AN UNMET NEED FOR CHAGAS' DISEASE DIAGNOSTICS

Chagas' disease is a kinetoplastid disease caused by the ***Trypanosoma cruzi*** parasite, predominantly spread by the blood-sucking triatomine bug. It is characterised by two distinct stages: acute and chronic Chagas' disease. Symptoms in the acute stage are often mild or absent, resulting in under-diagnosis. Left untreated, infected individuals will progress to the chronic second stage, and 20-30% will develop life-threatening complications.

In 2019, Chagas was responsible for an estimated 9,488 deaths and caused more than 275 thousand Disability-Adjusted Life Years, concentrated in tropical Latin America.[1] A significant portion of the death and disability caused by Chagas' disease could be prevented with more effective treatments and improved diagnosis and detection of infected individuals, with the latter serving as the focus of this snapshot.

Existing Chagas' diagnostics do not address the full range of clinical use cases

Existing Chagas diagnostics – mostly serological tests, but also molecular and direct parasitological tests – do not properly meet the needs of endemic regions, leaving an urgent need for the following classes of product:

TARGET 1: A test for monitoring treatment response and evaluating new treatments

There is a strong consensus from stakeholders, including the WHO NTD roadmap and the Drugs for Neglected Diseases Initiative (DND*i*),[2] on the need for a Chagas test which can be used to measure patients' response to treatment, both as an end in itself and as an input into the development of improved treatments.

The ideal product in this space should function as both an early assessment of treatment response and as a test of cure while offering increased, pan-geographic accuracy in a single application relative to the current standard-of-care serological tests, which are based on limited sets of parasite antigens. Alternatively, multiple products might be required to fill these gaps in the Chagas diagnostic landscape.

TARGET 2: A diagnostic for chronic Chagas disease

Accurate detection of Chagas' disease in its chronic phase currently requires a cumbersome confirmation process via two distinct serological tests. Experts identify the need for a point-of-care diagnostic capable of detecting chronic-phase Chagas, either as a standalone product or as a feature of the treatment evaluation diagnostic discussed above.[3]

1 Institute for Health Metrics and Evaluation, Global Burden of Disease 2019 Results Tool.

2 See, for example Porrás, et al. 'Target Product Profile (TPP) for Chagas Disease Point-of-Care Diagnosis and Assessment of Response to Treatment'. Edited by Alain Debrabant. *PLOS Neglected Tropical Diseases* 9, no. 6 (4 June 2015).

3 Including Picado, Albert, et al. 'Development of diagnostics for Chagas disease: where should we put our limited resources?' *PLoS neglected tropical diseases* 11.1 (20170.

TARGET 3: Tools for diagnosing acute, congenital, and reactivated Chagas' disease

In the absence of high quality standardised commercial kits, existing serological tests cannot reliably be used to diagnose acute asymptomatic infection outside of large urban centres. For acute neonatal infections, standard sero-diagnostic methods have low positive predictive value until 8–9 months after birth due to passive transfer of maternal antibodies.

Experts therefore identify a Chagas test capable of detecting congenital cases as a high priority, ideally as a feature of a reliable general-purpose acute-phase test.[4]

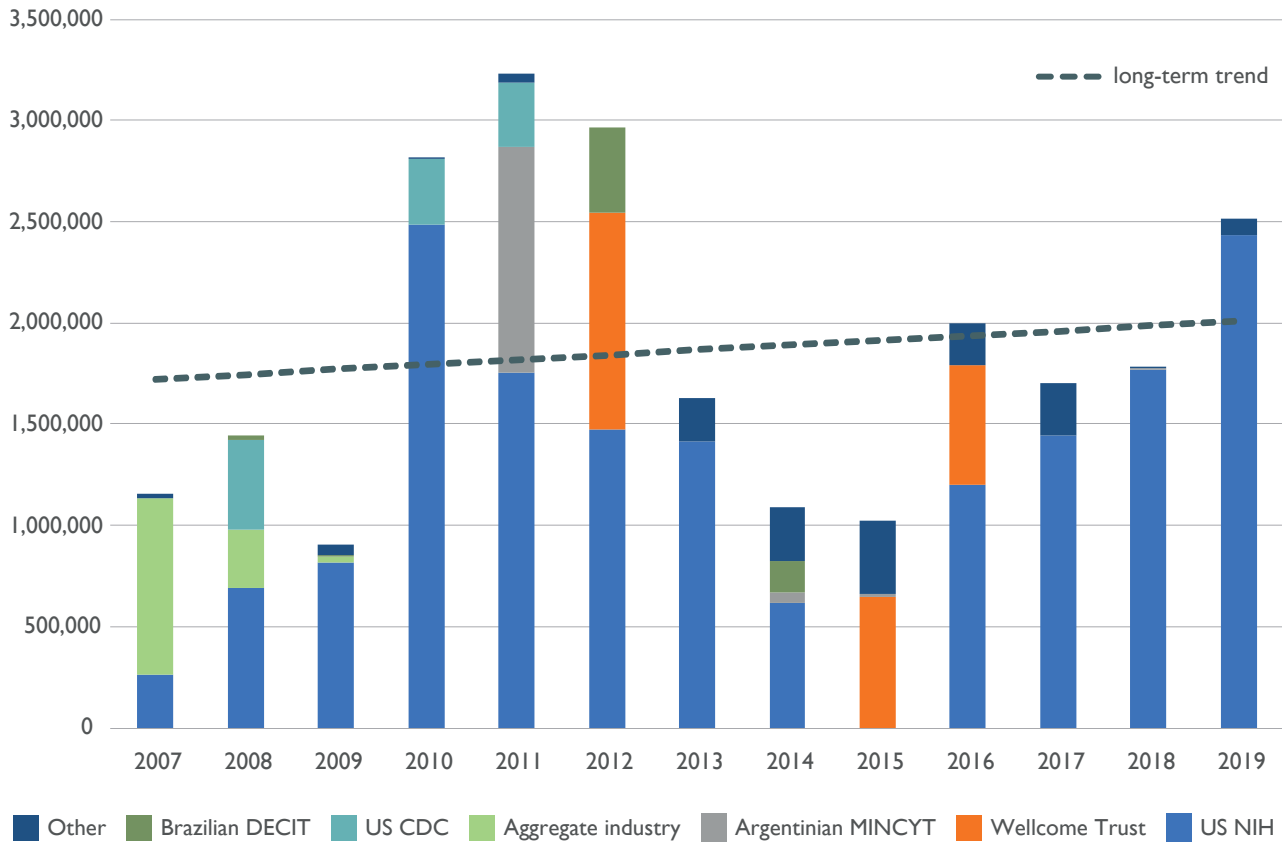
Lower-priority diagnostic needs

Alongside these consensus high-priority unmet needs, some sources identify other potential areas of need: a test for drug-resistance in Chagas, a tool for identifying patients at high risk of (or suffering from) Chagas-induced organ damage, and a test tailored to screening blood and organ donors for chronic Chagas infection.[5]

Funding trends for Chagas' disease diagnostics

Funding for Chagas' diagnostics reached $2.5m in 2019 – the most recent year for which funding data is available – following two consecutive years of growth. This left funding substantially above its long-term average of $1.9m, but still well below its 2010-2012 peak, when it averaged nearly $3m a year.

FIGURE 1 **Funders of Chagas' diagnostics R&D, 2007-2019**



4 Also covered in the publications referenced in notes 1 & 2.

5 See, especially, Picado et al., see supra note 2, in which a survey of experts ranked these as "low priority" products.

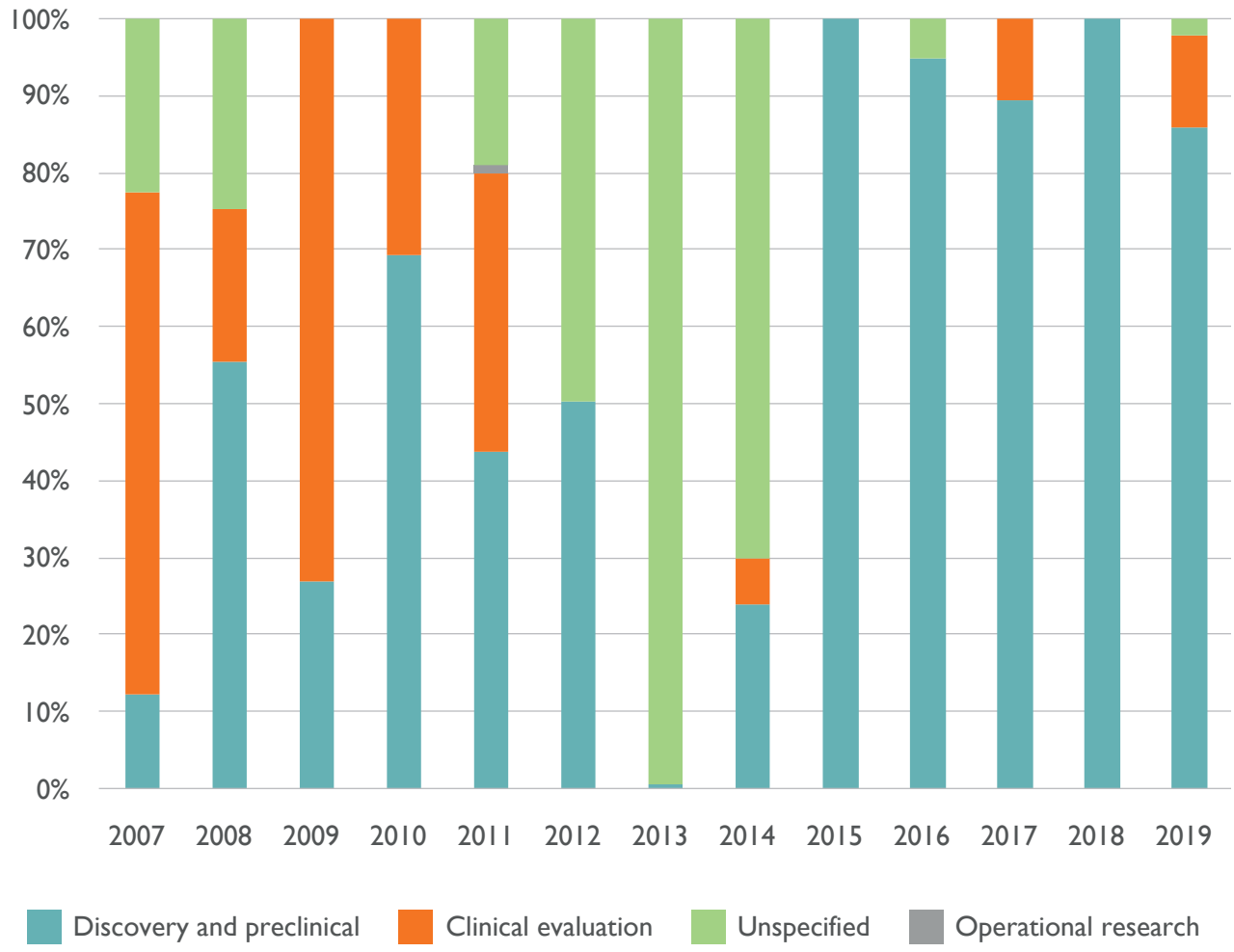
Like Chagas' disease R&D generally, funding for Chagas diagnostics has historically been dominated by the US National Institutes of Health (NIH), which has contributed more than two-thirds of all funding since 2007, and more than 95% in each of the last two years.

Much of the remaining funding was provided to the Drugs for Neglected Diseases Initiative (DND*i*) by the UK's Wellcome Trust, which provided more than three-fifths of funding in 2015 – the only year without NIH funding – but which has not disbursed any additional funding since 2016.

The third largest historical funder, the Argentinian Ministry of Science, Technology and Innovation (MINCYT), provided nearly 5% of total funding, the vast majority of which was disbursed in 2011, contributing to that year's record funding – with around a third going specifically to the development of neonatal diagnostics.[6] The US Centers for Disease Control (CDC) – which provided 4.5% of total historical funding – also appears to have ceased investing in Chagas diagnostics, with its last disbursement coming in 2011.

Together with the apparent withdrawal of the private sector from Chagas diagnostics R&D – with industry providing the vast majority of its recorded funding in 2007, and none at all since 2009 – this has left the sector almost completely dependent on the US NIH.

FIGURE 2 **Chagas' diagnostics R&D funding by stage, 2007-2019**



6 The MINCYT did not participate in the G-FINDER survey of 2019 funding, meaning that any funding it provided in that year is not captured in the figures presented here.

Historically, three-fifths of funding for Chagas diagnostics has been for discovery & preclinical research, with a further 18% going to clinical evaluation and 22% not identifying a specific R&D stage. Over the last five years the share of funding going to clinical evaluation has fallen sharply, with discovery & preclinical R&D receiving 94% of all funding and clinical evaluation just 5%.

In keeping with its dominant share of overall funding, the US NIH was the main funder of both discovery & preclinical research (66% of the total) and clinical evaluation (54%). The other top funders of preclinical & discovery broadly mirror the list of overall top funders – the Wellcome Trust, Argentina's MINCYT, Brazil's Department of Science and Technology (DECIT) and the US CDC.

The pipeline for Chagas diagnostics

The pipeline for Chagas diagnostics contains six products in various stages of development, which offer the potential for addressing the unmet needs identified above, as summarised in the table below.

R&D Target 1: Monitoring treatment response

R&D Target 2: Diagnostic for chronic disease

R&D Target 3: Diagnostics for acute, congenital, and reactivated disease

R&D Stage: Discovery and Prelinical		R&D Stage: Clinical Evaluation
Concept and research	**Design and development**	**Clinical validation and launch**
InfYnity Chagas (DNDi)	Chagas Urine Nanoparticle Test ("Chunap") (Johns Hopkins University)	Loopamp *Trypanosoma cruzi* Detection Kit (FIND, LSHTM)
	Shed Acute Phase Antigen ("SAPA") (Instituto Nacional de Parasitología de Argentina)	LAMP Chagas (CONICET)
		Stat-Pak (Chembio)

Only one pipeline product is explicitly aimed at the first R&D target – the unmet need for a tool for monitoring treatment response: DND*i*'s **InfYnity Chagas** is at the concept and research stage and aims to provide a test of cure for Chagas treatments. It was, however, recently put on hold while discrepancies between results from different platforms were being investigated, leaving a significant gap in the pipeline which is also likely to slow the development of improved Chagas treatments.

There is likewise only one product aiming to meet the second R&D target – a diagnostic for chronic Chagas disease, though its progress is much more advanced: ChemBio's **Stat-Pak** rapid diagnostic test is undergoing testing for launch readiness following a succesful 2019 trial in Colombia. Pending details of its practicality and accessibility in low-and middle-income environments, Stat-Pak may represent a significant step forward in the monitoring and management of chronic Chagas' disease.

Of the products addressing the range of unmet needs covered by the third R&D target, the **Chagas Urine Nanoparticle Test ("Chunap")**, from a group of researchers led by Johns Hopkins University, is currently being evaluated for the detection of Chagas in infants, but may also be adaptable for use with acute and reactivated cases.

The same is true of the Argentinian Instituto Nacional de Parasitología's **Shed Acute Phase Antigen ("SAPA")**, which is primarily intended as a congenital Chagas diagnostic at this stage of its development.

The **Loopamp *Trypanosoma cruzi* Detection Kit**, under development by a consortium including the Foundation for Innovative New Diagnostics (FIND) and the London School of Hygiene and Tropical Medicine (LSHTM), has the potential to address the broader set of unmet needs captured in the third R&D priority: it is currently undergoing clinical validation as a tool for detection of congenital, acute and reactivated Chagas' disease.

LAMP Chagas, backed by Argentina's National Scientific and Technical Research Council (CONICET), has also been explitly tested for use with acute and reactivated forms of the disease, as well as congentinal cases, and may ultimately be useable for chronic disease. Its development, however, has remained stalled at the clinical validation stage since 2018.

Further investment in clincial evaluation is needed

While a number of products in the Chagas diagnostic pipeline appear to offer promising solutions to the unmet needs in endemic areas, ensuring their successful launch will require funders to address the dwindling support for clinical evaluation, and renewed involvement from funders other than the US NIH.

One area of concern is that the sole candidate targeting the unmet need for a diagnostic which can monitor response to treatment and function as test of cure (DND*i*'s InfYnity Chagas), is currently stalled at the concept stage. This is a particularly important area of need because it feeds into the successful development of improved treatments. An absence of reliable tests of treatment response and cure, limits the effectiveness of ongoing trials of new regimens and repurposed drugs.

Two further areas of need – tests for acute and reactivated Chagas' disease – are currently addressed by only a single candidate, and as such remain entirely reliant on its successful clinical validation – or potentially the adaptation of tests currently intended for congenital Chagas' disease.

While the existence of some late-stage diagnostic candidates designed to address two of the three consensus unmet needs gives some cause for hope, continued funding and development is necessary to allow reliable diagnosis of all forms of Chagas' disease, and to assist in the development of effective treatments.