Validation of a Transthyretin Amyloid Cardiomyopathy (ATTR-CM) United States Claims-Based Coding Algorithm (ValidATTR-US)

John Isaiah Jimenez,[1] Gracia Fahed,[1] Nixuan Cai,[1] Margarita Udall,[2] Hiroki Kitakata,[1] Kevin M. Alexander[1]

[1]Stanford Amyloid Center, Stanford University School of Medicine, Stanford, CA, USA; [2]BridgeBio Pharma, Inc., San Francisco, CA, USA

Poster: RWD109

Scan QR code to access a PDF of the poster

INTRODUCTION

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive disease characterized by misfolded proteins that form toxic amyloid fibrils in the heart, causing cardiomyopathy and heart failure[1]
  - ATTR-CM is categorized into wild-type (ATTRwt-CM) and variant (ATTRv-CM) forms[1]
- With the emergence of disease-modifying therapies, there is a growing need to understand the burden, prevalence, and treatment patterns of ATTR-CM beyond the clinical trial setting, thus requiring accurate identification of these patients in real-world data sources[2]
- Administrative claims databases are among the most widely used secondary data sources for characterizing real-world disease burden, treatment patterns, and outcomes across diverse patient populations in the United States (US)[3]
- Coding complexity has resulted in substantial variability in how ATTR-CM is identified across real-world studies[3]
  - **There are no International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes specific for ATTR-CM**; instead, ATTR-CM is typically coded using combinations of nonspecific amyloidosis or cardiac codes, which can result in variability in how ATTR-CM is identified[3,4]

OBJECTIVE

- To develop and validate a US claims-based coding algorithm that maximizes the identification of patients with ATTR-CM within administrative claims and electronic health record (EHR) datasets

METHODS

Algorithm Development

- An algorithm for identifying patients with ATTR-CM within US claims databases (ValidATTR-US) was developed based on previously published studies using ICD-10-CM codes and iteratively refined to optimize sensitivity and specificity against a clinically confirmed patient registry[4-7]
  - Inclusion and exclusion criteria are shown in **Figure 1**

Study Cohorts

- **Index cohort:** The algorithm was applied to the Stanford Research Repository (STARR), a claims/EHR-linked database that has compiled clinical data at Stanford since 1998, to identify the index cohort of patients meeting ATTR-CM coding criteria
- **Validation cohort:** The Stanford ATTR-CM Patient Registry is a well-phenotyped registry of patients confirmed to have ATTR-CM through standardized diagnostic workup; this registry served as the validation cohort against which algorithm-identified patients in the index cohort were cross-referenced

Algorithm Performance

- Algorithm performance was assessed by cross-referencing patients captured in the index cohort (STARR) against confirmed cases in the validation cohort as follows:
  - True positives (TP) were in the index and validation cohorts
  - True negatives (TN) were in neither
  - False positives (FP) were in the index but not the validation cohort
  - False negatives (FN) were in the validation but not the index cohort
- Performance metrics: accuracy (TP+TN/total), specificity (TN/[TN+FP]), and sensitivity (TP/[TP+FN])
  - Good performance was defined as >80% sensitivity and specificity[8,9]

Subgroup and Sensitivity Analyses

- Algorithm performance was assessed by ATTR-CM subtype (ATTRwt-CM and ATTRv-CM)
  - Inclusion/Exclusion criteria were the same as those shown in **Figure 1** with the following exceptions: ATTRwt-CM classification required the ICD-10-CM diagnosis code E85.82 and ATTRv-CM required E85.[0, 1, 2]

Predictive Modeling

- The predictive value of individual ICD-10-CM codes (**Table 1**) within the algorithm was assessed using logistic regression; each amyloidosis code was factored and evaluated independently against a reference group with no amyloidosis code
- Predictive performance was assessed for the following two prespecified outcomes: ATTR-CM case status (ATTR-CM vs no ATTR-CM) and genotype classification (ATTRwt-CM vs ATTRv-CM)
- Model discrimination was evaluated using receiver operating characteristic (ROC) analysis and area under the curve (AUC)

Table 1. ICD-10-CM Codes in ValidATTR-US

Code	Definition
E85.0	Non-neuropathic heredofamilial amyloidosis
E85.1	Neuropathic heredofamilial amyloidosis
E85.2	Heredofamilial amyloidosis, unspecified
E85.4	Organ-limited amyloidosis
E85.82	ATTRwt-CM

ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

CONCLUSIONS

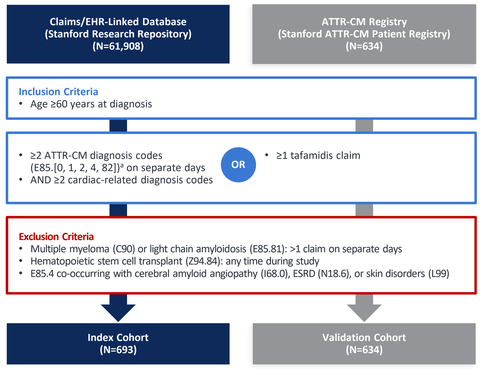
- ValidATTR-US, a validated algorithm, provides a standardized and replicable approach for identifying ATTR-CM in US administrative claims and EHR databases
- Future research should include external validation within other institutions and health systems (eg, community settings, different geographic regions, and enrollment-based claims databases)
- Broader application of ValidATTR-US could improve real-world understanding of ATTR-CM epidemiology in the US and support earlier identification of patients who may benefit from diagnostic evaluation and disease-modifying therapy

RESULTS

Algorithm Index and Validation Cohorts

- Application of ValidATTR-US to STARR identified 693 patients (index cohort); 634 patients in the ATTR-CM Registry served as the validation cohort (**Figure 1**)

Figure 1. Index and Validation Cohort Identification



aCodes defined in **Table 1**.
ATTR-CM, transthyretin amyloid cardiomyopathy; EHR, electronic health record; ESRD, end-stage renal disease.

- In both cohorts, patients with ATTRwt-CM were older than those with ATTRv-CM, and most patients were male (**Table 2**)
  - Most patients with ATTRwt-CM were White
  - For patients with ATTRv-CM, approximately 50% were Black and 37% were White

Table 2. Baseline Characteristics of the Index and Validation Cohorts[a]

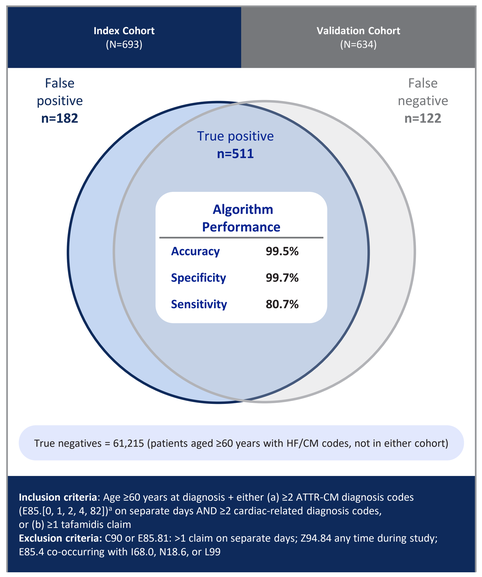
Characteristic	Index cohort (N=512)[b]		Validation cohort (N=634)	
	ATTRv-CM (n=97)	ATTRwt-CM (n=360)	ATTRv-CM (n=130)	ATTRwt-CM (n=437)
Age, years				
Mean (SD)	70.3 (7.5)	79.1 (7.4)	69.4 (8.1)	78.8 (7.5)
Median (min-max)	72 (48-87)	79 (60-99)	71 (40-87)	79 (54-99)
IQR	63-81	68-80	65-75	74-84
Sex, n (%)				
Female	22 (22.7)	27 (7.5)	29 (22.3)	34 (7.8)
Male	75 (77.3)	333 (92.5)	101 (77.8)	403 (92.2)
Race, n (%)				
White	36 (37.1)	302 (83.9)	48 (36.9)	364 (83.3)
Black	52 (53.6)	16 (4.4)	66 (50.8)	23 (5.3)
Asian	3 (3.1)	15 (4.2)	8 (6.2)	18 (4.1)
Other[c]	6 (6.2)	27 (7.5)	8 (6.2)	32 (7.3)

aCohorts include patients with known genotypes (ATTRv-CM and ATTRwt-CM) based on genetic testing, as well as patients with unknown genotype; baseline characteristics are shown for patients with known genotypes. bData shown for the 512 true positives within the overall index cohort (N=693). cConsists of native Hawaiian, American Indian, Alaska Native, >1 race, or unknown/not reported.
ATTR-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy.

Algorithm Performance

- Overall accuracy was 99.5%, specificity was 99.7%, and sensitivity was 80.7% for detecting patients with ATTR-CM (TP, n=511; TN, n=61,215; FP, n=182; FN, n=122)
- ValidATTR-US exceeded the a priori performance threshold of >80% for sensitivity and specificity (**Figure 2**)

Figure 2. ValidATTR-US Performance



aCodes defined in **Table 1**.
ATTR-CM, transthyretin amyloid cardiomyopathy; CM, cardiomyopathy; HF, heart failure.

Predictive Modeling

- Predictive modeling was conducted for ATTR-CM case status (ATTR-CM vs no ATTR-CM)
  - E85.82 (ATTRwt-CM) was the strongest individual predictor (odds ratio [OR], 4.68; 95% CI, 2.69-8.61), followed by E85.2 (heredofamilial amyloidosis, unspecified) (OR, 2.66; 95% CI, 1.21-6.33) (**Table 3**)
  - Sex (female) was considered a predictor (OR, 0.71; 95% CI, 0.54-0.95) for ATTR-CM case status (**Table 4**)
  - ROC analysis for identifying patients with ATTR-CM demonstrated strong model discrimination with an AUC of 0.84 (95% CI, 0.82-0.86) (**Figure 3**)
- Predictive modeling was conducted for genotype classification (ATTRv-CM vs ATTRwt-CM)
  - E85.2 (heredofamilial amyloidosis, unspecified) (OR, 77.43; 95% CI, 19.41-532.00) and E85.1 (neuropathic heredofamilial amyloidosis) (OR, 29.49; 95% CI, 10.43-98.86) were the strongest predictors (**Table 3**)
  - Age (OR, 0.92; 95% CI, 0.89-0.94) and race (Black: OR, 10.42; 95% CI, 6.11-18.03 and other: OR, 3.04; 95% CI, 1.73-5.30) were considered predictors for ATTR-CM genotype status (**Table 4**)
  - ROC analysis for variant identification demonstrated strong model discrimination with an AUC of 0.88 (95% CI, 0.85-0.91) (**Figure 4**)

Table 3. ValidATTR-US Algorithm Predictor Effects[a,b]

Outcome	Predictors, odds ratio (95% CI)				
	E85.0	E85.82	E85.1	E85.2	E85.4
ATTR-CM case status	2.15 (0.52-9.74)	**4.68 (2.69-8.61)**	1.89 (0.78-4.91)	**2.66 (1.21-6.33)**	0.92 (0.670-1.268)
ATTR-CM genotype status	0.28 (0.05-1.71)	0.58 (0.30-1.11)	**29.49 (10.43-98.86)**	**77.43 (19.41-532.00)**	**1.84 (1.01-3.34)**

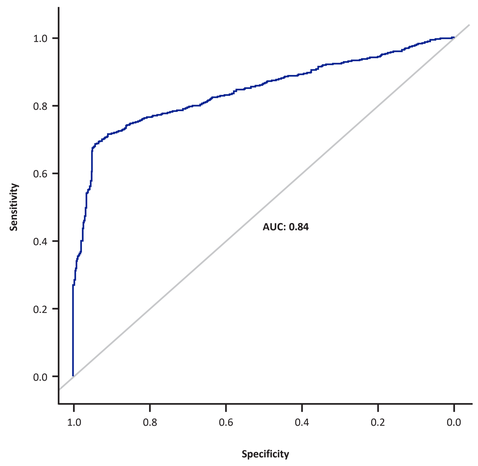
Bolding indicates $P<0.05$.
[a]The wide CIs observed are due to limited sample size. [b]Codes defined in **Table 1**.
ATTR-CM, transthyretin amyloid cardiomyopathy.

Table 4. Age, Sex, and Race Algorithm Predictor Effects[a]

Outcome	Predictors, odds ratio (95% CI)				
	Age	Sex (female)[b]	Race[c]		
			Black	Asian	Other
ATTR-CM case status	1.01 (0.99-1.02)	**0.71 (0.54-0.94)**	1.21 (0.78-1.90)	0.86 (0.57-1.28)	0.85 (0.59-1.22)
ATTR-CM genotype status	**0.92 (0.89-0.94)**	1.27 (0.67-2.37)	**10.42 (6.11-18.03)**	0.39 (0.07-1.52)	**3.04 (1.73-5.30)**

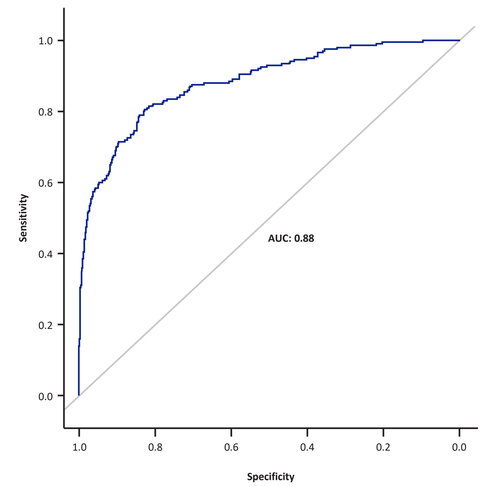
Bolding indicates $P<0.05$.
[a]The wide CIs observed are due to limited sample size. [b]Reference is male. [c]Reference is White.
ATTR-CM, transthyretin amyloid cardiomyopathy.

Figure 3. Algorithm Predictor Effects: Identifying Patients With ATTR-CM



ATTR-CM, transthyretin amyloid cardiomyopathy; AUC, area under the curve.

Figure 4. Algorithm Predictor Effects: ATTR-CM Genotype Classification



ATTR-CM, transthyretin amyloid cardiomyopathy; AUC, area under the curve.

DISCUSSION

- This is the first US claims-based coding algorithm for ATTR-CM to be validated against a clinically confirmed patient registry
  - ValidATTR-US achieved accuracy of 99.5%, specificity of 99.7%, and sensitivity of 80.7%
- Development of a validated algorithm directly addresses a recognized gap in ATTR-CM real-world evidence, where variability in claims-based identification has limited comparability across studies[3]
  - Because ValidATTR-US relies exclusively on diagnosis codes and pharmacy claims, it is readily implementable across US administrative claims and EHR databases without requiring access to clinical notes or imaging data
- Application of ValidATTR-US in clinical and research settings has the potential to improve how ATTR-CM is identified, studied, and managed in real-world populations

LIMITATIONS

- ValidATTR-US was refined and validated at a single academic institution in the US, therefore additional validation is encouraged across other institutions
- EHR-based data sources (such as STARR) lack continuous enrollment information, which may result in incomplete capture of diagnosis codes and affect algorithm performance
- Claims-based research is dependent on the accuracy of coded diagnoses

PRESENTING AUTHOR: John Isaiah Jimenez

REFERENCES: 1. Ruberg FL, et al. *J Am Coll Cardiol*. 2019;73(22):2872-2891. **2.** Tschöpe C, et al. *J Clin Med*. 2025;14(13):4785. **3.** Coleman CI, et al. *Curr Med Res Opin*. 2025;41(11):2013-2024. **4.** Damy T, et al. *Orphanet J Rare Dis*. 2023;18(1):345. **5.** Huda A, et al. *Nat Commun*. 2021;12(1):2725. **6.** Witteles RM, et al. *Front Cardiovasc Med*. 2025;12:1638380. **7.** Jaiswal V, et al. *JACC Adv*. 2024;3(12):101405. **8.** In brief: sensitivity and specificity. Accessed March 23, 2026. https://www.ncbi.nlm.nih.gov/books/NBK611900/. **9.** Rogers P, et al. *J Med Internet Res*. 2023;25:e43486.

ACKNOWLEDGMENTS: The authors thank all the patients and caregivers for their participation in this study and acknowledge the collaboration and commitment of all investigators and their research support staff. This study was funded by BridgeBio Pharma, Inc. All authors contributed to and approved the presentation; writing and editorial assistance were provided by Emma Hinkle, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by BridgeBio Pharma, Inc. The authors thank Charlotte Baker, PhD, MPH, for providing statistical support and guidance.

DISCLOSURES: JIJ, **GF**, **NC**, and **HK**: No relevant financial relationships to disclose. **MU**: Employee and stockholder of BridgeBio Pharma, Inc. and stockholder of Pfizer. **KMA**: Received consulting fees from Alexion Pharmaceuticals, Alnylam Pharmaceuticals, Bayer, BridgeBio Pharma, Inc., Novo Nordisk, and Pfizer.

Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2026; May 17-20, 2026; Philadelphia, PA, USA.