

Diagnostic Yield of Genetic Testing in an Unselected Cohort of 1,376 HCM Patients

Juha Koskenvuo, Julie Hathaway, Inka Saarinen, Jonna Tallila, Eija H Seppälä, Sari Tuupanen, Hannu Turpeinen, Tiia Kangas-Kontio, Jennifer Schleit, **Johanna Tommiska**, Eveliina Salminen, Pertteli Salmenperä, Johanna Sistonen, Mikko Muona, Massimiliano Gentile, Ville Kytölä, Samuel Myllykangas, Jussi Paananen, Tero-Pekka Alastalo
Blueprint Genetics, Biomedicum 1, Tukholmankatu 8, Helsinki, 00290, Finland

Introduction

Genetic testing in Hypertrophic Cardiomyopathy (HCM) is a published guideline-based recommendation¹. In the last decade, next generation sequencing has broadened testing options; expanded panels now contain not only the core HCM genes, but also a wide range of syndromic and metabolic etiologies. Patients with a clinical suspicion of HCM referred for genetic testing likely represent a more general, unselected HCM population compared to previously published HCM cohorts. We describe the diagnostic findings and variables significantly affecting the genetic testing yield in a heterogeneous HCM patient cohort.

Methods

This was a retrospective review of cases with a clinical suspicion of HCM sent for genetic testing between 2013 and 2018. Genetic test results and variant classification were summarized. Variants classified as pathogenic (P) or likely pathogenic (LP) at the time of reporting were considered diagnostic. Patient variables including age, gender, documented arrhythmias, type of medical device and patient outcomes (transplant, VF arrest) were compiled as reported by the ordering provider. The Fisher’s exact test or Mann-Whitney U test was used to determine statistical significance of variables on the diagnostic yield. A Bonferroni corrected P-value of <0.05 was considered significant.

Results

A total of 1376 cases with a clinical suspicion of HCM were sent for genetic testing. For half the patients (51%), a broad cardiomyopathy panel was ordered; 46% had an HCM specific panel and 3% had a comprehensive cardiology panel (cardiomyopathy and arrhythmia genes). The overall diagnostic yield was 26.2%. Altogether, 373 diagnostic findings were identified in 29 genes. Most diagnostic variants were identified in *MYH7* and *MYBPC3* (69%) (Figure 1a). The majority of diagnostic variants were in genes encoding proteins of the sarcomere (86%), however 8% of variants were in genes related to a metabolic disease or a RASopathy (Figure 1b). Five percent of diagnostic variants were in genes found only on the broad cardiomyopathy/comprehensive cardiology panels.

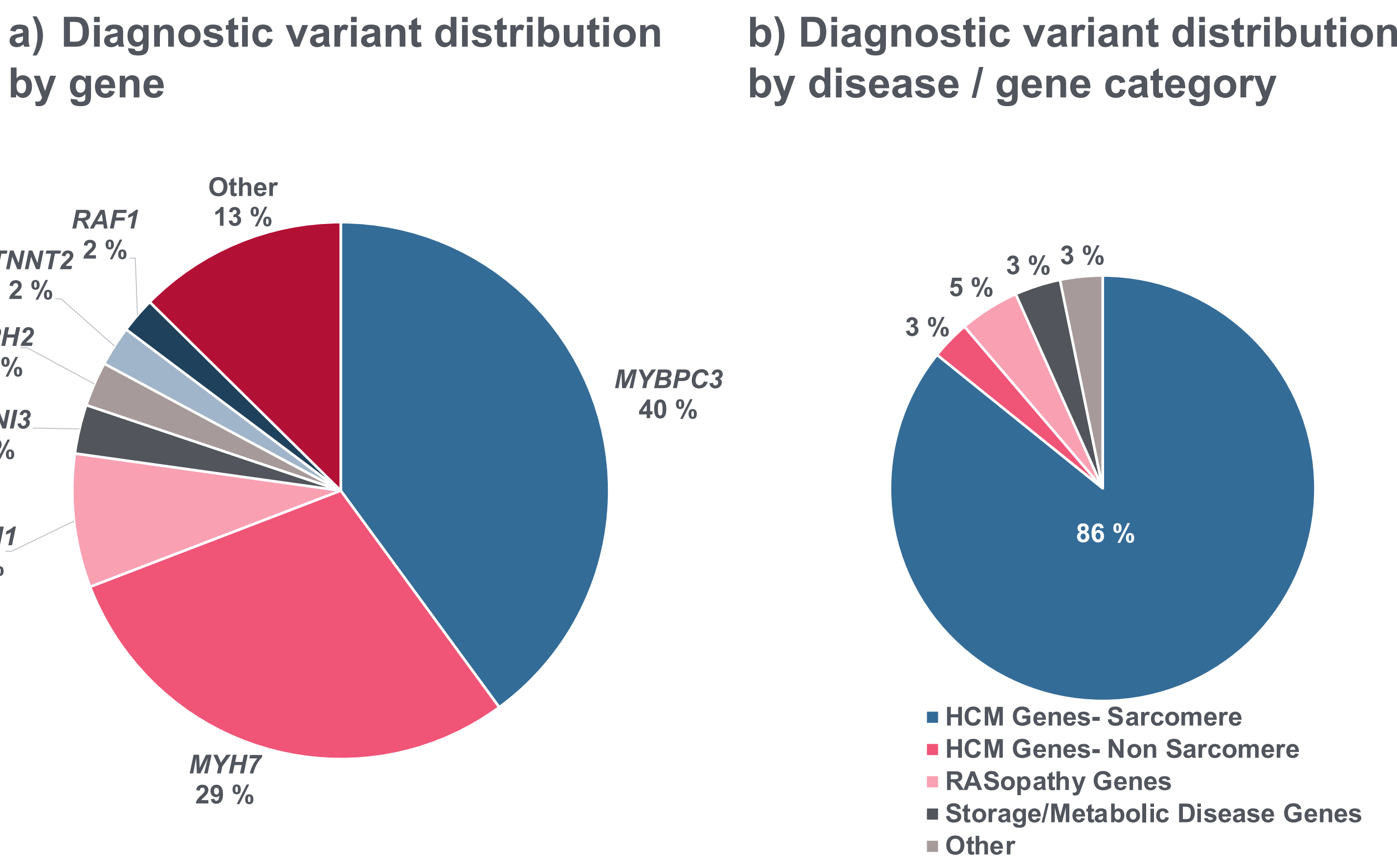


Figure 1. Diagnostic Findings by Gene (a) and by Disease/Gene Category (b)

Results

The diagnostic yield was significantly higher in those with a family history (36% vs. 22%, P-value 9.4 e-07), in those without hypertension (28% vs.14% P-value 0.016) and in those with an intracardiac defibrillator (40% vs. 25% P-value 0.02). A young age at diagnosis (Figure 2) and maximum wall thickness (Figure 3) also significantly affected the diagnostic yield (P-value 1.1 e-09 and 1.8 e-05 respectively).

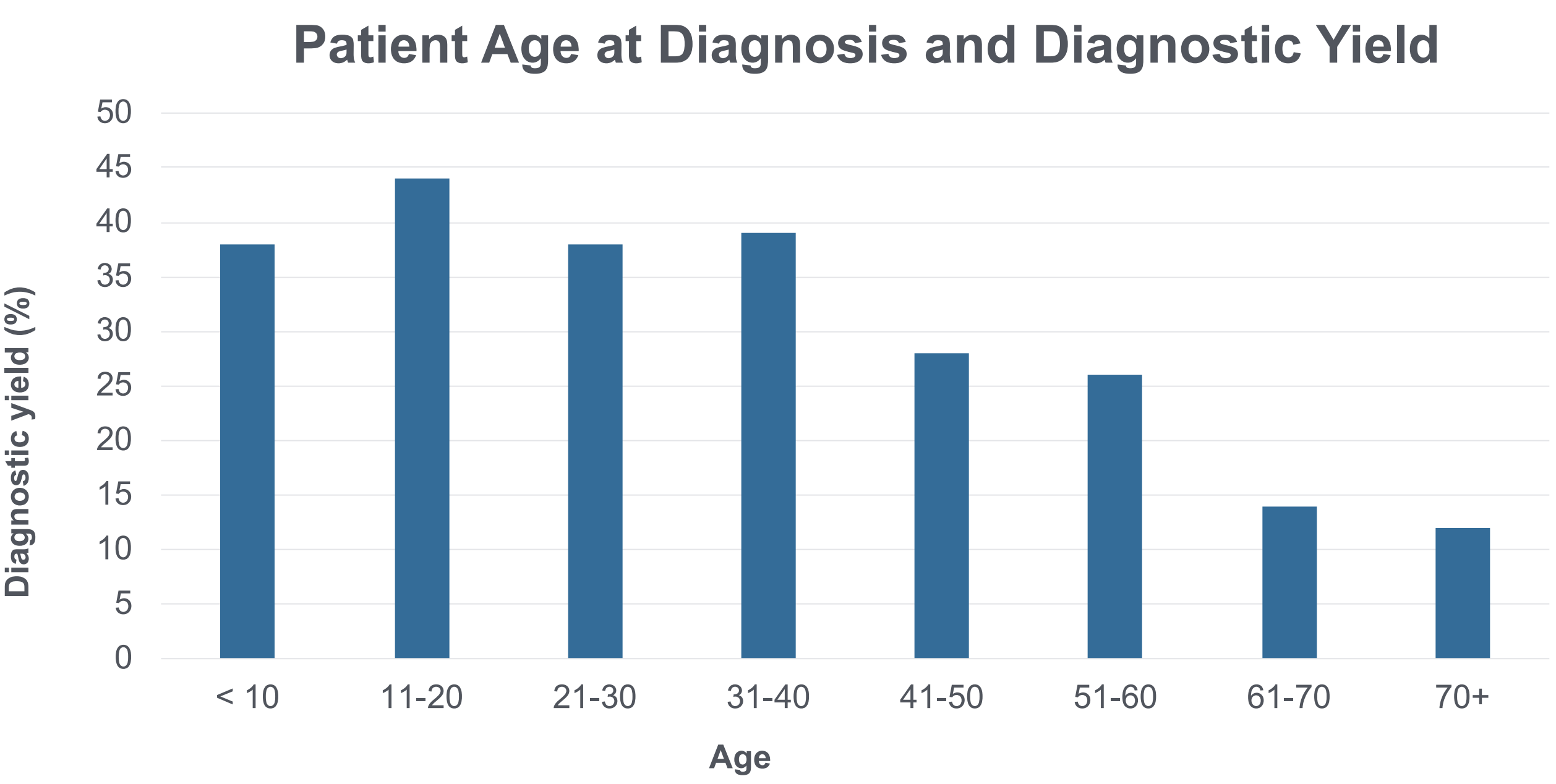


Figure 2. Patient Age at Time of Diagnosis and Diagnostic Yield (P-value 1.1 e-09)

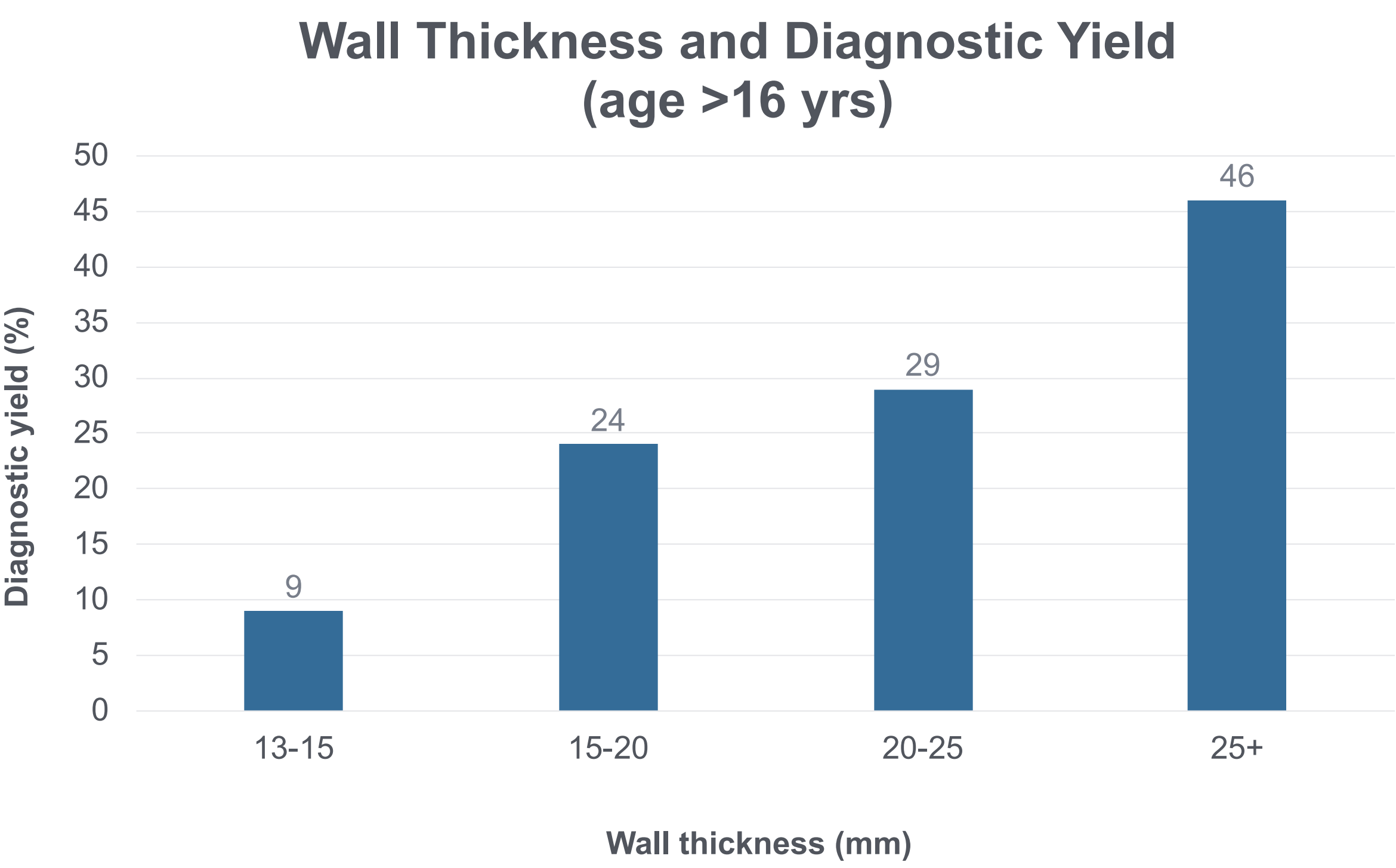


Figure 3. Maximum Wall Thickness and Diagnostic Yield (Patients ≥ 16 years, P-value 1.8 e-05)

Conclusion

- The diagnostic yield of genetic testing in this cohort of patients with HCM is comparable to other commercial laboratory reports² but lower than in well characterized populations
- One in 12 patients** had a diagnostic finding in a RASopathy or metabolic disease gene, underlining the importance of pre- and post-test counseling
- One in 20 patients** had a diagnostic finding in a gene not included on the HCM panel, further highlighting the heterogeneity of this cohort and the importance of utilizing broad panels in certain clinical circumstances
- Variables affecting the diagnostic yield were similar to a published validated scoring system used to predict the likelihood of a diagnostic test result³

References:

1. Hershberger RE *et al.* Genet Med 2018;20(9):899-909.
2. Alfares AA *et al.* Genet Med 2015; 17(11):880-888.
3. Bos JM *et al.* Mayo Clin Proc 2014; 89(6):727-737
Conflict of interest statement: All authors are employed by Blueprint Genetics.