Precision medicine opportunities for familial arrhythmias and cardiomyopathies identified when cost of genetic testing is removed as a barrier

Thomas E. Callis[1], Rebecca Truty[1], Edward D. Esplin[1], Ana Morales[1], John Garcia[1], Matteo Vatta[1], Robert L. Nussbaum[1]
[1]Invitae, San Francisco, CA

141

Eliminating cost as a barrier to genetic testing identifies actionable variants for 1 in 5 cardiology patients.

detect Cardiomyopathy and Arrhythmia

INVITAE

Background

- Genetic testing is not widely utilized in cardiovascular practice despite it being recognized to improve diagnosis and inform management for inherited cardiovascular disease by professional societies.[1-6]
- To reduce barriers to genetic testing and facilitate implementation of existing guidelines, we initiated a program of counseling-supported, sponsored genetic testing at no cost to patients suspected of having a genetic arrhythmia or cardiomyopathy.
- Here, we describe the variant prevalence and clinical utility of the findings.

Methods & Demographics

- With IRB approval, de-identified genetic and clinical data were reviewed from 1,606 probands referred for testing through the **Detect Cardiomyopathy and Arrhythmia genetic testing program** between July 2019 and January 2020.
- Testing consisted of a comprehensive cardiomyopathy and arrhythmia panel of up to 150 genes detecting single nucleotide, small indels, and copy number variants.
- Demographics:
  - Mean age at testing: 40.8 years (range 0 to 90)
  - Gender: 44% female; 56% male
  - 3.5% (56/1,606) of cases were tested postmortem

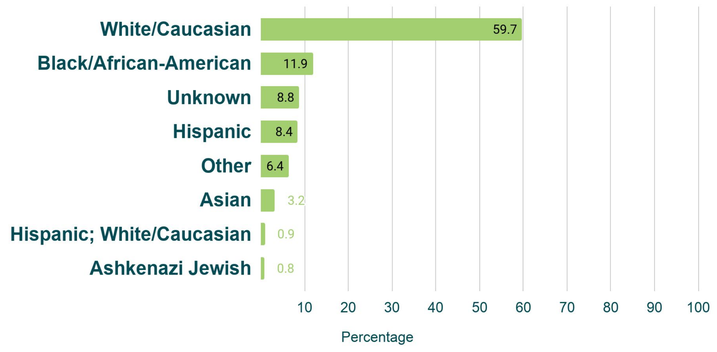

Figure 1: Self-reported ancestry among 1,606 program participants.

Results

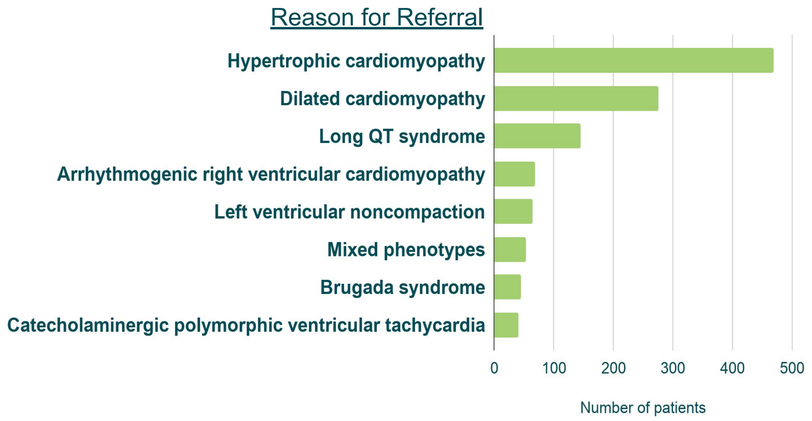

Figure 2: Reasons for referral for genetic testing. Hypertrophic and dilated cardiomyopathy were most common reasons for genetic testing referral.

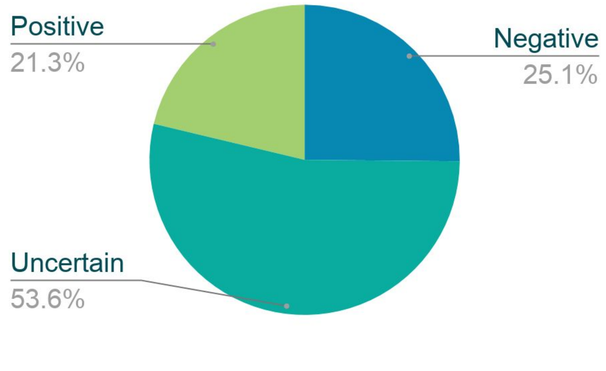

Figure 3: Diagnostic yield of genetic testing. Approximately 1 in 5 probands received a positive molecular diagnosis.

Gene	Number of positive probands	Yield	Common disease associations
MYBPC3	73	4.55%	HCM, DCM, LVNC
TTN	46	2.86%	DCM, muscular dystrophy
MYH7	41	2.55%	HCM, DCM, LVNC, Laing distal myopathy
KCNQ1	20	1.25%	LQTS, Afib, SQTS, Jervell and Lange-Nielsen syndrome
LMNA	15	0.93%	DCM, muscular dystrophy
PKP2	15	0.93%	ARVC, DCM
TTR	14	0.87%	transthyretin amyloidosis
SCN5A	12	0.75%	Brugada syndrome, LQTS, DCM, Afib
TNNI3	11	0.68%	HCM, DCM, RCM
DSP	10	0.62%	ARVC, DCM
FLNC	8	0.50%	HCM, DCM, RCM
KCNH2	6	0.37%	LQTS, SQTS
RYR2	5	0.31%	CPVT, ARVC, LVNC
TNNT2	5	0.31%	HCM, DCM, RCM, LVNC

Table 1: Most frequently identified genes and disease associations.

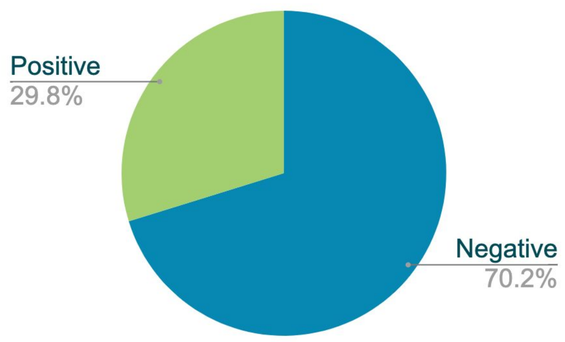

Figure 4: Identification of at-risk family members after a positive result. 29.8% (70/235) of family members received a positive molecular diagnosis.

Conclusion

- These data demonstrate eliminating cost as a barrier to comprehensive genetic testing identifies actionable variants in 21.3% of cardiology patients.
- A positive result confers eligibility for gene-specific precision therapies, guides implementation of established management recommendations, and enables identification of at-risk family members.

References: 1) Towbin JA *et al*. 2019 HRS Expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm.* 2019. doi:10.1016/j.hrthm.2019.05.007 **2)** Al-Khatib SM *et al*. 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2018;72:e91-e220. **3)** Priori SG *et al*. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes.. *Heart Rhythm.* 2013;10:1932-63. **4)** Gersh BJ *et al*. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: Executive summary. *J Am. Coll Cardiol*. 2011;58:2703-38. **5)** Ackerman MJ *et al*. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Heart Rhythm.* 2011;8;1308-39. **6)** Hershberger, RE *et al.* Genetic Evaluation of Cardiomyopathy-A Heart Failure Society of America Practice Guideline. *J. Card. Fail.* 2018;24,281-302.

Disclosures: Authors are stockholders and employees of Invitae.

Corresponding author:
Tom Callis tom.callis@invitae.com