TARGET PRODUCT PROFILE
for a point-of-care diagnostic test for dermal leishmaniases

World Health Organization

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1. Epidemiology

Localized cutaneous leishmaniasis and its evolving forms (diffuse cutaneous leishmaniasis, mucosal leishmaniasis and cutaneous leishmaniasis recidivans), together with the sequela of visceral leishmaniasis (post-kala-azar dermal leishmaniasis), account for about one million cases of dermal leishmaniases per year worldwide. Although not lethal, the dermal leishmaniases cause chronic, disfiguring skin lesions which are an important cause of morbidity and stigma.

Microscopy remains the reference test for diagnosis of dermal leishmaniases; however, it has low and variable sensitivity and requires well-trained personnel. The technical complexity and cost of the more sensitive molecular techniques (e.g. polymerase chain reaction) limit their application for routine diagnosis in endemic areas *(1)*. As a result, a high number of patients are put on treatment without laboratory confirmation, exposing a variable number of them to unnecessary toxic treatment *(2, 3)*.

A great need thus exists for point-of-care tests for early diagnosis of dermal leishmaniases in order to benefit both patients and communities by early identification of those who need treatment, thereby reducing the risk of both sequelae and ongoing *Leishmania* transmission.

2. Public health response

In 2007, the Sixtieth World Health Assembly adopted resolution WHA60.13 on control of leishmaniasis, urging Member States, among other actions:

- to strengthen prevention, active detection and treatment of cases of both cutaneous and visceral leishmaniasis in order to decrease the disease burden; and
- 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.

Furthermore, the WHO Director-General was requested 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 …".

3. Available diagnostic tools

Microscopy of Giemsa-stained samples from lesions, including skin scrapings, fine-needle aspirates or slit-skin smears, remains the reference test for diagnosis of the different forms of dermal leishmaniasis. However, microscopy has significant shortcomings, and more sensitive molecular tests have not yet been widely adopted. Other simpler tests for detection of leishmanial DNA, such as loop-mediated isothermal amplification, have yet to be implemented. Other potential approaches include serology, which may be useful for screening of post-kala-azar dermal leishmaniasis and mucosal leishmaniasis, but cannot be used for confirmation, as presence of antibodies may be due to previous episodes or exposure to the parasite by living in endemic areas. The leishmanin (Montenegro) skin test can also aid in the diagnosis of cutaneous leishmaniasis, but again the test is not a marker of active infection, and therefore has limited value *(1)*.

In 2016, FIND involved a panel of 47 international experts on leishmaniasis in a survey to rank diagnostic priorities. A rapid test for cutaneous leishmaniasis was identified among the top priorities *(4)*. Currently there is an FDA-cleared and CE-marked rapid test targeting *Leishmania* antigen that is designed for diagnosis of cutaneous leishmaniasis: the CL *Detect*™ Rapid Test for Cutaneous Leishmaniasis (InBios International Inc., Seattle (WA), USA; https://inbios.com/cl-detecttm-rapid-test-for-cutaneous-leishmaniasis-intl/). Studies have shown high specificity, but unfortunately the sensitivity is quite variable across Leishmania species and endemic regions *(5–8)*.

4. The WHO Diagnostic Technical Advisory Group for Neglected Tropical Diseases

The WHO Department of Control of Neglected Tropical Diseases manages a diverse portfolio of 20 diseases and disease groups, each with its own unique epidemiological and diagnostic challenges.

At its 12th meeting (Geneva, 29–30 April 2019), the Strategic and Technical Advisory Group for Neglected Tropical Diseases, the principal advisory group to WHO on the control, elimination and eradication of neglected tropical diseases (NTDs), decided to establish a single WHO working group to ensure use of a unified approach to identify and prioritize diagnostic needs and to inform WHO strategies and guidance on the subject *(9)*. The Diagnostic Technical Advisory Group (DTAG) was thus established as the principal advisory group to WHO on NTD diagnostics. At its inaugural meeting (Geneva, 30–31 October 2019), the DTAG identified the following diagnostic needs for dermal leishmaniases *(10)*:

- a rapid test for post-kala-azar dermal leishmaniasis – to distinguish this form of the disease from other skin conditions; and
- a rapid test for confirmation of suspected cases of cutaneous leishmaniasis at peripheral health facilities.

This target product profile (TPP) for a point-of-care diagnostic test for dermal leishmaniases was developed in response to those needs.

5. NTD road map 2021–2030

Cutaneous leishmaniasis is targeted for control in the new road NTD map for 2021–2030. The main target for 2030 is to detect, report and treat at least 87% of cases. At least 64 countries are expected to be validated for elimination of visceral leishmaniasis as a public health problem by 2030; which means that post-kala-azar dermal leishmaniasis (which plays an important role in transmission) must be specifically addressed in the Indian subcontinent and in some countries in eastern Africa *(11)*.

To achieve these goals, more effective and user-friendly diagnostics for cutaneous and post-kala-azar dermal leishmaniasis are needed. Enabling decentralized testing is essential for both individual cases and mass screening in the context of near-elimination of visceral leishmaniasis; i.e. testing in public health centres and/or among communities.

A rapid test targeting *Leishmania* antigens common across *Leishmania* species will address major diagnostic needs for dermal leishmaniasis, and, by addressing post-kala-azar dermal leishmaniasis, may also contribute to the control and elimination of visceral leishmaniasis.

6. Background and scope for the TPP

There is thus a great need for point-of-care tests for early diagnosis of dermal leishmaniases in order to benefit both patients and communities by early identification of those who need treatment, thereby reducing the risk of both sequelae and ongoing Leishmania transmission. It is therefore important that new point-of-care tests be developed to meet the needs of the target population and the requirements for implementation in resource-limited settings, where most cases of dermal leishmaniasis occur. This TPP for a point-of-care test for dermal leishmaniases was defined through several rounds of discussions and by consensus with stakeholders and experts in dermal leishmaniases from different types of organizations and endemic regions.

7. Audiences engaged and external consultations to develop the TPP

A draft TPP was developed by leishmaniasis experts at FIND and DNDi and presented at the second redeLEISH Meeting (Medellín, Colombia, July 2015) for discussion with a panel of 70 experts on leishmaniasis *(12)*. The draft was then refined based on the inputs from the experts and a new document was shared with a second panel of experts comprising 31 experts from different organizations and endemic regions. Consensus was reached to define a TPP with 29 priority features *(1)*. The TPP was presented at different stakeholder meetings, including the 6th World Congress on Leishmaniasis in 2017 *(13, 14)* and the biennial meeting of the Global Buruli Ulcer Initiative in 2017 *(15)*.

In the same period, more specifically in March 2016, and as part of a consultation to develop FIND's leishmaniasis strategy, 40 experts on leishmaniasis helped to identify and rank diagnostic priorities. The experts had experience in the different forms of leishmaniasis from different endemic regions and represented academia, international organizations and product development partnerships, among others. The experts identified a rapid point-of-care test for dermal leishmaniasis as one of the highest priorities. This was further discussed at the 6th World Congress on Leishmaniasis *(13, 14)*.

After further refinement, the TPP was published in *Parasite Epidemiology and Control* with authors from FIND, DND*i* and WHO in 2019 *(1)*.

When the WHO Department of Control of Neglected Tropical Diseases began work on TPPs, the leishmaniasis TPP published in 2019 *(1)* was subsequently reviewed by its lead author Dr Isra Cruz in line with the WHO guide for TPP development. The draft was then submitted to DTAG for comments before finalization and publication for online consultation (23 November–24 December 2021). No feedback was received. The TPP was therefore considered final.

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TPP for a point-of-care diagnostic test for dermal leishmaniases

1. Scope of the test	Minimum	Ideal	Annotations
1.1 Goal of test. Intended use	Detection of active localized cutaneous leishmaniasis (LCL)	Detection of active cutaneous leishmaniasis (CL, any form) or post-kala-azar dermal leishmaniasis (PKDL) with the purpose of initiating treatment during the same clinical encounter (or same day)	LCL is the most prevalent of dermal leishmaniases (> 80% of cases). This clinical form is present in all CL-endemic regions. All *Leishmania* species cause LCL. Other forms of CL usually evolve from LCL
1.2 Target population	Individuals with clinical signs suggestive of LCL	Individuals with clinical signs suggestive of any form of CL, or PKDL	
1.3 Target operator of test	Trained laboratory staff	Health worker at primary health care level without laboratory training	Most patients go to health facilities with limited human resources
1.4 Lowest setting for implementation	Decentralized health care facilities with minimum laboratory infrastructure	Decentralized health care facilities with no laboratory infrastructure, or mobile team	This test could replace microscopy, as has happened with other diseases (e.g. malaria)
1.5 Target analyte to be detected	*Leishmania* antigen		
2. Performance characteristics	Minimum	Ideal	Annotations
2.1 Clinical sensitivity	95% in parasitologically-confirmed cases	100% in parasitologically-confirmed cases	Measured in frozen or fresh samples from parasitologically-confirmed patients (microscopy and/or culture and/or PCR from skin scrapings, swabs, biopsies, aspirates, etc.). A combined reference standard according to each region should be considered
2.2 Clinical specificity	> 90%	> 95%	Tested against reference standard (according to each endemic setting), including subjects with other diseases affecting the skin
2.3 *Leishmania* species-specificity	*Leishmania* genus-specific	*Leishmania* species-specific	Different treatment options might be needed for different species
2.4 Type of analysis. Quantitation	Qualitative		There is no need for quantification as parasite burden will not guide therapy

3. Test procedure	Minimum	Ideal	Annotation
3.1 Training needs. Time dedicated to training session for end-users	One day for any level of health care worker. Job aid provided	Less than half a day for any level of health care worker. Job aid provided	
3.2 Sample type	Lesion fine-needle aspirate, skin scrapping, biopsy, etc.	Lesion swab	Minimally invasive sampling procedures will be preferred
3.3 Sample preparation. Total steps	3–5 simple steps	Direct testing from lesion swab	
3.4 Number of steps to be performed by operator	< 10; 1 timed step	< 3; 1 timed step	
3.5 Need for operator to transfer a precise volume of sample	Acceptable with a disposable transfer device provided	No	Sample may need to be eluted in specific buffer (included in the kit)
3.6 Time to result	< 1 h	< 20 min	
3.7 Internal control	Included		Positive control to confirm validity of the test
3.8 Reading system. Interpretation of results	Visual (naked eye) or simple reading device	Visual (naked eye)	See 3.9
3.9 Auxiliary equipment	Test reader (for lateral flow assay, dual path platform or similar)	None, instrument free (required materials are included in the kit)	There are rapid diagnostic tests that generate a fluorescent signal that increases sensitivity; a reader is needed to detect this signal. In these cases a connectivity option could be desirable, enabling sending results to a reference laboratory, coordinator, reporting system, etc. thresholds
3.10 Power requirements	Battery operated	None required	If a reading device is needed it should be a small, portable or hand-held instrument (< 1 kg) that can operate on rechargeable battery or solar power lasting at least 4 h (8 h preferred)
3.11 Need for maintenance/spare parts	None		

4. Operational characteristics	Minimum	Ideal	Annotations
4.1 Operating conditions	–40 °C, up to 80% relative humidity (RH), 0–2000 m above sea level	5–50 °C, up to 90% RH, 0–4000 m above sea level	High environmental temperatures and high humidity are often a problem in countries where CL is endemic. Some laboratories for CL diagnosis are located at high altitude (e.g. La Paz, Bolivia [Plurinational State of])
4.2 Reagent kit transport	No cold chain required; tolerance of transport stress for a minimum of 48 h at –15 °C to 50 °C	No cold chain required; tolerance of transport stress for a minimum of 72 h at –15 °C to 50 °C	Refrigerated transport is costly and often cannot be guaranteed during the entire transportation process. Frequent delays in transport are common
4.3 Reagent kit storage/stability	No cold chain required. Up to 12 months at 40 °C, up to 70% RH	No cold chain required. Up to 24 months at 50 °C, up to 90% RH	Should be able to tolerate transport stress (48 h at 50 °C). To include test quality detector (for surpassed temperature or humidity)
4.4 Reagents reconstitution. Need to prepare the reagents before use	A few simple steps	All reagents ready-to-use	Simple steps like resuspension of lyophilized reagent
4.5 In-use stability	> 1 h for single use test after opening the pouch		High environmental temperatures and high humidity are often a problem in countries where CL is endemic
4.6 Biosafety requirement. Level of protection to be made available for the staff and the samples	No need for biosafety cabinet. Standard biosafety precautions when handling potentially infectious materials. No contraindications to routine use		
5. Pricing	Minimum	Ideal	Annotations
5.1 Maximum price for individual test	< 5 US$ per test	< 1 US$ per test	Assumption that the test is produced at a large scale, transport costs from manufacturing company not included
5.2 Maximum price for instrumentation, if needed	< 2000 US$	< 2000 US$	In case a test reading device is needed
5.3 Expected scale of manufacture	1.0 million tests/year	2.5 million tests/year	Based on 0.7–1.2 million estimated CL cases; and provided the test has better performance than microscopy

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