

Target Product Profile:

Point-of-Care Malaria Infection Detection Test

For rapid detection of low-density, subclinical malaria infections

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Acronyms

BCTD	blood collection and transfer device
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
FIND	Foundation for Innovative New Diagnostics
FTAT	focused testing and treatment
HCW	health care worker
ICH	International Conference on Harmonisation
ID	infection detection
IDT	infection detection test
LOD	limit of detection
MACEPA	Malaria Control and Evaluation Partnership in Africa
MTAT	mass testing and treatment
PCD	passive case detection
PCR	polymerase chain reaction
<i>Pf</i>	<i>Plasmodium falciparum</i>
<i>Ppan</i>	<i>Plasmodium pan</i>
PPV	positive predictive value
<i>Pv</i>	<i>Plasmodium vivax</i>
QC	quality control
RDT	rapid diagnostic tests
SRA	stringent regulatory authority
TPP	target product profile
USFDA	United States Food and Drug Administration
WHO	World Health Organization

Context

Defining the need for a point-of-care infection detection test for malaria

Malaria control efforts have yielded significant progress toward reducing the burden of malaria. In the last decade alone, there are an estimated 274 million fewer cases and 1.1 million fewer malaria-related deaths [1]. However, the emergence of multiple forms of resistance, the cost of sustained control efforts, and a long history of malaria resurgence [2] following near elimination have fueled recent policy, guidance [3], and funding dedicated to achieving elimination and eradication goals.

As national malaria control programs contemplate their options for shifting tactics and tools to support malaria elimination [4], it is imperative that the malaria community reassess diagnostic priorities in reduced-prevalence settings. The epidemiology of malaria changes significantly as regions transition from control to pre-elimination phase prevalence levels [5]. Infections tend to become focused by defined geographic areas, are frequently imported from higher-transmission regions, and become increasingly dependent on behavioral risks associated with certain subpopulations. In low-prevalence regions, a larger proportion of ongoing transmission is attributed to low density and subclinical infections that cannot be readily detected by currently available rapid diagnostic tests (RDTs) or microscopy [6,7]. In high-prevalence regions, low-mortality and low-morbidity goals can be achieved with existing malaria diagnostic tools that detect symptomatic cases. However, the challenge of blocking transmission in low-prevalence settings requires finding subclinical cases with more sensitive assays.

Accordingly, passive case detection strategies that drive diagnostic use in control programs need to be augmented by active infection detection (ID) tactics and more accurate diagnostic tools in an elimination context. Currently available microscopy and RDTs have insufficient analytical sensitivity required to identify the subclinical cases targeted by active ID tactics. A limit of detection of approximately one-tenth that detectable by current RDTs is estimated to be appropriate to identify most of the low-density, subclinical infections that active ID tactics are targeting.

The proposed infection detection test (IDT) is intended for qualitative detection of *Plasmodium falciparum* (*P. falciparum*; *Pf*) infections. Specifically, the test is intended for use in active ID interventions aimed at identifying and treating subclinical, low parasite density infected populations that serve as reservoirs of parasite biomass. The proposed IDT will use human blood from a finger-stick sample on a lateral-flow immunochromatographic (RDT) assay format and include HRP2 as a target antigen and one other *Pf* antigen to ensure the strongest correlation with transmission risk.

Executive Summary Table

Variable	Minimal requirement	Optimistic specification
1. Product Use Summary/Differentiation Strategy		
1.1 Intended use(s)	Active infection detection (ID) interventions aimed at low-density and subclinical infection detection.	<ul style="list-style-type: none"> Active ID interventions aimed at low-density and subclinical infection detection. Passive case detection for clinical diagnosis and management. Epidemiological surveys.
1.2 Proposed target population	Individuals with <i>Plasmodium falciparum</i> (<i>P. falciparum</i> ; Pf) infection, whether or not they have symptoms of infection.	Individuals with any malaria species infection, whether or not they have symptoms of infection.
1.3 Lowest infrastructure level	The test will be performed under zero-infrastructure conditions including community health centers, households, and outdoor conditions.	Same.
1.4 Lowest level user	The test will be performed by community health workers, trained lay persons, and community volunteers.	All adults.
2. Design		
2.1 Format	Lateral-flow immunochromatographic strip in cassette format.	Same.
2.2 Target analyte	HRP2 and one other Pf specific antigen.	HRP2, one other Pf specific antigen, plus a <i>Plasmodium</i> pan or vivax antigen.
2.3 Sample type/collection	Peripheral whole blood from finger stick (heel prick for infants).	Less invasive sample types that do not include finger stick (e.g., saliva, buccal).
2.4 Sample volume	1–50 µl.	1–25 µl.
2.5 Detection	Minimal requirement: High-contrast, clear results for naked-eye, indoor and outdoor reading; battery-powered reader (only if necessary to achieve minimal limit of detection [LOD] requirements).	High-contrast, clear results for naked-eye, outdoor reading; reader compatible to aid with data handling for surveillance.
2.6 Quality control	Process control line; tests should be compatible with existing positive control wells for lot-to-lot quality control (QC).	Endogenous process control line; tests should be compatible with existing positive control wells for lot-to-lot QC. Colorimetric indicator to identify excessive heat exposure.
2.7 Supplies needed	All reagents and supplies are included in self-contained kit.	Same.
2.8 Lancet	Included in kit. Auto-retracting style. Adequate to achieve specified blood volumes.	Same.
2.9 Blood collection and transfer device	Included in kit. Adequate to collect and transfer specified blood volumes.	No device necessary; specimen transfer directly from finger stick.
2.10 Portability	Highly portable.	Same.

Variable	Minimal requirement	Optimistic specification
2.11 Safety	Auto-retracting lancet. No mixing well needed. Strip contained within a cassette. No buffer-mixture leakage from cassette. Normal use does not create additional hazards to the operator when Universal Blood Safety precautions are observed.	Transfer device made from unbreakable materials.
3. Performance		
3.1 Species differentiation	<i>Pf</i> only.	<i>Pf/Pv/Ppan</i> .
3.2 Analytic sensitivity/limit of detection	Limit of detection required is 10 times better than the current rapid diagnostic tests (RDT) or 10 p/μL. For HRP2, the requirement is 12 ng/ml.	LOD is 5 p/μL. For HRP2, this translates to 6 ng/ml.
3.3 Diagnostic/Clinical sensitivity	97%	99%
3.4 Diagnostic/Clinical specificity	90%	99%
3.5 Time to results	Less than 30 minutes.	Less than 15 minutes.
3.6 Throughput	Seven tests per hour; at least 70% of the throughput of existing RDTs.	More than 10 tests per hour; better than throughput of existing RDTs.
3.7 Target shelf life/stability	18 months at temperatures between 2°C and 30°C; stable for 2 weeks at 40°C.	36 months at temperatures between 2°C and 40°C; stable for 2 weeks at 50°C; time-temperature monitors included on each kit.
3.8 Ease of use	Two or fewer timed steps; instructions should include diagram of method and results interpretation.	One or no timed steps; instructions should include diagram of method and results interpretation.
3.9 Ease of results interpretation	Clear positive/negative readout in indoor and outdoor lighting conditions; language-appropriate instructions.	Same.
3.10 Operating temperature	20°C to 35°C.	10°C to 40°C.
4. Validation/Configuration/Format/Other		
4.1 Reference methods	Composite reference composed of HRP2 ELISA; other antigen ELISA; and a lab-validated, peer-reviewed quantitative polymerase chain reaction (qPCR) assay.	Same.
4.2 Data handling	None.	Alternative specification is compatibility with readers for cloud-based interface, real-time data availability.
4.3 Shipping conditions	Conformance to applicable requirements of ASTM D4169-05 and ISO 11607-1: 2006.	Same.
4.4 Training requirements	Less than one day for any level of provider. Language-appropriate training materials, results guide, and job aid should be made available via the Internet.	One hour for health care workers familiar with RDTs and half day for lay person.

Variable	Minimal requirement	Optimistic specification
4.5 Instrumentation requirements	No instrumentation desired or required unless a reader is necessary to achieve performance specifications.	Alternative specification is compatibility with readers for cloud-based interface and real-time data availability.
4.6 Instrumentation weight and size	No instrumentation desired or required unless a reader is necessary to achieve performance specifications.	Alternative specification is that infection detection test (IDT) should be compatible with RDT readers for cloud-based interface and real-time data availability.
4.7 Calibration	No instrumentation desired or required unless a reader is necessary to achieve performance specifications.	Alternative specification is compatibility with readers for cloud-based interface and real-time data availability.
4.8 Service and support	No instrumentation desired or required unless a reader is necessary to achieve performance specifications.	Alternative specification is compatibility with readers for cloud-based interface and real-time data availability.
4.9 Waste disposal	Does not include material that cannot be disposed of in the normal laboratory waste streams.	Does not include material that cannot be disposed of in the normal laboratory waste streams and the material is biodegradable.
4.10 Precision/ concordance	Individual test lines should be 95% concordant with a validated ELISA test (for the same target antigen) that has been validated at or below the same LOD as the IDT.	Individual test lines should be 99% concordant with a validated ELISA test (for the same target antigen) that has been validated at or below the same LOD as the IDT.
4.11 Power requirements	Self-contained kit operates independent of mains power.	Same.
4.12 Water requirements	Self-contained kit operates independent of water.	Same.
4.13 Labelling	Conformance with United States Food and Drug Administration (USFDA) labelling guidance and recommendations from the Enhanced Malaria RDT Harmonization Procurement & Supply Chain Management Working Group where appropriate.	Same.
5. Product Costs and Channels to Market		
5.1 Target pricing per test	Less than US\$2.00 (at volumes of 10 M).	Less than US\$1.00 (at volumes of 10 M).
5.2 Capital cost	None, unless a reader is required to achieve performance specifications.	Zero capital cost.
5.3 Target launch countries	Kenya, Senegal, Swaziland, Zambia.	Additional countries contemplating elimination of <i>Pf</i> and other species.
5.4 Product registration path	Country-level regulatory requirements apply for target countries.	USFDA 510(k) for class II device or other relevant stringent regulatory authority clearance; Clinical Laboratory Improvement Amendments waived; World Health Organization prequalified.
5.5 Channels to market	Campaign-driven distribution channels.	Shares same distribution channels as clinical-use RDTs.
5.6 Supply, service, and support mechanisms	None.	None.

1. Product Use Summary/Differentiation Strategy

1.1 Intended use-case scenario

Minimal requirement:

- Active infection detection (ID) interventions aimed at low-density and subclinical infection detection.

Optimistic specification:

- Active ID interventions aimed at low-density and subclinical infection detection.
- Passive case detection (PCD) for clinical diagnosis and management.
- Epidemiological surveys.

Annotation:

PCD methods relying on self-referred, symptomatic individuals significantly underestimate infection rates [8], and do not adequately support the aims of elimination [3]. Disrupting transmission in highly endemic regions necessitates the identification of malaria infection, whether symptomatic or subclinical [3]. Because subclinical individuals are not likely to seek treatment, elimination programs must include tactics to detect and treat reservoirs of subclinical infections that can sustain transmission from one season to the next [9,10]. Accordingly, active ID tactics have been developed to find both unreported clinical and subclinical infections in geographically and demographically defined reservoirs (termed hotspots and hotpops, respectively). These tactics become increasingly important as elimination is approached.

Figure 1 provides an overview of the taxonomy and diagnostic use scenarios common to elimination programs. A framework for multiple target product profiles (TPPs) and an overview of key requirements for elimination tests are provided in Table 1. Table 1 identifies three distinct TPPs whereas this document focuses on just one of these: Point-of-Care Infection Detection. Active ID tactics described in Figure 1 are grouped together based on their shared requirements for rapid time to results, high sensitivity, low limit of detection (LOD), and portability.*

While the minimal requirements in this TPP consider only active ID uses, the optimistic specifications include uses for active ID as well as surveys and PCD. It is likely that users from these additional two use scenarios (surveys and PCD) will desire a test with improved performance characteristics (ease of use, sensitivity, specificity, LOD); however, pricing will likely determine uptake in those markets. Lower pricing would improve the likelihood that the product is suitable for these markets. Increased demand and higher sales volumes from PCD and survey markets

* Conceptually, epidemiological surveys, aimed at identifying the extent of malaria in an area of unknown prevalence, do not require rapid results for treatment. However, in practice, ethical considerations often imply a treatment component for survey subjects identified as malaria positive. Nonetheless, since rapid treatment is not a requirement of the survey itself, we exclude surveys from further discussion in this TPP but acknowledge that a product meeting the requirements in this TPP would likely serve survey needs very well.

would enable economies of scale for manufacturing and distribution, resulting in a further reduction in infection detection test (IDT) costs.

As identified in Figure 1, active ID is subdivided into reactive ID in response to an index case and proactive ID to identify and treat infected individuals in hotspots and hotpops.

Reactive ID:

Reactive tactics triggered by one or more passively identified index cases are often referred to as reactive *case detection* [11,12,13]. Here, we propose adoption of the term reactive *infection detection* when this tactic is intended to quickly identify (and subsequently treat) both symptomatic *cases* and, importantly, subclinical infections in a general area defined around a confirmed index case. Reactive *ID* tactics are recommended by the World Health Organization (WHO) for low- and very-low-prevalence regions, especially in areas of high receptivity [14]. Reactive ID may involve either neighborhood, household, or workplace testing to identify and treat all infections associated with a “community-based” index case or network testing to identify and treat all infected persons traveling with a migrant worker or “mobile” index case.

Proactive ID:

Demographically targeted proactive ID tactics aimed at eliminating specific hotpops include testing and treating individuals at fixed locations such as border crossings [15,16,17], workplace, or other time/location testing and chain-referral sampling [5,18].

Demographically targeted proactive ID tactics such as mass testing and treatment (MTAT) and focused testing and treatment (FTAT) are aimed at eliminating transmission in specific hotspots and often cover larger regions than reactive ID. FTAT has been evaluated as a tactic to eliminate malaria and contain the spread of artemisinin resistance in identified, noncontiguous, high-risk hotspots [19]. MTAT is similar in method to FTAT but is applied at a larger, more contiguous scale. MTAT has been a component of successful elimination interventions [20]. WHO guidance includes consideration of MTAT where there is credible evidence of artemisinin resistance [21].

Both reactive and proactive tactics place increased emphasis on more portable technologies that enable rapid, low-density ID which promotes immediate treatment without the loss to follow-up associated with transporting samples to centralized testing facilities.

Figure 1. A proposed outcome-oriented use-scenario framework for malaria infection detection.

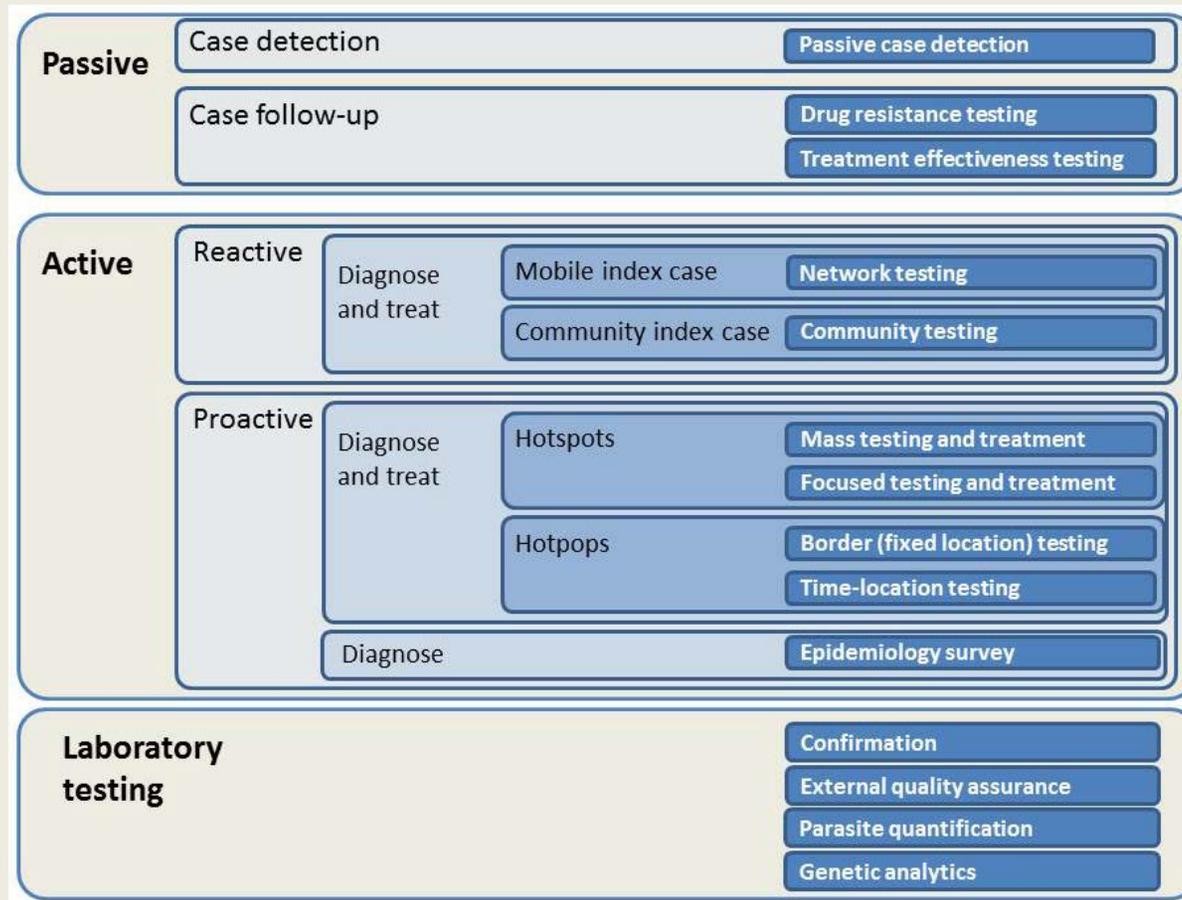


Figure 1 note: Control-phase activities require a robust, passive case-detection system at the point of care to reduce mortality and morbidity associated with the disease. As prevalence declines, malaria elimination and eradication programs place increased emphasis on active ID techniques to decrease transmission. Active ID is subdivided into reactive ID in response to an index case and proactive ID used both to diagnose and treat geographically and demographically defined reservoirs (hotspots and hotpops) and to define the local epidemiology and assess transmission risk. Network and community testing are frequently proposed reactive ID tactics to identify and treat infections associated with mobile index cases (e.g., migrant workers) or community-based index cases, respectively. Mass testing and treatment and focused testing and treatment are tactics used to detect and treat hotspot infections. Border and time-location testing are used to detect and treat hotpop infections. Surveys are used to assess regional transmission and establish priorities. Laboratory-based tests are frequently used for confirmation, external quality assurance, parasite quantification, and genetic analytics to assess infection origin and drug resistance.

Table 1. Proposed target product profile framework for malaria elimination diagnostics.

Target product profile	Point-of-care case detection	Point-of-contact infection detection	High-throughput infection detection
Defining requirements	Low cost, ease of use, rapid time to results, specificity	High sensitivity, low limit of detection, portability, rapid time to results	High sensitivity, high specificity, standardization, low limit of detection, high throughput
Use scenarios	Passive case detection and case follow-up	Network testing, community testing, mass testing and treatment, focused testing and treatment, border testing, time-location testing, surveys (if treatment is planned)	Surveys (when rapid treatment is not a priority), laboratory confirmation, external quality assurance, parasite quantification

Table 1 note: This target product profile (TPP) framework is organized by each TPP's defining attributes related to accuracy, cost, ease of use, portability, throughput, and time to results. Specific requirements for ideal tests will be detailed in TPPs currently in development by the authors. Use scenarios for drug-resistance testing and other genetic analytics are not included in this TPP framework because their analytical requirements vary considerably.

1.2 Proposed target population

Minimal requirement: Individuals with *Plasmodium falciparum* (*Pf*) infection, whether or not they have symptoms of infection.

Optimistic specification: Individuals with any malaria species infection, whether or not they have symptoms of infection.

The frequency and relevance of submicroscopic[†] carriage was recently reviewed by Okell, et al. [9]. The authors concluded that microscopy detects only about 54% of all polymerase chain reaction (PCR)–detectable malaria infections. Low-transmission settings have proportionately greater submicroscopic carriage rates. Two published studies [10,22] and one unpublished study [9] found that human-to-mosquito transmission rates are from 4 to 16 times lower from submicroscopically infected individuals as compared to infected individuals with parasite levels detectable by microscopy. Nonetheless, combining these estimates with relative submicroscopic carriage rates suggests that as malaria prevalence decreases, submicroscopic infections contribute increasingly to the human infectious reservoir. Submicroscopic infections may contribute to 20% to 50% of transmission in pre-elimination and elimination settings [9].

Active ID techniques are used at prevalence levels below and above a 5% slide

[†] For the purpose of this TPP, we avoid the use of the term sub-patent (original language used by the authors of this study) and instead use the term submicroscopic to describe parasite levels that are not easily detected by existing techniques available at the clinic level, specifically microscopy and RDTs. The reason we avoid the use of the term sub-patent is that there are several conflicting definitions that make the term ambiguous, especially in the context of the proposed IDT which is intended to identify infections at levels previously classified as sub-patent.

	positivity rate (the standard definition of pre-elimination). Therefore, to establish a practical reference population with suitably high infection rates for clinical validation of the IDT, a reference population between 10% and 30% is suggested. [‡]
<p>1.3 Lowest infrastructure level</p> <p>Minimal requirement: The test will be performed under zero-infrastructure conditions including community health centers, households, and outdoor conditions.</p> <p>Optimistic specification: Same.</p>	Reactive ID, MTAT, and FTAT are all conducted under zero-infrastructure conditions including community health centers, households, and outdoor conditions.
<p>1.4 Lowest level user</p> <p>Minimal requirement: The test will be performed by community health workers, trained lay persons, and community volunteers.</p> <p>Optimistic specification: All adults.</p>	<p>Operational research has been conducted using active ID tactics under mostly ideal conditions relying on well-trained diagnostic test users. We anticipate that scaled, real-world application of active ID tactics will have wide variation in user skills and training.</p> <p>Field research conducted by PATH (unpublished data, 2013) identified that operational reactive- and proactive-ID teams vary and may be composed of any combination of minimally trained malaria workers with as little as one to two weeks of professional training. Potential users include nurses, clinicians, laboratory technicians, community health workers, volunteers, and malaria control program managers.</p>

[‡] Additional samples from populations where prevalence is low (less than a 5% slide positivity rate) or very low (less than 1%) will be necessary to establish whether expressed antigens levels from infections in these populations differs from that of higher-prevalence-level populations.

2. Design

<p>2.1 Format</p> <p>Minimal requirement: Lateral-flow immunochromatographic strip in cassette format.</p> <p>Optimistic specification: Same.</p>	<p>Since their introduction in the mid-1990s, the number of procured rapid diagnostic tests (RDTs) for malaria has increased substantially. The number of RDTs supplied by manufacturers increased from 88 million in 2010 to 205 million in 2012. A total of 48 countries reported deployment of RDTs at the community level in 2013 (UNITAID, unpublished data, 2014). RDTs are easy to use by minimally trained workers and have no infrastructure requirements. With high adoption rates and high acceptability, the RDT (a.k.a., lateral-flow immunochromatographic strip) format is ideal for the proposed IDT. The introduction of an alternative format into malaria programs could create confusion.</p> <p>In addition to the requirements established in this TPP, IDT design should take into consideration the packaging and presentation characteristics prioritized by the Roll Back Malaria RDT harmonization working group. Draft recommendations from this working group are included as Appendix A to this TPP and should be updated when new drafts become available.</p>
<p>2.2 Target analyte</p> <p>Minimal requirement: HRP2 and one other <i>Pf</i>-specific antigen.</p> <p>Optimistic specification: HRP2, one other <i>Pf</i>-specific antigen, plus a <i>Plasmodium pan</i> (<i>Ppan</i>) or <i>Plasmodium vivax</i> (<i>Pv</i>) antigen.</p>	<p>Advantages of HRP2:</p> <ul style="list-style-type: none"> • HRP2 is a well-characterized target analyte that is produced in abundance in infected individuals and circulates in peripheral blood. • HRP2 correlates to total parasite biomass better than infected red blood cell concentration [23]. • HRP2 levels are a good predictor of severity of infection [24]. • Due to antigen persistence (long half-life), HRP2 levels are a strong proxy for infection and for onward transmission risk. • HRP2 levels remain nearly constant despite sequestration. Visual parasites, on the other hand, can sequester out of circulation. Other antigens and target DNA and RNA have sufficiently low persistence that they also fall to undetectable levels due to sequestration. • HRP2 is uniquely <i>Pf</i> species specific. <p>Disadvantages of HRP2:</p> <ul style="list-style-type: none"> • HRP2 is uniquely <i>Pf</i> species specific. • Long half-life can result in false positive results following treatment for up to four weeks. • Low repeat <i>Pf</i> varieties of HRP2 present binding challenges and, therefore, demonstrate low

affinity and avidity, leading to false negatives [25].

- HRP2 gene deletions have been reported to cause PfHRP2 RDT failure (false negative diagnoses) in Peru [26,27], Mali [28], India [29], Brazil [30], and Senegal [31], prompting the Centers for Disease Control and Prevention (CDC) to discourage RDT use when rates of HRP2 negativity of 10% or greater are detected in a region [32].
- Single-axis diagnose and treat tactics get what they select for, meaning that regional populations of *Pf* might develop detection resistance if these tactics select for *Pf* clones that are the most difficult or impossible to detect.
- Market supply of the best-performing mAbs (C-13) comes from a limited number of suppliers while the larger manufacturers have developed in-house, proprietary methods for antibody production.

The limitations of HRP2 should be mitigated in IDT tests by adding a second, *Pf*-specific, non-HRP2 test line as indicated by the minimal requirement. The *Pf*-specific, non-HRP2 target analyte will mitigate false negative results due to HRP2-negative sub-strains. Table 2 below identifies the proposed results interpretation scheme:

Table 2. Proposed result interpretation.

		HRP2	
		pos	neg
non-HRP2 Pf antigen	pos	positive	positive, likely attributed to HRP2 deletion or low HRP2 epitope repeats
	neg	positive, likely due to higher sensitivity of HRP2 analyte	negative

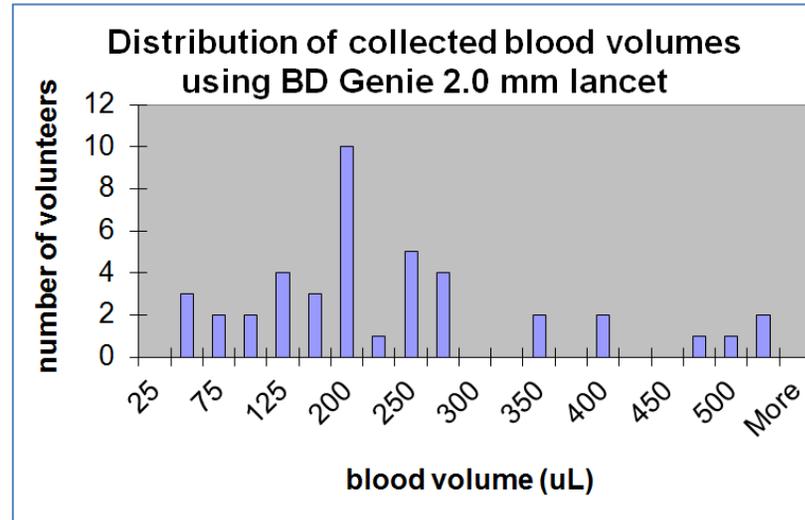
Table 2 note: Any test without a visible control line is determined to be “invalid.”

	<p>Further developments beyond the scope of this project might consider the optimistic specification of adding <i>Ppan</i>- or <i>Pv</i>-specific detection which might broaden the product market and benefit treatment selection and surveillance data. The value of <i>Ppan</i>, <i>Pv</i>, and other species-specific configurations is regionally specific.</p>
<p>2.3 Sample type/collection</p> <p>Minimal requirement: Peripheral whole blood from finger stick (heel prick for infants).</p> <p>Optimistic specification: Less-invasive sample types that do not include finger stick (e.g., saliva, buccal).</p>	<p>The degree to which invasiveness is tolerated is often inversely related to the personal benefit gained from a procedure. For the proposed IDT use scenarios aimed at identifying subclinical individuals, the personal benefits of diagnosis and treatment may be trivial. Thus, the sample type and volume requirements are a balance between an acceptable level of invasiveness and performance requirements. While higher volumes of blood might afford improved LOD, finger-stick collection is the highest level of invasiveness tolerable. Venous blood draw is not acceptable.</p> <p>Recent interviews of health care workers (HCWs) (PATH, unpublished data, 2013) identified their concern about how finger stick pain might lead to population fatigue after multiple detect-and-treat interventions on subclinical populations. The optimistic specification suggests use of less-invasive sample types should be considered, though it is unlikely other blood compartments can achieve the minimal performance requirements.</p>
<p>2.4 Sample volume</p> <p>Minimal requirement: 1–50µL</p> <p>Optimistic specification: 1–25µl</p>	<p>Very low sample volumes can yield false negative results due to the statistical distribution of low-density target analytes. However, the relative abundance of antigen analytes is often high compared with parasite density and even DNA density, so a lower bound of 1 µl is acceptable.</p> <p>Larger sample volumes are desirable to achieve the highest likelihood of detecting low-density infections. However, the upper sample volume threshold is established by the practical limit of finger-stick sampling. In a recent PATH study of 140 volunteers in Uganda, investigators observed that 95 µL of blood could be successfully collected from a BD Microtainer® Contact-Activated lancet finger prick and transferred only 89.1% of the time (PATH, unpublished data, 2011). There was an increased number of failures experienced by novice specimen collectors when compared to their expert counterparts. Therefore, additional focused training alone could significantly increase the successful collection of specimens from 89.1% to 95%.</p> <p>In another PATH study conducted with novice specimen collectors, maximum blood volumes from a BD Genie™ 2.0-mm lancet finger stick were collected in capillary tubes and measured. A frequency distribution of the results is shown in Figure 2 below. Of the 42 specimens collected, the average volume was 211 µL; the standard deviation was 125 µL. One hundred percent of the specimens collected were less than 25 µl; 93% were less than 50 µL, 88% were less than 75 µL, and 83% were less</p>

than 100 µL.

Anecdotal evidence suggests that the highest, most-consistent volumes are attained using contact-activated lancets.

Figure 2. Distribution of collected blood volumes using a BD Genie™ 2.0-mm lancet.



Note that while a higher volume may be beneficial to test performance, a lower blood volume is preferred as explained elsewhere in this section and because achieving higher blood volumes typically requires more expensive lancets.

2.5 Detection

Minimal requirement: High-contrast, clear results for naked-eye, indoor and outdoor reading; battery-powered reader (only if necessary to achieve minimal

Naked-eye detection is preferred; however, an automated reader may be needed to achieve test performance targets.

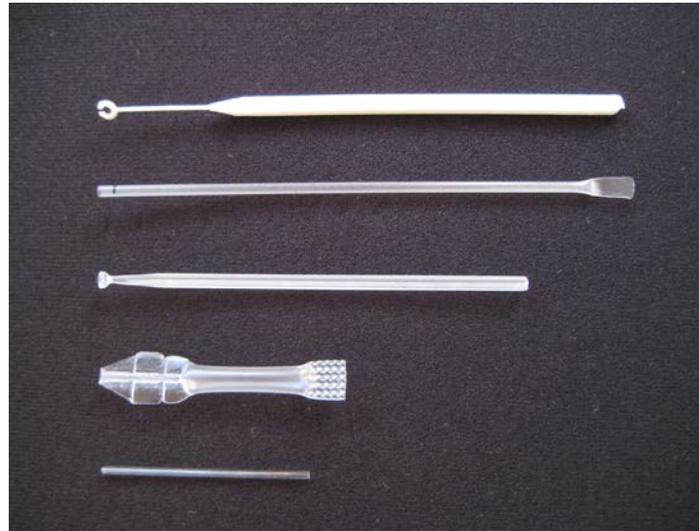
Field research (PATH, unpublished data, 2013) indicates that poor indoor lighting conditions are a barrier to accurate reading of current RDTs in some active ID scenarios. Therefore, high-contrast test lines should be readable in low indoor light levels as well as in sunlight.

The optimistic specification acknowledges that there are use scenarios where a reader may be more desirable (i.e., to provide global access to real-time data). Since the protocols for active ID use

<p>LOD requirements).</p> <p>Optimistic specification: High-contrast, clear results for naked-eye, outdoor reading; reader-compatible to aid with data handling for surveillance.</p>	<p>scenarios are rapidly evolving, the optimistic specification for a reader to support reporting needs (versus performance needs) is identified as “reader-compatible.”</p>
<p>2.6 Quality control</p> <p>Minimal requirement: Process control line; tests should be compatible with existing positive control wells for lot-to-lot quality control (QC).</p> <p>Optimistic specification: Endogenous process control line; tests should be compatible with existing positive control wells for lot-to-lot QC. Colorimetric indicator to identify excessive heat exposure.</p>	<p>Typical RDTs have a process control line that provides information on proper test completion (i.e., adequate volume of sample added, process steps performed correctly) and on the general integrity of immobilized bio-reagents.</p> <p>The control line does not confirm the ability to detect parasite antigen. Visual identification of the control line only allows the reader to infer that the analyte-specific activities of the RDT are still functional; it is not a direct test.</p> <p>Positive control wells are in late-stage development and may be useful to detect out-of-specification product lots. In anticipation of widespread uptake of positive control wells, the minimum requirement indicates that a newly developed test should be compatible with QC for positive control wells (i.e., the antibodies used should recognize the recombinant antigens in available positive controls wells equivalently to the native antigens in a clinical sample).</p> <p>The optimistic specification for an endogenous control extends the capacity of the test line to confirm that human blood has been processed as a sample adequacy control.</p> <p>Stakeholder feedback (PATH, unpublished data, 2013) indicates that HCWs were concerned about buffer color changes and were unclear whether this implied the buffer was out of specification. Therefore, the optimistic specification includes colorimetric indicators in the buffer or on the buffer bottle (e.g., time-temperature indicators) that indicate cumulative heat exposure relative to a threshold value that indicates the test should not be used.</p>
<p>2.7 Supplies needed</p> <p>Minimal requirement: All reagents and supplies are</p>	<p>Stakeholder feedback (PATH, unpublished data, 2013) indicates that RDT users across multiple use scenarios recounted errors in quantity and type of buffer used due to frequent changes in RDT brands. Furthermore, HCWs expressed preference for RDT kits rather than bulk packaging for ease of use, for ease of transport, and to ensure that all supplies needed were available. Therefore, all reagents and supplies necessary for the test should be contained in the RDT kit and clearly marked “for use only</p>

<p>included in self-contained kit. Optimistic specification: Same.</p>	<p>with XXX test kit.”</p>
<p>2.8 Lancet Minimal requirement: Included in kit. Auto-retracting style. Adequate to achieve specified blood volumes. Optimistic specification: Same.</p>	<p>Lancet selection should include consideration of trade-offs between cost, safety, user preference, and blood volume requirements. Stakeholders from a field study (PATH, unpublished data, 2013) preferred a trigger lancet over a contact-activated lancet because they were fearful of pushing the lancet into the finger. In addition, obtaining samples from young children was difficult using a contact-activated lancet; the children could visibly observe the sharp point and became fearful, causing them to pull their finger away at the moment of puncture, thus establishing distrust between the child and the HCW. In addition, trigger lancets with auto-retracting blades are much safer to use and they mitigate dangerous reuse practices as HCWs must often store used lancets at their home for a period of time before transporting them to a health facility for disposal.</p>
<p>2.9 Blood collection and transfer device Minimal requirement: Included in kit. Adequate to collect and transfer specified blood volumes. Optimistic specification: No device necessary; specimen transfer directly from finger stick.</p>	<p>A 2007 study of four blood collection and transfer device (BCTD) options for malaria RDTs identified that there is high variability in blood volume collected by the devices. The straw and the loop, the most preferred devices, usually transferred volumes greater than intended, while the glass capillary tube and the plastic pipette transferred less volume than intended or none at all. The study identified that blood volume variations affect RDT sensitivity, especially when the transferred volume is very low. Since none of the assessed BCTDs performed consistently well, the study authors recommend development of improved designs to be used by remote health workers [33]. A more recent study [34] found that the inverted cup design achieved the highest overall performance, while the loop also performed well. PATH research (unpublished data, 2013) indicates that there are regional preferences for BCTDs, and preference depends on skill level. Figure 3 below displays the various BCTD options.</p>

Figure 3. Blood collection and transfer devices.



From top to bottom: the loop, straw pipette, inverted cup, calibrated pipette, and glass capillary [34].

The TPP does not make specific recommendations for BCTD supplies since device selection will be highly dependent on sample volume. Beta prototypes of the kit should be evaluated in real-world conditions with several leading BCTD options to ensure the kit is optimized.

The optimistic specification indicates that eliminating a separate BCTD component could simplify the kit and the test process.

2.10 Portability

Minimal requirement: Highly

As regional elimination is approached, transmission will become isolated to areas termed “far-away malaria” characterized by long distances from urban populations. Accordingly, active ID will increasingly occur in areas that require multiple transportation methods (e.g., truck, boat, bike, foot)

<p>portable.</p> <p>Optimistic specification: Same.</p>	<p>over challenging terrain. Therefore, a high degree of portability is essential.</p> <p>Devices should be portable such that a single user can carry a full day's test load (60 tests) and a reader (if required) 10 kilometers overland into a community.[§]</p>
<p>2.11 Safety</p> <p>Minimal requirement: Auto-retracting lancet. No mixing well needed. Strip contained within a cassette. No buffer-mixture leakage from cassette. Normal use does not create additional hazards to the operator when Universal Blood Safety precautions are observed.</p> <p>Optimistic specification: Transfer device made from unbreakable materials.</p>	<p>WHO/Foundation for Innovative New Diagnostics (FIND) Malaria RDT performance evaluations [35] rate RDT safety across three attributes:</p> <ol style="list-style-type: none"> 1. Mixing wells involved. 2. Retractable needle. 3. Strip contained in a card or cassette (i.e., no exposed strip). <p>PATH field work identified a fourth safety issue which relates to cassette integrity. HCWs complained about blood-buffer mixture leaking from the cassette. Thus, the specification includes no leakage.</p> <p>Because some BCTDs (e.g., capillary tube) are a sharps hazard when broken, the minimum specification includes BCTDs made from unbreakable materials.</p>

3. Performance

<p>3.1 Species differentiation</p> <p>Minimal requirement: <i>Pf</i> only.</p> <p>Optimistic specification: <i>Pf/Pv/Ppan</i>.</p>	<p>Initial focus of the proposed IDT platform is <i>Pf</i>. By narrowing the focus to only <i>Pf</i>, accelerated development of a platform product provides an opportunity for enormous impact toward eliminating the <i>Plasmodium</i> subspecies with the highest associated mortality. A <i>Pf</i>-only focus prioritizes rapid product development over multifunction capability.</p> <p>Platform advances that evolve for the <i>Pf</i> product will be leveraged to accommodate the addition of other subspecies or <i>Ppan</i> detection <i>after</i> a <i>Pf</i>-only product has been validated. As such, the optimistic specification indicates <i>Pf/Pv/Ppan</i>.</p>
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[§] Note that size and weight benchmarks are identified in section 4.6 of this TPP.

3.2 Analytic sensitivity/limit of detection

Minimal requirement: LOD required is 10 times better than the current RDT or 10 p/μL. For HRP2, the requirement is 12 ng/ml.

Optimistic specification: LOD is 5 p/μL. For HRP2; this translates to 6 ng/ml.

Evidence suggests that submicroscopic infections are a significant contribution to ongoing transmission in low-prevalence regions [20]. Evidence also suggests that there is a threshold gametocyte density below which improvements in LOD have diminishing returns (see Figure 4) [36].

However, existing data are limited, and there is no universal agreement on an exact threshold LOD because the dynamics of transmission from a single mosquito bite are complex, highly heterogeneous (regional and individual variations), and multi-factorial (involving Poisson distribution statistics, and variations in human gametocyte density). That said, there is general agreement that the proposed IDT should be significantly improved over existing microscopy and RDTs. Thus the minimal requirement is set at approximately one-tenth of the detection limit of existing RDTs which is generally agreed to be 100 p/μl. Thus, this TPP establishes a LOD requirement of 10 p/μl.

Further translating this limit into a meaningful LOD for the primary target analyte, HRP2, requires an approximation of HRP2 to p/μl. Here are some assumptions [37,38,39]:

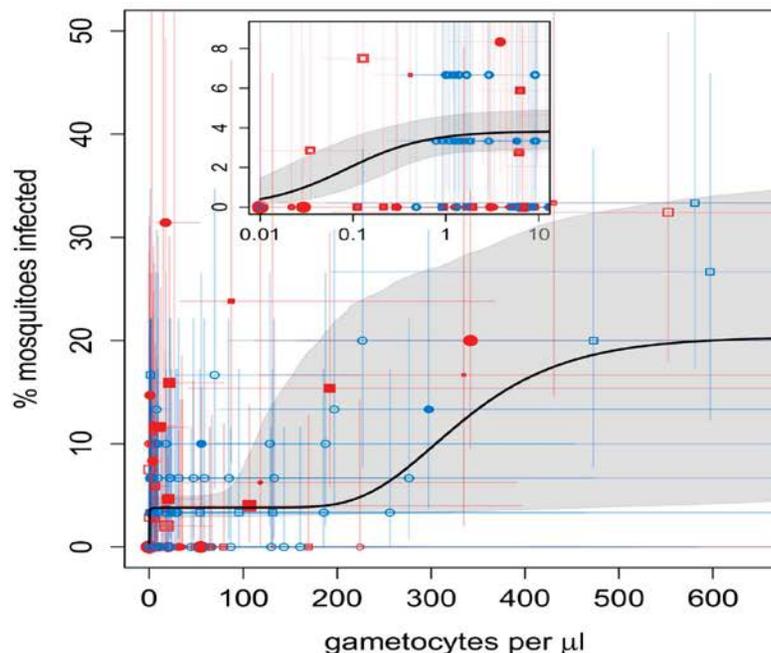
- Parasite density of 10 p/μl = parasitemia of 0.0002%
- 0.0002% parasitemia ≈ 12-400 ng/mL HRP2**

Thus, on the very conservative side, we set the HRP2 requirement at 12 ng/ml.^{††} For the optimal specification, the LOD is set at half of the requirement, 6 ng/ml. As a reference, the lowest published HRP2 LOD value identified is 4 ng/mL [37]. Unpublished values as low as 1 ng/mL have been achieved (personal communication with Harold Noedl, Associate Professor at Medical University of Vienna, July 2013).

** A wide HRP2 density range is listed because HRP2 does not correlate well to parasite density for the following reasons: HRP2 production levels vary based on a number of factors (e.g., subspecies, parasite stage), HRP2 does not sequester, and HRP2 has a long half-life.

†† Note that 12 ng/mL translates to $\sim 10^{11}$ molecules/μl HRP2, thus Poisson distribution will not affect results.

Figure 4. Mosquito infectivity rates as a function of gametocyte density.



A slope transition in the curve at ~1 g/μl suggests that there may be a threshold gametocyte density below which improved LOD has diminishing returns. Translating this to p/μl is challenging given a wide variability in gametocyte density as a fraction of asexual stage density (ranging from ~1% to 5%). Actual gametocyte:asexual stage parasite ratios are highly dependent on sub-strain, season, region, and individual/host interactions.

High sensitivity is required to achieve high effectiveness for active ID interventions.

3.3 Diagnostic/Clinical sensitivity^{‡‡}

The actual sensitivity of the IDT will be highly dependent on the population selected because average parasite density varies as a function of population prevalence. Therefore, the clinical sensitivity requirement of 97% should be validated with a reference population with analyte density of greater

^{‡‡} In sections 3.3 and 3.4, we discuss clinical sensitivity and specificity of a new IDT as compared to “truth.” A true positive is defined by the case definition. For the IDT, the case definition is a *P. falciparum* infection that is capable of transmitting disease between humans (*not* someone who is showing clinical signs and symptoms and *not* someone who tests positive by a particular test).

<p>Minimal requirement: 97%</p> <p>Optimistic specification: 99%</p>	<p>than five times the analytical sensitivity (LOD) to account for the fact that any test’s clinical sensitivity is not optimized at the target LOD.^{§§} This means that infections that have analyte density less than five times the LOD requirement established in section 3.2 will not be included in the denominator of the sensitivity calculation.^{***}</p> <p>The reference population for establishing clinical sensitivity is described in section 1.2. The composite reference described in section 4.1 will be used to determine true infection.</p> <p>The optimistic specification, 99%, acknowledges the need to detect and treat most, if not all, infections.</p>
<p>3.4 Diagnostic/Clinical specificity^{†††}</p> <p>Minimal requirement: 90%</p> <p>Optimistic specification: 99%</p>	<p>To achieve the desired LOD, it is likely that an IDT will have to be engineered in a way that may increase the number of false positives due to the relaxed binding stringency required to capture and report on a greater fraction of the analytes as compared to a test that has been optimized for a less-demanding LOD. Thus, the trade-off for a low LOD is reduced specificity. Therefore, a minimal requirement is set at 90% specificity.</p> <p>It is important to assess the positive predictive values (PPVs) of key levels of sensitivity and specificity at low prevalence rates. Table 3 below is provided to illustrate this.</p>

^{§§} Note that BinaxNOW® labeling indicates that sensitivity and specificity were determined at a threshold of 5,000 p/µl, or approximately five times the product LOD. Thus further revisions of the TPP need to reevaluate whether the threshold of ten times the LOD here is practical.

^{***} This clarification acknowledges that a test of 97% sensitivity does not indicate that it should be 97% sensitive for populations with parasite density levels near the LOD.

^{†††} The reference population for establishing clinical sensitivity is described in section 1.2. The composite reference described in section 4.1 will be used to determine true infection.

Table 3. Illustrative examples of positive predictive value as a function of prevalence rate, sensitivity, and specificity.

Phase	prevalence rate (%)	detection parameters	PPV (%)
control	30	Sensitivity: 97% Specificity: 90%	81
	20	Sensitivity: 97% Specificity: 90%	71
	10	Sensitivity: 97% Specificity: 90%	52
pre-elimination	5	Sensitivity: 97% Specificity: 90%	34
		Sensitivity: 97% Specificity: 95%	51
	1	Sensitivity: 99% Specificity: 99%	50
elimination	0.1	Sensitivity: 99% Specificity: 99%	9

The optimistic specification of 99% is set to achieve greater than 50% PPV at low prevalence levels down to 0.1%. A high-specificity test may also be useful as a confirmatory test for PCD when paired with a high-sensitivity primary test in low-prevalence regions. These high levels of specificity in the PCD use scenario would be useful to prevent deploying resources to investigate false positive index cases. A test that is 99% sensitive and 99% specific results in a PPV of just 9% at the elimination threshold (tested population prevalence of 0.1%) meaning that only 9 out of 100 positive results is a true positive. Otherwise stated, at these levels, a program might conduct approximately nine investigations pursuing false positives for each investigation on a true positive index case.

3.5 Time to results

Minimal requirement: Less than

Time to results as reported by the WHO/FIND round 4 results [35] indicate a range of 15 to 30 minutes for 48 tested malaria RDT products. The average was 20.2 minutes with a standard deviation of 4.4 minutes.

<p>30 minutes.</p> <p>Optimistic specification: Less than 15 minutes.</p>	<p>The minimum time to results requirement is set at the high end of comparable products tested because time to results is a lower priority than other performance requirements (e.g., sensitivity and LOD). Time to results may be a trade-off in achieving these higher-priority requirements.</p> <p>The optimistic specification represents a “best-in-class” target that addresses a common complaint expressed by HCWs interviewed in the field (PATH, unpublished data, 2013) that even 15 to 20 minutes was too long for active ID where HCWs have a high workload and need to move to the next house.</p>
<p>3.6 Throughput</p> <p>Minimal requirement: 7 tests per hour; at least 70% of the throughput of existing RDTs.</p> <p>Optimistic specification: More than 10 tests per hour; better than throughput of existing RDTs.</p>	<p>There is limited data on active ID throughput requirements. Recent Malaria Control and Evaluation Partnership in Africa (MACEPA) test-and-treat protocols set a goal of 10 households a day for an RDT testing team of two people. Given an average household size of six persons in Zambia, this goal would require the test team to perform 60 tests per day. However, a daily throughput rate does not reflect travel time between households and other factors such as staggered batch processing.</p> <p>Our assumption is that staggered batch processing of existing RDTs yields approximately 10 finished tests per hour. Recognizing that throughput and other performance characteristics are design trade-offs, the relaxed throughput requirement demonstrates that performance criteria are a higher priority than throughput. The minimal requirement is 7 tests per hour.</p> <p>The optimistic specification identifies higher throughput compared with existing RDTs at more than 10 tests per hour. This higher throughput would increase work flow efficiency and translate to cost savings for the intervention program.</p> <p>To validate this requirement, a time-motion study should be conducted comparing several commercialized RDTs (reference standard) to the new IDT product in a laboratory.</p>
<p>3.7 Target shelf life/stability</p> <p>Minimal requirement: 18 months at temperatures between 2°C and 30°C; stable for 2 weeks at 40°C.</p> <p>Optimistic specification: 36 months at temperatures between</p>	<p>WHO endorses the International Conference on Harmonisation (ICH) guidelines for climatic Zones III (hot/dry) and IV (hot/humid) for pharmaceuticals [40], which commonly share supply lines with diagnostics.</p> <ul style="list-style-type: none"> • For climatic Zones III, ICH guidelines recommend a minimum stability for one year at 30°C and 35% humidity [41,42]. • For climatic zone IV, ICH guidelines recommend a minimum stability for one year at 30°C and 65% humidity [41,42]. <p>For practical purposes and because product shelf life/stability were frequently cited by stakeholders</p>

<p>2°C and 40°C; stable for 2 weeks at 50°C; time-temperature monitors included on each kit.</p>	<p>as a major product constraints (PATH, unpublished data, 2013), minimal stability requirements are set to exceed ICH guidelines. High temperature excursions due to cold chain failure are expected during transport to many regions conducting active ID interventions, thus the requirement includes 2-week stability at 40°C.</p> <p>WHO recommends that kits should not require refrigeration and should tolerate temperatures of at least 40°C and peaks of up to 50°C which may occur not only during storage but also prolonged transport under tropical conditions [43]. A combined guideline by WHO, FIND, and the CDC recommends stability testing up to 45°C for a minimum of 2 to 6 months [44]. Optimistic specifications are established to reflect these recommendations. The optimistic specification also includes time-temperature monitors as a means of establishing product viability, especially in situations when cold chain requirements cannot be assured.</p>
<p>3.8 Ease of use</p> <p>Minimal requirement: Two or fewer timed steps; instructions should include a diagram of method and results interpretation.</p> <p>Optimistic specification: One or no timed steps; instructions should include a diagram of method and results interpretation.</p>	<p>Ease of use as evaluated by the WHO/FIND round 4 testing [35] assessed instruction quality, number of timed steps, and inclusion of descriptive diagrams in the instructions. Most products tested had only one timed step. The relaxed minimal requirement (two timed steps) enables inclusion of a sample-concentrating step to achieve performance requirements.</p> <p>The following frequently cited RDT ease-of-use constraints identified in PATH field work (unpublished data, 2013) should also be considered in new product design:</p> <ul style="list-style-type: none"> • Buffer spills when opening pouch. • Retained buffer in cap of pouch after it is opened. • Difficulty with blood transfer due to undersized sample wells resulting in incomplete dispensing of specimen. • Difficulty drawing and dispensing exact quantity of blood using blood transfer device. • Inadequate space on RDT cassette to write patient details. <p>The optimistic specification, one timed step, sets ease of use on par with most products evaluated in round 4 testing.</p>
<p>3.9 Ease of results</p>	<p>Results interpretation as indicated in Table 2 in Section 2.2.</p> <p>In field research conducted by PATH (unpublished data, 2013), stakeholders expressed difficulty reading results on current RDTs in poor lighting conditions. Additionally, several HCWs shared that</p>

<p>interpretation</p> <p>Minimal requirement: Clear positive/negative readout in indoor and outdoor lighting conditions; language-appropriate instructions.</p> <p>Optimistic specification: Same.</p>	<p>instructions for RDT kits are printed in English, not in their local language, so they are unable to read the instructions.</p> <p>Instructions and clear diagrams should be available in local languages and should identify all possible resulting test lines and the proper interpretation.</p>
<p>3.10 Operating temperature</p> <p>Minimal requirement: 20°C to 35°C.</p> <p>Optimistic specification: 10°C to 40°C.</p>	<p>Devices designed to work in low-resource settings at ambient temperature have specifications in the approximate range of 10°C to 40°C (for example, the OptiGene Genie® II [45]).</p>

4. Validation/Configuration/Format/Other

<p>4.1 Reference methods</p> <p>Minimal requirement: Composite reference composed of HRP2 ELISA; other antigen ELISA; and a lab-validated, peer-reviewed quantitative polymerase chain reaction assay.</p> <p>Optimistic specification: Same.</p>	<p>For IDT validation, the biggest challenge lies in knowing what truth actually is. Current gold-standard assays do not have the low LODs required for an IDT, making them poor proxies for truth and unsuitable as stand-alone reference assays for the laboratory comparisons that are usually used to determine diagnostic accuracy. The irrelevance of clinical signs and symptoms to true infection, either at presentation or monitored in follow-up, means that longitudinal studies will not bridge this gap. Thus it is imperative that a new and better proxy for truth be formulated by combining several laboratory methods into a composite reference standard.</p> <p>A validated composite reference test should be compiled from the individual specimens from subclinical patients in low-prevalence regions who test positive by <i>at least two</i> of the following:</p> <ul style="list-style-type: none"> • Microscopy^{†††}
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^{†††} Microscopy results should be derived from a minimum of three Level-1 certified microscopists. Figure of merit for LOD may be derived from diluted panels.

	<ul style="list-style-type: none"> • HRP2 ELISA • Other (non-HRP2 <i>Pf</i>-specific) antigen ELISA • qPCR^{§§§} <p>All four characterization methods should include quantitative analysis. A bank of representative sequestered samples should be developed to illustrate and validate HRP2 detection as a means of detecting sequestered parasites. For potentially sequestered samples,^{****} three sets of samples should be taken at approximately 24-hour intervals.^{†††}</p> <p>Negative samples should be taken from non-endemic regions from individuals who have no malaria risk factors.</p>
<p>4.2 Data handling</p> <p>Minimal requirement: None.</p> <p>Optimistic specification: Alternative specification is compatibility with readers for cloud-based interface, real-time data availability.</p>	<p>Some use scenarios may place a priority on data handling. Access to real-time, geo-tagged prevalence maps would be useful for surveys of regions with unknown malaria prevalence and in areas with very low prevalence where PCD could immediately identify and trigger a regional response to an outbreak.</p> <p>In this case, the optimistic specification should be interpreted as an alternate specification as it is not necessarily a preferred configuration. Rather, instrumentation for cloud-based interface and real-time data availability is a specification that certain market segments may prefer while other markets segments may not want the added complexity.</p>
<p>4.3 Shipping conditions</p> <p>Minimal requirement: Conformance to applicable requirements of ASTM D4169-05</p>	<p>Shipping validation is mandatory for medical devices that are CE marked. Shipping simulation to ASTM D4169-05 Standard Practice for Performance Testing of Shipping Containers and Systems include:</p> <ul style="list-style-type: none"> • Air transport: Long haul. • Initial manual handling: ASTM D332-1, Schedule A: Drop on each side from 15 inches—visual

§§§ Parasitemia determined by lab-validated, peer-reviewed qPCR should be developed/calibrated consistent with MIQE guidelines. Initial lab figure of merit/performance results should be established with the WHO *Pf*DNA standard.

**** Potentially sequestered samples are identified as positive by HRP2 ELISA only. To characterize the specimens, it may be more practical to treat all specimens as potentially sequestered.

††† Within the three time-point samples, an individual is considered positive for infection if all three time-points samples have a positive HRP2 ELISA signal and at least one out of the three time-point samples has a positive signal by one of the non-HRP2 characterization methods. All three samples from a positive individual are considered positive.

<p>and ISO 11607-1: 2006.</p> <p>Optimistic specification: Same.</p>	<p>inspection.</p> <ul style="list-style-type: none"> • Vehicle stacking: ASTM 642-00, Schedule C: Calculate stacking load, compress—visual inspection. • Loose load vibration: ASTM D 999-01, Schedule F: Vibrate at 40 Hz for 40 minutes, turning twice—visual inspection. • Vehicle vibration: ASTM D 4782-01, Schedule E: Vibrate at 2 Hz to 200 Hz at RMS 0.52 G for 180 minutes, turning twice—visual inspection. • Final manual handling: ASTM D 5725-98, Schedule A: Drop each side from 15 inches and the base from 30 inches x 2—visual inspection.
<p>4.4 Training requirements</p> <p>Minimal requirement: Less than one day for any level of provider. Language-appropriate training materials, results guide, and job aid should be made available via the Internet.</p> <p>Optimistic specification: One hour for HCWs familiar with RDTs and half-day for a lay person.</p>	<p>As a benchmark, the CareStart guide for training in the use of the CareStart Malaria HRP2 (Pf) (G0141) Test at the village and clinic level [46] developed by WHO/FIND recommends the following time guidelines (a total of less than four hours) for training community-level workers with no prior RDT experience:</p> <ul style="list-style-type: none"> • Introduction: 20 minutes. • How to use an RDT: 60 minutes. • How to take a finger-prick blood sample: 30 minutes. • Practical: 60 minutes. • Reading results: 45 minutes. <p>That said, training is a long-term investment. Skill competence, a sliding-scale attribute, is a high priority in order to achieve high-performance effectiveness. Thus, minimal requirements reflect a prioritization of competence over training time.</p> <p>The optimistic specification assumes improved ease of use will decrease training requirements.</p>
<p>4.5 Instrumentation requirements</p> <p>Minimal requirement: No</p>	<p>A reader may be necessary to achieve performance specifications. If a reader is required, a separate TPP should be established for the reader that includes ISO 60601 and other electro-mechanical medical device requirements.</p> <p>In this case, the optimistic specification should be interpreted as an alternate specification as it is not necessarily a preferred configuration. Rather, instrumentation for a cloud-based interface and real-</p>

<p>instrumentation desired or required unless a reader is necessary to achieve performance specifications.</p> <p>Optimistic specification: Alternative specification is compatibility with readers for cloud-based interface and real-time data availability.</p>	<p>time data availability is a specification that certain market segments may prefer while other market segments may not want the added complexity.</p>
<p>4.6 Instrument size and weight</p> <p>Minimal requirement: No instrumentation desired or required unless a reader is necessary to achieve performance specifications.</p> <p>Optimistic specification: Alternative specification is that IDT should be compatible with RDT readers for cloud-based interface and real-time data availability.</p>	<p>Benchmarks:</p> <ul style="list-style-type: none"> • The Holomic reader weighs 0.23 kg (not including smartphone) (written communication with Holomic representative, March 2014). • Fio Deki reader dimensions: 225 mm x 128 mm x 104 mm; weight: 1.15 kg (written communication with Fio representative, February 2014). <p>A reader may be necessary to achieve performance specifications. If a reader is required, a separate TPP should be established for the reader that includes ISO 60601 and other electro-mechanical medical device requirements.</p> <p>In this case, the optimistic specification should be interpreted as an alternate specification as it is not necessarily a preferred configuration. Rather, instrumentation for a cloud-based interface and real-time data availability is a specification that certain market segments may prefer while other market segments may not want the added complexity.</p>
<p>4.7 Calibration</p> <p>Minimal requirement: No instrumentation desired or required unless a reader is</p>	<p>Servicing personnel are not available for calibration or other maintenance in the regions where the product will be introduced. Therefore, no instrumentation is desired unless a reader is necessary to achieve performance specifications. If an instrument is required, calibration should be performed by the user using proxy standards provided with the instrument. In this case, a separate TPP should be established for the reader that includes ISO 60601 and other electro-mechanical medical device requirements.</p>

<p>necessary to achieve performance specifications.</p> <p>Optimistic specification: Alternative specification is compatibility with readers for cloud-based interface and real-time data availability.</p>	<p>In this case, the optimistic specification should be interpreted as an alternate specification as it is not necessarily a preferred configuration. Rather, instrumentation for a cloud-based interface and real-time data availability is a specification that certain market segments may prefer while other market segments may not want the added complexity.</p>
<p>4.8 Service and support</p> <p>Minimal requirement: No instrumentation desired or required unless a reader is necessary to achieve performance specifications.</p> <p>Optimistic specification: Alternative specification is compatibility with readers for cloud-based interface and real-time data availability.</p>	<p>Servicing personnel are typically not available for calibration or other maintenance in the regions where the product will be introduced. Therefore, no instrumentation is desired. If instrumentation is required, then the instrumentation should have self-check features that identify when an instrument requires support, and the instrument should be swapped out for a new or refurbished instrument.</p> <p>In this case, the optimistic specification should be interpreted as an alternate specification as it is not necessarily a preferred configuration. Rather, instrumentation for a cloud-based interface and real-time data availability is a specification that certain market segments may prefer while other market segments may not want the added complexity.</p>
<p>4.9 Waste disposal</p> <p>Minimal requirement: Does not include material that cannot be disposed of in the normal laboratory waste streams.</p> <p>Optimistic specification: Does not include material that cannot</p>	<p>Normal laboratory waste streams are often not available in the communities where the tests are performed so the used tests need to be transported back to the laboratory for disposal. PATH field research (unpublished data, 2013) identified that waste is often burned or buried on site by either the HCW or the home owner or is carried back to the home of the HCW and stored until it can be transported to a health facility. Therefore, it is recommended that the labelling identify that used test material should be stored safely until proper laboratory disposal is completed.</p>

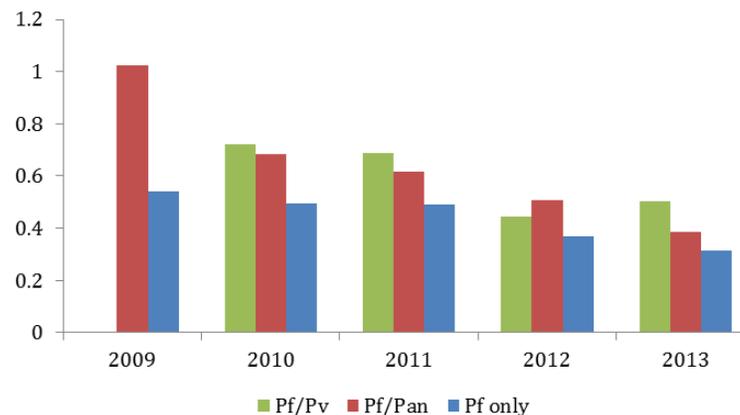
<p>be disposed of in the normal laboratory waste streams and the material is biodegradable.</p>	
<p>4.10 Precision/concordance</p> <p>Minimal requirement: Individual test lines should be 95% concordant with a validated ELISA test (for the same target antigen) that has been validated at or below the same LOD as the IDT.</p> <p>Optimistic specification: Individual test lines should be 99% concordant with a validated ELISA test (for the same target antigen) that has been validated at or below the same LOD as the IDT.</p>	<p>Concordance is more applicable than precision for the IDT.</p>
<p>4.11 Power requirements</p> <p>Minimal requirement: Self-contained kit operates independent of mains power.</p> <p>Optimistic specification: Same.</p>	<p>Mains power is not reliably available in many of the communities where the test will be used.</p>
<p>4.12 Water requirements</p>	<p>Clean water is not reliably available in many of the communities where the test will be used.</p>

<p>Minimal requirement: Self-contained kit operates independent of water.</p> <p>Optimistic specification: Same.</p>	
<p>4.13 Labelling</p> <p>Minimal requirement: Conformance with United States Food and Drug Administration (USFDA) labeling guidance [47] and recommendations from the Enhanced Malaria RDT Harmonization Procurement & Supply Chain Management Working Group (unpublished data, 2013) where appropriate.</p> <p>Optimistic specification: Same.</p>	<p>For specific details, see USFDA guidance document referenced in the requirement and RDT harmonization recommendations (see Appendix A).</p>

5. Product Costs and Channels to Market

<p>5.1 Target pricing per test</p> <p>Minimal requirement: Less than US\$2.00 (at volumes of 10 M).</p> <p>Optimistic specification: Less than US\$1.00 (at volumes of 10 M).</p>	<p>Downward pressure on RDT pricing for <i>clinical use</i> continues. For comparison, average prices for <i>Pf</i> RDTs were US\$0.37 and US\$0.32 in 2012 and 2013, respectively. For <i>Pf/pan</i> tests, weighted average prices were US\$0.51 and US\$0.38 in 2012 and 2013, respectively. As displayed in Figure 5, pricing has been decreasing dramatically, by 14% to 17% each year over the last four years (UNITAID, unpublished data, 2014).</p>
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Figure 5. Weighted average test prices (in US\$) by year for Pf only and combination RDTs.



The above cited RDT pricing for clinical use should be considered as the existing paradigm for PCD. These prices are marginally useful in determining price targets for a new class of IDT designated for active ID use in that many users will feel compelled to compare new product prices to the existing paradigm, clinical-use RDTs. That said, active ID use scenarios have very different cost drivers and (campaign-driven) procurement processes as compared to RDTs that have been scaled for clinical use. The minimum requirement of US\$2.00 is arbitrarily selected based on the paucity of data available to conduct a sensitivity analysis on the contributed cost of the test kit on the overall test-and-treat campaign cost.

The US\$1.00 optimal requirements sets a threshold whereby new IDTs may become competitive with existing RDTs for clinical and survey use—thus increasing the overall market size and further driving costs down through economy-of-scale efficiencies.

Production volumes of 10 million units are arbitrarily set as a reference to normalize quotes. Current global demand for these tests is less than 500 K per year.

Benchmarks:

- Fio Deki: Lease model with pricing based upon data type and size (written communication with Fio representative, February 2014).
- Holomic HRDR-200 reader, US\$995 (written communication with Holomic representative,

5.2 Capital cost

Minimal requirement: None, unless a reader is required to

<p>achieve performance specifications.</p> <p>Optimistic specification: Zero capital cost.</p>	<p>March 2014).</p>
<p>5.3 Target launch countries</p> <p>Minimal requirement: Kenya, Senegal, Swaziland, Zambia.</p> <p>Optimistic specification: Additional countries contemplating elimination of <i>Pf</i> and other species.</p>	<p>Currently MACEPA and University of California San Francisco are leading operational research in the use of active ID methods. Since active detect-and-treat tactics are evolving rapidly, it will be essential to validate and launch the IDT in these receptive, early adopter markets where the logistics of active ID tactics have already been worked out.</p>
<p>5.4 Product registration path</p> <p>Minimal requirement: Country-level regulatory requirements apply for target countries.</p> <p>Optimistic specification: USFDA 510(k) for class II device or other relevant stringent regulatory authority (SRA) clearance; Clinical Laboratory Improvement Amendments (CLIA) waived; WHO prequalified.</p>	<p>SRA approval is not required for commercialization of the device and could delay availability. Therefore, the minimal requirement is to meet only country-level registration requirements.</p> <p>Nonetheless, SRA registration would add a degree of credibility to the product and accelerate subsequent country adoption and WHO prequalification. Thus, the optimistic specification includes SRA clearance, CLIA waive certification, and WHO prequalification as these are all essential for global adoption of the IDT for active ID and other uses.</p> <p>There are only two tests cleared by the USFDA for malaria, an aid for staining blood specimens and the recently cleared BinaxNOW Malaria Rapid Antigen malaria RDT [48].</p> <p>Malaria RDTs are regulated by USFDA as class II medical devices [47]. In accordance with the USFDA code of federal regulations [49], the IDT can achieve 510(k) clearance by demonstrating substantial equivalence to a predicate device.</p> <p>Of note, USFDA guidance [47] suggests that product labeling identify the following when appropriate:</p> <ul style="list-style-type: none"> • “Testing should only be performed on patients with clinical symptoms of malaria.” • “This test is not intended for screening asymptomatic individuals.”

	<p>Because the intended use of the proposed IDT is different than the previously cleared BinaxNow predicate product, it will be important to gain clarity on the implications of this guidance with USFDA authorities as this may impact the regulatory pathway. The product developer should arrange a pre-investigational device exemption meeting with the USFDA early in the design process to clarify clinical evidence and labeling requirements.</p> <p>If USFDA regulatory approval is desired, the regulatory strategy should avoid design and labeling choices that force a class III, premarket approval process as this process is burdensome and incurs manufacturing requirements that would add exorbitant costs to the product.</p> <p>However, if the developer desires new indications and labeling claims beyond the predicate, the Food and Drug Modernization Act amended section 513(f) [50] provides a new mechanism for classifying new class III devices for which there is no predicate device. It allows the recipient of a not substantially equivalent letter to request a risk-based classification determination to be made for the device. In some cases, this allows a manufacturer to use the de novo process to submit a 510(k) for a new in vitro diagnostic that would otherwise require approval via the pre-market approval process.</p>
<p>5.5 Channels to market</p> <p>Minimal requirement: Campaign-driven distribution channels.</p> <p>Optimistic specification: Shares same distribution channels as clinical-use RDTs.</p>	<p>Distribution and channel-to-market details need to be worked out. Early adopter markets may not fit well with the procurement and distribution systems established for the scaled distribution of clinical-use RDTs, thus unique campaign-driven distribution channels may apply.</p> <p>The optimistic specification indicates that the IDT should follow the same distribution channels established for RDTs to benefit from the economies of scale and storage and logistics infrastructure that have been established.</p>
<p>5.6 Supply, service, and support mechanisms</p> <p>Minimal requirement: None.</p> <p>Optimistic specification: None.</p>	<p>WHO recommends that kits should not require refrigeration and should tolerate temperatures of at least 40°C and peaks of up to 50°C which may occur not only during storage but also during prolonged transport under tropical conditions [43].</p>

6. Change Management

Version	Key changes from previous version
EXAMPLE DD-MM-YYYY	UPDATE

Glossary

Active infection detection (active ID): The detection of malaria infections (clinical and subclinical) at community and household levels in population groups that are considered to be high risk.

Border testing: A proactive ID tactic aimed at preventing cross-border transmission at checkpoints. Border testing is frequently preceded by fever screening followed by testing of all patients with a recent history of malaria symptoms.

Community testing: A reactive ID tactic to identify and treat infected persons within a defined proximity to a community-based index case.

Elimination: The reduction to zero of the incidence of infection by human malaria parasites in a defined geographical area as a result of deliberate efforts. Continued measures to prevent reestablishment of transmission are required.

Eradication: A premeditated plan for global reduction to zero of all plasmodia parasites that are human pathogens.

Focused testing and treatment (FTAT): A focused testing for infection followed by treating all infected persons in a localized area such as a neighborhood or village irrespective of whether they have clinical symptoms. FTAT may be conducted broadly over non-contiguous areas on high-risk populations and hotspots.

Index case: A malaria case identified by parasitological confirmation via passive case detection.

Hotpops: Demographically clustered populations of malaria incidence. In an elimination context, hotpops are often associated with travel history and occupation.^{***}

Hotspots: Also referred to as foci, hotspots are large or small geographically clustered populations identified as having comparatively higher levels of transmission. Hotspots occur at every level of transmission and, therefore, are fractal in nature.

Limit of detection (alternatively, detection limit): The lowest quantity of an analyte that can be distinguished from the absence of that analyte (typically within a stated confidence limit, generally 1%).

Mass testing and treatment (MTAT): Mass testing for infection followed by treating all infected persons in a targeted contiguous area or population, irrespective of whether they are symptomatic. MTAT aims to reduce the size of the infectious reservoir in the targeted area.

Network testing: A reactive ID tactic to identify (and subsequently treat) all infected persons traveling with a mobile index case.

^{***} Adapted from the Malaria Elimination Group at the University of California San Francisco.

Passive case detection (PCD): The detection of malaria cases among patients who go to a health post for treatment on their own initiative, usually for febrile disease.

Proactive infection detection (proactive ID): Investigation tactics focused on populations defined by high-risk geography (hotspot) or high-risk demography (hotpop). Proactive ID may be preceded by fever screening of all patients with a recent history of malaria symptoms or by testing the target population without prior screening.

Reactive infection detection (reactive ID): The detection of malaria infections in community or occupation-based population groups in close proximity to an index case. Reactive ID involves testing (and subsequently treating) coworkers, household members, and neighbors of an index case. Reactive ID may be preceded by fever screening of all patients with a recent history of malaria symptoms or by testing the target population without prior screening.

Screening: An active ID practice used to select a subpopulation for testing based on each individual's recent history of malaria symptoms.

Time-location testing: A proactive ID tactic aimed at testing (and subsequently treating) a hotpop using prior knowledge of their occupation-specific location. This might include visits to mines, fishing docks, and forest camps, as well as mobile military units.

Transmission risk: The qualitative description of an individual's or population's ability to spread *Plasmodium*.

Use scenario: The outcome-oriented categorization of the interaction between a user, the setting, and a diagnostic tool.

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