Phenomapping of Patients With Heart Failure With Preserved Ejection Fraction Using Machine Learning-Based Unsupervised Cluster Analysis

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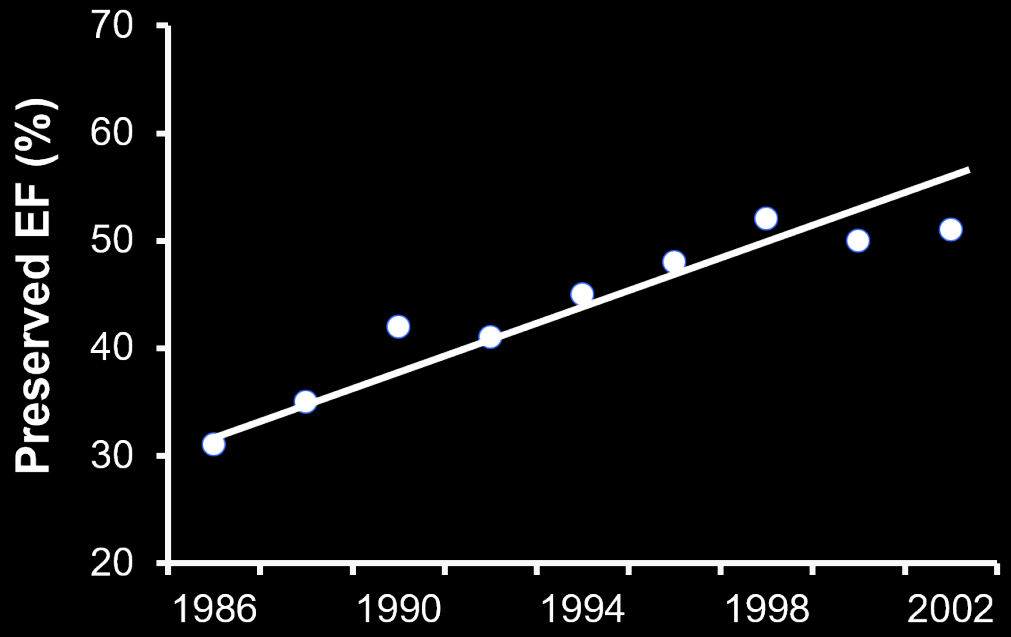
PGY-2, University of Texas Southwestern Medical Center

Disclosures: None

HFpEF: The New Face of HF

Increasing Prevalence



Owan, et al *NEJM* 2006

HFpEF: The New Face of HF

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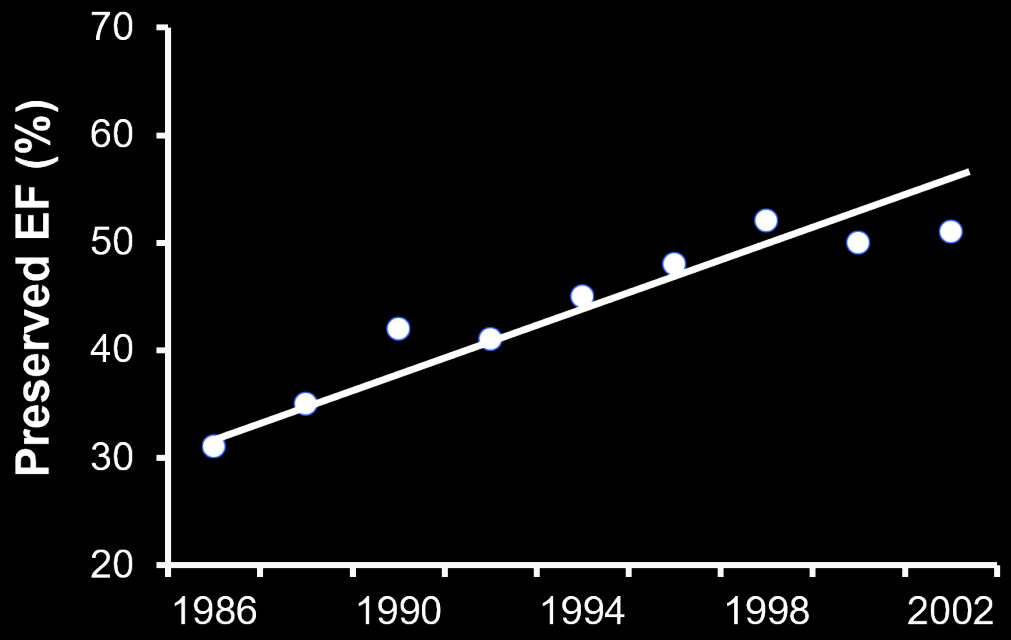
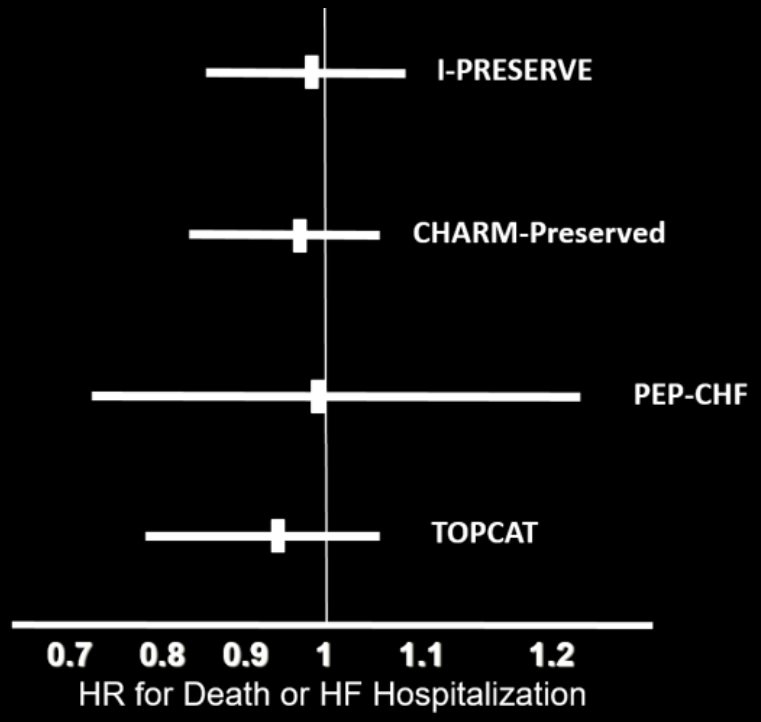


Refractory to Therapy



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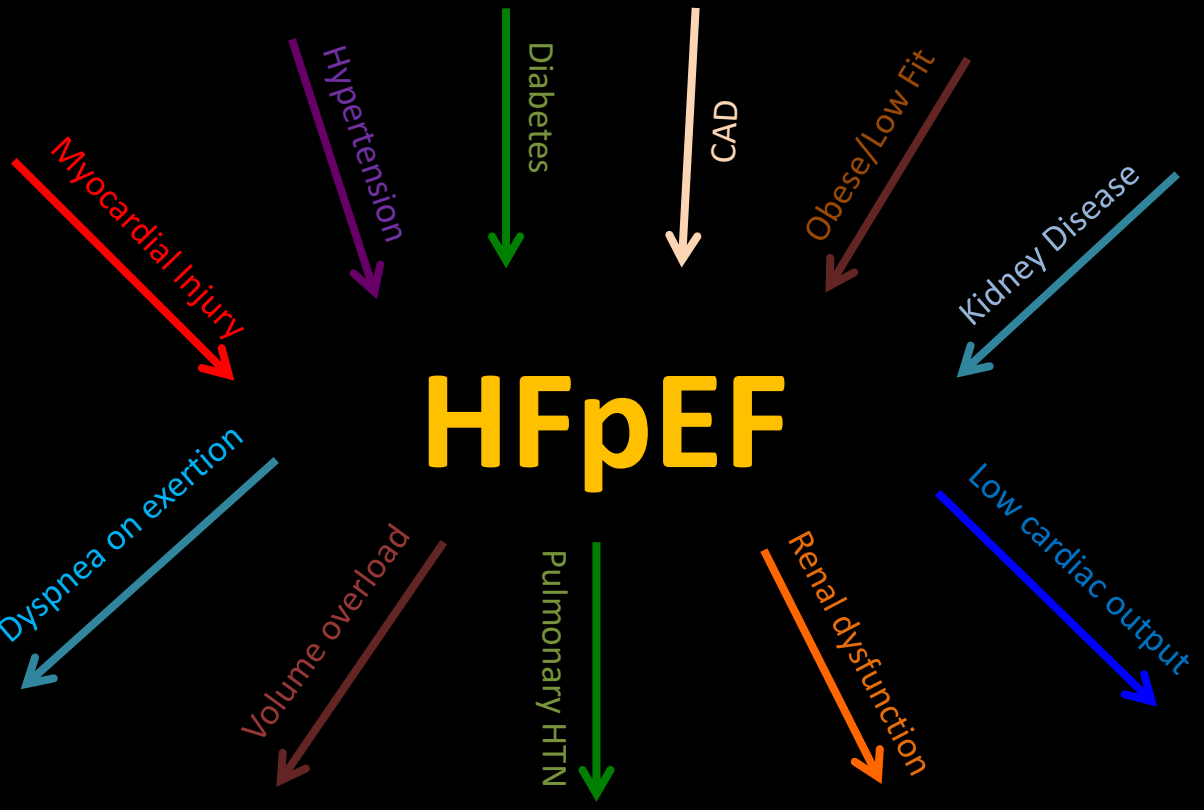
Different risk factors combinations leads to abnormal myocardial structure/function



Heterogenous clinical presentations

Shah SJ, et al. *Heart Fail Clin* 2014

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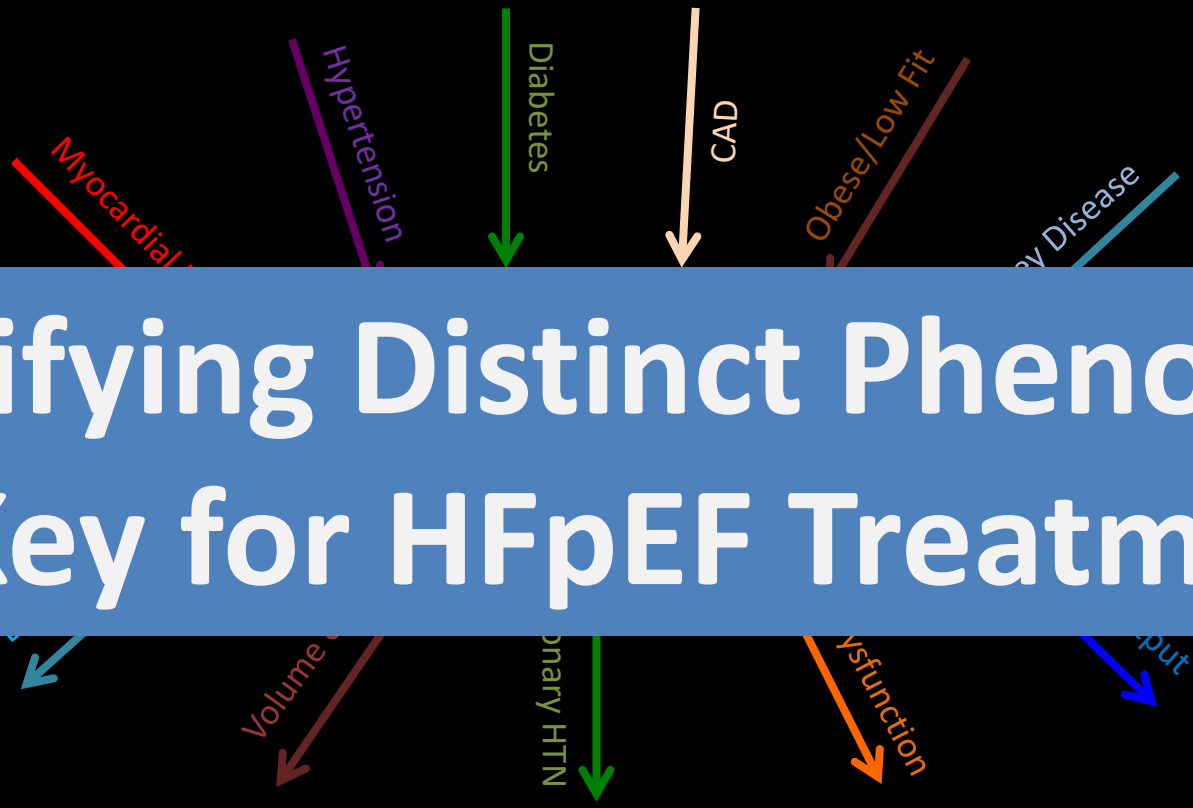


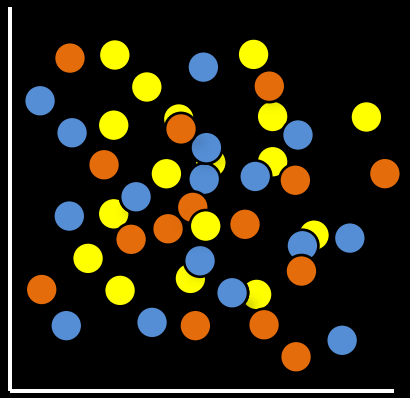
Identifying Distinct Phenotypes is Key for HFpEF Treatment

Heterogenous clinical presentations

Shah SJ, et al. *Heart Fail Clin* 2014

Central Hypothesis

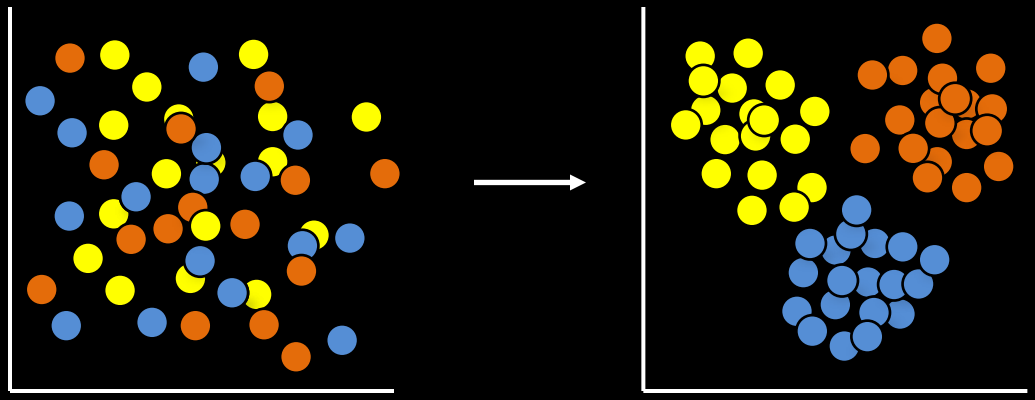
HFpEF Patients



Central Hypothesis

HFpEF Patients

Aim 1:
Determine Phenotypic Clusters



Central Hypothesis

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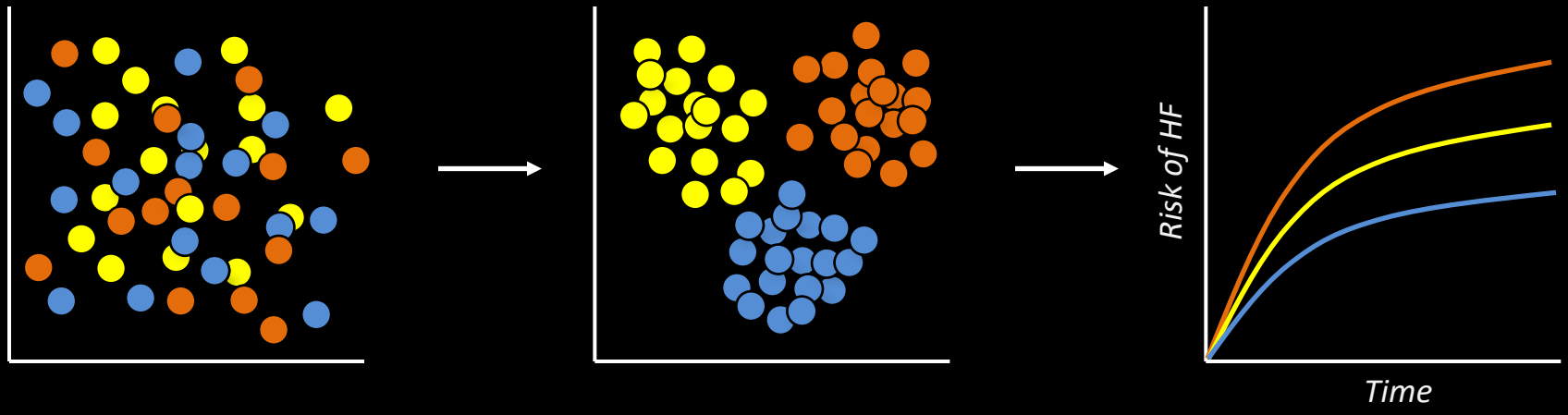
Aim 1:
Determine Phenotypic Clusters

Aim 2:
Unique Clinical Risk Profiles



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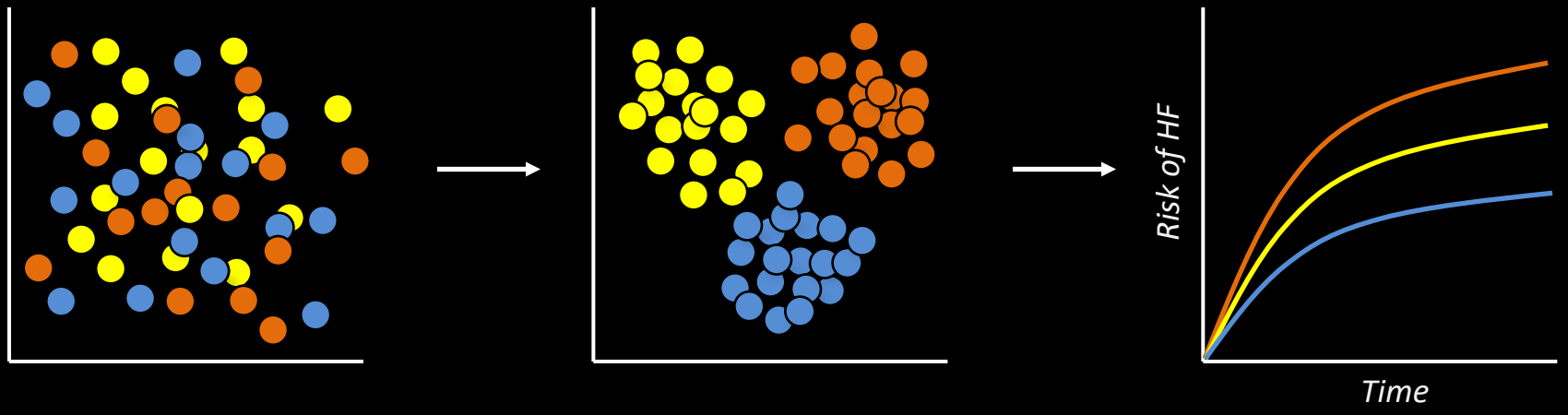
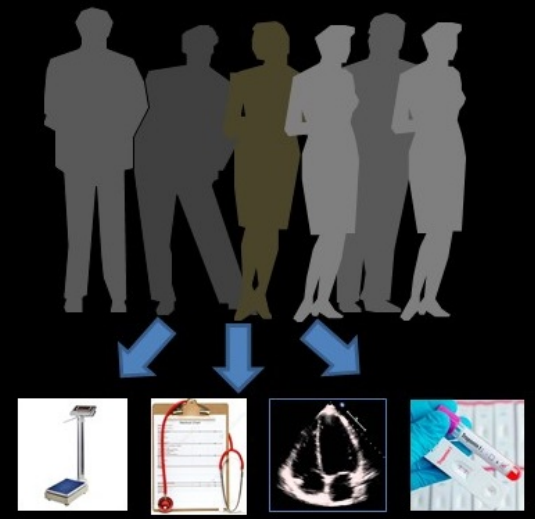


Hypothesis: Machine learning-based unsupervised clustering can identify distinct phenotypic subgroups in a mixed-data cohort of individuals with HFpEF.

Study Methodology

TOPCAT Trial
Stable HFpEF Patients (Americas)
(Spironolactone vs. Placebo)



Body size | Clinical parameters | Echo | Labs

61 non-collinear variables
<10% missingness

N = 654

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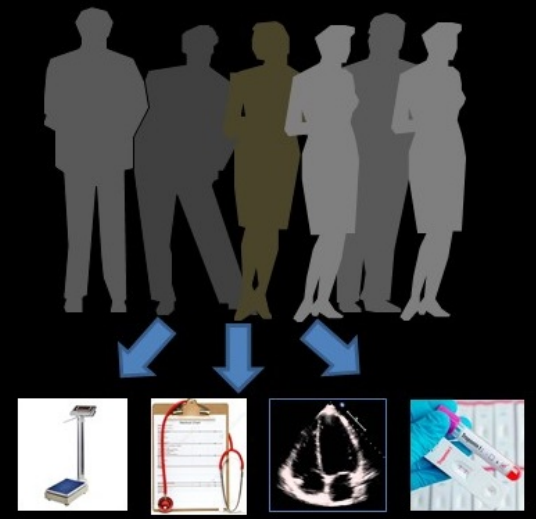

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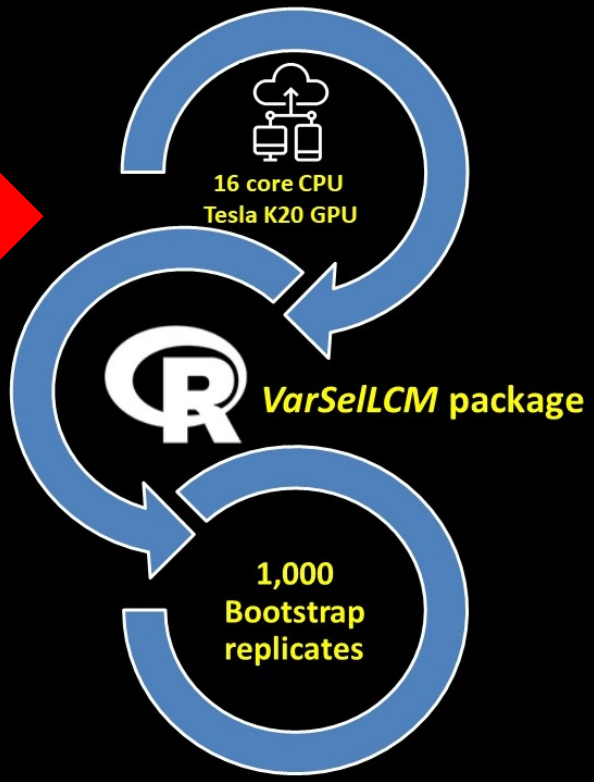
Machine Learning
Cluster Analysis



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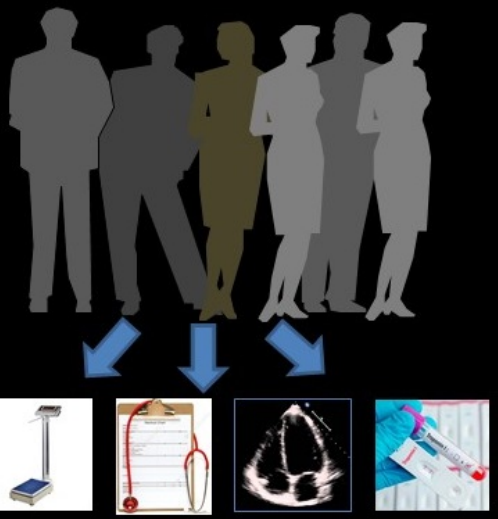

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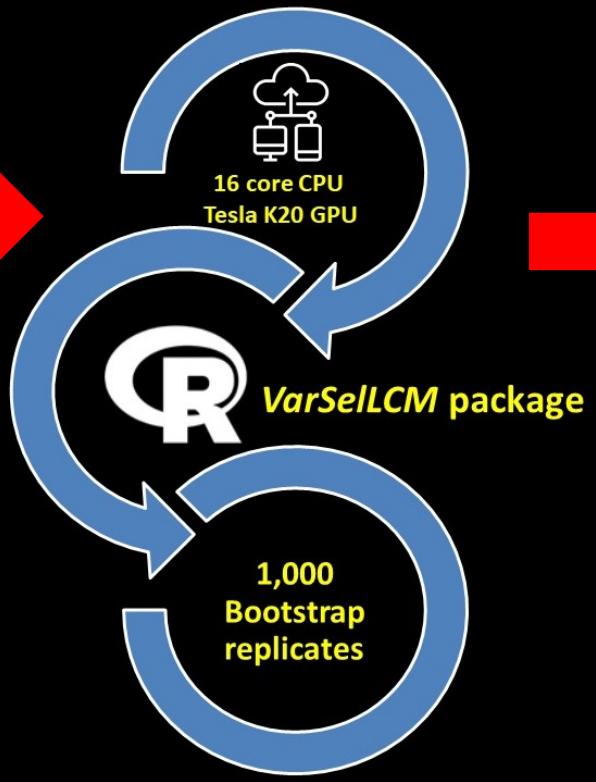
Machine Learning Cluster Analysis



Distinct Phenogroups

- **Phenogroup 1**
- **Phenogroup 2**
- **Phenogroup 3**

Clinical Characteristics of the Phenogroups

Phenogroup 1 (N = 136)

- Highest burden of CV risk factors:
  - Anemia
  - BMI
  - T2DM
  - eGFR
  - ASCVD
  - BNP/NT-ProBNP
- Echocardiographic:
  - Highest LV mass

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Phenogroup 2 (N = 108)

- Lowest burden of:
  - T2DM
  - Dyslipidemia
  - ASCVD
- Echocardiographic:
  - Highest diastolic dysfunction

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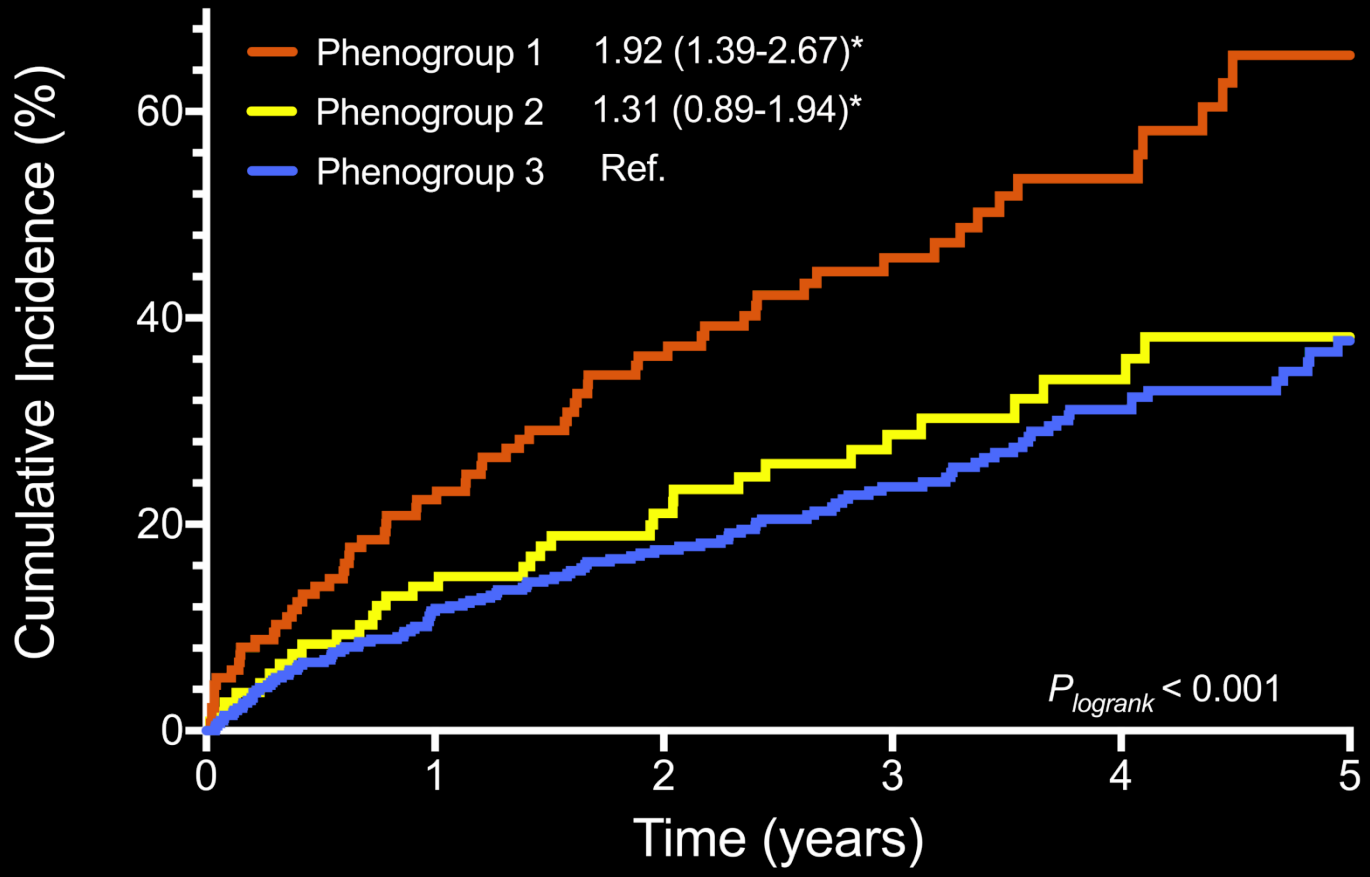
  - T2DM
  - Dyslipidemia
  - ASCVD
- Echocardiographic:
  - Highest diastolic dysfunction

Phenogroup 3 (N = 410)

- Lowest burden of:
  - Obesity
  - BNP/NT-ProBNP
- Echocardiographic:
  - Lowest diastolic dysfunction
  - Lower LA size
  - Lower PA pressure

Clinical Validity of the Phenomapping Approach

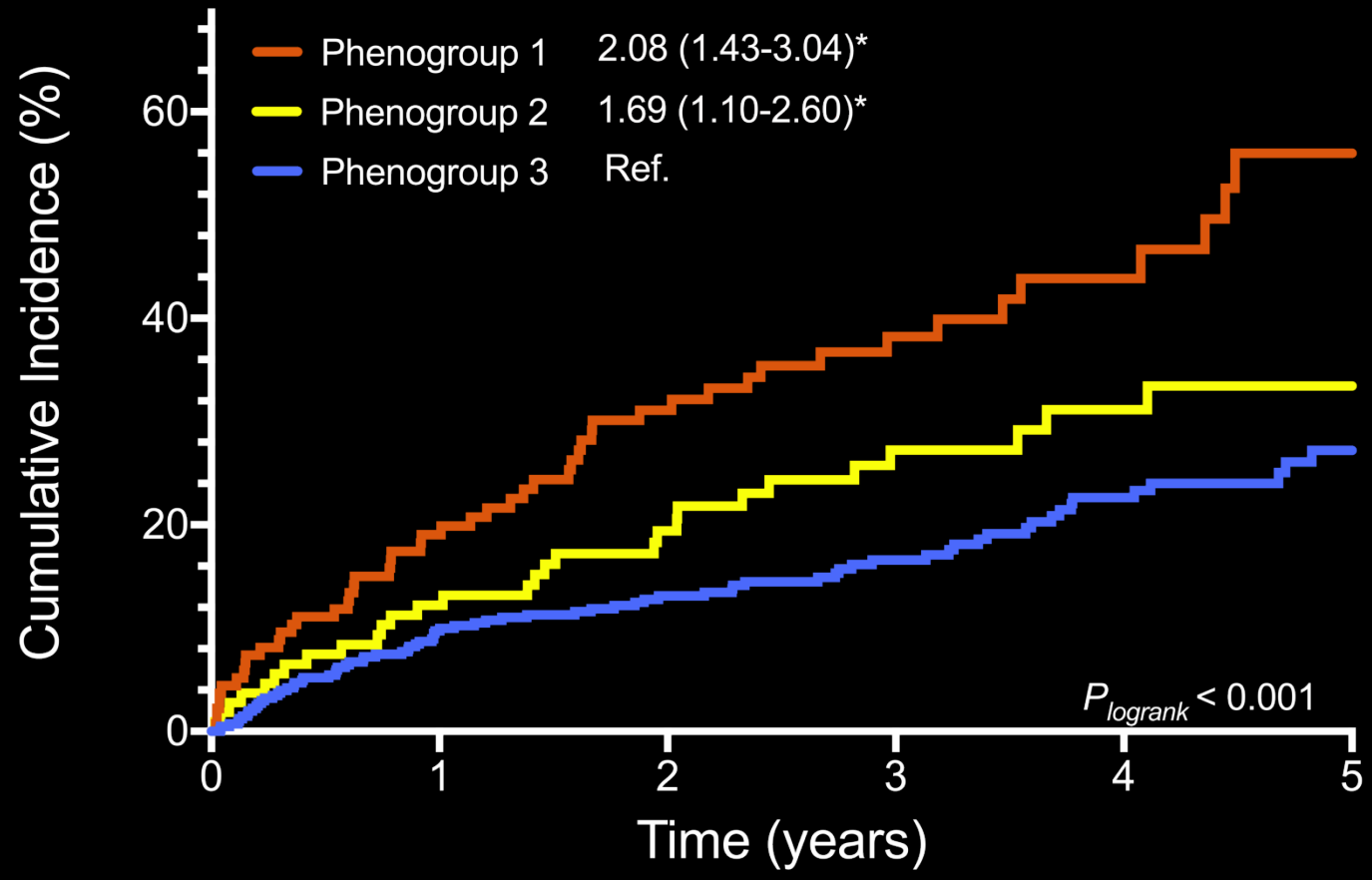
Primary composite endpoints[#] (N = 209)



**Hazard ratio for outcome adjusted for age, diabetes status, randomization strata, and treatment arm*
#Composite of aborted cardiac arrest, HF hospitalization, or CV death.

Clinical Validity of the Phenomapping Approach

HF hospitalization (N = 157)



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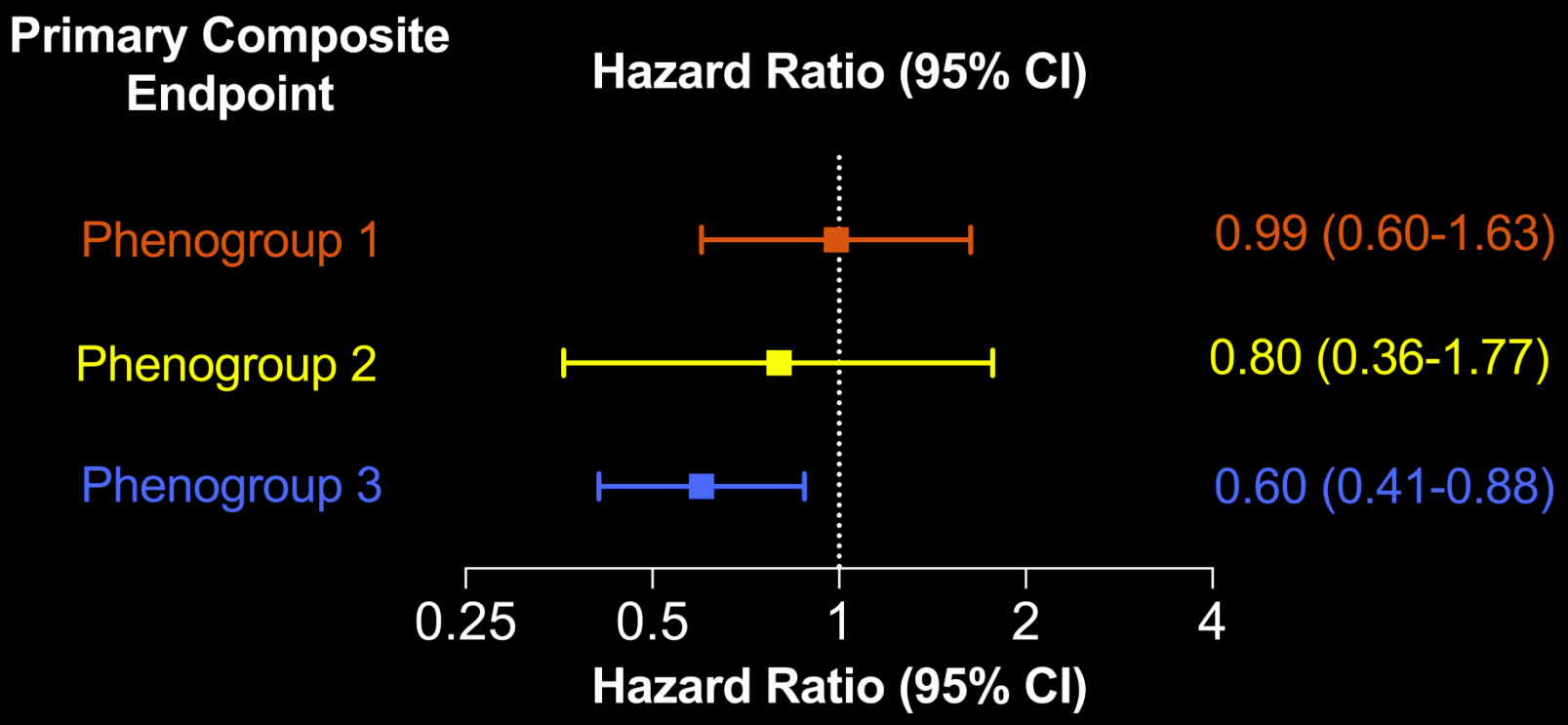
Efficacy of Spironolactone across Phenogroups

P-interaction (Treatment arm X Phenogroup): 0.10



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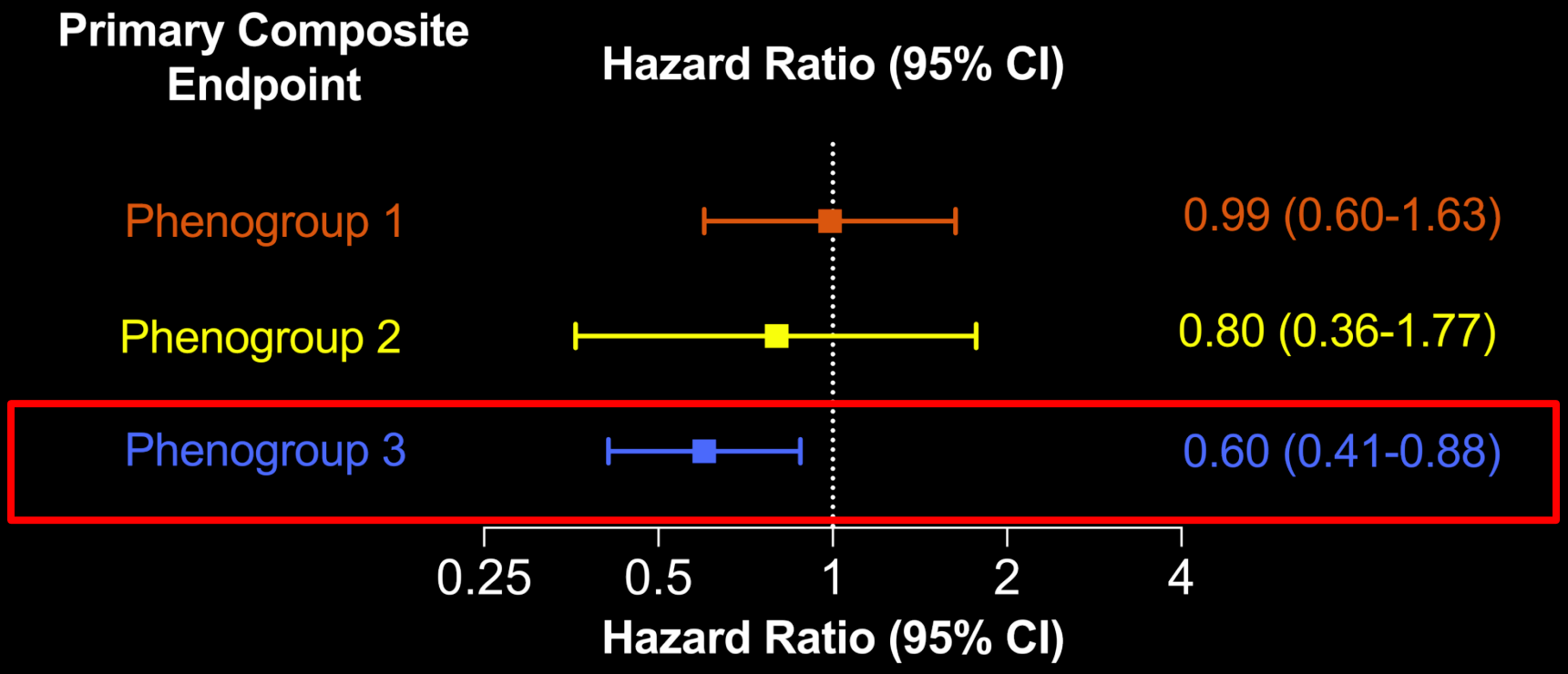

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Composite of aborted cardiac arrest, HF hospitalization, or CV death.

External Validation of the Phenomapping Approach

RELAX Trial Cohort (N = 198 stable HFpEF patients)

Outcome

- Composite rank score during follow up (6 months) based on significant clinical events
  - Death
  - Time to CV hospitalization
  - Worsening HF symptoms

- Lower score indicates worse prognosis

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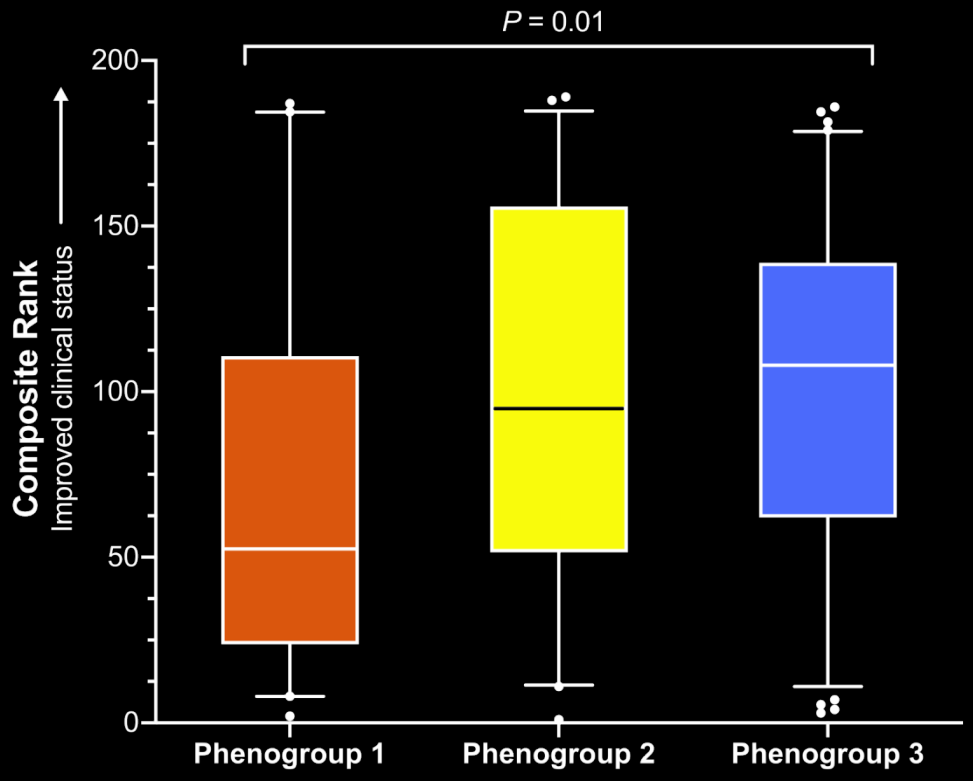

Limitations

- Exploratory analysis due to the negative primary results of the TOPCAT trial
- Missingness in other relevant clinical biomarkers
- Need larger cohort to test treatment interaction

Conclusion

- Machine learning-based cluster analysis can identify phenogroups of patients with HFpEF with distinct clinical characteristics and long-term outcomes.

Acknowledgements

Primary Mentor

- **Ambarish Pandey, MD**

UTSW

- Jarrett Berry, MD
- Justin Grodin, MD, MPH
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Computational/Resource Support

UT Southwestern Medical Center
Lyda Hill Department of Bioinformatics
BioHPC

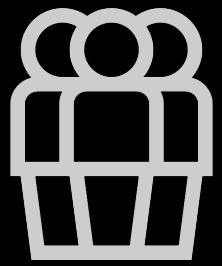
Research Funding Support

Southwestern Health Resources
Texas Health Resources®
UT Southwestern Medical Center

Clinical Characteristics of the Phenogroups

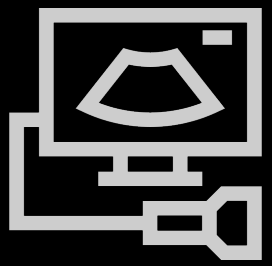
Baseline Characteristics	Phenogroup 1 (N =136)	Phenogroup 2 (N = 108)	Phenogroup 3 (N =410)
BMI, kg/m2	35	33	31
NYHA Class III or above (%)	52	28	33
Diabetes (%)	74	26	44
Prior PCI (%)	22	10	19
Peripheral Arterial disease (%)	16	6	10
Dyslipidemia (%)	78	66	67
Glucose, mg/dl	138	109	123
Total Bilirubin, mg/dl	0.67	0.83	0.63
Estimated GFR, ml/min	52	66	67
NT-ProBNP, pg/ml	2913	1470	1419
Peak TR velocity, cm/s	311	292	266
LV mass, mg	236	210	222
Severe Diastolic dysfunction (%)	28	33	1.7

Methods



TOPCAT

- 3445 participants
- 156 variables

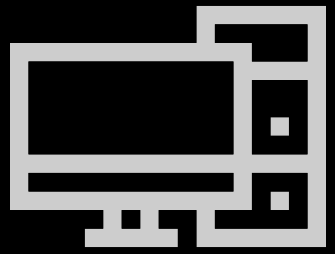


Echocardiographic

- 935 participants
- 156 variables

Americas

- 654 participants
- 82 variables



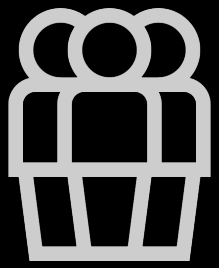
Final Analysis

- 654 participants
- 61 variables

Pitt, *et al.* "Spironolactone for HFpEF" *NEJM* (2014)

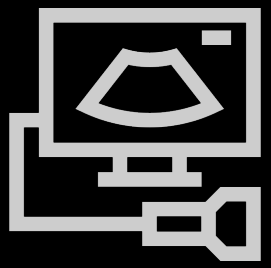
Pfeffer, *et al.* "Regional variation in TOPCAT" *Circulation* (2015)

External Validation



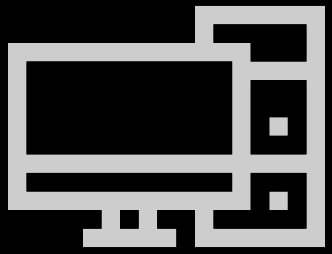
RELAX

- 216 participants
- 38 variables



Echocardiographic

- 214 participants
- 38 variables

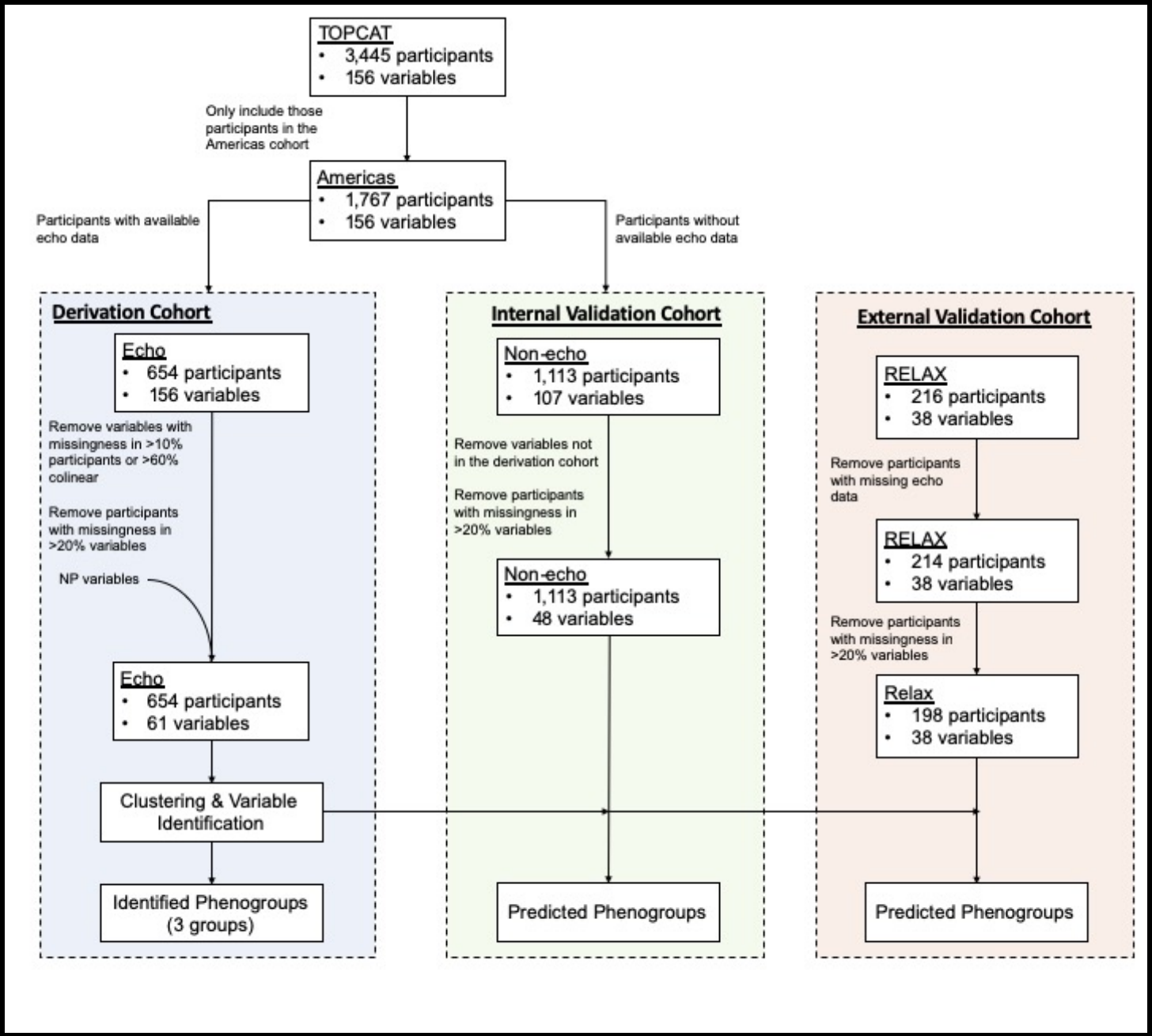


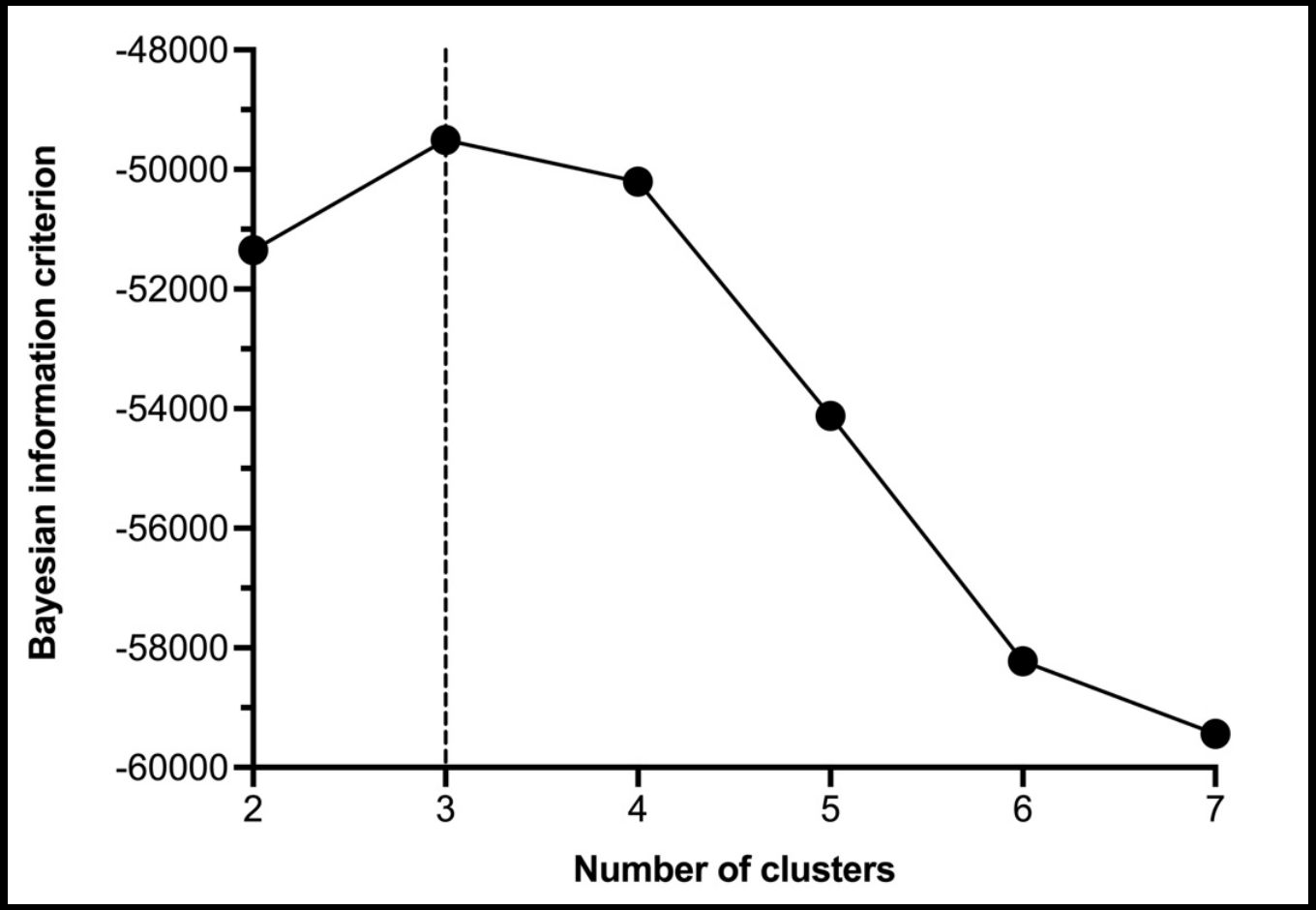
Final Analysis

- 198 participants
- 38 variables

Redfield, *et al.* "PDE-5 in HFpEF" *JAMA* (2013)

	TOPCAT (n=654)	RELAX (n=198)	P-value
Age, years	71.18 (9.85)	68.58 (10.20)	0.001
Male, n	339 (51.8)	99 (50.0)	0.710
History of MI, n	138 (21.1)	20 (10.1)	0.001
History of COPD, n	109 (16.7)	35 (17.7)	0.829
History of HTN, n	595 (91.1)	90 (45.5)	<0.001
History of PAD, n	70 (10.7)	29 (14.6)	0.167
History of ICD, n	14 (2.1)	1 (0.5)	0.22
Diabetes category, n			0.192
No diabetes	345 (52.8)	112 (56.6)	
Insulin dependent	159 (24.3)	36 (18.2)	
Non-insulin dependent	149 (22.8)	50 (25.3)	
Current smoker, n	41 (6.3)	25 (12.7)	0.005
Ever smoker, n	332 (54.2)	124 (62.9)	0.04
NYHA Class (III or above),	236 (36.3)	105 (53.0)	<0.001
HR, bpm	69.45 (11.64)	69.83 (11.73)	0.682
SBP, mmHg	126.89 (15.77)	127.88 (17.43)	0.451
BMI, kg/m^2	33.80 (7.99)	33.94 (7.02)	0.823
NA, mg/dL	139.47 (3.04)	139.68 (3.23)	0.405
K, mg/dL	4.15 (0.43)	4.32 (0.50)	<0.001
CO2, mg/dL	28.49 (3.63)	27.44 (3.22)	0.002
BUN, mg/dL	25.13 (12.29)	27.66 (14.18)	0.021
Glucose, mg/dL	123.95 (61.23)	123.45 (50.37)	0.923
BNP, pg/mL	364.92 (265.7)	413.0 (455.1)	0.410
Hb, U/L	12.71 (1.64)	12.90 (1.49)	0.135
AST, U/L	25.87 (14.35)	29.07 (14.44)	0.007
Total bilirubin, U/L	0.67 (0.45)	0.63 (0.34)	0.269
Albumin, U/L	3.84 (0.44)	3.98 (0.52)	0.002
QRS duration, ms	106.53 (31.09)	106.85 (33.65)	0.902
ACE inhibitor, n	343 (52.4)	88 (44.4)	0.058
ARB, n	189 (28.9)	55 (27.8)	0.829
Beta blocker, n	530 (81.0)	147 (74.2)	0.048
Calcium channel blocker, n	252 (38.5)	59 (29.8)	0.031
Diuretic, n	586 (89.6)	171 (86.4)	0.254
Aspirin, n	372 (56.9)	122 (61.6)	0.271
Statin, n	443 (67.7)	127 (64.1)	0.392
Warfarin, n	229 (35.0)	83 (41.9)	0.092
SSRI, n	93 (14.2)	61 (30.8)	<0.001
Ejection fraction, %	59.58 (7.80)	60.81 (6.52)	0.044
LV diastolic diameter, cm	4.80 (0.57)	4.67 (0.65)	0.015
E/a ratio	1.35 (0.73)	1.87 (1.36)	<0.001
TR velocity, cm	281.31 (46.38)	287.69 (43.25)	0.163
LA area, cm^2	20.20 (5.63)	22.29 (7.06)	0.011
H2FPEF score	6.04 (1.94)	6.47 (1.21)	0.100


TOPCAT
• 3,445 participants
• 156 variables
Only include those participants in the Americas cohort
Americas
• 1,767 participants
• 156 variables
Participants with available echo data
Participants without available echo data
Derivation Cohort
Echo
• 654 participants
• 156 variables
Remove variables with missingness in >10% participants or >60% colinear
Remove participants with missingness in >20% variables
NP variables
Echo
• 654 participants
• 61 variables
Clustering & Variable Identification
Identified Phenogroups (3 groups)
Internal Validation Cohort
Non-echo
• 1,113 participants
• 107 variables
Remove variables not in the derivation cohort
Remove participants with missingness in >20% variables
Non-echo
• 1,113 participants
• 48 variables
Predicted Phenogroups
External Validation Cohort
RELAX
• 216 participants
• 38 variables
Remove participants with missing echo data
RELAX
• 214 participants
• 38 variables
Remove participants with missingness in >20% variables
Relax
• 198 participants
• 38 variables
Predicted Phenogroups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-50000
-52000
-54000
-56000
-58000
-60000
Bayesian information criterion
2
3
4
5
6
7
Number of clusters