Circulation: Genomic and Precision Medicine

ORIGINAL ARTICLE

# Long-Term Follow-Up Study on the Uptake of Genetic Counseling and Predictive DNA Testing in Inherited Cardiac Conditions

Lieke M. van den Heuvel, MSc; Maxiem O. van Teijlingen, MSc; Wilma van der Roest, BSc; Irene M. van Langen, MD, PhD; Ellen M.A. Smets, PhD; J. Peter van Tintelen, MD, PhD; Imke Christiaans, MD, PhD

**BACKGROUND:** Inherited cardiac conditions present with a wide range of symptoms and may even result in sudden cardiac death. Relatives of probands with a confirmed pathogenic genetic variant are advised predictive DNA testing to enable prevention and treatment. In 2 previous cohort studies of 115 probands with a pathogenic variant, family uptake of genetic counseling was assessed in the first year(s) after test result disclosure to the proband. This study assesses uptake in these cohorts in the 14 to 23 years following disclosure.

**METHODS:** Uptake was determined retrospectively using patient records. First-degree relatives, and second-degree relatives of a deceased first-degree relative suspected of having an inherited cardiac condition, were considered eligible.

**RESULTS:** Of 717 eligible relatives (598 first-degree and 119 second-degree relatives), 60% attended genetic counseling. Most of them (68.6%) attended genetic counseling in the first year. A total of 98.4% of counseled relatives pursued predictive DNA testing. A total of 49.2% was identified as carrier. Median time between disclosure to the proband and counseling of relatives was 6 months (range: 0–187 months). Attending genetic counseling was observed more frequently in first-degree relatives, female relatives, primary arrhythmia syndromes, relatives with manifest inherited cardiac condition, relatives without children and families with sudden cardiac death in first-degree relatives <40 years.

**CONCLUSIONS:** During median follow-up of 16 years, 60.0% of relatives attended genetic counseling, with 41.0% in the first year. Our results may suggest that some relatives are not or inadequately informed or that barriers against genetic counseling are present. Further research is needed into interventions facilitating family communication, increasing awareness among families and healthcare professionals, and lowering thresholds for genetic counseling.

**Key Words:** cardiomyopathies ■ death ■ DNA ■ genetics ■ risk

Inherited cardiac conditions (ICCs), including cardiomyopathies and primary arrhythmia syndromes, may present with a wide range of symptoms and can even result in sudden cardiac death (SCD) at young age without any previous symptoms.[1,2] Even within families, ICCs show a high variability in expression and incomplete penetrance, and they can affect people at all ages.[1,2] Since options are available for prevention and treatment, including pharmaceutical treatment, lifestyle adjustments, and implantation of a cardiac defibrillator, identifying who in a family is at risk is paramount for preventing severe cardiac events, including SCD.[2,3] In the majority of ICC probands a pathogenic variant in one of the associated genes can be detected.

Genetic counseling to discuss predictive DNA testing is recommended for first-degree relatives allowing

Correspondence to: Imke Christiaans, MD, PhD, Department of Clinical Genetics, University Medical Center Groningen, Hanzeplein 1, 9713 GZ, Groningen, the Netherlands. Email i.christiaans@umcg.nl

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCGEN.119.002803.

For Sources of Funding and Disclosures, see page 529.



*Circulation: Genomic and Precision Medicine* is available at www.ahajournals.org/journal/circgen

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **HCM** | hypertrophic cardiomyopathy |
| **ICC** | inherited cardiac condition |
| **SCD** | sudden cardiac death |

carriers of the familial pathogenic variant to be regularly monitored by a cardiologist and to receive treatment if needed.[4,5] Noncarriers can be reassured and do not need cardiac evaluation and predictive testing of offspring.[5] Second- and further-degree relatives can subsequently be counseled and, if desired, tested as well, referred to as cascade genetic testing.[5] Current clinical genetic practice relies on the proband (the first affected person in a family to have a DNA test) to inform at-risk relatives when a (likely) pathogenic genetic variant is identified. This is referred to as the family mediated approach.[6] In the Netherlands, a family letter is generally provided by the clinical geneticist or genetic counselor to assist the proband in informing relatives.[6,7]

Two previous cohort studies have assessed the uptake of genetic counseling and predictive DNA testing in the Netherlands using this family mediated approach. These studies were performed in 97 patients with hypertrophic cardiomyopathy (HCM) and 18 patients with different types of ICCs in whom a (likely) pathogenic variant was identified.[4,8] Findings indicated that uptake of genetic counseling was relatively low, with less than half of relatives attending genetic counseling in the first year(s) after disclosure. Other studies assessing uptake in ICCs and other autosomal dominant diseases have reported similar uptake percentages in the first years after disclosure.[5,9–12]

However, previous studies investigating the uptake of genetic counseling and predictive DNA testing in ICCs assessed this over relatively short follow-up periods of <5 years.[4,8,10] Research on relatives' intentions concerning predictive DNA testing, primarily conducted in the context of hereditary types of cancer, suggests that, amongst other factors, life stage transitions may cause relatives to postpone genetic counseling and predictive DNA testing, for example, because of college or job choices, or because of life or long-term disability insurances.[6,13,14] This may be explanatory for the low short-term uptake in ICCs as well, besides relatives not being informed at all or later than desirable. Our study, therefore, aimed to (1) assess the uptake of genetic counseling and predictive DNA testing over time in the families included in the studies of Christiaans et al[4] and van der Roest et al[8] after a median follow-up period of 16 years and (2) investigate which factors influence the uptake of genetic counseling in ICCs.

# METHODS

The data that support our study findings and methods are available from the authors on reasonable request. Our study was exempt from medical ethical approval, based on the Dutch Medical Research Involving Human Subjects Act. Full methods are described in the Data Supplement.

# RESULTS

## Study Population

Table 1 shows the characteristics of the study population. In total, 115 ICC probands with a likely pathogenic or pathogenic genetic variant were included: 104 (90.4%) with HCM, 7 (6.1%) with long-QT syndrome, 3 (2.6%) with Brugada syndrome, and one (0.9%) with catecholaminergic polymorphic ventricular tachycardia. In the 115 families, 717 relatives (median=5.00 relatives per family; range: 2–17) were eligible for genetic counseling and predictive DNA testing at the time of disclosure of the test result to the proband. This included 349 (48.7%) male relatives and 362 (50.5%) female relatives. For 6 relatives (0.8%), gender was unknown from the pedigree. In total, 598 (83.4%) were first-degree relatives and 119 (16.6%) were second-degree relatives. The mean age of relatives at time of disclosure of the test result to the proband was 43.9 years (range: 0–98, SD 19.3). Four hundred seventy-three relatives (66.0%) had children; parenthood status was unknown for 106 relatives (14.8%). Families were mostly of white descent (111 families, 96.5%). Eighty-seven (12.1%) relatives died during follow-up; 30 of them did not attend genetic counseling until the date of death. Seven (1.0%) were living abroad based on the Dutch population registry.

In families with HCM, 34 relatives (15 males, 44.1%) were younger than 10 years of age at the time of disclosure of the test result to the proband, and turned 10 years of age after the test result was communicated to the proband. Mean age was 3.62 years (SD 3.15). Almost all children (33 out of 34, 97.1%) were first-degree relatives of the proband and of White descent (32 out of 34, 94.1%). For 15 children (44.1%), a first-degree relative had passed away due to SCD.

## Uptake of Genetic Counseling

Median follow-up time was 191 months (range: 5–257 months). In total, 430 eligible relatives (60.0%) attended genetic counseling (median=3.00 relatives per family). In first-degree relatives, uptake of genetic counseling was 63.7% (381/598), in second-degree relatives this was lower (49/119, 41.2%). In total, 75 relatives were clinically diagnosed with the ICC themselves before the follow-up period. When these relatives were excluded from the analysis, uptake was 58.1%.

**Table 1. Sociodemographic and Clinical Characteristics of Studied Families**

| | Probands, N (%) | Relatives, N (%) |
|---|---|---|
| Individuals | 115 | 717 |
| Gender | | |
| Male | 64 (55.7) | 349 (48.7) |
| Female | 51 (44.3) | 362 (50.5) |
| Unknown | 0 (0.0) | 6 (0.8) |
| Mean age (SD)* | 43.8 (14.6) | 43.9 (19.3) |
| Ethnicity | | |
| White | 111 (96.5) | 677 (94.4) |
| Other | 4 (3.5) | 40 (5.6) |
| Parenthood | | |
| Yes | 92 (80.0) | 473 (66.0) |
| No | 21 (18.3) | 138 (19.2) |
| Unknown | 2 (1.7) | 106 (14.8) |
| ICC type | | |
| HCM | 104 (90.4) | 644 (89.8) |
| LQTS | 7 (6.1) | 47 (6.6) |
| BS | 3 (2.6) | 18 (2.5) |
| CPVT | 1 (0.9) | 8 (1.1) |
| SCD in FDR of proband | | |
| Yes | 56 (48.7) | 376 (52.4) |
| No | 59 (51.3) | 341 (47.6) |
| Kinship degree with proband | | |
| FDR | … | 598 (83.4) |
| SDR | … | 119 (16.6) |
| ICC clinical diagnosis in eligible relative | | |
| Yes | … | 75 (10.5) |
| No | … | 642 (89.5) |

BS indicates Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; FDR, first-degree relative; HCM, hypertrophic cardiomyopathy; ICC, inherited cardiac condition; LQTS, long-QT syndrome; SCD, sudden cardiac death; and SDR, second-degree relative.

*Age at disclosure of test result to proband.

For relatives attending genetic counseling, the median time between disclosure of the individual test result to the proband and the relative attending genetic counseling was 6 months (range: 0–187 months). In all, 41.0% of eligible relatives (N=295/717) attended genetic counseling in the first year, while 5.2% of eligible relatives (N=37) attended counseling in the second year (conditional uptake: 37/422, 8.8%). From 5 years post disclosure up to the end of the follow-up period, only a small number of relatives attended genetic counseling (N=40, 5.6%; conditional uptake: 40/321, 12.5%), as shown in the Figure.

Table 2 shows the associations observed between clinical and demographic variables and the uptake of genetic counseling based on multivariable Cox regression analysis (N=611 relatives). Uptake was significantly higher in first-degree relatives ($P$<0.001, aHR [95% CI]=1.75 [1.68–1.83]), female relatives ($P$<0.001, aHR [95% CI]=1.27 [1.24–1.30]), relatives with a primary arrhythmia syndrome in their family ($P$<0.001, aHR [95% CI]=2.16 [2.10–2.22]), relatives without children ($P$<0.001, aHR [95% CI]=1.23 [1.20–1.27]), relatives with an ICC diagnosis themselves ($P$<0.001, aHR [95% CI]=1.53 [1.47–1.59]), and relatives with SCD in a first-degree relative of the proband below the age of 40 years ($P$<0.001, aHR [95% CI]=2.10 [2.04–2.16]). Based on univariate cox regression, relatives who were older than 18 years of age at disclosure of the test result of the proband showed a significant different uptake over time compared to minor-aged relatives in primary arrhythmia syndromes ($P$<0.001, HR [95% CI]=1.69 [1.61–1.82]). For HCM, this analysis was not possible because of violation of the proportional hazards assumption.

## Uptake of Predictive DNA Testing

Of the 430 relatives attending genetic counseling, 423 (98.4%) proceeded with predictive DNA testing. Hence, the uptake of predictive DNA testing was 59.0% of all eligible relatives. Of these, 208 relatives (49.2%) were identified as a carrier. In first-degree relatives, uptake of predictive DNA testing was 62.9% (376/598). In second-degree relatives, uptake was 39.5% (47/119).

In HCM families, 19 out of 34 relatives (55.9%) below the age of 10 at time of disclosure to the proband attended genetic counseling with their parents. Of these children, 10 children were also tested below the age of 10, often because they were tested at the same time as an older sibling.

# DISCUSSION

This study assessed the uptake of genetic counseling and predictive DNA testing in ICCs. Predictive DNA testing is important from a public health perspective because it allows for identification of carriers, who can be monitored and if needed, timely treated, and noncarriers, who can be reassured. Predictive DNA testing as part of a clinical screening strategy is also considered cost-effective, as investigated in HCM[15,16] and long-QT syndrome.[17] Our findings show that a majority of relatives attends genetic counseling in the first year with a slight increase thereafter at a fast-declining rate. After a median follow-up period 16 years, 60% of eligible relatives attended genetic counseling, yet 40% was not counseled nor tested. Almost all relatives who attended genetic counseling also pursued predictive DNA testing. Being a first-degree relative, female relatives, relatives with a primary arrhythmia syndrome in the family, relatives with children, SCD in a first-degree relative of the proband under the age of 40, and having a clinical ICC diagnosis themselves before genetic diagnosis in the proband were significantly associated with a higher uptake. Our findings indicate that relatives who experienced the severity of

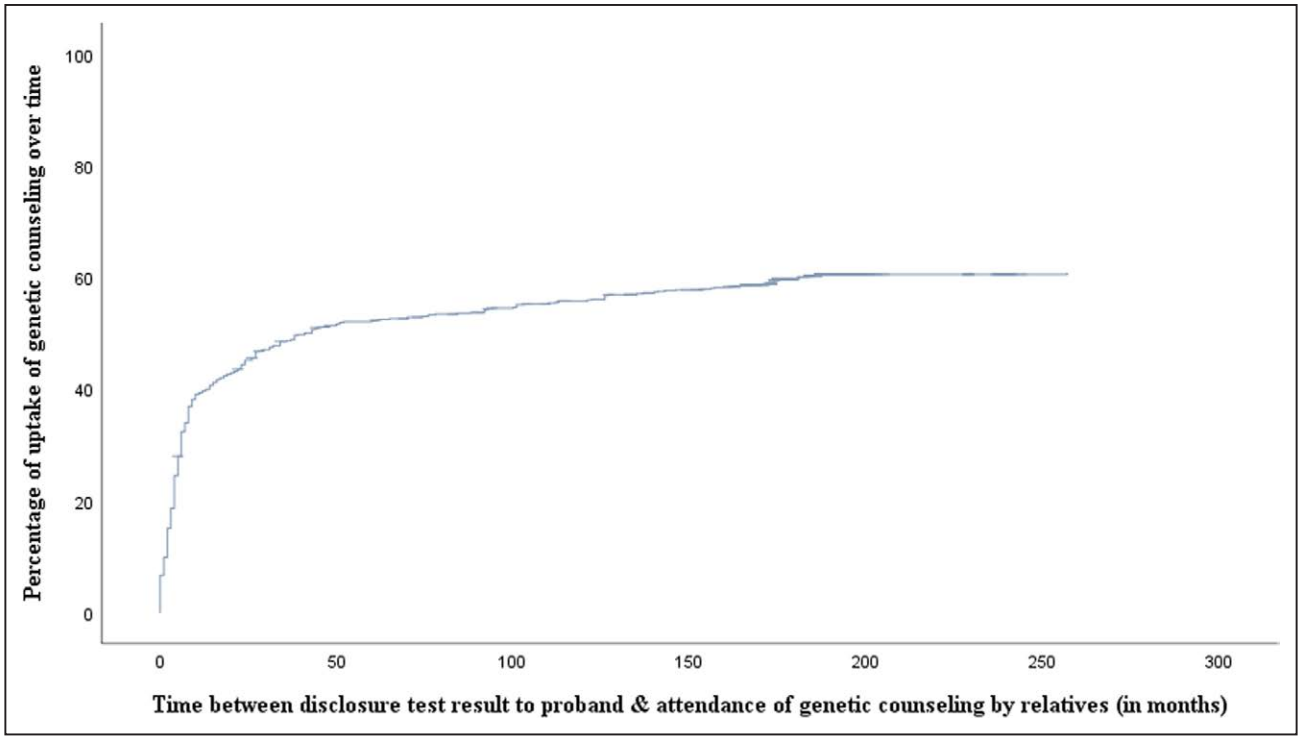


**Figure. Uptake during a median follow-up period of 191 mo (16 y).**

the disease themselves or in their families (in case of SCD) are more inclined to attend genetic counseling and have predictive DNA testing. Having this experience may influence the perceived importance of the information on genetic risks.

This study with long-term follow-up shows that after the first few years, only a limited number of additional relatives attended genetic counseling. For the first years, our findings are comparable to those of previous studies with relatively short follow-up investigating uptake in ICCs[5,10] and hereditary types of cancer.[9,11,12,18,19] The few studies available on uptake in primary arrhythmia syndromes also suggest a higher uptake of genetic counseling and predictive DNA testing compared with inherited cardiomyopathies.[5,10]

It is possible that relatives not attending genetic counseling have made a conscious and well-informed decision not to have predictive DNA testing. Some relatives may refrain from genetic counseling due to logistical or financial barriers such as the costs of genetic counseling and predictive DNA testing or potential insurance issues. In many healthcare systems, relatives currently have to finance (part of) genetic counseling and predictive DNA testing themselves. Since predictive DNA testing for ICCs has been proven to be cost-effective, incorporating the costs of genetic counseling and predictive DNA testing into the current healthcare systems could overcome financial barriers.[15–17]

Studies investigating relatives' motives for predictive DNA testing suggest that among other factors such as anxiety, fear for insurance issues and educational or job choices are important motives for postponing predictive DNA testing when being informed until insurances have been arranged or those choices have been made.[6,13,14] Our findings, however, may suggest that part of the relatives with these types of motives to postpone predictive DNA testing also may not attend genetic counseling in the decade after the initial family letter, while these motives may have been resolved or are no longer relevant. A total uptake of genetic counseling of 60.0% with only a small increase in uptake over time may also suggest that some relatives might not have been informed (albeit unintentionally), which is in line with previous literature on nondisclosure by probands.[10,20,21] van der Roest et al,[8] however, indicate that respectively 88% of relatives are informed by the proband, based on self-reported measures of probands. The study of Burns et al[8,10] reports that only 10% of participants indicated that at least one first-degree relative had not been informed. It is also possible that some of these relatives are informed generally but that the amount of information is insufficient to make an informed decision regarding counseling and predictive DNA testing. As illustrated by Burns et al[22] and Christiaans et al,[4] the process of informing at-risk relatives is complex and involves multiple parties. The proband has to understand the information about genetic risks for at-risk relatives sufficiently and has to be able to correctly communicate this information to relatives. Relatives then have to understand the information adequately and connect this to appropriate services.[4,22]

Previous research has suggested that healthcare professionals directly informing at-risk relatives can lead

**Table 2. Factors Associated With Uptake of Genetic Counseling During Follow-Up**

| | | Number Counseled (%)* | Median Follow-Up (Min–Max; mo) | Univariate | | | Multivariable† | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | B (SE) | *P* Value‡ | HR (95% CI) | B (SE) | *P* Value‡ | aHR (95% CI) |
| First-degree relative | | | | | | | | | |
| Yes | | 381/598 (63.7) | 189.5 (17–257) | 0.78 (0.02) | <0.001‡ | 2.17 (2.09–2.26) | 0.56 (0.21) | <0.001‡ | 1.75 (1.68–1.83) |
| No | | 49/119 (41.2) | 196.0 (5–241) | … | … | … | … | … | … |
| Relatives' gender | | | | | | | | | |
| Female | | 224/362 (61.9) | 191.0 (5–257) | 0.17 (0.01) | <0.001‡ | 1.19 (1.16–1.22) | 0.24 (0.01) | <0.001‡ | 1.27 (1.24–1.30) |
| Male | | 206/349 (59.0) | 190.0 (17–257) | … | … | … | … | … | … |
| ICC in proband | | | | | | | | | |
| Primary arrhythmia syndrome§ | | 62/73 (84.9) | 215.0 (90–257) | 0.80 (0.01) | <0.001‡ | 2.23 (2.16–2.29) | 0.77 (0.02) | <0.001‡ | 2.16 (2.10–2.22) |
| HCM | | 368/644 (57.1) | 187.0 (5–244) | … | … | … | … | … | … |
| Parenthood | | | | | | | | | |
| Yes | | 315/473 (66.6) | 188.0 (5–257) | −0.16 (0.01) | <0.001‡ | 0.85 (0.83–0.88) | −0.21 (0.02) | <0.001‡ | 0.81 (0.79–0.83) |
| No | | 103/138 (74.6) | 193.0 (17–257) | … | … | … | … | … | … |
| ICC clinical diagnosis in eligible relative | | | | | | | | | |
| Yes | | 57/75 (76.0) | 183.0 (17–244) | 0.45 (0.02) | <0.001‡ | 1.56 (1.51–1.62) | 0.43 (0.02) | <0.001‡ | 1.53 (1.47–1.59) |
| No | | 373/642 (58.1) | 191.5 (5–257) | … | … | … | … | … | … |
| SCD in FDR of proband | | | | | | | | | |
| Yes | | 241/376 (64.1) | 194.5 (5–257) | 0.24 (0.10) | 0.013 | 1.27 (1.05–1.54) | … | … | … |
| No | | 189/341 (55.4) | 187.0 (17–244) | … | … | … | … | … | … |
| SCD in FDR <40 of proband | | | | | | | | | |
| Yes | | 130/192 (67.7) | 193.5 (26–241) | 0.42 (0.01) | 0.001‡ | 1.51 (1.47–1.56) | 0.74 (0.02) | <0.001‡ | 2.10 (2.04–2.16) |
| No | | 300/525 (57.1) | 191.0 (5–257) | … | … | … | … | … | … |
| Age‖ | | | | | | | | | |
| HCM¶ | 0–18 y | 44/77 (57.1) | 192.0 (17–240) | … | … | … | … | … | … |
| | 19–81 y | 342/601 (56.9) | 187.0 (5–244) | … | … | … | … | … | … |
| Arrhythmias# | 0–18 y | 14/15 (93.3) | 220.0 (195–257) | −0.53 (0.03) | <0.001‡ | 0.59 (0.55–0.62) | … | … | … |
| | 19–81 y | 47/57 (82.5) | 210.5 (90–257) | … | … | … | … | … | … |

BS indicates Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; FDR, first-degree relative; HCM, hypertrophic cardiomyopathy; ICC, inherited cardiac condition; LQTS, long-QT syndrome; and SCD, sudden cardiac death.

*Not all data add up to total number of eligible relatives due to missing values.

†For multivariable analysis, the total number of relatives included was 611.

‡Significant difference based on Bonferroni corrected *P* value <0.006 (*P*=0.05/8 tests). Eight tests were used, since the HCM and arrhythmia age groups concern different datasets and were therefore counted as 1 test.

§Primary arrhythmia syndrome—includes LQTS, BS, and CPVT.

‖Age at disclosure individual test result to proband. Age groups were analyzed using univariate cox regression and not included in the multivariable model, since this analysis was conducted on two different sets of data.

¶The total number of relatives of HCM families in the ICC in proband section and the age section differ, because relatives below 10 at disclosure of the test result to the proband were included in the comparison of age groups 0–18 and 19–81. Univariate cox regression analysis was not possible due to violation of the proportional hazard assumption.

#The total relatives of arrhythmia families in the ICC in proband section and the age section slightly differ, because for one relative, not attending genetic counseling, age was missing.

to increased uptake.[23–26] Studies assessing these more active approaches showed almost double the uptake of genetic counseling.[23,24,26] It has to be noted, however, that these studies were registry based or were performed in the context of population screening. This means that, for these relatives, no costs were involved in having predictive DNA testing and that they were already known in the genetic center when they consented to participate in the registry. Furthermore, ethical issues such as the relatives' right not to know, (non)-directive counseling and the probands' right to privacy might be at stake when using a direct contact approach.[27–29] In addition, healthcare professionals contacting at-risk relatives may be unaware of their personal circumstances with the risk of harming them. A few intervention studies focusing on improving the support provided to probands in informing relatives at-risk that included follow-up contact with the proband and the possibility of direct contact with at-risk relatives by the genetic counselor reported an increase in uptake.[30,31] Follow-up contacts by healthcare professionals with the proband (and relatives carrying the familial variant) regarding informing at-risk relatives may also improve

uptake, since barriers regarding informing relatives can be discussed and support can be offered to overcome them.[30–32] Considering the uptake over time, particularly the steep declining rate after the first year, follow-up contacts should ideally take place after 2 months and again after 1 or 2 years following disclosure of the test result to the proband, for example, as proposed in the study of Nieuwhof et al[33] that describes a cardiogenetic follow-up clinic. Unfortunately, limited research has been performed on how effective interventions are in improving family communication.[24,25,30–32] Further research is, therefore, needed into the effectiveness of these interventions for improving the approach used to inform at-risk relatives.

Our findings additionally show that almost all relatives who attend genetic counseling also pursue predictive DNA testing. This may indicate that relatives who decide to ask their general practitioner for a referral to a cardiogenetic clinic have often already decided in favor of predictive DNA testing. It may also be a result of less nondirectiveness in genetic counseling in ICCs for which treatment and preventive options are available. Although the family letter provides some basic information on the condition in the family, its inheritance and potential complications, genetic counseling is considered important for relatives to provide additional information and support for making an informed decision regarding predictive DNA testing and cardiac screening. Information provision for relatives before genetic counseling might, therefore, be important to enhance informed decision-making. The provision of information and genetic counseling may become more easily accessible through the use of technological innovations, such as video or telephone counseling and online platforms that can provide more easily accessible genetic information or counseling chatbots.[32,34,35] These may enable relatives to make a better informed decision regarding predictive DNA testing. It is also paramount that cardiologists and general practitioners adequately inform probands and their relatives about the possibility of genetic counseling to discuss the pros and cons of predictive DNA testing.[36] Educating healthcare professionals about the genetic causes of cardiac diseases, the possibility of (predictive) DNA testing, and procedure and consequences of DNA testing is, therefore, important.

## Limitations

Dutch clinical genetic practice is uniquely organized with genetic counseling and predictive DNA testing being solely performed in specialized genetic centers and laboratories, in contrast to other countries. This means that even if a relative was tested in another center, this information is available. We, therefore, have the ideal situation to assess uptake. In consequence reported uptake from other countries is likely to be an underestimation of the true uptake. Still, also in our study not all data could be collected for relatives living abroad and attending genetic counseling and having predictive DNA testing outside the Netherlands (N=7, 1.0%). Since we only investigated the uptake of genetic counseling and predictive DNA testing, relatives who were referred to a cardiologist and decided to not have a DNA test but had cardiac screening were therefore not taken into account. Finally, some demographic data as well as clinical data (eg, SCD among relatives during follow-up) was missing for relatives who did not attend genetic counseling or had predictive DNA testing. We, therefore, could not assess what demographic and clinical differences there were in relatives who did not pursue predictive DNA testing, compared with relatives who did not.

## Conclusions

We have shown that, after a median follow-up of 16 years, the uptake of genetic counseling by relatives at-risk of ICCs in whose family a likely pathogenic or pathogenic variant was identified after the first year is limited, resulting in a total uptake of only 60.0%. This relatively low uptake over a long follow-up period, with a limited increase in uptake with time, is worrisome since it may suggest that some of the not counseled relatives are not or insufficiently informed, or that practical or psychological barriers may have prevented these relatives from attending genetic counseling. In order for relatives to make an informed decision regarding predictive DNA testing and preventive measures in case of carriership, the approach used to inform them needs to be improved and practical barriers need to be removed. This would increase the number of relatives enabled to make an informed decision at an earlier stage and possibly prevent SCD in families with ICCs.

## ARTICLE INFORMATION

Received October 14, 2019; accepted July 2, 2020.

### Affiliations

Department of Clinical Genetics (L.M.v.d.H., M.O.v.T., J.P.v.T., I.C.), Department of Medical Psychology (E.M.A.S.), Amsterdam UMC, University of Amsterdam. Netherlands Heart Institute, Utrecht (L.M.v.d.H.). Department of Genetics, University Medical Center Utrecht, Utrecht University (L.M.v.d.H., J.P.v.T.). Department of Clinical Genetics, University Medical Center Groningen/University of Groningen, the Netherlands (W.v.d.R., I.M.v.L., I.C.).

### Acknowledgments

We acknowledge the support of K. McIntyre for editing the article.

### Sources of Funding

This study was financially supported by the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation, CVON2015-12 eDETECT.

### Disclosures

None.

## REFERENCES

1. Bezzina CR, Lahrouchi N, Priori SG. Genetics of sudden cardiac death. *Circ Res.* 2015;116:1919–1936. doi: 10.1161/CIRCRESAHA.116.304030

2. Wilde AA, Behr ER. Genetic testing for inherited cardiac disease. *Nat Rev Cardiol*. 2013;10:571–583. doi: 10.1038/nrcardio.2013.108
3. Maron BJ, Rowin EJ, Casey SA, Link MS, Lesser JR, Chan RH, Garberich RF, Udelson JE, Maron MS. Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. *J Am Coll Cardiol*. 2015;65:1915–1928. doi: 10.1016/j.jacc.2015.02.061
4. Christiaans I, Birnie E, Bonsel GJ, Wilde AA, van Langen IM. Uptake of genetic counselling and predictive DNA testing in hypertrophic cardiomyopathy. *Eur J Hum Genet*. 2008;16:1201–1207. doi: 10.1038/ejhg.2008.92
5. Miller EM, Wang Y, Ware SM. Uptake of cardiac screening and genetic testing among hypertrophic and dilated cardiomyopathy families. *J Genet Couns*. 2013;22:258–267. doi: 10.1007/s10897-012-9544-4
6. Leenen CH, Heijer Md, van der Meer C, Kuipers EJ, van Leerdam ME, Wagner A. Genetic testing for Lynch syndrome: family communication and motivation. *Fam Cancer*. 2016;15:63–73. doi: 10.1007/s10689-015-9842-8
7. Menko FH, Aalfs CM, Henneman L, Stol Y, Wijdenes M, Otten E, Ploegmakers MM, Legemaate J, Smets EM, de Wert GM, et al; Dutch Society for Clinical Genetics. Informing family members of individuals with Lynch syndrome: a guideline for clinical geneticists. *Fam Cancer*. 2013;12:319–324. doi: 10.1007/s10689-013-9636-9
8. van der Roest WP, Pennings JM, Bakker M, van den Berg MP, van Tintelen JP. Family letters are an effective way to inform relatives about inherited cardiac disease. *Am J Med Genet A*. 2009;149A:357–363. doi: 10.1002/ajmg.a.32672
9. Brooks L, Lennard F, Shenton A, Lalloo F, Ambus I, Ardern-Jones A, Belk R, Kerr B, Craufurd D, Eeles R, et al. BRCA1/2 predictive testing: a study of uptake in two centres. *Eur J Hum Genet*. 2004;12:654–662. doi: 10.1038/sj.ejhg.5201206
10. Burns C, McGaughran J, Davis A, Semsarian C, Ingles J. Factors influencing uptake of familial long QT syndrome genetic testing. *Am J Med Genet A*. 2016;170A:418–425. doi: 10.1002/ajmg.a.37455
11. Menko FH, Ter Stege JA, van der Kolk LE, Jeanson KN, Schats W, Moha DA, Bleiker EMA. The uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome: a systematic review of the literature and implications for clinical practice. *Fam Cancer*. 2019;18:127–135. doi: 10.1007/s10689-018-0089-z
12. Meijers-Heijboer EJ, Verhoog LC, Brekelmans CT, Seynaeve C, Tilanus-Linthorst MM, Wagner A, Dukel L, Devilee P, van den Ouweland AM, van Geel AN, et al. Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. *Lancet*. 2000;355:2015–2020. doi: 10.1016/s0140-6736(00)02347-3
13. Ormondroyd E, Oates S, Parker M, Blair E, Watkins H. Pre-symptomatic genetic testing for inherited cardiac conditions: a qualitative exploration of psychosocial and ethical implications. *Eur J Hum Genet*. 2014;22:88–93. doi: 10.1038/ejhg.2013.81
14. Schuurman AG, van der Kolk DM, Verkerk MA, Birnie E, Ranchor AV, Plantinga M, van Langen IM. Maximising the efficiency of clinical screening programmes: balancing predictive genetic testing with a right not to know. *Eur J Hum Genet*. 2015;23:1124–1128. doi: 10.1038/ejhg.2014.269
15. Ingles J, McGaughran J, Scuffham PA, Atherton J, Semsarian C. A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophiccardiomyopathy. *Heart*. 2012;98:625–630. doi:10.1136/heartjnl-2011-300368
16. Perez MV, Kumarasamy NA, Owens DK, Wang PJ, Hlatky MA. Cost-effectiveness of genetic testing in family members of patients with long-QT syndrome. *Circ Cardiovasc Qual Outcomes*. 2011;4:76–84. doi: 10.1161/CIRCOUTCOMES.110.957365
17. Evans DG, Binchy A, Shenton A, Hopwood P, Craufurd D. Comparison of proactive and usual approaches to offering predictive testing for BRCA1/2 mutations in unaffected relatives. *Clin Genet*. 2009;75:124–132. doi: 10.1111/j.1399-0004.2008.01146.x
18. Sanz J, Ramón y Cajal T, Torres A, Darder E, Gadea N, Velasco A, Fortuny D, López C, Fisas D, Brunet J, et al. Uptake of predictive testing among relatives of BRCA1 and BRCA2 families: a multicenter study in northeastern Spain. *Fam Cancer*. 2010;9:297–304. doi: 10.1007/s10689-009-9313-1
19. Sharaf RN, Myer P, Stave CD, Diamond LC, Ladabaum U. Uptake of genetic testing by relatives of lynch syndrome probands: a systematic review. *Clin Gastroenterol Hepatol*. 2013;11:1093–1100. doi: 10.1016/j.cgh.2013.04.044
20. Batte B, Sheldon JP, Arscott P, Huismann DJ, Salberg L, Day SM, Yashar BM. Family communication in a population at risk for hypertrophic cardiomyopathy. *J Genet Couns*. 2015;24:336–348. doi: 10.1007/s10897-014-9774-8
21. Clarke A, Richards M, Kerzin-Storrar L, Halliday J, Young MA, Simpson SA, Featherstone K, Forrest K, Lucassen A, Morrison PJ, et al. Genetic professionals' reports of nondisclosure of genetic risk information within families. *Eur J Hum Genet*. 2005;13:556–562. doi: 10.1038/sj.ejhg.5201394
22. Burns C, James C, Ingles J. Communication of genetic information to families with inherited rhythm disorders. *Heart Rhythm*. 2018;15:780–786. doi: 10.1016/j.hrthm.2017.11.024
23. Aktan-Collan K, Haukkala A, Pylvänäinen K, Järvinen HJ, Aaltonen LA, Peltomäki P, Rantanen E, Kääriäinen H, Mecklin JP. Direct contact in inviting high-risk members of hereditary colon cancer families to genetic counselling and DNA testing. *J Med Genet*. 2007;44:732–738. doi: 10.1136/jmg.2007.051581
24. Sermijn E, Delesie L, Deschepper E, Pauwels I, Bonduelle M, Teugels E, De Grève J. The impact of an interventional counselling procedure in families with a BRCA1/2 gene mutation: efficacy and safety. *Fam Cancer*. 2016;15:155–162. doi: 10.1007/s10689-015-9854-4
25. Sturm AC. Cardiovascular cascade genetic testing: exploring the role of direct contact and technology. *Front Cardiovasc Med*. 2016;3:11. doi: 10.3389/fcvm.2016.00011
26. Suthers GK, Armstrong J, McCormack J, Trott D. Letting the family know: balancing ethics and effectiveness when notifying relatives about genetic testing for a familial disorder. *J Med Genet*. 2006;43:665–670. doi: 10.1136/jmg.2005.039172
27. Lucassen A, Gilbar R. Alerting relatives about heritable risks: the limits of confidentiality. *BMJ*. 2018;361:k1409. doi: 10.1136/bmj.k1409
28. Mitchell C, Ploem MC, Hennekam RC, Kaye J. A duty to warn relatives in clinical genetics: arguably 'Fair just and reasonable' in English Law? *Tottels J Prof Neglig*. 2016;32:120–136.
29. Weaver M. The double helix: Applying an ethic of care to the duty to warn genetic relatives of genetic information. *Bioethics*. 2016;30:181–187. doi: 10.1111/bioe.12176
30. Forrest LE, Burke J, Bacic S, Amor DJ. Increased genetic counseling support improves communication of genetic information in families. *Genet Med*. 2008;10:167–172. doi: 10.1097/GIM.0b013e318164540b
31. Hodgson J, Metcalfe S, Gaff C, Donath S, Delatycki MB, Winship I, Skene L, Aitken M, Halliday J. Outcomes of a randomised controlled trial of a complex genetic counselling intervention to improve family communication. *Eur J Hum Genet*. 2016;24:356–360. doi: 10.1038/ejhg.2015.122
32. Schwiter R, Kulchak Rahm A, Williams JL, Curry Sturm A. How can we reach at-risk relatives? Efforts to enhance communication and cascade testing uptake: a mini-review. *Curr Genet Med Rep*. 2018;6:21–27.
33. Nieuwhof K, Birnie E, van den Berg MP, de Boer RA, van Haelst PL, van Tintelen JP, van Langen IM. Follow-up care by a genetic counsellor for relatives at risk for cardiomyopathies is cost-saving and well-appreciated: a randomised comparison. *Eur J Hum Genet*. 2017;25:169–175. doi: 10.1038/ejhg.2016.155
34. Schmidlen T, Schwartz M, DiLoreto K, Kirchner HL, Sturm AC. Patient assessment of chatbots for the scalable delivery of genetic counseling. *J Genet Couns*. 2019;28:1166–1177. doi: 10.1002/jgc4.1169
35. Otten E, Birnie E, Ranchor AV, van Langen IM. Online genetic counseling from the providers' perspective: counselors' evaluations and a time and cost analysis. *Eur J Hum Genet*. 2016;24:1255–1261. doi: 10.1038/ejhg.2015.283
36. Slade I, Subramanian DN, Burton H. Genomics education for medical professionals - the current UK landscape. *Clin Med (Lond)*. 2016;16:347–352. doi: 10.7861/clinmedicine.16-4-347