# Genetic Testing for HCM: Negative Results

OTTAWA CARDIO VASCULAR GENETICS

## The Bottom Line

As per the 2020 AHA/ACC guidelines [1]: "Family members of a patient where genetic testing is not done or is negative (i.e., no likely pathogenic or pathogenic variant is identified) also require clinical screening at regular intervals because there is considerable phenotypic heterogeneity in age of onset and disease progression within members of the same family"

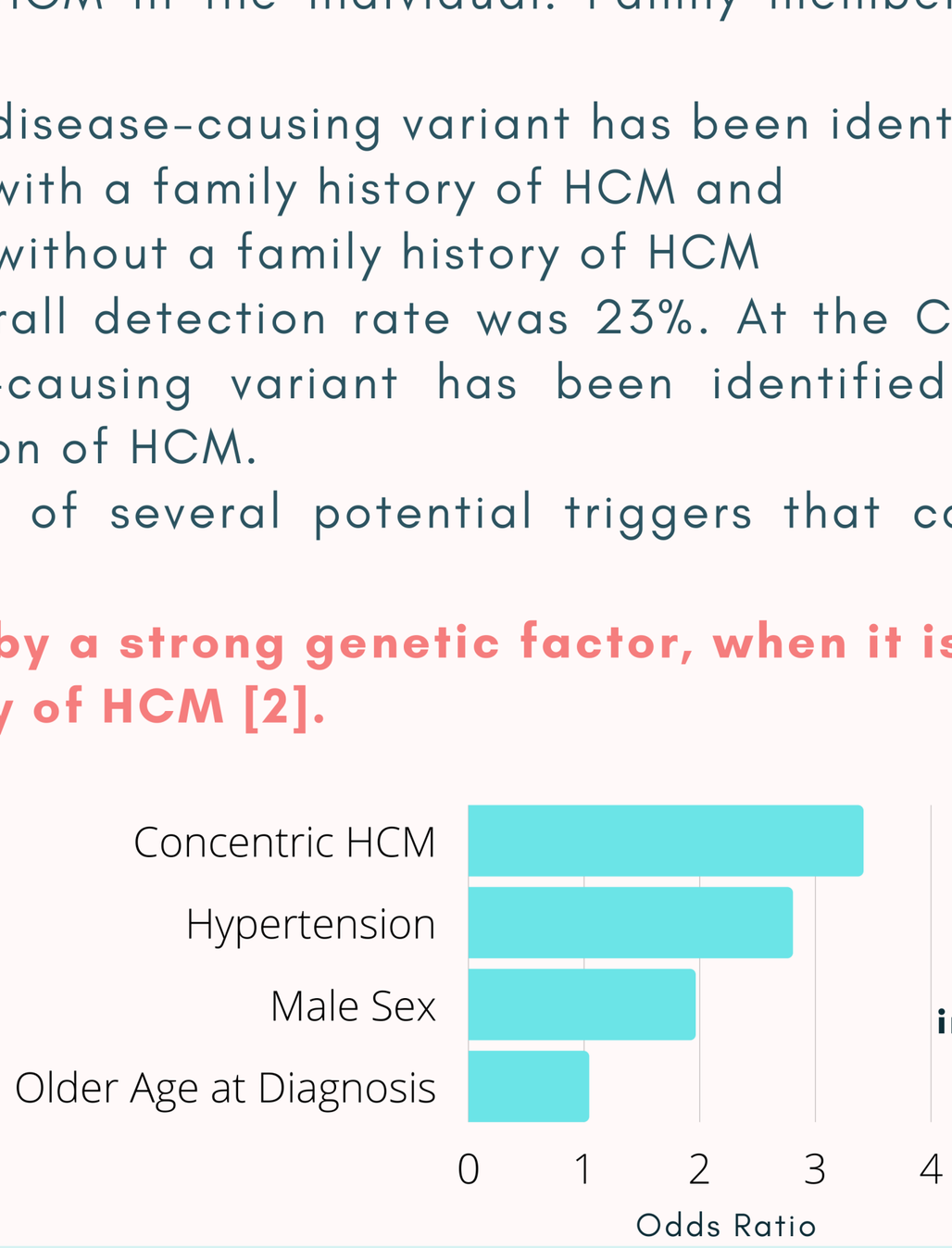
## Background on HCM

- HCM is a common condition which affects approximately 1/500 people.
- It affects both males and females and can present at any age, but is less common in children.
- Per the 2020 AHA/ACC guideline: For the first person diagnosed in the family, HCM is defined as an interventricular septum of 15mm or more "in the absence of another cardiac, systemic, or metabolic disease capable of producing the magnitude of hypertrophy evident in a given patient"

## What does a negative genetic result mean?

- **A negative result does not take away the diagnosis of HCM, nor does it mean that relatives are not at risk for HCM**. It just means that the current test is not good enough to find the genetic basis for the HCM in the individual. Family members must rely on cardiac screening.
- According to the literature [1,2], a disease-causing variant has been identified in:
  - 50-70% of affected individuals with a family history of HCM and
  - 20-30% of affected individuals without a family history of HCM
- In a very large cohort [3], the overall detection rate was 23%. At the CHEO Molecular Diagnostic Laboratory, a disease-causing variant has been identified in 15-20% of individuals referred for the indication of HCM.
  - A strong genetic factor is one of several potential triggers that can lead to the development of HCM [4].
- **HCM is more likely to be caused by a strong genetic factor, when it is diagnosed in an individual with a family history of HCM [2].**

Odds ratio for clinical feature association with <u>non-familial</u> HCM according to Ingles *et al.* 2017 [2]:




**An odds ratio=1 indicates the feature does not increase the odds of non-familial HCM**



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**If you have any questions, ask your health-care provider.**

# Genetic Testing for HCM: Negative Results

## What are recommendations for family members of patients with a negative result?

**International guidelines [1] recommend that for individuals with HCM:**

- All first degree relatives (parents, siblings and children) undergo ongoing screening (echocardiogram and ECG) organized by their own primary care provider.
- If the cardiac testing is normal, repeat the tests every 3-5 year for adults, more frequently for children and teens (who should be referred to pediatric cardiology)

While sometimes there is a known family history of HCM or red flags in the family history, many people with HCM do not know that they have HCM until they undergo cardiac screening by ECG and echocardiogram. This is why it is very important for all first degree relatives of someone with HCM to undergo cardiac screening before concluding that there is no family history. Moreover, HCM can present at different ages and with different symptoms even within the same family.

## Implications for Insurance

Health insurance in Canada (including OHIP and RAMQ) is not affected by someone's genetic results or by a diagnosis of a medical condition. Family members should know that a new diagnosis of HCM would have implications for how their doctor cares for them but could also affect future insurability (e.g. a new life, disability or travel insurance policy) beyond the potential implications of the family history of HCM.


**References**

**[1] Writing Committee Members et al. "2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines." The Journal of thoracic and cardiovascular surgery vol. 162,1 (2021): e23-e106. PMID: 33926766**

**[2] Ingles, Jodie et al. "Nonfamilial Hypertrophic Cardiomyopathy: Prevalence, Natural History, and Clinical Implications." Circulation. Cardiovascular genetics vol. 10,2 (2017): e001620. PMID: 28408708**

**[3] Dellefave-Castillo, Lisa M et al. "Assessment of the Diagnostic Yield of Combined Cardiomyopathy and Arrhythmia Genetic Testing." JAMA cardiology, e222455. 10 Aug. 2022, PMID: 35947370**

**[4]Maron, Bradley A et al. "What Causes Hypertrophic Cardiomyopathy?." The American journal of cardiology, S0002-9149(22)00651-8. 14 Jul. 2022, PMID: 35843734**




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