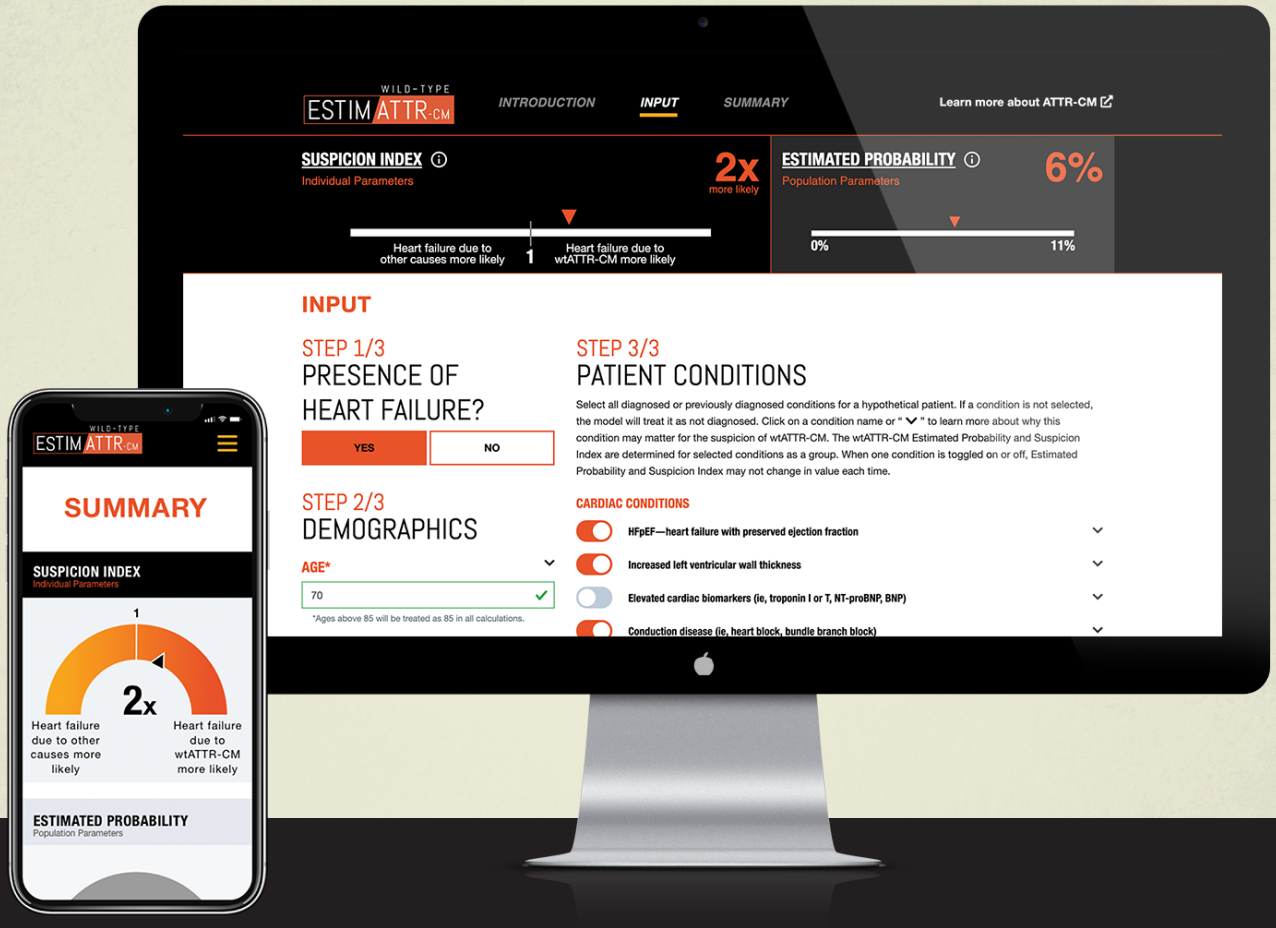
WILD-TYPE

ESTIM ATTR-CM

AN EDUCATIONAL, ONLINE TOOL TO ESTIMATE THE PROBABILITY OF wtATTR-CM IN HYPOTHETICAL HEART FAILURE PATIENTS



wtATTR-CM, wild-type transthyretin amyloid cardiomyopathy.

Pfizer Rare Disease

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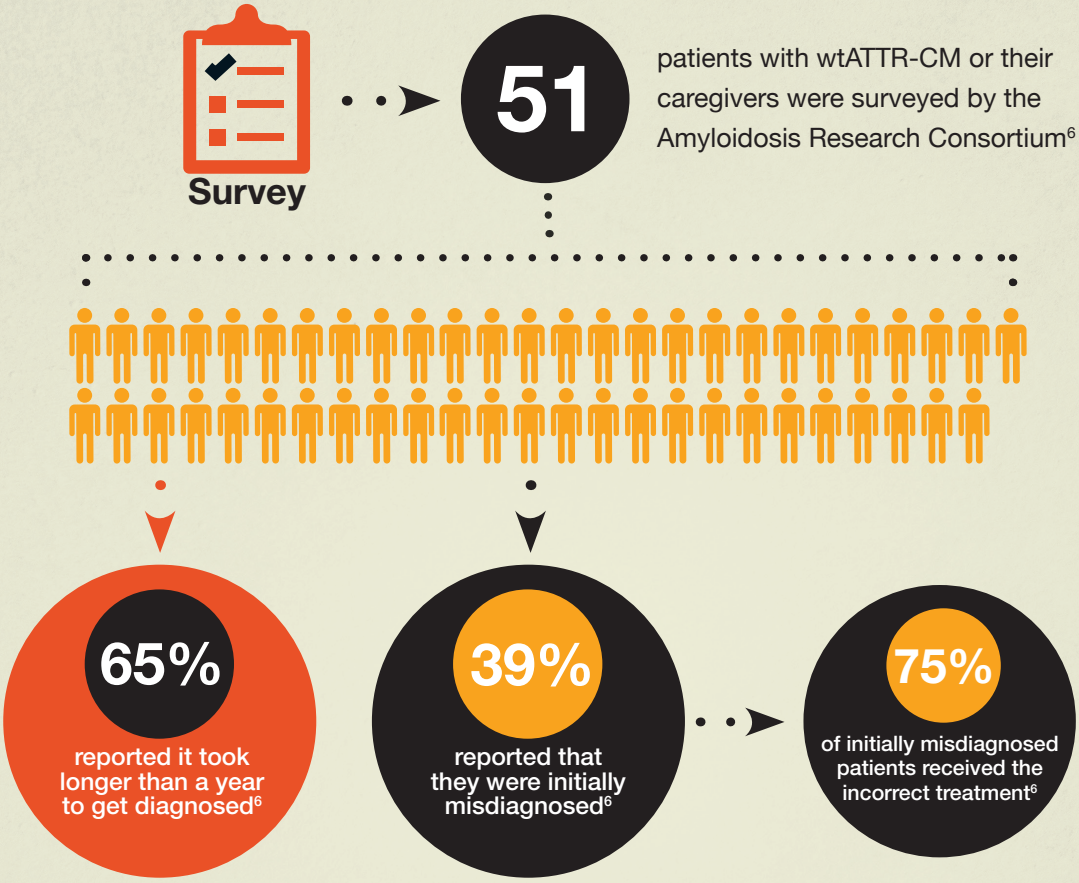
ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification.

BACKGROUND

IMPORTANCE OF MAINTAINING AN ELEVATED INDEX OF SUSPICION FOR wtATTR-CM

In clinical practice, the diagnosis of wtATTR-CM is often delayed or missed, potentially due to similarities between presentation of cardiac manifestations seen in wtATTR-CM and those seen in more common etiologies of heart failure (HF). Achieving a wtATTR-CM diagnosis is critical, as delay can lead to significant consequences for patients.[1,2] Once diagnosed, untreated patients with wtATTR-CM have a median survival of approximately 3.5 years.[3-5]

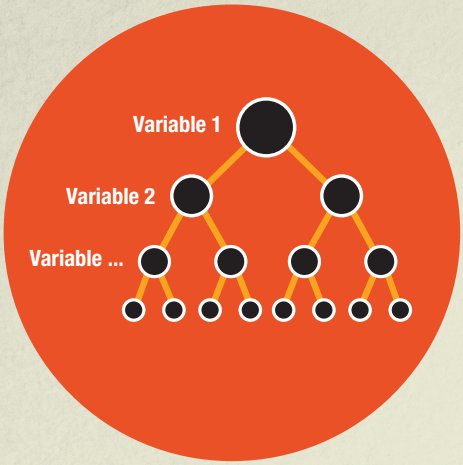


INTRODUCING THE wtATTR-CM estimATTR

The wtATTR-CM estimATTR uses an artificial intelligence/machine learning (AI/ML) approach to estimate the probability that a hypothetical patient with HF may have this condition, considering age, sex, and an estimated prevalence of wtATTR-CM among patients with HF, and the presence or absence of 11 different clinical conditions associated with wtATTR-CM.[7]

The wtATTR-CM estimATTR is only to be used as an educational tool to learn how different combinations of clinical conditions for hypothetical HF patients can yield different probability scores. It is not to be used in a clinical setting for the suspicion or diagnosis of wtATTR-CM in individual patients.

DEVELOPING A SIMPLIFIED MACHINE LEARNING MODEL

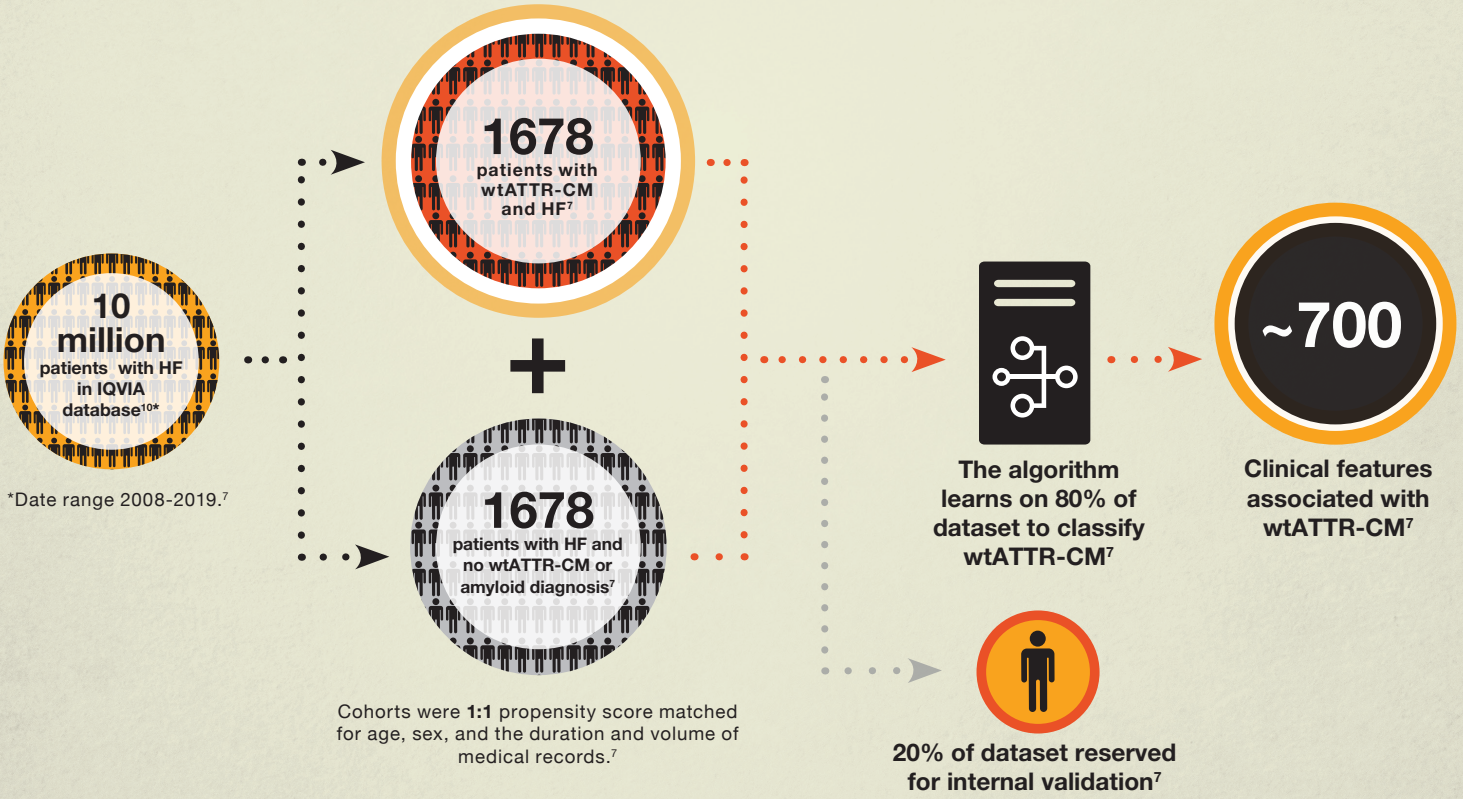


The wtATTR-CM estimATTR uses a **Random Forest (RF)** ML classification model to differentiate patients with wtATTR-CM from those with HF due to other causes.[7]

This algorithm takes predictor variables as inputs, which in this case are conditions associated with wtATTR-CM, and classifies the outcome, either wtATTR-CM or HF due to other causes, using an ensemble of trees. This method was chosen over other approaches because of its higher predictive accuracy and lower preprocessing requirements.[8,9]

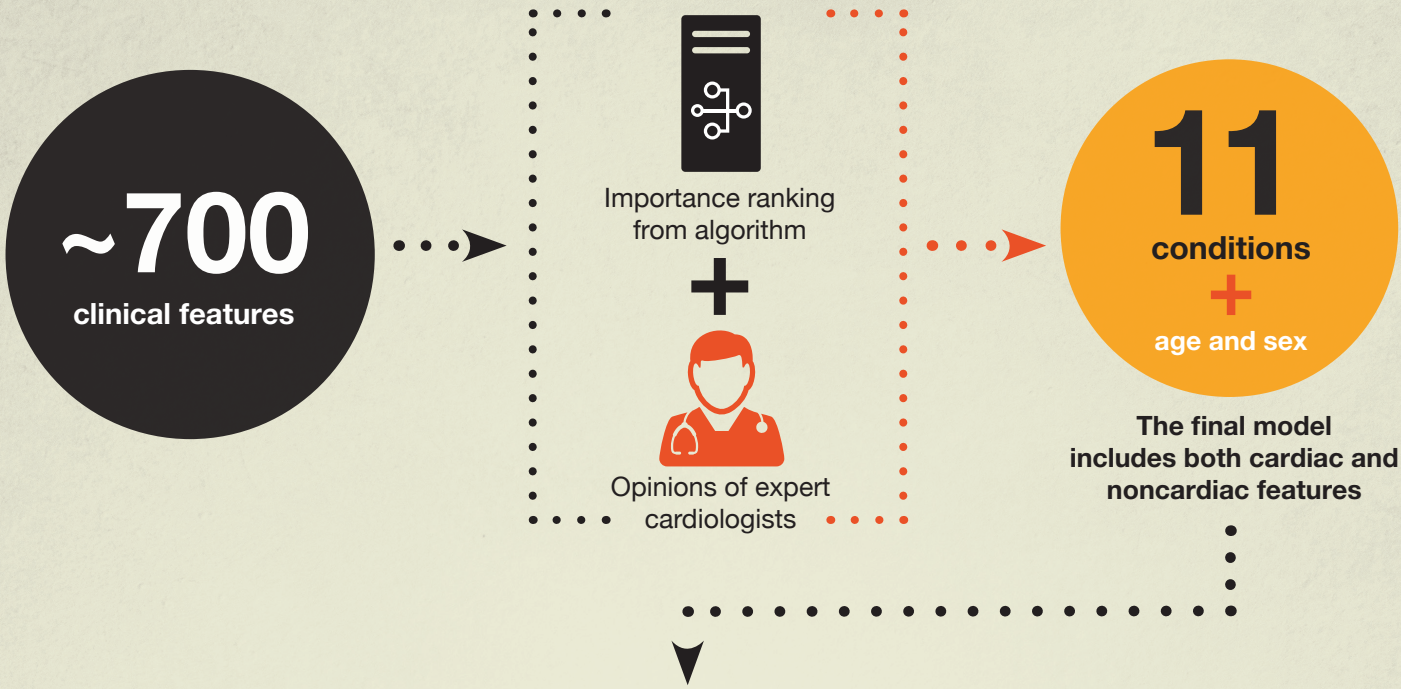
LEARNING TO IDENTIFY wtATTR-CM BASED ON REAL-WORLD MEDICAL CLAIMS DATA

The algorithm was trained on 2 patient cohorts derived from the IQVIA US medical claims database composed of (1) patients with diagnoses of both wtATTR-CM and HF and (2) a matched cohort of patients with HF alone without any amyloid diagnosis.[7]



CREATING THE MODEL

The model was created using a process called feature selection. The number of model features was systematically reduced to those with the greatest clinical and variable importance, in addition to age and sex, on the probability estimation.[7]



CARDIAC CONDITIONS

1. HFpEF—heart failure with preserved ejection fraction
2. Increased left ventricular wall thickness
3. Elevated cardiac biomarkers (ie, troponin I or T, NT-proBNP, BNP)
4. Conduction disease (ie, heart block, bundle branch block)
5. Atrial arrhythmias (ie, atrial fibrillation or flutter)
6. Pericardial effusion

NONCARDIAC CONDITIONS

7. Carpal tunnel syndrome (or history of corrective surgery)
8. Lumbar spinal stenosis (or surgical history)
9. Shoulder, hip, and/or knee degenerative joint disease
10. Nontraumatic tendon rupture (eg, biceps, achilles tendon) or history of surgical repair
11. Polyneuropathy (nondiabetic)

BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

INTERNAL VALIDATION AND PERFORMANCE PARAMETERS OF MODEL

The performance of the model was evaluated using a procedure called holdout evaluation. Twenty percent of each of the 2 patient cohorts were withheld from the model training procedure and used to test the accuracy of the model predictions.[7]

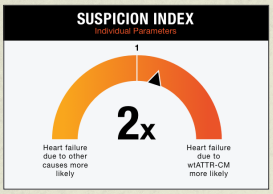
MODEL PERFORMANCE PARAMETER	DEFINITION	VALUE[7]
AUC ROC (area under the receiving operating characteristic curve)	A receiver operating characteristic (ROC) curve is a plot of the true positive rate (ie, sensitivity) on the y-axis and the false positive rate on the x-axis for all classification thresholds.[11] The AUC is the area under the ROC curve and represents the accuracy of the model. A model with an AUC of 1 would make 100% correct predictions.[11]	**0.82**
Sensitivity	The proportion of true positives that are correctly identified.[12]	**77%**
Specificity	The proportion of true negatives that are correctly identified.[12]	**72%**
Positive predictive value (PPV)	The proportion of patient profiles classified as wtATTR-CM that truly have wtATTR-CM.[13]	**71%**
Negative predictive value (NPV)	The proportion of patient profiles classified as not wtATTR-CM that truly do not have wtATTR-CM.[13]	**78%**
Classification model accuracy	The probability that a random example is correctly classified.[14]	**74%**

AUC, area under curve.

APPLYING THE MODEL IN HYPOTHETICAL HEART FAILURE PATIENT SCENARIOS

The AI/ML model has demonstrated the ability to differentiate hypothetical patient profiles with wtATTR-CM as the underlying cause of HF from those with HF due to other causes.[7] Based on probabilities computed from the model, the wtATTR-CM estimATTR provides 2 outputs for each profile evaluated: a Suspicion Index and an adjusted Estimated Probability.

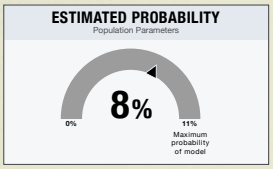
SUSPICION INDEX AND ESTIMATED PROBABILITY



The Suspicion Index is a metric that has been developed to assist in the interpretation of the Estimated Probability. It is a ratio of the likelihood that the selected group of conditions would be associated with wtATTR-CM relative to HF due to other causes.[7]

A Suspicion Index greater than 1 indicates that the group of conditions in a hypothetical profile is more likely to be associated with HF due to wtATTR-CM than HF due to other causes. The maximal value is approximately 24x, indicating that the presence of all 11 conditions is 24 times more likely to appear in a patient with wtATTR-CM than a comparable matched* patient with nonamyloid HF.[7,10]

*Control cohort were 1:1 propensity score matched by age, sex, and the duration and volume of medical records.



Probability estimates from the AI/ML model are based on the presence or absence of the 11 conditions included in the model for wtATTR-CM. To incorporate the estimated prevalence of wtATTR-CM among patients with HF and account for the differential risk of wtATTR-CM across age groups and sexes, the probability estimates from the AI/ML model were adjusted using a Naïve Bayesian approach.† Using the above assumptions, the maximum Estimated Probability of wtATTR-CM as the cause of HF given the presence of all 11 associated conditions is approximately 11%.[7,10]

†See Appendix for Naïve Bayesian formulation.

SUSPICION INDEX VALUE	DEFINITION	INTERPRETATION FOR A HYPOTHETICAL HF PATIENT PROFILE FROM THE GENERAL POPULATION
Less than 1	HF due to other causes is more likely than wtATTR-CM	wtATTR-CM is less likely for the hypothetical patient scenario (based on the conditions selected) than for a comparable patient with nonamyloid HF
Equal to 1	HF due to wtATTR-CM or due to other causes equally likely	wtATTR-CM is equally as likely for the hypothetical patient scenario (based on the conditions selected) as for a comparable patient with nonamyloid HF
Greater than 1	HF due to wtATTR-CM is more likely than other causes	wtATTR-CM is more likely for the hypothetical patient scenario (based on the conditions selected) than for a comparable patient with nonamyloid HF

LIMITATIONS

- Retrospective administrative data were used for the development of the calculator
- The Naïve Bayesian probability adjustment procedure assumes that age and sex are independent of the clinical features[7]
- Adjustment of the probability relies on the IQVIA data source for estimation of the proportion of HF patients with wtATTR-CM based on the age and sex of the hypothetical patient[7]
- Probability is further adjusted based on an estimated prevalence of wtATTR-CM among patients with HF, which is derived from the most current literature and expert opinion, as it is not yet well defined[7,15-17]

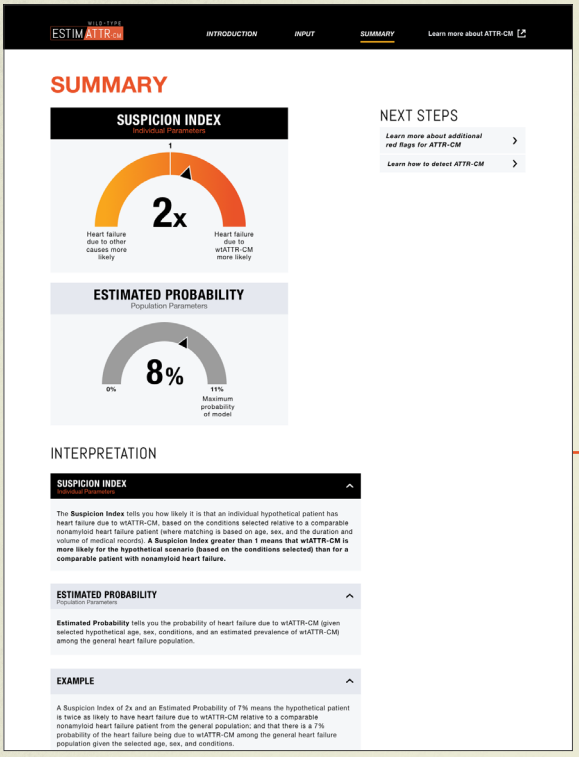
UNDERSTANDING THE wtATTR-CM estimATTR SUMMARY PAGE

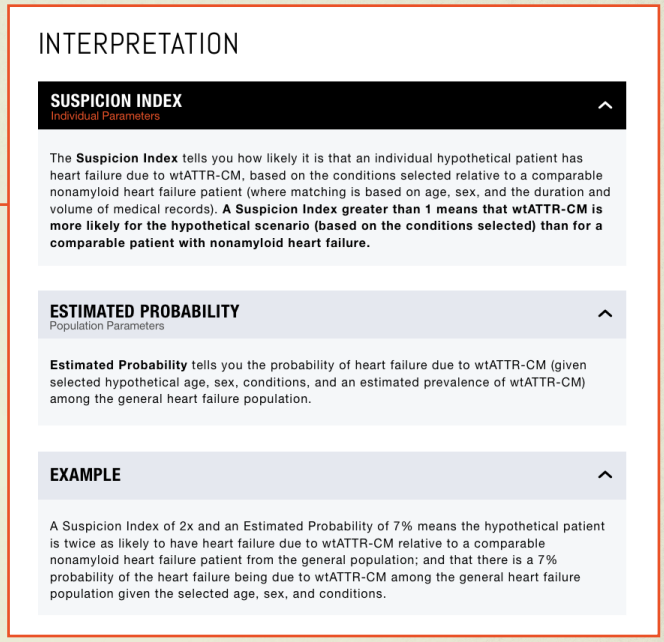
INTERPRETING THE RESULTS, INCLUDING EXAMPLE

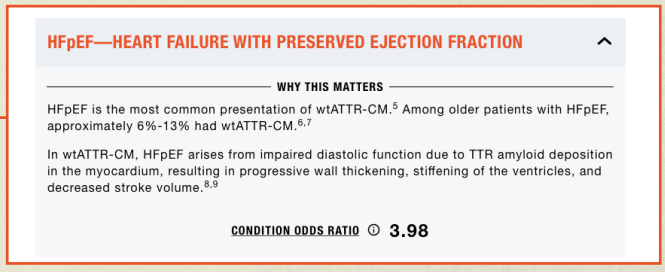
The wtATTR-CM estimATTR generates visualizations of the Suspicion Index and Estimated Probability data for the created hypothetical HF patient profile.

In addition, a list of the selected inputs is provided. Each is accompanied by the following:

1. An explanation of why the selected input may contribute to the risk of wtATTR-CM
2. An odds ratio that represents the odds that a hypothetical patient profile has HF due to wtATTR-CM compared to HF due to other causes based on this single clinical condition







APPENDIX

ICD-10-CM CODES (US) FOR CONDITIONS INCLUDED IN THE PREDICTION MODEL[10]

CONDITION NAME	ICD-10-CM CODES (US)
HFpEF—heart failure with preserved ejection fraction	• I5030 • I5032 • I5033 • I5031
Increased left ventricular wall thickness	• I517
Elevated cardiac biomarkers (ie, troponin I or T, NT-proBNP, BNP)	• R748 • R749
Conduction disease (ie, heart block, bundle branch block)	• I454 • I4589 • I4510 • I4439 • I450 • I4469 • I4430 • I444 • I4460 • I452 • I445 • I442 • I440 • I4519 • I459 • I455 • I453 • I441 • I447
Atrial arrhythmias (ie, atrial fibrillation or flutter)	• I481 • I4891 • I482 • I480 • I48 • I483 • I484 • I4892

CONDITION NAME	ICD-10-CM CODES (US)
Pericardial effusion	• I313
Carpal tunnel syndrome (or history of corrective surgery)	• G5603 • G5601 • G5602 • G5600
Lumbar spinal stenosis (or surgical history)	• M9963 • M48061 • M4806 • M4807 • M9933 • M9973 • M48062 • M9953
Shoulder, hip, and/or knee degenerative joint disease	• M25819 • M7611 • Z96649 • M7612 • M7050 • M25119 • M25751 • M25812 • M76891 • M25859 • M7071 • M7652 • M25752 • M7620 • M7601 • M222X2

CONDITION NAME	ICD-10-CM CODES (US)
Shoulder, hip, and/or knee degenerative joint disease (continued from previous page)	• Z96612 • M25761 • M7651 • Z96651 • M7650 • M7602 • M25159 • M7500 • M7061 • M222X1 • M25811 • Z96642 • M7060 • Z96652 • Z96611 • Z96641 • M7052 • M25852 • M25762 • M25861 • M76892 • M7501 • M7502 • M76899 • Z96659 • M7051 • M7610 • M25862 • M228X1 • M25851 • M25169 • M25869 • Z96653 • M769 • M7072 • M25152 • M7062 • R294 • M25111 • M7070 • Z96643 • Z96619

CONDITION NAME	ICD-10-CM CODES (US)
Nontraumatic tendon rupture (eg, biceps, achilles tendon) or history of surgical repair	• M75122 • M66879 • M75120 • M66369 • M66231 • M66321 • M66822 • M66259 • M66821 • M66371 • M66829 • M66311 • M75121 • M6688
Polyneuropathy (nondiabetic)	• G6289 • G629 • G63 • G64 • G6281

FORMULAS AND ASSUMPTIONS

SUSPICION INDEX FORMULA[7]

$$\text{Suspicion Index} = \frac{\text{RF Model Prob WT}}{\text{RF Model Prob HF}}$$

Explanation of variable names

- RF Model Prob WT = Generated probability estimate from the ML model that the hypothetical patient profile has wtATTR-CM
- RF Model Prob HF = Generated probability estimate from the ML model that the hypothetical patient profile has HF (and not wtATTR-CM) = (1 − RF Model Prob WT)

NAÏVE BAYESIAN PROBABILITY ADJUSTMENT FORMULA[7,10]

$$\text{Estimated Probability} = \text{RF Model Prob WT} \times \frac{\text{WT Prev} \times \frac{\text{\# WT Patients by Age, Sex}}{\text{\# WT Population}}}{\left[\text{WT Prev} \times \frac{\text{\# WT Patients by Age, Sex}}{\text{\# WT Population}} + \text{HF Prev} \times \frac{\text{\# HF Patients by Age, Sex}}{\text{\# HF Population}}\right]}$$

Explanation of variable names

- RF Model Prob WT = Generated probability estimate from the ML model that the hypothetical patient profile has wtATTR-CM
- WT Prev = Estimated prevalence of wtATTR-CM among the HF population = 5%
- HF Prev = (100% − WT Prev) = 95%
- # WT Population = Size of the wtATTR-CM and HF population from the IQVIA dataset = 1678
- # HF Population = Size of the HF (and not wtATTR-CM) population from the IQVIA dataset = 9,973,383
- # WT Patients by Age, Sex = The number of patients with wtATTR-CM and HF in the IQVIA dataset corresponding to the user-selected age and sex of the hypothetical patient profile
- # HF Patients by Age, Sex = The number of patients with HF (and not wtATTR-CM) in the IQVIA dataset matching the age and sex of the hypothetical patient profile

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