Harris Stephanie L (Orcid ID: 0000-0002-4222-6767)
Murad Andrea M (Orcid ID: 0000-0003-0423-4966)
Hansen Brittany (Orcid ID: 0000-0001-8810-6763)
Malinowski Jennifer (Orcid ID: 0000-0001-7500-2199)
Kelly Melissa A (Orcid ID: 0000-0003-4708-2261)
Christian Susan (Orcid ID: 0000-0001-5248-3049)
Cirino Allison L (Orcid ID: 0000-0002-7115-9532)

TITLE: The uptake and utility of genetic testing and genetic counseling for hypertrophic cardiomyopathy - a systematic review and meta-analysis

AUTHORS: Allison L Cirino*[1, 2], Stephanie L Harris*[3], Andrea M Murad[4], Brittany Hansen[5], Jennifer Malinowski[6], Jaime L Natoli[7], Melissa A Kelly[8], Susan Christian[9]

*authors contributed equally
[1]Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA
[2]MGH Institute of Health Professions, Boston, MA, USA
[3]Cardiology Division, Cardiovascular Genetics Program, Massachusetts General Hospital, Boston, MA, USA
[4]Division of Genetic Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA
[5]Center for Personalized Genetic Healthcare, Genomic Medicine Institute, Cleveland Clinic, Cleveland, OH, USA
[6]Write Inscite, South Salem, NY, USA
[7]Kaiser Permanente, Southern California Permanente Medical Group, Pasadena, CA, USA
[8]Geisinger, Genomic Medicine Institute, Danville, PA, USA
[9]Department of Medical Genetics, University of Alberta, Edmonton, AB, Canada

Corresponding Author:

Allison Cirino
MGH Institute of Health Professions
36 First Avenue
Boston, MA 02129
t: 617-726-1734
Email: acirino@mghihp.edu

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Running title: Genetic testing and genetic counseling for hypertrophic cardiomyopathy

ABSTRACT

Background: Genetic testing and genetic counseling are routinely indicated for patients with hypertrophic cardiomyopathy (HCM); however, the uptake and utility of these services is not entirely understood. This systematic review and meta-analysis summarize the uptake and utility of genetic counseling and genetic testing for patients with HCM and their at-risk family members, as well as the impact of genetic counseling/testing on patient reported outcomes (PROs). **Methods & Results:** A systematic search was performed through March 12, 2021. Meta-analyses were performed whenever possible; other findings were qualitatively summarized. Forty-eight studies met inclusion criteria (47 observational, 1 randomized). Uptake of genetic testing in probands was 57% (95% CI: 40, 73). Uptake of cascade screening for at-risk relatives were as follows: 61% for cascade genetic testing (95% CI: 45, 75), 58% for cardiac screening (e.g., echocardiography) (95% CI: 40, 73), and 69% for either/both approaches (95% CI: 43, 87). In addition, relatives of probands with a positive genetic test result were significantly more likely to undergo cascade screening compared to relatives of probands with a negative result (OR=3.17, 95% CI: 2.12, 4.76). Overall, uptake of genetic counseling in both probands and relatives ranged from 37-84%. Multiple studies found little difference in PROs between individuals receiving positive versus negative genetic test results; however, other studies found that individuals with positive genetic test results experienced worse psychological outcomes. Genetic testing may also inform life choices, particularly decisions related to reproduction and insurance. Genetic

counseling was associated with high satisfaction, increased perceived personal control and empowerment, and decreased anxiety. **Conclusions:** Approximately half to three-quarters of patients with HCM and their relatives undergo genetic testing or cascade screening. PROs after genetic testing varied and genetic counseling was associated with high satisfaction and improved PROs.

Keywords: cascade testing, genetic counseling, genetic testing, predictive genetic testing, systematic review, utility, Hypertrophic Cardiomyopathy

What is known about this topic

Genetic testing and counseling are recommended for patients with HCM and their at-risk relatives; however, previous research on outcomes of genetic testing and counseling in this population have been limited to small patient cohorts using diverse methodologies.

What this paper adds to the topic

This systematic evidence review and meta-analysis summarizes this data and identifies inadequacies in the uptake of cascade screening by at-risk relatives. Additionally, the uptake of genetic counseling is variable, but associated with high satisfaction and improved patient-reported outcomes.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant condition affecting approximately 1/500 individuals (Maron et al., 1995). The genetic basis of HCM was first-established in 1990 (Geisterfer-Lowrance et al., 1990) and over the past two

decades genetic testing and genetic counseling have become a recommended and routine part of clinical care for individuals with HCM (Hershberger et al., 2018; Landstrom et al., 2021; Ommen et al., 2021). Proband genetic testing can aid in confirmation of a diagnosis or distinguish HCM from various inherited or acquired phenocopies. Most importantly, proband genetic testing enables cascade genetic testing of at-risk relatives, which can identify relatives who are negative for the familial variant and can therefore avoid serial cardiac screening (e.g., echocardiography). In the absence of a causative variant, serial cardiac screening is recommended for all first-degree relatives of an individual diagnosed with HCM (Hershberger et al., 2018; Ommen et al., 2021).

Genetic counseling is defined as a "process of helping patients understand and adapt to the medical, psychological and familial implications of genetic contributions to disease" (Resta et al., 2006). Genetic counselors provide genetics expertise, patient education, and support patient's decision-making, adjustment to a new diagnosis, and communication of genetic risk to relatives. Cardiovascular genetic counselors are key members of the multi-disciplinary teams caring for families with inherited cardiovascular disease (Ahmad et al., 2019; Musunuru et al., 2020).

Previous studies investigating outcomes of genetic testing and counseling in patients with HCM and their at-risk relatives have been limited to small patient cohorts using diverse methodologies. This systematic review summarizes data on the uptake and utility of genetic testing and genetic counseling for patients with HCM and their at-risk relatives, reviews the impact of these services on PROs, and identifies future research priorities. In addition, the findings of this review will serve as the basis for a

forthcoming clinical practice guideline from the National Society of Genetic Counselors (NSGC).

METHODS

The methods reported herein are part of a larger systematic evidence review (SER) to address the overarching research question, "Do genetic testing and genetic counseling lead to improved outcomes for individuals diagnosed with HCM and their at-risk relatives?" A previous manuscript was published detailing the SER and meta-analysis for genetic testing detection rate, disease penetrance, and genotype-phenotype implications for prognosis (Christian et al., 2022). The present manuscript reports on the uptake of genetic testing by probands (defined as the percentage of index cases or affected individual who had genetic testing), the uptake of cascade screening by at-risk relatives (defined as the percentage of at-risk relatives who had genetic testing, cardiac screening [e.g., echocardiography], or a combination of the two), the uptake of genetic counseling by probands and at-risk relatives (defined as the percentage of individuals who received genetic counseling), the influence of genetic testing on family communication and cascade screening, and PROs following genetic testing and genetic counseling. PROs included quality of life (QOL); psychological outcomes, such as illness perception, anxiety, depression, and distress; and knowledge, satisfaction, and life choices.

This SER is aligned to the PRISMA 2020 reporting statement (Page et al., 2021). The research team included genetic counselors, a methodologist, and medical librarians. The population, interventions, comparators, outcomes, timing, and setting (PICOTS) for the full HCM SER were predefined by the research team and are presented in Supporting Information 1a. The initial search was performed on July 7,

2017 and updated through March 12, 2021. Databases searched included PubMed (MEDLINE), Embase, CINAHL, and Cochrane Central Library; the search query for PubMed (MEDLINE) is presented in Supporting Information 1b. We also reviewed references of included studies and relevant studies known to the authors to identify other publications that may have been missed by the database searches.

All phases of the review, data extraction process, and quality assessment were performed by blinded reviewers in duplicate, with disagreements resolved through discussion or with the aid of a third reviewer. Quality assessment was evaluated for observational studies using the Newcastle-Ottawa tool, which takes the selection of the study cohort(s), the comparability of the study cohort(s), and the measurement of the study outcomes into account (Wells et al., 2013). For the randomized controlled trial, the Cochrane Risk of Bias tool was used to identify the potential for bias at all stages of the project from selection and allocation of the study cohorts to reporting of study outcomes (Higgins et al., 2011). Citations from the initial search queries were deduplicated and uploaded to Rayyan (Ouzzani et al., 2016) for review according to pre-specified inclusion and exclusion criteria (Supporting Information 2). The updated queries were uploaded to a Covidence project for screening and review. Relevant data was extracted into Excel spreadsheets by reviewers.

The data analysis plan was pre-specified and outcomes for probands and at-risk relatives were analyzed separately. Data analysis was performed using R (v. 4.0.2) with 'meta,' 'metafor,' and 'stats' packages (Balduzzi S, 2019; R Core Team, 2021; Viechtbauer, 2010). Meta-analysis of continuous variables and multiple proportions were assessed using random-effects, inverse variance models, and meta-analyses of

single proportions were calculated using random-effects, generalized linear mixed models (Schwarzer et al., 2019). All meta-analysis results are reported as the pooled estimates with accompanying 95% confidence intervals (CI) and p-values for between-group comparisons. Heterogeneity was calculated as I^2 and τ^2 and are reported on the accompanying forest plots. Significance was set at $p<0.05$; no adjustment was made for multiple comparisons. If meta-analysis could not be performed for a particular outcome, data were narratively synthesized.

RESULTS

For the overall HCM SER, a total of 4662 non-duplicated abstracts were screened. Of these, 741 full-text articles were reviewed for possible inclusion, and 197 articles were accepted (Figure 1). Of the 197 publications, 149 articles focused on only detection rate, disease penetrance and genotype-phenotype implications for prognosis and are summarized by Christian et al. (2022). The present manuscript focuses on 48 publications that reported on uptake of genetic testing in probands (16 studies), uptake of cascade screening in at-risk relatives (25 studies), uptake of genetic counseling (7 studies), the influence of genetic testing on family communication (5 studies), PROs in probands (8 studies), and PROs in relatives (12 studies). A summary of all included studies is provided in Supporting Information 3. More comprehensive data, including quality assessments, are provided in Tables 1 and 2 and Supporting Information 4-6.

Synthesis of Evidence:
Uptake of Genetic Testing in Probands

Across 16 studies (10,770 individuals), the uptake of proband genetic testing was 57% (95% CI: 40, 73) and ranged from 13-99% (Figure 2, Supporting Information 2). Four studies specifically addressed the uptake of genetic testing in pediatric probands, which

ranged from 13-44% (Alashi et al., 2021; Fitzgerald-Butt et al., 2010; Tunca Sahin et al., 2021; Zhu et al., 2020).

Uptake of Cascade Screening

Twenty-five studies (6,535 individuals) reported on the uptake of cascade screening in at-risk relatives, including uptake of genetic testing, cardiac screening, or a combination of the two (Figure 3, Supporting Information 5). Across 16 studies, the uptake of genetic testing in at-risk relatives was 61% (95% CI: 45, 75) (Figure 3). Across five studies, the uptake of cardiac screening was 58% (95% CI: 40, 73), and across four studies the uptake of genetic testing and/or cardiac screening was 69% (95% CI: 43, 87) (Figure 3). An additional three studies, not included in the meta-analysis, reported on the uptake of cascade screening at a family level and uptake ranged from 56-73% (Christian et al., 2018; Knight et al., 2020; Ormondroyd et al., 2014)(Supporting Information 5).

Seven studies reported the uptake of genetic testing in pediatric patients at either an individual (n=5) or family level (n=2) and the results were highly variable, ranging from 8-93% (Charron et al., 2002; Christian et al., 2018; Jensen et al., 2013; Mathew et al., 2018; Norrish et al., 2019; Ormondroyd et al., 2014; van den Heuvel et al., 2020). One additional study found that 73% of families with at-risk children had cardiac screening and that cardiac screening occurred significantly more often in families when children had genetic testing (86% vs. 42%, respectively; $p<0.05$)(Christian et al., 2018). Another study found that 80% of children who underwent cascade genetic testing and were genotype-positive completed cardiac screening (Vermeer et al., 2017).

Uptake of Genetic Counseling

Seven studies (3,954 individuals) reported on the uptake of genetic counseling, which was delivered by a variety of healthcare providers, including genetic counselors,

cardiologists, and nurses (Table 1). The uptake of genetic counseling ranged from 37-68% in probands (Hudson et al., 2019; Khouzam et al., 2015; Otten et al., 2015) and 38-84% in at-risk relatives (Christiaans et al., 2008; Helio et al., 2020; Nieuwhof et al., 2017; van den Heuvel et al., 2020). Uptake of genetic counseling did not differ when counseling was provided by a genetic counselor/nurse versus a cardiologist (Nieuwhof et al., 2017). Finally, uptake of genetic counseling for pediatric patients was 56% (Christiaans et al., 2008; van den Heuvel et al., 2020).

Influence of Proband Genetic Testing on Family Communication and Cascade Screening

Five studies (675 individuals) reported on the influence of proband genetic testing or genetic counseling on family communication (Supporting Information 6). Batte et al. (2015) reported that genetic test results were not a predictor of family communication. Similarly, one study reported that 96% of patients with a positive result and 100% of patients with a negative result shared their results with family members (Wynn et al., 2018). In another study, only a small percentage of probands reported that they did not communicate family screening recommendations with their relatives regardless of whether the proband pursued genetic testing (Harris et al., 2019). However, in interviews of probands who underwent genetic testing, family communication seemed less challenging for individuals with positive results compared to individuals with uninformative results (Burns et al., 2017). An additional study found that awareness of family screening recommendations increased after genetic counseling (Ison et al., 2019).

Four studies (2,333 individuals) investigated the impact of proband genetic testing on the uptake of cascade screening (Figure 4, Supporting Information 5) (Harris

et al., 2019; Knight et al., 2020; Ko et al., 2018; van der Roest et al., 2009). Across three studies, relatives of genotype-positive probands were more likely to have undergone cascade screening than relatives of genotype-negative probands (OR=3.17, 95% CI 2.12, 4.76) (Figure 4). Further, at a family level, Knight et al. (2020) found that uptake of cascade screening was significantly higher in families with a genotype-positive proband (90%) compared to families where the proband had a negative or inconclusive result (67%), or probands who did not pursue testing or for whom testing status was unknown (43%) ($p<0.001$).

Patient-Reported Outcomes

Fifteen studies (1,235 patients) assessed the impact of genetic testing and genetic counseling on patient-reported outcomes (PROs) for probands and at-risk relatives (Table 2).

Quality of life

Four studies investigated the impact of genetic testing on QOL (Christiaans et al., 2009b; Hickey et al., 2014; Ingles, Yeates, et al., 2012; Spanaki et al., 2016). Two studies suggested that there are no significant differences in QOL between probands or relatives with a positive versus negative genetic test result (Hickey et al., 2014; Ingles, Yeates, et al., 2012). Christiaans et al. (2009b) reported worse QOL scores on some subscales for affected individuals who had undergone genetic testing after their diagnosis compared to the general population and compared to genotype-positive relatives ($p<0.05$ and $p<0.05$, respectively), some of whom were diagnosed with HCM after cascade genetic testing. Relatives who underwent cascade genetic testing did not have worse QOL than the general population, but relatives with a diagnosis of HCM after cascade genetic testing reported worse QOL on physical functioning and bodily

pain subscales compared to genotype-positive, phenotype-negative relatives ($p<0.05$). A fourth study in a pediatric population found no difference in QOL in genotype-positive, phenotype-negative relatives compared to the general population (Spanaki et al., 2016). No studies investigated the impact of genetic counseling on QOL.

Psychological outcomes

Eight studies reported on psychological outcomes of probands and relatives undergoing genetic testing (Bonner et al., 2018; Charron et al., 2002; Christiaans et al., 2009b; Hamang et al., 2012; Hickey et al., 2014; Jensen et al., 2013; MacLeod et al., 2014; Wynn et al., 2018). Hickey et al. (2014) found that illness perception, anxiety, and depression did not differ in probands with a positive versus negative genetic test result. However, Wynn et al. (2018) assessed psychological outcomes in probands and relatives who had undergone genetic testing and found that patients with a positive genetic test result, regardless of cardiomyopathy status, had greater distress and uncertainty and less positivity than patients with a negative result ($p<0.001$, $p<0.001$, $p=0.004$ respectively). Also, regardless of cardiomyopathy status patients with a positive genetic test result experienced more intrusive thoughts, avoidance, and hyperarousal than those with a negative result ($p=0.001$, $p=0.04$, $p=0.0004$)

Christiaans et al. (2009b) reported that affected individuals who had undergone genetic testing experienced more depression than genotype-positive relatives, some of whom were diagnosed with HCM after cascade genetic testing ($p<0.05$), but there was no significant difference in anxiety and both groups had lower anxiety scores than the general population. Hamang et al. (2012) found that individuals with a positive genetic-test result had higher levels of cardio-protective avoidance ($p=0.032$). Multiple interview-based studies found that most at-risk relatives reported minimal psychological impact

after cascade genetic testing, although some individuals experienced shock when receiving their result or worry about their children (Bonner et al., 2018; Charron et al., 2002; MacLeod et al., 2014). Jensen et al. (2013) measured anxiety and depression in three pediatric groups: genotype-negative relatives, genotype-positive relatives, and relatives of individuals with unknown genetic status; they found no significant differences in outcomes among the three groups.

Four studies investigated the impact of genetic counseling on psychological outcomes in probands and at-risk relatives (Hamang et al., 2012; Ison et al., 2019; Nieuwhof et al., 2017; Otten et al., 2015). One study found that probands had increased perceived personal control (PPC) and lower anxiety after group genetic counseling (Otten et al., 2015). Another study assessed PPC in at-risk relatives after genetic counseling when counseling was provided by a genetic counselor/nurse versus a cardiologist and found no significant difference between groups (Nieuwhof et al., 2017). Hamang et al. (2012) found that satisfaction with genetic counseling was associated with lower cardiac-related avoidance and attention ($p=0.037$ and $p=0.024$, respectively). Ison et al. (2019) found a significant increase in empowerment in probands and relatives after genetic counseling ($p<0.0001$).

Knowledge, Satisfaction and Life Choices

Five studies investigated the impact of genetic testing on knowledge, satisfaction, and life choices (Bonner et al., 2018; Burns et al., 2017; Christiaans et al., 2009a; MacLeod et al., 2014; Wynn et al., 2018). In interviews, Burns et al. (2017) found that probands with positive results expressed better understanding of their results compared to individuals with uninformative results. Wynn et al. (2018) assessed satisfaction in probands and relatives and found that 79% of participants reported complete

satisfaction with the decision to have genetic testing, regardless of genetic test results or proband status, although satisfaction was lower in individuals without cardiac symptoms compared to individuals with symptoms (p=0.04). The same study reported that 34% of individuals reported having made or were planning to make a life change after genetic testing, most often having a biological child and obtaining new life insurance. Participants with positive results more frequently made life changes compared to participants with negative results (p=0.01). MacLeod et al. (2014) and Bonner et al. (2018) also found that at-risk relatives undergoing cascade genetic testing found the information helpful for reproductive and insurance planning, as well as to guide exercise. Christiaans et al. (2009a) found that at-risk relatives did not experience pressure to proceed with cascade genetic testing or regret after testing.

Five studies assessed probands and relative's satisfaction with genetic counseling, with all studies reporting high levels of satisfaction (Christiaans et al., 2009a; Hamang et al., 2012; MacLeod et al., 2014; Nieuwhof et al., 2017; Otten et al., 2015). Nieuwhof et al. (2017) found that satisfaction was significantly greater for patients who received genetic counseling from a genetic counselor/nurse versus a cardiologist.

Quality Assessment and Risk of Bias:

The 48 studies included in this SER consisted of 47 observational studies and one randomized trial. The quality of individual studies using Newcastle-Ottawa tool was mostly low/poor or very low/very poor. Factors that contribute to a rating of 'poor quality' or 'high risk of bias' include: bias in measurement of the outcome, missing/bias in selection of the reported outcome data, and lack of representativeness of the study population to the population of interest. Studies included in this review varied in their

methodologies (quantitative versus qualitative, retrospective versus prospective), reported outcomes and measurement of those outcomes as well as cohort recruitment and inclusion criteria (participants with other inherited diagnoses, participants ascertained through clinic versus patient advocacy organizations, relatives ascertained via consultation versus pedigree analysis). While we did not exclude studies deemed to be of 'poor quality' or 'high risk of bias', the results reported in these studies may be less certain than the results reported by studies assessed as good quality or with a low risk of bias.

DISCUSSION

Summary of evidence

HCM is a routine indication for genetic testing and genetic counseling. However, our SER and meta-analyses found that only half to three-quarters of patients with HCM and their relatives undergo genetic testing or cascade screening. Furthermore, the reported uptake of genetic counseling was highly variable, but genetic counseling was associated with high satisfaction and improved PROs. Our results highlight the need for novel mechanisms to improve the uptake of genetic testing, cascade screening and genetic counseling for families with HCM.

Although just over half of probands completed genetic testing, uptake varied considerably across studies which may reflect differing genetic testing trends based on year, country, healthcare system, patient ascertainment, and demographics. Notably, few studies focused on probands' decision to pursue genetic testing. Khouzam et al. (2015) found that individuals were more likely to pursue testing if they were evaluated by a genetics professional, had a relative with HCM, had a known variant in the family, or if they perceived certain benefits to genetic testing such as it would satisfy curiosity,

provide reassurance, guide healthcare decisions, or serve as a motivator for a healthier lifestyle. Other factors that may influence the decision to pursue testing include education level and understanding of the inherited nature of HCM, as well as concerns about cost, insurance coverage, and genetic discrimination (Fitzgerald-Butt et al., 2010; Khouzam et al., 2015; Murphy et al., 2016). Uptake of genetic counseling by probands and at-risk relatives varied dramatically. Notably only one study specifically reported on the uptake of genetic counseling by a genetic counselor/nurse (Nieuwhof et al., 2017), highlighting the need for further research investigating access to and utilization of genetic counselors versus other health professionals.

Cascade screening in families with HCM is critical to identify relatives with subclinical disease who are at risk for SCD, heart failure, or stroke. When a genetic diagnosis is established in a family, cascade genetic testing can discriminate between relatives requiring serial cardiac screening and those who can be released from routine cardiac care. Our data demonstrates that the uptake of cascade screening is approximately 60-70%; thus, approximately a third of at-risk relatives do not seek care related to their family history of HCM. Reasons for not completing cascade screening are poorly understood. Studies suggest most probands share genetic risk information with their relatives regardless of genetic testing status or result (Batte et al., 2015; Harris et al., 2019; Wynn et al., 2018); however, a positive genetic test result in a proband is associated with greater uptake of cascade screening in their relatives, possibly indicating that a proband's positive result motivates at-risk relatives to seek evaluation.

These findings underscore the need for novel methods for disseminating genetic risk information in families and equipping relatives to act on this information. Numerous studies have investigated the acceptability and utility of direct-contact methods and technology interventions to assist with cascade screening (Haas et al., 2021; Jujjavarapu et al., 2021; Schmidlen et al., 2019; Sturm, 2016), and such approaches should continue to be explored. Although not specifically analyzed in this review, we identified five studies demonstrating the cost-effectiveness of genetic testing and cascade screening for HCM, derived from cessation of cardiac screening for genotype-negative relatives. These findings further highlight the benefit of genetic testing and cascade screening, not just for families, but for healthcare systems at large (Alejandra Restrepo-Cordoba et al., 2017; Alfares et al., 2015; Ingles, McGaughran, et al., 2012; Tomasov et al., 2014; Wordsworth et al., 2010).

Fifteen studies investigated the influence of genetic testing and genetic counseling on PROs, but these studies varied considerably in study design, cohort, outcomes and measures. Multiple studies found little difference in PROs between individuals receiving positive versus negative genetic test results (Hickey et al., 2014; Ingles, Yeates, et al., 2012; Jensen et al., 2013) suggesting that genetic test results may not contribute to worse outcomes. However other studies reported worse psychological outcomes in individuals with a positive genetic test result, and importantly Wynn et al. found this to be true regardless of cardiomyopathy status (Hamang et al., 2012; Wynn et al., 2018). Other studies suggested that worse outcomes may be related to having a clinical diagnosis of HCM or symptoms related to the disease (Christiaans et al., 2009b). A recent systematic review concluded that genetic testing across a diverse

group of inherited cardiovascular disorders does not negatively impact quality of life nor increase anxiety and distress (Oliveri et al., 2018). Additional research is needed to better understand predictors of worse psychological outcomes amongst individuals undergoing genetic testing for HCM.

Multiple studies noted that genetic testing may help guide life choices, including reproductive and insurance planning, and this may happen more often for individuals with a positive genetic test result (Bonner et al., 2018; MacLeod et al., 2014; Wynn et al., 2018). Additionally, studies reported high satisfaction with genetic counseling (Christiaans et al., 2009a; Hamang et al., 2012; Nieuwhof et al., 2017; Otten et al., 2015; Wynn et al., 2018) and found that genetic counseling was associated with increased perceived personal control and empowerment and decreased anxiety (Hamang et al., 2012; Ison et al., 2019; Otten et al., 2015). These findings suggest that genetic counseling is associated with improved PROs, although further research is needed to understand which patients may benefit most from genetic counseling and the impact of various genetic counseling service delivery models.

Limitations and Future Direction

All but one study included in this review were observational. Although large, randomized trials are often considered to be most rigorous approach to answering questions about the impact of testing and medical interventions on patient outcomes, they may have limited applicability for questions that relate to rare diseases such as HCM as well as interventions that are heavily dependent on patient preferences and autonomy. Secondly, many study cohorts were small or included participants with other inherited diagnoses. It is possible that conclusions drawn from studies including cohorts

of patients with various conditions may not be generalizable to strictly HCM populations. For some outcomes, particularly uptake of proband genetic testing, the outcome was not the primary focus of most of the studies included in this analysis. Studies assessing the uptake of cascade screening varied in their ascertainment of at-risk relatives, with some studies only including relatives that presented for consultation. Lastly, studies investigating relevant outcomes in patients with a variety of inherited diseases including HCM may not have been identified in our search.

Making comparisons and combining data across studies for analysis is limited by varying methodologies, inconsistent definitions and different outcomes of interest and measures. Collaboration by international cardiovascular genetics teams to prioritize outcomes of interest, define the optimal way to measure these outcomes, and harmonize data collection across institutions would strengthen research on the uptake and utility of genetic counseling and testing. Such collaborations would also allow for collection of disease-specific data with sufficient a sample size to provide meaningful results.

Conclusions

As genetic testing and genetic counseling have become routinely incorporated into the clinical care of patients with HCM and their relatives, numerous studies have investigated the impact of these services. This SER synthesizes the existing research on uptake and utility of genetic testing and genetic counseling for HCM. Overall, the findings suggest that many probands do not undergo genetic testing and many at-risk relatives do not undergo cascade screening. While the uptake of genetic counseling varied, satisfaction with genetic counseling was high. Lastly, though studies had

inconsistent findings, most studies indicate that genetic testing does not lead to worse PROs and genetic counseling may improve PROs.

This SER highlights future research needs, including studies focused on probands' decision-making around genetic testing, novel methods for promoting cascade screening, factors influencing psychological outcomes after genetic testing, and outcomes related to genetic counseling services, specifically when delivered by a genetic counselor. Importantly, future research would be strengthened by collaboration across cardiovascular genetic teams, ensuring systematic collection of outcomes using consistently defined variables and standardized reporting. When appropriate, more rigorous study designs, such as randomized control trials, could be considered. The study outcomes summarized herein have relevance for genetic counseling practice and as such, genetic counselors should play a central role in generating high quality genetic counseling research. The findings of this review will serve as the basis for a forthcoming National Society of Genetic Counselors clinical practice guideline.

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Author Contributions

Authors AC and SH confirm that they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors gave final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with Ethical Standards

Conflict of Interest Statement

- Susan Christian -No conflicts of interest to declare
- Allison Cirino -No conflicts of interest to declare
- Brittany Hansen – No conflicts of interest to declare
- Stephanie Harris - No conflicts of interest to declare
- Andrea Murad - AMM is a paid consultant for Concert Genetics.
- Jaime Natoli - No conflicts of interest to declare
- Jennifer Malinowski - JM is a contract methodologist for the NSGC with no other conflicts of interest to declare
- Melissa A Kelly - No conflicts of interest to declare

Human Studies and Informed Consent

No human studies were carried out by the authors of this article.

Animal Studies

No non-human animal studies were carried out by the authors for this article.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

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Table and Figure legends

Table 1: Uptake of Genetic Counseling in probands and relatives

Abbreviations: HCM=Hypertrophic cardiomyopathy; DCM=Dilated cardiomyopathy; ARVC=Arrhythmogenic right ventricular cardiomyopathy; RCM=Restrictive cardiomyopathy; BrS=Brugada syndrome; CPVT= Catecholaminergic polymorphic ventricular tachycardia

Note: Genetic counseling was provided by a variety of health care providers

[a]Data is from clinic cohorts with the exception of Khouzam et al and Hudson et al which both gathered self-reported data from a patient advocacy group cohort

[b]Number of families who had genetic testing

Table 2: Patient-reported outcomes in probands and relatives

Abbreviations: GT=genetic testing; GC=genetic counseling; G+=positive genetic test result, G-=negative genetic test result, P-=phenotype negative; VUS=variant of uncertain significance; HCM=Hypertrophic cardiomyopathy; DCM=Dilated cardiomyopathy; HD=Huntington's disease; HBOC=Hereditary breast and ovarian cancer; ARVC=Arrhythmogenic right ventricular cardiomyopathy; LQTS=Long QT syndrome; BrS= Brugada syndrome; FH=Familial Hypercholesterolemia; SCA=sudden cardiac arrest; Other=Born with Ventricular Septal Defect, Sudden Cardiac Death, Heart Attack, Pulmonary arterial hypertension; CM=cardiomyopathy; PRO=Patient-reported outcome; HRQL= Health-related quality of life; QoL=Quality of life; CAQ=Cardiac Anxiety Questionnaire; HADS=Hospital Anxiety and Depression Scale; IPQ-R=Illness Perception Questionnaire, Revised; STAI= State-Trait Anxiety Inventory; PPC=Perceived personal control; aMICRA=Multidimensional Impact of Cancer Risk Assessment; IES=Impact of events scale; DS14=Standard assessment of negative affectivity; CGS=Clinical genetics satisfaction indicator; SWD=Satisfaction with decision scale; GCOS=Genetic Counseling Outcome Scale

[a]Data from Groups A and S was excluded because patients with syndromic disease were included

[b]Satisfaction Indicator of the Dutch Clinical Genetics Association (VKGN)

Figure 1: PRISMA diagram

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) details the initial yield of the database searches and the process of selecting articles for inclusion in the systematic review.

Figure 2: Uptake of genetic testing in probands
Forest plot of the proportion of probands who undergo genetic testing

Figure 3: Uptake of cascade screening in at-risk relatives
Forest plot of the proportion of at-risk family members who undergo genetic testing, cardiac screening or a combination of either screening modality

Figure 4: Impact of proband genetic testing on cascade screening
Forest plot of studies reporting the uptake of cascade screening among at-risk relatives of genotype-positive probands compared to at-risk relatives of genotype-negative probands

Supporting information 1

- **a.** PICOTS for individuals with known or suspected diagnosis of HCM or for at-risk relatives of those patients
- **b.** MEDLINE search strategy for PubMed

Supporting information 2: Inclusion/exclusion criteria

Supporting information 3: Reference table of included articles

Supporting information 4: Uptake of genetic testing in probands
Abbreviations: HCM=Hypertrophic cardiomyopathy; DCM=Dilated cardiomyopathy;LQTS=Long QT syndrome
[a]data is from clinic cohorts with the exception of Khouzam et al and Batte et al which both gathered self-reported data from a patient advocacy group cohort
[b]Parent or child had testing; 62% (16/26) said they would consider testing after learning about it
[c] Genetic testing data was available for 305/306 patients
[d] Included individuals diagnosed with HCM (n=270/306, 88%) and at-risk relatives (n=36/306, 12%)
[e] Phase 1 data only
[f] Of the 52 who did not have testing, 22 were documented to have declined testing.
[g] Includes probands (222/398) and those referred for family screening (176/398)

Supporting information 5: Uptake of cascade screening in at-risk relatives
Abbreviations:G+= genotype positive; G-=genotype negative; GT=genetic testing
[a] HCM cohort is duplicated in these publications
[b] 46 HCM probands and 11 DCM probands
[c] some overlap of the HCM cohorts reported in these publications
[d] Number of families or parents who proceeded with predictive testing in minor age children
[e] as reported by probands recruited through a patient advocacy organization

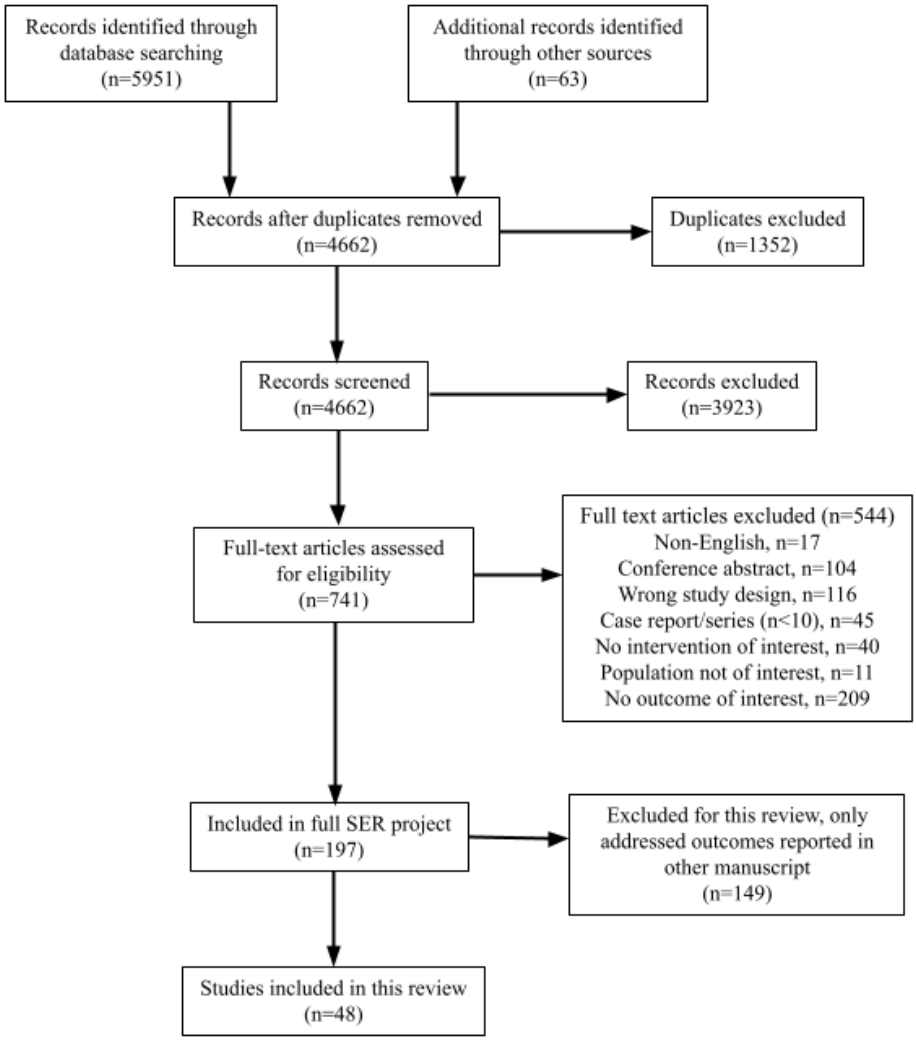
[f] Phase 1 data only

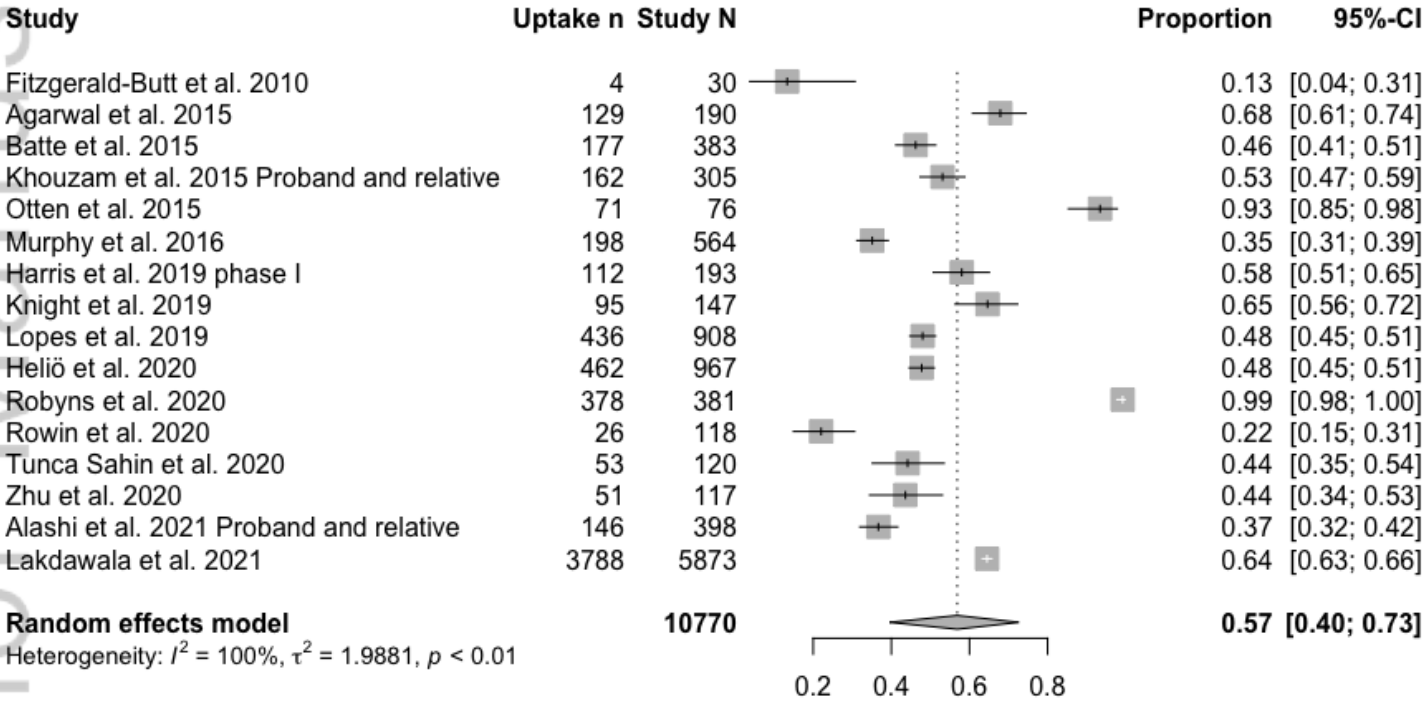
Supporting information 6: Impact of genetic testing or genetic counseling on family communication

Abbreviations: HCM=Hypertrophic cardiomyopathy; DCM=Dilated cardiomyopathy; LQTS=Long QT syndrome; FH=Familial Hypercholesterolemia; SCA=sudden cardiac arrest; Other=Ventricular septal defect, Sudden Cardiac Death, Heart Attack, Pulmonary arterial hypertension; CM=cardiomyopathy

Supporting information 7: PRISMA 2020 checklist

Supporting information 8: PRISMA 2020 abstract checklist





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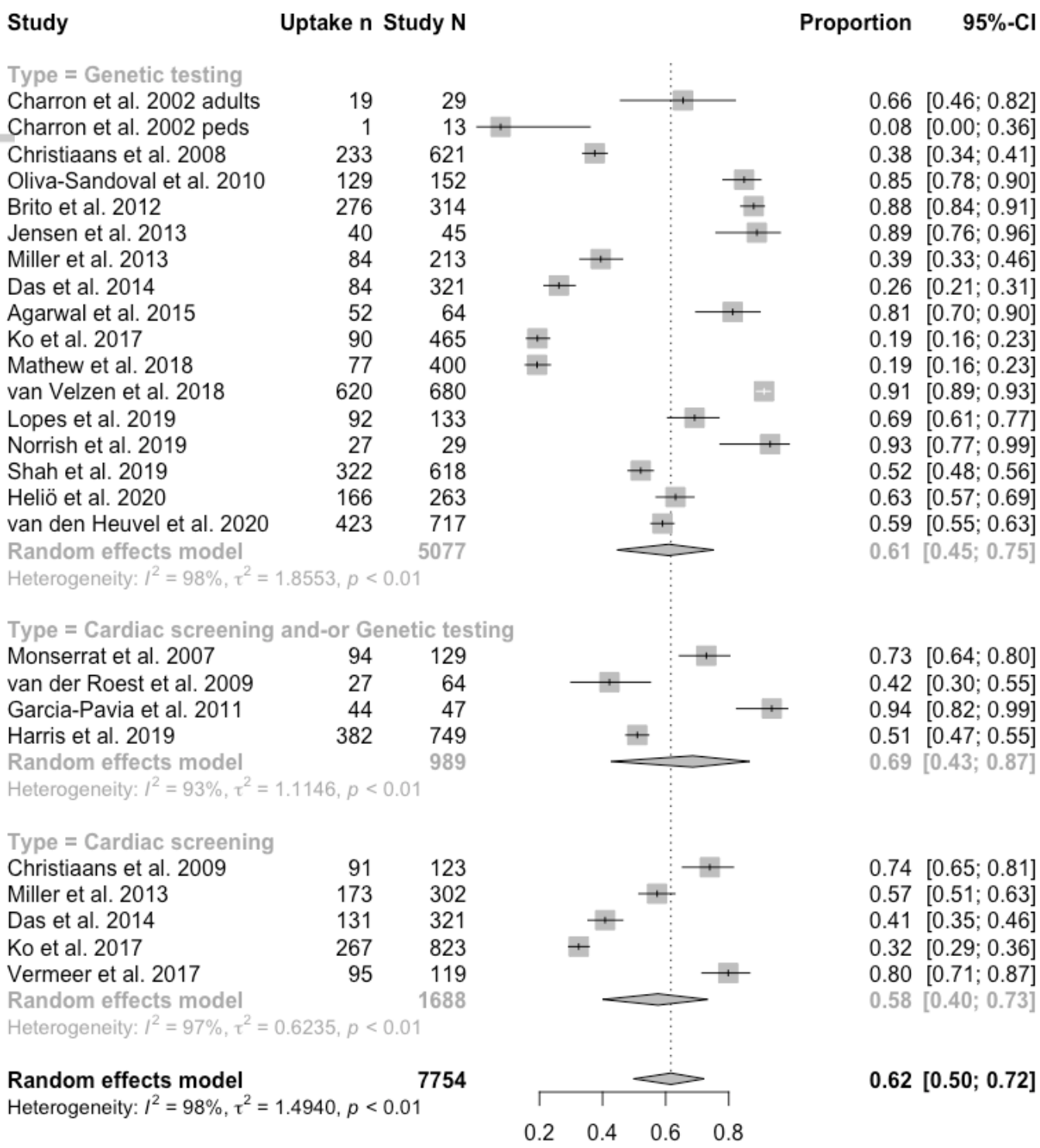

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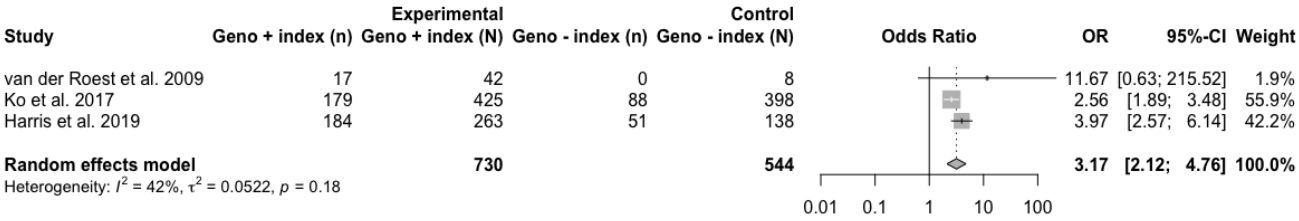

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