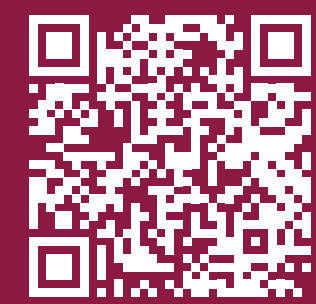


Cardiovascular Disease Burden Before Hereditary Transthyretin Amyloidosis Diagnosis

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BACKGROUND/INTRODUCTION

- Hereditary transthyretin amyloidosis (hATTR or ATTRv [variant]) is a progressive and fatal disease often associated with infiltrative cardiac involvement^{1,2}
- Cardiac involvement in ATTRv is associated with poor survival^{1,3,4}
- Patients often have long-standing cardiac symptoms prior to their amyloidosis diagnosis, and it has been shown that diagnostic delay can result in increased disease burden and progressive myocardial injury and failure^{1,3}
- Real-world evidence focusing on cardiac manifestations throughout the ATTRv patient journey is limited^{1,3}
- Nurses who work closely with patients with heart failure are positioned to recognize the symptoms and early signs that should raise clinical suspicion and uncover an underlying diagnosis of ATTRv

OBJECTIVE

- To determine whether patients with ATTRv demonstrate significant cardiovascular symptom manifestations and health care utilization before diagnosis

METHODS

Study design and data source

- Retrospective claims analysis of IBM® MarketScan® Commercial and Medicare Supplemental* data (US) from 1/1/2011-12/31/2017

Patient identification

Eligibility criteria

- Adult patients (≥18 years of age) newly diagnosed with ATTRv identified using a claims-based algorithm as follows:
 - ≥1 medical claim with relevant amyloidosis diagnosis code (ICD-10-CM: E85.0-4, E85.89, E85.9; excluding light chain and wild type) during identification (ID) period of 1/1/2016-12/31/2017, and the occurrence of ≥1 qualifying criteria during any time in study period:
 - ≥15 days diflunisal use without >30-day gap or liver transplantation
 - Patients with specific claim codes E85.1 (neuropathic hereditary amyloidosis) or E85.2 (hereditary amyloidosis, unspecified) at any time did not require additional qualifier
 - Study index date was defined as the date of first claim with an amyloidosis diagnosis in ID period
 - A look-back period during the 5 years prior to the index date was used to examine cardiovascular manifestations leading up to diagnosis
 - Patients had continuous health plan enrollment during the look-back period

Exclusion criteria

- To ensure that only patients with a new diagnosis were included, those with an ICD-9/10 amyloidosis code during the look-back period were excluded

Disease-free control group

- To serve as a reference group, an ATTRv-free cohort was created that included patients without ATTRv diagnosis and matched 3:1 to patients with ATTRv based on age, gender, and region
- The same index and enrollment requirements as patients with ATTRv were used for matched patients

Study measures

- Frequency of selected cardiovascular conditions (hypotension, aortic stenosis, congestive heart failure, dyspnea, edema, stroke [ischemic, hemorrhagic], bleeding, hypertrophic cardiomyopathy, restrictive cardiomyopathy, ventricular hypertrophy, atrial fibrillation/flutter, syncope, chest pain, bradycardia) during the 5-year look-back period
- Frequency of diagnostic testing (blood/urine testing and cardiac imaging [i.e., pyrophosphate imaging, cardiac magnetic resonance imaging (MRI), and echocardiogram]), hospitalization, and emergency department (ED) visits were determined during the 5-year look-back period
- Demographics and Charlson comorbidity index (CCI) were determined 1 year prior to or on the index date

Statistical analysis

- Descriptive statistics generated for pre-index measures during each year of look-back period
- The cumulative probability of occurrence of selected comorbidities and diagnostic testing since 5 years before the index date was generated

*MarketScan is a trademark of IBM Corporation in the United States and other countries.

Baseline demographics and comorbidities during the 1-year pre-index period (Table 1)

- Among 141 patients with ATTRv and 423 matched controls meeting inclusion criteria, mean (SD) age was 62.5 (14.2) years, with most (76%) having a diagnosis at age 55 years or older; 53.9% were female
- Mean CCI for patients with ATTRv was 2.7 (3.0) vs 1.1 (1.9) for matched controls

Table 1. Baseline demographic and comorbidities during 1-year pre-index period

	Newly Diagnosed Patients with ATTRv N=141	Matched Controls* N=423
Age, year, mean (SD)	62.5 (14.3)	62.5 (14.2)
18-34, n (%)	6 (4.3)	18 (4.3)
35-54	27 (19.1)	81 (19.1)
55-64	52 (36.9)	156 (36.9)
65+	56 (39.7)	168 (39.7)
Female, n (%)	76 (53.9)	228 (53.9)
Region, n (%)		
Midwest	26 (18.4)	78 (18.4)
Northeast	47 (33.3)	141 (33.3)
South	55 (39.0)	165 (39.0)
West	13 (9.2)	39 (9.2)
Insurance type, n (%) ^b		
PPO/POS	99 (70.2)	239 (56.5)
HMO/EPO	8 (5.7)	30 (7.1)
CDHP/HDHP	14 (9.9)	72 (17.0)
Comprehensive	20 (14.2)	80 (18.9)
Charlson comorbidity index, mean (SD)	2.7 (3.0)	1.1 (1.9)
Number of chronic conditions, mean (SD)	5.1 (2.7)	3.2 (2.3)
Usual physician specialty, n (%)		
Primary care	65 (46.1)	230 (54.4)
Cardiologist	5 (3.5)	10 (2.4)
Dermatologist	4 (2.8)	16 (3.8)
Gastroenterologist	6 (4.3)	6 (1.4)
Neurologist	6 (4.3)	2 (0.5)
Rheumatologist	5 (3.5)	6 (1.4)
Other ^c /Unknown	50 (35.5)	153 (36.2)

ATTRv: hereditary transthyretin amyloidosis; CDHP/HDHP: consumer-directed health plan/high deductible health plan; EPO: exclusive provider organization; HMO: health maintenance organization; PPO/POS: preferred provider organizations/point of service.

*Matched with age, gender, and region.

^bTwo matched controls had missing/unknown insurance type.

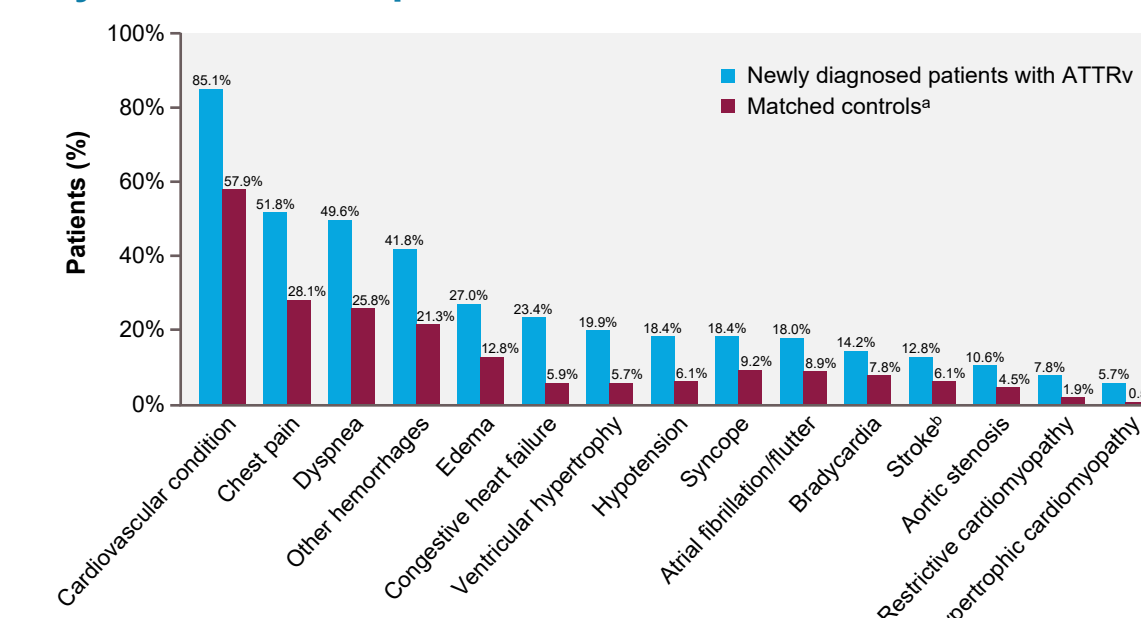
^cIncludes podiatrists and individual specialties with count <5.

RESULTS

Healthcare utilization and cardiovascular comorbidities during the 5-year look-back period

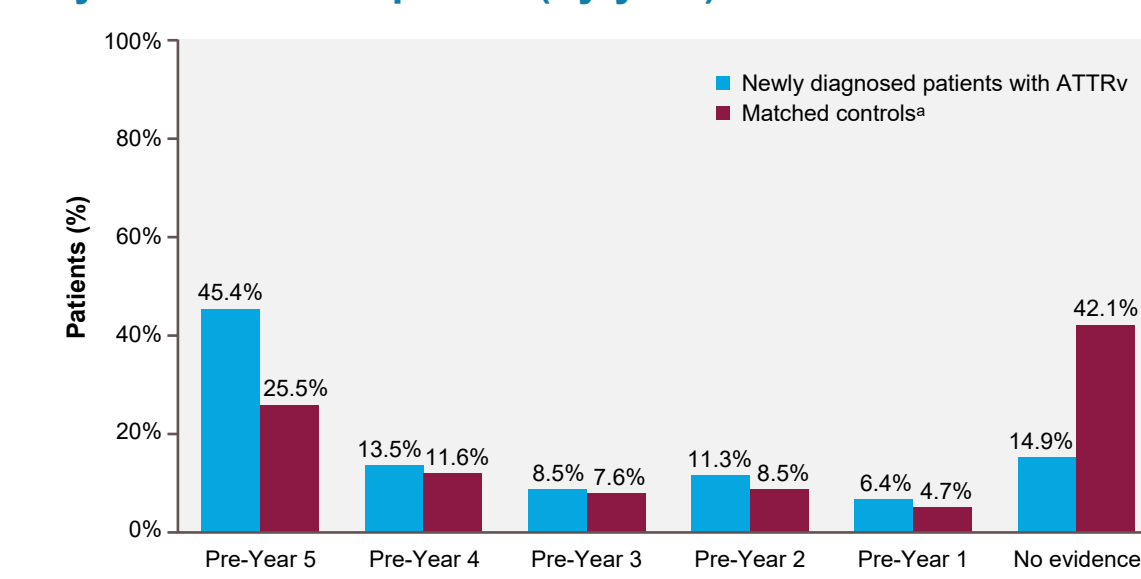
- Cardiovascular manifestations were common among patients with ATTRv prior to diagnosis
 - A higher proportion of patients with ATTRv vs. matched controls had each cardiovascular condition during the look-back period (Figure 1)
 - Cardiovascular conditions were relatively higher for patients with ATTRv vs. matched controls in each look-back year (Figure 2)
- First observed occurrence of the cardiovascular conditions was often early in the 5-year look-back period prior to diagnosis of ATTRv
 - Median time from first occurrence of a cardiovascular condition to diagnosis of ATTRv ranged from 15.4 months for patients with hypertrophic cardiomyopathy to 43.0 months for patients with chest pain (Figure 3)
 - Many of the cardiovascular conditions start to appear multiple (e.g., 3-5) years before a diagnosis of ATTRv, with dyspnea and chest pain most common throughout this period. Manifestation of certain conditions, such as bleeding, congestive heart failure, and hypotension, became more frequent in the year prior to diagnosis (Figure 4)
- First observed occurrence of diagnostic testing, such as cardiac MRI, echocardiogram, and blood-urine testing, was also common several years before an ATTRv diagnosis; pyrophosphate imaging did not occur until the year before diagnosis among a few patients (Figure 5)
- Hospitalization (47.5% vs. 24.3%), ED visits (60.3% vs. 47.0%), and cardiac imaging (56.7% vs. 27.0%) were more frequent among patients with ATTRv during the look-back period compared with matched controls (results not shown)
 - Echocardiography was the most common form of imaging performed in patients with ATTRv (56.7%), followed by cardiac MRI (7.1%), and pyrophosphate imaging (2.1%) (results not shown)

Figure 1. Cardiovascular conditions identified during the 5-year look-back period



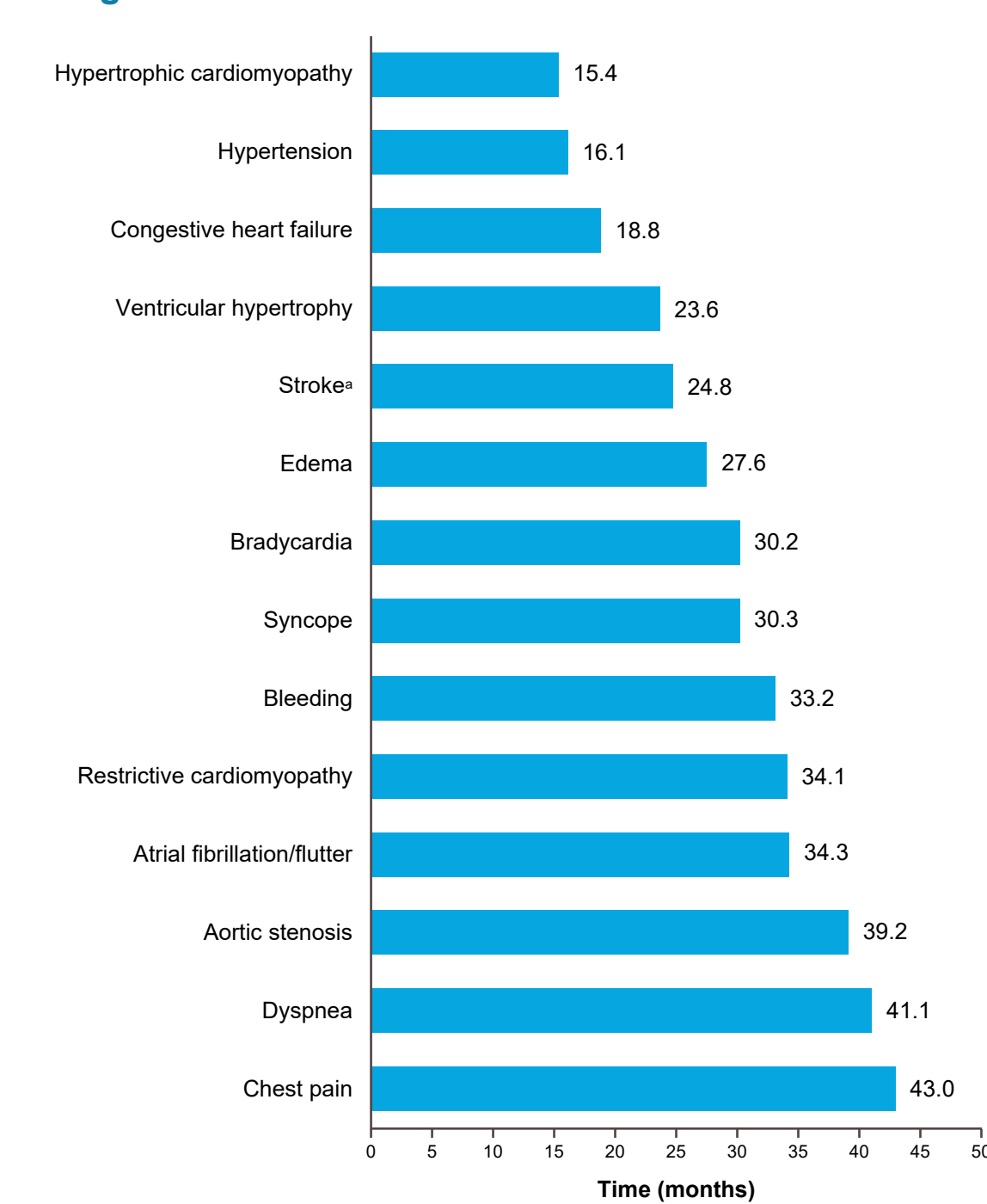
ATTRv: hereditary transthyretin amyloidosis.
*Matched with age, gender, and region.
^bIncludes ischemic and hemorrhagic stroke.

Figure 2. Cardiovascular conditions identified during the 5-year look-back period (by year)



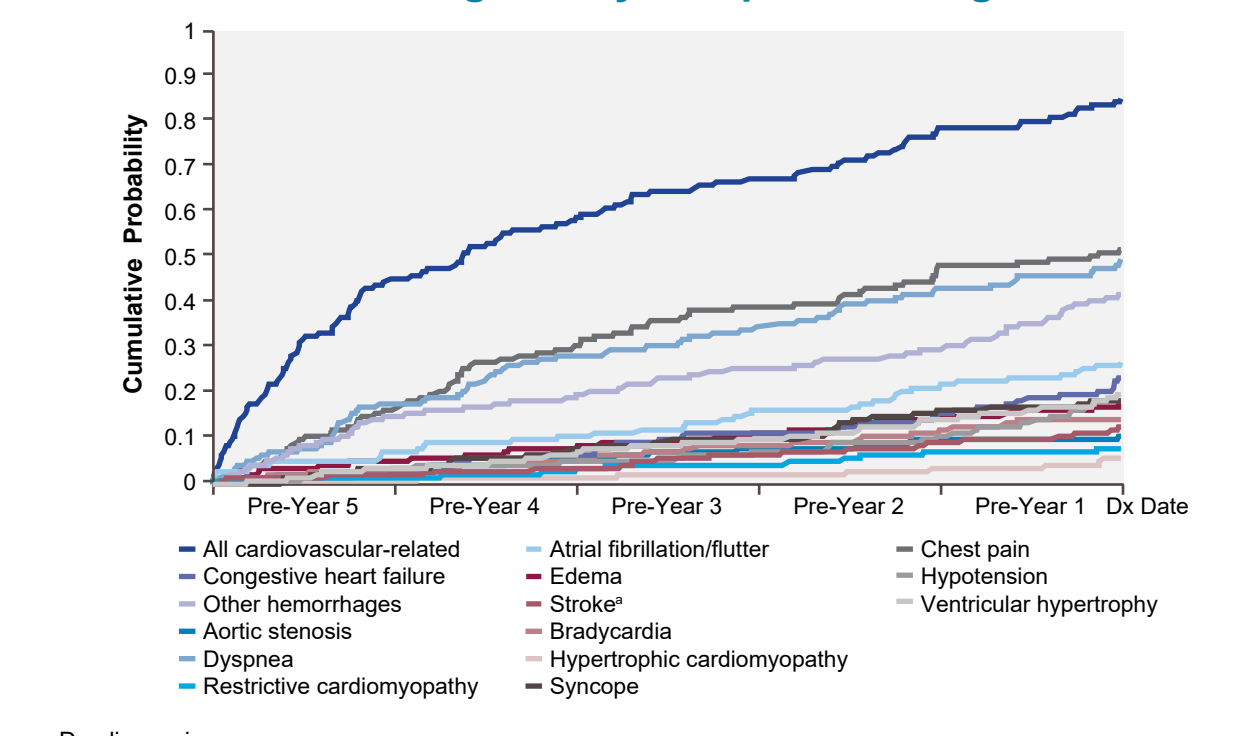
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Figure 3. Median time (months) from first occurrence of cardiovascular conditions to diagnosis among patients newly diagnosed with ATTRv



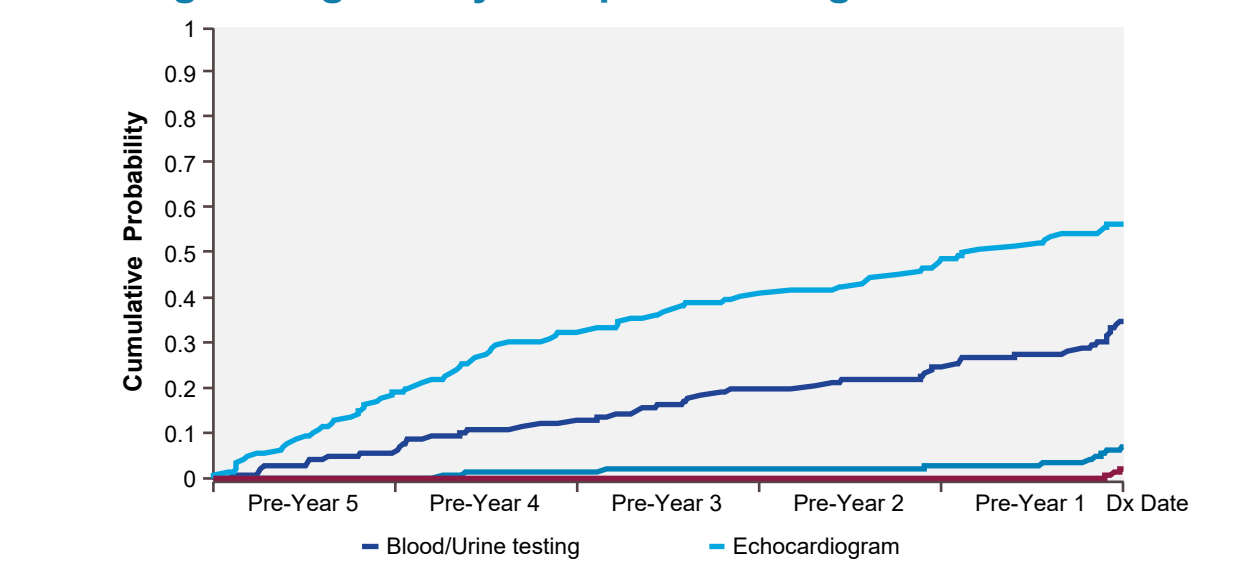
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^bIncludes ischemic and hemorrhagic stroke.

Figure 4. First observed occurrence of cardiovascular comorbidities during the 5 years prior to diagnosis



Dx: diagnosis.
^bIncludes ischemic and hemorrhagic stroke.

Figure 5. First observed occurrence of diagnostic testing during the 5 years prior to diagnosis



Dx: diagnosis; MRI: magnetic resonance imaging.

CONCLUSIONS

- Patients diagnosed with ATTRv have considerable cardiovascular disease burden in the 5 years preceding diagnosis
- Increased awareness of characteristic cardiovascular manifestations among nurses may increase clinical suspicion, leading to early diagnosis and prompt intervention
- This study has potential limitations:
 - As the look-back period was only 5 years prior to diagnosis, pre-existing conditions (and other outcomes) may have been misclassified as first occurring during that period
 - Results may not be generalizable to patients without continuous enrollment in a healthcare plan or to those with other types of insurance coverage

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DISCLOSURES

M. Vera-Llonch: Employee; Company Relationship; Akcea Therapeutics. Stock or Stock Options; Company Relationship; Akcea Therapeutics. J.T. Ortiz-Pérez: Speakers Bureau; Company Relationship; General Electric, Akcea Therapeutics SL, Medical Dospilus SL, AstraZeneca SL, Bristol Myers Squibb/Pfizer, Psyma Iberica Marketing Research. Board Membership; Company Relationship; Akcea Therapeutics SL. S.R. Reddy: Consultant; Company Relationship; Akcea Therapeutics. E. Chang: Consultant; Company Relationship; Akcea Therapeutics. M.H. Tarbox: Consultant; Company Relationship; Akcea Therapeutics. M.R. Pollock: Employee; Company Relationship; Akcea Therapeutics. Stock or Stock Options; Company Relationship; Akcea Therapeutics. J. Nativi-Nicolau: Grant/Research Support; Company Relationship; Pfizer, Eidos Therapeutics, Akcea Therapeutics, Alnylam Pharmaceuticals. Consultant; Company Relationship; Akcea Therapeutics, Eidos Therapeutics, Alnylam Pharmaceuticals, Pfizer. N.M. Fine: Grant/Research Support; Company Relationship; Akcea Therapeutics, Pfizer, Alnylam Pharmaceuticals. Consultant; Company Relationship; Akcea Therapeutics, Pfizer, Alnylam Pharmaceuticals.