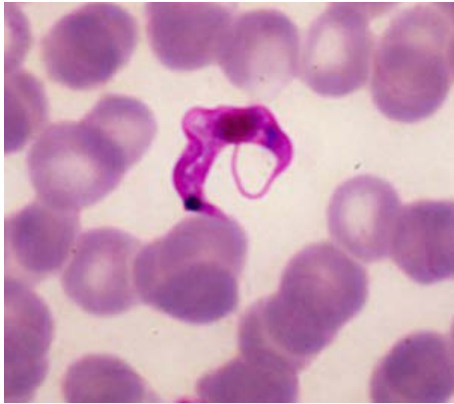


Chagas Disease



Trypanosoma cruzi

Norman Beatty, MD

Infectious Diseases Fellow

University of Arizona
College of Medicine

July 25th 2018



Triatoma recurva



Learning Objectives

- Background, transmission, clinical manifestations, diagnosis, and treatment/management
- Chagas disease in the United States
- Chagas disease in Arizona
- Chagas disease research in Arizona



Romaña's sign



Triatoma protracta

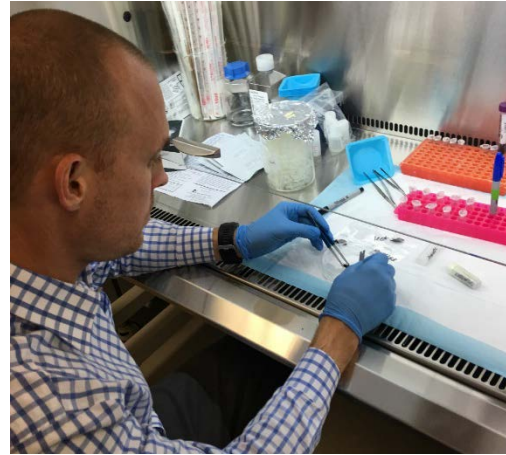


UA Kissing Bug Research Team



Disclosures

None to declare



Triatoma protracta



Triatoma rubida

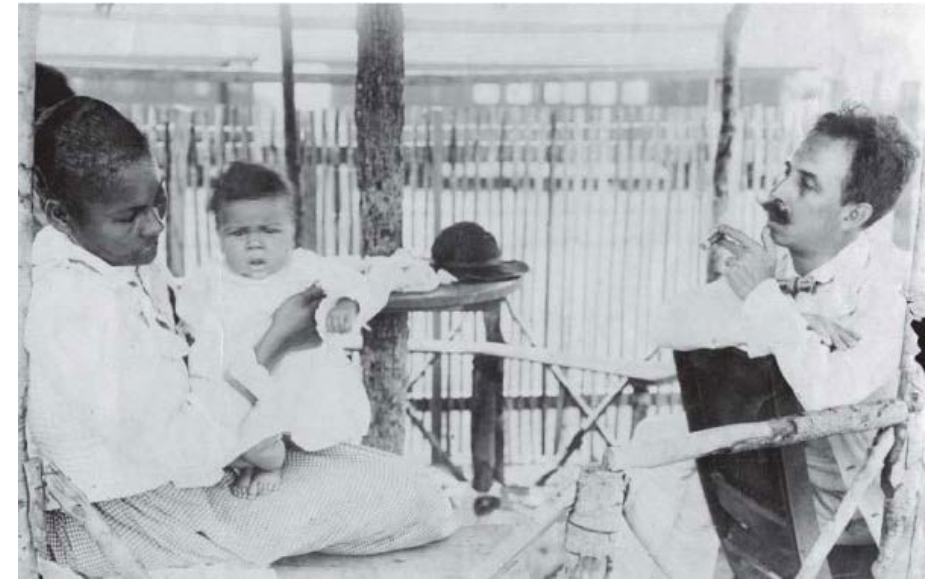


Bisbee, AZ



Chagas disease

This disease is named after **Dr. Carlos Chagas**
- Brazilian physician and epidemiologist

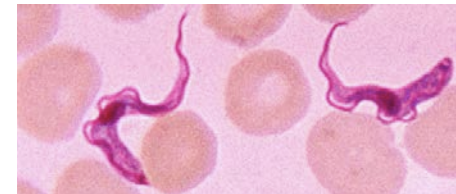


Dr. Chagas interviewing a villager, 1909

In **1909** he was sent to a small city in the **Amazon** to combat a malaria outbreak where he worked with villages for two years.

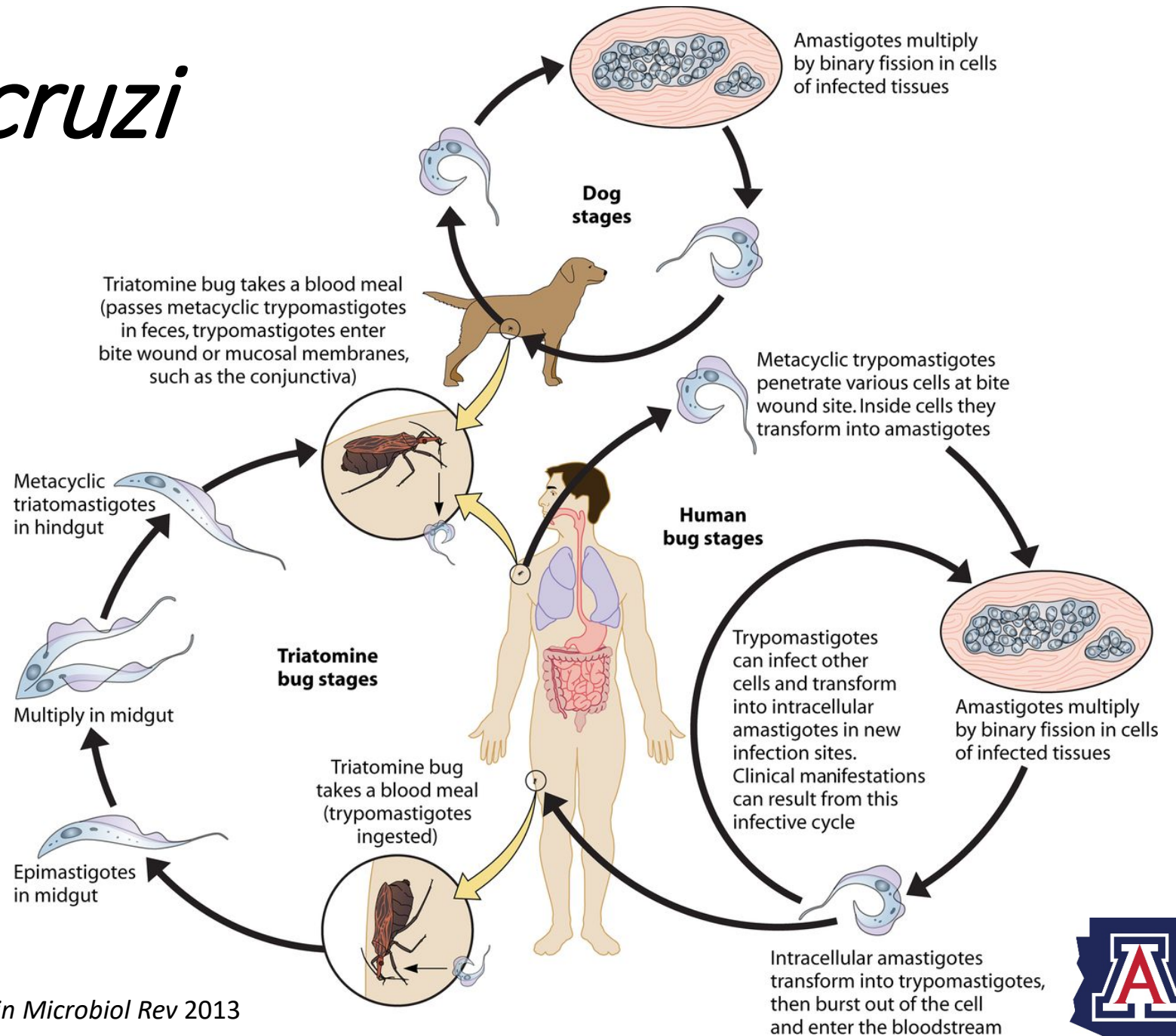
- He noticed during this field work a **blood sucking** insect feeding on the faces of these villagers at night.

- Demonstrated transmission of the protozoan parasite to **marmoset monkeys** that were bitten by an infected triatomine bugs.



Trypanosoma cruzi

- Kinetoplastid protozoan
- Infects mammalian hosts during defined stages in its complex life cycle
- Dogs serve as primary domestic reservoir



Adapted from Peterson et al. *Clin Microbiol Rev* 2013



Kissing bugs (Triatominae)



ENCONTROU UM DESTES INSETOS?



Não mate-o!

Proteja as mãos para pegar o inseto. Coloque-o em um pote com furos na tampa e entregue em um **POSTO DE INFORMAÇÃO DE TRIATOMÍNEOS/BARBEIROS (PIT)**.

- Harbor the **parasite** that can cause Chagas disease
- “Kissing bugs” are found throughout the **Americas**
- In Latin-America also known as “**vinchuca**” or “**barbeiro inseto**”
- 130+ triatomine can be infected by *T. cruzi*.¹

¹Bern et al. *Clin Microb Rev* 2011



Transmission of *T. cruzi* to Humans

Vector-borne via infected triatomines

- Feces contains parasite, enters through the bite site or mucous membranes

Congenital transmission

- Mother to Fetus

Blood transfusion

- Prior to 2007, countries that do not screen

Organ-transplantation

- Donor with *T. cruzi* infection

Oral ingestion

- Contaminated foods (contain the infected bug and/or feces)
- Açai palm fruit, guava juice, and juice prepared from sugarcane



Rhodnius prolixus taking a blood meal with **fecal drop** (courtesy of WHO)



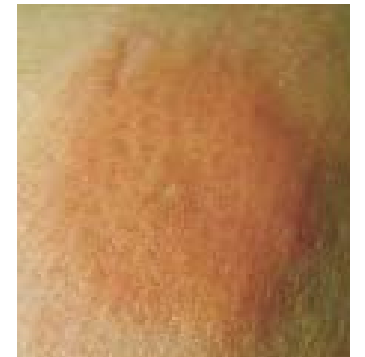
Chagas disease



Triatoma infestans biting human

Acute infection

- A person can be asymptomatic or develop a febrile illness
- Symptoms can last weeks to months then resolve
- **Signs/symptoms include: fever, enlarged lymph nodes, and fatigue**
- Patients with a weakened immune system can develop severe infections
 - Typically involving brain and heart
- **Chagoma** area of local inflammation at the site of **entry** of the parasite
- **Romaña's sign** can be seen when infection enters the mucosa near eye



Chagoma

Indeterminate Phase

- After acute infection some people enter the indeterminate phase
- These patients are **asymptomatic and with low-grade parasitemia**
- This lasts many years and may resolve spontaneously or **progress to chronic disease**

Chronic Chagas disease

- Affects two major organ systems, the **cardiac and gastrointestinal systems**



Chronic Chagas disease

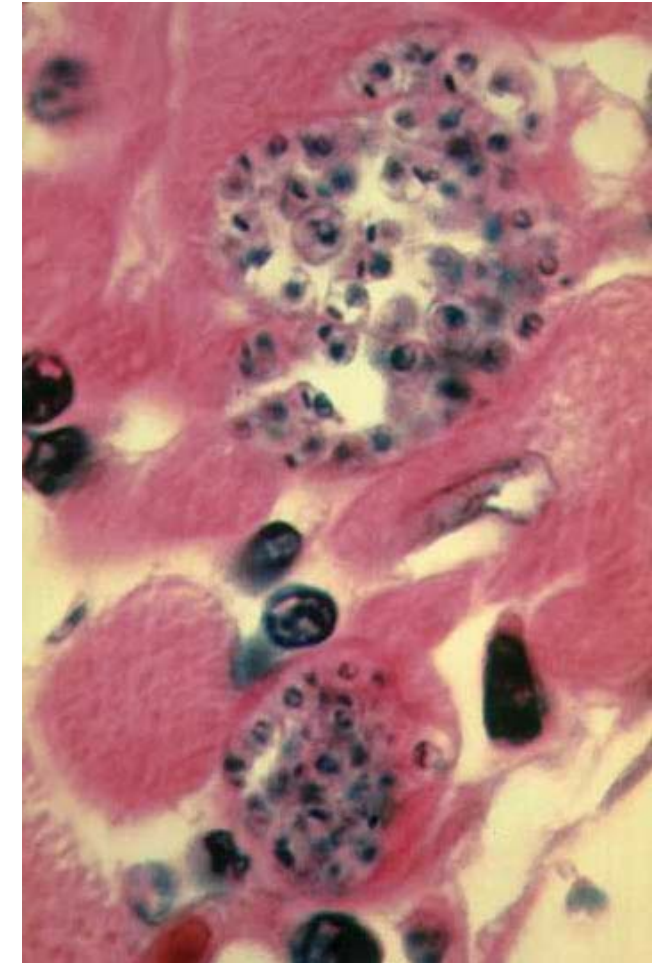
Heart involvement

- Manifested by abnormal heart rhythms
- Dilated heart chambers causing heart failure
- Most **deaths** are due to **cardiac involvement**

Gastrointestinal tract

- Can affect the **esophagus down to the colon**
- Difficult and painful swallowing and regurgitation
- Constipation, abdominal pain, or perforation.

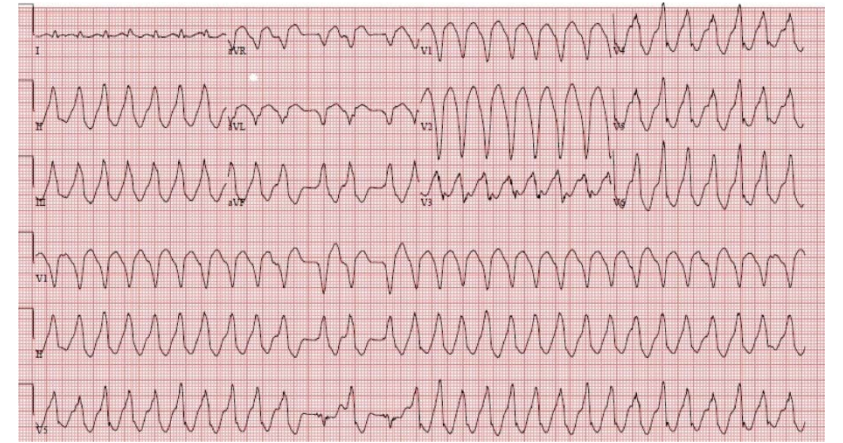
Approximately up to 30% of people infected with *T. cruzi* will develop chronic Chagas disease



T. cruzi amastigotes in cardiac tissue



Chagas heart disease



Electrical abnormalities typically arise first

- Right bundle branch block >> Left bundle branch block
- 1st degree, 2nd degree and complete heart block
- Feared complication is development of sudden cardiac arrest from **ventricular fibrillation**
- **ICD placement is a consideration in some patients**
- Amiodarone is the antiarrhythmic of choice
- Ablation and cardiac resynchronized therapies have been used, efficacy leaning toward benefit

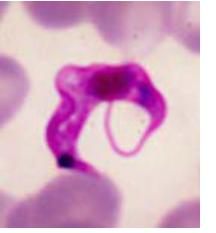
Progressive heart failure

- Generally left-sided, **progressive reduced ejection fraction**, warrants standard medical management
- Ventricular aneurysm can occur
- **Heart transplant has now successfully been done, reactivation is rare cause of death**

Thromboembolic disease (stroke and pulmonary embolism)

- **Higher** compared to other types of cardiomyopathy
- Anticoagulation has been used in those at-risk

Diagnosis of Chagas disease



T. cruzi trypomastigote

- **Direct visualization of parasite** (blood smear, tissue pathology)
 - Uncommon, typically only acute phase
- **Culture of *T. cruzi* in laboratory setting** (extremely uncommon)
- **Detection of *T. cruzi* DNA via PCR**
 - Utilized to monitor those who have received organ from a donor who was found to have Chagas after the fact
 - Can be used on blood or tissue specimens
 - New research showing undetectable DNA levels after administration of Benznidazole
- **Serology (IgM and IgG)**
 - **Screening tests** – a single assay, used for testing in a population low prevalence
 - **Confirmatory tests** – typically highly specific, only available at CDC in the US
 - **Point-of-care rapid test** (InBios Chagas Detect Plus)



Diagnosis of Chagas disease - Serology



- **Two serological tests** based on **different antigens** (whole-parasite lysate and recombinant antigens) and/or **techniques** (ELISA and IFA) are used in parallel
- **Reference labs in the United States:**
 - FDA-cleared ELISA tests:
 - Ortho *T. cruzi* ELISA, Wiener Chagatest ELISA Recombinante, Hemagen ELISA
 - **Associated regional university pathologists** (ARUP) – IgM (IFA), IgG (ELISA)
 - **Mayo clinic laboratories** – IgG (Hemagen)
 - **Quest diagnostics** – IgG (EIA)
 - **FDA-cleared rapid assay** – **InBios Chagas Detect Plus**
- **Confirmatory tests in the United States: CDC**
 - *T. cruzi* IgG (EIA) – 100% sensitive, 98.7% specific
 - Tripomastigote excreted and secreted antigen (TESA) – 97.6% sensitive, 96.6% specificity



Chagas disease – Treatment

Table 1. Recommendations for antiparasitic treatment of *T. cruzi* infection

Clinical group	Treatment recommendation [44]	Recommendation, evidence level [24]
Infants with congenital infection	Treat	I, B
Any acute phase	Treat	I, B
Reactivation in immunocompromised	Treat	I, C
Children in chronic indeterminate phase	Treat	I, A
Adolescents in chronic indeterminate phase	Treat	IIa, B
Seropositive organ donors	Treat	I, C
Recipients of organs from seropositive donors	Probable treat	IIa, C
Laboratory accidents	Treat	IIa, C
Women of childbearing age	Treat	NA
Chronic indeterminate phase, adults 19–50 years old without cardiomyopathy (Kuschnir 0)	Probable treat	IIa, B
Chronic phase, cardiomyopathy without advanced heart disease (Kuschnir I, II)	Probable treat	IIb, C
Chronic phase with advanced cardiomyopathy (Kuschnir III)	Probable non treat	III, C
Chronic indeterminate phase, adults older than 50 without advanced cardiomyopathy (Kuschnir 0, I, II)	Possible treat; case-by-case evaluation	IIb, C [20]
Early digestive involvement without advanced cardiomyopathy (Kuschnir 0, I, II)	Probable treat	IIa, C
Pregnant women	Definite non-treat	III, C



Chagas disease – Treatment

Table 1. Recommendations for antiparasitic treatment of *T. cruzi* infection

Clinical group	Treatment recommendation [44]	Recommendation, evidence level [24]
Infants with congenital infection	Treat	I, B
Any acute phase	Treat	I, B
Reactivation in immunocompromised	Treat	I, C
Children in chronic indeterminate phase	Treat	I, A
Adolescents in chronic indeterminate phase	Treat	IIa, B
Seropositive organ donors	Treat	I, C
Recipients of organs from seropositive donors	Probable treat	IIa, C
Laboratory accidents	Treat	IIa, C
Women of childbearing age	Treat	NA
Chronic indeterminate phase, adults 19–50 years old without cardiomyopathy (Kuschnir 0)	Probable treat	IIa, B
Chronic phase, cardiomyopathy without advanced heart disease (Kuschnir I, II)	Probable treat	IIb, C
Chronic phase with advanced cardiomyopathy (Kuschnir III)	Probable non treat	III, C
Chronic indeterminate phase, adults older than 50 without advanced cardiomyopathy (Kuschnir 0, I, II)	Possible treat; case-by-case evaluation	IIb, C [20]
Early digestive involvement without advanced cardiomyopathy (Kuschnir 0, I, II)	Probable treat	IIa, C
Pregnant women	Definite non-treat	III, C



Chagas disease – Treatment

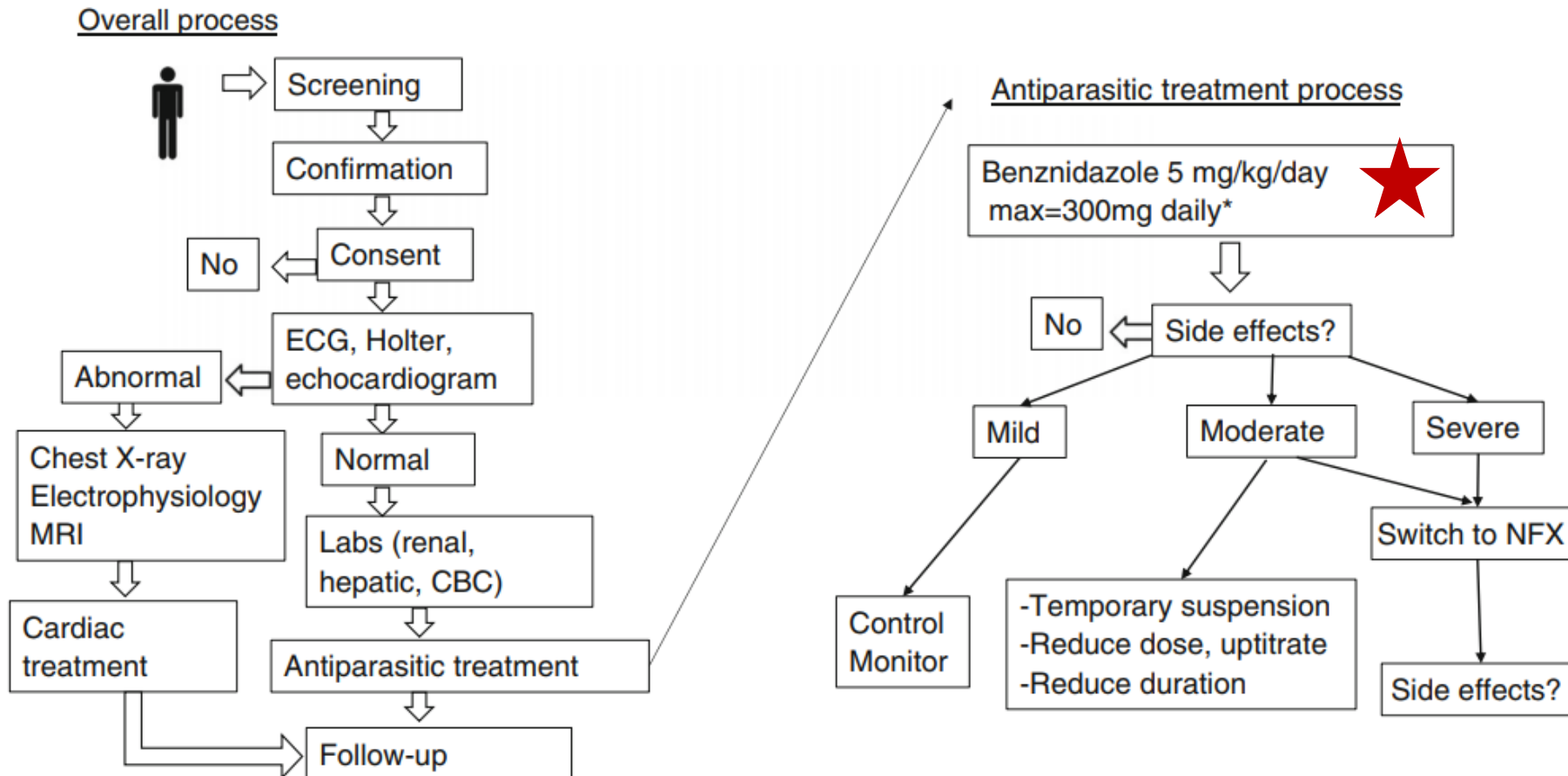
Table 1. Recommendations for antiparasitic treatment of *T. cruzi* infection

Clinical group	Treatment recommendation [44]	Recommendation, evidence level [24]
Infants with congenital infection	Treat	I, B
Any acute phase	Treat	I, B
Reactivation in immunocompromised	Treat	I, C
Children in chronic indeterminate phase	Treat	I, A
Adolescents in chronic indeterminate phase	Treat	IIa, B
Seropositive organ donors	Treat	I, C
Recipients of organs from seropositive donors	Probable treat	IIa, C
Laboratory accidents	Treat	IIa, C
Women of childbearing age	Treat	NA
Chronic indeterminate phase, adults 19–50 years old without cardiomyopathy (Kuschnir 0)	Probable treat	IIa, B
Chronic phase, cardiomyopathy without advanced heart disease (Kuschnir I, II)	Probable treat	IIb, C
Chronic phase with advanced cardiomyopathy (Kuschnir III)	Probable non treat	III, C
Chronic indeterminate phase, adults older than 50 without advanced cardiomyopathy (Kuschnir 0, I, II)	Possible treat; case-by-case evaluation	IIb, C [20]
Early digestive involvement without advanced cardiomyopathy (Kuschnir 0, I, II)	Probable treat	IIa, C
Pregnant women	Definite non-treat	III, C



Chagas disease – Treatment / Management

Treatment of Chagas Disease in the USA *Meymandi et al.*



Nifurtimox can be requested from CDC via a donation from PAHO



Chagas disease in the 21st Century

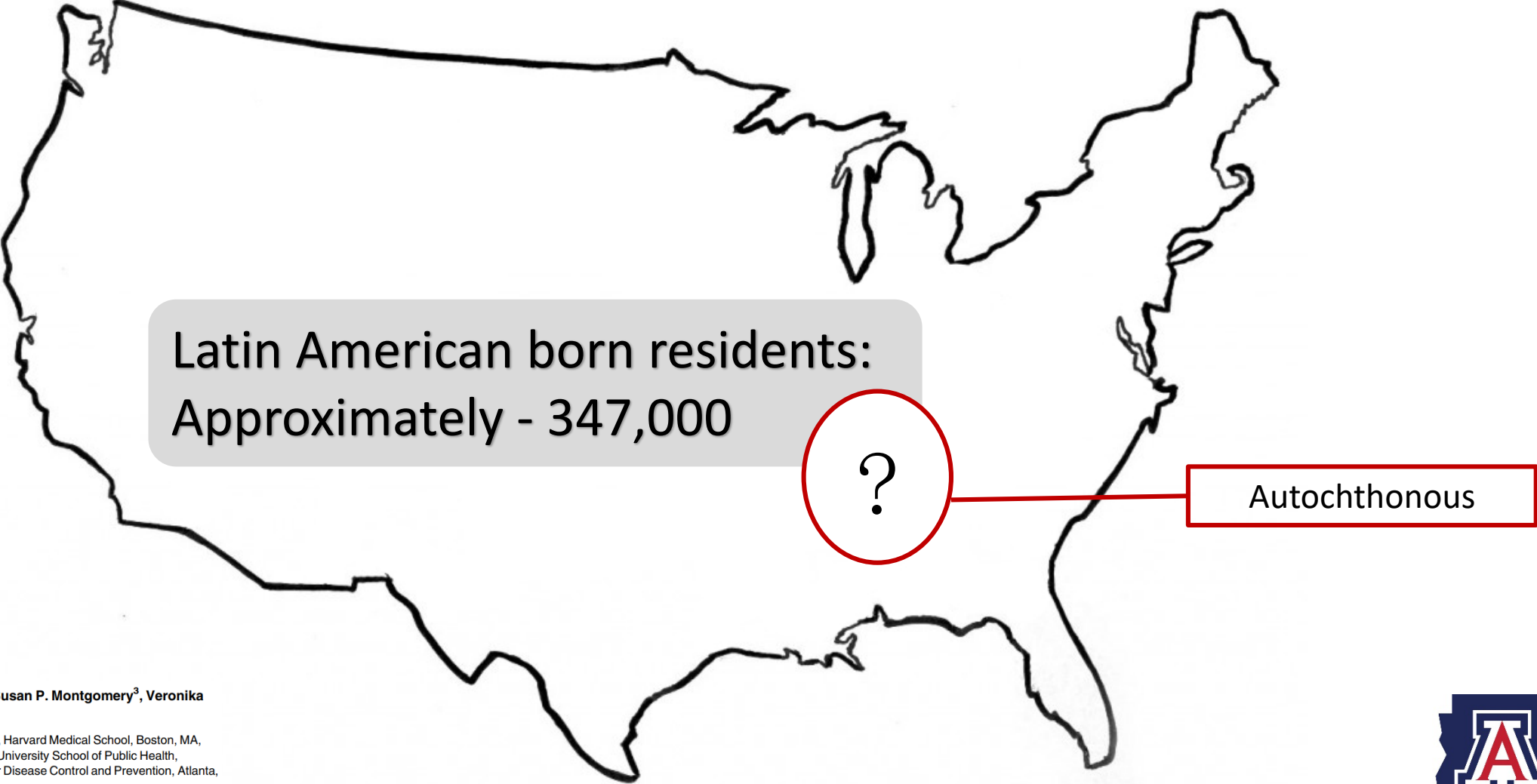
- **WHO estimates 8-10 million people globally**
- 180,000 people infected with *T. cruzi* in 2016
- WHO 2015 > 1 million have Chagas heart disease
- Mainly rural populations living in poverty
- Emigrants from endemic regions
- **Worldwide < 1% actually receive any treatment**



David Kuhn



Chagas disease in the United States



Jennifer Manne-Goehler^{1*}, Chukwuemeka A. Umeh², Susan P. Montgomery³, Veronika J. Wirtz²

¹ Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States of America, ² Department of Global Health, Boston University School of Public Health, Boston, MA, United States of America, ³ United States Centers for Disease Control and Prevention, Atlanta, GA, United States of America



Chagas disease in the United States

California – 70,000

Texas – 37,000

Florida – 18,000

New York – 17,000

Illinois – 9,000

New Jersey – 8,600

Virginia – 7,300

Arizona – 6,400

Maryland – 6,000

Total US Burden – 347,000

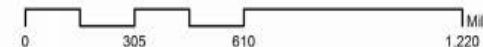


Chagas Estimate

0 - 999

1000 - 4999

5,000 - 71,000



Jennifer Manne-Goehler^{1*}, Chukwuemeka A. Umeh², Susan P. Montgomery³, Veronika J. Wirtz²

¹ Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States of America, ² Department of Global Health, Boston University School of Public Health, Boston, MA, United States of America, ³ United States Centers for Disease Control and Prevention, Atlanta, GA, United States of America

Chagas disease in the United States



- CDC has indicated that from 2007 to 2013 there have been **1,908 cases** reported to them¹
- **422 courses of either benznidazole or nifurtimox during this period¹**
- **Los Angeles County** – largest prevalence study out of UCLA²
 - Screened 4,755 Latin American-born, Overall prevalence 1.24%
 - Salvadorans – 3.45%
 - Mexican participates – Oaxaca 4.65%, Zacatecas 2.2%
 - **Estimating > 30,000 people may be infected in Los Angeles**



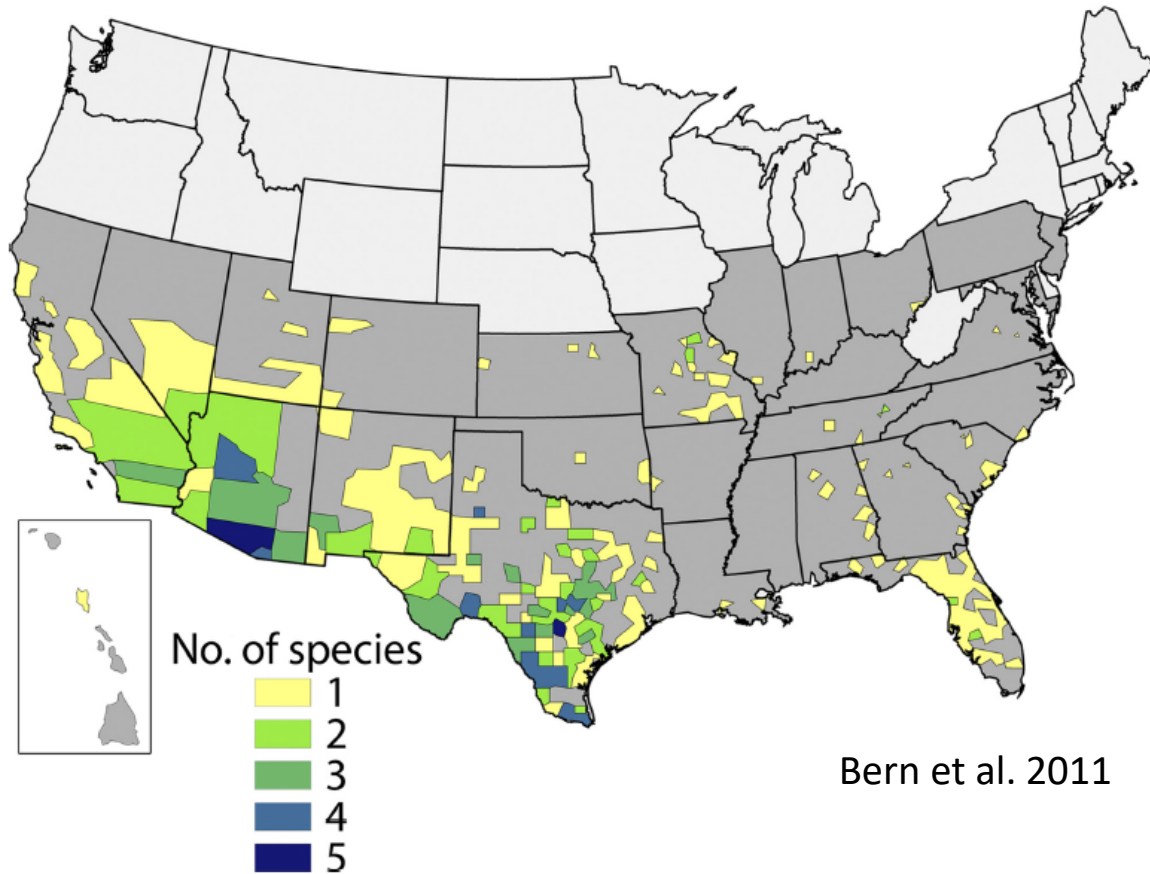
¹Manne-Goehler et al. Access to Care for Chagas Disease in the United States: A Health Systems Analysis. AJTMH 2015

²Meymandi et al. Prevalence of Chagas Disease in the Latin American-born Population of Los Angeles. CID 2017



Kissing Bugs in the United States

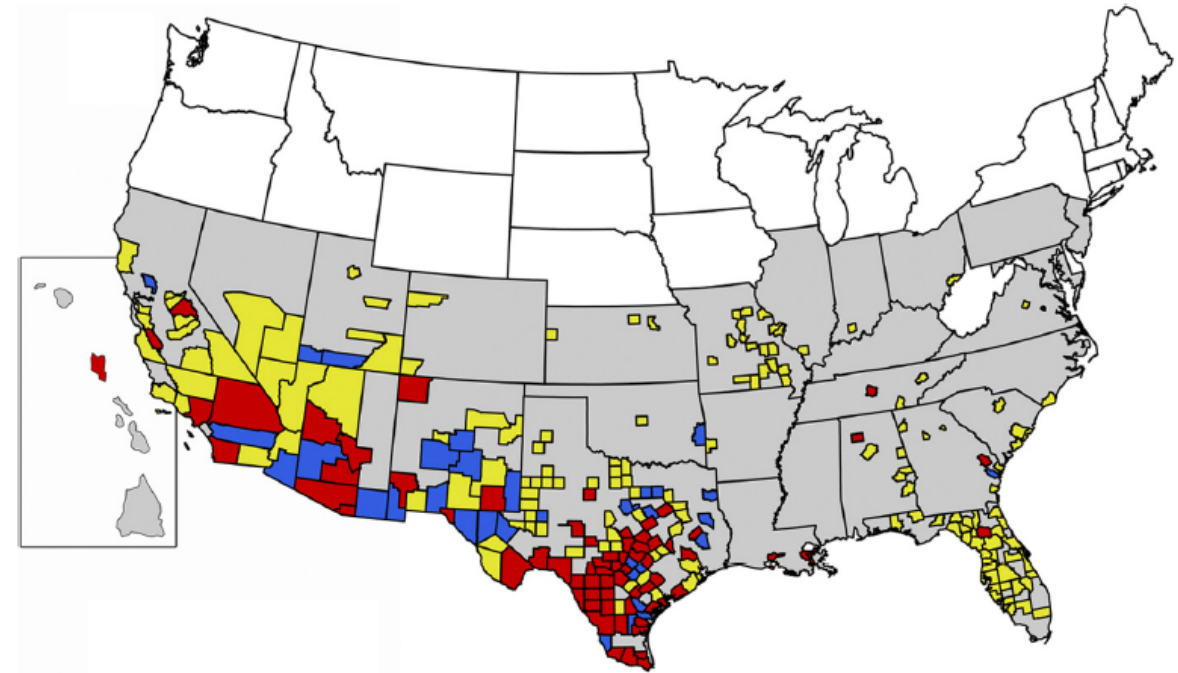
A.



Bern et al. 2011

Triatomine species per U.S. county

B.



Bern et al. 2011



Kissing bug exposure in Arizona



Triatoma recurva



Triatoma rubida



Triatoma protracta

Three most common species



5th instar – *T. rubida*

- Annual life-cycle
- 5 nymphal stages precede adult
- **Dispersal period (May through July)**
- Typically with each feed will mature to next stage
- Lay eggs summer months

Sylvatic, peridomestic, and domestic exposure reported throughout Arizona



Kissing bug bites



Beatty N, Klotz S. The Midnight Bite! A kissing bug nightmare. Am J Med. 2018 Feb;131(2)

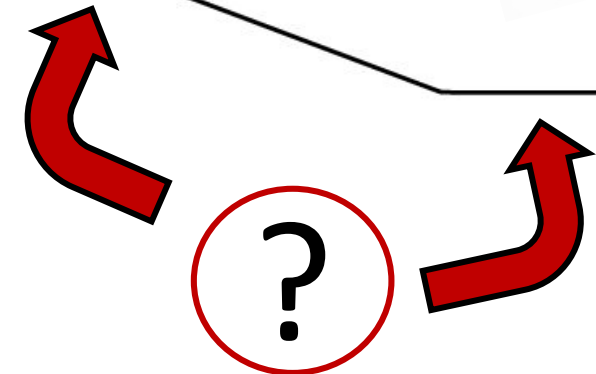
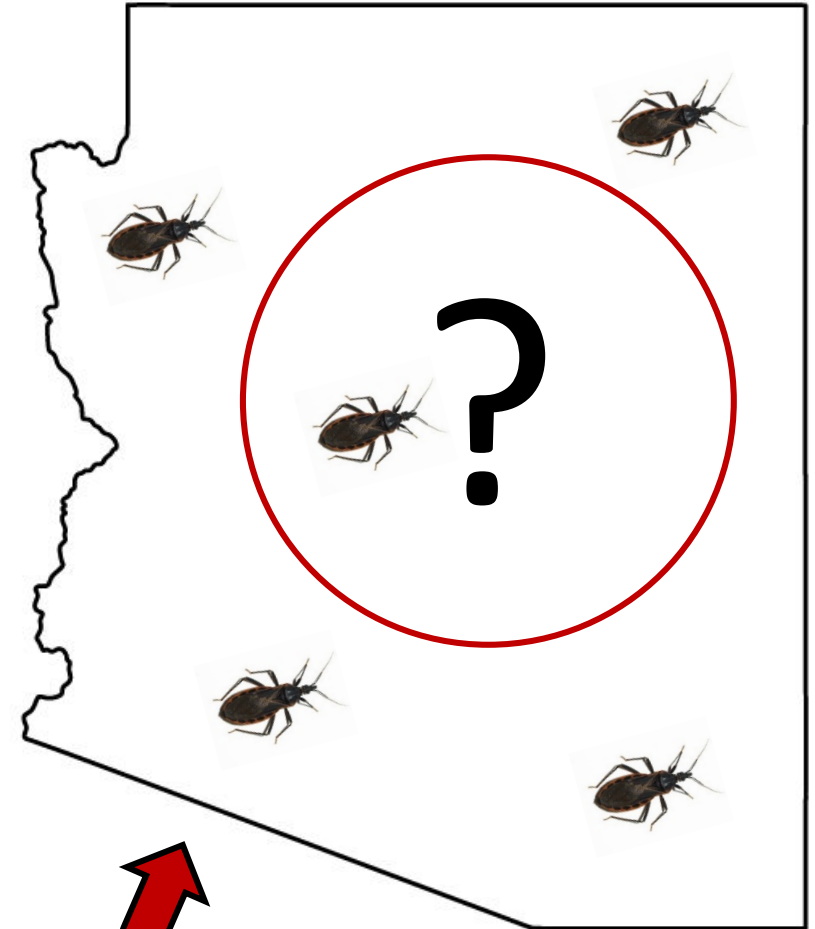
- **Typically painless during the bite**
- Local reaction, edema, erythema, raised papule or patch
- Systemic symptoms can occur; diffuse puritis, anxiety, tachycardia
- Anaphylaxis is known

Erythema and ecchymosis may take 2-3 weeks to resolve completely



Chagas disease in Arizona

- Very little is known about Chagas disease in Arizona
- We have at least **four *Triatoma* spp.** that harbor *T.cruzi*¹
- **Arizona Poison Control Center** receives approximately **100-150 calls** a year regarding bites from “kissing bugs”²



¹Bern et al. *Clin Microb Rev* 2011

²Unpublished data provided by Dr. Mazad Shirazi



Chagas disease reported to ADHS

- Reportable disease since 2008
- **Case definition updated 2017** – centered on laboratory evidence of *T. cruzi* infection

Confirmed case:

- Isolation of *T. cruzi* by microscopy OR culture OR detection DNA via PCR OR
- Confirmatory serology performed at CDC

Probable case:

- Evidence of *T. cruzi* antibodies on serologic assays, OR
- Reactive blood donor screen AND a secondary positive supplemental assay



Chagas disease reported to ADHS

- **79 unique cases** reported to ADHS since **2007** via concern for Chagas disease and/or laboratory evidence of possible *T. cruzi* infection
 - **61 cases had a positive *T. cruzi* test**
 - 13 cases negative *T. cruzi* testing
 - 4 unknown testing, 1 no testing done (after being bitten by kissing bug)
- **46 cases reported from blood bank screening**
 - (UBS=34, ARC=9, UBS/ARC=1, Mexico=1, unknown=1)
 - **38 cases without or unknown confirmatory testing done**
- **21/79 (26.5%) lost to f/u at some point during investigation**
- **18 cases where testing was requested due to concern for Chagas disease**
 - 6 cases due to kissing bug bite exposure (Arizona=3, Peru=1, Trinidad=1, unknown location=1)

5 confirmed cases as of 05/2018

- Heart transplant=2
- Lost f/u=1
- Asymptomatic=1
- **Autochthonous=1**

2 cases sudden cardiac death, positive *T. cruzi* serology and clinical suspicion, (confirmatory unable to be sent)



Chagas disease in Arizona

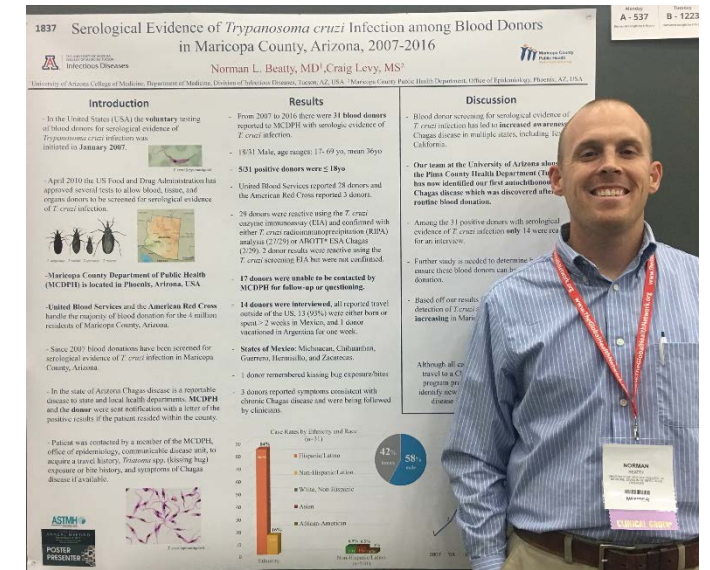
Serological evidence of *Trypanosoma cruzi* Infection among Blood Donors in Maricopa County, Arizona, 2007-2016

Norman L Beatty¹, Craig Levy²

¹University of Arizona College of Medicine, Tucson, Arizona, USA

²Maricopa County Public Health Department, Phoenix, Arizona, USA

- **31 donors** reported to MCPHD from blood service banks
- 14/31 were reached for questioning, **17 lost to follow-up** (58.5%)
- **5/31 (16%) ≤ 18 years-old**
- Median age 36yo, 58% male
- All had travel outside of the US, 13 were either born or spent > 2 weeks in Mexico, and 1 donor vacationed in Argentina
- **3/14 were manifesting clinical signs/symptoms of chronic Chagas disease**



Chagas disease in Arizona

Reported cases by county:

Maricopa - 59

Pima – 7

- 1 local (confirmed)

- 1 local (suspected)

Pinal – 7

Coconino – 3

Mohave – 1

- 1 local (suspected)

La Paz – 1

Yavapai – 1

Yuma – 0

Gila – 0

Santa Cruz – 0

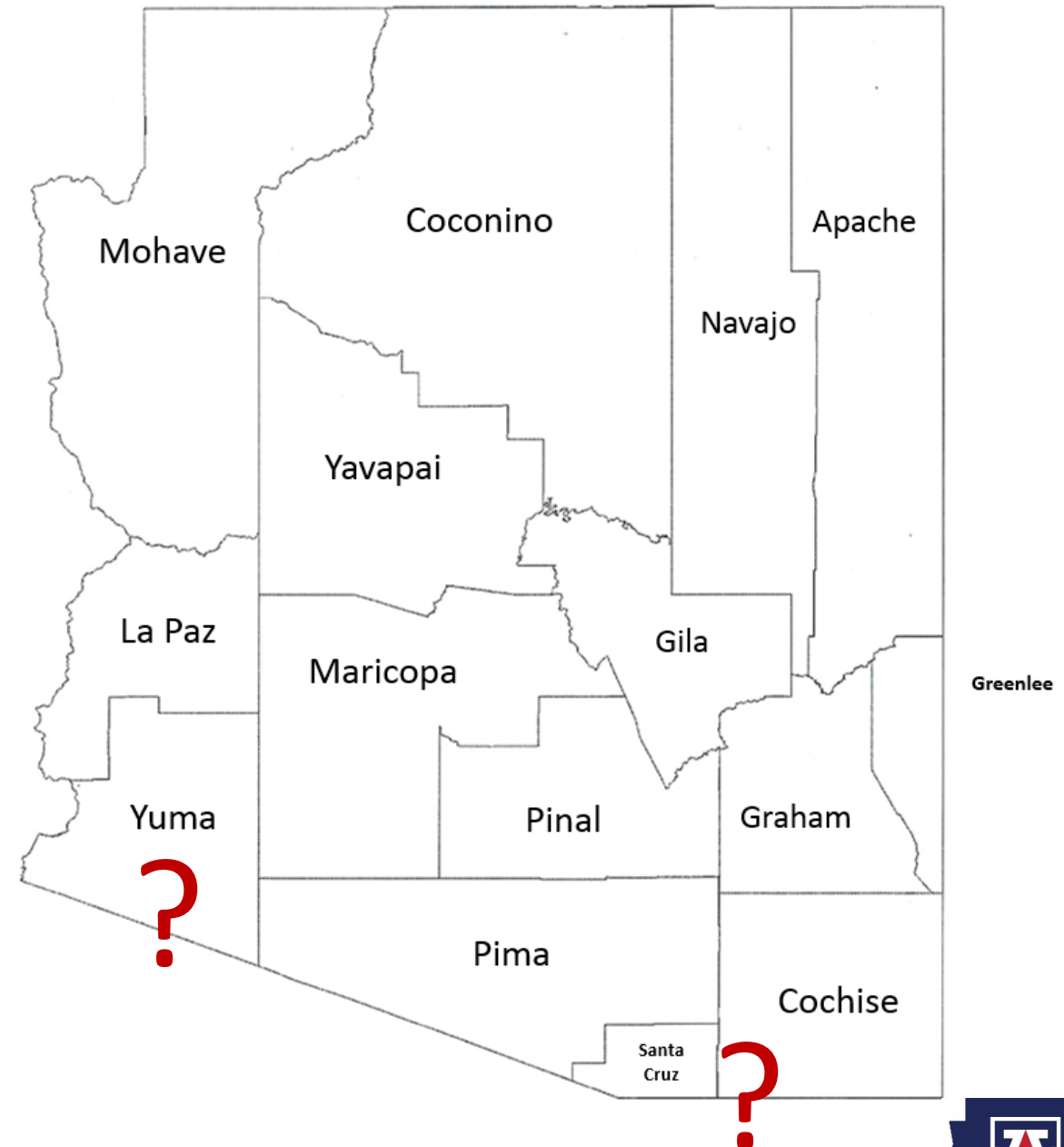
Cochise – 0

Graham – 0

Greenlee – 0

Navajo – 0

Apache – 0



Are we testing at-risk populations?



Chagas disease in Arizona

Evidence of Autochthonous Transmission of Chagas Disease in Arizona

Norman L. Beatty¹, Carlos M. Perez-Velez², Hayley D. Yaglom³, Sharon Carson², Eugene Liu⁴, Zain I. Khalpey⁵, Stephen A. Klotz¹, Sean P. Elliott⁶

¹University of Arizona College of Medicine, Department of Medicine, Division of Infectious Diseases, Tucson, Arizona, USA

²Pima County Health Department, Tucson, Arizona, USA

³Arizona Department of Health Services, Office of Infectious Disease Services, Bureau of Epidemiology & Disease Control, Phoenix, Arizona, USA

⁴Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

⁵University of Arizona College of Medicine, Department of Surgery, Division of Cardiothoracic Surgery, Tucson, AZ, USA

⁶University of Arizona College of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Tucson, Arizona, USA

- 16yo F, no past medical history, native to Tucson, AZ
- **Donated blood to American Red Cross (October 2016), Routine screening was positive**
- Further confirmatory testing at CDC was also positive for *T. cruzi* infection
- Patient received benznidazole therapy (6wks)
- **Extensive kissing bug exposure while living in Tucson:**

History “pack-rat” infestation at home, kissing bug sightings inside/outside home

Current home located in foothills of Santa Catalina Mountains

Kissing bugs collected at current home including nymphs – **all were positive for *T. cruzi* via PCR**

Only significant travel was to “rocky point” Mexico for a family vacation for three days

Stayed in modern hotel on the beach, No camping, no animal exposure

No other travel outside the US to endemic regions of *T. cruzi*

No other significant exposure risks (raw/unprocessed foods), Mother tested negative for serological evidence of *T. cruzi*



ASTMH
AMERICAN SOCIETY OF TROPICAL MEDICINE & HYGIENE
ADVANCING GLOBAL HEALTH SINCE 1918

**THE AMERICAN JOURNAL OF
TROPICAL MEDICINE AND HYGIENE**
official Journal of the American Society of
Tropical Medicine and Hygiene



Morbidity and Mortality Weekly Report (MMWR)

[CDC](#) > [MMWR](#)

Chagas Disease Surveillance Activities – Seven States, 2017

State	Year reporting began	Primary objectives for Chagas disease surveillance	Reasons for initiating Chagas disease surveillance
Arizona	2008	Identify source of infection; monitor acute and chronic disease burden	Presence of <i>T. cruzi</i> -positive triatomines in the state
Arkansas	2013	Identify source of infection; monitor acute and chronic disease burden	Understand the potential burden of locally acquired, congenital, and imported cases; create awareness among physicians working with populations at risk
Louisiana	2013	Identify source of infection; monitor incident cases	Monitor incident cases; assess risk factors for local autochthonous transmission
Mississippi	2010	Identify source of infection; monitor acute and chronic disease burden	Determine whether cases identified by blood banks are caused by local autochthonous transmission; monitor extent of Chagas disease testing occurring at laboratories throughout the state
Tennessee	2010	Identify source of infection; monitor acute and chronic disease burden	Identification of <i>T. cruzi</i> -infected triatomines and nonhuman hosts during a serosurvey
Texas	2013	Identify source of infection; monitor acute and chronic disease burden	Monitor incident cases; assess risk factors for local autochthonous transmission; increase awareness of physicians working with populations at risk
Massachusetts	2008	Monitor chronic disease phase burden	Ensure that blood donors identified through screening are referred for appropriate care

Chagas disease research in Arizona



Home News Events

KISSING BUGS

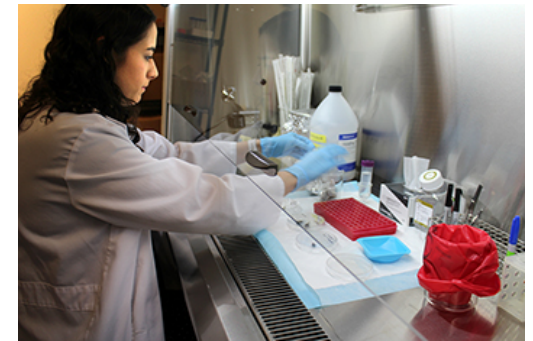
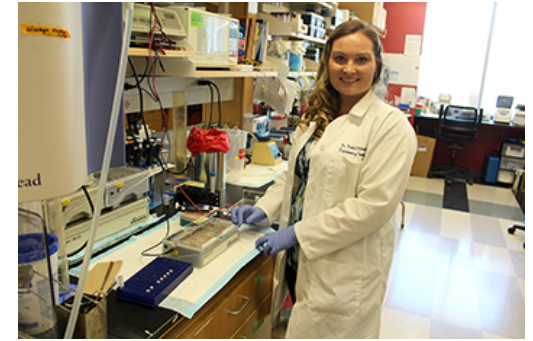
CHAGAS DISEASE

RESEARCH &
PUBLICATIONS

OUR TEAM

GET INVOLVED

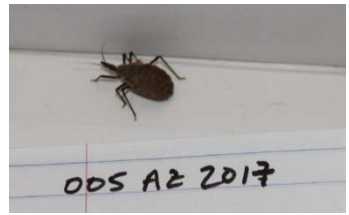
CONTACT US



Kissingbug.arizona.edu



Chagas disease research in Arizona



Carriage Rates of *Trypanosoma cruzi* among Kissing Bugs in Southern Arizona¹

219 kissing were dissected (*T. rubida*, N=114; *T. recurva*, N=87; *T. protracta*, N=18)

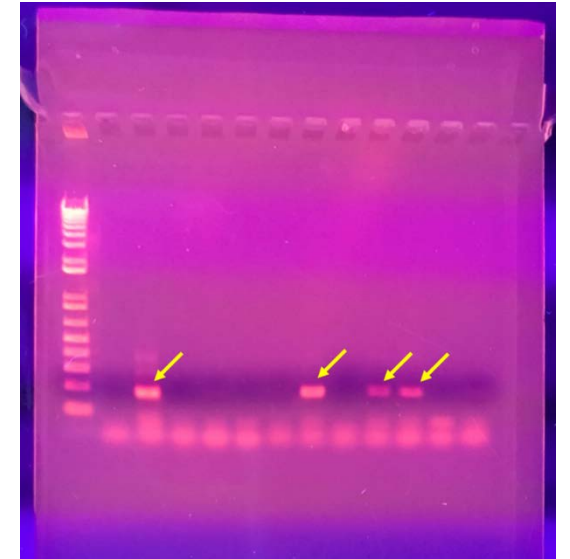
Specimens were provided from our citizen science program and field collections

28.8% (63/219) positive for *Trypanosoma cruzi*

T. rubida - **41.2%** (47/114)

T. protracta - 22.2% (4/18)

T. recurva - 13.8% (12/87)



54.7% (29/53) of *T. rubida* collected from Tucson were positive

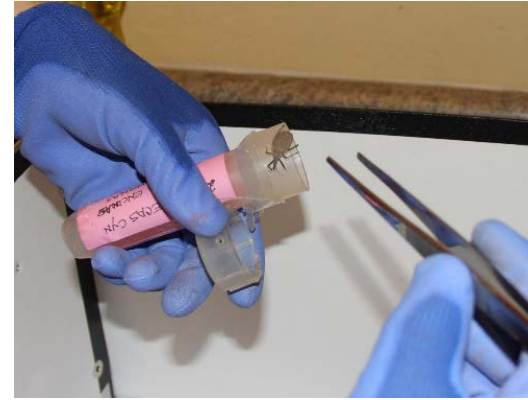
¹Beatty et al. Abstract presentation ASTHM 2018



Citizen Science Project



UA undergraduate research assistant, Fernanda Egurrola



- Inviting community members to safely collect kissing bugs
- Complete home and bite surveys



Tucson and Bisbee Projects

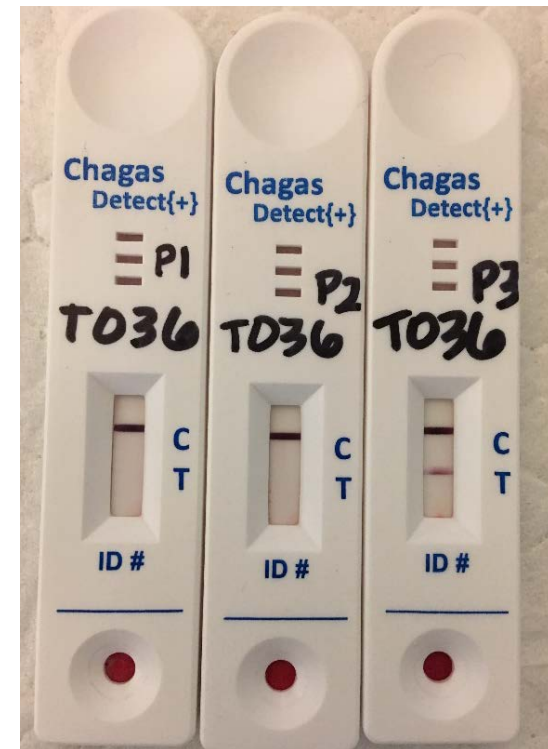
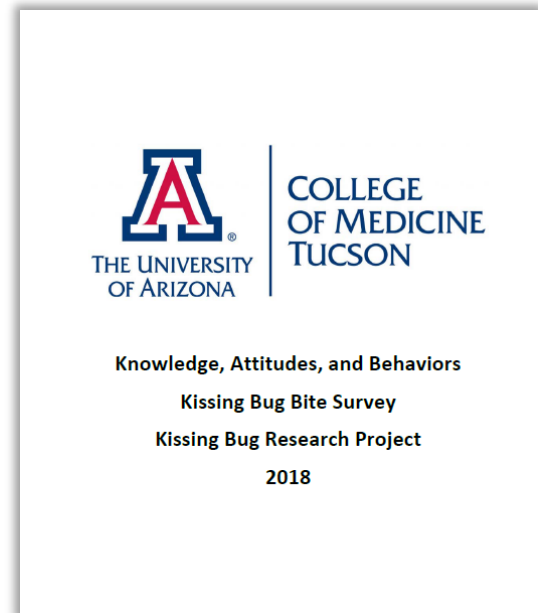
- **Collecting survey data:**
 - Knowledge, attitudes, behaviors with regards to kissing bugs
 - Kissing bug bites; reactions...
 - Environmental/housing and ecological factors
- **Kissing bugs collected from homes being tested for *T. cruzi***
 - Received over 300 bugs from both projects
 - Infestation is suspected in several participate homes
 - Bisbee cohort primarily bitten by *T. recurva*
 - Tucson/southern Arizona primarily bitten by *T. rubida*
- **Individuals who have been bitten are offered testing for *T. cruzi* infection**
InBios Chagas Detect Plus
 - N=71 tested in Tucson (goal >100)
 - N=34 tested in Bisbee (goal >50)
- **Project timeline:** ongoing and recruiting
 - Anticipate ending both projects and the end of Aug 2018



Triatoma recurva



Triatoma rubida



Kissingbug.arizona.edu

Chagas disease - Summary

- Chagas disease is caused by *Trypanosoma cruzi* infection
- Spread to humans primarily through the **kissing bug**
- Often patients remain asymptomatic but approximately **30% will develop chronic disease**
- **Kissing bugs are found in Arizona and up to 50% are positive for *T. cruzi***
- Blood donation is a source of screening the population but further study is needed
- Major gaps persist in the current knowledge of Chagas disease in the U.S.
- **Antitrypanosomal treatment is available and warranted in certain infected individuals**
- Patients who are infected should be monitored annually for the development of chronic disease



Special Thanks



- Dr. Mazda Shirazi



- Hayley Yaglom
- Dr. Heather Venkat



- Dr. Nafees Ahmad
- Dr. Nicole Bradley



- Dr. Susan Montgomery
- Dr. Eugene Liu



- Dr. Rebecca Sunenshine
- Craig Levy



- Dr. Stephen Klotz
- Maria Love
- Shannon Smith



- Dr. Sarah Hamer

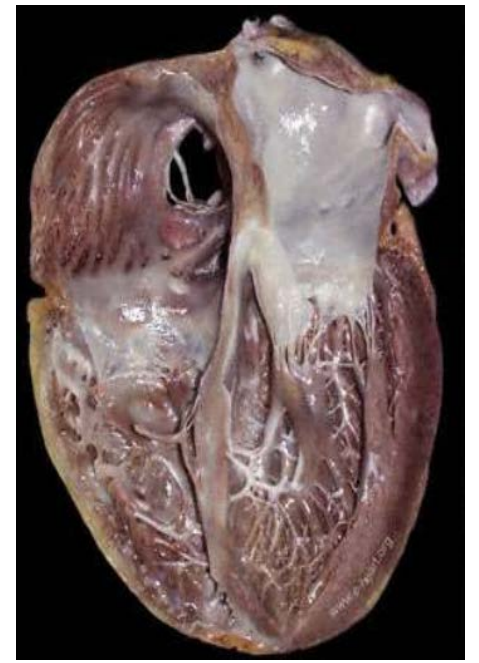


- Dr. Carlos Perez-Velez
- Sharon Carson



- Dr. Patricia Dorn





Thank you

Questions?

