Diagnostic Gaps and Recommendations for Leprosy

Assessment of user needs, use cases, and the diagnostic landscape
Acknowledgment
This report was written by PATH and supported in whole or part by a grant from the Bill & Melinda Gates Foundation. The views expressed herein are solely those of the authors and do not necessarily reflect the views of the Gates Foundation.

Suggested citation

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**Acronyms**

BB  mid-borderline leprosy  
BL  borderline lepromatous leprosy  
BT  borderline tuberculoid leprosy  
CMI  cell mediated immunity  
DAWLY  disability-adjusted working life years  
DNA  deoxyribonucleic acid  
ELISA  enzyme-linked immunosorbent assay  
IFNγ  interferon-gamma  
LL  lepromatous leprosy  
MB  multibacillary  
MDT  multidrug therapy  
NTD  neglected tropical disease  
PB  paucibacillary  
PCR  polymerase chain reaction  
rPCR  real-time polymerase chain reaction  
PNL  pure neural leprosy  
POC  point-of-care  
RDT  rapid diagnostic test  
TT  tuberculoid leprosy  
QA/QC  quality assurance/quality control  
WHO  World Health Organization
Executive summary

Leprosy is a chronic infectious disease that results in nerve damage, muscle weakness and atrophy, and permanent disability and disfigurement, causing sufferers to be stigmatized and isolated by their communities. Provision of multidrug therapy and follow-up care has resulted in a dramatic decline in the prevalence of leprosy; however, there are close to 200,000 new cases of this curable disease each year, often diagnosed after permanent disability has already developed.

The World Health Organization (WHO) 2020 goal is to eliminate leprosy as a public health problem (defined as prevalence <1 case per 10,000). The WHO set a number of goals for the Neglected Tropical Diseases (NTD) to be achieved by 2020, and the London Declaration on NTDs backed these goals with commitments from public and private institutions, notably for leprosy Novartis committed to donate antibiotic drugs to treat leprosy in endemic countries. The 3rd progress report of the London Declaration indicated that “priorities for progress” towards reaching leprosy goals include an urgent need for field-friendly diagnostic tests for leprosy.

In support of the London Declaration goals, PATH aims to catalyze engagement of the diagnostics industry and product development efforts. As part of this work, PATH assessed needs and landscaped potential solutions to improve diagnostic tools used to support leprosy elimination efforts. We conducted literature reviews, a product development landscape, and interviews with key stakeholders in the leprosy community to identify use cases for leprosy diagnostics, understand current practices, and analyze progress toward more robust diagnostics. The findings were used to develop recommendations to improve availability, access, and adoption of leprosy diagnostic tools.

PATH identified four use cases for leprosy diagnostics: diagnosing subclinical infection, diagnosing symptomatic infection including paucibacillary (PB) and multibacillary (MB) disease, and treatment monitoring. We found that current diagnostic tools and practices for leprosy are unlikely to support achievement of elimination goals. There are no POC tools commercially available for leprosy diagnosis. Tools currently in late-stage development are not applicable to all symptomatic leprosy infections and there is growing interest in new tools that can detect subclinical infections and monitor treatment outcomes. Based upon these findings, we have developed the following recommendations:

1. **Bring to market antibody-detecting rapid tests to aid health workers in the confirmation of MB infections.** Prototypes are in late-stage development and would identify the most transmissible and debilitating infections. Implementation and market research may be needed to support optimal uptake and use of these tools.

2. **Develop new diagnostic tools that identify all symptomatic leprosy infections.** These tools are necessary to ensure prompt treatment and cure of all leprosy cases.

3. **Support further research to understand feasibility and utility of diagnostic tools for subclinical infections and post-treatment monitoring of immunologic reactions and relapse.**
Introduction

Leprosy, or Hansen’s disease, is a chronic infectious disease caused by the bacterium *Mycobacterium leprae*. Leprosy has been associated with isolation and fear throughout history. If left untreated, the disease can cause nerve damage, leading to muscle weakness and atrophy, as well as permanent disability and disfigurement. There are currently between one and two million people visibly and irreversibly disabled from leprosy.\(^1\) The global prevalence of leprosy at the end of 2013 was 180,618 cases on record for treatment in 105 countries with the majority of those cases (127,295) in India (see Figure 1). The number of new cases reported globally in 2013 was 215,656; this incidence has remained largely unchanged since 2000.\(^2\) A modified method that accounts for disability-adjusted working life years (DAWLYs) estimated that among leprosy-affected patients, an average of 28.6 years or 30 percent of their productive working years are lost to disability.\(^3\)

**Figure 1. New case detection rates for leprosy.** Data reported to the World Health Organization as of January 2014.\(^4\)

Recent years have seen a dramatic decline in the prevalence of leprosy, due largely to control efforts that include improved diagnosis, provision of multidrug therapy, and follow-up care. Better patient counseling and community education has decreased the stigma associated with leprosy in some places and increased self-reporting. Demonstrated success in some countries suggests that the elimination of leprosy as a public health problem may be a feasible goal.

The 2012 World Health Organization (WHO) Neglected Tropical Disease (NTD) Roadmap puts forward the goal of elimination of leprosy as a public health problem, defined as achieving prevalence less than 1
case per 10,000 population, by the year 2020. Shortly after the release of the NTD Roadmap, 20 public and private institutions that support global health and international development—including pharmaceutical companies, donors, governments from endemic countries, nonprofit organizations, and others—joined the efforts to reach the 2020 goals for 10 of the 17 diseases, in a document known as the London Declaration on Neglected Tropical Diseases. The London Declaration represents a commitment from these institutions to sustain, expand, and extend programs that ensure the necessary supply of drugs and other interventions to achieve the NTD Roadmap goal for elimination of leprosy as a public health problem by 2020.

The London Declaration 3rd Report identified an urgent need for field-friendly diagnostics for leprosy. In response to this need, PATH conducted a diagnostic landscape analysis to identify gaps and evaluated current and emerging leprosy diagnostics that may provide solutions. This analysis was informed by a review of literature and interviews with organizations in the leprosy community. The literature review included peer-reviewed scientific publications, policies and guidelines, documents from expert meetings hosted by the Novartis Foundation, country case studies, and a review of the technology landscape. The peer-reviewed literature was searched for studies that evaluated diagnostic tools and algorithms in leprosy clinical management. Key grey literature documents include country-level guidelines and strategies from India and the Philippines. The review of the technology landscape was conducted through January 2016.

Key organizations in the leprosy community were identified through their roles in global and country-level programs, academic research, participation in consultative meetings, and through referral from other key stakeholders. Identified stakeholders were interviewed with a semi-structured interview guide focusing on several themes identified through the literature review. These themes included disease progression and treatment, access to care, diagnostic use cases and user needs, and existing technologies and technology gaps. Information from the literature review, product development landscape, and stakeholder interviews was compiled to:

- Identify use cases and understand current leprosy diagnostic practices and tools associated with each use case.
- Analyze progress toward robust diagnostics for leprosy across different biomarkers.
- Develop recommendations for steps to improve the availability, access, and adoption of leprosy diagnostic tools.
Diagnostic landscape

Disease course and transmission

Leprosy is caused by *M. leprae*, a slow-growing mycobacterium that targets human skin, peripheral nerves, nasal mucosa, upper respiratory tract, and eyes. The average period of incubation of *M. leprae* is three to five years, and the disease can take as long as ten years to progress. Leprosy is a long-lasting infection that causes episodic and damaging immune responses and can lead to chronic or permanent nerve damage, the effects of which can have debilitating physical, social, and psychological consequences. Leprosy is spread person-to-person with the main point of entry and exit being the upper respiratory tract. Other modes of transmission of *M. leprae* may include skin-to-skin contact with an infected person, aerosols/droplets, and shedding of bacteria into the environment such as transmission of dust to small wounds.

The infection may be subclinical, in which no disease symptoms appear. Subclinical infections may progress into a paucibacillary (PB) or multibacillary (MB) infection, which is the two-category WHO operational classification of leprosy created to simplify the five-category Ridley-Jopling classification. The distinction between the PB and MB disease stage depends on the number of skin lesions and extent of nerve damage, which impacts duration of treatment. See Figure 2 for a summary of disease progression and clinical management.

**Figure 2. Disease progression and clinical management relating to need for diagnostic tools.**

The disease course is complicated by variation in the host immune response, between individuals and over the course of infection. Genetic variability impacts the regulation of the innate immune response, which has a key role in determining susceptibility to leprosy. Additionally, at the onset of infection, cell-mediated immune responses are increased, characterized by IL-2 and IFNγ. In the MB stage, antibody responses are increased as *M. leprae* is more abundant in tissue, characterized by IL-4 and IL-10 responses. The clinical outcome after *M. leprae* infection is determined by the balance of pro- and anti-inflammatory cytokines in response to *M. leprae*.
Leprosy is a spectral disease and the clinical manifestations are dependent on the host immune response.\textsuperscript{18,19} At one end of the spectrum, lepromatous leprosy (LL) patients exhibit a higher bacterial index (BI), high titers of \textit{M. leprae}–specific antibodies, and limited or no specific cell-mediated immunity (Figure 3). By contrast, tuberculoid leprosy (TT) patients demonstrate no detectable BI, low or absent titers of \textit{M. leprae}–specific antibodies, and significant specific cell-mediated immunity (CMI).\textsuperscript{20–22} Between LL and TT patients, leprosy patients can also be classified as borderline tuberculoid (BT); mid-borderline (BB); and borderline lepromatous (BL). See Figure 3 for an overview of the host immune response by disease classification.

\textbf{Figure 3. Host immune response by disease classification.} From Lockwood and Saunderson, 2012.\textsuperscript{20}

Beyond genetic susceptibility (there is widespread natural immunity to leprosy), there are social determinants that impact overall health and immunity, leading to disease. Factors related to poverty, such as malnutrition, crowded living conditions, and other coinfections may be associated with disease. However, these factors may also worsen after diagnosis, as a result of stigma, disability, and depression due to unemployment or community isolation.\textsuperscript{16}
Diagnosis

The diagnosis of leprosy is currently based on clinical manifestations. These include the presence of skin lesions, sensory loss, or thickened peripheral nerves. Clinical diagnosis can be complemented by techniques such as evaluation of skin sensitivity. No laboratory test alone is considered *sine qua non* to diagnose leprosy or its clinical form. In inconclusive cases, skin smear, Mitsuda intradermal reaction, and histopathology often make it possible to confirm the diagnosis of leprosy and classify its clinical form. New tools are currently available for research purposes, including serological tests and polymerase chain reaction (PCR), with several primers aiming at different genomic targets of *M. leprae*.\(^{23,24}\)

The timely diagnosis of leprosy is complicated by several factors. For one, care-seeking on the part of patients is delayed due to stigma and other barriers. The historical and ongoing implications of stigma associated with leprosy are well documented. Stigma can lead to isolation, poor mental health, and declines in socio-economic status.\(^{25-27}\) Leprosy patients may conceal their condition and withdraw from their families or communities—factors that can delay care-seeking.\(^{27}\) In addition, patients may not detect skin lesions or experience enough discomfort to seek care from a health center.\(^{28}\) Finally, many leprosy patients face other barriers to accessing care in rural areas including distance to care, poverty, and low health literacy.\(^{27}\)

Secondly, accurate diagnosis through clinical manifestations relies on the expertise of trained leprologists. Given that the prevalence of leprosy has declined dramatically in recent years, fewer and fewer practitioners have the requisite skills and experience with leprosy patients needed to identify the early signs of the disease. Moreover, leprosy patients often live in rural or remote areas without effective systems for identification and referral. As the pool of leprosy expertise gets smaller due to the declining prevalence of the disease, so too does the likelihood that suspected patients will have access to skilled leprologists.\(^{29}\) Lack of leprosy expertise becomes a particularly important issue as more diagnostic and treatment programs are integrated into primary care systems. A challenge with diagnosing based on host immune responses is its variability over disease course, moving from cell-mediated immunity to humoral immunity. Ultimately, differential diagnosis may rely on slit-skin smears or skin biopsies, which are not widely available.

Delayed diagnosis is particularly detrimental to leprosy patients due to the nerve damage that can occur throughout the disease course. Because nerve damage is immune mediated, it can occur before, during, and after antibiotic treatment, and it results in the physical deformities of the face and limbs that are typical late-stage features of leprosy.\(^{20}\) Although the disease is curable, delaying diagnosis and the initiation of treatment leads to permanent nerve damage and disability, which can further lead to severe social consequences.\(^{30,31}\) Leprosy strategies highlight the need to ensure all existing and new cases get and continue appropriate treatment.

Finally, a reliance on clinical manifestations precludes any diagnosis or initiation of treatment in asymptomatic individuals who may be vulnerable to disease progression. At a meeting hosted by the Novartis Foundation in 2015, experts characterized leprosy infection as a tiered structure of patients and potential patients with varying levels of exposure and associated risk of infection.\(^{32}\) The largest tier of the
cascade represents those who are susceptible to infection or exposed to the bacteria. Smaller tiers beneath that represent the subset of those people who will become infected and an even smaller subset of those people who will progress to a symptomatic infection. As indicated in the patient cascade, there are potentially large groups of exposed or infected individuals who will not be diagnosed as long as diagnosis relies on the experience of symptoms. There are currently no guidelines that support treatment for these groups, which may represent missed opportunities to intervene and interrupt transmission, prevent new cases of leprosy, or halt the progression of nerve damage and disability.

Treatment

Leprosy is curable and treatment can prevent the progression of deformities and disability. Infected individuals are no longer infectious shortly after initiating treatment as drug therapy also interrupts transmission of the disease. Leprosy is treated with a multidrug therapy (MDT) that includes rifampicin, clofazimine, and dapsone, due to the potential for the development of drug resistance. See Table 1 for leprosy classifications and corresponding MDT. These drugs are supplied free of cost by Novartis to leprosy patients in all endemic countries.

Table 1. WHO operational classification of leprosy and the corresponding multidrug therapy (MDT).
Adapted from Walker and Lockwood, 2006.

<table>
<thead>
<tr>
<th>Type of leprosy</th>
<th>Number of skin lesions</th>
<th>Drug treatment Monthly supervised</th>
<th>Drug treatment Daily, self-administered</th>
<th>Duration of treatment (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paucibacillary</td>
<td>1–5</td>
<td>Rifampicin 600 mg</td>
<td>Dapsone 100 mg</td>
<td>6</td>
</tr>
<tr>
<td>Multibacillary</td>
<td>6 or more</td>
<td>Rifampicin 600 mg, Clofazimine 300 mg</td>
<td>Clofazimine 50 mg, Dapsone 100 mg</td>
<td>12</td>
</tr>
</tbody>
</table>

Reactions to leprosy treatment are a function of the immune response and can lead to permanent nerve damage. Steroids and other anti-inflammatory drugs may be necessary to manage reactions. While the antibiotics used to treat leprosy are free to patients, the steroids needed to manage leprosy reactions are not and accessing them may be a barrier to effective treatment. Proper management of reactions and patient education are critical to the effectiveness of treatment and to stop transmission.

Following the observance of antimicrobial resistance with dapsone-only regimes, multidrug regimens were introduced in 1982. Though the duration of MDT was decreased by the WHO in 1989, there is still some uncertainty in this recommendation due to concerns with incomplete treatment and relapse. Currently, multiple antibiotics are used to prevent the development of resistance to a single drug. These challenges along with the stigma associated with leprosy reinforce the critical role of diagnostic tools, as health care providers are unwilling to treat patients without a clear and reliable diagnosis.
Use cases

The integration of leprosy diagnosis and care into general health services is important to decrease stigma and support elimination efforts, and as such is an essential part of the WHO’s global strategy for elimination. Any future diagnostic tools must be designed with the parameters of primary care settings in mind. This analysis identified four unique use cases for leprosy diagnostics: diagnosis of subclinical infections, PB infections, or MB infections, as well as post-treatment monitoring.

Figure 4: Use cases for leprosy diagnostics

Subclinical infection
Identifying subclinical (or asymptomatic) infections requires active surveillance of household contacts and communities. There is significant evidence to suggest that subclinical infections are more common than symptomatic infections and that these infections represent a critical link in transmission. However, many subclinical infections will be resolved on their own, necessitating the distinction between subclinical infections likely to progress versus those likely to clear. There are currently no diagnostic tools that can detect subclinical infections nor are there guidelines that recommend the initiation of treatment for this stage of infection. Optimal biomarkers are still being investigated and potential tests could utilize host cytokines and chemokines, or nucleic acid amplification specific to \textit{M. leprae}. Several research groups are engaged in this early discovery phase of product development (see Current Diagnostic Tools). Interest in this area of research is further supported by the Novartis Foundation, which recommended the development of a predictive test or a test to detect asymptomatic leprosy cases at its expert meetings in November 2014 and August 2015. Diagnosis at this stage would be done by minimally trained health workers in a surveillance or community setting.

Paucibacillary (PB) infection
Identifying PB infections would prevent the progression of the disease and potentially prevent permanent nerve damage or disability. It would align with the strategic goal of early diagnosis and also reduce the number of new cases as it could facilitate the initiation of treatment early. Diagnosis at the PB stage would ideally be performed by health workers in a clinic or health post setting. A test to supplement clinical signs would give health workers with minimal experience with diagnosing leprosy improved confidence in the accuracy of their diagnosis.

Because most leprosy patients do not show visible changes at early stages of infection and clinical manifestations are dependent on the host immune response, early diagnosis would involve some clinical
signs and could be strengthened by biomarkers, including those specific to *M. leprae*, or nucleic acid amplification. Lateral flow assays for detection of IP-10/IL-10 cellular immunity against *M. leprae* have potential to distinguish pathogenic immune responses from earlier evidence of infection by *M. leprae* and thus diagnose PB cases.²⁸ PCR methods have also shown some utility in detecting scarce *M. leprae* bacilli in difficult-to-diagnose patients using clinical specimens such as skin biopsy samples, skin smears, nerves, urine, oral or nasal swabs, blood, and ocular lesions.²⁹,³⁰ Noninvasive point-of-care (POC) tests are necessary to improve upon the complexity of current skin biopsy practices. Ultrasound technology may also be used to detect enlarged nerves, offering a quantitative measure of disease progression.³¹-³³ These diagnostic methodologies are still in the research stage of product development.

**Multibacillary (MB) infection**

Accurate and timely diagnosis of MB infection also offers an opportunity to reduce transmission and prevent permanent disability. In addition, as treatment recommendations differ between PB and MB infection classifications, it is critical to differentiate between the two stages.

Diagnosis at this stage is most often by clinical signs such as skin lesions and nerve involvement, though other techniques are useful like microscopy and testing for antibodies to *M. leprae* antigens. Several studies demonstrated that the presence of anti-PGL-1 antibodies reflects bacillary load and helps classify clinical forms, since MB patients show high antibody titers and PB patients show scarce or absent titers. The *M. leprae* immunodominant antigen PGL-1, due to its glycolipid nature, induces a humoral immune response, resulting in the production of antibodies.³⁴ Subsequently, researchers synthesized PGL-1 as mono-, di-, and trisaccharide compounds, used it in a flow test and further synthesized the chimeric fusion protein Leprosy IDRI Diagnostic 1 (LID-1). LID-1 is an antigen specifically recognized by sera from leprosy patients from geographically and ethnically diverse populations, with a direct correlation between seroreactivity and bacterial index.³⁵-³⁷ In conjunction with Orange Life, Rio de Janeiro, IDRI created simple immunochromatographic lateral flow tests using an NDO-LID-1 fusion protein that detected larger proportions of MB and PB leprosy than an alternative, Standard Diagnostics leprosy test and showed increased specificity.³⁸ Currently these products are not available in the market, but IDRI is collaborating with CTK Biotech on a similar product. Additionally, the quantifiable nature of the NDO-LID test using a Smart Reader platform showed utility for detection and monitoring of MB leprosy.³⁹ CTK Biotech’s NDO-LID-1 based rapid diagnostic test (RDT) is in prototype development though not commercially available as of the time of this report.

**Post-treatment monitoring**

Given the continued occurrence of immunologic reactions even after leprosy treatment is initiated, there is a need to monitor patients post-treatment to identify immunologic reactions or, in rare cases, reinfection. Health care providers manage these reactions with steroids and anti-inflammatory drugs to reduce permanent disability. Reinfection would require additional treatment with antibiotics. From the patient perspective, painful reactions after treatment initiation sometimes cause patients to believe the treatment is ineffective and discourage patients from complying fully with the long course of MDT. Tools
to identify immune reactions may help to reassure patients that their clinical care is effective and to encourage follow through. More research on this use case is needed at this time.

Current diagnostic tools

Commercially available products for leprosy diagnosis are very limited, and no POC tools are available. The development of good diagnostic tests for leprosy is challenged by the diversity of the cellular and humoral responses, varying from high to low and non-responders and thus, both serological and immunological tests that rely on antibodies or a cell-mediated immune (CMI) response have limitations. See Table 2 for an overview of the leprosy diagnostic landscape.

Cell-mediated immunity

CMI responses offer a promising range of diagnosis options in the early stages of leprosy infection. Antibody responses are not easily detected in most PB cases but these patients do exhibit cell-mediated immunity, secreting high levels of IFNγ, pro-inflammatory (IP-10) and anti-inflammatory/regulatory (IL-10), after in vitro stimulation with specific *M. leprae* antigens or a peptide fraction. However, one problem in early diagnosis is that most household contacts show a similar pattern of IFNγ secretion to the PB patients. Studies indicated no significant difference in CMI response when compared between endemic healthy controls and *M. leprae*-infected subjects, and the test procedure is associated with high turnaround time and high cost. For MB forms, patients do not produce CMI response but have high bacillary loads that are easily identified by PCR or anti-PGL-I detection.

Antibody detection

The distinction between PB and MB infection through a clinical exam is challenging but essential for specific multidrug therapy. The transition from PB to MB infection is marked by the decline of a CMI response and subsequent increase in the antibody response. Several studies have identified that anti-PGL-I or its synthetic mimetic conjugated to the recombinant fusion protein product of the *M. leprae* genes can help in the classification of MB and PB leprosy patients to orient the choice of treatment, and could ultimately aid leprosy control programs by allowing greater numbers of individuals to be tested and treated at a greater frequency. Together, such applications of the test would effectively lower disease prevalence and reduce leprosy morbidity. However, antibody detection methods will miss the majority of PB leprosy, and antibodies can remain present long after treatment. Thus antibody detection methods cannot be used for post-treatment monitoring.

Nucleic acid amplification

PCR can be valuable in diagnosing difficult cases like pure neural leprosy (PNL), PB leprosy, and patients with atypical clinical presentation and histopathological features compatible with leprosy. It can also be used to detect *M. leprae* DNA in samples from the household contacts of leprosy patients.
a positive PCR result is not sufficient to confirm the disease outcome, it can indicate increased risk of developing the disease and could alert the clinicians to follow these contacts more closely or begin chemoprophylaxis. However, this technique is limited to research centers due to the high cost of reagents and the need for specific equipment and qualified technicians.\textsuperscript{52,53}

**Ultrasound technology**

Neurological involvement is present throughout the leprosy clinical spectrum and nerve impairment is responsible for leprosy-associated disability. Currently, nerve palpation detection requires expertise, and diagnoses based on this technique are subjective even among trained professionals. Ultrasound technology presents one way to overcome this barrier to a clear and differential diagnosis. There is a growing interest in ultrasound as a diagnostic tool for peripheral neuropathies.\textsuperscript{42} However, as recent studies have revealed that thickening and asymmetry are common in leprosy patients and that these abnormalities occur at similar frequencies in PB and MB patients, ultrasound may not be able to distinguish between PB and MB infection and guide treatment decisions.\textsuperscript{54} Further studies are needed with larger cohorts to first determine the diagnostic cutoff for nerve enlargement using POC ultrasound technology, and then to measure the performance of this technology to differentiate symptomatic leprosy patients from individuals without disease.
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Candidates</th>
<th>Sample type</th>
<th>Format</th>
<th>Stage of product development</th>
<th>Use case</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| **Clinical signs** | Exam | Clinical assessment of disease stage according to WHO grading system | Exam | Clinical exam | NA | • Detect symptomatic cases | • Expert leprologist needed for PB detection  
• Neural leprosy hard to detect by lesion |
| **Nerve enlargement** | | Quantify nerve enlargement by sonography | Cross section of peripheral nerve | High definition ultrasound probe | Pilot study in India ongoing (American Leprosy Mission) | • Detect PB and MB | • More clinical evaluations and product development needed |
| **Bacteria (M. leprae)** | Whole | Direct visualization | Skin biopsy | Acid fast staining and microscopy | Lab-based gold standard | • Detect MB | • Dead bacteria remain in skin 3-5 years after tx initiation  
• Time-consuming, need expertise |
| | Antigens | Skin test to M. leprae antigen | Inactive M. leprae antigen | Dermal injection | Lepromin test available | • Detect MB and late PB | • Many cases don’t progress to MB (no detectable Ab) |
| | Nucleic acid | DNA targets: repetitive element (RLEP), superoxide dismutase A (sodA), proline-rich antigen (pra) 36 kDa, 65 kDa, 18 kDa, Ag85B, DNA polymerase subunit with TTC repeat | Split skin smear, urine, nerve, nasal swabs, blood, ocular lesions, etc. | Lab- or field-based molecular method: PCR, rtPCR | In research stage (various researchers) | • Detect MB and PB  
• Detect asymptomatic cases | • Presence of DNA ≠ disease  
• Asymptomatic cases may not progress to disease  
• Dead bacteria can remain for >5 years post tx (high false positive)  
• Less field-friendly |
| **Host immune markers** | Antibodies (Ab) | Recombinant protein/peptide targets: PGL-I, ML0405, ML2331, NDO-LID-1, ML2028, ML2038, ML0286 | Whole blood | ELISA, lateral flow | ELISA: available (Inbios); RDT: in development (Infectious Disease Research Institute (IDRI)-CTK biotech; IDRI-Chembios) | • Detect MB and late PB | • RDT at advanced stage of development  
• Many cases don’t progress to MB (no detectable Ab)  
• Antibody remains positive after tx  
• Orange Life product stopped (QC/QA failure) |
| | Cytokines and chemokines | IP-10, IL-10 | Whole blood, serum | Lateral flow | In research stage (Geluk and other researchers) | • Detect early PB  
• Detect asymptomatic cases | • Useful to screen community/household contacts  
• Enables early tx of symptomatic cases  
• Asymptomatic cases may not progress to disease  
• No tx guidelines for asymptomatic cases  
• More lab-intensive, long incubation time, high cost |
| | Combination of Ab and cytokine | NDO-LID and IP10, IL10 | Serum | Multiplex lateral flow | In research stage (various researchers) | • Detect MB and PB  
• Detect asymptomatic cases | • Enables tx of all symptomatic cases  
• Identifies all leprosy infections  
• No tx guidelines for asymptomatic cases  
• More lab-intensive, long incubation time |
Conclusions

Current diagnostic tools and practices are unlikely to achieve the goals for the elimination of leprosy set forth in the WHO NTD Roadmap, because existing methods fail to fill critical use cases. There are no POC diagnostic tools available to aid in the diagnosis of leprosy, and the potential value of such tools is significant. See Table 3 for a summary of product attributes of needed diagnostics. In order to support elimination efforts, PATH proposes the following recommendations to the leprosy research community. See Figure 5 for an overview of the proposed diagnostic recommendations.

Figure 5. Proposed diagnostic recommendations to the leprosy research community.

1. Focus on bringing to market antibody-detecting rapid tests that are in late-stage development to aid in the confirmation of MB infections, which would identify the most transmissible and debilitating infections.

In the short term, better support for access to and subsequent adoption of an antibody detection RDT will have an immediate impact on identifying infections, interrupting transmission, and limiting morbidity. The limitation with antibody detection is that mostly MB cases would be detected. However, there is still progress to be made in the identification of all MB cases, and exploiting the utility of this low-cost, user-friendly platform may provide an incremental improvement for some programs where confirming a leprosy diagnosis is challenging. MB cases with a higher bacterial load are thought to be more infectious, so identifying and treating a greater proportion of these cases may significantly impact transmission and reduce the number of new cases.

Furthermore, in the absence of any commercially available diagnostic tool for leprosy, the necessary systems to support their proper and continued use are also missing. Issues like quality assurance and quality controls, technician and patient education and training, and support for integration into ongoing country-led programs are important supportive activities to the introduction, as well as to long-term access and adoption of new diagnostic tools. Once systems have been established, improved versions of diagnostic tools can be integrated into current practices with greater ease. Additionally, significant regulatory and commercialization support may be required beyond product launch. The development of these critical systems and their integration into country-led control programs should move forward in parallel with technology development efforts.
2. Develop new diagnostic tools that identify all symptomatic leprosy infections, which would enable the prompt treatment and cure of all leprosy cases.

In the long term, product development will be required to meet elimination goals. Beyond current antibody-based RDTs, new diagnostic tools for detecting all symptomatic infections are needed. There is consensus among leading leprosy stakeholders and organizations that it is necessary to detect all leprosy cases to achieve elimination. Diagnosing these cases will require new tools that may detect host immune factors such as antibodies and cell-mediated immunity, low levels of bacteria-specific markers such as nucleic acid, or early disease features such as nerve enlargement.

3. Conduct further research to understand feasibility and utility of diagnostic tools for subclinical infections and post-treatment monitoring.

Also in the long term, further product development may be warranted to address diagnostic needs for subclinical infections and treatment monitoring. There is increasing consensus that elimination goals may not be reached if transmission among those with subclinical infections is not interrupted. Currently no treatment recommendations exist for those with subclinical infections, though this may change in the near future. There is some evidence to support the chemoprophylactic use of a single dose of rifampicin to reduce the risk of developing leprosy but other regimes along with post-exposure prophylaxis need to be further explored. If new tools that can either identify subclinical infections or monitor patients after treatment are deemed feasible and useful, their development and introduction would require concomitant changes in policies, guidelines, and practices to support their use.

Table 3. Summary of recommendations: product attributes of needed diagnostic tools for leprosy.

<table>
<thead>
<tr>
<th>Use case</th>
<th>MB infection</th>
<th>All symptomatic infections (PB and MB)</th>
<th>Subclinical infections and post-treatment monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen</td>
<td>Blood</td>
<td>Blood; physical feature</td>
<td>To be determined</td>
</tr>
<tr>
<td>Marker/manufacturer</td>
<td>Antibody tests</td>
<td>• Antibody and CMI dual test (in research stage) • Other potentials (PCR, ultrasound)</td>
<td>To be determined</td>
</tr>
<tr>
<td>Context of use</td>
<td>Primary care</td>
<td>Primary care</td>
<td>Active screening programs; treatment programs</td>
</tr>
<tr>
<td>Value proposition</td>
<td>A point-of-care tool that would: ▪ Aid in the diagnosis of MB and late PB infections for immediate treatment and cure ▪ Be less invasive than current methods ▪ Help identify the most transmissible and debilitating infections by less skilled health care workers</td>
<td>A point-of-care tool to detect all infections that require treatment to prevent further transmission and enable the elimination of leprosy as a public health problem</td>
<td>A better understanding of the feasibility and utility of diagnostic tools for subclinical infections and post-treatment monitoring is needed to inform product development for these use cases</td>
</tr>
</tbody>
</table>
References


