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