

## Technologies for Malaria Case Management and Elimination

Malaria remains a major cause of morbidity and mortality worldwide, with an estimated 282 million cases and more than 600,000 deaths reported globally in 2024, the majority occurring in sub-Saharan Africa.<sup>1</sup> Despite substantial progress over the past two decades, sustained control and eventual elimination depend on timely, accurate, and scalable diagnosis to guide case management, surveillance, and targeted interventions. Rapid diagnostic tests (RDTs) have transformed malaria care by enabling decentralized diagnosis without microscopy. However, biological vulnerabilities, declining sensitivity at low parasite densities, and market constraints increasingly challenge the adequacy of current tools for routine care and elimination settings.<sup>1</sup>

A growing body of evidence highlights vulnerabilities in widely deployed HRP2-based RDTs. Deletions in the *pfhrp2* and *pfhrp3* genes have been documented across multiple endemic regions and can lead to false-negative results in HRP2-targeting tests.<sup>2,3</sup> These deletions undermine confidence in HRP2-based RDTs and have prompted World Health Organization (WHO) recommendations to transition to non-HRP2 biomarkers in affected settings.<sup>3</sup> Additionally, diagnostic sensitivity declines as parasitemia decreases, and species differentiation remains limited at low parasite densities, particularly for mixed infections and non-*falciparum* species.<sup>4,5</sup> These limitations are most consequential in areas approaching elimination, where low-density and asymptomatic infections contribute disproportionately to onward transmission.

Beyond biological constraints, structural and market dynamics strongly shape what malaria diagnostics can realistically achieve at scale. Malaria RDTs are procured in extremely high volumes at prices well below US\$1 per test, making affordability a binding constraint for innovation at scale.<sup>1</sup> WHO guidance emphasizes that diagnostics must maintain high sensitivity and specificity while remaining feasible in peripheral settings characterized by limited infrastructure, high ambient temperatures, and constrained supply chains.<sup>1,6</sup> As countries transition from burden reduction to elimination strategies, diagnostic tools must also support mass screen-and-treat (MSAT) campaigns, active surveillance, and rapid response to focal outbreaks, all of which place additional demands on throughput, robustness, and data integration.

Global policy makers have outlined performance requirements for malaria diagnostics across case management and surveillance contexts, including minimum sensitivity and specificity thresholds and expectations for stability and ease of use.<sup>6</sup> In practice, high-impact innovation opportunities include pan-*Plasmodium* antigen detection tests (e.g., pLDH-based assays or equivalent biomarkers) that maintain performance in the context of HRP2/3 deletions; ultra-low-cost formats capable of sustainable sub-US\$1 manufacturing; and tools that enable detection at transmission-relevant parasite densities.

Screening and diagnosis in malaria are closely linked within programmatic workflows, particularly in MSAT and elimination campaigns, where tools must deliver accurate results at high throughput with minimal operator burden. High-throughput screening approaches, including novel device-based or noninvasive sensing modalities, may offer pathways to identify asymptomatic infections where conventional RDT workflows become logistically limiting, provided they achieve sensitivity aligned with elimination thresholds and operationally meaningful time-to-result.

Crucially, all malaria diagnostic innovation is constrained by economics at scale. To remain viable within national malaria control programs, tools must achieve ultra-low per-test costs compatible with existing procurement mechanisms and supply chains. Innovations must therefore combine analytical performance with sustainable manufacturing pathways. WHO and partners have consistently emphasized that diagnostics must be affordable, simple to use, stable under field conditions, and deployable without reliance on laboratory infrastructure.<sup>1,6</sup> Cost-disruptive innovation in malaria is defined not by marginal performance gains alone, but by approaches that materially reset cost,

throughput, or sustainability while meeting real-world operational requirements. Incremental modifications to existing RDT formats that do not materially improve performance in the context of HRP2/3 deletions, low-density infections, throughput, or manufacturing sustainability are unlikely to meet the bar for impact.

Recent advances in digital health, sensing technologies, and device engineering offer opportunities to strengthen malaria diagnostic performance without substantially increasing consumable costs. AI-enabled or digitally augmented RDT platforms have demonstrated potential to reduce interpretation error, improve read accuracy, enable semi-quantitative interpretation, and enhance data capture for surveillance and program monitoring.<sup>7,8</sup> When designed appropriately, such approaches can improve reliability and workflow efficiency without increasing per-test cost. Similarly, novel sensing modalities and reusable device-based platforms may enable rapid detection of low-density infections or support high-throughput screening in asymptomatic populations, if they can meet WHO performance expectations and preserve affordability at scale.

For malaria case management and elimination, cost-disruptive innovation encompasses tools that address biological vulnerabilities such as HRP2/3 deletions; improve detection of low-density or asymptomatic infections; enhance reliability, interpretation, or workflow efficiency through digital augmentation; or materially strengthen manufacturing sustainability while maintaining ultra-low per-test costs. Success will be defined by diagnostic tools that can be deployed at population scale while maintaining WHO-aligned performance for case management and elimination, functioning reliably in real-world field conditions, and achieving ultra-low per-test costs compatible with existing national procurement mechanisms. Technologies of interest are those capable of supporting high-coverage diagnosis, screening, or surveillance at population scale without imposing unsustainable economic or operational burdens on endemic health systems.

## References

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