Epidemiology and Population Health Strategies for Cardiac Amyloidosis

Sandesh Dev, MD
Overview

• How common is it? Incidence, prevalence
  • hATTR, wtATTR, AL

• What is population health? Who should be screened? Screening strategies
  • What is the ideal risk group?
    • LVH
    • Biomarkers
  • Operationalizing ‘clinical red flag’s
    • E.g. bilateral carpal tunnel
    • Spinal stenosis
    • Orthopedic
    • ECG
    • hATTR

• Screening tools/strategies

• Tissue carpal tunnel, spinal stenosis
  • Predictive scores, mayo
  • AI, Huda, UCLA
    • imaging
    • EMR
    • ECG

• Benefits, Risks, Costs
  • HF clinical
Why population health?

• ‘However, reliance on the appropriate and timely diagnosis by individual clinicians may continue to underperform.’
• Patients identified 39 months after cardiac symptoms develop (Lane)
• Most patients identified at stage II or III

Patients
Cardiac Amyloidosis HF Hospitalizations Are Increasing with Geographic Variation

- Medicare, 2002 to 2012
- Increase in prevalence rate (8 to 17 per 100,000 person-yr)
- Increase in incidence rate (18 to 55 per 100,000 person-yr)
- Increase most in men, those >=75 years old, Black populations
Geographic Disparities In Death Rates: Mirrors referral centers and Southern U.S. lags
Deep South and Southwest USA are underperforming
## Distribution of cardiac amyloidosis hospitalization: highest in Black men, women

<table>
<thead>
<tr>
<th></th>
<th>Incidence (95% CI)</th>
<th>Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (No. of patients in each cohort in 2012)</td>
<td>4746</td>
<td>15 737</td>
</tr>
<tr>
<td>Overall patients (per 100 000 person-years)</td>
<td>16.6</td>
<td>55.2</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>18.3</td>
<td>69.6</td>
</tr>
<tr>
<td>Women</td>
<td>15.4</td>
<td>43.8</td>
</tr>
<tr>
<td>Race and sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White women</td>
<td>14.2</td>
<td>36.2</td>
</tr>
<tr>
<td><strong>Black women</strong></td>
<td><strong>29.5</strong></td>
<td><strong>128.9</strong></td>
</tr>
<tr>
<td>White men</td>
<td>17.2</td>
<td>62.6</td>
</tr>
<tr>
<td><strong>Black men</strong></td>
<td><strong>35.6</strong></td>
<td><strong>174.0</strong></td>
</tr>
<tr>
<td>Other race women</td>
<td>12.6</td>
<td>33.8</td>
</tr>
<tr>
<td>Other race men</td>
<td>13.1</td>
<td>44.5</td>
</tr>
<tr>
<td>Geography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>16.2</td>
<td>54.4</td>
</tr>
<tr>
<td><strong>Northeast</strong></td>
<td><strong>24.0</strong></td>
<td><strong>87.4</strong></td>
</tr>
<tr>
<td>South</td>
<td>13.5</td>
<td>40.5</td>
</tr>
<tr>
<td>West</td>
<td>14.5</td>
<td>44.2</td>
</tr>
</tbody>
</table>
Overview

• How common is it? Incidence, prevalence
  • hATTR, wtATTR, AL

• What is population health? Who should be screened? Screening strategies
  • What is the ideal risk group?
    • LVH
    • Biomarkers
  • Operationalizing ‘clinical red flag’s
    • E.g. bilateral carpal tunnel
    • Spinal stenosis
    • Orthopedic
    • ECG
    • hATTR

• Screening tools
  • Predictive scores, mayo
  • AI, Huda, UCLA
    • imaging
    • EMR
    • ECG

• Benefits, Risks, Costs
  • HF clinical
  • Genotype, phenotype
Diagnosis: Clinical Clues Across Organ Systems But Not Specific for Amyloid

Clinicians and health system need predictive tools to identify patients at risk
Moving towards early detection of ATTR CM
## Pertinent History for Cardiac Amyloid

### Orthopedic
- Carpal tunnel syndrome
- Spinal stenosis
- Biceps tendon rupture
- Trigger finger
- Rotator cuff tear
- Hip/knee/shoulder replacement

### Neuropathic
- Numbness in lower extremities
- Orthostatic symptoms
- Erectile dysfunction
- Diarrhea

### Eye
- Periorbital purpura
- Vitreous opacities/vitrectomy

### Cardiac
- History of pacemaker
- History of atrial fibrillation/ablation
**Amyloidosis Algorithm for Biopsy During Carpal Tunnel Release**

**Tier 1**
- Male age ≥ 50 years old
- Female age ≥ 60 years old
- Bilateral carpal tunnel symptoms

**Tier 2**
- Spinal stenosis
- Biceps tendon rupture
- Atrial fibrillation or flutter (active or previous history)
- Pacemaker
- Congestive heart failure
- Family history of ATTR amyloidosis

**TWO characteristics from Tier 1 OR ONE characteristic from Tier 1 PLUS any ONE from Tier 2**

Tenosynovial and/or TCL tissue biopsy with Congo red (or Thioflavin-S) staining

**Amyloid Typing** (mass spectrometry)

Amyloid (+) → Referral to amyloid expert
Amyloidosis Algorithm for Biopsy During Carpal Tunnel Release

Tier 1
- Male age ≥ 50 years old
- Female age ≥ 60 years old
- Bilateral carpal tunnel symptoms

Tier 2
- Spinal stenosis
- Biceps tendon rupture
- Atrial fibrillation or flutter (active or previous history)
- Pacemaker
- Congestive heart failure
- Family history of ATTR amyloidosis

TWO characteristics from Tier 1

OR

ONE characteristic from Tier 1 PLUS any ONE from Tier 2

Tenosynovial and/or TCL tissue biopsy with Congo red (or Thioflavin-S) staining

**Amyloid Typing** (mass spectrometry)

Amyloid (+)

Referral to amyloid expert
Orthopedic manifestations

• Tufts
• 13% SS,
High risk populations TAVR

• 11.8%
• Clinical risk score:
High risk populations TAVR

• 11.8%

• Clinical risk score:

• Population: 407 patients with AS patients, at 3 sites, referred for TAVR evaluation, underwent DPD scintigraphy

• Outcome: death, predictors of CA

High risk populations TAVR

• Results:
  • mean age 83, 50% men
  • 1 in 8 patients had AS-CA
    • +DPD in 11.8% (n=48) (2/3 were grade 2/3) all ATTR except 1 AL
  • Intervention: 84% underwent TAVR/SVR and 16% medical management (odds of receiving TAVR =2 for lone AS vs. AS-CA)

• Outcomes:
  • 1-year Mortality (irrespective of treatment): 24.5% vs 13.9% (p=0.05) AS-CA vs lone AS
  • For those undergoing TAVR, no diff. in survival from lone AS
Outcomes after AVR vs. Medical Therapy
AS-CA patients have distinct profile compared to lone AS patients

- Older age, more men, history of carpal tunnel syndrome, lower prevalence of PAD/CAD, functional status (6 min walk), higher NTproBNP and hsTnT, lower voltage, voltage/mass ratio, low-flow/low-gradient AS more prevalent, worse remodeling (LV mass index), impaired contractility (SV)

Score $\geq 2$ Specificity 52% and Sensitivity 94%
RAISE Score of $\geq 2$ Suggested to Prompt CA screening in TAVR Referrals

Score $\geq 2$  Specificity 52% and Sensitivity 94%
RAISE Score of 2 As Screening Tool in TAVR Referrals

<table>
<thead>
<tr>
<th>Score</th>
<th>Specificity</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥6 points</td>
<td>100%</td>
<td>14.9%</td>
</tr>
<tr>
<td>≥5 points</td>
<td>98.9%</td>
<td>23.4%</td>
</tr>
<tr>
<td>≥4 points</td>
<td>95.0%</td>
<td>42.6%</td>
</tr>
<tr>
<td>≥3 points</td>
<td>83.6%</td>
<td>72.3%</td>
</tr>
<tr>
<td>≥2 points</td>
<td>52.1%</td>
<td>93.6%</td>
</tr>
<tr>
<td>≥1 point</td>
<td>16.7%</td>
<td>97.9%</td>
</tr>
</tbody>
</table>
High risk populations – HF, TAVR

• 13% of HFpEF, LVH
• Sharma
Systematic Screening for Amyloidosis in HFpEF Increases Disease Detection

Figure 2. Prevalence of Transthyretin Amyloid Cardiomyopathy (ATTR-CM) in Heart Failure With Preserved Ejection Fraction

Error bars indicate 95% CIs.
Black patients higher risk

Spinal Stenosis Surgery: ATTR common in Ligamentum Flavum but ATTR CA is rare

• 13% (43/324) in US study, any site SS, had ATTR in ligamentum flavum (mass spec)
  • Of 43, 4 had ATTR (11%) and 78% were equivocal scans (grade 1 PYP), 11% grade
  • Age > 65, 21% ATTR
  • Patients with ATTR were older, had CTS, and non-cervical SS

• 37% (93/250) in Swedish study, lumbar SS, had ATTR (immunohistochemistry) and no ATTR CA (MRI)

ATTR DEPOSITION MAY BE EARLY SYSTEMIC DISEASE, LONG TERM DEVELOPMENT OF ATTR CA UNKNOWN

Central Illustration: Overview of Study Background, Hypothesis, and Results

Prevalence of Cardiac Amyloidosis (CA) 5-15 Years After Surgery for Bilateral Carpal Tunnel Syndrome (CTS)

**Background:**
Screening for CA at time of CTS surgery has shown a relatively low yield of CA (2%) but a high proportion of amyloid transthyretin (ATTR) deposits in the carpal ligaments (10%).

**Hypothesis:**
Cardiac evaluation will detect higher prevalence of CA if conducted 5-15 years after surgery for bilateral CTS.

**Results:**
- Prevalence of ATTR-CA:
  - 4.8% in total
  - 8.8% in males
  - 21.2% in males ≥70 years
  - BMI <30 kg/m²


Screening for cardiac amyloidosis (CA) was performed 5 to 15 years after surgery for bilateral carpal tunnel syndrome (CTS). The prevalence of early stage wild-type transthyretin amyloidosis (ATTR) was 4.8% in total, and 8.8% in males. Subgroup analysis of nonobese men aged ≥70 years showed a 21.2% prevalence, suggesting potential for systematic screening. BMI – body mass index.
Prior Bilateral Carpal Tunnel Surgery Is a High-Yield Target for ATTR CA screening

• What is prevalence of undiagnosed, early-stage CA 5-15 yrs after bilateral CTS?
  • Denmark, 250 subjects, M:F 1:1 by design, age 60-85 yrs, prior CTS, invited to undergo complete CA screening including PYP, excluding: known amyloidosis, secondary CTS [wrist fracture, ganglion, pregnancy, childbirth within 1 year of CTS]
  • Results: 36% participated, median age 70 yrs, 50% female, median time between CTS surgery and baseline 9.0 yrs
  • CA in 4.8% (n=12), all wtATTR, 1 female
    • One patient with suspected AL was PYP negative but biopsy positive for ATTR
  • Subgroups:
    • Men: 8.8%
    • Men >=70 yrs, BMI <30 kg/m2: 21.2%
    • Most patients had lowest disease severity score
Prior Bilateral Carpal Tunnel Surgery Is a High-Yield Target for ATTR CA screening

• Limitations: real world population, prevalence lower as more women have CTS
• Only 1/3 patients agreed with CA screening
• Subgroup analysis was not prespecified, must be interpreted with caution

Most patients had early stage ATTR CA
False negatives can occur with PYP scintigraphy in very mild disease (i.e., screening population), hence multimodal approach
Maximizing Diagnostic Yield in Late Screening of CTS Surgical Patients

Higher Age, male sex, normal BMI are highly predictive of CA in this population.
Progression from Tenosynovial Amyloid to CA?

- Prevalence of ATTR wt in men resembles tenosynovial deposits in carpal ligament in men at time of CTS surgery (8.8% vs 9.8%)
- Requires prospective study
- If true, need trials of therapy at time of amyloid diagnosis in the wrist would prevent development of CA
Autopsy data shows higher likelihood of wtATTR in HFrEF patients vs. non-HF controls

5% of HFrEF patients had moderate-severe interstitial wtATTR deposition whereas 12% had mild or intramural coronary deposition

Epidemiology: Cardiac Amyloid Increasingly Recognized Condition due to New Drugs and Imaging

- 13% of hospitalized heart failure (HF) with preserved ejection fraction patients
- 15% of patients > age 80 undergoing transcatheter aortic valve replacement

*However, disease burden in entire U.S. or VA population is not known*

Gonzalez-Lopez E, et al Eur Heart J 2015; Hahn V et al JACC Heart Failure 2020; Castano A et al Eur Heart J 2017
Epidemiology – increasingly recognized condition

• ATTR-CM common in older HFpEF patients
• 13% of hospitalized HFpEF pts > age 60 with LVH > 1.2 cm
• 15% of patients > age 80 undergoing transcatheter aortic valve replacement

Gonzalez-Lopez E, et al Eur Heart J 2015; Hahn V et al JACC Heart Failure 2020; Castano A et al Eur Heart J 2017
Diagnosis and Recognition: Past and Current Trends

• Historically considered rare
  • Frequently underrecognized
  • Need for biopsy
  • Attribution to aging, hypertension, hypertrophic cardiomyopathy, HFpEF, lack of approved treatment

• Current, ‘no longer a zebra’:
  • Noninvasive detection available without need for biopsy
  • Studies indicating significant proportion of HF patients have transthyretin amyloid cardiomyopathy (ATTR-CM)
  • Therapies approved for ATTR-CM

*Circulation. 2020;142:e7–e22. DOI: 10.1161/CIR.0000000000000792*
Overview

• How common is it? Incidence, prevalence
  • hATTR
  • wtATTR
  • AL

• Who should be screened? Screening strategies
  • What is the ideal risk group?
    • LVH
    • Biomarkers
  • Operationalizing ‘clinical red flag’s
    • E.g. bilateral carpal tunnel

• Screening tools
  • Predictive scores, mayo
  • AI
    • imaging
    • EMR
    • ECG

• Benefits
• Risks
  • Costs
  • HF clinical
### Epidemiology: wild-type TTR most common followed by hereditary (30%)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Age at Onset, y</th>
<th>Sex Distribution</th>
<th>National/Ethnic Predominance</th>
<th>Cardiac Involvement</th>
<th>Other Organ Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val30Met (V30M) or pV50M</td>
<td>&lt;30 in early onset &gt;60 in late onset</td>
<td>Slight F&gt;M</td>
<td>Portuguese, Swedish, and Japanese</td>
<td>Conduction disease more common than heart failure</td>
<td>Peripheral neuropathy Autonomic neuropathy</td>
</tr>
<tr>
<td>Val122Ile (V122I) or pV142I</td>
<td>60–65 (older age at onset in women)</td>
<td>Slight M&gt;F</td>
<td>Afro-American Afro-Caribbean</td>
<td>Common</td>
<td>Peripheral neuropathy likely Bilateral carpal tunnel syndrome</td>
</tr>
<tr>
<td>Thr60Ala (T60A) or pT80A</td>
<td>&gt;60</td>
<td>Unknown</td>
<td>Irish</td>
<td>Common</td>
<td>Autonomic and peripheral neuropathy</td>
</tr>
<tr>
<td>TTRwt</td>
<td>70–75</td>
<td>80%-90% male</td>
<td>None</td>
<td>Common</td>
<td>Bilateral carpal tunnel syndrome, spinal stenosis, biceps tendon rupture</td>
</tr>
</tbody>
</table>

Val122Ile is the most important mutation in United States, in 3-5 % of African-Americans
Diagnosis: Clinical Clues Across Organ Systems

Cardiac
- Heart failure
- Atrial fibrillation
- Bradyarrhythmias/conduction abnormalities/pacemakers

Musculoskeletal
- Carpal tunnel syndrome
- Back pain/lumbar spinal stenosis
- Ruptured distal biceps tendon/Popeye sign
- Shoulder, knee and hip pain or surgery
- Trigger finger

Polyneuropathy
- Painful neuropathy in hands and feet
- Muscle weakness, difficulty walking, and falls

Autonomic Dysfunction
- Orthostatic hypotension/insensitivity to blood pressure meds
- Chronic diarrhea/constipation/weight loss
- Erectile dysfunction

Nativi-Nicolau, Karam, Khella, Maurer. Heart Failure Reviews, 2021;Feb 20.
Frailty common in wild-type TTR

Figure 2. Frequency of frailty, and the relationships between frailty and organ impairment in patients with A-TTRwt-CA. The prevalence of frailty among patients with ATTRwt-CA can be explained by the amyloid fibril infiltration of various organs and tissues, particularly the heart, integumentary system, and nerves. FAB: frontal assessment battery, GDS: geriatric depression scale, IADL: instrumental activity of daily living, MNA: mini nutritional assessment, NYHA: New York heart association, SEGA: short emergency geriatric assessment SPPB: short physical performance battery, 7-CDT: 7-clock drawing test.
Early diagnosis is critical in amyloid:

*Red flags often predate diagnosis by years*
Proposed timeline of disease process

11C-PIB indicates Pittsburgh compound B; 99mTc-DPD, 99mtechnetium-3,3-diphosphono-1,2-propanodicarboxylic acid; 99mTc-HMDP, hydroxymethylene diphosphonate; 99mTc-PYP, technetium pyrophosphate; ATTR-CM, transthyretin amyloidosis with predominant cardiomyopathy (either wild-type or hereditary); CA, cardiac amyloidosis; ECG, electrocardiography; LVST, left ventricular septal thickness; and TTR, transthyretin.
Frailty common in wild-type TTR and prognostic of poor outcomes

Figure 2. Frequency of frailty, and the relationships between frailty and organ impairment in patients with A-TTRwt-CA. The prevalence of frailty among patients with A-TTRwt-CA can be explained by the amyloid fibril infiltration of various organs and tissues, particularly the heart, integumentary system, and nerves. FAB: frontal assessment battery, GDS: geriatric depression scale, IADL: instrumental activity of daily living, MNA: mini nutritional assessment, NYHA: New York heart association, SEGA: short emergency geriatric assessment SPPB: short physical performance battery, 7-CDT: 7-clock drawing test.
ECG findings have low predictive value in isolation

atrial fibrillation, low voltage in the limb leads, and a pseudoinfarct pattern with Q waves in leads V1-V2.

doi:10.3949/ccjm.84.s3.02
Overview

• How common is it? Incidence, prevalence
  • hATTR, wtATTR, AL

• What is population health? Who should be screened? Screening strategies
  • What is the ideal risk group?
    • LVH
    • Biomarkers
  • Operationalizing ‘clinical red flag’s
    • E.g. bilateral carpal tunnel
    • Spinal stenosis
    • Orthopedic
    • ECG
    • hATTR

• Screening tools
  • Predictive scores, mayo
  • AI, Huda, UCLA
    • imaging
    • EMR
    • ECG

• Benefits, Risks, Costs
  • HF clinical
  • Genotype, phenotype
AI for ECG and Echocardiogram is Promising to Aid Detection

Artificial intelligence-enabled fully automated detection of cardiac amyloidosis using electrocardiograms and echocardiograms

Shinichi Goto, Keitaro Mahara, Lauren Beussink-Nelson, Hidehiko Ikura, Yoshinori Katsumata, Jin Endo, Hanna K. Gaggin, Sanjiv J. Shah, Yuji Itabashi, Calum A. MacRae & Rahul C. Deo

High-Throughput Precision Phenotyping of Left Ventricular Hypertrophy With Cardiovascular Deep Learning

Grant Duffy, BS; Paul P. Cheng, MD, PhD; Neal Yuan, MD; Bryan He, BS; Alan C. Kwan, MD; Matthew J. Shun-Shin, PhD; Kevin M. Alexander, MD; Joseph Ebinger, MD; Matthew P. Lungren, MD; Florian Rader, MD, MSc; David H. Liang, MD, PhD; Ingela Schnitter, MD; Euan A. Ashley, MBChB, DPhil; James Y. Zou, PhD; Jignesh Patel, MD, PhD; Ronald Witteles, MD; Susan Cheng, MD, MPH; David Ouyang, MD
**Simple score**

**Figure 1. Description of the Transthyretin Amyloid Cardiomyopathy (ATTR-CM) Score**

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If 60-69</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>If 70-79</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>If ≥80</td>
<td>+4</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>+2</td>
</tr>
<tr>
<td>Hypertension diagnosis</td>
<td>Present</td>
<td>-1</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>&lt;60%</td>
<td>+1</td>
</tr>
<tr>
<td>Posterior wall thickness</td>
<td>≥12 mm</td>
<td>+1</td>
</tr>
<tr>
<td>Relative wall thickness&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;0.57</td>
<td>+2</td>
</tr>
</tbody>
</table>

High-risk score ≥6

Description of the ATTR-CM score components and point allocations for each component.

<sup>a</sup> If variable is absent, points = 0.

<sup>b</sup> Sum of septal and posterior wall thickness divided by left ventricular end diastolic diameter.
• Random forest machine learning model to identify transthyretin cardiomyopathy using medical claims
• Derivation: 1071 cases, 1071 non-amyloid controls
• Validation: 3 national cohorts (9412 cases, 9421 controls), EMR cohort (261 cases, 39393 controls)
ML Model Outperformed Clinical Model though PPV was Low

Table 3 Prediction of cardiac amyloidosis in the Northwestern Medicine Enterprise Data Warehouse Heart Failure Cohort using the wild-type ATTR-CM Random Forest prediction model.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Probability cutoff for the diagnosis of ATTR-CM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>69.7</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>75.6</td>
</tr>
<tr>
<td>PPV, %</td>
<td>1.9</td>
</tr>
<tr>
<td>NPV, %</td>
<td>99.7</td>
</tr>
<tr>
<td>Accuracy, %</td>
<td>75.5</td>
</tr>
<tr>
<td>LR+</td>
<td>2.86</td>
</tr>
<tr>
<td>LR−</td>
<td>0.40</td>
</tr>
</tbody>
</table>

ATTR-CM amyloidogenic transthyretin cardiomyopathy, LR+ positive likelihood ratio, LR− negative likelihood ratio, NPV negative predictive value, PPV positive predictive value.

Table 4 Areas under the receiver operating characteristic curve for various prediction models in the Northwestern Medicine Enterprise Data Warehouse Heart Failure Cohort.

<table>
<thead>
<tr>
<th>Model</th>
<th>N</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATTRwt-CM RF model</td>
<td>39,654</td>
<td>0.80</td>
</tr>
<tr>
<td>ATTRwt-CM RF model, age &gt; 70 years</td>
<td>23,570</td>
<td>0.82</td>
</tr>
<tr>
<td>Age only</td>
<td>39,624</td>
<td>0.54</td>
</tr>
<tr>
<td>Age + sex</td>
<td>39,618</td>
<td>0.62</td>
</tr>
<tr>
<td>Age + sex + ethnicitya</td>
<td>39,203</td>
<td>0.70</td>
</tr>
<tr>
<td>Age + sex + ethnicity + logBNPb</td>
<td>20,419</td>
<td>0.73</td>
</tr>
<tr>
<td>Age + sex + ethnicity + logBNP + abnormal troponin-l²</td>
<td>15,046</td>
<td>0.73</td>
</tr>
<tr>
<td>ATTRwt-CM RF model + age + sex + ethnicity</td>
<td>39,203</td>
<td>0.83</td>
</tr>
<tr>
<td>ATTRwt-CM RF model + age + sex + ethnicity + total number of encounters</td>
<td>38,337</td>
<td>0.83</td>
</tr>
</tbody>
</table>

ATTRwt-CM amyloidogenic transthyretin (wild-type), AUROC area under the receiver operating characteristic curve, RF Random Forest, BNP B-type natriuretic peptide.
aEthnicity categories: non-Hispanic White, non-Hispanic Black, Hispanic, Asian, others.
bHighest BNP value in the electronic health record, log-transformed.
cBased on the highest troponin-l in the electronic health record (abnormal defined as >0.04 ng/ml).
A machine learning model for identifying patients at risk for wild-type transthyretin amyloid cardiomyopathy

Ahsan Huda, Adam Castaño, Anindita Niyogi, Jennifer Schumacher, Michelle Stewart, Marianna Bruno, Mo Hu, Faraz S. Ahmad, Rahul C. Deo, & Sanjiv J. Shah
Time course of non-cardiac and cardiac phenotypes prior to HF diagnosis
Potential Projects

1. Epidemiology
   Incidence, prevalence, predictors
   Disparities, Geographic and facility level variation

2. AI/ML Prediction Tool Using EHR data, Implementation of Clinical Decision Support

3. Prognostic staging, phenotyping

4. Comparative effectiveness, pharmacoepidemiology

Other:
Quality of life
Health economics, cost effectiveness, extremes of age
Quality of care, diagnosis
High Medicare Part D out-of-pocket costs

Figure 5. Projected Medicare Part D beneficiary monthly out-of-pocket costs for tafamidis. Projected annual out-of-pocket expenses were calculated using the standard 2019 Medicare Part D plan including: (1) an initial $415 deductible; (2) an initial coverage period until drug costs reach $3,810; (3) a coverage gap ("donut hole") with 25% cost sharing until out-of-pocket costs reach $5,160; and (4) catastrophic coverage with 5% cost sharing without an upper limit. Monthly insurance premiums and the costs of other medications were not included in this projection.