All Black Adults Should NOT Undergo Genetic Screening for TTR Variants

Katherine Hunt Brendish, PhD, MS, CGC

Director, ASU Genetic Counseling Program & Clinical Professor

khuntbrendish@asu.edu

Why all Black adults should not be offered TTR genetic screening

- Multiple types of genetic testing options, all of which lead to complex results
- Pre-symptomatic genetic testing requires pre and post test genetic counseling and currently there are no established protocols in clinics to address this need
- Significant barriers exist for Black adults to access genetic services
- Individuals undergoing genetic testing need to fully understand benefits, risks and limitations before proceeding with testing
  - Researchers still have limited understanding of clinical utility of some types of genetic results from most minority groups, including the Black population

Hereditary Transthyretin Amyloidosis

- Clinical features and classifications:
  - ATTR amyloid neuropathy
  - ATTR cardiac amyloidosis- **Familial amyloid cardiomyopathy**
  - ATTR leptomeningeal/CNS amyloidosis

- *TTR* gene- 18q12.1
  - Nearly 150 ***TTR*** single-nucleotide variants and one in-frame microdeletion have been identified in individuals with hereditary ATTR **amyloidosis**

- Autosomal dominant
  - 50% chance to pass pathogenic variant to offspring
  - *De novo* mutation rate is unknown
  - Some affected individuals are homozygous for pathogenic variants

Sekijima Y. Hereditary Transthyretin Amyloidosis. 2001 Nov 5 [Updated 2021 Jun 17]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews®
https://www.ncbi.nlm.nih.gov/books/NBK1194/

Familial amyloid cardiomyopathy

❖Clinical features: Cardiac amyloidosis is mainly characterized by progressive cardiomyopathy (**penetrance is not 100%)**

- Cardiomegaly
- Conduction block
- Arrhythmia
- Anginal pain
- Congestive heart failure
- Sudden death

Genotypes:

Val142Ile

Val140Ile	His76Arg
Asp38Asn	Gly77Arg
Ala65Thr	Ala101Thr
Ala65Ser	Ala101Val
His108Arg	Glu112Lys
Arg123Ser	Leu131Met

❖Prevalence of p.Val142Ile

- Val142Ile variant is present in **3.0-3.9% of Blacks** and more than 5.0% of population in West Africa and is most common amyloid-associated *TTR* variant worldwide
- In the US, the frequency of Val142Ile in the white and Hispanic populations is 0.44% and 1.0%, respectively

Sekijima Y. Hereditary Transthyretin Amyloidosis. 2001 Nov 5 [Updated 2021 Jun 17]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® Available from: https://www.ncbi.nlm.nih.gov/books/NBK1194/

Which test is best to order and what are the consequences?

- Types of genetic testing:
  - Targeted gene testing- Identify specific genetic variant only (Val142Ile)
  - Single–gene testing- Sequence analysis of ***TTR*** *variants (150-130 variants)*
  - Multi-gene panel- Include multiple genes associated with Familial amyloid cardiomyopathy & other inherited cardiomyopathies
  - Full genome sequencing

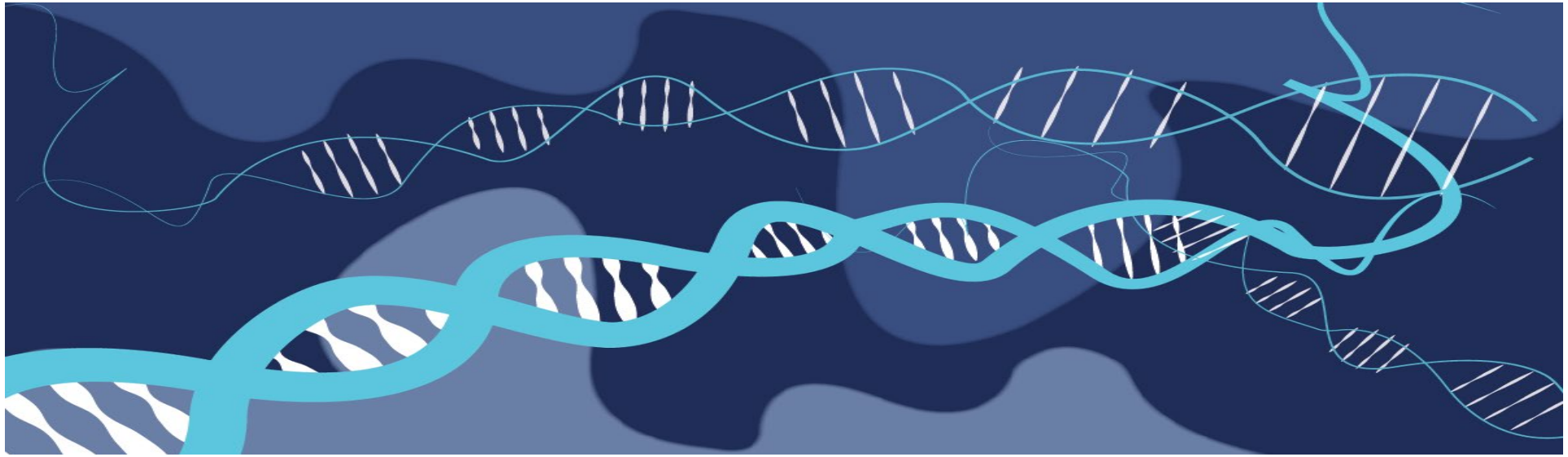
- Interpretation of genetic test result:
  - **Pathogenic/Likely pathogenic**
  - ***Variant of unknown significance***
  - **Benign/Likely benign**

Clinical implications of results

- **Positive** ---**Pathogenic/Likely pathogenic variant**
  - Can be used in medical decision making, along with other clinical information
  - Some diseases are not 100% penetrant and have variable expressivity
- **Negative** ---**Benign/Likely benign variant**
  - Not the cause of the patient's disorder
  - Utilize clinical information and the variant to conclude that it is not the cause of the patient's disorder
  - "True negative"-used when a known pathogenic variant has already been identified in relative and individual does not carry this pathogenic variant

Clinical implications of results

- **Uncertain significance ---*Variant of unknown significance***
  - Should NOT be used in clinical decision making
  - While variant is being re-classified, patient can continue to be monitored
  - Variants will be re-classified, therefore it is important to establish a mechanism to recontact the patient



Potential for complex result(s)

- Interpretation of genetic test result:
  - **Depends on type of test performed**
    - Targeted gene testing- might miss a TTR variant for an individual with mixed-background *(providing false reassurance)*
    - Single-gene testing- higher likelihood to identifying a VUS or complex result *(homozygous pathogenic variants)*
    - Possibility to identify a pathogenic variant and/or a VUS in another gene not associated with familial amyloid cardiomyopathy *(complicates follow-up management)*
    - Sensitivity of the diagnostic test will vary by lab

Decision about genetic testing

- Based on personal medical history & family history
  - Will take into account an individuals background
- Decision to undergo genetic testing will also largely be based on the preferences of the patient and their family

Pre-symptomatic genetic testing protocol

- **Pre test genetic counseling overview (informed consent)**
  - Purpose of test (diagnostic, carrier, pre-disposition)
  - Cost
  - Turn around time
  - Documentation of results
  - Predictive value of a positive, negative or indeterminate result
  - Overview of how medical management will change
  - Possible psychological reactions
  - Implications to family members
  - Insurance and job discrimination concerns
- **Post-test genetic counseling**
  - Interpretation of genetic test results
  - Communication with family members about results (subsequent genetic testing of at-risk relatives
  - Medical management recommendations
  - Potential for a variant reclassification (who will contact the patient with updated results?)

Barriers for Black adults to access genetic services

- Black Americans have a negative history with research which make it less likely they will pursue genetic testing, even when offered
  - Among Black women offered genetic testing for hereditary breast cancer, participation of genetic testing was viewed negatively, primarily because of lack of trust in the use of their genetic information (Glenn B., et al.)
  - Black Americans (and other minority groups) have a low participation in genetic research, which leads to limited understanding of many of the variants identified during genetic testing and thereby reducing the clinical utility of the results
    - 32 biobank participants who self-identified as Black or Hispanic were provided results of a pathogenic TTR variant (Soper, ER, et al.)
      - Findings suggested penetrance was lower than expected
      - Still left with many unknown variables (other genetic variants/environmental interactions?)

Glenn B., et al. *Ethnicity Dis.* 2012;22:267–273
Soper ER., et al. *J Pers Med*. 2021 Jan 15;11(1):49

Additional barriers when considering genetic testing for minority groups

- Socioeconomic barriers
  - Concerns over loss of job or health insurance can be barriers to seeking genetic screening/testing
  - Strained communication/relationships prohibit sharing of genetic information
- Health disadvantages
  - Limited access to care for individuals at-risk to receive appropriate screening and follow-up management
  - Limited data whether early identification and intervention for V142I results in improved cardiovascular outcomes (Reza N., et al)

Reza N., et al. *JACC: Cardiooncology*, 2021

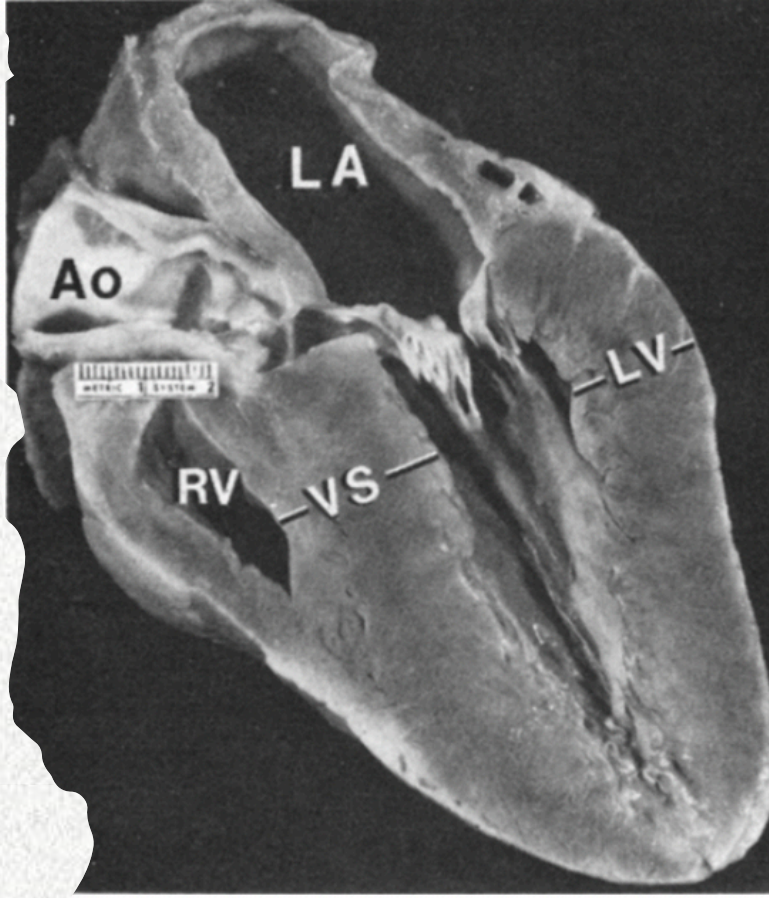
While population-based screening may be on the horizon… it's not ready for prime time *just yet*

- Additional research is needed to better understand the clinical significance of different TTR variants and develop subsequent medical management recommendations based on age at presentation, penetrance of gene, etc.
- Need to establish pre-symptomatic genetic testing protocols where individuals have access to a genetic counselor
- Continue to find ways to increase trust between medical community and Black communities so that individuals are more likely to participate in research and consider genetic testing
- Ensure appropriate access to care following a positive result

All Black Adults Should NOT (Routinely) Be Offered TTR Genetic Testing

Marc A. Silver, MD, FACC, FAHA, FHFSA
Professor of Medicine, University of Arizona-PHX
Banner University, Advanced Heart Failure Program-PHX
Marc.Silver@Bannerhealth.com

My Perspective on Cardiac Amyloid, Circa 1982



ardiac amyloidosis simulating hypertrophic card
is view of heart in a 55-year-old woman (WMC
n well until 6 months before death when she de
urpura, pedal edema, and right-arm pain. When
onth later, she was hospitalized and found to have
lectrocardiography disclosed both atrial and ve
nd electrophysiologic studies disclosed distal H
congestive heart failure. On the day of death
soon thereafter had fatal cardiac arrest. T
nd it had the typical amyloid consistency. A
he ventricular septum (VS) is thicker than
wall. The left atrium (LA) is dilated. Ao = a
avity.

Survival Following Implantable Cardioverter-Defibrillator Implantation in Patients With Amyloid Cardiomyopathy

Angela Y. Higgins, MD; Amarnath R. Annapureddy, MD; Yongfei Wang, MS; Karl E. Minges, PhD, MPH; Rachel Lampert, MD; Lynda E. Rosenfeld, MD; Daniel L. Jacoby, MD; Jeptha P. Curtis, MD; Edward J. Miller, MD, PhD; James V. Freeman, MD, MPH, MS

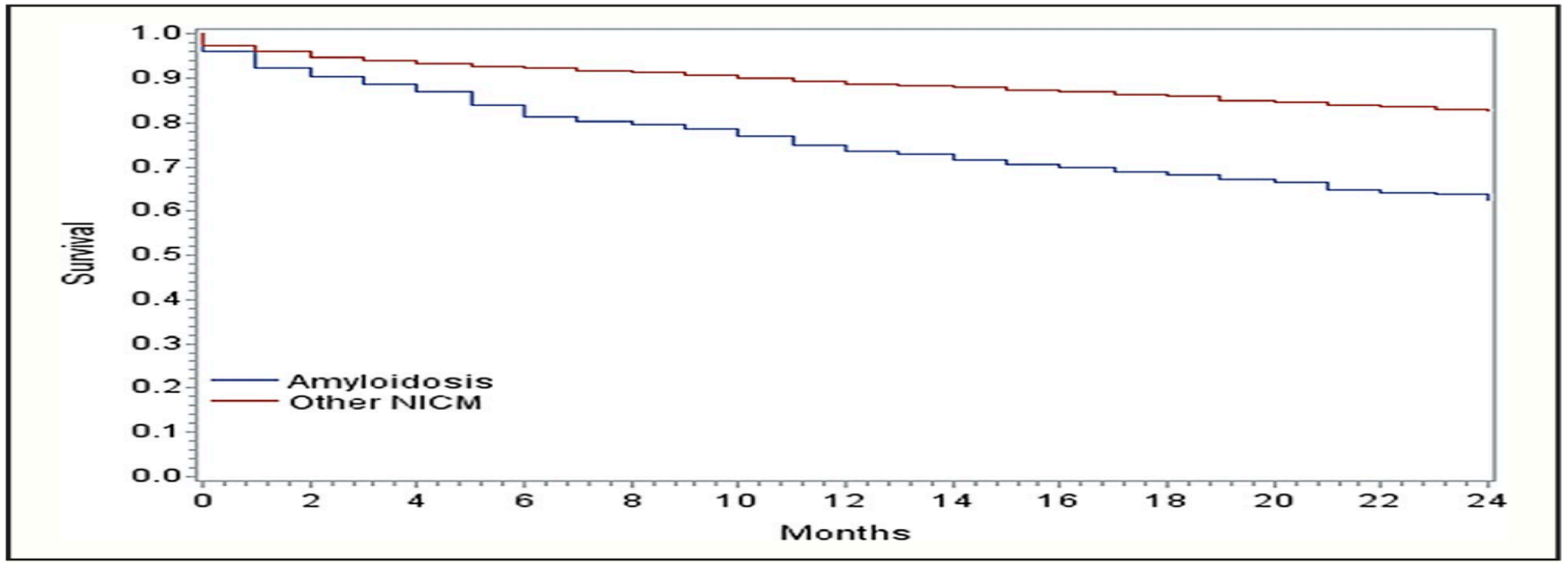


Figure 2. Probability of survival.
Kaplan–Meier curves for survival following implantable cardioverter-defibrillator implantation stratified by type of cardiomyopathy. Survival in patients with cardiac amyloidosis was significantly lower than the propensity-matched cohort of patients with NICMs. NICM indicates nonischemic cardiomyopathy.

J Am Heart Assoc. 2020;9:e016038. DOI: 10.1161/JAHA.120.016038

Fast Forward to 2016, THAOS Registry

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 68, NO. 2, 2016

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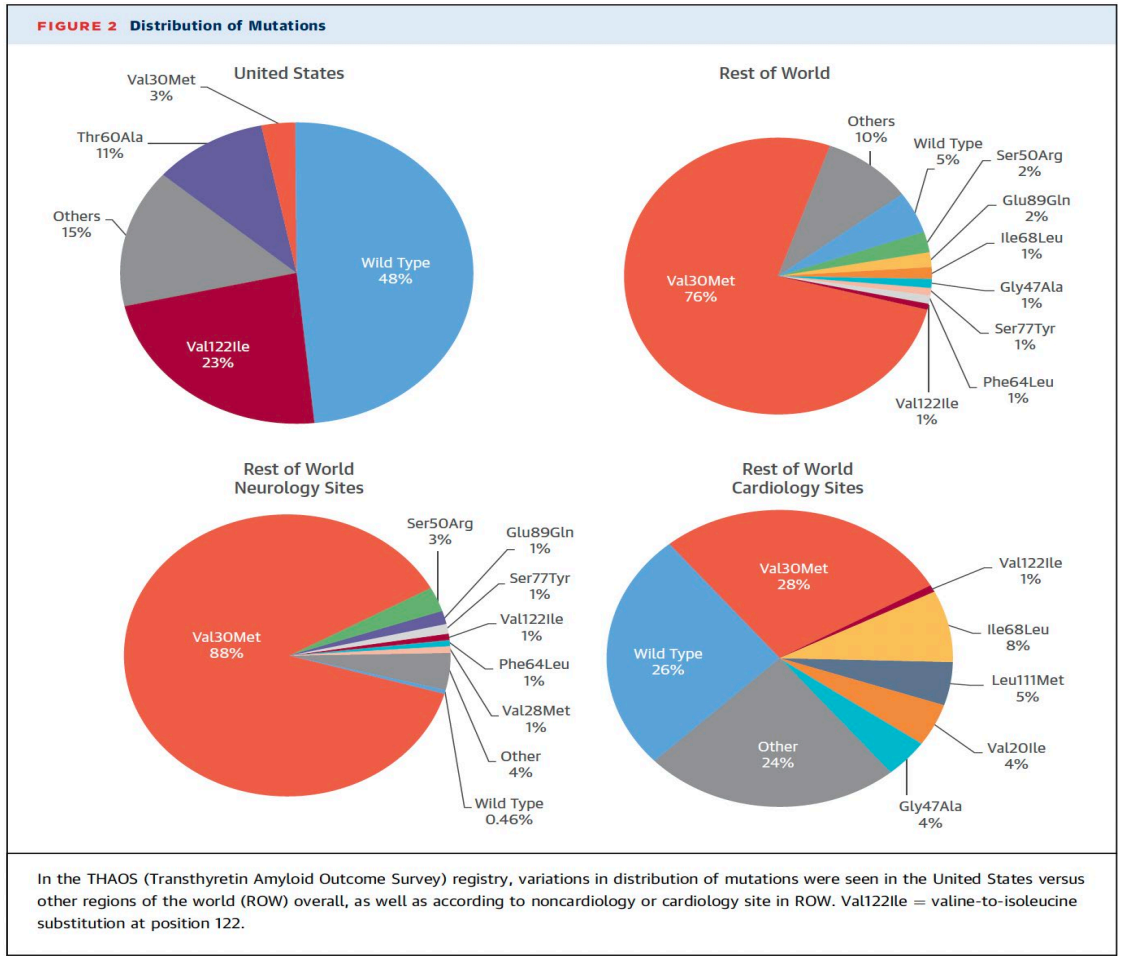
Geno
Cardi

THAOS

Mathew S. Ma es, MD,[d]
Brian Drachm ah, MD,[i]
D. Eric Steidle [n]
Savitri Fedson, MD,[o] Scott L. Hummel, MD,[p,q] Arnt V. Kristen, MD,[r] Thibaud Damy, MD, PhD,[s]
Violaine Planté-Bordeneuve, MD, PhD,[s] Teresa Coelho, MD,[t] Rajiv Mundayat, MS,[u] Ole B. Suhr, MD,[v]
Márcia Waddington Cruz, MD,[w] Claudio Rapezzi, MD,[x] on behalf of the THAOS Investigators

CONCLUSIONS—In the THAOS registry, ATTR in the United States is overwhelmingly a disorder of older adult males with a cardiac-predominant phenotype. Val122Ile is the most common TTR mutation, and neurologic phenotypic expression differs between wild-type disease and Val122Ile, but survival from enrollment in THAOS does not.

Should NOT, because….



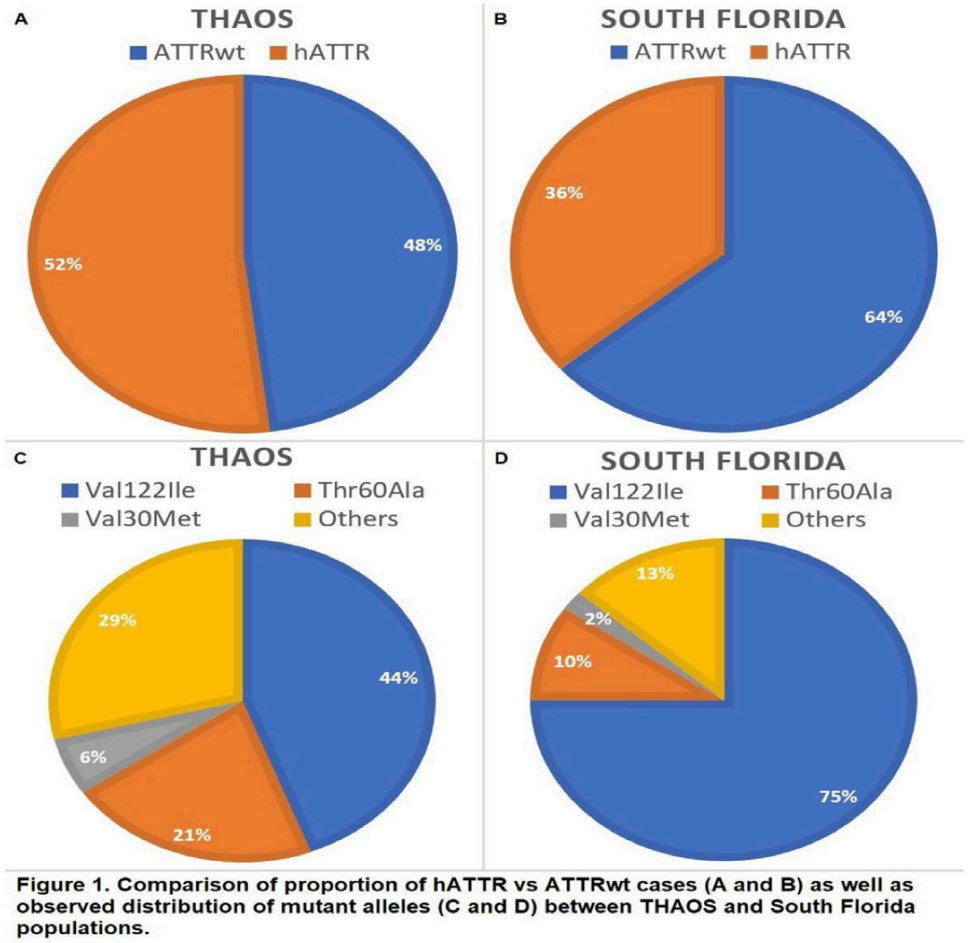


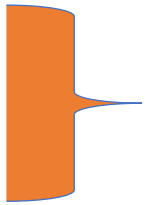
Figure 1. Comparison of proportion of hATTR vs ATTRwt cases (A and B) as well as observed distribution of mutant alleles (C and D) between THAOS and South Florida populations.

(J Am Coll Cardiol 2016;68:161–72)

Should NOT, because…

Of all self-identified Black patients sampled, how many have a pathogenic result?

- 32% Negative.
- 54% VUS.



86 %

- 15% Pathogenic/Likely Pathogenic.
- Out of the P/VLP, 20% had TTR mutations.
- All of the TTR positive patients were reported to be African American.

For 100 patients screened, 15 P/VLP but only 3/100 have TTR. Is this the correct population focus?

Data,Courtesy of Ambry Genetics

What lies downstream of a Positive Genetic Test?

Diagnostic Test ≠ Genetic Counseling

Genetic Counseling ≠ Rx (Affordability, Coverage or Compliance)

Financial Burden

- In patients with ATTR-CM
  - Tafamidis reduces all-cause mortality and cardiovascular hospitalizations and slows decline in quality of life compared with placebo
  - Tafamidis is the most expensive cardiovascular drug ever launched in the United States
- In a simulation model of US adults, tafamidis therapy for ATTR-CM
  - Estimated to cost $880 000 per quality adjusted life-year gained compared with usual care
  - Increased annual health care costs by $32.3 billion (including a 9.3% increase in total spending on all prescription drugs over 2018 levels)
- A 92.6% reduction in drug price from $225,000 annually to $16,563 would be necessary to meet a $100,000 per quality-adjusted life-year threshold

Should NOT, because….Summary

- Testing currently identifies a limited proportion of patients with TTR
- Testing does not translate into diagnosis, counseling or treatment
- The costs of therapy (existing and emerging) relegate treatment to more of a “tease” than a realistic treatment opportunity.
- The cost of the testing resource would be better directed towards population awareness to the many clinical “clues” of amyloid heart disease.

Rebuttal Slides

Rebuttal….Well, maybe….

CardioNext®: Analyses of 92 Genes Associated with Inherited Cardiomyopathies and Arrhythmias

RESULTS	
TTR	**Pathogenic Mutation: p.V142I**

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **p.V142I (c.424G>A)** pathogenic mutation in the *TTR* gene.

Rebuttal….Well, maybe….

- Background: (pV142I)

A 76-year-old male (Black) with past medical history including **systolic and diastolic HF-**

- The patient has had **multiple emergency department visits with shortness of breath and thoracenteses.**
- **Orthopnea and sleeping in a chair** since discharged from the hospital in April 2023.
- **ECGs show low voltage in all limb leads**.
- **Bilat carpal tunnel with repairs**.
- **Echo thick walls with thickening of MV and AV leaflets**.
- **Recurrent Pleural effusions**
- **Family History**:
- **He had 6 siblings who <u>all had carpal tunnel</u>, and some were diagnosed with "fluid buildup". His youngest sister died last year from "fluid in her lungs".**
- **Multiple older relatives with "dropsy" but they never knew what caused it. (several generations).**

- He has 5 children
- 3 sons
- 2 daughters. Oldest daughter is 41 years old and already had carpal tunnel surgery. (After patients' diagnosis she had genetic testing and has the same genetic abnormality.)