Access Plan for Benznidazole in the United States: Expanding Access to Treatment for Chagas Disease

ACCESS PLAN FOR BENZNIDAZOLE IN THE UNITED STATES: EXPANDING ACCESS TO TREATMENT FOR CHAGAS DISEASE

KOTA YOSHIOKA

A DELTA Doctoral Thesis Submitted to the Faculty of

The Harvard T.H. Chan School of Public Health

in Partial Fulfillment of the Requirements

for the Degree of *Doctor of Public Health*

Harvard University

Boston, Massachusetts.

May, 2019

Dissertation Advisor: Dr. Michael R. Reich Kota Yoshioka

ACCESS PLAN FOR BENZNIDAZOLE IN THE UNITED STATES: EXPANDING ACCESS TO TREATMENT FOR CHAGAS DISEASE

Abstract

Approximately 300,000 persons are infected with the causal agent of Chagas disease (CD) in the United States (US) but less than 1% of them are estimated to have been treated. In 2017, the US Food and Drug Administration approved benznidazole, a medicine for CD treatment, and Exeltis USA began supplying it commercially in May 2018. Despite this FDA approval, access to CD treatment remains limited to date. This Access Plan was developed as a Doctor of Public Health DELTA project to provide a strategic guide to expand access to benznidazole in the US. The project applies the access framework found in the public health literature to understand barriers, facilitators, and key actors that shape CD patients' ability to obtain and use benznidazole. In addition, key barriers to CD diagnosis are also examined.

The Access Plan identifies seven key barriers to benznidazole: 1) no formal structure to facilitate collaboration between key actors, 2) physician's failure to use specific paper forms to order benznidazole, 3) lack of emergency benznidazole delivery, 4) uncertain financial sustainability of Exeltis' drug subsidy program, 5) limited number of treaters offering CD treatment, 6) obstacles for patients seeking medical appointments, and 7) inadequate evaluation of patient eligibility for treatment. The project also found five key barriers to diagnosis: 1) limited screening opportunities at the primary care level, 2) limited access to physicians for seropositive blood donors, 3) limited physician knowledge about diagnostic procedures, 4) uncertain affordability of testing, and 5) unknown reliability of the currently used diagnostics.

To overcome these barriers, the Access Plan proposes eight areas of strategic actions in which Exeltis and Fundación Mundo Sano could take actions in collaboration with other actors. These areas are intended to: 1) establish emergency benznidazole delivery, 2) ensure financial sustainability of the drug subsidy program, 3) organize and educate treaters, 4) promote patient networking, 5) implement pilot screening projects, 6) educate providers about diagnostic testing, 7) promote development of guidelines for screening, diagnosis and treatment, and 8) facilitate multi-sectorial coordination. Taking the actions proposed in this Access Plan will contribute to expanding access to CD treatment in the US.

Table of Contents

List of Figures

List of Tables

Acknowledgements

The opportunity for this DELTA Project was created and supported by Fundación Mundo Sano and Exeltis USA. I, as the author, deeply thanks Silvia Gold, Marcelo Abril, Sebastián Cañon, Salustiano Pérez, Kenneth Abreu and Martin Manfredi for their generosity, engagement, dedication, and curiosity in this DELTA Project.

I extend acknowledgements to those who are devotedly working for Chagas disease in the United States. Their sense of responsibility to fight against social inequity, as embodied in Chagas diseases, impressed me. They provided variable information and insights to this project.

I would also like to express my appreciation to my thesis committee: Michael Reich, James Maguire, and Jennifer Manne-Goehler, who taught, guided and encouraged me. Their vision, professionalism, intelligence, and patience were all critical to accomplishing this DELTA Project.

Special thanks to my family. We shared every good and difficult time living in Boston. Without their existence, I could not have completed my life as a graduate student.

Finally, I hope that this document serves to improve the well-being of the people who live with the risk of Chagas disease in the United States.

ACCESS PLAN FOR BENZNIDAZOLE IN THE UNITED STATES: EXPANDING ACCESS TO TREATMENT FOR CHAGAS DISEASE

1. Introduction

The United States (US) has about 300,000 persons infected with *Trypanosoma cruzi*, the etiologic agent of Chagas disease (CD), primarily due to migration from Latin American countries (Bern & Montgomery, 2009; Manne-Goehler, Umeh, Montgomery, & Wirtz, 2016). Epidemiological data are limited, but for example, one study found that 1.24% of non-random Latin American-born residents of Los Angeles County were infected with *T. cruzi* (Meymandi et al., 2017). At the national level, less than 1% of those who are estimated to be infected have been identified (Manne-Goehler, Reich, & Wirtz, 2015), implying that access to treatment is extremely limited. In addition, access to health care in the US is generally difficult for people without health insurance and for undocumented immigrants. CD-related annual health-care costs are estimated to be $118 million in the US, which is second only to Brazil and nearly 20% of the global estimates (Lee, Bacon, Bottazzi, & Hotez, 2013). CD is an important public health burden for the US society and antiparasitic treatment in the early stage of disease progression can avert the high public health burden.

Two antitrypanosomal agents, benznidazole and nifurtimox, offer benefits for some CD patients (Bern, 2015). Historically, both drugs have experienced global supply chain problems, such as suspended production, drug shortages and lack of approvals from health authorities such as the US Food and Drug Administration (FDA) (Alpern, Lopez-Velez, & Stauffer, 2017). In the US until recently, both drugs were only available through the Centers for Disease Control and Prevention (CDC) for compassionate use (i.e., use of drugs that are being tested but have not been approved by the FDA, and provision is tightly restricted to people who meet certain conditions). From October 2011 to May 2018, CDC released benznidazole to treat 365 patients (providing the drug at no cost to patients) (Herwaldt et al., 2018). Physicians have reported that the CDC's investigational protocol was

time-consuming because it required them to work with CDC to assess each patient's individual eligibility for treatment (Manne-Goehler et al., 2015).

On August 29, 2017, the FDA approved benznidazole for use in children ages 2 to 12 years old with a 7-year market exclusivity expiring on August 29, 2024 (U.S. Food and Drug Administration, n.d.). The FDA granted a neglected tropical disease priority review voucher (PRV) to the drug manufacturer, Chemo Research, now renamed Insud Pharma. According to the manufacturer and its collaborators, a substantial part of the financial benefits from the sale of the PRV is to be directed towards enhancing access to CD treatment and improving patient health in other disease areas (DNDi, 2017).

The FDA approval changed the supply chain of benznidazole in the US substantially. On May 14, 2018, CDC stopped its compassionate use program for benznidazole and Exeltis USA began to sell Insud Pharma's Benznidazole Tablets® (100 mg and 12.5 mg). Exeltis is a private company based in New Jersey with experience in selling branded medicines in the areas of women's health and dermatology. The new commercial availability of benznidazole allows a physician to obtain the medicine based on his or her own criteria and judgment. Despite the FDA's approved indication for pediatric use, a physician can use benznidazole for patients older than 12 years old, a medically common practice called "off-label" use. Exeltis offers free or low-cost drug supply options to uninsured or underinsured patients.

The FDA approval made obtaining benznidazole less complex for physicians and is expected to increase the use of benznidazole in the US. The average number of benznidazole prescriptions per month increased from 4.6 to 13.1 after its commercialization in May 2018 (Figure 1). This increase is still small compared to the large number of estimated people infected with *T. cruzi* living in the US, although not every infected person needs benznidazole treatment. Even after the drug's approval, it is likely that several health system barriers from the pre-license period (Manne-Goehler et al., 2015) remain unchanged, contributing to limited access to CD diagnosis and treatment.

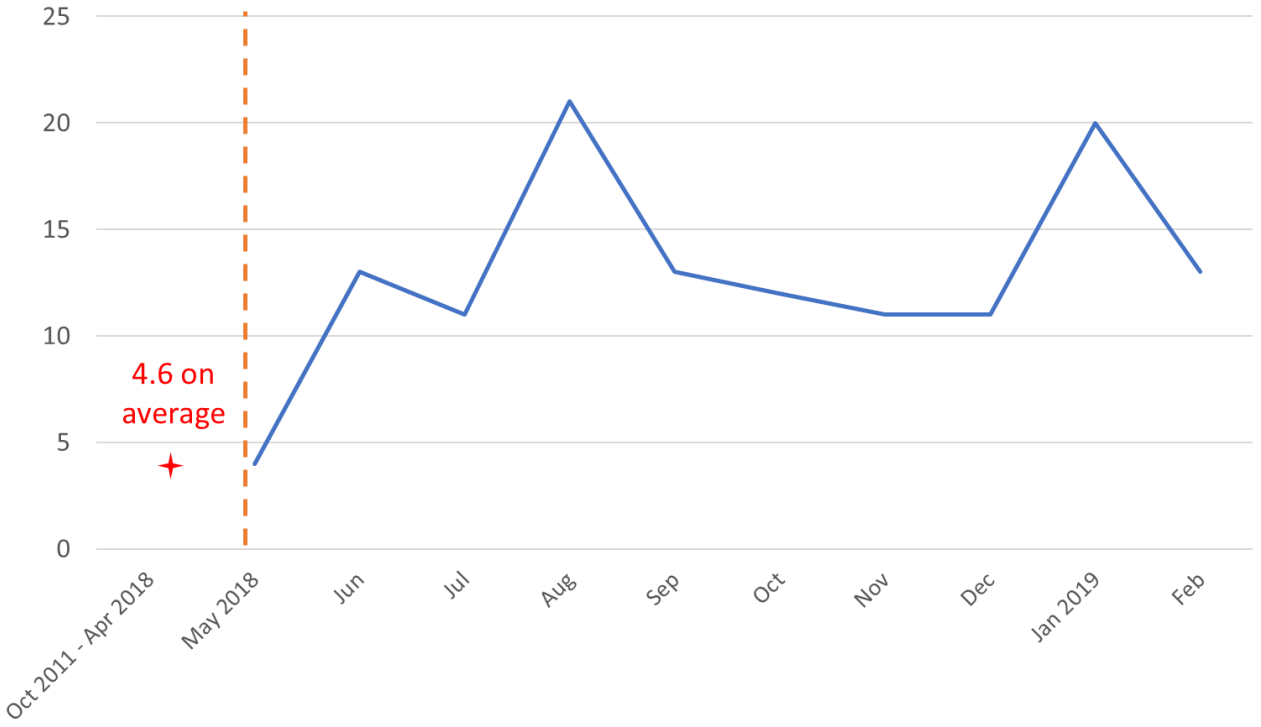

Figure 1: Number of benznidazole prescriptions before and after its commercialization in May 2018.

Source: Herwaldt, Dougherty, et al., 2018 & Exeltis USA

In this context, Fundación Mundo Sano (FMS) agreed to support the development of this Access Plan, a written document which recommends strategic actions to expand access to benznidazole in the US, as the DELTA project of a Doctor of Public Health candidate. FMS is an Argentina-based non-profit private foundation, which seeks to improve the well-being of populations affected by neglected diseases globally, through the development of effective management models for prevention, diagnosis, and treatment. Both Exeltis and FMS operate under the organizational umbrella of Insud Pharma.

This Access Plan has been prepared from a public health perspective to serve as an operational and strategic guide for Exeltis and FMS with the purpose of expanding access to benznidazole in the US. Exeltis and FMS are the intended main actors who can consider the actions proposed in this document. In addition, this Access Plan also suggests actions that Exeltis and FMS

can take in coordination with other key US actors.

This Access Plan has been developed using the best available information at the time of writing. It draws on various sources of information, including: 1) the published literature, 2) interviews and e-mail exchanges with key informants, including health service providers, researchers and government officers, 3) the "Rethinking Chagas" workshop held at the Harvard T.H. Chan School of Public Health on October 22, 2018, and 4) discussion with and data provided by Exeltis USA and FMS. This Access Plan should be considered a flexible and dynamic tool that can be regularly revised and reshaped in the future, as new circumstances arise and as the broader context for CD in the US evolves (Frost & Reich, 2008). The Access Plan is meant to systematically prioritize and propose next steps that would expand access to benznidazole in the US.

This document is organized as follows: Chapter 1 introduces the Access Plan. Chapter 2 provides a conceptual framework adapted from the public health literature (Frost & Reich, 2008) to structure both a discussion and recommendations on increasing access to benznidazole. Using this conceptual framework, Chapter 3 analyzes key barriers, facilitators and actors involved in processes to create access to benznidazole and summarizes actions to consider. Chapter 4 briefly discusses current challenges to access to CD diagnosis in the US. Taken together, Chapter 5 proposes eight areas for strategic actions to address the key barriers identified in this document.

2. Access framework for benznidazole

This Access Plan applies the access framework, adapted from Frost and Reich (2008), to plan activities for expanding access to benznidazole in the United States (Figure 2). According to Frost and Reich (2008), "a deeper understanding of the facilitators, barriers and key actors […] is necessary for better access planning" (p. 18) and the access framework can be used as a prescriptive tool to "propose key activities […] and develop strategies for guiding the [health] technology to the end-user" (p. 34).

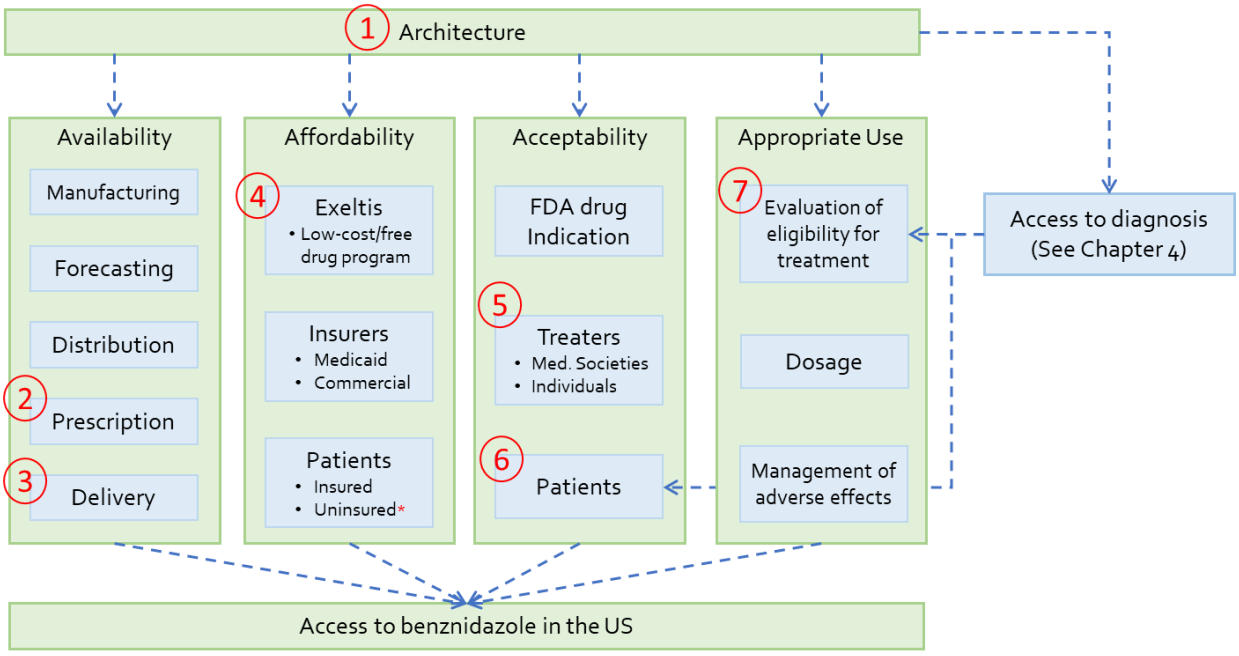

Figure 2: Access Framework for benznidazole in the United States.

Note: The numbers in circles indicate where this Access Plan identifies key access barriers for treatment. The numbers correspond to the numbers assigned to the key barriers described in Chapter 3 (e.g., Barrier T1) and do not imply any order of priority.

Frost and Reich (2008) defines access as "an end-user's ability to consistently obtain and appropriately use good quality health technologies when they are needed" (p. 219). Barriers are "factors that limit the abilities of end-users" (p. 220) and facilitators are "factors that promote the ability of end-users" (p. 223) to successfully obtain and appropriately use a health technology. This Access Plan adopts their definitions, and thus, access to benznidazole refers to CD patients' ability to obtain and appropriately use benznidazole when they require antiparasitic treatment. In Chapter 2 and 3 where this access framework is applied, CD patients refer to those who have already been diagnosed and are looking for treatment.

According to Frost and Reich (2008), there are five relevant activity streams[1] that shape

[1] The original access framework describes four activity streams and "appropriate use" is considered as a

access to health technologies. This Access Plan adapted them for the case of benznidazole in the US. The five activity streams are defined as follows:

Architecture

Organizational structures and relationships established with the purpose of coordinating and steering the various activities necessary to ensure access to benznidazole. Creating access requires Exeltis and FMS to work with other key actors, establishing a division of labor and roles, channels of communication, decision-making, accountability, and monitoring and evaluation.

Availability

The degree to which benznidazole reaches CD patients through the process of making, ordering, storing, prescribing and delivering treatment. Access requires well-structured logistics to move benznidazole from its manufacture in Spain to CD patients living in the US.

Affordability

The degree to which the cost of benznidazole and related services influences the ability of CD patients to receive treatment. For ensuring access, the cost of drug and related services are shared among Exeltis/FMS, public and commercial insurers, and CD patients.

Acceptability

The degree to which benznidazole is accepted and demanded across multiple levels of the health system. In addition to FDA approval, access to benznidazole requires demand from treating

subcomponent of "acceptability (adoption)" stream. The original framework recognizes that end-users' behavior can affect benefits of health technologies. For benznidazole, however, appropriate use is not determined only by end-user's behavior, but also by physician decisions. Thus, this access plan separates "appropriate use" from "acceptability." Given frequent and severe adverse effects of benznidazole, appropriate use should be emphasized in this Access Plan.

physicians and CD patients.

Appropriate use

The degree to which benznidazole is effectively and safely used, in the manner intended to produce health benefits. Successful access to benznidazole requires appropriate initial evaluation of patients to establish eligibility for treatment, adequate dosing and duration, and management of adverse effects.

In addition, access to benznidazole requires access to CD diagnosis, whose process, barriers and facilitators will be examined separately in Chapter 4.

3. Access to benznidazole

This chapter will summarize the current situation of barriers and facilitators that affect access to benznidazole, as well as recent activities by Exeltis. The chapter focuses on CD patients who have already been diagnosed and are looking for treatment. For access to diagnosis, see Chapter 4.

3-1. Architecture

Architecture refers to the network of organizations that steer and connect activities to expand access to benznidazole. Frost and Reich (2008) suggest that key actors need to be organized into effective relationships and partnerships, which can require establishing a clear governance structure among partners, transparency in decision-making, and program accountability.

3-1-1. Summary of current actors and their relationships

Below is the list of key actors that are currently shaping access to benznidazole in the US.

List of key actors

Pharmaceutical industry

- Exeltis USA: A private company in NJ, responsible for commercializing benznidazole in the US. Exeltis is owned by Insud Pharma, a pharmaceutical company group based in Argentina and Spain.
- Foundation Care: A specialty pharmacy based in St. Louis, MO, which is contracted by Exeltis USA to provide warehousing services, manage physicians' orders for benznidazole and ship benznidazole to users.

Government agencies

- FDA: Currently reviewing the application to expand the indication for benznidazole.
- CDC: Confirmatory CD diagnosis is available only at CDC. It stopped releasing benznidazole in a compassionate use program in May 2018, when the drug became commercially available.

Non-governmental organizations

- Fundación Mundo Sano (FMS): A non-profit organization seeking to expand access to CD treatment globally. FMS was created and is funded by Insud Pharma to pursue the company's social responsibility. FMS supports Exeltis' benznidazole initiative in the US.
    - DND*i*: A non-profit research and development organization that is developing new treatments for neglected diseases. In relation to CD treatment in the US, DND*i* is focused on research, mainly in collaboration with CECD (see next bullet).

Specialized treatment centers[2]

- Center of Excellence for Chagas Disease (CECD): The first treatment center in the US specialized for Chagas disease, based at Olive View-UCLA Medical Center, Los Angeles, CA. CECD is also active in research and currently trying to organize a local patient network.
- Latin American Society of Chagas (LASOCHA): Established to provide follow-up care to the patients who were identified through the Johns Hopkins seroprevalence study. LASOCHA aims to provide access to free treatment in the metropolitan Washington, DC, area and to raise awareness of Chagas disease within the at-risk population and the medical community.
- Boston Medical Center (BMC): Two physicians are actively treating CD patients referred from the East Boston Neighborhood Health Center (EBNHC), where adults and pregnant women are screened in primary care settings. BMC and EBNHC started to address CD as part of the East Boston Strong Heart Project, initially funded by FMS.

Academic institutions (only those who have or will have agreements with FMS are listed)

- Dr. Caryn Bern at the University of California San Francisco (UCSF) has been contracted by FMA as a consultant and is one of the key opinion leaders in the scientific community for Chagas disease.
- Harvard T.H. Chan School of Public Health was funded by FMS to organize the "Rethinking Chagas" workshop held on October 22, 2018 and received support from FMS for the development of this Access Plan by a DrPH candidate.
- Dr. Paula Stigler Granados at Texas State University is proposing a study aiming to screen about 40,000 mothers and create a physician network in Texas. The idea of this study emerged during the "Rethinking Chagas" workshop.

[2] 22.5% of CD treatment with benznidazole occurred at these three centers (Exeltis data, as of February 28, 2019).

Multi-actor networks

- Chagas Consortium: An informal group of about 20 researchers and clinicians in the US committed to improving the availability of diagnosis and treatment. The group has contacted Ortho Diagnostics, one of the diagnostic test makers for CD, to propose resuming the production of CD diagnostics.
- Texas Chagas Task Force: Created in 2015 with CDC funding, this group consists of researchers, public health agencies, entomologists, veterinarians, and health care providers in Texas. It aims to raise awareness of CD and improve screening and treatment (Forsyth, Stigler Granados, Pacheco, Betancourt, & Meymandi, 2019). Online quarterly meetings are coordinated by Dr. Paula Stigler Granados.

The actors listed above potentially share the same goal of expanding access to appropriate CD treatment in the US. Currently, two networks, namely, the Chagas Consortium and the Texas Chagas Task Force, are facilitating informational exchanges among their members. However, there is no structured form of collaboration at the national level with explicit participation from government agencies or companies **[Barrier T1]**. The need to strengthen coordination among the US actors has been recognized in various occasions, including the "Rethinking Chagas" workshop.

In October 2018, a new organizational structure, called the "US Chagas Alliance[3]," was proposed during the "Rethinking Chagas" workshop. This proposal, however, may be difficult to achieve due to its financial requirements. Instead of creating a new organization, this Access Plan recommends expanding the existing Chagas Consortium as a national-level platform for regular information exchanges among key actors, including the CDC and Exeltis, and potentially, blood

[3] The proposed US Chagas Alliance may have a broader scope than access to CD treatment. It potentially can cover other topics such as domestic vector-borne transmission, blood safety, development of new diagnostics and drugs, and other issues.

banks, commercial laboratories and manufacturers of diagnostics.

3-1-2. Proposed actions in Architecture

- There is no structured form of coordination among different actors at the national level in which private companies can participate actively. This Access Plan recommends expanding the existing Chagas Consortium so that this informal network can coordinate interests not only for researchers and clinicians but also for government agencies and companies.
- The Access Plan also recommends that Exeltis improve its relationships with other actors. In the US, government officials, clinicians and researchers may feel uncomfortable to work directly with a pharmaceutical company. Exeltis needs to build trust and work closely with the CDC, physicians and researchers, and potentially with blood banks and other companies, to implement activities recommended in this Access Plan. Exeltis should try to promote more effective relationships among key actors in the public, private and academic sectors.

3-2. Availability

Availability refers to the degree to which benznidazole reaches CD patients. Benznidazole needs to be manufactured with adequate demand forecasting, distributed from the manufacturer to pharmacies, ordered by physicians using a specific form, and delivered to patients.

3-2-1. Barriers, facilitators, actors and recent activities

Benznidazole for the US market is manufactured by Insud Pharma's plants in Spain. *Quimica Sintetica* produces active pharmaceutical ingredients for *Liconsa CMO* which fabricates Benznidazole Tablets®. From Spain, benznidazole is exported to Foundation Care in St. Louis, MO. This model of production and distribution facilitates the consistent and timely supply of

benznidazole to the US market. Drug shortage is not a problem.[4]

For demand forecasting, Exeltis roughly estimated 200 patients per year. Exeltis has imported 2,000 bottles of benznidazole (1,600 bottles of 100 mg tablets and 400 of 12.5 mg), which are approximately equivalent to treating 1,000 patients. As of February 2019, the average number of benznidazole prescriptions was 13.1 per month, suggesting that the annual number of prescriptions would not reach 200. Compared to the actual demand level, Exeltis is experiencing oversupply, which will yield surplus stock and potential expiration of benznidazole. However, this is not an access barrier since the surplus stock will not affect directly the ability of patients to obtain drugs.

Prescription of benznidazole requires physicians to submit a two-page order form available on the Exeltis website.[5] Compared to the CDC's protocol, Exeltis' form is much shorter.[6] However, some physicians try to prescribe benznidazole without using the Exeltis form and fail to provide drugs to patients,[7] as exemplified by the case in Box 1. There is no information available on how many benznidazole prescriptions are currently rejected at pharmacies, but the failure to use the form could be one barrier in obtaining benznidazole **[Barrier T2]**.

For emergency situations such as acute transplant-transmitted infections or reactivation disease in the setting of HIV, benznidazole or nifurtimox needs to be delivered to the patient as soon as possible. Emergency situations do not occur frequently (probably less than 10 cases annually) but the lack of readily available benznidazole on an emergency basis could result in life-threatening events for patients **[Barrier T3]**. Exeltis is trying to find a solution; Foundation Care identified a company that can offer a same-day drug delivery service and is currently

[4] Interview, Exeltis USA, Aug/1/2018
[5] Exeltis USA website; https://www.benznidazoletablets.com/assets/pdf/Fast_Access_Forms.pdf
[6] Interview, BMC, Aug/16/2018
[7] Paramedics who help ordering benznidazole at CECD and BMC confirmed that the use of Exeltis form is necessary to obtain drug.

assessing its costs.[8]

In summary, the system to supply and deliver benznidazole in the US seems to be largely reliable, but only when health service providers use the right order form. There is no formally established mechanism to deliver benznidazole for emergency use.

3-2-2. Proposed actions in Availability

- Prescribing physicians must use the order form which is only available on the Exeltis' benznidazole website to obtain the drugs. More visibility of the Exeltis website and physician awareness of the form is necessary.
- An emergency benznidazole delivery system is required for patients who need it immediately. Exeltis is responsible for developing a mechanism for the same-day delivery of benznidazole.

3-3. Affordability

Affordability refers to the degree to which CD patients can pay for benznidazole and related services. In the US, the main payers involve Exeltis, public and commercial insurers and CD patients. Appropriate cost-sharing is necessary for patients to get affordable CD treatment.

3-3-1. Barriers, facilitators, actors and recent activities

As of March 2019, the price of benznidazole is US$ 300 for a bottle of 100 mg tablets and US$ 250 for 12.5 mg (100 tablets per bottle). The doses needed for treatment depend on patient body weight, but Exeltis estimates that the drug cost per prescription would be US$ 600 on average.

To assure benznidazole affordability to CD patients, Exeltis launched a drug subsidy program called FastAccess. This program limits patients' co-payments up to US$ 60 when their

[8] E-mail, Foundation Care, Mar/01/2019

health insurance covers benznidazole and provides free drugs when patients have no insurance, or their insurance does not cover benznidazole.[9] As of the second week in March 2019, the total amount paid for benznidazole has been shared among FastAccess (43%), commercial insurance companies (34%), government insurance programs (14%), and patients (8%). The FastAccess program and expanded insurance coverage for benznidazole have been key facilitators in Affordability.

The FastAccess program is financed by FMS, using benefits from the Priority Review Voucher granted with the FDA approval of benznidazole. The FastAccess budget is not unlimited but FMS and Exeltis have not calculated the program's financial sustainability. In the future, the program's discontinuation could be a critical barrier for Affordability**,** which will need to be addressed **[Barrier T4]**.

Financial reliance on the FastAccess program can be decreased by increasing insurance coverage of benznidazole. Major public and private insurers now cover benznidazole (Table 1), but Exeltis needs to advance negotiations with other insurers that have not yet decided to cover benznidazole. Medicaid decisions about coverage are on a state by state basis.

[9] The subsidy is not applied to patients covered by Medicaid/Medicare because of the anti-kickback law.

Table 1: List of public and private insurers that cover benznidazole, as of January 18, 2019.

Type	Insurer	Population covered
Medicaid	CA Medicaid	1,900,000
	NY Medicaid	687,000
	FL Medicaid	133,000
	TX Medicaid	111,000
	VA Medicaid	2,300,000
	MA Medicaid	6,000,000
Commercial	Express Scripts (PBM)	85,000,000
	CVS Caremark (PBM)	79,000,000
	Prime/BCBS (PBM)	23,000,000
	OptumRx (PBM)	8,000,000
	United Healthcare	21,200,000
	BCBS MI	2,600,000
	Horizon	1,800,000
	CareSource	2,000,000
	Highmark	1,800,000
	Magellan Health (PBM)	150,000
	EnvisionRx (PBM)	671,000
	MedImpact (PBM)	1,000,000
	Kaiser Permanente	4,000,000
	Prescription Solutions	300,000
	AARP	6,000,000

Note: This list was created by the former Executive Director at Exeltis USA but may not include all insurers. Source: Exeltis USA.

Costs of medical services can also be problematic particularly for uninsured patients. Table 2 provides a rough estimate of the costs of services related to CD diagnosis and treatment. Uninsured patients could be required to pay for all these services out of their own money, which can be prohibitive for many patients. In addition, uninsured patients may decide not to seek CD treatment if they perceive the risk of hospitalization due to adverse effects as being unaffordable (Manne-Goehler et al., 2015). The issue of unaffordable health care stems from the nature of the US health system, and this Access Plan does not address those broader problems. Solutions may be locally found: some private insurers offer affordable plans for people living with low income (see Box 1), and some grassroots organizations also provide financial support for underserved populations (Appendix 1).

Table 2: Rough estimation of diagnosis and treatment costs per patient with chronic CD.

Services	Cost	Source
PCP visit for screening	$166	MEPS
Serological tests	$60	(Stillwaggon, Perez-Zetune, Bialek, & Montgomery, 2018)
Confirmatory testing at CDC	$0	(Edwards, Stimpert, & Montgomery, 2017; Manne-Goehler et al., 2015)
MD visit for baseline medical check	$166	MEPS
Cardiologist examination (not always needed)	$303	MEPS
Electrocardiogram	$220	(Stillwaggon et al., 2018)
Monitoring every 15 days (4 ID visits)	$1,240	MEPS
Total	$2,155	

PCP: primary care physician, ID: infectious disease physician, MEPS: Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality, U.S. Department of Health & Human Services (https://meps.ahrq.gov/data_files/publications/st484/stat484.shtml).
Note: The table does not include costs for general lab tests, nursing, and costs related to manage adverse effects (prescriptions or hospitalization). The estimates in this table may not represent many situations, since costs of health services in the US widely vary depending on states, hospitals, health insurance, and other factors.

In summary, the Exeltis' FastAccess program is a key facilitator for benznidazole affordability, but the program's financial sustainability is not clearly established. The costs of medical services, including physician visits, can be prohibitive particularly for uninsured patients, but this Access Plan does not address the problems due to the broader US health system.

3-3-2. Proposed actions in Affordability

- Exeltis and FMS need to calculate the financial resources required by the FastAccess program to sustain this program as long as possible.
- Exeltis should continue to seek to decrease the financial reliance of CD patients on the FastAccess program by expanding insurance coverage for benznidazole, including more state Medicaid programs and more private insurance companies.

3-4. Acceptability

Acceptability involves creating demand for benznidazole from government actors, providers and patients (Frost & Reich, 2008). In the US, acceptability of benznidazole is shaped by the FDA's approved indications, endorsement of treatment guidelines by medical societies, knowledge of treating physicians, and patients' understanding of CD and benznidazole. In addition, patients may need logistical or emotional support to seek care within the complex US health system.

3-4-1. Barriers, facilitators, actors and recent activities

Implications of FDA approval

In August 2017, the FDA approved benznidazole for use in children ages 2 to 12 years old (U.S. Food and Drug Administration, 2017). Although the approval is a key access facilitator, the indication for pediatric patients has two important implications.

First, the narrow indication may limit physician demand, because uncertainty around treating adult patients remains. As Table 3 shows, most patients who have been treated in the US are over 12 years old. Although the CDC recommends treatment for adults up to 50 years old with chronic infection who do not already have advanced Chagas cardiomyopathy (CDC-Centers for Disease Control and Prevention, 2018) and some experts support treatment of adult chronic indeterminate cases in the US (for example, see Meymandi, Hernandez, Park, Sanchez, & Forsyth, 2018), robust scientific evidence is still lacking to demonstrate health benefits from treatment with antiparasitic drugs in adult patients. Just recently, the phase II clinical trial in Bolivia (called BENDITA) found that 2-week treatment with benznidazole showed efficacy for adult patients with chronic CD (DNDi, 2019), however this finding needs to be confirmed by a larger study. Decisions whether to treat adult patients should be individualized and physicians may avoid making difficult decisions without a clear message from the FDA or from definitive scientific studies. As of March 2019, Exeltis continues to pursue additional indications at the FDA and they

may be approved by the end of 2019.[10]

Second, the narrow indication limits the ability of Exeltis to increase physician demand because Exeltis cannot promote "off-label" use of benznidazole. In contrast to the limitations for Exeltis, medical communities can discuss "off-label" use to educate health service providers. Collaboration with clinical educators would be critically important for Exeltis to increase physician acceptability of benznidazole. Exeltis has little business experience in the field of parasitic diseases and needs to develop relationships with key clinical educators.

Table 3: Distribution of patients treated with benznidazole by age group, before and after commercialization of benznidazole in May 2018.

	Oct 2011-May 2018 (CDC)		May 2018-Feb 2019 (Exeltis)	
Age group (yrs)	**No**	**%**	**No**	**%**
<2	1	0.3	0	0.0
2–12	2	0.5	5	3.9
13–18	29	7.9	2	1.6
19–50	236	64.7	80	62.0
>50	97	26.6	42	32.6
Total	**365**	**100**	**129**	**100**

Source: Herwaldt, Dougherty, et al., 2018, Exeltis USA

Physician acceptance of benznidazole

Since its launch in May 2018, benznidazole has been requested by a limited number of physicians in the US. As of December 2018, 11 physicians treated two or more patients and 59 physicians treated one patient. The number of knowledgeable physicians who can treat CD patients is limited (Forsyth et al., 2019) **[Barrier T5]**. Poor physician awareness and knowledge about CD are repeatedly emphasized in the US (Amstutz-Szalay, 2017; Edwards, Abanyie, & Montgomery,

[10] E-mail, Exeltis, Mar/05/2019.

2018; Manne-Goehler et al., 2015; Stimpert & Montgomery, 2010; Verani, Montgomery, Schulkin, Anderson, & Jones, 2010). There is no CD treatment guideline that is endorsed by key medical societies, such as the Infectious Disease Society of America (IDSA) or the American Society of Tropical medicine & Hygiene (ASTMH). A review article published in JAMA (Bern et al., 2007) and the CDC website are currently used to make treatment decisions, but there is a gap on how to manage adverse effects.[11]

Organizing a physician network could help increase the number of providers offering treatment and also improve physician acceptance of benznidazole (Forsyth et al., 2019). In January 2019, Exeltis proposed to share the list of prescribers with a group of CD experts at UCSF, CECD, LASOCHA and BMC, so that this expert group could approach them, briefly check their treatment practices and invite them to join a treater network.[12] The network is intended to provide clinical advice to other healthcare providers who are new to CD treatment.

Patient acceptance of benznidazole

Understanding CD is sometimes difficult for patients. One patient in East Boston believed that s/he acquired the disease from bedbugs in the US.[13] Another patient's husband doubted that the parasites can persist in human bodies for such a long time and believed that commercially available colloid silver could treat his wife (Box 1). Despite such confusion, patients seem to be willing to take benznidazole, according to interviews conducted with a treating physician and a pharmacist in BMC.[14] A more important challenge for many patients seems to be making medical appointments for treatment.[15]

In East Boston, for example, CD patients are identified at the East Boston Neighborhood

[11] Interview, BMC, Aug/16/2018
[12] Online call, Exeltis and others, Jan/30/2019
[13] Interview, East Boston Strong Heart Project, Aug/13/2018
[14] Interview, BMC, Aug/16/2018
[15] Interview, East Boston Strong Heart Project, Aug/13/2018

Health Center and then referred to Boston Medical Center for treatment. The referral often triggers several problems, such as difficulties to accommodate the patient's job or childcare duties within the limited time windows of infectious disease specialists, high transportation and opportunity costs due to long distances to travel, and different insurance requirements applied for the different hospitals.[16] Similar problems, including transportation difficulties and limited time off, are reported among patients identified at CECD in Los Angles (Forsyth et al., 2018). Patients in the US can face various obstacles in making medical appointments and can thus become discouraged from seeking care **[Barrier T6]**. Support for patients is critical to keep patients engaged and encouraged during the process of seeking medical treatment for CD.

One potential solution is "patient peer support" (provision of help and support from treated patients to others) that has been used to improve cancer care. This strategy has been shown effective to address system-level barriers such as fragmented care, financial constraints, and transportation costs as well as to decrease emotional distress (Kowitt et al., 2019). A similar strategy may work for CD, and some initiatives have emerged locally; for instance, LASOCHA and CECD have ideas to organize patients in the metropolitan Washington area and in Los Angeles, respectively[17] but clear strategies to introduce peer support programs are yet to be developed within these two organizations. In addition, there is no CD patient association at the national level in the US.

For national-level networking, Exeltis has an idea to add an online hub function to its benznidazole website. This hub function is intended to help connect new healthcare providers with experienced CD treaters as well as to connect people who are seeking CD diagnosis and treatment with treated patients. As of March 15, 2019, Exeltis is revising the website with a website developer (Vizion Advertising). One potential concern is how physicians and patients

[16] Interview, East Boston Strong Heart Project, Aug/13/2018
[17] E-mail, CECD, Mar/03/2019

will perceive the industry-led networking effort.

In summary, demand for benznidazole by physicians and patients needs to be effectively stimulated even though benznidazole is FDA-approved. The limited number of physicians offering treatment, coupled with the lack of treatment guidelines and uncertainty around treating adult patients, are identified as key access barriers. Another barrier is practical obstacles (related to financial and time constraints) that patients can face when they seek medical appointments for treatment. Exeltis could become engaged in education and networking of physicians and patients to address these issues, while a caution is required because Exeltis is not allowed to promote the off-label use of benznidazole.

3-4-2. Proposed actions in Acceptability

- To increase the number of physicians offering CD treatment, development of an experienced treater network that can give clinical advice to new healthcare providers will be helpful. Dr. Bern is taking a leadership to organize this provider network.
- In addition, development of materials for physician education, in particular treatment guidelines endorsed by key medical societies, could help improve physician acceptance of benznidazole.
- To improve patient acceptance, particularly to ensure linkage to care, development of a patient peer support program may be useful, so that patients seeking care or under treatment can learn from other patients' experiences who already completed treatment.
- An online hub function to connect new treaters with experienced treaters as well as to connect people who are seeking care with treated patients would help expand these networks at the national level, thus enhancing the acceptability of benznidazole. Whether this online hub function can be located on the Exeltis website or not should be carefully assessed and decided.

3-5. Appropriate use

Appropriate use refers to the degree to which benznidazole is effectively and safely used. Inappropriate use of benznidazole can result in severe adverse effects, discontinued medication and treatment failure. Appropriate use requires providers to evaluate patient eligibility for treatment, synthesizing the results of confirmatory diagnosis, medical history, physical examination, presence of advanced cardiac or digestive complications, patient's age, and pregnancy, among others (Bern et al., 2007). In addition, appropriate use of benznidazole also requires appropriate dose and duration, and frequent medical checkups to manage adverse effects. Since CDC no longer offers gatekeeping services (limiting access to benznidazole when physicians do not adhere to the standard of care), efforts to improve quality of care are important to reduce inappropriate use of benznidazole.

3-5-1. Barriers, facilitators, actors and recent activities

Before May 2018, CDC worked with providers to assess eligibility for treatment for each patient before it released benznidazole. Currently, no institution is playing this gatekeeping role in the US, and physicians can obtain benznidazole from Exeltis after completing the prescription form. Some CD experts are concerned about the potential misuse of benznidazole by physicians who do not follow the standard of care for CD treatment.

Several anecdotal cases illustrate these expert concerns. In the case of one patient (Box 1), the patient's physician prescribed benznidazole, but neither assessed her treatment eligibility nor explained adverse effects and need for periodic follow-up evaluation. In another case, while efficacy might not outweigh adverse consequences for patients over 50 years old (Bern et al., 2007), benznidazole was used to treat an 88-year-old patient who died within one month after initiating the drug administration.[18] As an overall tendency, the proportion of patients over 50 years old who are being treated with benznidazole increased from 26.6% to 32.6% in nine

[18] Exeltis, Periodic Adverse Drug Experience Report for Benznidazole Tablet, Dec/18/2018

months after the commercial launch of benznidazole (Table 3). Inadequate evaluation by healthcare providers to establish patient eligibility for CD treatment seems to be a key barrier in Appropriate use **[Barrier T7]**. Currently, Exeltis is planning to upload information on eligibility for treatment to its website, so that prescribers can self-check their decisions before they download the order forms.

Information is not enough to assess appropriate use of benznidazole, including dosage and management of adverse effects. Foundation Care collects information on the quantity of benznidazole dispensed, however, Exeltis cannot calculate dosage and treatment duration because patient weights are not reported. The post-marketing safety surveillance of benznidazole is performed via the FDA Adverse Event Reporting System, where patients or providers voluntarily report adverse events to the FDA and to the manufacturer, but this report does not provide information to assess whether physicians are providing adequate medical supervision during drug administration. The abovementioned expert group from UCSF, CECD, LASOCHA and BMC is planning to collect more information to understand how benznidazole is currently used by physicians.[19]

In summary, it appears there are examples of inappropriate use of benznidazole. Key barriers involve inadequate evaluation by health care providers of patient eligibility for treatment. Collaboration with researchers and physicians could be developed to collect more information and ensure quality of CD care.

3-5-2. Proposed actions in Appropriate use

- Exeltis can update its website to make sure that prescribers have adequate information on how to evaluate patient eligibility for treatment, before they download the order forms.
- Data collection on appropriate use of benznidazole and appropriate management of adverse

[19] Online call, Exeltis, UCSF, CECD, LASOCHA and BMC, Jan/30/2019

effects could help understand current treatment practices after benznidazole was commercialized.

- Expanded education of health care providers could help prevent misuse of the drug and improve quality of CD care.

4. Access to diagnosis

This chapter will review the process, barriers and facilitators for accessing CD diagnosis in the US. Access to diagnosis is largely shaped by the marketing strategies of the commercial labs and test makers. However, these companies' strategies were not available at the time of developing this Access Plan, which made it difficult to apply the access framework presented in Chapter 2. Instead, this chapter draws on the process by which a person potentially infected with *T. cruzi* can obtain a confirmatory diagnosis (Figure 3). Key barriers are defined as conditions that can block a potential patient's progress in following this diagnostic process.

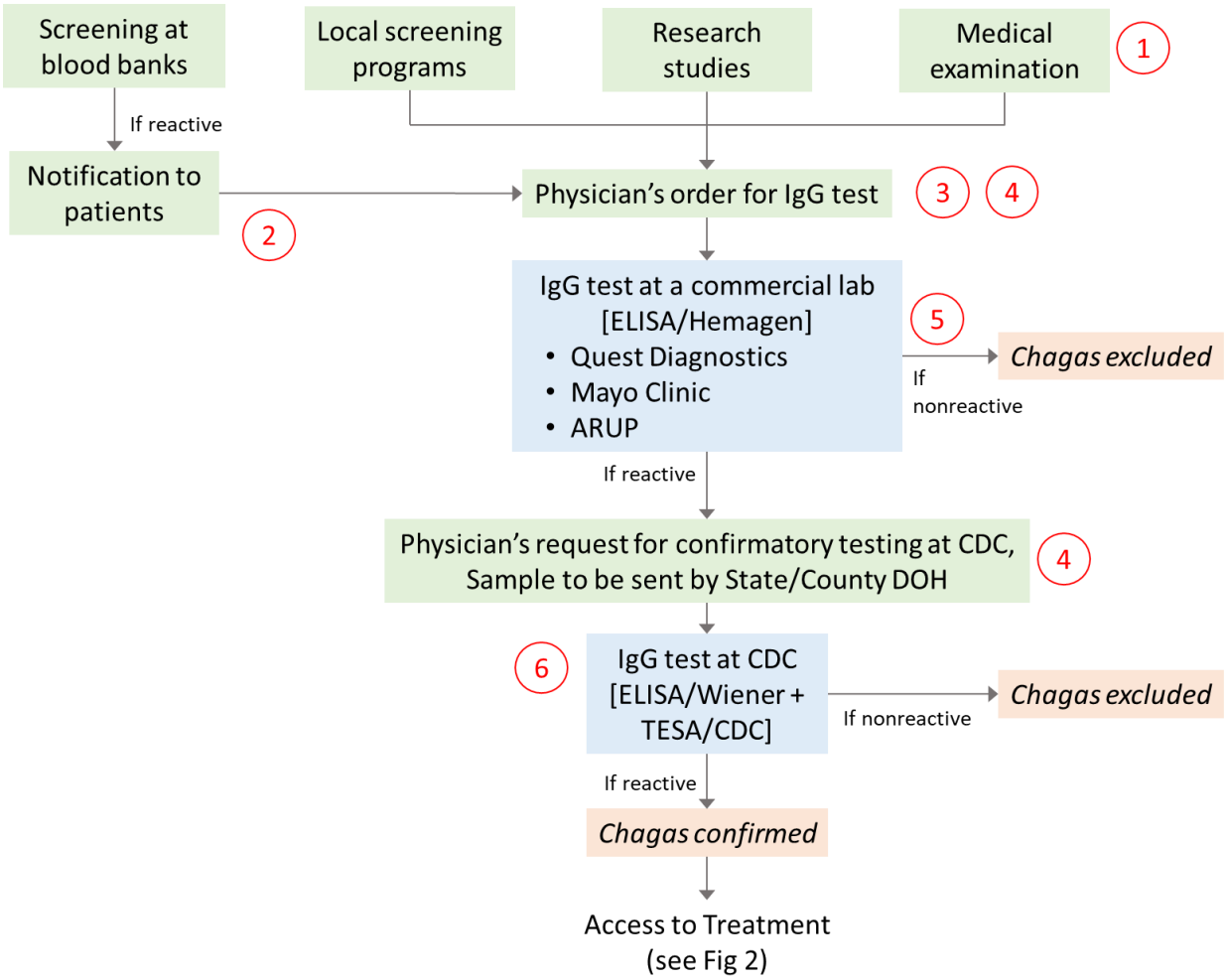

Figure 3: Process to diagnose chronic Chagas disease in the United States.

The numbers in circles indicate access barriers to diagnosis. Modified from Manne-Goehler et al. (2015).

4-1. Key access barriers to diagnosis

Barrier D1: Limited screening opportunities at the primary care level

The detection of potential CD patients can occur through blood bank screening (Dodd et al., 2018), local screening programs like the East Boston Strong Heart Project, research studies, or medical examination of patients with or without clinical manifestations. Except for blood donors, screening opportunities are ad-hoc in the US (Forsyth et al., 2019; Manne-Goehler et al., 2015). The lack of screening guideline for clinical settings is impeding the scaling-up of screening efforts (Manne-Goehler et al., 2015). In addition, CD screening at the primary care level often requires providers who

take the time to explain what the disease is, and if the test results are positive, then refer patients to treating physicians. Primary care providers have limited time (e.g., 20 minutes) to attend one patient per visit and testing for CD can be perceived as an additional burden to an already saturated schedule. There are no incentives for primary care providers to give the same level of priority to CD as HIV, TB, or diabetes.[20] CD screening needs to be recognized as a higher priority at the hospital or clinic level.

Barrier D2: Limited access to physicians for positive blood donors

Nearly 100 donors are found to be seropositive annually as part of blood bank screening after 2014.[21] Blood donation agencies notify donors about their test results and donors then need a medical appointment to confirm their diagnosis. Serological tests used at blood banks are not necessarily approved by the FDA for diagnostic use. For example, the American Red Cross uses three tests, namely Abbott PRISM Chagas, Ortho *T. cruzi* ELISA and Abbott enzyme strip assay Chagas (Dodd et al., 2018), but only the Ortho test is FDA-cleared for diagnostic use. Therefore, CDC requires all test-positive blood donors to follow the diagnostic procedures illustrated in Figure 3. However, it is likely that some donors, particularly when they are uninsured, have no or limited access to a physician who can order diagnostic testing.

Barrier D3: Limited physician knowledge on diagnostic procedures

CD diagnosis requires at least two different serological assays that use different antigen preparations. Physicians must order the first serological test, which is provided by three commercial laboratories. However, there are no guidelines for CD diagnosis and often physicians do not know which test to order or which laboratory offers tests. The Box 1 describes a case where the physician was not aware of the need to confirm the diagnosis and therefore skipped the entire diagnostic process. When the

[20] Interview, EBNHC, Aug/17/2018
[21] AABB data

first test result is positive, the provider must request confirmatory testing at CDC, but there could be providers who do not know the procedures used by government entities to send blood samples to CDC.

Barrier D4: Uncertain affordability of testing

Uninsured or underinsured patients may not be able to afford the costs related to testing. Currently, Quest Diagnostics charges $60-100 per test, which may not be covered by insurers.[22] Assessing the affordability of testing requires an understanding of the market strategies set by the commercial labs and test makers.

Barrier D5: Unknown reliability of currently available diagnostics

There are four FDA-cleared assays for clinical use (Table 4), but the accuracies of these assays in the US population are unknown (Forsyth et al., 2019). These assays were largely developed with South American *T. cruzi* strains while a large amount of CD patients in the US come from Central America and Mexico where different *T. cruzi* strains are prevalent. The difference in *T. cruzi* strains is suspected to affect the performance of serological tests. False negatives by these assays would be a critical barrier for patients, because CDC receives only those samples positive to the first serological test. Currently, Hemagen test is the only one that is commercially available. The Chagas Consortium has advocated resuming production of the Ortho assays and the company may make their tests available in July 2019 at the earliest.[23] Researchers at UCSF are planning a comparative evaluation of FDA-cleared assays with funds from FMS.

[22] E-mail, LASOCHA, Dec/11/2018
[23] E-mail, Chagas Consortium, Dec/10/2018

Table 4: Four *T. cruzi* assays cleared for clinical use in the United States

	Hemagen ELISA	Ortho ELISA	Wiener Chagatest ELISA recombinant	InBios Chagas Detect Plus (rapid test)
Manufacturer	Hemagen Diagnostics, Columbia, MD	Ortho Clinical Diagnostics, Raritan, NJ	Laboratorio Wiener, Rosario, Argentina	InBios, Seattle, WA
Sensitivity/Specificity (insert)	100/98.7 (South American sample)	100/99.9 (mixed sample)	99.3/98.7 (SA sample)	95.1/98.7 (SA sample)
Other studies	100/95.56 (Otani et al. 2009)	98.9/99.4 (510K application) 99.2/99.1 (do Brasil et al. 2016)	98.81/99.62 (Otani et al. 2009) 90/100 (Duarte et al. 2014) 93.7/99 (do Brasil et al. 2016)	99.3/96.9 (Shah et al. 2014, Bolivian serum)
Key concerns	Concerns about specificity	Currently not being manufactured for clinical use; potentially high cost	No U.S. distributor; very low sensitivity reported in Vera Cruz study (Guzman-Gomez et al. 2015)	Unknown specificity (Central American/Mexican /US patients)

Source: Forsyth C, Strengthening Diagnosis of Chagas Disease in the United States: Gaps and Needs. PowerPoint presentation for "Rethinking Chagas" workshop at Harvard T.H. Chan School of Public Health.

Potential barrier D6: Centralized confirmatory diagnosis at CDC

For confirmatory diagnosis, the provider must send the patient's blood sample to CDC via the State or Country Department of Health. Currently, CDC is the only laboratory where the second and third assays are available: Wiener tests imported from Argentina and TESA assays developed by CDC (Montgomery, 2017). CDC offers these tests for free and then faxes the test results to the provider who requested the testing.

The centralized confirmatory diagnosis is not a current access barrier, because CDC's budget seems to be adjusted to the current level of demand. However, if the demand for CD testing increases in the future, it is uncertain to what extent CDC can manage the increased requests. Wider scaling-up of CD testing may require a decentralization of confirmatory diagnosis (Forsyth et al., 2019).

Potentially, any CLIA[24]-regulated laboratory could perform confirmatory testing if they can use two or more different serologic tests.[25]

4-2. Proposed actions in Access to Diagnosis

Access to CD diagnosis would be improved by the following activities:

- Evaluation of the performance of the currently available diagnostics,
- Collaboration with blood banks to improve communications with potentially infected blood donors.
- Collaboration with commercial labs and test makers to ensure availability and affordability of reliable testing,
- Development of screening and diagnosis guidelines,
- Physician education on CD diagnosis, particularly through increasing continuing medical education (CME)[26] opportunities,
- Creation of incentives for primary care providers to expand and routinize screening,
- Possible decentralization of confirmatory testing.

A focus on maternal and newborn screening, as proposed during the "Rethinking Chagas" workshop, could provide an entry point for actions on diagnosis. Maternal screening, infant testing, and treatment of CD in the US are shown to be cost saving (Stillwaggon et al., 2018). Pregnant women and children have greater access to healthcare services in general and mothers are often key decision makers on family welfare in Latino culture. In addition, newborn screening can be used to establish

[24] Clinical Laboratory Improvement Amendments (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm)
[25] E-mail, CDC, Jul/06/2018
[26] Physicians are required by law to obtain CME credits in order to renew their medical license. However, physicians can choose any topics that they are interested in. How to encourage physicians to select CD-related materials is a further challenge.

maternal serostatus. This focus is also promoted by the Pan American Health Organization's new framework for eliminating mother-to-child transmission (PAHO/WHO, 2017). Experience at the East Boston Neighborhood Health Center (EBNHC) provides lessons about conditions necessary to implement maternal screening programs at primary healthcare centers (Box 2).

4-3. Proposed actions for screening and diagnosis

- FMS provides funding to the study proposed by Dr. Caryn Bern at UCSF, to comparatively evaluate the performance of FDA-cleared diagnostics using samples from blood banks. This project is expected to be completed by the end of 2019.
- Following the consensus at the "Rethinking Chagas" workshop, Dr. Paula Stigler at Texas State University, who is also a coordinator of Texas Chagas Task Force, is developing a proposal to investigate the epidemiology of maternal prevalence and congenital transmission and create a physician network in Texas. The proposal is under review by FMS.
- SMT, Inc., a consulting company in New Jersey, proposed a project to work with Health Resources Service Administration (HRSA) to implement screening programs at six Federally Qualified Health Centers (FQHCs). Compared to the newborn screening proposed by Texas State University, the HRSA-based screening has an advantage that screening will occur only after physicians agree to identify infected people, thus access to care is more guaranteed for patients. On the other hand, it is not clear whether FQHCs are able to start CD screening with their financial constraints and FQHCs-based screening can cover limited geographical areas. SMT helped Exeltis develop the benznidazole dossier for its FDA application. Exeltis is considering this proposal.
- Some researchers and physicians have started to develop CME materials to expand physician knowledge on CD screening (e.g. Edwards et al., 2017).

5. Areas for strategic actions

To address barriers and facilitators summarized in the previous two chapters, this Access Plan organizes access activities into eight areas. Each of the eight areas addresses one or more access barriers (Table 5). This chapter presents brief descriptions of the eight areas for strategic actions, in which Exeltis USA and FMS can develop specific activities.

Table 5: Areas for strategic actions addressing key access barriers

	Key barriers that will be addressed by strategic actions												
	Access to benznidazole							Access to diagnosis					
	Arch.	Availability		Afford.	Acceptability		App. use						
Areas for Strategic Actions	T1. No formal structure to facilitate collaborations	T2. Failure to use the Exeltis ordering form	T3. Lack of emergency delivery	T4. Unclear financial sustainability of FastAccess	T5. Limited number of treaters offering CD treatment	T6. Obstacles for patients seeking med. appointments	T7. Inadequate evaluation of patient eligibility for treatment	D1. Limited routine screening at the primary care level	D2. Limited access to physicians for test-positive donors	D3. Limited physician knowledge about diagnostic procedures	D4. Uncertain affordability of testing	D5. Unknown reliability of diagnostics	(D6) Centralized confirmatory diagnosis
A1. Establish emergency benznidazole delivery			X										
A2. Ensure financial sustainability of FastAccess				X									
A3. Organize and educate treaters		X			X		X			X			
A4. Promote patient networking						X		X	X				
A5. Implement pilot screening projects								X		X			
A6. Educate physicians for diagnostic testing						X		X	X	X			
A7. Promote development of guidelines for screening, diagnosis and treatment					X			X		X		X	X
A8. Facilitate muti-sectorial coordination	X				X		X		X	X	X		X

Area #1: Establish emergency benznidazole delivery system

CDC has expected Exeltis to develop same-day emergency delivery of benznidazole for rare cases such as acute transplant-transmitted infections, reactivation disease in the setting of HIV, or severe congenital CD. Exeltis can explore delivery options with Foundation Care and develop an effective emergency service that would meet the request from CDC.

Area #2: Ensure the financial sustainability of the FastAccess Program

The future financial sustainability of the Exeltis FastAccess Program is critical to keep benznidazole affordable. Exeltis and FMS can calculate the program's financial projection and develop a plan to ensure sustainability. Exeltis can continue expanding insurance coverage of benznidazole to reduce reliance on FastAccess program.

Area #3: Organize and educate treating providers

Education of health care providers should be the top priority for Exeltis to ensure and increase appropriate use of benznidazole, as well as to gain trust from the scientific and clinical community. Exeltis can undertake website development (uploading physician's self-assessment sheet before ordering benznidazole and adding an online hub function for physician networking) and collaborate with researchers to investigate how benznidazole is currently used as compared to the standard of care.

Area #4: Promote patient networking

Exchange of information and experiences among patients and those who are seeking care will be useful to improve patient acceptance of diagnosis and treatment. Exeltis can start collaborating with LASOCHA to develop a local patient network. Exeltis can also create an online hub function in the website where care seekers can virtually meet treated CD patients.

Area #5: Implement pilot screening projects

Expanding screening opportunities requires some pilot projects to demonstrate effective models of intervention. A focus can be given to maternal and newborn screening at a few FQHCs in California and Texas. Exeltis can consider developing a project proposal, with or without the participation of the consulting company. In parallel, FMS can work with Texas State University to do an epidemiological

survey on maternal prevalence and congenital transmission in Texas.

Area #6: Educate providers for diagnostic testing

To expand access to CD diagnosis, systematic education of primary care providers can be strengthened. Continuous Medical Education (CME) opportunities for CD can be expanded by developing materials (published papers, online videos, etc.). Exeltis and FMS can identify physicians who can help to develop materials as well as other potential funders, including companies interested in increasing demand for CD diagnostic testing.

Area #7: Promote development of guidelines for screening, diagnosis and treatment

Official guidelines for screening, diagnosis and treatment can help persuade more providers and hospitals to find and provide care for CD patients. Development of the guidelines will require data from the comparative evaluation study of the four FDA-cleared diagnostic assays, currently being done at the UCSF with FMS' funding. Once the study's results are shared and recognized, FMS can support the process of organizing a draft committee, a group of experts who will write guidelines and get them endorsed by key medical societies.

Area #8: Facilitate multi-sectorial coordination

A structured network could assist researchers, physicians, CDC and Exeltis in working together towards a common goal. This could be accomplished by expanding the existing informal network (Chagas Consortium). This network can invite blood banks and companies in the diagnostic market that may be willing to join in efforts to expand access to CD diagnosis. Exeltis can also participate in this network and share its progress in implementing this Access Plan, so that the company's efforts are widely recognized and supported in the Chagas community in the US.

Box 1: Struggling to get benznidazole: a patient's experience

In late 2017, Valentina (fictitious name) decided to donate blood, and the blood center informed her that she was possibly infected with *T. cruzi*. She is originally from Central America and has lived in the US for more than ten years. She is undocumented and had no health insurance.

Many months after Valentina was notified by the blood bank, she visited one of the Federally Qualified Health Centers close to her home. Her physician checked Valentina with a blood test (not including a *T. cruzi* antibody test) and prescribed benznidazole. Unfortunately, the physician was not knowledgeable about Chagas disease. He did not order *T. cruzi* antibody testing, evaluate her for cardiac or gastrointestinal disease, or explain the potential adverse effects of benznidazole.

With the prescription in her hands, Valentina went to a commercial pharmacy. There, she found that benznidazole would cost $400. She decided to pay for it, but the pharmacy couldn't process the order. Her physician had to fax an order form directly to Foundation Care, a specialty pharmacy. Valentina's physician did not know how to order benznidazole; as a result, Valentina did not take benznidazole.

Unable to purchase the medication, Valentina sought help and contacted the author (K. Yoshioka). When the author spoke to her, Valentina believed that her blood bank testing was enough for her to take benznidazole at home, on her own. The author explained that she would need different blood tests at CDC to confirm her infection. She was concerned about using CDC's services, because she was applying to obtain legal civil status and she had heard that the US government was declining applications from people getting benefits from government agencies. Her husband also asked several questions to the author, including whether the parasite can persist for decades in a patient's body and whether a commercially available silver colloid can kill the parasite. When Valentina understood the risk of taking benznidazole, she agreed to seek

confirmatory testing at CDC.

Valentina wanted to have an assigned physician who could offer continued care to her. She found private health insurance which provided an affordable option for people living below a certain level of income. The company's agent told her that Valentina should pay only $105 a month to cover her and her husband and she decided to get enrolled. In March 2019, Valentina visited her newly assigned primary care physician, who then referred her to a specialist. Within a few days, she saw an infectious disease specialist who assessed her cardiac conditions and ordered a serological test.

(updated as of March 26, 2019)

Box 2: Experience of maternal screening at East Boston

A focus on maternal and newborn screening could provide an entry point to expand access to screening and diagnosis for Chagas disease. The experience at East Boston Neighborhood Health Center (EBNHC), where 200-300 pregnant women have been screened every month since 2017,[27] provides a useful case study. At EBNHC, Chagas disease testing is incorporated into routine prenatal screening, and it does not consume providers' time in explaining about Chagas disease and obtaining specific patient consent. The costs of testing are covered by Medicaid (MassHealth) and no financial problems have been observed. Infected mothers and newborns are referred to specialists at Boston Medical Centers for mother's treatment and babies' diagnosis.

EBNHC is a Federally Qualified Health Center (FQHC), which receives funds from the federal government to provide primary care services in underserved areas, in exchange for meeting a set of requirements set by the Health Resources & Services Administration.[28] The EBNHC case shows that prenatal screening of Chagas disease can be routinized in FQHCs. The fishbone diagram (Figure 4, prepared by the author) shows the conditions that need to be addressed in order to routinize prenatal screening in an FQHC, based on the EBNHC's experiences.

This diagram can be used to guide the implementation of prenatal screening in other FQHCs, for example in Texas, the geographic focus recommended by the "Rethinking Chagas" workshop. However, its application to Texas requires careful attention because 1) EBNHC is one of the largest, well-resourced FQHCs in the US and the low-cost clinics in Texas are often unable to support a screening program due to the costs of testing and intensive management resources needed for treatment (Forsyth et al., 2019), and 2) Texas Medicaid only covers low-income

[27] Interview, EBNHC, Oct/5/2018
[28] Health Resources & Services Administration. https://www.hrsa.gov/opa/eligibility-and-registration/health-centers/fqhc/index.html

pregnant women with health-care benefits during pregnancy and up to two months after birth,[29] implying that some pregnant women and infected mothers would not continue to be insured at the time of screening and treatment, respectively.

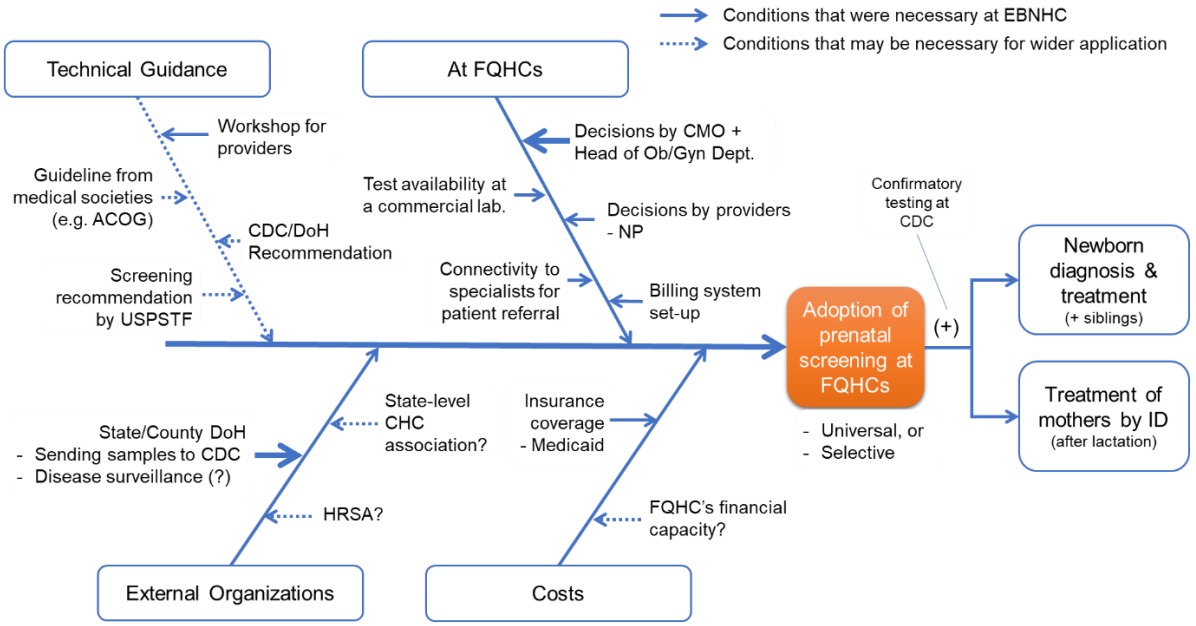

Figure 4: Conditions needed to adopt routine prenatal screening for Chagas disease at the East Boston Neighborhood Health Center.

ACOG: The American College of Obstetricians and Gynecologists, CDC: U.S. Center for Disease Control & Prevention, CHC: Community Health Centers, HRSA: Health Resources & Services Administration, FQHC: Federally Qualified Health Center, CMO: Chief Medical Officer, DoH: Department of Health, ID: Infectious disease physician, NP: Nurse practitioner, Ob/Gyn: Obstetrics and Gynecology, USPSTF: U.S. Preventive Services Task Force.

[29] Texas Health and Human Services. https://yourtexasbenefits.hhsc.texas.gov/programs/health/women/pregnant

Appendix 1: List of Organizations that may be able to help with medication and financial assistance for under-resourced patients.

This list is generated by the National Organization for Rare Disorders (NORD) Information Services
www.rarediseases.org

NeedyMeds
Dedicated to helping people who cannot afford medicine or health care costs.

P.O. Box 219
Gloucester, MA 01931
Phone: 800-503-6897

Patient Access Network (PAN)
Helps uninsured people with life-threatening, chronic, and rare diseases obtain medications and treatment.

PO Box 221858
Charlotte, NC 28222
Phone: 866-316-7263
Email: contact@panfoundation.org

The Patient Advocate Foundation (PAF)
Provides professional case management services to Americans with chronic, life threatening and debilitating illnesses. Patients can call PAF's case management team for personalized assistance resolving their healthcare issues at 1-800-532-5274 during business hours.

The PAF Co-Pay Relief Program, one of the self-contained divisions of PAF, provides direct financial assistance to insured patients who meet certain qualifications to help them pay for the prescriptions and/or treatments they need. This assistance helps patients afford the out-of-pocket costs for these items that their insurance companies require. Call directly at 1-866-512-3861 - option 1

421 Butler Farm Road
Hampton, VA 23666
Phone: 800-532-5274
Fax: 757-873-8999

RxAssist
Offers a database of patient assistance programs, as well as practical tools, news, and articles so that health care professionals and patients can find the information they need.

Email info@rxassist.org

The HealthWell Foundation
Addresses the needs of individuals with insurance who cannot afford their co-payments, coinsurance, and premiums for important medical treatments.

PO Box 4133
Gaithersburg, MD 20885-4133
Phone: 800-675-8416

Hill-Burton Free and Reduced Cost Health Care
Provides services to people who are unable to pay for hospitals, nursing homes, and other facilities.

5600 Fishers Lane
Rockville, MD 20857
Phone: 800-221-9393

Patient Services, Inc. (PSI)
Helps patients living with specific chronic illnesses by locating health insurance, subsidizing the cost of health insurance premiums, providing pharmacy and treatment co-payment assistance, assisting with Medicare Part D Co-insurance, and helping with advocacy for Social Security Disability.

P.O. Box 5930
Midlothian, VA 23112
Phone: 800-366-7741
Email: uneedpsi@uneedpsi.org

Need Help Paying Bills
Provides information on assistance programs, charity organizations, and other resources that can help with paying bills, mortgage, and debt expenses. You will have to go to their website to view the information:

http://www.needhelppayingbills.com/

Free or Reduced Cost Medical Care
The National Association of Free Clinics (NAFC) focuses on the issues and needs of the more than 1,200 free clinics and the people they serve in the United States.

1800 Diagonal Road
Suite 600
Alexandria, VA 22314
Phone: 703-647-7427
Email: info@nafcclinics.org

Bibliography

Alpern, J. D., Lopez-Velez, R., & Stauffer, W. M. (2017). Access to benznidazole for Chagas disease in the United States—Cautious optimism? *PLoS Neglected Tropical Diseases*, *11*(9). https://doi.org/10.1371/journal.pntd.0005794

Amstutz-Szalay, S. (2017). Physician Knowledge of Chagas Disease in Hispanic Immigrants Living in Appalachian Ohio. *Journal of Racial and Ethnic Health Disparities*, *4*(3), 523–528. https://doi.org/10.1007/s40615-016-0254-8

Bern, C. (2015). Chagas' Disease. *New England Journal of Medicine*, *373*(5), 456–466. https://doi.org/10.1056/NEJMra1410150

Bern, C., & Montgomery, S. P. (2009). An estimate of the burden of Chagas disease in the United States. *Clinical Infectious Diseases*, *49*(5), e52-54. https://doi.org/10.1086/605091

Bern, C., Montgomery, S. P., Herwaldt, B. L., Rassi, A., Marin-Neto, J. A., Dantas, R. O., … Kirchhoff, L. V. (2007). Evaluation and treatment of Chagas disease in the United States: a systematic review. *Jama*, *298*(18), 2171–2181.

CDC-Centers for Disease Control and Prevention. (2018, May 15). CDC - Chagas Disease - Antiparasitic Treatment. Retrieved August 14, 2018, from https://www.cdc.gov/parasites/chagas/health_professionals/tx.html

DNDi. (2017, August 31). U.S. FDA approves Chemo Group's benznidazole to treat children with Chagas disease. Retrieved February 22, 2019, from DNDi – Best science for the most neglected website: https://www.dndi.org/2017/media-centre/press-releases/fda-approves-benznidazole-chagas-children/

DNDi. (2019, March 14). Study shows dramatically shorter treatment for Chagas disease could be just as effective, and significantly safer. Retrieved March 15, 2019, from DNDi – Drugs for Neglected Diseases initiative website: https://www.dndi.org/2019/media-centre/press-releases/study-shows-dramatically-shorter-treatment-chagas-effective-and-safer/

Dodd, R. Y., Groves, J. A., Townsend, R. L., Notari, E. P., Foster, G. A., Custer, B., … Stramer, S. L. (2018).

Impact of one-time testing for *Trypanosoma cruzi* antibodies among blood donors in the United States: ONE-TIME ANTI- *TRYPANOSOMA CRUZI* DONOR TESTING. *Transfusion*. https://doi.org/10.1111/trf.15118

Edwards, M. S., Abanyie, F. A., & Montgomery, S. P. (2018). Survey of Pediatric Infectious Diseases Society Members About Congenital Chagas Disease. *The Pediatric Infectious Disease Journal*, *37*(1), e24–e27. https://doi.org/10.1097/INF.0000000000001733

Edwards, M. S., Stimpert, K. K., & Montgomery, S. P. (2017). Addressing the Challenges of Chagas Disease: An Emerging Health Concern in the United States. *Infectious Diseases in Clinical Practice*, *25*(3), 118. https://doi.org/10.1097/IPC.0000000000000512

Forsyth, C. J., Hernandez, S., Flores, C. A., Roman, M. F., Nieto, J. M., Marquez, G., … Meymandi, S. (2018). "It's Like a Phantom Disease": Patient Perspectives on Access to Treatment for Chagas Disease in the United States. *The American Journal of Tropical Medicine and Hygiene*, *98*(3), 735–741. https://doi.org/10.4269/ajtmh.17-0691

Forsyth, C. J., Stigler Granados, P., Pacheco, G. J., Betancourt, J. A., & Meymandi, S. (2019). Current Gaps and Needs for Increasing Access to Healthcare for People with Chagas Disease in the USA. *Current Tropical Medicine Reports*. https://doi.org/10.1007/s40475-019-0170-1

Frost, L. J., & Reich, M. (2008). *Access: how do good health technologies get to poor people in poor countries?* Cambridge, Mass: Harvard Center for Population and Development Studies : Distributed by Harvard University Press.

Herwaldt, B. L., Dougherty, C. P., Allen, C. K., Jolly, J. P., Brown, M. N., Yu, P., & Yu, Y. (2018). Characteristics of Patients for Whom Benznidazole Was Released Through the CDC-Sponsored Investigational New Drug Program for Treatment of Chagas Disease — United States, 2011–2018. *MMWR. Morbidity and Mortality Weekly Report*, *67*. https://doi.org/10.15585/mmwr.mm6729a3

Kowitt, S. D., Ellis, K. R., Carlisle, V., Bhushan, N. L., Black, K. Z., Brodar, K., … Fisher, E. B. (2019). Peer support opportunities across the cancer care continuum: a systematic scoping review of recent peer-reviewed literature. *Supportive Care in Cancer*, *27*(1), 97–108.

https://doi.org/10.1007/s00520-018-4479-4

Lee, B. Y., Bacon, K. M., Bottazzi, M. E., & Hotez, P. J. (2013). Global economic burden of Chagas disease: a computational simulation model. *The Lancet Infectious Diseases*, *13*(4), 342–348. https://doi.org/10.1016/S1473-3099(13)70002-1

Manne-Goehler, J., Reich, M. R., & Wirtz, V. J. (2015). Access to Care for Chagas Disease in the United States: A Health Systems Analysis. *The American Journal of Tropical Medicine and Hygiene*, *93*(1), 108–113. https://doi.org/10.4269/ajtmh.14-0826

Manne-Goehler, J., Umeh, C. A., Montgomery, S. P., & Wirtz, V. J. (2016). Estimating the Burden of Chagas Disease in the United States. *PLoS Neglected Tropical Diseases*, *10*(11), e0005033. https://doi.org/10.1371/journal.pntd.0005033

Meymandi, S., Forsyth, C. J., Soverow, J., Hernandez, S., Sanchez, D., Montgomery, S. P., & Traina, M. (2017). Prevalence of Chagas Disease in the Latin American–born Population of Los Angeles. *Clinical Infectious Diseases*, *64*(9), 1182–1188. https://doi.org/10.1093/cid/cix064

Meymandi, S., Hernandez, S., Park, S., Sanchez, D. R., & Forsyth, C. (2018). Treatment of Chagas Disease in the United States. *Current Treatment Options in Infectious Diseases*, *10*(3), 373–388. https://doi.org/10.1007/s40506-018-0170-z

Montgomery, S. (2017, September). *Diagnosis of Chagas Disease in the United States - CDC*. PowerPoint Presentation presented at the Chagas disease in the United States: Improving patient diagnosis and treatment.

PAHO/WHO. (2017, July). *EMTCT Plus: Framework for Elimination of Mother-to-Child Transmission of HIV, Syphilis, Hepatitis B, and Chagas*. Retrieved from http://iris.paho.org/xmlui/bitstream/handle/123456789/34306/PAHOCHA17009-eng.pdf?sequence=1&isAllowed=y

Stillwaggon, E., Perez-Zetune, V., Bialek, S. R., & Montgomery, S. P. (2018). Congenital Chagas Disease in the United States: Cost Savings through Maternal Screening. *The American Journal of Tropical Medicine and Hygiene*, *98*(6), 1733–1742. https://doi.org/10.4269/ajtmh.17-0818

Stimpert, K. K., & Montgomery, S. P. (2010). Physician Awareness of Chagas Disease, USA. *Emerging Infectious Diseases*, *16*(5), 871–872. https://doi.org/10.3201/eid1605.091440

U.S. Food and Drug Administration. (2017, August 29). Press Announcements - FDA approves first U.S. treatment for Chagas disease [WebContent]. Retrieved August 13, 2018, from https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm573942.htm

U.S. Food and Drug Administration. (n.d.). Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Retrieved February 22, 2019, from https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=209570

Verani, J. R., Montgomery, S. P., Schulkin, J., Anderson, B., & Jones, J. L. (2010). Survey of Obstetrician-Gynecologists in the United States About Chagas Disease. *The American Journal of Tropical Medicine and Hygiene*, *83*(4), 891–895. https://doi.org/10.4269/ajtmh.2010.09-0543