Title

742. Evaluation of Chagas Disease Diagnostic Testing Practices in Four Hospital Systems in California and Texas

Journal

Open Forum Infectious Diseases, 8(Supplement_1)

ISSN

2328-8957

Authors

Kelly, Emily A

Alegre, Jose I Echeverri

Promer, Katherine

et al.

Publication Date

2021-12-04

DOI

10.1093/ofid/ofab466.939

The Journal of Infectious Diseases

BRIEF REPORT

Chagas Disease Diagnostic Practices at Four Major Hospital Systems in California and Texas

Emily A. Kelly,[1,a] Jose I. Echeverri Alegre,[2,a] Katherine Promer,[3] Jesica Hayon,[4] Roumen Iordanov,[4] Khuzaima Rangwalla,[5] Jerry J. Zhang,[6] Zian Fang,[6] Cindy Huang,[6] Cassiana E. Bittencourt,[7] Sharon Reed,[3,8] Rosa M. Andrade,[9] Caryn Bern,[10] Eva H. Clark,[4] and Jeffrey D. Whitman[1]

[1]Department of Laboratory Medicine, University of California, SanFrancisco, San Francisco, California, USA; [2]School of Medicine, Baylor College of Medicine, Houston, Texas, USA; [3]Department of Medicine, Division of Infectious Diseases and Global Public Health, University of California, San Diego, San Diego, California, USA; [4]Department of Medicine, Section of Infectious Diseases, Baylor College of Medicine, Houston, Texas, USA; [5]School of Medicine, University of California, SanFrancisco, San Francisco, California, USA; [6]School of Biological Sciences, University of California, Irvine, Irvine, California, USA; [7]Department of Pathology, University of California, Irvine, Irvine, California, USA; [8]Department of Pathology, University of California, San Diego, San Diego, California, USA; [9]Department of Medicine, Division of Infectious Diseases, University of California, Irvine, Irvine, California, USA; and [10]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California, USA

Background. Chagas disease (CD) is a parasitic disease that affects ~300 000 people living in the United States. CD leads to cardiac and/or gastrointestinal disease in up to 30% of untreated people. However, end-organ damage can be prevented with early diagnosis and antiparasitic therapy.

Methods. We reviewed electronic health records of patients who underwent testing for CD at four hospital systems in California and Texas between 2016 and 2020. Descriptive analyses were performed as a needs assessment for improving CD diagnosis.

Results. In total, 470 patients were tested for CD. Cardiac indications made up more than half (60%) of all testing, and the most frequently cited cardiac condition was heart failure. Fewer than 1% of tests were ordered by obstetric and gynecologic services. Fewer than half (47%) of patients had confirmatory testing performed at the Centers for Disease Control and Prevention.

Discussion. Four major hospitals systems in California and Texas demonstrated low overall rates of CD diagnostic testing, testing primarily among older patients with end-organ damage, and incomplete confirmatory testing. This suggests missed opportunities to diagnose CD in at-risk individuals early in the course of infection when antiparasitic treatment can reduce the risk of disease progression and prevent vertical transmission.

Keywords. Chagas disease; *Trypanosoma cruzi*; diagnosis; serology; United States.

Chagas disease (CD) is a neglected infectious disease caused by the protozoan parasite *Trypanosoma cruzi*. An estimated 6 million people have CD worldwide, including 300 000 living in the United States [1, 2]. *T. cruzi* is transmitted primarily by triatomine insect vectors in endemic regions of continental Latin America, but it can also be acquired congenitally and through organ transplantation or blood product transfusion [1, 3–5]. Untreated *T. cruzi* infection leads to cardiac and/or gastrointestinal disease in up to 30% of infected persons [6, 7]. In the United States, most patients present with cardiac manifestations, given their country of origin (Mexico and Central America), where gastrointestinal disease is rarely reported. At-risk individuals should be screened as early in the course of infection as possible, as antitrypanosomal treatment can reduce the risk of disease progression and vertical transmission.

Diagnosis of chronic *T. cruzi* infection is based on concordant positive results by ≥2 distinct serologic tests [8]. The diagnostic workflow in the United States commonly begins with a clinician ordering the first *T. cruzi* serologic assay through a commercial reference laboratory. If the result is positive, a second specimen should be sent for confirmatory serologic testing, which is available through the US Centers for Disease Control and Prevention (CDC). The CDC reference laboratory performs testing by means of enzyme-linked immunosorbent assay, immunoblot, and indirect florescent antibody assay, if needed for tie-breaker testing [1].

Though autochthonous transmission has been reported in the southern United States, the vast majority of *T. cruzi*–infected persons in the United States are immigrants from endemic areas of Latin America, who are disproportionately uninsured or underinsured and often lack regular access to robust healthcare services [9, 10]. Most are unaware of their risk and the need for screening, and the lack of awareness and knowledge of CD among US medical providers may also lead to missed or delayed diagnoses [11]. Furthermore, the diagnostic process is challenging and time consuming for both patients and clinicians, and patients may be lost to follow-up while awaiting results.

The objective of this study is to describe CD diagnostic practices among healthcare providers at 4 major hospital systems in California and Texas, which provide tertiary care and are each associated with >400 hospital beds: the University of California

Received 23 May 2023; editorial decision 12 September 2023; accepted 15 September 2023; published online 19 September 2023

[a]E. A. K. and J. I. E. A. contributed equally to this work.

Correspondence: Jeffrey D. Whitman, MD, MS, Department of Laboratory Medicine, University of California, San Francisco, 1001 Potrero Ave, Bldg 5, Room 2 M, San Francisco, CA 94110 (jeffrey.whitman@ucsf.edu); Caryn Bern, MD, MPH, Department of Epidemiology and Biostatistics, University of California, San Francisco, 550 16th St, San Francisco, CA 94158 (caryn.bern2@ucsf.edu).

The Journal of Infectious Diseases® 2024;229:198–202

https://doi.org/10.1093/infdis/jiad404

(UC) Irvine (UCI), UC San Francisco (UCSF), UC San Diego (UCSD), and the Harris Health System (HHS) in Houston, Texas. Our results illustrate barriers to the identification and testing of patients at risk for CD.

METHODS

Research teams at UCSF, UCI, UCSD, and HHS extracted and reviewed electronic health records (EHRs) systematically for all patients tested for CD in their respective health systems from 2016 to 2020, excluding pretransplantation screening. All sites used standardized data collection forms. Age, sex, and ethnicity were captured from each patient's EHR demographics. Country of birth, travel history, and test indications were identified from provider notes. Test date, specialty of ordering provider, and test results were linked to each electronic order.

At UCSF, patients tested for CD during the review period were identified through the clinical laboratory information system. At UCI, UCSD, and HHS, patients were identified using the front-end application, SlicerDicer (Epic Systems). All UC clinical data were stored in a UCSF REDCap (Research Electronic Data Capture) database with data user groups for each site, and all HHS clinical data were stored in the Baylor College of Medicine REDCap [12]. Descriptive analyses were performed using Stata 14.2 software. Institutional review boards at UCSF and the Baylor College of Medicine approved this study; UCI and UCSD were approved for reliance on the UCSF institutional review board.

RESULTS

Between 2016 and 2020, a total 470 patients were tested for CD at the 4 major hospital systems reviewed (Table 1). Of California patients, 39%–52% identified as Hispanic, and 91% identified as Hispanic at HHS. Country of birth data were documented incompletely in California (17%–38% missing) but were available for all HHS patients.

For the 470 patients who underwent CD workup, a total of 625 individual commercial diagnostic tests were ordered (155 at UCSF, 139 at UCSD, 40 at UCI, and 291 at HHS). Providers who ordered CD testing were frequently in the cardiology department at all California sites and the internal medicine department at HHS (Table 1). Gastroenterology providers ordered CD diagnostic testing infrequently (<5% of orders). Fewer than 1% of tests were ordered by obstetrics and gynecology providers.

Cardiac indications made up more than half of all testing indications at each site, and the most frequently cited cardiac indication was heart failure. The most common gastrointestinal indications for testing were dysphagia at UCSF, UCSD, and HHS and abdominal pain at UCI (Table 1).

Forty-seven patients (10%) had an initial positive result by commercial serology assay (Table 2). Thirteen (28%) underwent repeated commercial testing, and 22 (47%) had confirmatory testing performed at the CDC. Sixteen of 22 samples (73%) sent to the CDC were confirmed positive.

DISCUSSION

Latin American immigrant communities have the highest risk of CD in the United States [13]. Addressing this problem is complicated by inadequate access to healthcare, complicated diagnostic algorithms, and lack of CD knowledge and awareness among US providers [8, 11].

Quantifying CD diagnostic gaps is challenging without precise estimates of underlying prevalence. However, our results illuminate several important gaps, including (1) low volume of CD testing among healthcare systems serving large at-risk populations, (2) infrequent completion of confirmatory testing, (3) predominance of testing by subspecialties managing older patients with end-organ manifestations rather than by those in the position to screen younger at-risk individuals who would more likely benefit from antiparasitic treatment, and (4) lack of comprehensive CD risk assessment and documentation in the EHR.

The small number of patients tested (an average of 59 total patients tested for CD per year across 3 major university health systems in California and 44 per year in Harris County) despite large at-risk populations served by these health centers strongly suggests undertesting [13]. For patients who did receive CD testing in California, 33%–40% had repeated serologic testing at the same commercial laboratory, which does not confirm CD when the same test is used and is therefore not recommended. In contrast, providers in Texas did not order repeated commercial testing through the same laboratory for patients with positive screening results. Fewer than half (22 of 47) of all patients with initial positive CD serologic results underwent CDC confirmatory testing, possibly owing to providers' unfamiliarity with the chronic CD diagnosis algorithm or to patient loss to follow-up [8].

The types of subspecialists ordering CD testing varied by site and were likely determined by institutional workflow standards and setting (ie, inpatient vs outpatient), as well as individual provider practices regarding laboratory orders. At all sites, regardless of ordering provider, the most common indication for CD testing was cardiac disease. Nevertheless, the underlying etiology likely goes unrecognized in a large proportion of the estimated 57 000 cases of Chagas cardiomyopathy in the United States [13]. Our findings of an older median age of patients, the specialties of ordering providers (ie, primarily cardiology), and medical indications (ie, primarily heart failure or GI disease) suggest that providers focus testing on patients who already have characteristic end-organ damage.

The importance of testing at-risk patients as early as possible in their lifetime should be emphasized during healthcare provider education, with the goal of treating patients with

Table 1. Demographics and Risk Factors for Chagas Disease (CD) Among Patients Tested for CD at 4 Major Hospitals Systems in California and Texas—2016–2020

Demographic Characteristics and Risk Factors	Patients, No. (%)				
	UCSF (n = 136)	UCSD (n = 123)	UCI (n = 35)	HHS (n = 176)	All Sites (n = 470)
Sex					
Male	86 (63)	86 (70)	19 (54)	113 (64)	304 (65)
Female	50 (37)	37 (30)	16 (46)	63 (36)	116 (35)
Age at initial test, median (IQR), y	50 (36, 63)	55 (39, 63)	52 (32, 65)	41 (35, 53)	…
Ethnicity					
Hispanic	53 (39)	64 (52)	18 (51)	60 (91)	295 (63)
Non-Hispanic	77 (57)	58 (47)	17 (49)	16 (9)	168 (36)
Declined/unknown	6 (4)	1 (1)	0 (0)	0 (0)	7 (1)
Region of birth					
South America	4 (3)	4 (3)	0 (0)	5 (3)	13 (3)
Central America	8 (6)	8 (7)	4 (11)	85 (48)	105 (22)
Mexico	22 (16)	39 (32)	6 (17)	60 (34)	127 (27)
United States	35 (26)	24 (20)	14 (40)	22 (13)	95 (20)
Other	15 (9)	9 (7)	5 (14)	4 (2)	33 (7)
Unknown	52 (38)	39 (32)	6 (17)	0 (0)	97 (21)
Travel history					
South America/Central America/Mexico	47 (35)	28 (23)	12 (34)	27 (15)	114 (24)
Other[a]	14 (10)	11 (9)	5 (14)	3 (2)	33 (7)
None/not recorded	75 (55)	84 (68)	18 (51)	146 (83)	323 (69)
Test indication[b]					
Heart failure	34 (25)	63 (51)	13 (37)	82 (47)	192 (41)
Other cardiac[c]	41 (30)	16 (13)	7 (20)	26 (15)	90 (19)
Dysphagia	3 (2)	5 (4)	3 (9)	10 (6)	21 (4)
Abdominal pain	2 (1)	1 (1)	4 (11)	6 (3)	13 (3)
All other	56 (41)	38 (31)	8 (23)	52 (29)	154 (33)
Ordering provider[b]					
Cardiology	66 (49)	70 (57)	13 (37)	25 (14)	174 (37)
Gastroenterology	4 (3)	1 (1)	1 (3)	1 (1)	7 (1)
Infectious diseases	10 (7)	5 (4)	4 (11)	37 (21)	56 (12)
Hematology/oncology	16 (12)	16 (13)	0 (0)	0 (0)	32 (7)
Internal medicine	5 (4)	14 (11)	9 (26)	107 (61)	135 (29)
OB/GYN	0 (0)	1 (1)	0 (0)	1 (1)	2 (0)
Other	35 (26)	16 (13)	8 (23)	5 (3)	64 (14)

Abbreviations: HHS, Harris Health System; IQR, interquartile range; OB/GYN, obstetrics and gynecology; UCI, UC Irvine; UCSD, UC San Diego; UCSF, UC San Francisco.

[a]Travel destinations documented, none of which are located in endemic regions of South America, Central America, or Mexico.

[b]Of initial commercial tests. The total numbers of tests and patients were 155 and 136, respectively, for UCSF, 139 and 123 for UCSD, 40 and 35 for UCI, and 291 and 176 for HHS.

[c]Cardiac test indication other than heart failure.

confirmed CD before end-organ damage develops. Primary care and routine perinatal testing were rare among the studied hospital systems. Risk-based screening in the primary care setting, rather than symptom-based diagnosis in specialty clinics, affords the greatest opportunity for prevention and early intervention. In addition, gynecologic and prenatal care visits provide timely opportunities to screen at-risk reproductive-age women for CD, allowing screening of infants and other children of infected women and early treatment of the women themselves. Preconception treatment has been shown to decrease the likelihood of vertical transmission by >95% [14].

In addition to diagnostic gaps, our data show gaps in documentation that impede the identification of at-risk patients. None of the health systems in the study mandated standard documentation of country of origin. While birth in an endemic region is an incomplete estimate of CD risk, it can help identify the population likely to benefit from screening and, consequently, gaps in appropriate testing. More than two-thirds of Hispanic people in the United States were born in the continental United States or Puerto Rico and therefore have a risk of *T. cruzi* infection similar to that of other non-Hispanic US residents [15]. As such, birth in an endemic country is a more appropriate screening criterion for CD than Hispanic ethnicity.

The strengths of this study include involvement of multiple major healthcare systems across two states serving large patient populations from continental Latin America and systematic

Table 2. Regional Associations and Outcomes Following Initial Positive Result With Commercial Assay

Patient and Test Factors	Initial Tests Ordered, No. (%)				
	UCSF (n = 136)	UCSD (n = 123)	UCI (n = 35)	HHS (n = 176)	All Sites (n = 470)
Initial test positivity	12 (9)	15 (12)	6 (17)	14 (8)	47 (10)
Initial test positivity stratified by region of birth					
South America	0/4 (0)	0/4 (0)	0/0 (–)	1/5 (20)	1/13 (8)
Central America	3/8 (38)	2/8 (25)	2/4 (50)	9/85 (11)	16/105 (15)
Mexico	5/22 (23)	9/39 (23)	1/6 (17)	4/60 (7)	19/127 (15)
United States	2/35 (6)	3/24 (13)	2/14 (14)	0/22 (0)	7/95 (7)
Other	1/15 (7)	0/9 (0)	1/5 (20)	0/4 (0)	2/33 (6)
Unknown	1/52 (2)	1/39 (3)	0/6 (0)	0/0 (–)	2/97 (2)
Initial test positivity stratified by test indication					
Heart failure	9/34 (26)	10/63 (16)	2/13 (15)	6/82 (7)	27/192 (14)
Other cardiac	3/41 (7)	2/16 (13)	3/7 (43)	3/26 (12)	11/90 (12)
Dysphagia	0/3 (0)	1/5 (20)	0/3 (0)	2/10 (20)	3/21 (14)
Abdominal pain	0/2 (0)	0/1 (0)	1/4 (25)	2/6 (33)	3/13 (23)
Other	0/56 (0)	2/38 (5)	1/8 (13)	2/52 (4)	5/154 (3)
Outcome after initial positive result[a]					
No subsequent testing	4 (33)	6 (40)	3 (50)	7 (50)[b]	20 (43)
Repeated commercial testing	4 (33)	6 (40)	2 (33)	1 (7)[c]	13 (28)
Confirmatory testing sought at CDC	6 (50)[d]	7 (47)[e]	3 (50)[d]	6 (43)	22 (47)
Confirmed positive by CDC testing	4 (33)	4 (27)	2 (33)	6 (43)	16 (34)

Abbreviations: CDC, Centers for Disease Control and Prevention; HHS, Harris Health System; UCI, UC Irvine; UCSD, UC San Diego; UCSF, UC San Francisco.

[a]Percentages for outcomes are the percentage of initial positive tests. The percentage for each outcome will not add up to 100% when repeated commercial testing and CDC confirmation were sought for the same patients. See subsequent footnotes.

[b]For 3 patients, infectious diseases physician wrote that they intended to order confirmatory testing at CDC, but tests were not found in the electronic health record.

[c]This patient had send-out testing performed by 2 commercial laboratories using 2 different tests, which would be considered confirmatory (rather than simple "repeat" testing, which is not confirmatory when the same test is run twice).

[d]Two patients had both repeated commercial testing and CDC confirmatory testing.

[e]Four patients had both repeated commercial testing and CDC confirmatory testing.

collection of data using laboratory information systems and electronic health records. Limitations include possible incomplete capture of testing events that fell outside the 5-year study period or were not documented in the health record (eg, CDC confirmatory testing not uploaded to the EHR). In addition, data on clinical setting (ie, inpatient or outpatient) and antiparasitic treatment were not extracted from the EHR.

Ultimately, our findings indicate that healthcare systems serving large at-risk populations should improve CD screening and diagnostic testing practices. Published recommendations [15] suggest that standardized screening programs should be implemented for the following groups: (1) patients—particularly younger patients—reporting >6 months of residency in an endemic area or born to a mother from an endemic area and (2) at-risk reproductive age women during prenatal care or in primary care settings. Precedent exists for standardized screening to prevent potential CD transmission events, including widespread blood donation and allograft transplant screening, but this is not yet the standard of care for other at-risk patient groups.

The problem of incomplete confirmatory testing could be addressed through clinical laboratories, which provide testing oversight for individual healthcare systems. Laboratory directors could implement test result comments or provide clinical consultation to ensure appropriate follow-up testing for initial positive results. Electronic ordering systems could be used to standardize saving serum samples for reflex testing to obviate the need for additional blood collection when the screening test result is positive. Such approaches are relatively simple and inexpensive solutions that can help overcome the current lack of confirmatory testing and patient loss to follow-up.

This study underscores widespread undertesting for CD, particularly for at-risk people early in their lives, before irreversible structural sequelae develop, as well as gaps in documentation that impair identification of at-risk patients. Future prospective studies are needed to address the magnitude of undertesting and develop interventions to improve knowledge, awareness, and diagnosis of this neglected infectious disease.

Notes

Financial support. This work was supported by a Grant for Emerging Researchers/Clinicians Mentorship (G.E.R.M.) Program award through the Infectious Diseases Society of America.

Potential conflicts of interest. C. B. receives royalties from Wolters Kluwer publishers for UpToDate topics on epidemiology and management of Chagas disease. All other authors

report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Bern C, Messenger LA, Whitman JD, Maguire JH. Chagas disease in the United States: a public health approach. Clin Microbiol Rev **2019**; 33:10–128.
2. World Health Organization. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. Wkly Epidemiol Rec **2015**; 90:33–44.
3. Nunes MCP, Beaton A, Acquatella H, et al. Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American heart association. Circulation **2018**; 138:e169–209.
4. Lynn MK, Bossak BH, Sandifer PA, Watson A, Nolan MS. Contemporary autochthonous human Chagas disease in the USA. Acta Trop **2020**; 205:105361.
5. Voelker R. Congenital Chagas disease reported in United States. JAMA **2012**; 308:443.
6. Nunes MCP, Dones W, Morillo CA, Encina JJ, Ribeiro AL, Council on Chagas Disease of the Interamerican Society of Cardiology. Chagas disease: an overview of clinical and epidemiological aspects. J Am Coll Cardiol **2013**; 62: 767–76.
7. Meymandi S, Hernandez S, Park S, Sanchez DR, Forsyth C. Treatment of Chagas disease in the United States. Curr Treat Options Infect Dis **2018**; 10:373–88.
8. Pan American Health Organization. Guidelines for the diagnosis and treatment of Chagas disease. Washington, DC: Pan American Health Organization, **2019**.
9. Khullar D, Chokshi DA. Challenges for immigrant health in the USA—the road to crisis. Lancet **2019**; 393:2168–74.
10. Mills RM. Chagas disease: epidemiology and barriers to treatment. Am J Med **2020**; 133:1262–5.
11. Stimpert KK, Montgomery SP. Physician awareness of Chagas disease, USA. Emerg Infect Dis **2010**; 16:871–2.
12. Harris PA, Taylor R, Minor BL, et al. The REDCap Consortium: building an international community of software platform partners. J Biomed Inform **2019**; 95:103208.
13. Irish A, Whitman JD, Clark EH, Marcus R, Bern C. Updated estimates and mapping for prevalence of Chagas disease among adults, United States. Emerg Infect Dis **2022**; 28:1313–20.
14. Fabbro DL, Danesi E, Olivera V, et al. Trypanocide treatment of women infected with *Trypanosoma cruzi* and its effect on preventing congenital Chagas. PLoS Negl Trop Dis **2014**; 8:e3312.
15. Forsyth CJ, Manne-Goehler J, Bern C, et al. Recommendations for screening and diagnosis of Chagas disease in the United States. J Infect Dis **2022**; 225:1601–10.