Project brief

PARADIGM

Lab to market support for the next generation of malaria rapid diagnostic tests

Early and accurate diagnosis of malaria is essential for case management and surveillance. In collaboration with national malaria programs, manufacturers, and global stakeholders, the PATH Partnership for Acceleration of Innovative Diagnostics for Malaria (PARADIGM) project is advancing the availability of sensitive diagnostic tests that address current and evolving needs to diagnose, control, and eliminate malaria.

A biological threat and the need for improved sensitivity

Antigen-detecting rapid diagnostic tests (RDTs) are affordable and easy-to-use for confirming infection at the point of care. However, the majority of RDTs that detect *Plasmodium falciparum* malaria—which contributes to the greatest burden of malaria mortality globally—rely on detection of the histidine-rich protein 2 (HRP2) antigen expressed by the parasite. The emergence of histidine-rich protein 2 and 3 (*hrp2/3*) gene deletions in *P. falciparum* allows parasites to effectively become invisible to RDTs. Patients infected with these parasites are not diagnosed as positive and therefore not treated. These false-negative test results cause preventable morbidity and mortality as well as ongoing malaria transmission. Parasites with *hrp2/3* gene deletions have been observed in Latin America, Africa, and Asia, and are predicted to spread.

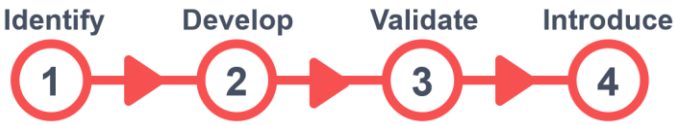
While tests exist that detect lactate-dehydrogenase (LDH), an essential enzyme expressed by all malaria species, LDH-based tests are typically less sensitive at detecting malaria compared to HRP2-based tests.

Additionally, diagnosis of other malaria species such as *P. vivax* has mostly relied on the detection of LDH resulting in the lower sensitivity of RDTs for non-*P. falciparum* infections and a higher number of false-negative test results in people infected with these species.

To address these challenges, new RDTs are emerging that fill these gaps by improving: (1) the diagnosis of *P. falciparum* infections through combined and more accurate detection of HRP2 and *P. falciparum*-specific LDH and/or (2) the diagnosis of *P. vivax* and other forms of malaria through more sensitive *P. vivax*-specific LDH or all-species (pan) LDH detection.

PARADIGM supports manufacturers' efforts to develop more reliable RDTs that will enable national programs to reach their malaria control and elimination goals. Our work supports product development throughout the product development cycle (Figure 1) including identification and assessment of novel biomarkers, research and development (R&D), clinical validation, and market introduction.

Figure 1. Lab-to-market pathway

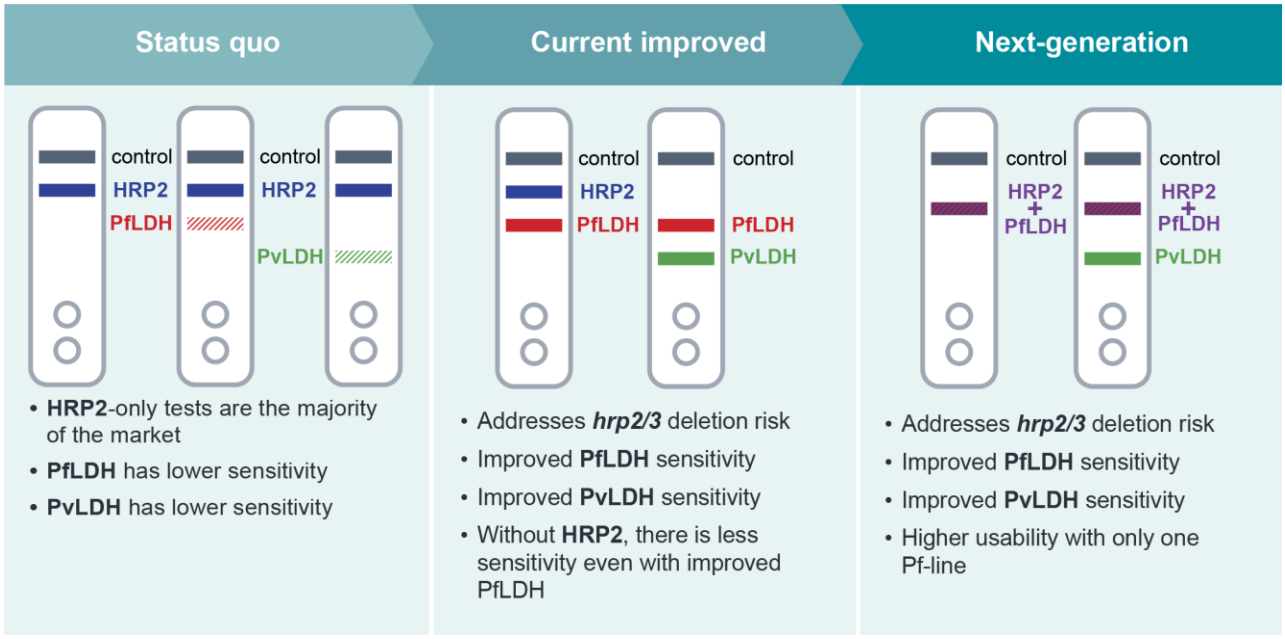


Assessment of new biomarkers

New biomarkers have the potential to transform malaria control and elimination strategies by allowing diagnostics to achieve higher sensitivity. However, investments in innovative technologies are often opportunistic and limited in scope rather than strategic.

PARADIGM is developing a framework for a realistic assessment of how biomarkers may perform and what is needed to objectively evaluate and spur further development of promising candidates. This work—which includes landscaping technologies, identifying risks and benefits of change, and estimating timelines—leverages our expertise in comparative analytical performance evaluation and work throughout the product development pathway and value chain for RDTs.

Figure 2. Schematic of status quo RDTs to next generation RDTs



Product development support

To support manufacturers with R&D for new RDTs with enhanced LDH sensitivity, PARADIGM is conducting independent benchmarking evaluations of RDTs using established panels for analytical sensitivity and performance assessments. This allows manufacturers and donors/investors to verify progress in R&D toward a fit-for-purpose competitive product. PARADIGM will also be providing manufacturers with an easily sourced core RDT performance assessment reagent panel. These panels standardize samples for sensitivity evaluation and provide access to cultured samples containing *hrp2/3* single- and double-deletions and control proteins to check selectivity in the presence of non-target *Plasmodium* species antigens.

Clinical validation

As products advance through development, evidence of clinical performance is critical for supporting regulatory dossiers and demonstrating the value proposition of new products in key use cases. To support this, PARADIGM provides technical support to manufacturers in the planning and execution of clinical studies. PARADIGM is also leading and sponsoring clinical studies in Ethiopia and Malawi to evaluate the clinical performance of pipeline products in key populations, including populations where *hrp2/3* deletions are common.

PARAGIDM is also supporting manufacturers in the clinical validation of new RDTs through lighter-touch engagement, such as retrospective evaluations on frozen specimens, technical assistance in study design and development, and access to a repository of open-access research tools.

Catalyzing adoption of new RDTs

PARADIGM is engaging national malaria programs, the WHO, researchers, implementers, companies, donors, and procurers to identify uptake challenges improved malaria RDTs will face entering health systems. The project has leveraged PATH's multicounty presence and partnerships in high-burden countries to engage national programs and listen to their opinions on the need for improved RDTs and challenges they face with *hrp2/3* deletions. PARADIGM is coordinating market shaping interventions with manufacturers, procurers, and social finance firms and sharing market intelligence with manufacturers on the demand for improved RDTs to ensure a healthy, competitive market for malaria diagnostics.

PATH

PATH is a global nonprofit dedicated to achieving health equity. With more than 40 years of experience forging multisector partnerships, and with expertise in science, economics, technology, advocacy, and dozens of other specialties, PATH develops and scales up innovative solutions to the world's most pressing health challenges.

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