# ONCHOCERCIASIS: DIAGNOSTIC TARGET PRODUCT PROFILE

to support preventive chemotherapy

World Health Organization

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# Contents

# 1. Epidemiology

Onchocerciasis, also known as river blindness, affects an estimated 21 million people, with 99% of cases reported in 31 sub-Saharan countries (WHO, 2020a). The disease is caused by the filarial worm *Onchocerca volvulus*, which is transmitted by *Simulium* flies. Adult worms live in nodules, some of which are subcutaneous. Conversely, the embryos (microfilariae) can migrate through the skin, causing debilitating pruritus and skin disease, and to the eyes, leading to progressive and permanent blindness. Onchocerciasis is also hypothesized to lead to neurological disorders including epilepsy (Chesnais, 2020), nodding syndrome (Geelhand de Merxem, 2020) and stunted growth.

# 2. Public health response

Currently, at least 217.5 million people live in areas known to be endemic for onchocerciasis (WHO, 2019). Morbidity is controlled by annual mass drug administration (MDA) of ivermectin, with 157 million treatments delivered in 2018 (WHO, 2019). Ivermectin temporarily blocks transmission of infection by clearing microfilariae but does not kill the adult worms, which have a reproductive lifespan of about 10 years, requiring MDA to be continued for over a decade.

In 2010, based on progress towards the elimination of transmission of onchocerciasis in the Region of the Americas as well as in a few foci in sub-Saharan Africa, global targets were revised from the control of morbidity to elimination (interruption of transmission) (WHO, 2010). In 2020, following several rounds of public consultation, WHO published the draft road map for neglected tropical disease 2021–2030 (WHO, 2020b), which the Seventy-third World Health Assembly is expected to endorse. The road map identifies as a critical action the mapping of suspected onchocerciasis-endemic areas, with launch of MDA wherever indicated. It further identifies as critical the development of improved diagnostics to facilitate mapping and decision-making (WHO, 2020b; Fig. 12). The principal disease-specific target for onchocerciasis is to increase the number of countries verified as having interrupted transmission from four (12%)[1] in 2020 to 12 (31%) in 2030 (WHO, 2020b; Table).

This shift requires treatment to be expanded to include hypo-endemic settings which were previously excluded from MDA. Hypo-endemic areas are defined as having a palpable subcutaneous nodule prevalence < 20%, corresponding to a microfilariae prevalence of approximately < 35% (Zouré, 2014). Some of these hypo-endemic areas have been mapped, while others have not, and the maps are not necessarily current, leading to an uncertainty in the total number of people who must be reached. It is estimated that in 2011, 98 million people lived in areas in which the prevalence of palpable subcutaneous nodules was 0–4.9%, 77 million in areas of 5–20% nodule prevalence and 62 million in areas of > 20% nodule prevalence (Zouré, 2014).

# 3. Available diagnostic tools and their limitations

The main diagnostics for onchocerciasis fall into the following categories.

1. Analysis of skin biopsies, also known as skin snips, by microscopy or molecular techniques is considered to be definitive but is relatively insensitive, has low throughput and can be painful for the patient if appropriate equipment and techniques are not ensured. Populations are reluctant to participate in skin snipping, especially when onchocerciasis is not viewed by the locals as a problem and/or when children are involved.

[1] Colombia, Ecuador, Guatemala and Mexico.

2. Nodule palpation has been a main driver of the African Program for the Elimination of Onchocerciasis, being used for the rapid epidemiological assessment or rapid evaluation and monitoring of onchocerciasis. A prevalence of approximately 5% of people having palpable nodules of other etiologies makes this technique acceptable for meso- and hyper-endemic areas but insufficiently specific for hypo-endemic areas.
3. The DEC patch is a diethylcarbamazine-containing transdermal patch that kills microfilariae in the skin, triggering a reactive urticaria (the Mazzotti reaction) that can be visualized. The fact that it requires 2 days in the field[1] to monitor skin reactions is a limitation, and there are specificity issues in areas co-endemic with *L. loa* (Ozoh, 2007). "Ready-to-use" DEC patches (Awadzi, 2015) made under good manufacturing practice conditions by a manufacturer specialized in transdermal-delivery systems are available to health ministries requesting them from WHO (TDR contact: Dr A.C. Kuesel). Large-scale evaluation of the DEC patch has to date only occurred in populations that were skin snip negative (Diawara, 2009) and needs to be conducted in populations with different levels of skin microfilariae density to assess its performance and safety.
4. Ov16 serology is part of the current WHO criteria for stopping MDA, alongside entomological investigations (WHO, 2016). Identification of hypo-endemic areas is also under consideration. The third meeting of the WHO Onchocerciasis Technical Advisory Subgroup (Geneva, 26–28 February 2019) summarized the results of the evaluation of different Ov16 assays in a variety of programmatic contexts and identified differences in performance with different types of specimen and concerns of accuracy (WHO, 2020c). The enzyme-linked immunosorbent assay (ELISA) always requires dried-blood spots; a rapid diagnostic test performs better with dried-blood spots than with whole blood. One issue is the lack of standardization across different versions of these serological tests.
5. Entomological identification of ongoing transmission consists of detecting infective or infected *Simulium* flies by polymerase chain reaction (PCR). It requires trained personnel for laboratory work and field teams knowledgeable about methodologies for finding and capturing flies.

# 4. Diagnostic Technical Advisory Group

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, diagnostic and control challenges. In 2019, WHO's Strategic and Technical Advisory Group for Neglected Tropical Diseases, the Organization's principal advisory group on neglected tropical diseases (NTDs), recommended the establishment of a Diagnostic Technical Advisory Group to help ensure a consistent approach to identifying and prioritizing diagnostic needs and to inform WHO strategies and guidance on the subject. The first meeting of the Group (Geneva, 30–31 October 2019) discussed priorities for the year ahead as well as how to manage the complexity of supporting the diagnostics agenda across the entirety of the WHO portfolio of NTDs. It was clear that all NTDs had diagnostic needs which would have to be addressed in due course. One of the recommendations was to create a sub-committee dedicated to onchocerciasis, with an initial mandate to define the target product profiles of new diagnostics necessary to reach the 2030 goals.

[1] One day for setting the patch, the next day for readout.

# 5. Need for novel target product profiles

With more than 150 million doses of ivermectin distributed each year, the fight against onchocerciasis is a major international public health programme. Means to identify all populations in need of treatment are still required, and new diagnostics are needed to support all programmatic activities, especially in areas of low prevalence or low intensity of infection. The 2020 road map recognizes the critical need "to develop improved diagnostics to facilitate mapping and decisions to eliminate transmission" of onchocerciasis (WHO, 2020b; Fig. 12).

***Mapping***. A sensitive, specific assay is required to map onchocerciasis in hypo-endemic areas and to overcome the limitations of the existing tools. The WHO Onchocerciasis Technical Advisory Subgroup recommended establishing a biological threshold of 2% antibody prevalence in adults for decisions to start treatment (WHO, 2020c). To have confidence of estimates around this threshold, sensitive and specific tests are critical. Field-based operational research to generate empirical data to validate or refine starting and stopping thresholds is under way.

***Monitoring and evaluation***. In areas of higher endemicity, progress is evaluated with skin snips (microscopy or PCR) or using serology. Serology is performed in children as sentinel groups. It is recognized that generally children are less exposed to infection than adults (e.g. working outdoors), but for serology, adults cannot be used as a sentinel group because of the long-lasting nature of the Ov16 response. In areas of low endemicity, serology may not be sufficiently sensitive for characterizing communities, but monitoring of infected or infective vectors may be appropriate. Target product profiles for human and vector-based diagnostics are needed to advance monitoring and evaluation agendas. Unlike mapping, which is done only once, monitoring must be continued for at least a decade, and therefore the new tools need to be especially affordable.

***Stopping MDA***. In 2016, WHO published guidelines for stopping MDA and verifying elimination of human onchocerciasis (WHO, 2016). The guidelines require that both entomology and serology be used to demonstrate the interruption of transmission of *O. volvulus* for the purpose of stopping MDA.

- **Entomology** ("strong recommendation, high certainty of evidence"): O-150 PCR (Poolscreen) testing in black flies should be used to demonstrate interruption of transmission of *O. volvulus*, with an upper bound of the 95% confidence interval of a prevalence of vectors carrying infective larvae of 0.05%. Research priorities for entomological evaluations include standardizing the PCR diagnostic test itself and the protocols for fly catching.
- **Ov16 serology** ("strong recommendation, low certainty of evidence"): Ov16 ELISA[1,2] should meet a threshold of 0.1% positivity in children aged 10 years or younger (upper bound 95% confidence interval). Evidence to support this threshold and age group is low, and research is ongoing to identify the most informative age groups and define associated thresholds in different epidemiological settings (Coffeng, 2019). Research priorities identified in the WHO guidelines also include investigating the sero-reversion of Ov16 responses and validating the Ov16 rapid diagnostic test.

Stopping should ideally be a one-time event, and one may justifiably use more resources or more expensive tests for the sake of supporting appropriate decision-making on MDA cessation.

[1] This guideline related to a single ELISA with a sensitivity of < 50%.

[2] With follow-up with skin biopsies on Ov16-positive participants.

***Post-treatment surveillance***. These tests are conducted 12 months after the last round of MDA and at the time in which parasite transmission, if still occurring, would be at its peak. After a period of post-treatment surveillance of 3–5 years, and on the advice of the national oversight committee, interruption of transmission is confirmed, by entomological (O-150 PCR Poolscreen) test and, if necessary, by additional serological (Ov16) testing. It is only when such surveillance is completed for all transmission foci within a country that, upon submission of a dossier by the Ministry of Health, WHO can grant elimination status.

***Post-elimination surveillance***. Next, a national programme establishes a post-elimination surveillance system to detect possible renewal of parasite transmission (recrudescence or reintroduction) both in previously endemic and in non-endemic areas as well as in areas where imported cases might be expected to occur. Such post-elimination surveillance can be centred on entomological assessments by the demonstration of the absence of infective-stage larvae of *O. volvulus* in the vector population as determined by O-150 PCR using *O. volvulus*-specific DNA probes. Such assessments should be conducted at regular intervals until elimination is verified in all countries in the relevant WHO region, or at least until any risk of recrudescence or reintroduction can substantially be excluded.

With many countries still being far from interruption of transmission, diagnostics specifically designed for post-elimination surveillance are regarded as a lower priority at this time. However, there will eventually be a need for a tool that can detect either transmission or human infection at very low prevalence levels, or with low intensity of infections, and identify individuals carrying fecund adult female parasites so that they may be individually treated. It is likely that in a post-elimination surveillance setting, few resources will be available and that transmission or entomology may be too expensive and technically demanding to be routinely performed. It would therefore be desirable to have a diagnostic that can be easily integrated with other surveillance programmes.

# 6. Conclusion

One of the challenges posed by the current diagnostics is the difficulty of comparing epidemiological data obtained with different techniques, i.e. skin biopsies, versus rapid evaluation and monitoring of onchocerciasis, versus serology. Rather than having different diagnostics for mapping, monitoring and stopping decisions, it would be more effective to have a single platform that could support all these functions, while providing longitudinal data.

All activities described in the WHO 2016 guideline are to be applied to onchocerciasis "transmission foci" or "transmission zones", but currently there are no WHO-recommended protocols to delineate such foci.

Addressing onchocerciasis in areas endemic for L. loa, where ivermectin can lead to severe adverse events, remains a major problem (Vinkeles Melchers, 2020). Unless new treatments are identified that are suitable for use within MDA campaigns and not microfilaricidal, diagnostics for L. loa infection are needed to exclude those at risk of severe and serious adverse reactions to microfilaricides. This holds particular importance for areas in which onchocerciasis is hypo-endemic and L. loa is co-endemic, which will need to be included in interventions for elimination of onchocerciasis, where the risks associated with distribution of ivermectin may outweigh the benefits.

**Table 1. TPP ONCHO Mapping**

| 1. Product use summary | Ideal | Minimum | Background, annotation re requirement risk, etc. |
|---|---|---|---|
| 1.1 Intended use | An in vitro **point-of-care** test to map onchocerciasis and identify areas with > 2% prevalence of analyte(s). | An in vitro **laboratory-based** test to map onchocerciasis and identify areas with > 2% prevalence of analyte(s). | NB: A point-of-care test is highly preferred, but a laboratory-based test is acceptable if there are no other options. |
| 1.2 Targeted population | All ages of individuals resident in the population living in the defined geographical area. | Sentinel groups of school-aged children living in the defined geographical area. | |
| 1.3 Lowest infrastructure level | The test will be performed under "zero-infrastructure" conditions including but not limited to community health centres, households and outdoor conditions. | If the required levels of performance necessitate a laboratory-based test, tests can be performed in a centralized laboratory. | |
| 1.4 Lowest user level | This test will be performed by health personnel and community health workers. | If testing must be performed in a centralized laboratory, the test will be performed by trained laboratory technicians. | |
| 1.5 Training requirements | One day for community volunteers and lay persons; testing job aid/instructions for use should be made available via the internet for download (i.e. are publicly available). | If testing must be performed in a centralized laboratory, < 2 weeks for training laboratory technicians; testing job aid/instructions for use should be made available via the Internet for download (i.e. are publicly available). | |
| 2. Design | Ideal | Minimum | Annotation |
| 2.1 Portability | Highly portable with no specialized transport needs. | If needed to obtain the required levels of performance, a laboratory-based test is acceptable. | |
| 2.2 Instrument/ power requirement | Self-contained kit operates independently of any mains power. | If a laboratory-based test is required, access to mains power is acceptable. | |
| 2.3 Water requirement | Self-contained kit operates independently of any water supply. | If a laboratory-based test is required, access to laboratory-grade water is acceptable. | |
| 2.4 Maintenance and calibration | No maintenance required (i.e. disposable) and no calibration required. | If a laboratory-based test is required, periodic maintenance and calibration of any instrumentation must be available in the countries and should not be needed more frequently than once a year. | |
| 2.5 Sample type/ collection | Peripheral whole-blood from finger-stick or other easily collectable samples (e.g. urine, saliva). | If a laboratory-based blood test is required, peripheral whole-blood from finger stick, EDTA/heparinized sample or dried blood spot. No venipuncture sampling. | If EDTA/heparinized sample, would need to ensure there is the ability to either transport immediately or store suitably. |
| 2.6 Sample preparation/transfer device | Sample preparation should not exceed transfer of specimen to the testing device, either directly or by use of a predefined and provided device (e.g. inverted cup, transfer loop; may provide their own validated transfer device) | If a laboratory-based blood test is required, preparation of serum/plasma from EDTA/heparin anticoagulated blood or elution from dried blood spot is acceptable. | |

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|---|---|---|---|
| 2.7 Sample volume | If whole blood: 5–50 µL | If whole blood: 1–100 µL | |
| 2.8 Target analyte | Antigen(s) or other biomarker(s) specific for live, adult *O. volvulus* female worms | Biomarker(s) to detect exposure to *O. volvulus.* | |
| 2.9 Type of analysis | Quantitative | Qualitative | Even for an ideal case, qualitative analysis may suffice. |
| 2.10 Detection | High contrast, clear result for naked eye; indoor and outdoor reading of a signal. | If a laboratory-based test is required, may include instrument-based detection of a signal that provides a "yes/no" result. | |
| 2.11 Quality control | A reference control sample shall be made available to verify that the test (lot) has retained its desired analytical sensitivity. If the test is a rapid diagnostic test, it will have a control line. | A reference control sample shall be made available to verify that the test (lot) has retained its desired analytical sensitivity. If the test is a rapid diagnostic test, it will have a control line. | **The positive control can have a shelf-life different from that of the assay.** |
| 2.12 Supplies needed | All reagents and supplies included in kit, with minimal import restrictions (e.g. animal-free) | All reagents and supplies included in kit, with minimal import restrictions (e.g. animal-free) | |
| 2.13 Safety | All materials used for sampling must adhere to universal safety precautions. If lancets are included, they should be auto-retracting. | All materials used for sampling must adhere to universal safety precautions. If lancets are included, they should be auto-retracting. | |
| 3. Performance | Ideal | Minimum | Annotation |
| 3.1 Species differentiation | Can differentiate *O. volvulus from Wuchereria, Loa* and *Mansonella spp.* | Can differentiate *O. volvulus from Wuchereria, Loa* and *Mansonella spp.* | |
| 3.2 Diagnostic/ clinical sensitivity | ≥ 60 % | ≥ 60 % | · The test should detect at least 60% of people who have proven infection as demonstrated by the presence of microfilarial DNA in the skin.<br>· The sensitivity criteria and specificity criteria were calculated with the assumptions that mass drug administration should start above a 2% prevalence threshold, and that overtreating is acceptable 10% of the time, while undertreating should not occur more than 5% of the time. |
| 3.3 Diagnostic/ clinical specificity | ≥ 99.8% | ≥ 99.8% | To be demonstrated with > 95% confidence |
| 3.4 Time to results | < 0.5 h to developed test result | If a laboratory test is required, < 48 h to developed test result | 48 h is based on eluting dried blood spots on the first day and running an enzyme-linked immunosorbent assay the following day. Does not include the time to ship/receive samples. |
| 3.5 Result stability | Developed test result remains stable for 24 h | Developed test result remains stable for 0.5 h | Ability to interpret final test results in a manner not constrained by timed steps helps greatly in resource-constrained settings. |

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| 3.6 Throughput | ≥ 10 tests per hour and per operator | If a laboratory test is required, 120 tests/day per operator. If field-based test, ≥ 7 tests/h per operator. | The 120 tests/day figure is based on running three enzyme-linked immunosorbent assay plates, each with 40 samples in duplicate. |
| 3.7 Target shelf-life/ stability | Stable for 36 months at 4–40 °C. Tolerates excursions to 50 °C for 2 weeks | If laboratory based: ≥ 12 months at 4 °C; temperature excursion of 50 °C for one week acceptable.<br>If field deployable: Stable for 18 months at 4–37 °C, tolerates excursions to 50 °C for 1 week. | Acknowledging that other tests (e.g. filariasis test strip for lymphatic filariasis) have a 12-month shelf-life; logistical problems have been encountered with that test as well as with medicines having a 24-month shelf life due to shipping, customs clearance, transport and/ or field staff availability. |
| 3.8 Ease of use | One timed step; ≤ 10 user steps; instructions for use should include diagram of method and results interpretation. For field-based test, must be able to use in an unprotected external environment. | If a laboratory test is required, ≤ 5 timed steps; ≤ 15 user steps, instructions for use should include diagram of method and results interpretation. | |
| 3.9 Ease of results interpretation | Interpreted by unaided eye; does not require discrimination of one colour from another. | If a laboratory test is required, results can be interpreted by a suitable instrument. | |
| 3.10 Operating temperature | 15-40 °C | May have to control temperature for laboratory-based test. | |
| 3.11 Equivalence of matrices | If the test is intended for one matrix (e.g. blood) but performance will be assessed in the laboratory with another matrix (e.g. serum), then equivalence between the two matrices shall be demonstrated. | If the test is intended for one matrix (e.g. blood) but performance will be assessed in the laboratory with another matrix (e.g. serum), then equivalence between the two matrices shall be demonstrated. | |
| 4. Product configuration | Ideal | Minimum | Annotation |
| 4.1 Shipping conditions | Conformance to applicable requirements of ASTM D4169–05 (for shipping) and ISO 11607–1:2006 (for sterile packaging, if needed); no cold-chain shipping required. | If a laboratory-based test is required, cold-chain shipping (e.g. 0–4 °C) is acceptable. | If a laboratory-based test is required, the samples preferrably should be able to be shipped to the laboratory at ambient temperature. |
| 4.2 Storage conditions | Ambient storage conditions, 4-40 °C. Colourimetric or other indicators to identify excessive heat/humidity exposure. | If a laboratory-based test is required, cold storage is acceptable. Colourimetric or other indicators to identify excessive heat/humidity exposure. | It is recommended that the temperature indicator goes on the carton, while the moisture indicator should be inside the pouch (e.g. moisture indicating silica gel). |
| 4.3 Service and support | None required (though can be made available). | If laboratory-based test, support must be available from the manufacturer. | |
| 4.3 Service and support | None required (though can be made available). | If laboratory-based test, support must be available from the manufacturer. | |
| 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. | |

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| 4.5 Labelling and instructions for use | Compliance required per in vitro diagnostic device regulation and, if applicable, WHO prequalification; product insert shall be available in relevant local language(s) and shall include instructions for use of the test; if appropriate, photos of example test results (i.e. positive, weak positive, negative) should be included in the instructions. | Compliance required per in vitro diagnostic device regulation and, if applicable, WHO prequalification; product insert shall be available in relevant local language(s) and shall include instructions for use of the test; if appropriate, photos of example test results (i.e. positive, weak positive, negative) should be included in the instructions. | |
| 5. Product cost and channels | Ideal | Minimum | Annotation |
| 5.1 Target pricing per test | Mapping: < US$ 1 | Mapping: < $2.50 | Cost does not include personnel. Please note that requirements for cold-shipping may increase cost to beyond acceptable. |
| 5.2 Capital cost | No capital costs | To be determined | |
| 5.3 Product lead times | < 4 weeks | < 6 weeks | Time needed from receipt of purchase order to assays being ready to ship. |
| 5.4 Target launch countries | N/A | N/A | |
| 5.5 Product registration (i.e. substantiation to regulatory body of product claims) | · CE/In Vitro Diagnostic Regulation<br>· Any registration required for export from country of origin (e.g. Korea Food and Drug Administration, etc.)<br>· WHO prequalification (if required/applicable)<br>· Country-level registration (if required/applicable for target countries) | Same | An effort is ongoing to ensure that the WHO prequalification process will apply to NTDs. More and more countries are requiring registration of diagnostics within country, and the prequalification process would simplify things. As of 2020, a letter of no objection from the importing contry is used as a workaround, but this may not be a sustainable solution. |
| 5.6 Procurement | Available for procurement from all endemic countries with no restriction. | Available for procurement from all endemic countries with no restriction. | |
| 5.7 Cost | · Standardized pricing quoted by manufacturer available to all stakeholders<br>· Absence of distributor or third-party mark up | · Standardized pricing quoted by manufacturer available to all stakeholders<br>· Absence of distributor or third-party mark up | |

**Table 2. TPP ONCHO Stopping**

| 1. Product use summary | Ideal | Minimum | Background, annotation, requirement risk, etc |
|---|---|---|---|
| 1.1 Intended use | An in vitro **point-of-care** test to support decision for stopping mass drug administration and certifying areas with < 1% prevalence of analyte(s). | An in vitro **laboratory-based** test to support decision for stopping mass drug administration and certifying areas with < 1% of analyte(s). | Historically, different methods have been employed for different phases of the programme (nodules, skin snips, serology), and this has complicated the analysis of trends. A rapid diagnostic test with > 89% sensitivity and > 99.8% specificity may have the potential to support all of the following programme needs: mapping, monitoring and evaluation, stopping. |
| 1.2 Targeted population | All ages of individuals resident in the population living in the defined geographical area. | Sentinel groups of school-aged children living in the defined geographical area. | |
| 1.3 Lowest infrastructure level | The test will be performed under "zero-infrastructure" conditions including but not limited to community health centres, households and outdoor conditions. | If the required levels of performance necessitate a laboratory-based test, tests can be performed in a centralized laboratory. | |
| 1.4 Lowest user level | This test will be performed by health personnel and community health workers. | If testing must be performed in a centralized laboratory, the test will be performed by trained laboratory technicians. | |
| 1.5 Training requirements | One day for community volunteers and lay persons; testing job aid/instructions for use should be made available via the Internet for download (i.e. are publicly available). | If testing must be performed in a centralized laboratory, < 2 weeks for training laboratory technicians; testing job aid/instructions for use should be made available via the Internet for download (i.e. are publicly available) | |
| 2. Design | Ideal | Minimum | Annotation |
| 2.1 Portability | Highly portable with no specialized transport needs. | If needed to obtain the required levels of performance, a laboratory-based test is acceptable. | |
| 2.2 Instrument/ power requirement | Self-contained kit operates independently of any mains power. | If a laboratory-based test is required, access to mains power is acceptable. | |
| 2.3 Water requirement | Self-contained kit operates independently of any water supply. | If a laboratory-based test is required, access to laboratory-grade water is acceptable. | |
| 2.4 Maintenance and calibration | No maintenance required (i.e. disposable) and no calibration required. | If a laboratory-based test is required, periodic maintenance and calibration of any instrumentation must be available in the countries and should not be needed more frequently than once a year. | |
| 2.5 Sample type/ collection | Peripheral whole blood from finger-stick or other easily collectable samples (e.g. urine, saliva). | If a laboratory-based blood test is required, peripheral whole blood from finger-stick, EDTA/heparinized sample, or dried blood spot. No venipuncture sampling. | If EDTA/heparinized sample, would need to ensure there is the ability to either transport immediately or store suitably. |

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|---|---|---|---|
| 2.6 Sample preparation/transfer device | Sample preparation should not exceed transfer of specimen to the testing device, either directly or by use of a predefined and provided device (e.g. inverted cup, transfer loop, etc.; may provide their own validated transfer device.) | If a laboratory-based blood test is required, preparation of serum/plasma from EDTA/heparin anticoagulated blood or elution from dried blood spot is acceptable. | |
| 2.7 Sample volume | If whole blood: 5–50 µL | If whole blood: 1–100 µL | |
| 2.8 Target analyte | Antigen(s) or other biomarker(s) specific for live, adult *O. volvulus* female worms | Biomarker(s) to detect exposure to *O. volvulus*. | |
| 2.9 Type of analysis | Quantitative | Qualitative | Even for an ideal case, qualitative may suffice. |
| 2.10 Detection | High contrast, clear result for naked eye; indoor and outdoor reading of a signal. | If a laboratory-based test is required, may include instrument-based detection of a signal that provides a "yes/no" result. | |
| 2.11 Quality control | A reference control sample shall be made available to verify that the test (lot) has retained its desired analytical sensitivity. If the test is a rapid diagnostic test, it will have a control line. | A reference control sample shall be made available to verify that the test (lot) has retained its desired analytical sensitivity. If the test is a rapid diagnostic test, it will have a control line. | The positive control can have a shelf life different from that of the assay. |
| 2.12 Supplies needed | All reagents and supplies included in kit, with minimal import restrictions (e.g. animal-free) | All reagents and supplies included in kit, with minimal import restrictions (e.g. animal-free) | |
| 2.13 Safety | All materials used for sampling must adhere to universal safety precautions. If lancets are included, they should be auto-retracting. | All materials used for sampling must adhere to universal safety precautions. If lancets are included, they should be auto-retracting. | |
| 3. Performance | Ideal | Minimum | Annotation |
| 3.1 Species differentiation | Can differentiate *O. volvulus* from *Wuchereria, Loa* and *Mansonella* spp. | If a laboratory-based test is required, may include instrument-based detection of a signal that provides a "yes/no" result. | |
| 3.2 Diagnostic/clinical sensitivity | ≥ 89 % | ≥ 89 % | The test should detect at least 89% of people who have proven infection as demonstrated by the presence of microfilarial DNA in the skin. The sensitivity criteria and specificity criteria were calculated with the assumptions that mass drug administration can cease below a 1% prevalence threshold, and that overtreating is acceptable 10% of the time, while undertreating should not occur more than 5% of the time. |
| 3.3 Diagnostic/clinical specificity | ≥ 99.8% | ≥ 99.8% | |

| | | | |
|---|---|---|---|
| 3.4 Time to results | < 0.5 h to developed test result | If a laboratory test is required, < 48 h to developed test result | 48 h is based on eluting dried blood spots one day and running an enzyme-linked immunosorbent assay the following day. Does not include the time to ship/receive samples. |
| 3.5 Result stability | Developed test result remains stable for 24 h | Developed test result remains stable for 0.5 h | Ability to interpret final test results in a manner not constrained by timed steps helps greatly in resource-constrained settings. |
| 3.6 Throughput | ≥ 10 tests per hour and per operator | If a laboratory test is required, 120 tests/day per operator. If field-based test, ≥ 7 tests/h per operator. | The 120 tests/day figure is based on running three enzyme-linked immunosorbent assay plates, each with 40 samples in duplicate. |
| 3.7 Target shelf-life/ stability | Stable for 36 months at 4–40 °C. Tolerates excursions to 50 °C for 2 weeks | If laboratory based: ≥ 12 months at 4 °C; temperature excursion of 50 °C for one week acceptable.<br>If field deployable: Stable for 18 months at 4–37 °C; tolerates excursions to 50 °C for 1 week. | Acknowledging that other tests (e.g. filariasis test strip for lymphatic filariasis) have a 12-month shelf-life, logistical problems have been encountered with that test as well as with medicines having a 24-month shelf-life due to shipping, customs clearance, transport and/ or field staff availability. |
| 3.8 Ease of use | One timed step; ≤ 10 user steps, instructions for use should include diagram of method and results interpretation. For field-based test, must be able to use in an unprotected external environment. | If a laboratory test is required, ≤ 5 timed steps; ≤ 15 user steps, instructions for use should include diagram of method and results interpretation. | |
| 3.9 Ease of results interpretation | Interpreted by unaided eye, does not require discrimination of one color from another | If a laboratory test is required, results can be interpreted by a suitable instrument. | |
| 3.10 Operating temperature | 15–40 °C | May have to control temperature for laboratory-based test. | |
| 3.11 Equivalence of matrices | If the test is intended for one matrix (e.g. blood) but performance will be assessed in the laboratory with another matrix (e.g. serum), then equivalence between the two matrices shall be demonstrated. | If the test is intended for one matrix (e.g. blood) but performance will be assessed in the laboratory with another matrix (e.g. serum), then equivalence between the two matrices shall be demonstrated. | |
| 4. Product configuration | Ideal | Minimum | Annotation |
| 4.1 Shipping conditions | Conformance to applicable requirements of ASTM D4169-05 (for shipping) and ISO 11607-1:2006 (for sterile packaging, if needed); no cold-chain shipping required. | If a laboratory-based test is required, cold-chain shipping (e.g. 0–4 °C) is acceptable. | The test should detect at least 89% of people who have proven infection as demonstrated by the presence of microfilarial DNA in the skin. The sensitivity criteria and specificity criteria were calculated with the assumptions that mass drug administration can cease below a 1% prevalence threshold, and that overtreating is acceptable 10% of the time, while undertreating should not occur more than 5% of the time. |
| 4.2 Storage conditions | Ambient storage conditions, 4–40 °C. Colourimetric or other indicators to identify excessive heat/humidity exposure. | If a laboratory-based test is required, cold storage is acceptable. Colourimetric or other indicators to identify excessive heat/humidity exposure. | |

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| 4.3 Service and support | None required (though can be made available). | If laboratory-based test, support must be available from the manufacturer. | |
| 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. | |
| 4.5 Labeling and instructions for use | Compliance required per in vitro diagnostic device regulation and, if applicable, WHO prequalification; product insert shall be available in relevant local language(s) and shall include instructions for use for the test; if appropriate, photos of example test results (i.e. positive, weak positive, negative) should be included in the instructions. | Compliance required per in vitro diagnostic device regulation and, if applicable, WHO prequalification; product insert shall be available in relevant local language(s) and shall include instructions for use for the test; if appropriate, photos of example test results (i.e. positive, weak positive, negative) should be included in the instructions. | |
| 5. Product cost and channels | Ideal | Minimum | |
| 5.1 Target pricing per test | < US$ 2 | < US$ 3 | Cost does not include personnel. Please note that requirements for cold-shipping may increase cost to beyond acceptable. For the test to be applicable also to monitoring and evaluation activities, the cost should be < US$ 2 (mass drug administration stopping decisions, which are done only once, tolerate a higher price-point than monitoring and evaluation activities that are repeatedly performed over a decade). |
| 5.2 Capital cost | No capital costs | To be determined | |
| 5.3 Product lead times | < 4 weeks | < 6 weeks | Time needed from receipt of purchase order to assays being ready to ship. |
| 5.4 Target launch countries | N/A | N/A | |
| 5.5 Product registration (i.e., substantiation to regulatory body of product claims) | · In vitro diagnostic device regulation<br>· Any registration required for export from country of origin (e.g., KFDA)<br>· WHO prequalification (in due course)<br>· Country-level registration (if required/ applicable for target countries) | · In vitro diagnostic device regulation Any registration required for export from country of origin (e.g., KFDA)<br>· WHO prequalification (in due course)<br>· Country-level registration (if required/ applicable for target countries) | An effort is ongoing to ensure that the WHO prequalification process will apply to NTDs. More and more countries are requiring registration of diagnostics within country, and the prequalification process would simplify things. As of 2020, a letter of no objection from the importing country is used as a workaround, but this may not be a sustainable solution. |
| 5.6 Procurement | Available for procurement from all endemic countries with no restriction. | Available for procurement from all endemic countries with no restriction. | |
| 5.7 Cost | · Standardized pricing quoted by manufacturer available to all stakeholders<br>· Absence of distributor or third-party mark up | · Standardized pricing quoted by manufacturer available to all stakeholders<br>· Absence of distributor or third-party mark up | |

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