Target product profile

for a diagnostic test to confirm visceral leishmaniasis

World Health Organization

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Declarations of interest

All contributors completed the WHO Declaration of Interest form, which was reviewed by WHO/NTD before the meeting. Dr Emily Adams declared that she works for the Liverpool School of Tropical Medicine and later joined (part-time) Global Access Diagnostics. Her declarations were assessed, and she did not participate in the decision-making meetings of the subgroup.

1. Background

Leishmaniasis is caused by protozoan parasites which are transmitted by the bite of infected female phlebotomine sandflies. The disease is poverty-related and is associated with poor housing, migration and population displacement of nonimmune people into areas with existing endemic or enzootic transmission cycles, environmental and climate changes, protein–energy malnutrition, weakness of the immune system, and lack of resources.

There are three main forms, namely visceral leishmaniasis (VL) also known as kala-azar, which is the serious form because it is fatal if not treated timely, cutaneous leishmaniasis which is the most common form causing skin ulcers, and mucocutaneous leishmaniasis which affects the mouth, nose and throat *(1)*.

Visceral leishmaniasis is characterized by irregular bouts of fever, weight loss, enlargement of the spleen and liver, and anaemia. Most cases occur in Brazil, Eastern Africa and India. It is estimated that 50 000–90 000 new cases occur worldwide annually *(2)*.

Early detection and appropriate treatment are key strategies for control of visceral leishmaniasis. Signs and symptoms of the infection are non-specific; diagnosis is therefore confirmed by combining clinical signs with *Leishmania*-specific laboratory tests. Diagnostic policy for health services in endemic areas depends on the level of the health system. Two serological tests – the direct agglutination test and the rK39 antigen-based immunochromatographic tests – are developed for field use in most endemic areas *(3)*. A rapid diagnostic test (RDT) detects antibodies and is a simple test that can be used at both peripheral and central levels. A scientific review of published studies estimates that the sensitivity of RDTs varies with the eco-epidemiological regions, especially its low sensitivity in East Africa *(4,5)*. Given the persistence of antibodies for long periods after cure, all serological tests have limitations because they cannot reliably diagnose relapse, and a significant proportion of healthy people living in endemic areas with no history of visceral leishmaniasis test positive for antileishmanial antibodies due to asymptomatic infections. Therefore, antibody-based tests must therefore always be used in combination with a standardized clinical case definition for visceral leishmaniasis diagnosis.

Thus, there is a need for an in vitro point-of-care test to confirm or exclude active cases for early diagnosis to confirm or exclude diagnosis in all transmission settings, thus benefitting both patients and communities in terms of clinical outcomes and limiting the risk of *Leishmania* transmission.

2. Public health response

In 2007, the Sixtieth World Health Assembly adopted resolution WHA60.13 on the Control of Leishmaniasis, urging Member States where leishmaniasis is a public health problem, among other actions:

- to strengthen prevention, active detection and treatment of cases of both visceral and cutaneous leishmaniasis in order to decrease the disease burden;
- to strengthen the capacity of peripheral health centres to deliver primary and secondary care so that they provide appropriate affordable diagnosis and treatment and act as sentinel surveillance sites;

and requested the WHO Director-General

- to promote research pertaining to leishmaniasis control, including in the areas of safe, effective and affordable vaccines, diagnostic tools and medicines with less toxicity, and dissemination of the findings of that research *(6)*.

3. Available diagnostic tools

Signs and symptoms of visceral leishmaniasis are not specific enough to differentiate from clinical conditions such as chronic malaria or other systemic infections. In patients with HIV coinfection, the clinical features may be atypical. Therefore, *Leishmania*-specific laboratory tests are required for diagnostic confirmation.

The minimal platform for techniques for the diagnosis of visceral leishmaniasis in endemic areas depends on the health system level. The most commonly used is the rK39 antigen-based immunochromatographic test in primary health-care centres. At the district level, rK39 RDTs, the direct agglutination test and microscopy on bone marrow, spleen or lymph node aspiration are used. At the tertiary level, additional serological (IFAT, ELISA) and molecular tests (PCR) can be used.

The sensitivity of RDTs varies with the eco-epidemiological endemic regions, especially its low sensitivity in East Africa. Because antibodies persist for long periods after cure, serological tests cannot distinguish between active cases and relapse in previously treated cases. These limitations mean that a negative result in patients with advanced HIV infection cannot rule out the diagnosis of VL, and a significant proportion of healthy people living in endemic areas with no history of visceral leishmaniasis may test positive for antileishmanial antibodies due to asymptomatic infections. Antibody-based tests must therefore always be used in combination with a standardized clinical case definition for diagnosis of visceral leishmaniasis.

4. Development of the target product profiles

This TPP was developed according to a process based on the WHO Target Product Profiles, Preferred Product Characteristics, and Target Regimen Profiles: Standard Procedure, version 1.03 dated 7 December 2021.

The WHO Global Neglected Tropical Diseases Programme (WHO/NTD) set up the Diagnostic Technical Advisory Group (DTAG) as the principal advisory group to WHO on diagnostics for neglected tropical diseases (NTDs). The Group works to ensure unified methods for solving NTD diagnostic needs and to direct WHO strategies in developing efficient diagnostic tools. At its first meeting (Geneva, 30–31 October 2019), the Group discussed priorities for the year ahead and how to manage the complexity of supporting the diagnostics agenda across the entirety of WHO's portfolio of NTDs. Recommendations were made, based on the understanding that they would be reviewed at the next meetings, as it had been made clear that all NTDs had diagnostic needs that would have to be addressed in due course *(7)*. At its second meeting (13 October 2020), the Group recommended constituting a subgroup on visceral leishmaniasis to cater to diagnostic requirements specially in the context of elimination *(8)*. Following this, WHO issued a public notice calling for experts to share their résumés for consideration of a diagnostic TPP for visceral leishmaniasis. The public call was extended for another 4 weeks to accommodate adequate geographical and gender representation. WHO/NTD received more than 40 résumés from interested experts. The DTAG Coordination Committee of WHO/NTD selected 14 experts as members and eight experts as observers. All members completed the WHO declaration of interests form, with the provision that feedback from members with declared interests in this field would be analysed separately. All the meetings were held online and in each virtual meeting members were asked to update their declaration of interests.

At its first meeting on 11 October 2021, the TPP Development Group reviewed the currently available diagnostic tests, diagnostic practices and needs for the current epidemiological situation. It identified two use cases: (i) a diagnostic test for confirmation of visceral leishmaniasis and (ii) a diagnostic test to confirm cure of visceral leishmaniasis. The Group formed two subgroups to deliberate on (i) use case characterization and (ii) diagnostic capability landscape. From October 2021 to September 2022, a draft TPP was developed and all comments and input from the members were reviewed and incorporated when appropriate and feasible. In October 2022, the draft was presented to the TPP Development Group and observers; 4 weeks were given for any final comments and review. Once no additional comments were received, WHO posted the draft TPP for public consultation[1] over 8 weeks during March and May 2023. Anyone could respond by identifying themselves and listing their comments and suggested amendments. The draft TPP was also shared with DTAG members for their review and suggestions. All comments and suggestions from the public and DTAG members were reviewed and the TPP was revised when appropriate and feasible.

WHO then released the current version of the TPP (Table 1).

5. Purpose of the target product profiles

The purpose of this target product profile (TPP) is to communicate the minimum and ideal characteristics desired to meet the need for an in vitro point-of-care diagnostic test for confirmation of visceral leishmaniasis disease caused by infection with *L. donovani* or *L. infantum*.

[1] https://www.who.int/news-room/articles-detail/call-for-public-consultation-----target-product-profiles-(tpp)-for-visceral-leishmaniasis-diagnostics

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Table 1. Characteristics of a needed diagnostic test for confirmation of VL

1. Product use summary	Minimum	Ideal	Background, annotation re requirement risk, etc.
1.1 Intended use	An in vitro point-of-care test for the detection of analyte specific to *L. donovani* or *L. infantum* to enable detection of VL disease.	An in vitro point-of-care test for the detection of analyte specific to *L. donovani* or *L. infantum* to enable detection of VL disease.	The objective is to enable detection of active VL disease.
1.2 Targeted population	All ages and genders of individuals with clinical symptoms of VL regardless of case history, e.g. new, relapsed, geography, patient immune status (such as HIV coinfected, immunosuppression status), etc.	All ages and genders of individuals with clinical symptoms of VL regardless of case history, e.g. new, relapsed, geography, patient immune status (such as HIV coinfected, immunosuppression status), etc.	
1.3 Lowest infrastructure level	The test will be performed under "zero-infrastructure" conditions including but not limited to households, community health centres, and potentially outdoor conditions.	The test will be performed under "zero-infrastructure" conditions including but not limited to households, community health centres, and potentially outdoor conditions.	"Zero infrastructure" conditions are those where no prior requirements must be fulfilled for proper operation of the test.
1.4 Lowest level user	This test will be performed by health personnel, community health workers and community volunteers.	This test will be performed by health personnel, community health workers and community volunteers.	
1.5 Training requirements	One day or less for health personnel, community health workers and community volunteers; testing job aids/instructions for use should be made available via the Internet for download (i.e. are publicly available).	One day or less for health personnel, community health workers and community volunteers; testing job aids/instructions for use should be made available via the Internet for download (i.e. are publicly available).	It is not a requirement to have Internet access to obtain job aids/instructions for use since these must be included with the test itself (per Requirement 4.5), but rather that job aids/instructions for use should always be available via the Internet.

2. Design	Minimum	Ideal	Annotation
2.1 Portability	Highly portable with no specialized transport needs.	Highly portable with no specialized transport needs.	"Portability" implies those characteristics described in 2.2–2.4 as well as no locational limitations to where the test can be performed.
2.2 Instrument/power requirement	Self-contained kit operates independent of any mains power.	Self-contained kit operates independent of any mains power.	
2.3 Water requirement	Self-contained kit operates independent of any water supply.	Self-contained kit operates independent of any water supply.	
2.4 Maintenance and calibration	No maintenance required (i.e. disposable) and no test calibration required.	No maintenance required (i.e. disposable) and no test calibration required.	
2.5 Sample type/ collection	Peripheral whole blood from finger stick, venipuncture blood, urine or saliva.	Peripheral whole blood from finger stick, urine or saliva.	Venipuncture sampling may require support beyond that available as described in Requirements 1.4 and 1.5, which would necessitate having suitably trained technicians or health workers available. It can be assumed that if the test performs well on whole blood, it will also perform well on serum/plasma. The biomarker could be of any nature (antigen, antibody, DNA), and blood is the desired sample. Biobank samples will have blood, sera/plasma.
2.6 Sample preparation/ transfer device	· Sample preparation should not exceed transfer of whole blood (finger stick or venous draw), urine or saliva to the testing device. · Transfer of the sample volume to the testing device shall occur by use of a predefined and provided single-use transfer device (e.g. inverted cup, disposable fixed-volume transfer pipet, etc.)	· Sample preparation should not exceed transfer of whole blood (finger stick or venous draw), urine or saliva to the testing device. · Transfer of the sample volume to the testing device shall occur by use of a predefined and provided single-use transfer device (e.g. inverted cup, disposable fixed-volume transfer pipet, etc.)	
2.7 Sample volume	1–100 µL	1–10 µL	"Sample volume" represents the volume introduced to the test device itself; the original collected sample volume may exceed this volume limit.

2.8 Target analyte	Biomarker(s) specific for infection from *L. donovani* or *L. infantum* that results in VL disease.	Biomarker(s) specific for infection from *L. donovani* and *L. infantum* that results in VL disease.	Analytes based on antigens or other biomarker types (e.g. some nucleic acid-based markers) will presumably provide more favourable half-life kinetics and thus enable more accurate determination of clinical infection from *L. donovani* and/or *L. infantum* in all age groups and genders. For example, current IgG-based serology biomarkers may possess kinetics that enable reliable determination of prior infection from *L. donovani* and/or *L. infantum* but their half-life may preclude their use as markers of apparent clinical infection. If existing VL biomarkers (e.g. antigen-based or otherwise) are further developed or if new biomarkers are discovered and proposed, their qualification and validation will require significant time and effort going forward. For this reason, this is a high-risk requirement.
2.9 Type of analysis	Qualitative	Quantitative	
2.10 Detection	High contrast, clear result for naked eye; indoor and outdoor reading of a signal that provides a definitive result without the need for colour discrimination.	High contrast, clear result for naked eye; indoor and outdoor reading of a signal that provides a definitive result without the need for colour discrimination.	
2.11 Quality control	· Internal process control indicator (e.g. control line on an RDT)	· Internal process control indicator · Colorimetric or other indicator to identify excessive heat/humidity exposure.	For further consideration (i.e. beyond TPP scope): definition of how endogenous positive controls should/would be used if they are to be included with a test (e.g. will there be a community-wide quality panel, centralized reporting of results, etc.).
2.12 Supplies needed	All reagents and supplies included in test kit, with minimal import restrictions (e.g. animal-free, reagents free from toxicity levels that trigger import restrictions)	All reagents and supplies included in test kit, with minimal import restrictions (e.g. animal-free, reagents free from toxicity levels that trigger import restrictions).	Supplies needed: Assumed that all materials are included, including sample collection devices.
2.13 Safety	Normal use of the test does not create any additional hazards to the operator when observing Universal Blood Safety/Body Fluid precautions.	Normal use of the test does not create any additional hazards to the operator when observing Universal Blood Safety/Body Fluid precautions.	
3. Performance	**Minimum**	**Ideal**	**Annotation**
3.1 Species differentiation/detection	*L. donovani* **and** *L. infantum*	*L. donovani* **and** *L. infantum*	The test should be able to detect both *L. donovani* and *L. infantum*, because both species may overlap endemically. However, there should be particular focus to ensure no interference from other *Leishmania* species, particularly those that cause cutaneous and mucocutaneous leishmaniasis.

3.2 Diagnostic/clinical sensitivity	95%	98%	For the evaluation of sensitivity and specificity requirements, the following are assumed: · Range of pre-test probability (PTP) of positive result/ true positive prevalence: 10–70% of symptomatic individuals.· · "Minimum" predictive value requirements are for PPV ≥ 75% and NPV ≥ 95%; "Ideal" predictive requirements are for PPV ≥ 90% and NPV ≥ 95%· · Sensitivity was fixed at 95% for "Minimum". The Se and Sp values shown under "Minimum" are capable of achieving those PPV (≥ 75%) and NPV (95%) requirements, but only over the range of 10–50% PTP; < 90% NPV is achieved once the PTP reaches 70%. The Se and Sp values shown under "Ideal" are capable of achieving those PPV (90%) and NPV (95%) requirements, but this can be achieved over the entire range of 10–70% PTP. It is recommended that the 5%+ difference in meeting the ≥ 95% NPV target for both "Minimum" and "Ideal" in these extremely high pre-test probability conditions will be more than compensated for by the fact that diagnosis depends not only on the test result but also patient assessment that adheres to the clinical description promulgated by in *WHO Technical Report Series 949: Control of the Leishmaniases (2010), which states: "An illness with prolonged irregular fever, splenomegaly and weight loss as its main symptoms. In endemic malarious areas, visceral leishmaniasis should be suspected when fever lasts for more than 2 weeks and no response has been achieved with antimalarial medicines (assuming that drug-resistant malaria has also been considered)."* NOTE: Sensitivity values below 95% were evaluated for their ability to achieve NPV and PPV requirements. Both "Minimum" and "Ideal" PPV requirements can be met at lower Se values of 90% and 85%, but at the expense of a substantial narrowing of the PTP range covered at the predictive values required. NOTE: The minimum specificity was set at 96.5% to account for the range of species and presentations. In some regions the specificity of a diagnostic algorithm combining clinical suspicion (fever, splenomegaly) and a diagnostic test may be higher than 96.5%.
3.3 Diagnostic/clinical specificity	96.5%	99%	

3.4 Time to results	< 2 hours to developed test result	< 0.5 hour to developed test result	
3.5 Result stability	Developed test result remains stable for 0.5 hour	Developed test result remains stable for 24 hours or provides capacity to digitally upload test results (e.g. through a mobile phone application).	· Ability to interpret final test results in a manner not constrained by timed steps helps greatly in resource-constrained settings. · Having remote connectivity for transfer of point-of-care test results would provide centralized data analysis (e.g. for programmatic evaluations) as well as enabling long-term "result stability" (via digital storage) of test results.
3.6 Throughput	≥ 7 individuals tested per hour per tester	≥ 10 individual tested per hour per tester	"Throughput" represents how many tests can be run in parallel within an hour and is *separate from* the time to results.
3.7 Target shelf life/ stability	≥ 18 months, 2–40 °C, 75% relative humidity (no cold chain required); temperature excursion/ prolonged deviation of 50 °C for 2 weeks acceptable.	≥ 24 months, 2–40 °C, 75% relative humidity (no cold chain required); temperature excursion/ prolonged deviation of 50 °C for 2 weeks acceptable.	
3.8 Ease of use	Less than or equal to two timed steps; eight or fewer user steps, instructions for use should include diagram of method and results interpretation. Must be able to use in an unprotected and potentially harsh external environment (e.g. high temperature, high humidity; see Requirement 3.10).	Less than or equal to one timed step; five or fewer user steps, instructions for use should include diagram of method and results interpretation. Must be able to use in an unprotected and potentially harsh external environment.	
3.9 Ease of results interpretation	For point-of-care tests, a definitively interpreted "yes/no" result is achieved by meeting requirements defined in 2.10 "Minimum".	For point-of-care tests, a definitively interpreted "yes/no" result is achieved by meeting requirements defined in 2.10 "Minimum".	
3.10 Operating temperature	15–40 °C, 75% relative humidity	15–40 °C, 75% relative humidity	

4. Product configuration	Minimum	Ideal	Annotation
4.1 Shipping conditions	Conformance to applicable requirements of ASTM D4169-05 and ISO 11607-1:2006 (or equivalent); no cold-chain shipping required.	Conformance to applicable requirements of ASTM D4169-05 and ISO 11607-1:2006 (or equivalent); no cold-chain shipping required.	
4.2 Storage conditions	Ambient storage conditions, 2–40 °C; no cold storage required.	Ambient storage conditions, 2–40 °C; no cold storage required.	
4.3 Service and support	None required.	None required.	
4.4 Waste disposal	Does not include material that cannot be disposed of in normal laboratory biohazard waste streams.	· Does not include material that cannot be disposed of in normal laboratory biohazard waste streams. · Daily throughput needs are considered in the packaging so as to minimize the need to dispose of extraneous product waste and/or disposal of unused tests (also refer to Requirement 5.1).	
4.5 Labelling and instructions for use (IFUs)	· Compliance required per **relevant** CE Mark/ IVDR requirements (or other SRA, e.g. 21 CFR 820) and WHO prequalification guidance (see *WHO TGS-5: Designing instructions for use for in vitro diagnostic medical devices*) · Product insert shall be available in relevant local language(s) and shall include IFUs for the test. · Must provide accurate MSDS information on components that are potentially toxic.	· Compliance required per **relevant** CE Mark/ IVDR requirements (or other SRA, e.g. 21 CFR 820) and WHO prequalification guidance (see *WHO TGS-5: Designing instructions for use for in vitro diagnostic medical devices*) · Product insert shall be available in relevant local language(s) and shall include IFUs for the test. · Must provide accurate MSDS information on components that are potentially toxic.	Labelling and instructions for use (IFUs): WHO prequalification label/IFU guidance should be applied, regardless of whether test is prequalified by WHO or not.

5. Product cost and channels	Minimum	Ideal	Annotation
5.1 Target pricing per test	< US$10	< US$ 2	· Actual price details will depend on other factors separate from the test itself, which include shipping, storage, quantities purchased and other factors commonly encountered in national procurement for NTD programmes. · Low-volume test usage in certain situations creates the need for packaging that allows one-at-a-time use of tests to avoid creating significant price pressure from wasting of unused tests (e.g. tests are packaged for individual use as opposed to a larger number packaged together that must be used shortly after opening (also refer to Requirement 4.4)).
5.2 Capital cost	None required.	None required.	
5.3 Product lead times	< 12 weeks	< 12 weeks	"Lead time" includes fulfillment and delivery of ordered tests to procurer. NOTE: May be adjusted to longer lead times provided shelf-life is of sufficient duration (e.g. 2 years).
5.4 Target launch countries	WHO prioritized countries	WHO prioritized countries	
5.5 Product registration (i.e. substantiation to regulatory body of product claims)	· CE Mark/IVDR (or other SRA) as *relevant* · Any registration required for export from country of origin (e.g. KMFDS from Republic of Korea, etc.) · WHO prequalification, *if required/applicable* · Country-level registration, *if required/ applicable for targeted countries*	· CE Mark/IVDR (or other SRA) as *relevant* · Any registration required for export from country of origin (e.g. KMFDS from Republic of Korea, etc.) · WHO prequalification, *if required/applicable* · Country-level registration, *if required/ applicable for targeted countries*	

ASTM: American Society for Testing and Materials; IFU: instruction for use; IVDR: In Vitro Diagnostics Regulation; KMFDS: Korean Ministry of Food and Drug Safety; MSDS: material safety data sheet; NPV: negative predictive value; PPV: positive predictive value; PTP: pre-test probability; SRA: Stringent Regulatory Authority; VL: visceral leishmaniasis..

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