and chronic lung disease (2). Data from a service for over 1000 patients with suspected primary immunodeficiency in Asia showed that families had often lost one or more children to undiagnosed immunodeficiency before the current diagnosis (3). Long delays in diagnosis and many infectious episodes can reduce the quality of life and result in permanent functional impairment (1). In a cohort of 2212 patients with common variable immunodeficiency, each year of diagnostic delay and each year of age at diagnosis were associated with a 1.7% and a 4.5% increase in the risk of death, respectively. Long delays in diagnosis and many infectious episodes can reduce the quality of life and result in permanent functional impairment (1).

Does this test meet a medical need? Primary immunodeficiency can often be diagnosed with two simple blood tests – a complete blood count with differential white cell count and serum immunoglobulin levels (3); however, although these

tests are inexpensive, they are not necessarily available in all countries. Criteria for fast, reliable diagnosis of primary immunodeficiency include physicianfriendly algorithms (4), with multi-stage diagnostic protocols for different clinical presentations so that patients are referred early for therapy (3). The target population is people with primary immunodeficiency, who have no protection against common pathogens and have life-threatening infections and increasing, permanent damage to various body organs, especially the lungs and intestines, making them more susceptible to severe infections. Many of the conditions that are present in childhood are genetic, and parental consanguinity is a risk factor for primary immunodeficiency. A positive family history is an important indication for screening.

How the test is used: The IVD is used in protocols to ensure swift diagnosis according to the clinical presentation. Examples of peer-reviewed published diagnostic protocols are reported in references 4 and 5.

Public health relevance

Prevalence: Primary immunodeficiency comprises over 350 inherited disorders, due to malfunction of components of the immune system. The condition may be more common than previously estimated, with as many as 1% of the population affected.

Socioeconomic impact: Diagnostic delays lead not only to deterioration of the patient's condition and difficulty for carers but also to inappropriate use of health resources, including avoidable visits to specialists for recurring infections. Early diagnosis resulted in lower costs than in the previous year, even if regular immunoglobulin replacement therapy was required. The annual saving by the health care system for each diagnosed patient was US\$ 85 882 (6). In a study of early diagnosis and management of primary immunodeficiency in the USA, the average annual cost to the health care system for each patient with undiagnosed primary immunodeficiency was US\$ 102 552; early diagnosis and treatment saved an average of US\$ 79 942 per patient per year (7).

WHO or other clinical guidelines relevant to the test None reported

Test purpose	In the diagnosis of primary and secondary immunodeficiency disorders
Test format	Flow cytometry

Basic test characteristics

Specimen types	5 mL EDTA blood sample
Equipment required	Flow cytometer: many brands are available. Various pipettes; 12 x 75 mm polystyrene test tubes and caps (Elkay Laboratory Products). Various pipettes; 12 x 75 mm polystyrene test tubes and caps. Centrifuge, water bath, vortex mixer, sample rotator
Regulatory status	Commercially available flow cytometers are approved by many regulatory bodies
Global availability	Broad
Price per test range	US\$ 20–60
Instrument price range	Same as for CD4 cell enumeration.

Table continued

Evidence for clinical usefulness and impact

Use of these tests in the diagnosis of immunodeficiency is well established in international practice and recommended by the American Academy of Allergy, Asthma and Immunology, the Jeffrey Modell Foundation and the European Society for Immunodeficiencies as best practice.

Evidence for economic impact and/or cost-effectiveness

Few comparative data are available on cost-effectiveness for this large group of rare diseases. Flow cytometry requires high initial costs for analysers and staff and may be suitable only for hub laboratories in resource-poor areas. The typical cost is £ 50-70 (US\$ 64-90) in the United Kingdom. In India, the cost to the hospital is 720–940 INR (US\$ 10–13), and that to the patient is 900 INR (US\$ 12.45).

This technique requires significant manpower, training and maintenance and a dedicated machine. Expertise and significant training are required for interpretation.

Ethics, equity and human rights issues

Consent is required to obtain a blood sample. Antibody deficiency disorders are chronic and rare and are often diagnosed late or not at all, even in developed countries with effective, widely available access to health care. Once primary immunodeficiency is diagnosed, the right treatment can be prescribed, and, according to their doctor's advice. patients can lead a normal life with a lower risk of infections. A prompt diagnosis is the priority, as it increases the chances of appropriate treatment, management and care. About 60% of patients require

life-long treatment with immunoglobulin replacement therapy, which are WHO essential medicines for both adults (8) and children (9). The proposed IVD tests would help to close the gap between access to diagnosis and treatment and would probably be cost–effective. They would also help to reduce under-diagnosis: it is estimated that 70–90% of people worldwide have undiagnosed primary immunodeficiency (10). In the USA, the average time from symptom onset to diagnosis of primary immunodeficiency is 12.4 years (11).

The first recommendation of the Asia-Pacific Economic Cooperation for enhancing access to safe therapy for people with immunodeficiency and bleeding disorders is to improve laboratory diagnosis (12). Inclusion of these tests would enable faster diagnosis of primary immunodeficiency and therefore increase equity for this patient population.

SAGE IVD evidence review

No detailed evidence or summary of evidence was submitted to support this intended use. There is evidence of the accuracy and value of flow cytometry in differentiating lymphocyte subsets, particularly for diagnosis of leukaemia, extended to HIV infection and lymphoma. There is also clear evidence of the importance of accurate, early diagnosis in reducing morbidity and mortality and of cost–effectiveness. As flow cytometry is a routine diagnostic technique, with immunoglobulin estimation in high-income settings, the test has not been investigated individually. Its importance has been accepted by association.

SAGE IVD considerations for recommendation

Immunodeficiency consists of a wide variety of conditions and is underdiagnosed even in high-income countries. It contributes to a significant disease burden, which can often be relieved if the condition diagnosed early and treated appropriately. While estimates of immunoglobulin are widely used, they do not identify the cellular-based abnormalities, and a combined diagnostic approach is required. Both specific treatment and long-term care of chronically infected patients are expensive, with wide implications for the families of sufferers.

The capital costs of a flow cytometric facility are high, as a dedicated laboratory with access to a reliable power supply and consumables is required. A flow cytometry facility for following up HIV patients and/or for diagnosis of leukaemia can also be used for immunodeficiency testing.

This IVD for enumeration of lymphocyte subtypes is used in protocols to ensure swift diagnosis according to the clinical presentation; however, the technique requires significant manpower, training and maintenance, a dedicated machine and expertise and training for interpretation. The test is used and is recommended by a number of professional associations.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended conditional inclusion on the EDL of the IVD for enumeration of lymphocyte subtypes for diagnosis of immunodeficiency, pending submission of evidence for its clinical usefulness and use in LMICs.

The Group noted that the test is expensive and requires highly skilled laboratory technicians. No evidence was provided of its use in LMICs. Furthermore, the submission did not include an evaluation of evidence that patients were treated with the associated EML drugs as a result of use of the test, and no evidence was given for its diagnostic accuracy or safety. No guidelines for its use appear to be available.

Recommended test purpose

As an aid in the diagnosis of primary and secondary immunodeficiencies

References

- 1. Jiang F, Torgerson TR, Ayars AG. Health-related quality of life in patients with primary immunodeficiency diseases. Allergy Asthma Clin Immunol. 2015;11:27.
- 2. Kobrynski L, Waltenburg Powell R, Bowen S. Prevalence and morbidity of primary immunodeficiency diseases, United States 2001–2007. J Clin Immunol. 2014;34(8):954–61.
- 3. Chapel H, Prevot J, Gaspar HB, Español T, Bonilla FA, Solis L, et al. Primary immune deficiencies principles of care. Front Immunol. 2014;5:627.
- Bousfiha AA, Jeddane L, Ailal F, Al-Herz W, Conley ME, Cunningham-Rundles C, et al. A phenotypic approach for IUIS primary immunodeficiency classification and diagnosis: guidelines for clinicians at the bedside. J Clin Immunol. 2013;33:1078–87.
- De Vries E, Clinical Working Party of the European Society for Immunodeficiencies (ESID). Patientcentred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists. Clin Exp Immunol. 2011;167:108–19.
- 6. Modell V, Orange JS, Quinn J, Modell F. Global report on primary immunodeficiencies: 2018 update from the Jeffrey Modell Centers Network on disease classification, regional trends, treatment modalities, and physician reported outcomes. Immunol Res. 2018;66:367–80.
- 7. Condino-Neto A, Espinosa-Rosales FJ. Changing the lives of people with primary immunodeficiencies (PI) with early testing and diagnosis. Front Immunol. 2018;9:1439.
- 8. 20th Model List of Essential Medicines. Geneva: World Health Organization; 2017 (http://apps. who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1, accessed April 2019).
- 9. 6th Model List of Essential Medicines for Children: Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/handle/10665/273825/EMLc-6-eng.pdf?ua=1, accessed April 2019).
- Primary immunodeficiencies (PID) driving diagnosis for optimal care in Europe. European reference paper. London: World PI week; 2019 (http://worldpiweek.org/sites/default/files/basic_ page_documents/PI_European_Reference_Paper.pdf, accessed April 2019).

- Primary immune deficiency diseases in America: 2007. The third national survey of patients. Towson (MD): Immune Deficiency Foundation; 2009 (https://primaryimmune.org/wp-content/ uploads/2011/04/Primary-Immunodeficiency-Diseases-in-America-2007The-Third-National-Survey-of-Patients.pdf, accessed April 2019).
- 12. APEC recommendations for enhancing access to safe therapy for persons with immunodeficiency and bleeding disorders. Singapore: Asia–Pacific Economic Cooperation; 2018 (http://blood.apec.org/wp-content/uploads/2018/01/17_lsif2_agn05.7_Access-to-Safe-Therapy-recommendations-FINAL.-docx.pdf, accessed July 2019).

Plasma levels of immunoglobulins G, A and M

Test category

Nephelometry or turbidimetry with capillary zone electrophoresis for plasma levels of IgG, IgA and IgM

Addition, change or deletion

Addition

Proposed test purpose

For diagnosis of primary and secondary immunodeficiency disorders, identification of patients with low levels of immunoglobulin levels and monitoring replacement

Applicant organization(s)

IPOPI and International Union of Immunological Societies

Background

Disease condition and impact on patients: In a study of 32 patients with primary immunodeficiency, more than two thirds experienced diagnostic delay, which led to serious morbidity, including pneumonia, meningitis, osteomyelitis and septicaemia (1). In the USA, the proportion of hospital admissions for primary immunodeficiency increased each year between 2001 and 2005, and patients had significantly longer hospital stays. The most common comorbidities included non-specific fever, splenomegaly and failure to thrive, respiratory infections, pathogen-specific infections and chronic lung disease (2). Data from a service for over 1000 patients with suspected primary immunodeficiency in Asia showed that families had often lost one or more children to undiagnosed immunodeficiency before the current diagnosis (3). Long delays in diagnosis and many infectious episodes can reduce the quality of life and result in permanent functional impairment (1).

Does this test meet a medical need? Primary immunodeficiency can often be diagnosed with two simple blood tests – a complete blood count with differential

white cell count and serum immunoglobulin levels (3); however, although these tests are inexpensive, they are not necessarily available in all countries. Criteria for fast, reliable diagnosis of primary immunodeficiency include physicianfriendly algorithms (4), with multi-stage diagnostic protocols for different clinical presentations so that patients are referred early for therapy (3). The target population is people with primary immunodeficiency, who have no protection against common pathogens and have life-threatening infections and increasing, permanent damage to various body organs, especially the lungs and intestines, making them more susceptible to severe infections. Many of the conditions that are present in childhood are genetic, and parental consanguinity is a risk factor for primary immunodeficiency. A positive family history is an important indication for screening.

How the test is used: The IVDs listed in this application are part of diagnostic protocols to optimize a swift diagnosis. Examples of peer-reviewed published diagnostic protocols are reported in references 4 and 5.

Public health relevance

Prevalence: Primary immunodeficiency comprises over 350 inherited disorders due to malfunction of components of the immune system. The condition may be more common than previously estimated, with as many as 1% of the population affected.

Socioeconomic impact: Diagnostic delays lead not only to deterioration of the patient's condition and difficulty for carers but also to inappropriate use of health resources, including avoidable visits to specialists for recurring infections. Early diagnosis resulted in lower costs than in the previous year, even if regular immunoglobulin replacement therapy was required. The annual saving by the health care system for each diagnosed patient was US\$ 85 882 (6). In a study of early diagnosis and management of primary immunodeficiency in the USA, the average annual cost to the health care system for each patient with undiagnosed primary immunodeficiency was US\$ 102 552; early diagnosis and treatment saved an average of US\$ 79 942 per patient per year (7).

WHO or other clinical guidelines relevant to the test None reported

Basic test characteristics

Test purpose

Diagnosis of primary and secondary immunodeficiency disorders to identify patients with low immunoglobulin levels and monitor replacement therapy

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Test format	Nephelometry, ELISA, centrifugal analysis, radial immunodiffusion
Specimen types	Plasma 2 mL serum for quantification of immunoglobulins; 2 mL serum and 5 mL urine for electrophoresis
Equipment required	Basic automated instruments
Regulatory status	Commercially available products have CE, FDA
Global availability	Broad
Price per test range	US\$ 0.5–7
Instrument price range	US\$ 1 000–8 500

Table continued

Evidence for clinical usefulness and impact

Use of these tests in the diagnosis of immunodeficiency is well established in international practice and in the recommendations of the American Academy of Allergy, Asthma and Immunology, the Jeffrey Modell Foundation and the European Society for Immunodeficiencies.

Evidence for economic impact and/or cost-effectiveness

Few comparative data on the cost-effectiveness of the test for these rare diseases were available. Nephelometry or turbidimetry to measure plasma levels of IgG, IgA and IgM involves high start-up costs for analysers and staff and may be suitable only for hub laboratories in resource-poor areas. The typical cost is £ 8-12 (US\$ 10-15.5) in the United Kingdom and, in India, 75 INR (US\$ 1.03) per test to the hospital and 100 INR (US\$ 1.38) to the patient. Serum-free light chain involves high initial costs for analysers and staff and may be suitable only for hub laboratories in resource-poor areas. The typical cost is £ 8-12 (US\$ 10-15.5) in the United Kingdom and, in India, 400 INR (US\$ 5.55) per test for the laboratory and 500 INR (US\$ 6.93) would be charged to the patient. The typical cost of radial immunodiffusion is £ 5.00 (US\$ 6.4) in the United Kingdom and, in India, 175 INR (US\$ 2.43) per test for the laboratory and 100 INR (US\$ 1.39) to the patient. All the techniques require significant manpower, training and maintenance. Some, such as immunoglobulin measurement or ELISA/EIA for antibody detection in vaccine responses, are performed on multi-analyte platforms, which have many other uses. Automated tests are performed on random access platforms, with minimal hands-on time required, and semi-automated tests are performed on batch analysers, with slightly more hands-on time required. Nevertheless, these instruments must be operated by skilled and trained personnel. Expertise and

significant training are required for interpreting the results. Significant skill and time are required to perform manual analyses.

Ethics, equity and human rights issues

Consent is required to obtain a sample. Antibody deficiency disorders are chronic and rare and are often diagnosed late or not at all, even in developed countries with effective, widely available access to health care. Once primary immunodeficiency is diagnosed, the right treatment can be prescribed. A prompt diagnosis is the priority, as it increases the chances of appropriate treatment, management and care. About 60% of patients require life-long treatment with immunoglobulin replacement therapy, which are WHO essential medicines for both adults (8) and children (9). The proposed IVD tests would help to close the gap between access to diagnosis and treatment and would probably be cost–effective. They would also help to reduce under-diagnosis: it is estimated that 70–90% of people worldwide have undiagnosed primary immunodeficiency (10). In the USA, the average time from symptom onset to diagnosis of primary immunodeficiency is 12.4 years (11).

The first recommendation of the Asia-Pacific Economic Cooperation for enhancing access to safe therapy for people with immunodeficiency and bleeding disorders is to improve laboratory diagnosis (12). Inclusion of these tests would enable faster diagnosis of primary immunodeficiency and therefore increase equity for this patient population.

SAGE IVD evidence review

No detailed evidence or summary of evidence was provided to support this submission; however, the method has been the reference standard for estimation of immunoglobulins. Supporting evidence for inclusion of these tests is provided by the trials considered by the EML for listing immunoglobulin therapies based on reported low values of IgG, IgM and IgA.

SAGE IVD considerations for recommendation

Counterpart immunoglobulin replacement therapies are listed in the WHO EML for both adults and children. Use of the tests for diagnosis of immunodeficiencies is well established in international practice and incorporated into the best practice recommendations and diagnostic criteria of the American Academy of Allergy, Asthma and Immunology, the Jeffrey Model Foundation and the European Society for Immunodeficiencies. The test is recommended by a number of professional associations.

The test methods have been standardized against the certified reference material in human serum of the Institute for Reference Materials and Measurements.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended conditional inclusion on the EDL of the IVD for measuring plasma levels of IgG, IgA and IgM for diagnosis of immunodeficiency, pending submission of evidence of its clinical usefulness, with testing in various regions in field surveys.

The Group noted that use of the test is expensive and requires highly skilled laboratory technicians. No evidence was provided of its use in LMICs, except in a few countries in Central America. Furthermore, the submission did not include an evaluation of evidence that patients were treated with the associated EML drugs as a result of use of the test, and no evidence was given for its diagnostic accuracy or safety. No guidelines for its use appear to be available.

Recommended test purpose

To identify patients with low immunoglobulin levels and monitor replacement.

References

- 1. Jiang F, Torgerson TR, Ayars AG. Health-related quality of life in patients with primary immunodeficiency diseases. Allergy Asthma Clin Immunol. 2015;11:27.
- 2. Kobrynski L, Waltenburg Powell R, Bowen S. Prevalence and morbidity of primary immunodeficiency diseases, United States 2001–2007. J Clin Immunol. 2014;34(8):954–61.
- 3. Chapel H, Prevot J, Gaspar HB, Español T, Bonilla FA, Solis L, et al. Primary immune deficiencies principles of care. Front Immunol. 2014;5:627.
- Bousfiha AA, Jeddane L, Ailal F, Al-Herz W, Conley ME, Cunningham-Rundles C, et al. A phenotypic approach for IUIS primary immunodeficiency classification and diagnosis: guidelines for clinicians at the bedside. J Clin Immunol. 2013;33:1078–87.
- De Vries E, Clinical Working Party of the European Society for Immunodeficiencies (ESID). Patientcentred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists. Clin Exp Immunol. 2011;167:108–19.
- Modell V, Orange JS, Quinn J, Modell F. Global report on primary immunodeficiencies: 2018 update from the Jeffrey Modell Centers Network on disease classification, regional trends, treatment modalities, and physician reported outcomes. Immunol Res. 2018;66:367–80.
- 7. Condino-Neto A, Espinosa-Rosales FJ. Changing the lives of people with primary immunodeficiencies (PI) with early testing and diagnosis. Front Immunol. 2018;9:1439.
- 20th Model List of Essential Medicines. Geneva: World Health Organization; 2017 (http://apps. who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1, accessed April 2019).
- 6th Model List of Essential Medicines for Children: Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/handle/10665/273825/EMLc-6-eng.pdf?ua=1, accessed April 2019).
- Primary immunodeficiencies (PID) driving diagnosis for optimal care in Europe. European reference paper. London: World PI week; 2019 (http://worldpiweek.org/sites/default/files/basic_ page_documents/PI_European_Reference_Paper.pdf, accessed April 2019).

- Primary immune deficiency diseases in America: 2007. The third national survey of patients. Towson (MD): Immune Deficiency Foundation; 2009 (https://primaryimmune.org/wp-content/ uploads/2011/04/Primary-Immunodeficiency-Diseases-in-America-2007The-Third-National-Survey-of-Patients.pdf, accessed April 2019).
- 12. APEC recommendations for enhancing access to safe therapy for persons with immunodeficiency and bleeding disorders. Singapore: Asia–Pacific Economic Cooperation; 2018 (http://blood.apec. org/wp-content/uploads/2018/01/17_lsif2_agn05.7_Access-to-Safe-Therapy-recommendations-FINAL.-docx.pdf, accessed July 2019).

Plasma and urine protein electrophoresis and immunofixation

Test description

Plasma and urine protein electrophoresis and immunofixation

Addition, change or deletion

Addition

Proposed test purpose

In the diagnosis of primary and secondary immunodeficiency disorders and monoclonal plasma cell disorders (e.g. multiple myeloma) and for differential diagnosis of primary antibody deficiency

Applicant organization(s)

IPOPI and International Union of Immunological Societies

Background

Disease condition and impact on patients: In a study of 32 patients with primary immunodeficiency, more than two thirds experienced diagnostic delay, which led to serious morbidity, including pneumonia, meningitis, osteomyelitis and septicaemia (1). In the USA, the proportion of hospital admissions for primary immunodeficiency increased each year between 2001 and 2005, and patients had significantly longer hospital stays. The most common comorbidities included non-specific fever, splenomegaly and failure to thrive, respiratory infections, pathogen-specific infections and chronic lung disease (2). Data from a service for over 1000 patients with suspected primary immunodeficiency in Asia showed that families had often lost one or more children to undiagnosed immunodeficiency before the current diagnosis (3). Long delays in diagnosis and many infectious episodes can reduce the quality of life and result in permanent functional impairment (1).

Does this test meet a medical need? Primary immunodeficiency can often be diagnosed with two simple blood tests – a complete blood count with differential

white cell count and serum immunoglobulin levels (3); however, although these tests are inexpensive, they are not necessarily available in all countries. Criteria for fast, reliable diagnosis of primary immunodeficiency include physicianfriendly algorithms (4) with multi-stage diagnostic protocols for different clinical presentations, so that patients are referred early for therapy (3). The target population is people with primary immunodeficiency, who have no protection against common pathogens and have life-threatening infections and increasing, permanent damage to various body organs, especially the lungs and intestines, making them more susceptible to severe infections. Many of the conditions that are present in childhood are genetic, and parental consanguinity is a risk factor for primary immunodeficiency. A positive family history is an important indication for screening.

How the test is used: The IVDs listed in this application are part of diagnostic protocols to optimize a swift diagnosis. Examples of peer-reviewed published diagnostic protocols are reported in references 4 and 5.

Public health relevance

Prevalence: Primary immunodeficiency comprises over 350 inherited disorders, due to malfunction of components of the immune system. The condition may be more common than previously estimated, with as many as 1% of the population affected.

Socioeconomic impact: Diagnostic delays lead not only to deterioration of the patient's condition and difficulty for carers but also to inappropriate use of health resources, including avoidable visits to specialists for recurring infections. Early diagnosis resulted in lower costs than in the previous year, even if regular immunoglobulin replacement therapy was required. The annual saving by the health care system for each diagnosed patient was US\$ 85 882 (6). In a study of early diagnosis and management of primary immunodeficiency in the USA, the average annual cost to the health care system for each patient with undiagnosed primary immunodeficiency was US\$ 102 552; early diagnosis and treatment saved an average of US\$ 79 942 per patient per year (7).

WHO or other clinical guidelines relevant to the test

None reported

Test purpose	In diagnosis of primary and secondary immunodeficiency
	and monoclonal plasma cell disorders (e.g. multiple myeloma)
	Differential diagnosis of primary antibody deficiency

Test format	Urine dipstick and light microscopy
Specimen types	Electrophoresis: 2 mL serum, 5 mL urine Identification of paraproteins (monoclonal gammopathy) in serum and urine by immunofixation: 2 mL serum, 5 mL urine
Equipment required	Basic automated instruments
Regulatory status	CE, FDA
Global availability	Broad
Price per test range	US\$ 0.5–16
Instrument price range	Not stated
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Table continued

Evidence for clinical usefulness and impact

Use of these tests in the diagnosis of immunodeficiency is well established in international practice and in the recommendations of the American Academy of Allergy, Asthma and Immunology, the Jeffrey Modell Foundation and the European Society for Immunodeficiencies.

Evidence for economic impact and/or cost-effectiveness

Few comparative data on the cost–effectiveness of the test for these rare diseases were available. The typical cost of capillary zone electrophoresis is £ 5.00 (US\$ 6.4) in the United Kingdom. The high initial cost of analysers and staff may make this test suitable only for hub laboratories in resource-poor areas. In India, the cost is 120 INR (US\$ 1.66) per test for the laboratory and 150 INR (US\$ 2.08) charged to the patient. Identification of paraproteins (monoclonal gammopathy) in serum and urine by immunofixation involves moderate initial cost for analysers and staff. The typical cost is £ 10–20 (US\$ 13–26) in the United Kingdom and, in India, 750 INR (US\$ 10.40) per test for the laboratory and 1 000 INR (US\$ 13.8) charged to the patient.

All the techniques require significant manpower, training and maintenance, and some, such as capillary zone electrophoresis, require dedicated machines. Automated tests are performed on random access platforms, with minimal hands-on time required, and semi-automated tests are performed on batch analysers, with slightly more hands-on time required. Nevertheless, these instruments must be operated by skilled and trained personnel. Expertise and significant training are required for interpretation of results. Significant skill and time are required to perform manual analyses.

Ethics, equity and human rights issues

Consent is required to obtain a sample. No ethical issues are associated with capillary zone electrophoresis or identification of paraproteins in serum and urine by immunofixation, as long as the patient is aware that investigation of immunodeficiency involves excluding a malignancy and provides informed consent.

Antibody deficiency disorders are chronic and rare and are often diagnosed late or not at all, even in developed countries with effective, widely available access to health care. Once primary immunodeficiency is diagnosed, the right treatment can be prescribed, and, according to their doctor's advice, patients can lead a normal life with a lower risk of infections. A prompt diagnosis is the priority, as it increases the chances of appropriate treatment, management and care. About 60% of patients require life-long treatment with immunoglobulin replacement therapy, which are WHO essential medicines for both adults (8) and children (9). The proposed IVD tests would help to close the gap between access to diagnosis and treatment and would probably be cost–effective. They would also help to reduce under-diagnosis: it is estimated that 70–90% of people worldwide have undiagnosed primary immunodeficiency (10). In the USA, the average time from symptom onset to diagnosis of primary immunodeficiency is 12.4 years (11).

The first recommendation of the Asia-Pacific Economic Cooperation for enhancing access to safe therapy for persons with immunodeficiency and bleeding disorders is to improve laboratory diagnosis (12). Inclusion of these tests would enable faster diagnosis of primary immunodeficiency and therefore increase equity for this patient population.

SAGE IVD evidence review

No detailed evidence or summary of evidence was provided to support this submission.

SAGE IVD considerations for recommendation

Not applicable.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended rejection of the submission for inclusion on the EDL of plasma and urine protein electrophoresis and immunofixation for use in the diagnosis of primary and secondary immunodeficiency and monoclonal plasma cell disorders.

The Group noted that no evidence was provided to support the application and concluded that it would be more appropriate for it to consider a complete application, including full references to guidelines, the evidence base and an algorithm for its use in the diagnosis of multiple myeloma.

References

- 1. Jiang F, Torgerson TR, Ayars AG. Health-related quality of life in patients with primary immunodeficiency diseases. Allergy Asthma Clin Immunol. 2015;11:27.
- 2. Kobrynski L, Waltenburg Powell R, Bowen S. Prevalence and morbidity of primary immunodeficiency diseases, United States 2001–2007. J Clin Immunol. 2014;34(8):954–61.
- Chapel H, Prevot J, Gaspar HB, Español T, Bonilla FA, Solis L, et al. Primary immune deficiencies principles of care. Front Immunol. 2014;5:627.
- Bousfiha AA, Jeddane L, Ailal F, Al-Herz W, Conley ME, Cunningham-Rundles C, et al. A phenotypic approach for IUIS primary immunodeficiency classification and diagnosis: guidelines for clinicians at the bedside. J Clin Immunol. 2013;33:1078–87.
- De Vries E, Clinical Working Party of the European Society for Immunodeficiencies (ESID). Patientcentred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists. Clin Exp Immunol. 2011;167:108–19.
- 6. Modell V, Orange JS, Quinn J, Modell F. Global report on primary immunodeficiencies: 2018 update from the Jeffrey Modell Centers Network on disease classification, regional trends, treatment modalities, and physician reported outcomes. Immunol Res. 2018;66:367–80.
- 7. Condino-Neto A, Espinosa-Rosales FJ. Changing the lives of people with primary immunodeficiencies (PI) with early testing and diagnosis. Front Immunol. 2018;9:1439.
- 8. 20th Model List of Essential Medicines. Geneva: World Health Organization; 2017 (http://apps. who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1, accessed April 2019).
- 6th Model List of Essential Medicines for Children: Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/handle/10665/273825/EMLc-6-eng.pdf?ua=1, accessed April 2019).
- Primary immunodeficiencies (PID) driving diagnosis for optimal care in Europe. European reference paper. London: World PI week; 2019 (http://worldpiweek.org/sites/default/files/basic_ page_documents/PI_European_Reference_Paper.pdf, accessed April 2019).
- Primary immune deficiency diseases in America: 2007. The third national survey of patients. Towson (MD): Immune Deficiency Foundation; 2009 (https://primaryimmune.org/wp-content/ uploads/2011/04/Primary-Immunodeficiency-Diseases-in-America-2007The-Third-National-Survey-of-Patients.pdf, accessed April 2019).
- 12. APEC recommendations for enhancing access to safe therapy for persons with immunodeficiency and bleeding disorders. Singapore: Asia–Pacific Economic Cooperation; 2018 (http://blood.apec.org/wp-content/uploads/2018/01/17_lsif2_agn05.7_Access-to-Safe-Therapy-recommendations-FINAL.-docx.pdf, accessed July 2019).

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Response to tetanus and pneumococcus vaccines

Test category Vaccine response test (tetanus and pneumococcus)

Addition, change or deletion Addition

Proposed test purpose

Diagnosis of antibody failure after vaccination against hepatitis B and tetanus and with extracts of *Salmonella* and *Pneumococcus* cell walls

Applicant organization(s) IPOPI

Background

Disease condition and impact on patients: In a study of 32 patients with primary immunodeficiency, more than two thirds experienced diagnostic delay, which led to serious morbidity, including pneumonia, meningitis, osteomyelitis and septicaemia (1). In the USA, the proportion of hospital admissions for primary immunodeficiency increased each year between 2001 and 2005, and patients had significantly longer hospital stays. The most common comorbidities included non-specific fever, splenomegaly and failure to thrive, respiratory infections, pathogen-specific infections and chronic lung disease (2). Data from a service for over 1000 patients with suspected primary immunodeficiency in Asia showed that families had often lost one or more children to undiagnosed immunodeficiency before the current diagnosis (3). Long delays in diagnosis and many infectious episodes can reduce the quality of life and result in permanent functional impairment (1).

Does this test meet a medical need? Primary immunodeficiency can often be diagnosed with two simple blood tests – a complete blood count with differential white cell count and serum immunoglobulin levels (3); however, although these tests are inexpensive, they are not necessarily available in all countries. Criteria for fast, reliable diagnosis of primary immunodeficiency include physician-friendly algorithms (4), with multi-stage diagnostic protocols for different clinical presentations so that patients are referred early for therapy (3). The target population is people with primary immunodeficiency, who have no protection against common pathogens and have life-threatening infections and increasing, permanent damage to various body organs, especially the lungs and intestines, making them more susceptible to severe infections. Many of the conditions that are present in childhood are genetic, and parental consanguinity is a risk

factor for primary immunodeficiency. A positive family history is an important indication for screening.

How the test is used: The IVD is part of diagnostic protocols to optimize a swift diagnosis. Examples of peer-reviewed published diagnostic protocols are reported in references 4 and 5.

Public health relevance

Prevalence: Primary immunodeficiency comprises over 350 inherited disorders due to malfunction of components of the immune system. The condition may be more common than previously estimated, with as much as 1% of the population affected.

Socioeconomic impact: Diagnostic delays lead not only to deterioration of the patient's condition and difficulty for carers but also to inappropriate use of health resources, including avoidable visits to specialists for recurring infections. Early diagnosis resulted in lower costs than in the previous year, even if regular immunoglobulin replacement therapy was required. The annual saving by the health care system for each diagnosed patient was US\$ 85 882 (6). In a study of early diagnosis and management of primary immunodeficiency in the USA, the average annual cost to the health care system for each patient with undiagnosed primary immunodeficiency was US\$ 102 552; early diagnosis and treatment saved an average of US\$ 79 942 per patient per year (7).

WHO or other clinical guidelines relevant to the test None reported

Test purpose	Diagnosis of antibody failure to hepatitis B, tetanus and extracts of <i>Salmonella</i> and <i>Pneumococcus</i> cell walls In the diagnosis of antibody immunodeficiency
Test format	Vaccine response, ELISA
Specimen types	2 mL serum
Equipment required	Basic automated instruments
Regulatory status	No information available
Global availability	Broad
Price per test range	US\$ 1.7–5
Instrument price range	US\$ 1 000–12 000

Basic test characteristics

Evidence for clinical usefulness and impact

Use of these tests in the diagnosis of immunodeficiency is well established in international practice and in the recommendations of the American Academy of Allergy, Asthma and Immunology, the Jeffrey Modell Foundation and the European Society for Immunodeficiencies.

Evidence for economic impact and/or cost-effectiveness

Few comparative data on cost-effectiveness were available. The typical cost per test was £ 10–20 (US\$ 13–26) in the United Kingdom and 500–1250 INR (US\$ 7–17) in India for the laboratory and 100–1500 INR (US\$ 1.5–21) charged to the patient. The initial cost for analysers and staff is moderate for semiautomated operation, but ELISA can be conducted with low-cost manual methods. All the techniques require significant manpower, training and maintenance. Some, like ELISA/EIA for antibody detection in vaccine responses, are performed on multi-analyte platforms, which have many other uses. Automated tests are performed on random access platforms, with minimal hands-on time required, and semi-automated tests are performed on batch analysers, with slightly more hands-on time required. Nevertheless, these instruments must be operated by skilled and trained personnel. Expertise and significant training are required for interpretation of results. Significant skill and time are required to perform manual analyses.

Ethics, equity and human rights issues

Consent is required to obtain a serum sample. Antibody deficiency disorders are chronic and rare and are often diagnosed late or not at all, even in developed countries with effective, widely available access to health care. A prompt diagnosis is the priority, as it increases the chances of appropriate treatment, management and care. About 60% of patients require life-long treatment with immunoglobulin replacement therapy, which are WHO essential medicines for both adults (8) and children (9). The proposed IVD tests would help to close the gap between access to diagnosis and treatment and would probably be cost–effective. They would also help to reduce under-diagnosis: it is estimated that 70–90% of people worldwide have undiagnosed primary immunodeficiency (10). In the USA, the average time from symptom onset to diagnosis of primary immunodeficiency is 12.4 years (11).

The first recommendation of the Asia-Pacific Economic Cooperation for enhancing access to safe therapy for people with immunodeficiency and bleeding disorders is to improve laboratory diagnosis (12). Inclusion of these tests would enable faster diagnosis of primary immunodeficiency and therefore increase equity for this patient population.

SAGE IVD evidence review

No evidence was provided of how accurately vaccine response tests are linked to particular diagnoses or appropriately measure immune response. Use of these tests appears to be based largely on expert judgement.

SAGE IVD considerations for recommendation

There is evidence that vaccine response tests appropriately measure immune response; however, no link to clinical diagnoses has been made, apart from expert judgement by clinical immunologists. In view of the large number of primary immunodeficiency disorders, it would be difficult to obtain strong empirical evidence.

SAGE IVD recommendation, with rationale

The SAGE IVD did not recommend inclusion on the EDL of the ELISA for response to vaccines against tetanus and pneumococcus in the absence of evidence that the test changes the way in which patients are managed or its diagnostic accuracy at screening level. More evidence that these tests accelerate the diagnostic pathway would be required.

References

- 1. Jiang F, Torgerson TR, Ayars AG. Health-related quality of life in patients with primary immunodeficiency diseases. Allergy Asthma Clin Immunol. 2015;11:27.
- 2. Kobrynski L, Waltenburg Powell R, Bowen S. Prevalence and morbidity of primary immunodeficiency diseases, United States 2001–2007. J Clin Immunol. 2014;34(8):954–61.
- 3. Chapel H, Prevot J, Gaspar HB, Español T, Bonilla FA, Solis L, et al. Primary immune deficiencies principles of care. Front Immunol. 2014;5:627.
- Bousfiha AA, Jeddane L, Ailal F, Al-Herz W, Conley ME, Cunningham-Rundles C, et al. A phenotypic approach for IUIS primary immunodeficiency classification and diagnosis: guidelines for clinicians at the bedside. J Clin Immunol. 2013;33:1078–87.
- 5. De Vries E, Clinical Working Party of the European Society for Immunodeficiencies (ESID). Patientcentred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists. Clin Exp Immunol. 2011;167:108–19.
- 6. Modell V, Orange JS, Quinn J, Modell F. Global report on primary immunodeficiencies: 2018 update from the Jeffrey Modell Centers Network on disease classification, regional trends, treatment modalities, and physician reported outcomes. Immunol Res. 2018;66:367–80.
- 7. Condino-Neto A, Espinosa-Rosales FJ. Changing the lives of people with primary immunodeficiencies (PI) with early testing and diagnosis. Front Immunol. 2018;9:1439.
- 8. 20th Model List of Essential Medicines. Geneva: World Health Organization; 2017 (http://apps. who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1, accessed April 2019).
- 6th Model List of Essential Medicines for Children: Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/handle/10665/273825/EMLc-6-eng.pdf?ua=1, accessed April 2019).

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10. Primary immunodeficiencies (PID) – driving diagnosis for optimal care in Europe. European reference paper. London: World PI week; 2019 (http://worldpiweek.org/sites/default/files/basic_page_documents/PI_European_Reference_Paper.pdf, accessed April 2019).

- Primary immune deficiency diseases in America: 2007. The third national survey of patients. Towson (MD): Immune Deficiency Foundation; 2009 (https://primaryimmune.org/wp-content/ uploads/2011/04/Primary-Immunodeficiency-Diseases-in-America-2007The-Third-National-Survey-of-Patients.pdf, accessed April 2019).
- 12. APEC recommendations for enhancing access to safe therapy for persons with immunodeficiency and bleeding disorders. Singapore: Asia–Pacific Economic Cooperation; 2018 (http://blood.apec. org/wp-content/uploads/2018/01/17_lsif2_agn05.7_Access-to-Safe-Therapy-recommendations-FINAL.-docx.pdf, accessed July 2019).

Sexually transmitted infections

Chlamydia trachomatis and Neisseria gonorrhoeae genomic DNA

Test category

Qualitative test for the detection and differentiation of genomic DNA from *Chlamydia trachomatis* and *Neisseria gonorrhoeae*

Addition, change or deletion Addition

Proposed test purpose

For the diagnosis of chlamydial and gonorrhoeal urogenital disease

Applicant organization(s) World Health Organization

WHO technical department Reproductive Health and Research

Background

Disease condition and impact on patients: Sexually transmitted infections compromise fertility, reproductive health and birth outcomes. Testing and treatment of these infections prevent these sequelae. Untreated women have chronic pelvic pain and may have ectopic pregnancies and be infertile. Infants born to untreated pregnant women may have eye infections (gonococcal ophthalmia) or pneumonia and be premature, with a low birth weight.

Does this test meet a medical need? Diagnosis of gonorrhoea and chlamydia in symptomatic and asymptomatic people guides treatment and management of both patients and partners. High-risk women on HIV pre-exposure

prophylaxis should be tested for these infections for prevention of mother-tochild transmission.

How the test is used: Single test for symptomatic testing and asymptomatic screening.

Public health relevance

Prevalence: The prevalence of *C. trachomatis* is estimated at 3.8% in women and 2.7% in men, whereas that of *N. gonorrhoeae* is estimated to be 0.9% in women and 0.7% in men (1).

Socioeconomic impact: Costs are related to complications of untreated infections. *N. gonorrhoeae* shows AMR.

WHO or other clinical guidelines relevant to the test

The WHO Reproductive Health and Research department is conducting an independent evaluation in several countries of a molecular-based IVD for diagnosis of chlamydia and gonorrhoea to improve access to testing in populations mainly in LMICs.

Guidelines for sexually transmitted infections (2) recommend etiological diagnosis for *N. gonorrhoeae* (minimal standard); both *C. trachomatis* and *N. gonorrhoeae* are high-priority pathogens for surveillance.

Test purpose	Diagnosis of gonorrhoea and chlamydia in symptomatic and asymptomatic people to guide treatment and management of patients and their partners
Test format	PCR and other molecular technologies such as transcription-mediated amplification
Specimen types	Molecular tests may be validated for several or all the following specimen types: male and female urine, male and female urethral swabs, endocervical swab, vaginal swab collected by patient or a physician, male and female rectal swabs and male and female oropharyngeal swabs Liquid cytology specimens are usually validated for both symptomatic and asymptomatic chlamydia, i.e. for both diagnosis and screening.
Equipment required	Usually fully automated nucleic acid testing instruments, which may consist of high-throughput laboratory systems or small, cartridge-based bench-top instruments for points of care

Basic test characteristics

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Most commercial tests are CE and FDA approved. No WHO-prequalified test for gonorrhoea or chlamydia.
Yes
US\$ 15 for combined testing for gonorrhoea and chlamydia
Small point-of-care nucleic acid testing instruments: US\$ 5000–25 000 ≤ US\$ 150 000 for large automated instruments

Table continued

Evidence for clinical usefulness and impact

These IVDs are the primary means of screening for and diagnosing chlamydia and gonorrhoea in most countries with the necessary laboratory infrastructure. Evidence of impact may not be relevant. According to the US Centers for Disease Control and Prevention (*3*):

The sensitivity and specificity of the NAATs are higher than those of any other test, and there is no justification for use of tests such as EIAs or DNA probe assays, which have inferior performance. No point-of-care assays are available that are suitable for routine use, although some may be used in high-risk populations who require immediate treatment because of poor follow-up. Testing for both gonorrhoea and chlamydia should be available in at least some reference laboratories, as *N. gonorrhoeae* culture is the only method for monitoring resistance to current treatment regimens.

Evidence for economic impact and/or cost-effectiveness

Some training is required to conduct these tests, which are the gold standard for screening and diagnosis of chlamydia and gonorrhoea. Their inclusion in a health care system might require resources, particularly in countries where access to these diagnostics is not yet available or is limited. The cost varies by manufacturer, but the health benefits override the potential costs because of reduced cost for complications of untreated infection.

In high-prevalence settings, the cost-benefit ratio is acceptable. As infections may be asymptomatic, prevention of their spread and the associated morbidity justifies testing in all risk categories, as the ontological risk may be greater than the epistemological risk.

Ethics, equity and human rights issues Consent is required to obtain a sample.

SAGE IVD evidence review

The accuracy of these tests is difficult to assess in the absence of a good reference standard; assessments rely on methods such as latent class analyses or comparison with panels of alternative tests. Systematic reviews of the accuracy of these tests were unavailable. One study with a reasonable sample size supports the claim made in non-systematic reviews that laboratory-based tests are highly accurate (4). Many of the other supporting primary studies are based on very few cases. Additional evaluations, particularly for new cartridge-based methods, would be useful.

SAGE IVD considerations for recommendation

Although the analytical performance varies by assay, the sensitivity of tests for *C. trachomatis* is 91–100%, the specificity is 98–100%, the positive predictive value for symptomatic patients is > 90%, and the negative predictive value is > 98.8%; and the sensitivity of tests for *N. gonorrhoeae* is 97.7–100%, the specificity is 99.6–100%, the positive predictive value for symptomatic patients is 89.4–100%, and the negative predictive value is \geq 99.9%. The tests are FDA-approved or CE-marked, although local vendors might require validation or verification. No evidence was provided of the impacts of these tests in clinical practice. There are UNAIDS/WHO guidelines for the test for *N. gonorrhoeae*, and both organisms are high priorities for surveillance.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion on the EDL of nucleic acid testing for *C. trachomatis* and *N. gonorrhoeae*. They noted that the tests are reliable, with high diagnostic accuracy, that appropriate tests with high sensitivity are essential for surveillance of these diseases and that the tests have been on the market for a number of years.

The Group considered that the test should be included only for testing in tertiary laboratories but that it could be considered for use at primary care level in the future.

Recommended test purpose

For the diagnosis and screening of symptomatic or asymptomatic chlamydial and/or gonorrhoeal urogenital disease and extragenital infection.

References

 Rowley J, Vander Hoorn S, Korenromp E, Low N, Unemo M, Abu-Raddad LJ, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. Bull World Health Org. 2019;97:548–62.

- UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance. Strategies and laboratory methods for strengthening surveillance of sexually transmitted infections. Geneva: UNAIDS, World Health Organization; 2012 (https://apps.who.int/iris/bitstream/handle/10665/75729/ 9789241504478_eng.pdf?sequence=1, accessed September 2019).
- 3. Laboratory diagnostic testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Expert consultation meeting summary report. Atlanta (GA): Centers for Disease Control and Prevention; 2009.
- 4. Van Der Pol B, Liesenfeld O, Williams JA, Taylor SN, Lillis RA, Body BA, et al. Performance of the cobas CT/NG test compared to the Aptima AC2 and Viper CTQ/GCQ assays for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. J Clin Microbiol. 2012;50(7):2244–9.

Treponema pallidum antibodies: rapid diagnostic test for diagnosis or as an aid in diagnosis of syphilis

Test category

Rapid plasma reagin test, VDRL test, EIA, TPPA test and TPHA

Addition, change or deletion Additions

Proposed test purpose For use in the diagnosis of syphilis

Applicant organization(s) World Health Organization

WHO technical department Reproductive Health and Research

Background

Disease condition and its impact on patients: Over 50% of women with untreated syphilis will experience an adverse birth outcome. If left untreated, syphilis causes damage to the brain, eyes and nerves.

Does the test meet a medical need? The tests allow accurate diagnosis and differentiation between acute, latent and tertiary infections and other treponematoses. As a consequence of diagnosis, appropriate treatment and follow-up to prevent transmission, including mother-to-child transmission, may be given.

How the test is used: Syphilis testing can be performed in a laboratory with an algorithm that includes treponemal and non-treponemal antibody assays.

Patients are usually screened with a non-treponemal test, and positive results are confirmed by treponemal testing.

Public health relevance

Prevalence: Syphilis is the second most common infectious cause of stillbirth globally (1). Over 50% of women with untreated syphilis will experience an adverse birth outcome. In 2016, WHO estimated that > 350 000 adverse birth outcomes occurred among 1 million pregnant women with syphilis and 6.3 million new syphilis infections occurred among adults.

Socioeconomic impact: Untreated syphilis in pregnancy is a major cause of deaths and stillbirths, preterm or low-birth-weight infants, neonatal death and syphilis infections in infants. An IVD for diagnosis of treponemal disease would advance efforts towards the global elimination of congenital syphilis.

WHO or other clinical guidelines relevant to the test

2013. Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus.

2016. Global health sector strategy on sexually transmitted infections 2016–2021: towards ending STIs

2016. Report on global sexually transmitted infection surveillance.

2016. Guidelines for the treatment of Treponema pallidum (syphilis)

2017. Global guidance on criteria and processes for validation: elimination of mother-to-child transmission of HIV and syphilis.

2017. Guideline on syphilis screening and treatment for pregnant women. The recommended strategies include use of a rapid syphilis test (not included in the EDL submission), the rapid plasma reagin test, the VDRL test, TPPA and TPHA. EIA is not mentioned.

Test purpose (brief)	In diagnosis of syphilis
Test format	Rapid plasma reagin, VDRL, EIA, TPPA, TPHA
Specimen types	Serum, plasma, whole blood, cerebrospinal fluid
Equipment required	Rapid plasma reagin assay, VDRL test, automatic EIA, TPPA, TPHA Several companies manufacture these tests.

Basic test characteristics

Table continued	
Regulatory status	None are WHO prequalified. Some have stringent regulatory approval in the USA and other high-income countries They have been widely used for many years in all countries.
Global availability	Broad
Price per test range	From US\$ 0.10 for non-treponemal tests to US\$ 1.0 for treponemal tests
Instrument price range	Not stated

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Evidence for clinical usefulness and impact

The tests allow accurate diagnosis and differentiation between acute, latent and tertiary syphilis as well as other treponematoses. As a consequence of diagnosis, appropriate treatment and follow-up can be given to treat infections and prevent transmission, including from mother to child.

Evidence for economic impact and/or cost–effectiveness

The additional cost for extension of use of these tests will be outweighed by the cost of negative health outcomes.

Ethics, equity and human rights issues

Consent is required to obtain a blood sample. Lack of access to these essential testing modalities can result in inequitable care and treatment.

SAGE IVD evidence review

Supporting evidence is provided in the WHO guideline, which is based on many systematic reviews. The guideline provides appropriate testing algorithms with rapid plasma reagin, VDRL, TPPA and TPHA, which are based on a costeffectiveness model. Few relevant data were provided on the performance of each test.

SAGE IVD considerations for recommendation

Untreated syphilis in pregnancy is a major cause of death and stillbirths, preterm or low-birth-weight infants, neonatal death and syphilis infections in infants. Use of rapid plasma reagin, VDRL, TPPA and TPHA for the detection of T. pallidum is recommended in an evidence-based WHO guideline. A systematic review indicated high sensitivity of the qualitative point-of-care rapid plasma reagin test, and the accuracy of the rapid syphilis test is estimated to be higher.

Accuracy is difficult to determine, however, as it depends on the stage of syphilis and the type of test.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion in the EDL of serological tests for detection of *T. pallidum*, noting that the five proposed tests would be valuable for other uses. The rapid plasma reagin test is useful for screening, the VDRL for diagnosis of neurosyphilis, EIA for testing large blood volumes before transfusion and TPPA and TPHA for screening blood and for confirmatory testing.

Recommended test purposes

Non-treponemal test-rapid plasma reagin: For screening for syphilis, and for monitoring treatment effectiveness.

Non-treponemal VDRL test: For screening, diagnosis and confirmation of neurosyphilis.

TPHA test: For confirmation of syphilis infection and for diagnosis of early and late syphilis infection.

TPPA test: For confirmation of syphilis infection and for diagnosis of early and late syphilis infection.

Reference

 Laboratory diagnosis of sexually transmitted infection, including human immunodeficiency virus. Geneva: World Health Organization; 2013 (http://www.who.int/reproductivehealth/publications/ rtis/9789241505840/en/, accessed September 2019).

Zika virus infection

Zika virus: enzyme-linked immunoassay for immunoglobulin M

Test category

ZIKV IgM immunoassay in diagnosis of ZIKV infection

Addition, change or deletion Addition

Proposed test purpose As an aid in the diagnosis of ZIKV disease

Applicant organization(s) World Health Organization

WHO technical department

Health Emergencies, Infectious Hazards Management, High-threat Pathogens

Background

Disease condition and impact on patients: By 3 August 2017, about 217 000 cases of ZIKV disease and about 3400 cases of associated congenital syndrome had been reported in Latin America and the Caribbean (1). It has been projected that about 12.3 (0.7–162.3) million cases could be expected in Latin America and the Caribbean every year, which could result in about 64 400 cases of Guillain-Barré syndrome and about 4700 cases of microcephaly (2). Although non-congenital ZIKV disease is not generally fatal, the mortality rate among 602 suspected cases of congenital microcephaly in infants in Brazil during the first week of life was 51 per 1000 live births (3).

Does the test meet a medical need? Cases of ZIKV infection have been identified in Africa and Asia since the 1950s, and outbreaks of ZIKV disease were first recognized in the Pacific islands in 2007 and 2013. The 2015–2016 outbreak in the Americas further demonstrated the epidemic potential of ZIKV, with capacity for rapid global spread and birth defects, other adverse pregnancy outcomes and Guillain-Barré syndrome.

How the test is used: Diagnosis of ZIKV disease depends on the interval between symptom onset and specimen collection. Serum and/or urine specimens collected within 7 days of symptom onset are tested for the presence of viral RNA by RT-PCR. If the result is negative, specimens are tested for the presence of IgM antibodies, with possible confirmatory testing with neutralization assays. WHO guidance (4) is being updated to incorporate guidance on testing for dengue and chikungunya.

Public health relevance

Prevalence: The importance of monitoring and controlling ZIKV transmission globally was underscored when WHO declared ZIKV infection and its associated complications a PHEIC, which changed the emergency response into a long-term programme with a sustained global strategy. To date, 86 countries and territories have reported mosquito-borne ZIKV transmission, and 36 have confirmed ZIKV infection-associated microcephaly and congenital Zika syndrome. Congenital Zika syndrome has been reported in the Americas, the Pacific, South and Southeast Asia and sub-Saharan Africa. Evidence from epidemiological studies and animal models of infection with African and Asian ZIKV strains indicates a risk for maternal-fetal transmission and adverse pregnancy outcomes in all regions with ZIKV transmission.

Socioeconomic impact: The prospective economic burden of the neurological sequelae of ZIKV infection in South America and the Caribbean is estimated to be US\$ 2.3 (US\$ 0–159.3) billion per annum (2). In a separate analysis, it was estimated that an attack rate of 0.3% across the six states of Brazil at greatest risk would result in a total cost exceeding US\$ 0.5 billion, an attack rate of 1% would cost more than US \$1 billion, and an attack rate of 2% would cost more than US\$ 2 billion (3).

WHO or other clinical guidelines relevant to the test

WHO guidelines: laboratory testing for Zika virus infection. Interim guidance. 23 March 2016 (4)

Test purpose	Diagnosis of ZIKV infection
Test format	EIA, immunofluorescent assay
Specimen types	Serum and cerebrospinal fluid
Equipment required	Automated instrument
Regulatory status	FDA Emergency use authorized and FDA cleared
Global availability	No
Price per test range	US\$ 5–30
Instrument price range	US\$ 1000–3000
Equipment required Regulatory status Global availability Price per test range	Automated instrument FDA Emergency use authorized and FDA cleared No US\$ 5–30

Basic test characteristics

Evidence for clinical usefulness and impact

Discrimination between ZIKV and DENV infections is critical, as pregnant women with ZIKV infection should be managed for possible adverse outcomes, including fetal microcephaly, while those who test positive for DENV should be managed to reduce their risk for severe morbidity and mortality from acute DENV infection.

Evidence for economic impact and/or cost-effectiveness

The activities that will require resources and budgetary commitment are: purchase of equipment and reagents; training in use of the selected assays; appropriate storage conditions for reagents; collection, transport and storage of clinical specimens in optimal conditions for testing; maintenance of diagnostic equipment; and training of health care providers and public health programme managers in appropriate indications for use of tests and interpretation of results.

Ethical issues, equity and human rights issues

Consent is required for collection of a serum or cerebrospinal fluid sample. ZIKV infection may have serious implications in certain populations. For example, given the association with microcephaly and other poor pregnancy outcomes, a positive test is a serious, challenging situation for pregnant women. False-positive results may prompt unnecessary medical interventions or follow-up and exacerbate maternal anxiety, and false negative results may fail to identify high-risk pregnancies or proper diagnosis of congenital Zika syndrome. False-positive results may also incur use of limited public health resources for outbreak response and the economic loss associated with travel deferral if an area is identified as having active autochthonous ZIKV transmission. In addition to issues of clinical management, the absence of laboratory methods for detecting ZIKV infection may leave populations and public health programmes vulnerable to emergence and re-emergence of ZIKV transmission and adverse sequelae of congenital malformations and Guillain-Barré syndrome.

Reliable ZIKV diagnostic testing is still very limited, especially in resource-constrained settings. The availability of simple, affordable tests will improve detection of outbreaks, accurate diagnosis and appropriate strategies for prevention, patient care and disease control. Better-resourced settings have greater access to diagnostic tests and to maternal and child health care, including pregnancy and antenatal medical services (with prenatal ultrasound and other mechanisms to monitor pregnancies), thus differentially affecting the management of women with ZIKV infection. All commercially available ZIKV antibody tests for use in a laboratory or at points of care and those in the pipeline should be evaluated systematically for specificity, particularly in populations with a high prevalence of diseases caused by other flaviviruses, especially DENV.

SAGE IVD evidence review

Zika IgM IVDs have not been extensively validated, and the existing studies have not been published. The evidence base for ZIKV anti-IgM tests is unclear. At least one of the tests has poor performance in patients who are not infected with ZIKV, posing a risk of misdiagnosing dengue.

SAGE IVD considerations for recommendation

The importance of monitoring and controlling ZIKV transmission globally was underscored when WHO declared ZIKV infection and its associated complications a PHEIC. The tests are currently available under an FDA Emergency Use Authorization. Reliable diagnostic testing is still limited, especially in resource-constrained settings. The availability of simple, affordable tests will improve detection of outbreaks, accurate diagnosis and appropriate strategies for prevention, patient care and disease control.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended conditional inclusion on the EDL of the ELISA for ZIKV anti-IgM, pending provision of further evidence, including a clear recommendation in guidelines and an updated review of the available data.

The Group noted that caution should be used in interpreting the results of ZIKV anti-IgM tests, particularly for pregnant women, in the absence of prior NAT testing. The Group noted the high level of cross-reactivity of anti-IgM with ZIKV, DENV and other flaviviruses, the wide range of specificity and the persistence of Zika IgM antibody, which might reflect infection before pregnancy. False-negative and false-positive results may occur.

The test should be used only as an aid to diagnosis, with confirmation of positive tests, and should not be used on cerebrospinal fluid samples.

Recommended test purpose

As an aid in the diagnosis of suspected Zika virus infection.

References

- 1. Zika cumulative cases. Washington DC: WHO Regional Office for the Americas; 2016 (http://www.paho.org/hq/index.php?option=com_content&view=article&id=12390&Itemid=42090&Iang=en, accessed April 2018).
- 2. Colón-González FJ, Peres CA, Steiner São Bernardo C, Hunter PR, Lake IR. After the epidemic: Zika virus projections for Latin America and the Caribbean. PLoS Negl Trop Dis. 2017;11(11):e0006007.
- 3. França GV, Schuler-Faccini L, Oliveira WK, Henriques CM, Carmo EH, Pedi VD, et al. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. Lancet. 2016; 388: 891–7.
- WHO guidelines: laboratory testing for Zika virus infection. Interim guidance. 23 March 2016 (http://apps.who.int/iris/bitstream/handle/10665/204671/WHO_ZIKV_LAB_16.1_eng.pdf;jsessio nid=8BF6EDD420F9BEDD723CA4B1C2EB9566?sequence=1, accessed April 2019).

Test for Zika virus nucleic acid

Test category

ZIKV NAT for use in diagnosis of acute ZIKV infection

Addition, change or deletion Addition

Proposed test purpose To confirm ZIKV infection during onset of disease or to determine cause of death

Applicant organization(s) World Health Organization

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WHO technical department

Health Emergencies, Infectious Hazards Management, High-threat Pathogens

Background

Disease condition and its impact on patients: By 3 August 2017, about 217 000 cases of ZIKV disease and about 3400 cases of associated congenital syndrome had been reported in Latin America and the Caribbean (1). It has been projected that about 12.3 (0.7–162.3) million cases could be expected in Latin America and the Caribbean every year, which could result in about 64 400 cases of Guillain-Barré syndrome and about 4700 cases of microcephaly (2). Although non-congenital ZIKV disease is not generally fatal, the mortality rate among 602 suspected cases of congenital microcephaly in infants in Brazil during the first week of life was 51 per 1 000 live births (3).

Does the test meet a medical need? Cases of ZIKV infection have been identified in Africa and Asia since the 1950s, and outbreaks of ZIKV disease were first recognized in the Pacific islands in 2007 and 2013. The 2015–2016 outbreak in the Americas further demonstrated the epidemic potential of ZIKV, with capacity for rapid global spread and birth defects, other adverse pregnancy outcomes and Guillain-Barré syndrome.

How the test is used: Diagnosis of ZIKV disease depends on the interval between symptom onset and specimen collection. Serum and/or urine specimens collected within 7 days of symptom onset are tested for the presence of viral RNA by RT-PCR. If the result is negative, specimens are tested for the presence of IgM antibodies, with possible confirmatory testing with neutralization assays. WHO guidance (4) is being updated to incorporate guidance on testing for dengue and chikungunya.

Public health relevance

Prevalence: The importance of monitoring and controlling ZIKV transmission globally was underscored when WHO declared ZIKV infection and its associated complications a PHEIC and changed the emergency response into a long-term programme with a sustained global strategy. To date, 86 countries and territories have reported mosquito-borne ZIKV transmission; and 36 have confirmed ZIKV infection-associated microcephaly and congenital Zika syndrome. Congenital Zika syndrome has been reported in the Americas, the Pacific, South and Southeast Asia and sub-Saharan Africa. Evidence from epidemiological studies and animal models of infection with African and Asian ZIKV strains, indicate a risk for maternal-fetal transmission and adverse pregnancy outcomes in all regions with ZIKV transmission.

Socioeconomic impact: The prospective economic burden of the neurological sequelae of ZIKV infection in South America and the Caribbean is estimated to be US\$ 2.3 (US\$ 0–159.3) billion per annum (2). In a separate analysis, it was estimated that an attack rate of 0.3% across the six states of Brazil at greatest risk would result in a total cost exceeding US\$ 0.5 billion, an attack rate of 1% would cost more than US \$1 billion, and an attack rate of 2% would cost more than US\$ 2 billion (3).

WHO or other clinical guidelines relevant to the test

WHO guidelines: laboratory testing for Zika virus infection. Interim guidance. 23 March 2016 (4)

Test purpose	In the diagnosis of ZIKV infection	
Nucleic acid determination	NAT	
Specimen types	Available NATs have been validated with various specimens but most commonly with serum, plasma and urine, as stipulated on product labels. Evidence of persistence of ZIKV RNA in unfractionated (whole) blood for several months has been reported. This specimen type requires special buffers for dilution before NAT testing. Viral RNA has also been detected in semen, saliva, cerebrospinal fluid and amniotic fluid; however, these specimens may be less reliable and stable.	
Equipment required	Automated instruments	
Regulatory status	FDA Emergency use authorized, and FDA approved for blood donor product screening	
Global availability	Narrow	
Price per test range	US\$ 100–200	
Instrument price range	US\$ 3 000–20 000	

Basic test characteristics

Evidence for clinical usefulness and impact

Limited data are available from clinical settings. ZIKV persists in serum and plasma for only 5–7 days after symptoms appear, although it may persist for up to 14 days in urine and whole blood and up to 3 months in semen. Diagnosis of ZIKV infection is critical for tracking its emergence, re-emergence and global spread as a basis for recommendations to women of reproductive age

and the potential population-level risk to pregnant women. Diagnosis of ZIKV infection in pregnancy is important for clinical management in areas where there is ZIKV transmission, because of the risks for microcephaly and other complications, including preterm birth, stillbirth and the spectrum of malformations characterized as congenital ZIKV syndrome. As the symptoms of ZIKV infections tend to be mild and nonspecific, diagnostic testing is important for determining infection of pregnant women and monitoring transmission in the general population. No published studies with quantitative data are available. Cohort studies are in progress to address these issues.

Evidence for economic impact and/or cost-effectiveness

Studies of the cost–effectiveness of testing are not available, except for assessment during blood product screening.

Activities that will require resources and budgetary commitment are purchase of equipment and reagents; training in use of the assays; appropriate storage conditions for reagents; collection, transport and storage of clinical specimens in optimal conditions for testing; maintenance of diagnostic equipment; and training of health care providers and public health programme managers in appropriate use of the test, interpretation of results and appropriate counselling of patients.

Ethical issues, equity and human rights issues

Consent is required for taking samples. There are no vaccines or therapeutics for ZIKV infection and no treatments to reduce the risk of exposing fetuses. Positive maternal test results do not necessarily reflect fetal infection. Pregnant women are tested to provide information for clinicians and for the women to anticipate potential adverse outcomes, to decide whether more intensive monitoring of the pregnancy is needed and to guide decision-making. In areas with low or no transmission, false-positive results may prompt unnecessary medical interventions, such as elective termination of pregnancy, or exacerbate maternal anxiety. False-negative results might fail to identify high-risk pregnancies or might result in subsequent misdiagnosis of the cause of congenital malformations.

NAT is expensive and technically complex and is therefore limited to relatively sophisticated laboratories with well-trained, skilled technicians. Therefore, the test will not be widely available in many settings. Research and public health programmes are under way to develop simple, affordable pointof-care tests. Access to maternal and child health care, including pregnancy and antenatal medical services (with prenatal ultrasound or other means to monitoring of pregnancies), differs by region and socioeconomic status and thus differentially affects management of women with evidence of infection.

SAGE IVD evidence review

Two tests have published small evaluation studies which show agreement with confirmed PCR methods. Studies have been undertaken in small stored sample banks or spiked sera.

SAGE IVD considerations for recommendation

The importance of monitoring and controlling ZIKV transmission globally was underscored when WHO declared ZIKV infection and its associated complications a PHEIC. Several studies have shown valid results of ZIKV NAT tests in patients with acute infection, pregnant women, fetal deaths (stillbirths) and children born with neurological and other congenital clinical outcomes, as confirmed by PCR methods. Studies in selected, sometimes artificial samples provide some evidence for the accuracy of ZIKV NAT tests.

SAGE IVD recommendation, with rationale

The SAGE IVD recommended inclusion on the EDL of the test for ZIKV nucleic acid for diagnosis or confirmation of early ZIKV infection, noting that it is specific for confirming infection and detecting outbreaks; its sensitivity and specificity appear to be acceptable. There is no cross-reactivity with other flaviviruses.

The Group noted, however, that no studies of use in the field have been reported. Use of NAT for diagnosis of ZIKV infection is included in WHO laboratory guidance published in 2016 and in updated guidance by the WHO Regional Office for the Americas in 2018.

The Group also recommended that simple NAT tests be developed for use in primary care settings or in district hospitals.

Recommended test purpose

To diagnose acute ZIKV infection.

References

- 1. Zika cumulative cases. Washington DC: WHO Regional Office for the Americas; 2016 (http://www.paho.org/hq/index.php?option=com_content&view=article&id=12390&Itemid=42090&Iang=en, accessed April 2018).
- 2. Colón-González FJ, Peres CA, Steiner São Bernardo C, Hunter PR, Lake IR. After the epidemic: Zika virus projections for Latin America and the Caribbean. PLoS Negl Trop Dis. 2017;11(11):e0006007.
- 3. França GV, Schuler-Faccini L, Oliveira WK, Henriques CM, Carmo EH, Pedi VD, et al. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. Lancet. 2016; 388: 891–7.
- 4. WHO guidelines: laboratory testing for Zika virus infection. Interim guidance. 23 March 2016 (http://apps.who.int/iris/bitstream/handle/10665/204671/WHO_ZIKV_LAB_16.1_eng.pdf;jsessio nid=8BF6EDD420F9BEDD723CA4B1C2EB9566?sequence=1, accessed April 2019).

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Second Model List of Essential In Vitro Diagnostics (EDL)

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

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

Note: The specimen types listed for each diagnostic test category comprise all possible specimens for that category; however, not all test brands within each category will be validated for all the specimen types listed.

Immunoassays are available in various formats – manual microplate assays and automated platforms – with various types of chemical detection (e.g. turbidimetry, chemiluminescence and electrochemiluminescence assays).

I. List of Essential In Vitro Diagnostics (EDL): For community settings and health facilities without laboratories

These lists contain tests for community settings and health facilities that include health posts and centres, doctors' offices, outreach clinics, ambulatory care and home-based and self-testing. If laboratory facilities are available in community settings, please refer to the IVDs described in Section II. If laboratory facilities are not available, specimens may be collected, transported to and processed at a higher tier of the health system. The tests in this section of the EDL are also assumed to be available, in combination with the extended list in Section II, at healthcare facilities with laboratories. ..∎ 164

Discipline	Diagnostic test	Test purpose	Assay format	Specimen type
Blood typing	A, B and O and rhesus factor (Rh)	To determine A, B and O groups and Rh type	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 diagnose and screen for diabetes	Dipstick	Urine
		 To diagnose hypoglycaemia and screen for intermediate hyperglycaemia 	Glucose meter	Capillary whole blood
	Ketones	To diagnose diabetic ketoacidosis	Dipstick	Urine
	Haemoglobin A1c (HbA1c)	To diagnose and monitor diabetes mellitus	Handheld and small analyser	Capillary whole blood
	Whole blood lactate	To assess metabolic acidosis, diabetic keto-acidosis, sepsis and dehydration	Handheld analyser	Venous whole blood ¹
Haematology	Haemoglobin (Hb)	To diagnose and monitor anaemia	Haemoglobinometer	Capillary whole blood Venous whole blood ¹
		 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)	Dipstick	Urine
		 To aid in the diagnosis of intravascular haemolysis, renal conditions, rhabdomyolysis (myoglobinuria) 		

I.a General	I.a General IVDs for use in community settings and health facilities without laboratories continued								
Discipline	Diagnostic test	Test purpose	Assay format	Specimen type					
Microbiology	Urinalysis test strips	To detect urinary tract infections	Multi-parameter strips (dipstick)	Urine					
Pregnancy testing	Human chorionic gonadotropin (hCG)	To aid in the early detection of pregnancy	Rapid diagnostic test (RDT) (dipstick and cassette), latex agglutination	Urine (early morning)					

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

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Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cholera	Vibrio cholerae antigen	For initial detection or exclusion of a cholera outbreak (Not for use in case management)	RDT	Stool Rectal swab	N/A	Interim technical note: The use of cholera rapid diagnostic tests, (2016) https://www.who.int/cholera/ task_force/Interim-guidance- cholera-RDT.pdf
Hepatitis B virus (HBV) infection	Hepatitis B surface antigen (HBsAg)	To screen for acute and chronic HBV infection: infants > 12 months of age, children, adolescents and adults	RDT	Capillary whole blood Venous whole blood ¹	Public reports of WHO- prequalified IVDs https://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/hbsag/ public_report/en/	Guidelines on hepatitis B and C testing (February 2017) https://apps.who.int/iris/ handle/10665/254621
	Hepatitis B e antigen (HBeAg)	Staging to assess need for HBV treatment in chronic HBV infection	RDT	Capillary whole blood Venous whole blood ¹	N/A	-
Hepatitis C virus (HCV) infection	Anti-HCV antibody	To screen for HCV infection: infants > 18 months of age, children, adolescents and adults	RDT	Oral fluid Capillary whole blood Venous whole blood ¹	Public reports of WHO prequalified IVDs http://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/hcv/ public_report	Guidelines on hepatitis B and C testing (February 2017) https://apps.who.int/iris/ handle/10665/254621

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

¹ If a phlebotomist is available.

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents	
HIV infection	HIV 1/2 antibody (anti-HIV Ab)	HIV self-testing	RDT	Oral fluid Capillary whole blood Venous whole blood ¹	Public reports of WHO prequalified IVDs https://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/self-	Guidelines on HIV self-testing and partner notification (2016) https://apps.who.int/iris/ handle/10665/251655	
				biood	testing_public-report/en/	Consolidated guidelines on HIV testing services (July 2015)	
		To diagnose HIV infection: adults,	RDT	Oral fluid Capillary whole	Public reports of WHO prequalified IVDs	https://apps.who.int/iris/ handle/10665/179870	
		adolescents, children and infants > 18 months of age		blood Venous whole blood ¹	http://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/hiv-	WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection, module 10 for	
	Combined HIV antibody/p24 antigen (anti-	For the diagnosis of HIV infection: adults, adolescents,	RDT	Capillary whole blood Venous whole	rdts/public_report	testing providers (2017) http://www.who.int/hiv/pub/ prep/prep-implementation-tool	
	HIV/p24 Ag)	children and infants > 18 months of age		blood ¹		Consolidated guidelines on HIV testing services (2015)	
	Qualitative HIV virological nucleic acid test	For diagnosis of HIV infection in infants < 18 months of age	Point-of-care nucleic acid test	Capillary whole blood Venous whole blood ¹ Dried blood spots	Public reports of WHO prequalified IVDs http://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/hiv-vrl/ public_report	https://apps.who.int/iris/ handle/10665/179870	

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

¹ If a phlebotomist is available.

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Disease	Dia una attia	Test mum ess	A	Canadian an truc	WILLO mean wellified as	W/110 entry entities de europe
Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV infection continued	CD4 cell enumeration	 For staging advanced HIV disease For monitoring 	Point-of-care flow cytometry platform	Capillary whole blood Venous whole blood ¹	Public reports of WHO prequalified IVDs https://www.who.int/ diagnostics_laboratory/	Consolidated guidelines on HIV testing services (2015) https://apps.who.int/iris/ handle/10665/179870
		For monitoring plat response to antiretroviral therapy. (In settings where viral load is not available)			evaluations/pq-list/cd4/ public_report	Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy (2017) https://apps.who.int/iris/ handle/10665/255884
	Cryptococcal antigen	For screening and diagnosis of cryptococcal meningitis in people with advanced HIV disease	RDT	Capillary whole blood Venous whole blood ¹	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

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

¹ If a phlebotomist is available.

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Influenza	Influenza A and B antigen detection	To aid in the diagnosis of seasonal influenza infection	RDT Instrument-	Nasal swab Nasopharyngeal swab	N/A	Use of influenza rapid diagnostic tests (2010) https://apps.who.int/iris/
	acteenon	(Not recommended	based	Nasopharyngeal		handle/10665/44304/
		for surveillance testing)	point-of-care immunoassay	aspirate or wash		WHO recommendations on the use of rapid testing for influenza diagnosis:
	Influenza A and B nucleic acid test For diagnosis of seasonal influenza infection Point-of-care nucleic acid test Nasopharyngeal aspirate or wash Nasopharyngeal	N/A	https://www.who.int/influenza/ resources/documents/RapidTest Influenza_WebVersion.pdf			
				1 , 3		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: https://www.who.int/influenza/ resources/documents/WHO_ Epidemiological_Influenza_ Surveillance_Standards_2014.pd	
						Guidance on clinical management of influenza infections: https://www.who.int/influenza/ resources/documents/clinical_ management_2012

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

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Disease	Diagnostic 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	spp. antigens;one or more humanbloodprequalified IVDsspecies-malaria species (P.Venous wholehttp://www.who.int/specific (e.g.falciparum, P. vivax,blood 1diagnostics_laboratory/HRP2) and/orP. malariae, P. ovale)evaluations/pq-list/	prequalified IVDs http://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/	WHO guidelines for the treatment of malaria, third edition (2015) https://apps.who.int/iris/ handle/10665/162441		
	pan-species specific (e.g. pan-pLDH)	m	malaria/public_report	Malaria rapid diagnostic test performance. Results of WHO product testing of malaria RDTs: Round 8 (2016–2018) https://www.who.int/ malaria/publications/ atoz/9789241514965		
						WHO good practices for selecting and procuring rapid diagnostic tests for malaria (2011) https://apps.who.int/iris/ handle/10665/44530
					Information note on recommended selection criteria for procurement of malaria rapid diagnostic tests https://www.who.int/malaria/ publications/atoz/rdt_selection_ criteria	

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

¹ If a phlebotomist is available.

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products ¹	WHO supporting documents
Syphilis	Antibodies to Treponema pallidum	For diagnosis or as an aid in the diagnosis of <i>T. pallidum</i>	RDT	Capillary whole blood Venous whole blood ²	N/A	WHO laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus (2013) http://apps.who.int/iris/ bitstream/handle/10665/85343/ 9789241505840_eng.pdf
	Combined antibodies to <i>T. pallidum</i> and to HIV-1/2	For diagnosis or as an aid in the diagnosis of HIV-1/2 and/or <i>T. pallidum</i>	RDT	Capillary whole blood Venous whole blood ²	Public reports of WHO prequalified IVDs https:// www.who.int/diagnostics_ laboratory/evaluations/ pq-list/hiv_syphilis/en/	WHO Information note on the use of dual HIV/syphilis rapid diagnostic tests (RDT) (2017) http://apps.who.int/iris/ handle/10665/252849
Tuberculosis (TB)	Tuberculin skin (Mantoux) test (TST)	For diagnosis of latent TB infection	Intradermal test	N/A		Latent TB infection: updated and consolidated guidelines for programmatic management (2018) http://apps.who.int/iris/ bitstream/handle/10665/ 260233/9789241550239-eng.pdf
Visceral leishmaniasis	rK39 antigen test for visceral leishmaniasis	To aid in the diagnosis of clinically suspected visceral leishmaniasis (caused by <i>L. donovani</i> or <i>L. infantum</i> infection)	RDT	Serum ² Capillary whole blood Venous whole blood ²	N/A	WHO Technical Report Series 949 https://apps.who.int/iris/ handle/10665/44412

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

¹ All TB tests are evaluated and guidelines developed by the WHO global TB programme.

² If a phlebotomist is available.

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II. Health care facilities with clinical laboratories

These lists contain additional tests for 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 diagnostic 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 for use in clinical laboratories
- b) Disease-specific IVDs for use in clinical laboratories
- c) Disease-specific IVDs for blood screening laboratories

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Discipline	Diagnostic test	Test purpose	Assay format	Specimen type	WHO supporting documents
Anatomical pathology ¹	Histopathology	Assessment of tissue for infection, neoplasia, inflammatory and degenerative disorders	Macroscopic assessment of tissue and selection of areas for microscopic examination. 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	Surgical resection Biopsy Core biopsy Cell block	WHO priority medical devices for cancer management https://apps.who.int/iris/ handle/10665/255262 Basic histopathology and anatomical pathology services for developing countries with variable services https://apps.who.int/iris/ handle/10665/119675
	Cytology (cytopathology)	Assessment of cells for infection, neoplasia, inflammatory and degenerative disorders	Microscopy of stained cells on slides	Cervical specimen for Papanicolaou (Pap) smear Body fluids: e.g. cerebrospinal fluid, urine, pleural and peritoneal fluids	-
				Fine-needle aspirate (FNA) of lymph node, spleen, other tissues, bone marrow aspirate, sputum, bronchial brushings, bronchoalveolar lavage (BAL), skin samples	

II.a General IVDs for use in clinical laboratories

¹ Note: The tests described in this section require specialized anatomical pathology laboratories and trained anatomical pathologists.

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Discipline	Diagnostic test	Test purpose	Assay format	Specimen type	WHO supporting documents
Anatomical pathology ¹ continued	Immunohisto- chemistry (IHC)	Assessment of 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	Determination of cause of death and correlation with pre-mortem clinical features and investigations	Macroscopic assessment and microscopy of tissue sections. Procedures selected case by case	Cadaver	International guidelines for the determination of death – Phase I https://www.who.int/ patientsafety/montreal-forum- report.pdf

II.a General IVDs for use in clinical laboratories continued

¹ Note: The tests described in this section require specialized anatomical pathology laboratories and trained anatomical pathologists.

Discipline	Diagnostic test	Test purpose	Assay format	Specimen type
Bacteriology, mycology	Urinalysis test strips	Detection of urinary tract infections (UTIs)	Multi-parameter strips including nitrite test	Urine
and parasitology	Microscopy	Microbial morphology, presence or absence of white blood cells, red blood cells versus squamous epithelial cells for presumptive identification; presence of casts and crystals in urine	Microscopic examination of slides as wet preparations or treated with organism- specific chemical stains (e.g. Gram stain, Giemsa stain, modified Ziehl-Nielsen stain, stains for fungi)	Disease-appropriate specimens (e.g. venous whole blood, urine, stool, cerebrospinal fluid) or cultures
	Culture	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antibiotic 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, cerebrospinal fluid, etc.)
	Blood culture	For the detection of 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	For the identification of the genus or species of bacteria or fungi from cultured isolates	A range of biochemical tests that may be performed manually or on automated equipment.	lsolates from bacterial or fungal cultures
	susceptibilityafter species identification and interpretationistesting (AST)by EUCAST1 and CLSI guidelines2d		Antimicrobial susceptibility testing of isolates May be done manually by disc diffusion, gradient tests, broth microdilution	Microbial isolates
			or automated platforms	

II.a General IVDs for use in clinical laboratories continued

¹ EUCAST, European Committee on Antimicrobial Susceptibility Testing: Breakpoint tables for interpretation of MICs and zone diameters Version 9.0.

² CLSI, Clinical and Laboratory Standards Institute: CLSI M 100 Performance Standards for Antimicrobial Susceptibility Testing, 29th Edition.

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Discipline	Diagnostic test	Test purpose	Assay format	Specimen type
Clinical chemistry	Alanine amino- transferase (ALT)	To assess liver function	Optical methods, automated chemistry analyser if available	Serum Plasma
	Albumin	To detect or monitor malnutrition, kidney, liver disease or malabsorption	Optical methods, automated chemistry analyser if available	Serum Plasma
		To detect or monitor kidney disease	Optical methods, automated chemistry analyser if available	Urine
	Alkaline phosphatase (ALP)	To aid in diagnosis of hepatobiliary diseases and bone disorders	Optical methods, automated chemistry analyser if available	Serum Plasma
	Aspartate amino- transferase (AST)	To assess liver function	Optical methods, automated chemistry analyser if available	Serum Plasma
	Basic metabolic panel (BMP)	To measure the levels of glucose, sodium, potassium chloride, carbon dioxide, blood urea nitrogen (BUN), BUN:creatinine ratio, glomerular filtration rate (eGFR) and may include calcium	Photometric and colorimetric testing, ion-selective potentiometry (8-parameter automated clinical chemistry analyser)	Venous whole blood Serum Plasma
		Note: Result time sensitive for emergency and critical care		
	Bilirubin	To detect or monitor liver disease, bile duct disorders and red cell destruction	Optical methods, automated chemistry analyser if available	Serum Plasma
	Direct and indirect bilirubin	To detect or monitor liver disease, bile duct disorders and haemolytic anaemia and to differentiate between these causes of jaundice	Optical methods, automated chemistry analyser if available	Serum Plasma

Discipline	Diagnostic test	Test purpose	Assay format	Specimen type
Clinical chemistry	Blood pH and gases	To assess lung function, metabolic or kidney disorders and monitor oxygen therapy	Blood gas analysers, including portable analysers for emergency and critical care	Arterial whole blood
continued		To measure blood pH, O ₂ and CO ₂ , serum bicarbonate, anion gap		Venous whole blood
		Note: Result time sensitive for emergency and critical care		
Blood urea		To assess kidney function	Optical methods, automated chemistry	Serum
	nitrogen (BUN)	Note: Result time sensitive for emergency and critical care	analyser if available	Plasma
	Comprehensive metabolic panel (CMP)	To measure levels of basic metabolic panel parameters plus magnesium, total protein, albumin, globulin, albumin:globulin ratio, bilirubin (direct or total), alkaline phosphatase (ALP), alanine and aspartate aminotransferases (ALT and AST)	As for basic metabolic panel (14 or more parameter automated clinical chemistry analyser)	Venous whole blood Serum Plasma
	C-reactive protein	To detect inflammation as an indicator	RDT	Venous whole blood
	(CRP)	of various conditions, e.g. sepsis, upper respiratory infections	Latex agglutination assay	Serum Plasma
		Note: Result time sensitive for emergency and critical care	Immunoassay	

II.a General IVDs for use in clinical laboratories continued

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Discipline	Diagnostic test	Test purpose	Assay format	Specimen type
Clinical chemistry continued	Creatinine	 To estimate glomerular filtration rate (eGFR) and urine albumin:creatinine ratio (ACR) and urine protein:creatinine ratio 	Optical methods, automated chemistry analyser if available	Serum Urine
		 To monitor kidney function for management of severe infections (i.e. sepsis, Lassa fever) and antimicrobial regimen adjustment 		
		Note: Result time sensitive for emergency and critical care		
	Electrolytes (sodium,	To monitor fluid, electrolyte and acid-base balance	Automated chemistry analyser	Serum Plasma
	potassium, chloride, bicarbonate)	Note: Result time sensitive for emergency and critical care		
	Gamma-glutamyl	To assess hepatobiliary function	Optical methods, automated chemistry	Plasma
	transferase (GGT)	 To distinguish between bone and hepatobiliary causes of raised ALP 	analyser if available	Serum
	Glucose	To diagnose and screen for diabetes and intermediate hyperglycaemia, to diagnose hypoglycaemia	Optical methods, automated chemistry analyser if available	Plasma Serum
		Note: Result time sensitive for emergency and critical care		
	Glucose-6- phosphate dehydrogenase activity (G6PD)	For screening newborns for G6PD deficiency	Semi-quantitative fluorescent spot test	Venous whole blood

II.a General IVDs for use in clinical laboratories continued

Discipline	Diagnostic test	Test purpose	Assay format	Specimen type
Clinical chemistry	Haemoglobin A1c (HbA1c)	To diagnose and monitor diabetes mellitus	Immunoassay	Venous whole blood
continued Lipase	Lipase or amylase	To assess acute pancreatitis and other pancreatic disorders Note: Lipase result time sensitive for emergency and critical care	Optical methods, automated chemistry analyser if available	Serum Plasma Peritoneal fluid (amylase)
	Lipid profile	To assess risk of cardiovascular disease (CVD) by measuring cholesterol, triglycerides, low-density lipoproteins (LDL) and high- density lipoproteins (HDL)	Optical methods, automated chemistry analyser if available	Plasma Serum
	Phosphate	 To monitor chronic kidney disease To prevent and manage tumour lysis syndrome 	Optical methods, automated chemistry analyser if available	Serum Plasma
	Procalcitonin	To guide antibiotic therapy initiation or discontinuation in sepsis and lower	RDT	Serum Plasma
		respiratory tract infection (For use only in tertiary care facilities and above)	Point-of-care immunoassay instrument	Venous whole blood Capillary whole blood Plasma
			Immunoassay	Serum Plasma

II.a General IVDs for use in clinical laboratories continued

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II.a Gene	ral IVDs for use ir	clinical laboratories continued			
Discipline	Diagnostic test	Test purpose	Assay format	Specimen type	
Clinical chemistry continued	Thyroid- stimulating hormone (TSH)	To screen for hypothyroidism and hyperthyroidism	Immunoassay	Serum Plasma Capillary whole blood (neonates)	
			Immunoassay (handheld or large automated instrument)	Venous whole blood Serum Plasma	
	Uric acid	 To diagnose and monitor gout To prevent and manage tumour lysis syndrome	Optical methods, automated chemistry analyser if available	Serum Plasma	
	Urine chemistry	To detect and quantify substances in the urine associated with metabolic disorders, renal dysfunction or urinary tract infections	Automated chemical analyser	Urine	
		Note: Result time sensitive for emergency and critical care			

Discipline	Diagnostic test	Test purpose	Assay format	Specimen type
Haematology	Blood cross- matching	To determine blood compatibility for blood transfusions	Slide and/or tube agglutination test	Venous whole blood Capillary blood
		Note: Result time sensitive for emergency and critical care		
	Complete blood count (CBC) Automated	 To evaluate overall health and to detect a wide range of disorders, including anaemia, infections, leukaemias, red blood cell, white blood cell and platelet abnormalities and primary immune disorders 	Automated haematology analyser, total and differential counts of white blood cell (WBC), red blood cell (RBC), platelets, haemoglobin (Hb) and haematocrit (Hct)	Capillary whole blood Venous whole blood
		 To diagnose and monitor chemotherapy- associated myelotoxicity 		
		Note: Result time sensitive for emergency and critical care		
	D-Dimer	To diagnose disseminated intravascular coagulation	Immunoassay	Citrate plasma
	Direct antiglobulin test,	 To aid in the diagnosis of the cause of immune haemolytic anaemias 	Red blood cell agglutination	Venous whole blood
	(DAT) also known	 To investigate a blood transfusion reaction 		
	as direct Coombs test	 To diagnose haemolytic disease of the newborn 		
	Fibrinogen	To diagnose disseminated intravascular coagulation	Hand-held or automated coagulation analyser (fibrinogen activity)	Citrate plasma
			Enzyme immunoassay (EIA) (fibrinogen antigen)	

II.a General IVDs for use in clinical laboratories continued

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Discipline	Diagnostic test	Test purpose	Assay format	Specimen type	
Haematology continued	Haematocrit (Hct)	To diagnose and monitor anaemia	Micro-haematocrit method (if automated haematology analyser not available)	Capillary whole blood Venous whole blood	
		Note: Result time sensitive for emergency and critical care	Haematology analyser (preferred)		
	Haemoglobin (Hb)	 To diagnose and monitor anaemia and polycythaemia 	Haemoglobinometer, if automated haematology analyser not available	Capillary whole blood Venous whole blood	
		• To monitor the safety of certain drugs (e.g. zidovudine for HIV infection)	Haematology analyser (preferred)		
		 To screen potential blood donors 			
		 Clinical marker for certain severe infections (e.g. malaria, viral haemorrhagic fevers) 			
		 Aid in the diagnosis of intravascular haemolysis, renal conditions, rhabdomyolysis (myoglobinuria) 			
	Indirect antiglobulin test	• To screen for antibodies to red blood cells before a blood transfusion or in pregnancy	Red blood cell agglutination	Serum	
	 (IAT), also known as indirect Coombs test or red blood cell antibody screen 				

II.a General IVDs for use in clinical laboratories continued

Discipline	Diagnostic test	Test purpose	Assay format	Specimen type
Haematology Iron studies: continued Iron Ferritin Total iron-binding capacity (TIBC) or transferrin Calculated transferrin saturation		To diagnose iron deficiency and overload	Optical methods (iron and TIBC) Immunoassay ¹ (ferritin and transferrin)	Serum Plasma
	Partial thromboplastin time (PTT), also known as activated partial thromboplastin time (APTT)	 To diagnose a bleeding disorder or a thrombotic disorder To monitor anticoagulant therapy 	Hand-held or automated coagulation analyser	Citrate plasma
	Peripheral blood film examination	For detection of red blood cell, white blood cell and platelet abnormalities, malignancies and parasites and for white blood cell differential count	Romanowsky stained blood films	Capillary whole blood Venous whole blood

II.a General IVDs for use in clinical laboratories continued

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Discipline	Diagnostic test	Test purpose	Assay format	Specimen type	
Haematology Platelet count continued		• Diagnosis of thrombocytopenia or thrombocytosis	Haemocytometer, if automated haematology analyser is not available	Capillary whole blood Venous whole blood	
	 Marker to manage severe infection associated with bleeding and sep (e.g. viral haemorrhagic fever, meningococcaemia) and certain haematological disorders 		Haematology analyser (preferred)	-	
		Note: Result time sensitive for emergency and critical care			
	Prothrombin time and international normalized ratio (PT/INR)	To detect or diagnose a bleeding disorder or thrombotic disorder (prothrombin time (PT)); monitor performance of anticoagulant medications (International normalized ratio (INR))	Hand-held or automated coagulation analyser	Citrate plasma	
		Note: Result time sensitive for emergency and critical care			
	White blood cell count	To aid in the diagnosis of infections and leukaemias	Haemocytometer, if automated haematology analyser not available	Capillary whole blood Venous whole blood	
			Haematology analyser (preferred)	-	
	Sickle cell testing	To aid in the diagnosis of sickle cell anaemia,	Sodium metabisulfite slide test	Venous whole blood	
		sickle cell trait and other sickling disorders	Haemoglobin solubility	-	
	-	For the diagnosis of sickle cell anaemia, sickle cell trait and other sickling disorders	Haemoglobin electrophoresis	Venous whole blood	
Serology	Human chorionic	To detect and/or confirm pregnancy	Optical method	Serum	
	gonadotropin (hCG)	To detect germ cell neoplasms	Immunoassay	-	

II.a General IVDs for use in clinical laboratories continued

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
fetop (AFP)	Alpha- fetoprotein (AFP) immunoassay	For screening for hepatocellular carcinoma (HCC) in high-risk individuals with liver cirrhosis or with a family history,	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
		in conjunction with ultrasound For staging and disease monitoring of germ cell tumours				Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. 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. http://publications.iarc.fr/ Book-And-Report-Series/Who- larc-Classification-Of-Tumours/ Who-Classification-Of-Tumours/ Of-The-Urinary-System-And- Male-Genital-Organs-2016

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

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II.b Disease-specific IVDs for use in clinical laboratories continued								
Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents		
Cancer continued						WHO classification of tumours of female reproductive organs. WHO classification of tumours, 4th edition, volume 6. http://publications.iarc.fr/ Book-And-Report-Series/ Who-larc-Classification-Of- Tumours/WHO-Classification- Of-Tumours-Of-Female- Reproductive-Organs-2014		
	Basic panel for immunohisto- chemical (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)	Formalin-fixed paraffin- embedded tissue (FFPE) ¹	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- larc-Classification-Of-Tumours/ Who-Classification-Of- Tumours-Of-Haematopoietic- And-Lymphoid-Tissues-2017		

¹ Only for use in specialized anatomical pathology laboratories – see Anatomical Pathology section under II. a General IVDs for use in clinical laboratories.

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer continued	Basic panel of immunohisto- chemical (IHC) markers for diagnosis of	To aid in diagnosis, prognosis and treatment of solid tumours, especially childhood cancer	IHC testing Markers incl Desmin, Cytokeratin AE1/AE3, S100,	Formalin-fixed paraffin- embedded tissue (FFPE)1	N/A	WHO classification of tumours, 4th edition. http://publications. iarc.fr/Book-And-Report-Series/ Who-larc-Classification-Of- Tumours
	solid tumours	mours synaptophysin, myogenin		WHO list of priority medical devices for cancer management https://apps.who.int/iris/ bitstream/handle/10665/ 255262/9789241565462-eng.pdf		
	BCR-ABL1 and ABL1 transcripts	For diagnosis and therapeutic monitoring of chronic myelocytic leukaemia (CML) and CML variants (neutrophilic CML) and prognosis of acute lymphoblastic leukaemia (ALL)	Nucleic acid test	Whole blood	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-larc-Classification-Of- Tumours/Who-Classification-Of- Tumours-Of-Haematopoietic- And-Lymphoid-Tissues-2017
						20th Essential Medicines List (2017) https://apps.who.int/iris/ handle/10665/273826

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

¹ Only for use in specialized anatomical pathology laboratories – see Anatomical Pathology section under II. a General IVDs for use in clinical laboratories.

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II.b Dise	II.b Disease-specific IVDs for use in clinical laboratories continued								
Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents			
Cancer continued	Essential flow cytometry panel of antibodies to leukaemia (detect 10 unique items among 12 components for four-colour fluorochrome cytometry)	To aid in the diagnosis of acute leukaemias	Flow cytometry (CD10, CD19, CD45, CD34, CD7, CD33, CD117, myeloperoxi- dase, CD79a, cytoplasmic CD3)	Bone marrow Peripheral blood Body fluid Tissue Lymph node	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-larc-Classification-Of- Tumours/Who-Classification-Of- Tumours-Of-Haematopoietic- And-Lymphoid-Tissues-2017 WHO list of priority medical devices for cancer management. https://apps.who.int/iris/ handle/10665/255262			
	Faecal immunochemical test (FIT)	Screening for colorectal cancer	Latex agglutination immuno- turbidimetry	Stool	N/A	WHO priority medical devices for cancer management https://apps.who.int/iris/ handle/10665/255262			
						Colorectal cancer screening. IARC Handbooks of Cancer Prevention, volume 17 http://publications.iarc.fr/ Book-And-Report-Series/ Iarc-Handbooks-Of-Cancer- Prevention/Colorectal-Cancer- Screening-2019			

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Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer continued	Human chorionic gonadotrophin (hCG) plus beta- hCG		N/A	WHO classification of tumours of the urinary system and male genital organs. WHO classification of tumours, 4th Edition, Volume 8 http://publications.iarc.fr/ Book-And-Report-Series/ Who-larc-Classification-Of- Tumours/Who-Classification- Of-Tumours-Of-The-Urinary- System-And-Male-Genital- Organs-2016		
						WHO classification of tumours of female reproductive organs WHO classification of tumours 4th edition, volume 6 http://publications.iarc.fr/ Book-And-Report-Series/ Who-larc-Classification-Of- Tumours/WHO-Classification- Of-Tumours-Of-Female- Reproductive-Organs-2014

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

II.b Dise	ase-specific IVDs	for use in clinical l	aboratories co	ontinued		
Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer continued	Lactate dehydrogenase (LDH) activity	To aid in the prognosis and monitoring of haematological malignancies (lymphoma) and germ cell tumours	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- larc-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 http://publications.iarc.fr/ Book-And-Report-Series/Who- larc-Classification-Of-Tumours/ Who-Classification-Of-Tumours/ Of-The-Urinary-System-And- Male-Genital-Organs-2016

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer continued						WHO classification of tumours of female reproductive organs. WHO classification of tumours, 4th edition, volume 6 http://publications.iarc.fr/ Book-And-Report-Series/Who- larc-Classification-Of-Tumours/ WHO-Classification-Of-Tumours/ Of-Female-Reproductive- Organs-2014
	Oestrogen (ER) and progesterone (PgR) receptors	To aid in diagnosis, prognosis and treatment of breast cancer	lmmunohisto- chemical testing	Formalin- fixed paraffin embedded tissue (FFPE) ¹	N/A	WHO classification of tumours of the breast. WHO classification of tumours, 4th edition, volume 4. http://publications.iarc.fr/ Book-And-Report-Series/Who- larc-Classification-Of-Tumours/ WHO-Classification-Of- Tumours-Of-The-Breast-2012
						WHO list of priority medical devices for cancer managemen https://apps.who.int/iris/ handle/10665/255262/

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

¹ Only for use in specialized anatomical pathology laboratories – see Anatomical Pathology section under II. a General IVDs for use in clinical laboratories.

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Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer continued						WHO 20th Essential medicines List (2017) https://apps.who.int/iris/ handle/10665/273826/
						Guidelines for management of breast cancer. WHO Regional Office for the Eastern Mediterranean (2006) http://applications.emro.who. int/dsaf/dsa697.pdf
	Papanicolaou (Pap) smear test	For screening and as an aid in early diagnosis of cervical cancer	Microscopic examination of cervical cells on slides	Cervical smear from liquid cytology specimen	N/A	Guidelines for screening and treatment of precancerous lesion for cervical cancer prevention. WHO guidelines. (2013) https://apps.who.int/iris/ handle/10665/94830
	Prostate specific antigen (PSA)	To aid in diagnosis, prognosis and monitoring of prostate cancer	lmmunoassay	Peripheral blood	N/A	WHO classification of tumours of the urinary system and male genital organs. WHO classification of tumours, 4th edition, volume 8 http://publications.iarc.fr/ Book-And-Report-Series/Who- larc-Classification-Of-Tumours/ Who-Classification-Of-Tumours/ Of-The-Urinary-System-And- Male-Genital-Organs-2016

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Cancer continued	Tyrosine- protein kinase receptor (erbB-2) or human epidermal growth factor receptor 2 (HER-2) overexpression	To aid in diagnosis, prognosis and treatment of breast cancer	Immunohisto- chemical testing as confirmatory test	Formalin-fixed paraffin- embedded tissue (FFPE) ¹ (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 http://publications.iarc.fr/ Book-And-Report-Series/Who larc-Classification-Of-Tumours WHO-Classification-Of- Tumours-Of-The-Breast-2012 WHO list of priority medical devices for cancer management https://apps.who.int/iris/ handle/10665/255262
						WHO 20th Essential Medicines List (2017) https://apps.who.int/iris/ handle/10665/273826

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

II.b Disea	se-specific IVDs	for use in clinical la	boratories co	ntinued		
Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Hepatitis B	virus (HBV)acute and chronicbloodprequalified IVDssurface antigenhepatitis B virusPlasmahttp://www.who.(HBsAg)(HBV) infection:Serumdiagnostics_laborinfants > 12 monthsevaluations/pq-lis	acute and chronic hepatitis B virus	RDT	blood Plasma	Public reports of WHO prequalified IVDs http://www.who.int/ diagnostics_laboratory/	Guidelines on hepatitis B and C testing (February 2017) http://apps.who.int/iris/ handle/10665/254621
		 evaluations/pq-list/ hbsag/public_report 				
	Quantitative HBV virological nucleic acid test	Staging to assess the need for treatment in chronic HBV infection and monitoring of response to treatment	Nucleic acid test	Serum Plasma	N/A	
	Hepatitis BStaging to assess the need for treatment inImmunoassay PlasmaSerumN/A(HBeAg)chronic HBV infectionPlasma	N/A	-			
	lgM-specific antibodies to hepatitis B core antigen (IgM anti-HBc)	For the diagnosis of acute HBV infection – used for outbreak investigation	lmmunoassay	Serum Plasma		

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Hepatitis B continued	Antibodies to hepatitis B surface antigen (anti-HBs)	To determine effectiveness of HBV vaccination at individual and population levels. Also used as a marker of recovery from HBV infection	Immunoassay	Serum Plasma	N/A	

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

II.b Disea	se-specific IVDs	for use in clinical la	boratories co	ntinued		
Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
	()	Screening for 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 http://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/hcv/ public_report	Guidelines on hepatitis B and C testing (February 2017) http://apps.who.int/iris/ handle/10665/254621
			Immunoassay	Serum Plasma	_	
	Combined antibodies to HCV (anti- core antigenScreening for past or present HCV infection: infants > 18 months of age, core antigen (HCVcAg)Immunoassay PlasmaSerum PlasmaHCV (Anti- infection: infants core antigen (HCVcAg)> 18 months of age, and adults> 18 months of age, core antigen and adults					
	HCV core antigen (HCVcAg)	For diagnosis of viraemic HCV	Immunoassay	Serum Plasma	-	
	Qualitative or quantitative HCV virological nucleic acid	For diagnosis of viraemic HCV and monitoring of response to treatment, and as a test of cure	Nucleic acid test	Capillary whole blood Venous whole blood Serum Plasma	_	

Disease	Diagnostic 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)	For the diagnosis of HIV infection: adults, adolescents, children and infants	RDT	Venous whole blood Plasma Serum	Public reports of WHO prequalified IVDs https://www.who.int/ diagnostics_laboratory/	Guidelines on HIV self-testing and partner notification (2016) http://apps.who.int/iris/ handle/10665/251655
	> 18 months of	> 18 months of age	Immunoassay	Serum Plasma	 evaluations/pq-list/hiv- rdts/public_report 	Consolidated guidelines on HIV testing services (July 2015) https://apps.who.int/iris/ handle/10665/179870
						WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection, module 10 for testing providers (2017) http://www.who.int/hiv/pub/ prep/prep-implementation- tool
	Combined HIV antibody/p24 antigen (anti- HIV/p24 Ag)	For the diagnosis of HIV infection: adults, adolescents, children and infants	RDT	Venous whole blood Plasma Serum		Consolidated guidelines on HIV testing services (2015) https://apps.who.int/iris/ handle/10665/179870
		> 18 months of age	Immunoassay	Serum Plasma		

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

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Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV infection continued	Qualitative HIV virological nucleic acid test	For diagnosis of HIV infection in infants < 18 months of age	Nucleic acid test	Capillary whole blood Venous whole blood Dried blood spots Plasma	Public reports of WHO prequalified IVDs http://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/hiv- vrl/public_report	Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (2016) https://apps.who.int/iris/ handle/10665/208825
	Quantitative HIV virological nucleic acid test	 For monitoring response to antiviral treatment For diagnosis of HIV infection in infants < 18 months of age (only if validated by the manufacturer) 	Nucleic acid test	Dried blood spots (whole blood or plasma) Serum Plasma	-	
	CD4 cell enumeration • For staging advanced HIV disease Flow cytometry disease • For monitoring response to antiretroviral therapy. (In settings where viral load is not available) Flow cytometry	advanced HIV disease • For monitoring response to		Capillary whole blood Venous whole blood	Public reports of WHO prequalified IVDs https://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/cd4/ public_report	Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (2016) https://apps.who.int/iris/ handle/10665/208825
				Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy https://apps.who.int/iris/ handle/10665/208825		

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Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV infection continued	Cryptococcal antigen	For screening and diagnosis of cryptococcal meningitis in people living with advanced HIV disease	RDT	Cerebrospinal fluid Capillary whole blood Venous whole blood Serum Plasma Cerebrospinal fluid 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 antiretrovira therapy (2017) https://apps.who.int/iris/ handle/10665/255884
	Histoplasma antigen	To aid in the diagnosis of disseminated histoplasmosis	lmmunoassay	Urine	N/A	Guidelines for managing advanced HIV disease and rapid initiation of antiretrovira therapy (2017) https://apps.who.int/iris/ handle/10665/255884

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

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Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Human papilloma- virus (HPV) Infection	HPV nucleic acid test	For cervical cancer screening	Nucleic acid test	Cervical cells collected in test- specific transport fluid	Public reports of WHO prequalified IVDs https://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/ public_report_hpv	WHO human papillomavirus laboratory manual, first edition (2009) http://apps.who.int/iris/ handle/10665/70505
Influenza	Influenza A and B nucleic acid test	For diagnosis of seasonal influenza infection	Nucleic acid test	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: https://www.who.int/influenza/ resources/documents/WHO_ Epidemiological_Influenza_ Surveillance_Standards_2014.pdf
						Guidance on clinical management of influenza infections: https://www.who.int/influenza/ resources/documents/clinical_ management_2012

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Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Malaria	spp. antigens; one or species-specific malaria (e.g. HRP2) and/ (<i>P. falci</i>)	For diagnosis of one or more human malaria species (P. falciparum, P. vivax, P. malariae, P. ovale)	uman blood s Venous whole ? <i>vivax</i> , blood	blood Venous whole	Public reports of WHO prequalified IVDs http://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/ malaria/public_report	WHO guidelines for the treatment of malaria, third edition (2015) http://apps.who.int/iris/10665/ 162441 Malaria rapid diagnostic test performance: Results of WHO product testing of malaria RDTs: Round 8 (2016–2018) https://www.who.int/ malaria/publications/atoz/ 9789241514965
					Information note on recommended selection criteria for procurement of malaria rapid diagnostic tests https://www.who.int/ malaria/publications/atoz/ rdt_selection_criteria	
						WHO good practices for selecting and procuring rapid diagnostic tests for malaria (2011) http://apps.who.int/iris/ handle/10665/44530

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Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Malaria Plasmodia continued spp.	Plasmodium spp.	For diagnosis of one or more human malaria 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	WHO guidelines for the treatment of malaria, third edition (2015) http://apps.who.int/iris/10665/ 162441 Basic malaria microscopy Part I: Learner's guide (2010) http://apps.who.int/iris/ handle/10665/44208
				antitative blood orescent		Malaria microscopy standard operating procedures (2015) http://www.wpro.who.int/mvp/ lab_quality/mm_sop/en/
	Glucose-6- phosphate dehydrogenase (G6PD) activity	To determine G6PD activity (normal, intermediate, deficient) for a decision to administer 8-aminoquinoline group drugs for radical cure of <i>P. vivax</i> malaria	Semi- quantitative fluorescent spot test		WHO guidelines for the treatment of malaria, third edition (2015) http://apps.who.int/iris/10665/ 162441	

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

Disease	Diagnostic 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	Nucleic acid test	Serum Plasma Filter paper stored blood	N/A	Dengue: guidelines for diagnosis, treatment, prevention and control (2009) https://www.who.int/tdr/ publications/documents/
	Dengue virus antibody (immunoglo- bulin M) (IgM)	To aid in the diagnosis of dengue fever (always in combination with NS1) and for population surveys	RDT	Serum Venous whole blood	N/A	 dengue-diagnosis.pdf
			lmmunoassay	Venous whole blood Filter paper stored blood Dried blood spots (DBS) Saliva	_	
	antigen (NS1)	To aid in the diagnosis of dengue fever (always in combination with IgM) and for population surveys	RDT	Serum Venous whole blood	N/A	
			Immunoassay	Serum Plasma	_	

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II.b Disea	II.b Disease-specific IVDs for use in clinical laboratories continued								
Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents			
Neglected tropical diseases continued	Kato-Katz	For surveillance and diagnosis of soil- transmitted helminthiasis and schistosomiasis caused by Schistosoma mansoni, S. intercalatum, S. japonicum, S. mekongi	Microscope slide examination	Fresh stool	N/A	Video of Kato-Katz method https://www.who.int/ neglected_diseases/ preventive_chemotherapy/ Basic_Lab_methods_in_ human_parasitology/en/ index2.html			

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Primary Immuno- deficiencies	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
	Immunoglo- bulin plasma levels (IgG, IgA, IgM)	To identify patients with low Ig levels and monitor replacement	Radial immuno- diffusion (RID)	Serum	N/A	-
			Immunoassay	Serum Plasma	_	
	Lymphocyte subtype enumeration: CD4, CD8, CD20, CD16/56 cells, B cells, and NK cells	To aid in the diagnosis of primary and secondary immunodeficiencies	Flow cytometry	Venous whole blood	N/A	-
	(Refer to HIV infection for enumeration of CD4 cells only)					

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Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Sexually transmitted infections	Qualitative test for <i>Chlamydia</i> <i>trachomatis</i> (CT) and	For the diagnosis and screening of symptomatic or asymptomatic	Nucleic acid test	Urine, urethral swabs endocervical swabs,	N/A	WHO sexually transmitted infection laboratory manual https://apps.who.int/iris/ handle/10665/85343
	Neisseria gonorrhoeae (NG) infections	onorrhoeae or gonorrhoeal rectal swabs,		Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations https://apps.who.int/iris/ handle/10665/246200		
	Antibodies to Treponema pallidum	For diagnosis or as an aid in the diagnosis of syphilis	RDT	Venous whole blood Plasma Serum	N/A	WHO laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus (2013) http://apps.who.int/iris/ handle/10665/85343
			Immunoassay	Serum Plasma		
	Antibodies to <i>T. pallidum</i> and to HIV-1/2 (anti- HIV Ab)	For diagnosis or as an aid in diagnosis of HIV-1/2 infection and/or syphilis	RDT	Venous whole Public reports of WHO blood prequalified IVDs Plasma https://www.who.int/ Serum diagnostics_laboratory/ evaluations/pq-list/ hiv_syphilis/en/	prequalified IVDs https://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/	WHO Information note on the use of dual HIV/syphilis rapid diagnostic tests (RDT) (2017) http://apps.who.int/iris/ handle/10665/252849/
					hiv_syphilis/en/	Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations https://apps.who.int/iris/ handle/10665/246200

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Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Sexually transmitted infections continued	Non- treponemal rapid plasma reagin (RPR) test	For screening for syphilis and monitoring treatment effectiveness	Particle/ charcoal agglutination assay	Serum Plasma	N/A	WHO sexually transmitted infection laboratory manual https://apps.who.int/iris/ handle/10665/85343
	Non- treponemal venereal disease research laboratory (VDRL) test	For screening, diagnosis and confirmation of neurosyphilis	Flocculation test	Serum Plasma Cerebrospinal fluid	N/A	
	<i>T. pallidum</i> haemagglutina- tion (TPHA) test	For confirmation of syphilis infection and diagnosis of early and late synhilis	Red cell agglutination assay	Serum (preferred) Plasma	N/A	Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus https://www.who.int/ reproductivehealth/ publications/ rtis/9789241505840
	<i>T. pallidum</i> particle agglutination (TPPA) test	 and late syphilis infection 	Particle agglutination assay		N/A	

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II.b Diseas	e-specific IVDs	for use in clinical lal	ooratories co	ontinued		
Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products ¹	WHO supporting documents
Tuberculosis (TB)	<i>Mycobacterium tuberculosis</i> bacteria	For diagnosis, treatment and monitoring of active TB	Microscopy	Sputum or other specimen types	Implementing tuberculosis diagnostics: policy framework (2015)	Compendium of WHO guidelines and associated standards: Ensuring optimum
		For diagnosis and treatment monitoring of active TB including drug- resistant TB	Bacterial culture	Sputum or other specimen types	WHO meeting report of a technical expert consultation: non- inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/ RIF (2017) http://apps.who.int/iris/ handle/10665/254792 Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Policy update (2013) https://apps.who.int/iris/ handle/10665/112472	delivery of the cascade of care for patients with tuberculosis, second edition (2018) https://apps.who.int/iris/ handle/10665/272644
	<i>M. tuberculosis</i> DNA	For diagnosis of active TB and simultaneous detection of rifampicin resistance	Nucleic acid test	Sputum Broncho-alveolar lavage (BAL) or extra-pulmonary TB specimen types		 Implementing tuberculosis diagnostics: policy framework (2015) https://apps.who.int/iris/ handle/10665/162712

¹ All TB tests are evaluated and guidelines developed by the WHO global TB programme.

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products ¹	WHO supporting documents
Tuberculosis continued	<i>M. tuberculosis</i> DNA	For diagnosis of active TB	Loop- mediated isothermal amplification (LAMP)	Sputum	The use of loop- mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis: policy guidance (2016) http://apps.who.int/ iris/10665/249154	
	M. tuberculosisFor detection of resistance to first-line associated with resistanceMolecular line probe assay (LPA)	line probe	Sputum	The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin: policy update (2016) https://apps.who.int/iris/ handle/10665/250586	Compendium of WHO guidelines and associated standards: Ensuring optimum delivery of the cascade of care for patients with tuberculosis, second edition (2018) https://apps.who.int/iris/ handle/10665/272644	
						Implementing tuberculosis diagnostics: policy framework (2015) https://apps.who.int/iris/ handle/10665/162712

¹ All TB tests are evaluated and guidelines developed by the WHO global TB programme.

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Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products ¹	WHO supporting documents
Tuberculosis continue	<i>M. tuberculosis</i> DNA mutations associated with resistance	For detection of resistance for second-line anti-TB medicines	Molecular line probe assay (LPA)	Sputum	The use of molecular line probe assays for the detection of resistance to second-line anti- tuberculosis drugs: policy update (2016) http://apps.who.int/iris/ handle/10665/246131	
	Drug susceptibility testing with <i>M. tuberculosis</i> culture	To detect resistance to first-line and/or second-line anti-TB medicines	Drug susceptibility testing	Bacterial culture of <i>M. tuberculosis</i>	Technical report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis (2018) http://www.who.int/ tb/publications/2018/ WHO_technical_report_ concentrations_TB_ drug_susceptibility	

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¹ All TB tests are evaluated and guidelines developed by the WHO global TB programme.

Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products ¹	WHO supporting documents
Tuberculosis continued	Lipoarabino- mannan (LAM) antigen	To aid in the diagnosis of TB in seriously ill HIV-positive inpatients	is of urine lipoarabinomanna iously assay (LF-LAM) for the ositive diagnosis and screening ts of active tuberculosis in people living with HIV: policy update (2015)	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/	Compendium of WHO guidelines and associated standards: Ensuring optimum delivery of the cascade of care for patients with tuberculosis, second edition (2018) https://apps.who.int/iris/ handle/10665/272644	
						Implementing tuberculosis diagnostics: policy framework (2015) https://apps.who.int/iris/ handle/10665/162712
	Immune response by Interferon- gamma release assay (IGRA)	For diagnosis of latent TB infection	Immunoassay or ELISPOT assay	Venous whole blood		Latent TB Infection: updated and consolidated guidelines for programmatic management (2018) http://apps.who.int/iris/ handle/10665/260233

¹ All TB tests are evaluated and guidelines developed by the WHO global TB programme.

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Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Zika virus infection	Detection of IgM antibodies to Zika virus	To aid in the diagnosis of suspected Zika virus infection ¹	Immunoassay	Serum (Not to be used with cerebrospinal fluid)	N/A	Laboratory testing for Zika virus infection interim guidance https://www.who.int/csr/ resources/publications/zika/
	Virological detection of Zika virus	To diagnose acute Zika virus infection ^{2,3}	Nucleic acid test	Venous whole blood Serum Plasma Urine CSF	WHO listing through Emergency Use Assessment and Listing (EUAL) procedure: https://www.who.int/ diagnostics_laboratory/ eual-zika-virus/zika/en/	- laboratory-testing

¹ 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.

² 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.

³ 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.

Organism	Screening test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
Hepatitis B virus (HBV)	Hepatitis B surface antigen (HBsAg)	For screening blood donations for HBV	RDT ^{1,2}	Capillary whole blood Venous whole blood Plasma Serum	Public reports of WHO prequalified IVDs https://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/ hbsag/public_report	Screening donated blood for transfusion transmissible infections: recommendations (2009) http://apps.who.int/iris/ handle/10665/44202
			Particle aggluti- nation assay ^{1,2}	Plasma Serum	_	
			Immunoassay ¹	Plasma Serum	_	
Hepatitis C virus (HCV)	Antibodies to HCV (anti-HCV)	For screening blood donations for HCV	RDT ^{1,2}	Capillary whole blood Venous whole blood Plasma Serum	Public reports of WHO prequalified IVDs https://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/hcv/ public_report	
			Immunoassay ¹	Serum Plasma		
	Combined anti- bodies to HCV (anti-HCV) and HCV core antigen (HCV cAg)	For screening blood donations for HCV	Immunoassay ¹	Serum Plasma	-	

II.c Disease-specific IVDs for blood screening laboratories

¹ The only assays recommended for blood screening are those that have been validated for this purpose by the manufacturer.

² 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.

Annex 1

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Organism	Screening test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
HIV	Antibodies to HIV-1/2 (anti- HIV Ab) test	For screening blood donations for HIV	RDT ¹	Capillary whole blood Venous whole blood Serum Plasma	Public reports of WHO prequalified IVDs https://www.who.int/ diagnostics_laboratory/ evaluations/pq-list/hiv- rdts/public_report	Screening donated blood for transfusion transmissible infections: recommendations (2009) http://apps.who.int/iris/ handle/10665/44202
			Particle aggluti- nation assay ¹	Serum Plasma	_	
			Immunoassay ^{1,2}	Serum Plasma	-	
	Combined HIV antibody/p24 antigen (anti- HIV/p24 Ag) test	For screening blood donations for HIV	Immunoassay ^{1,2}	Serum Plasma		
Treponema pallidum	Antibodies to T. pallidum	For screening blood donations for syphilis	Immunoassay ^{1,2,3}	Serum Plasma	N/A	-
Other transfusion- transmitted organisms	human T-lymphot Zika virus, <i>Babesic</i>	<i>Trypanosoma cruzi,</i> tropic virus (HTLV I/II), a and West Nile virus ns, depending on local tion.	Immunoassay ^{1,2}	Serum Plasma	N/A	-

¹ The only assays recommended for blood screening purposes are those that have been validated for this purpose by the manufacturer.

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² May be performed in laboratories with small throughput, in remote areas or emergency situations.

³ 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). NOTE: Please refer to the Haematology section for information on General IVDs for blood transfusion.

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First WHO Model List of Essential In Vitro Diagnostics

WHO Technical Report Series, No. 1017, 2019 Website: https://www.who.int/medical_devices/diagnostics/selection_in-vitro

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This report presents the deliberations and findings of the Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD) meeting in March 2019, which was convened to make recommendations on the test categories to be included in the Second 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 scope and recommended use of the List and details of the methods, the criteria for prioritizing IVDs, and the procedures for establishing the List. It also includes the procedures for updating the List, its integration with other WHO initiatives and its adaption to national contexts. Finally, it contains recommendations from the SAGE IVD on test categories together with a full description of the evidence considered for each test submission, and the voting method for approval or rejection of submissions. In addition, it contains a description of discussions that took place during the open day of the SAGE IVD meeting, which was attended by various stakeholders, including representatives from member state governments, NGO's, the diagnostics industry, academia, and others.

