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ARTICLE

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Predicting personal cardiovascular disease risk based on family health history: Development of expert-based family criteria for the general population

Tetske Dijkstra[1], Lieke M. van den Heuvel[1,2,3], J. Peter van Tintelen[3], Christian van der Werf[4], Irene M. van Langen[1] and Imke Christiaans[1]✉

In inherited and familial cardiovascular diseases (CVDs), relatives without current symptoms can still be at risk for early and preventable cardiovascular events. One way to help people evaluate their potential risk of CVD is through a risk-assessment tool based on family health history. However, family criteria including inherited CVD risk to be used by laypersons are non-existent. In this project, we employed a qualitative study design to develop expert-based family criteria for use in individual risk assessment. In the first phase of the project, we identified potential family criteria through an online focus group with physicians with expertise in monogenic and/or multifactorial CVDs. The family criteria from phase one were then used as input for a three-round Delphi procedure carried out in a larger group of expert physicians to reach consensus on appropriate criteria. This led to consensus on five family criteria that focus on cardiovascular events at young age (i.e., sudden death, any CVD, implantable cardioverter-defibrillator, aortic aneurysm) and/or an inherited CVD in one or more close relatives. We then applied these family criteria to a high-risk cohort from a clinical genetics department and demonstrated that they have substantial diagnostic accuracy. After further evaluation in a general population cohort, we decided to only use the family criteria for first-degree relatives. We plan to incorporate these family criteria into a digital tool for easy risk assessment by the public and, based on expert advice, will develop supporting information for general practitioners to act upon potential risks identified by the tool.

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INTRODUCTION

Monogenic cardiovascular diseases (CVDs) such as long QT syndrome, cardiomyopathies, and familial hypercholesterolemia (FH) may manifest with severe symptoms or sudden death (SD) early in life [1]. However, disease symptoms and SD may also manifest at young age in multifactorial CVDs and, just as in in monogenic CVDs, impose a greater disease risk for relatives who share risk-related genetic and environmental factors [2–5]. People are often unaware of these predisposing genetic and familial risk factors, even though early detection could prevent severe disease manifestations [6, 7].

Facilitating personal risk prediction for CVD could decrease cardiovascular mortality and morbidity. Such a personal risk prediction should be based on traditional cardiovascular risk factors like hypertension and hypercholesterolemia and on genetic and familial risk factors. However, DNA-analysis of genetic risk factors is costly and not currently suitable for use in the general population. Family health history may be used as a proxy variable or predictor for the presence of genetic and familial risk factors and is known to be also associated with disease risk independent of genetic factors [8, 9]. In current practice, family health history is used in criteria for referral to clinical genetic centres and is evaluated to determine when DNA-diagnostics for monogenic disease is indicated. Use of family health history to identify actionable risks is being embraced in primary care, albeit slowly, but its adoption faces many barriers. Its use in the general population is even rarer even though widespread use could greatly benefit prevention goals as studies have shown that 42–82% of people are at increased risk for one or more diseases based on family health history [10–13].

A digital risk-prediction tool for CVD based on the presence of cardiovascular disease and events in the family might therefore allow for early disease detection and prevention in the general population. However, to our knowledge, a free-to-use digital tool for the general population including inherited CVDs has not yet been developed [3]. Likewise, family history criteria associated with an increased risk of CVD for use by clinicians exist, but there are no versions that can be used by lay people. We therefore aimed to develop and evaluate expert-based family criteria for CVD risk for use by the general population that can be implemented in a digital risk-prediction tool.

[1]Department of Clinical Genetics, University Medical Center Groningen / University of Groningen, Groningen, the Netherlands. [2]Department of Clinical Genetics, Academic Medical Center / University of Amsterdam, Amsterdam, the Netherlands. [3]Department of Biomedical Genetics, University Medical Center Utrecht / University Utrecht, Utrecht, the Netherlands. [4]Heart Center, Department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands. ✉email: i.christiaans@umcg.nl

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SUBJECTS AND METHODS

This study was carried out in three phases. Phase 1 was identification of family criteria by an online focus group of experts. In Phase 2 an online Delphi method was used to reach consensus on the family criteria in a larger group of experts. In Phase 3 we evaluated the family criteria in different cohorts.

Phase 1: Online focus group

In Phase 1, we organised a focus group to discover the areas of interest that form the basis of the family criteria for the tool. Eight expert physicians were approached via e-mail to participate in this online focus group based on their expertise on inherited and familial CVDs. The invitation e-mail contained information on the study, the study procedure and the time investment requested. Seven physicians then participated in the focus group: two cardiologists, two clinical geneticists, one vascular internist, and two general practitioners (GPs) with special expertise in CVDs.

The focus group was conducted by a psychologist (LMvdH) with experience in qualitative research. The psychologist used a semi-structured topic list, based on existing literature on referral criteria for familial and inherited CVDs (Supplementary Information). The focus group was organised online during the COVID pandemic but also to accommodate expert physicians in participation. To join, participants could login via a personal account to the Cisco platform Webex. The focus group was transcribed verbatim and analysed using thematic analysis by two researchers independently (TD and LMvdH) with Atlas.ti 5.0.

Phase 2: Delphi method

The areas of interest for potential family criteria that were discussed in the focus group were used as input for the Delphi method, which aimed to reach consensus among a larger group of expert physicians on the potential family criteria by filling in three rounds of questionnaires. We invited 51 experts (7 cardiologists, 7 clinical geneticists, 12 vascular internists, and 25 GPs) and 26 experts agreed to participate (6 cardiologists, 7 clinical geneticists, 6 vascular internists, and 7 GPs). The seven experts who participated in the focus group also participated in the Delphi method. Participants' mean age was 49 years (SD 8.3), 60% was female, and 90% had ≥ 10 years of professional experience (55% ≥ 15 years, and 20% ≥ 20 years).

The Delphi questionnaire included 21 statements covering four subjects: (a) experts' opinions on the usefulness of a digital risk-prediction tool based on family history (1 statement), (b) potential family criteria for risk assessment, including age limits (10 statements), (c) use of the family criteria in a pedigree (5 statements), and (d) needs for implementation of a digital risk-prediction tool (6 statements) (Supplementary Information). Participants were asked to score each statement on a 3-point scale (agree, doubting, disagree) and to give an obligatory motivation for their score. For each round, participants had 2 weeks to respond. After each round, statement scores were calculated and motivations were summarised and used as input for the following questionnaire. Three rounds of questionnaires were distributed, with each filled in by at least 20 experts.

We considered consensus to have been reached if ≥ 75% of the participants agreed or disagreed on a statement. For statements without consensus, scores and summarised motivations for each statement were fed back to participants in the next round of the questionnaire. Answers on statements for which consensus was reached in the previous questionnaire were summarised to indicate participants' general opinion.

Phase 3: Evaluation of family criteria

We evaluated the family criteria established in Phase 1 and 2 in two cohorts representing different CVD risk populations. The first was a cohort of individuals with a high a priori risk for genetic or familial CVD from the Department of Genetics of the University Medical Center Groningen, a tertiary referral centre with expertise in cardiogenetics. The second cohort was a general population cohort derived from the Lifelines population cohort. The Genetics department cohort was selected based on the following criteria: the referred patient was asymptomatic, the reason for referral was CVD or SD in the family matching genetic referral guidelines, and the referral had occurred in the last 15 years. We evaluated 81 randomly selected patients with different types of family history for CVD (SD, heart disease, aortic aneurysms) that reflected the diversity and distribution of patients seen at the Genetics department. Each patient's family was evaluated on the presence of potential family criteria in first- and second-degree relatives, and the advice from genetic counselling was retrieved. A positive score on the family criteria was defined as the presence of ≥ 1 family criteria in the family. Descriptive and frequency statistics were used to describe the data. We subsequently determined the concordance between positive or negative family criteria in first- and second-degree relatives, respectively, and a positive or negative counselling advice as the gold standard (i.e., whether there was advise to perform genetic testing in the family and/or cardiovascular evaluations reflecting a potential high risk).

The general population cohort was derived from the Lifelines cohort and biobank. Lifelines is a large multigenerational cohort study that has collected data and biomaterials of over 167,000 participants (~10% of the regional population) from the Northern Netherlands [14]. Self-reported questionnaire data gathered by Lifelines, including information such as family composition, family health, and personal health regarding CVDs, were used to determine the presence of potential family criteria (Supplementary Information).

Since Lifelines only collects information on first-degree relatives, we randomly selected 50 Lifelines participants without CVD whose parents also participate in Lifelines. For these 50 participants, we could construct a pedigree containing first- and second-degree relatives that could be evaluated for the presence of the potential family criteria in both first- and second-degree relatives. Additionally, from the entire Lifelines cohort, we looked at available information on CVD in first-degree relatives.

RESULTS

Phase 1: Online focus group findings

Two main themes were derived from the focus group, which we discuss and illustrate with quotes below.

Use of a digital risk-prediction tool based on family history

All focus group participants agreed that a digital risk-prediction tool based on family history could be useful. They felt the tool should not only focus on monogenic CVDs but also on CVDS that occur at a young age in a family.

When there is an increased risk, they thought the tool should refer users to their GP. Participants suggested that the GP could be helpful in examining the family history in more detail and in determining which further actions are necessary, e.g., a referral to a clinical geneticist or a cardiologist or cardiovascular risk management by the GP. One GP (Participant #4) indicated:

> "I think it is in principle useful to use a tool to see if someone should go to a clinical geneticist, but I can't imagine that that would be the only outcome. Sometimes you think something is not hereditary, but it is still good to have your cardiovascular risk profile checked, so I can also imagine there are other outcomes after using [the tool]."

A general opinion among participants that emerged several times during the focus group was to keep the tool as simple as possible by using a limited number of family criteria and simple language instead of medical terminology. As one cardiologist (Participant #2) explained:

> "I think if you want to fill in the tool and you want to capture multiple cardiogenetic diagnoses with different cut-off points for gender, age, phenotype, then you're actually already designing a very complicated app… I think the most important thing is that what is input is also correct. Perhaps this initiative provides more opportunity to really steer people with an obvious signal to cardiogenetics rather than focusing on vaguer things."

Participants advised us to additionally develop supporting information for GPs to help them make decisions about further management for users of the tool with a high risk. Participants believed that such information should contain, for example, a decision tree for referral and additional questions to differentiate

between possible cardiovascular conditions. One participant (#7, GP) said:

> "I see a lot [of benefit] in a two-step method, but in a slightly broader form than described by participant #5; you already capture a lot, for example, with an age limit of 50 for SCD and CVD, and if the answer is 'yes', you refer someone to the GP, and the GP should then have a good screening method to figure out the family history together with the patient [user]. So you keep it very simple for the family…, for the patient [user], like something cardiovascular before age 50, and then you offer tools and information for the GP."

Family criteria

Most participants believed that the family criteria should only include first-degree and possibly second-degree relatives. They found that medical information on more distant relatives is probably difficult to accurately obtain or know, as illustrated by a clinical geneticist (Participant #6):

> "Well, I wouldn't go much further than second [-degree], I think. Beyond that, people usually don't know anymore. Maybe you can develop an app where you press enter and the immediate output is a ready-made family tree for the GP in which it is clear who died at what age. That would definitely do a lot of work for the GP in advance."

All participants agreed that SD at young age should be included as a family criterium. The insertion of an implantable cardioverter-defibrillator (ICD) at young age was also considered a relevant family criterium, because indications for an ICD at young age include resuscitation and inherited CVDs. One cardiologist (Participant #5) said:

> "I would say an ICD at a young age is also a red flag. Hmm, but then you also have to know if this is a justified ICD, because there are a lot of people who I would not have given an ICD… but that is also not something that is common at a young age, so an ICD at a young age is a red flag."

Specific medical diagnoses, e.g., myocardial infarction, were thought to be too difficult to include as a family criterium in the prediction tool. An alternative suggestion was to ask about CVDs at young age in the family in a more general manner. This would probably increase the number of false positives (i.e., indication of high risk in people who do not have a high risk), for example if the CVD in the family is thrombosis. However, the expert GPs and vascular specialists in the focus group thought such a general criterium would be best despite the possible noise. A vascular specialist (Participant #1) explained:

> "And I think, yes, if we are going to take a serious look at a tool with which we are going to detect hereditary CVDs, then I would find it a bit of a missed opportunity to skip this [CVDs at a young age], precisely because it is so incredibly important to continue to recognise. So you do want to keep that in. If you only see '40 years and SD' you might be able to puzzle out a small part of what's missing, but yeah, you then also miss a lot of people with an important hereditary disorder."

Phase 2: Delphi method findings

The themes derived from the focus group were used as input for the statements in the Delphi method to reach consensus on family criteria and to provide more input on the implementation of the tool. Results of the statements on the usefulness and implementation of the tool are presented in the Supplementary Information.

The Delphi questionnaires contained statements on ten potential family criteria. For nine of these statements consensus was reached, for five on inclusion as family criterium and for four on exclusion (Table 1). No consensus was reached on the potential family criterium 'diagnostic characteristics of FH at young age'. Experts believed that FH in the family was associated with a high risk, but they considered it too difficult for laypeople to determine if relatives could have diagnostic characteristics of FH, like a very high cholesterol, tendon xanthomas and ocular signs, and too difficult to question this in lay language and reliably know the cholesterol level of a relative. The family criterium on high cholesterol and hypertension was consented to exclude because this would probably result in too many false positives. No consensus was reached on the age limit for two of the included family criteria (Table 1).

There was consensus to not apply the family criteria to third-degree relatives, but no consensus was reached on the use for second-degree relatives or on setting different age limits for males and females (Table 2).

Phase 3: Evaluation of family criteria

We then evaluated the five family criteria for which consensus for inclusion was reached in the Delphi method in two cohorts: 1) a high-risk cohort of patients referred to the UMCG Genetics

Table 1. Statements on potential family criteria indicating a high risk of cardiovascular disease.

A first-degree relative had/has…	Consensus	Defining young age
Sudden death at young age	Round 1: 85% agreed	50 years
A cardiovascular disease at young age	Round 2: 75% agreed	To be determined (no consensus)
An ICD inserted at young age	Round 1: 85% agreed	50 years
High cholesterol and/or hypertension at young age	Round 3: 80% disagreed	NA
A specific diagnosis related to inherited cardiovascular diseases at young age	Round 3: 85% agreed	To be determined (no consensus)
Diagnostic characteristics of familial hypercholesterolemia at young age	No consensus. Round 3: 30% agreed, 60% disagreed, 10% doubting	NA
A thoracic- or abdominal aortic aneurysm at young age	Round 3: 75% agreed	50 years
Physical characteristics for specific syndromes that are related to cardiovascular problems (e.g., Marfan syndrome)	Round 3: 80% disagreed	NA
Congenital heart defects	Round 3: 85% disagreed	NA

NA Not applicable.

Table 2. Statements on the use of family criteria in a pedigree.

Statement	Consensus
Apply different age cut-offs for women and men	No consensus. Round 3: 20% agreed, 65% disagreed, 15% doubting
Including second-degree relatives in the risk-prediction tool	No consensus. Round 3: 50% agreed, 30% disagreed, 20% doubting
More than one second-degree relative having one of the criteria should be used as a criterium	No consensus. Round 3: 55% agreed, 20% disagreed, 25% doubting
Including third-degree relatives in the risk-prediction tool	Round 1: 75% disagreed
More than one third-degree relatives having one of the criteria should be used as a criterium	Round 2: 90% disagreed
One (or more) second-degree relatives AND a third-degree relative should be used as a criterium.	Round 2: 80% disagreed

department because of a family history of CVD or SD, and 2) a population cohort derived from the Lifelines cohort. We did not evaluate the family criterium on diagnostic characteristics for FH, for which no consensus was reached in the Delphi method, as a separate family criterium, but it was included in the family criterium on 'a specific diagnosis related to inherited cardiovascular diseases'. Since no consensus was reached on an age limit for the criterium on inherited CVDs, we decided not to use an age limit, because an inherited CVD poses a risk to relatives irrespective of the age of diagnosis in the family. As there was also no consensus on an age limit for 'a CVD at young age', we evaluated the pedigrees for the two age limits most commonly mentioned in the Delphi method: 50 years (50% of answers) and 55 years for males and 65 for females (conform the definition of premature cardiovascular disease used in cardiovascular risk management, 30% of answers).

We evaluated the five family criteria in the high-risk cohort using the pedigrees of 81 patients without CVD: 49 were referred because of SD in the family and 32 because of CVD in the family. For patients with a positive score on ≥ 1 of the five family criteria in first-degree relatives using an age limit of 50 years for 'a CVD in the family', the family criteria corresponded with the counselling advice in 63 of 81 (78%) of families (Table 3A). In the remaining 18 patients that did not fulfil any family criterium but did receive advice for additional testing, the reason for the additional testing was that multiple relatives experienced SD or CVD above age 50. Using the age limit that conforms with the definition of premature CVD we showed that the family criteria corresponded with the counselling advice in 73 out of 81 (90%) patients (Table 3B). We did not identify patients with a positive score on the family criteria for first-degree relatives, that did not get advice for additional testing (Table 3A, B). No differences were observed when applying the family criteria on second-degree relatives (Table 3C, D).

We then looked at available questionnaire data on CVD in the family from the Lifelines population cohort: 42% of participants had a first-degree relative with a CVD at any age and 26% had one before age 60. We constructed pedigrees for 50 Lifelines participants who did not have CVD, including information on health in first- and second-degree relatives. In 8% of these pedigrees, we found a positive score on ≥ 1 of the family criteria for first-degree relatives when using the age limit of 50 years, and we found a positive score in 10% when using the age limit that conforms with the definition of premature CVD. Looking at only second-degree relatives in the families without a positive score on a family criterium in a first-degree relative, we observed an additional 42% and 52% with a positive score using the two different age limits, respectively. However, the self-reported Lifelines data contained the variable 'heart failure or cardiomyopathy', which we interpreted as an idiopathic cardiomyopathy and thus fulfilled the family criterium 'specific diagnosis related to an inherited CVD at any age', although we could not evaluate the idiopathic nature and exclude external causal factors like coronary artery disease. Ignoring the 'heart failure or cardiomyopathy' answers resulted in lower percentages of positive scores (8% became 2%, 10% became 4%, 42% became 22%, and 52% became 32%).

DISCUSSION

In our three-phase approach to develop expert-based family criteria for risk prediction on CVD based on family history, we started with a focus group with expert physicians. A main point that arose several times during this focus group was the need to keep the family criteria as simple as possible. In the Delphi method questioning a larger group of experts, all potential family criteria suggested by the focus group also reached consensus for use. The Delphi method ultimately led to consensus on five family criteria for first-degree relatives that showed substantial diagnostic accuracy in a high-risk cohort who had been referred based on genetic referral guidelines and thus could be used for risk prediction.

No consensus was reached on the criterium 'diagnostic signs for FH in a relative', the use of family criteria in second-degree relatives and on the age limit for'a CVD at young age in a relative'. We decided to include FH in the criterium 'a specific diagnosis related to inherited CVD in a relative'. Also relevant FH-related events would also be picked up by other consented family criteria. Use of the family criteria in second-degree relatives did not generate much additional diagnostic value in the high-risk cohort, and data from the general population cohort showed that use in second-degree relatives results in a large number of people with an increased risk based on the family criteria, probably generating many false positives. Furthermore, including second-degree relatives is not in line with the focus group's advice to keep the family criteria as simple as possible, and previous studies have shown that knowledge and accuracy of family history decrease with the degree of kinship [15–17].

We tested two different age limits for the family criterium 'a CVD at young age in a relative'. The age limit that conforms to the definition of premature CVD from cardiovascular risk management (55 years for males and 65 for females) resulted in a slight increase in diagnostic accuracy in the high-risk cohort, but data from the population cohort showed that 26% of respondents had a first-degree relative with CVD before age 60. It is thus likely that the age limit from cardiovascular risk management will also generate too many false positives, especially when used in the general population [10].

Existing digital tools to assess family health history are often only available for health-care professionals, for research studies, or on a paid subscription basis, limiting their use by the general public. The few free digital tools available to the public do not ask for CVD or only assess risk for coronary artery disease and not for inherited CVDs [3]. Assessment of family history of CVD in the general population can also be hampered by health literacy and disease knowledge [3, 10]. In our experience from

Table 3. Evaluation of the family criteria in a high-risk cohort using different kinship degrees and age limits.

A: Evaluation among *first-degree* relatives, age limit for cardiovascular disease 50 years.					**B: Evaluation among *first-degree* relatives, age limit for cardiovascular disease 55 years in males and 65 years in females.**				
Positive counselling advice					**Positive counselling advice**				
		+	−	**Total**			+	−	**Total**
Positive score on ≥ 1 family criterium	+	61	0	61	Positive score on ≥ 1 family criterium	+	71	0	71
	−	18	2	20		−	8	2	10
				81					81
C: Evaluation among *second-degree* relatives, age limit for cardiovascular disease 50 years.					**D: Evaluation among *second-degree* relatives, age limit for cardiovascular disease 55 years in males and 65 years in females.**				
Positive counselling advice					**Positive counselling advice**				
		+	−	**Total**			+	−	**Total**
Positive score on ≥ 1 family criterium	+	1	1	2	Positive score on ≥ 1 family criterium	+	2	1	3
	−	17	1	18		−	6	1	7
				20					10

clinical genetics, people can more accurately recall the type of cancer in a relative than the type of heart disease. It is thus important to use lay language, provide additional information on the diseases mentioned in the family criteria, and assess the understanding of family criteria in particular in people with low health literacy.

Future perspectives

In the next step in our research, we will further evaluate the age limit for 'a CVD at young age in a relative'. We will develop a prototype of the tool using the five accepted family criteria in first-degree relatives and evaluate the age limit among 1000 people who reflect the age and sex distribution of the general population. During development we will test the prototype in people with low health literacy and evaluate the tool's usability and psychological reactions in users. As suggested in the focus group, and further explored in the Delphi method, we will also develop online information for GPs to provide them with more information on familial and inherited CVDs and to support them in management of patients with a positive score on the family criteria.

Ideally, the family criteria could be combined with clinical risk factors for CVD in a digital risk-prediction tool, combined with family health history for other diseases, and possibly even polygenic risk scores. However, further studies are needed before combining different methods of risk assessment, as risks cannot simply be summed when risk mechanism partly overlap [3, 18].

Inclusion of the tool or its results in an individual's digital personal health environment, or in a health professionals electronic health record with for example automatic best practice advisory pop-ups, would probably be beneficial for the use of the family criteria and their effectiveness in disease prevention.

The capacity to connect and alert relatives using family connections via a digital risk-prediction tool could create a positive ripple effect like that seen in cascade genetic testing, especially for monogenic CVDs, and thereby extend the preventive potential of the tool. However, privacy aspects must be considered carefully before implementing such an option.

Limitations

We developed expert-based family criteria and thus cannot quantify the exact risk of CVD for each family criterium. Based on our evaluation in a high-risk and population cohort, we do think these family criteria are useful as a first-tier screening tool for the general population.

In eight patients from the high-risk cohort, we noticed missing data on the age at diagnosis or SD in ≥ 1 relatives. We decided not to exclude these patients because in six out of eight patients the remaining family data were already positive for a family criterium in a first-degree relative. In the other two families, a diagnosis in an affected relative within the age limits could only mean a higher diagnostic accuracy for the family criteria.

While the Lifelines cohort contains data of over 167,000 people, family history data are only available in a minority. Data on CVD in first-degree relatives is available for 52,453 participants (including 203 participants with marked missing data). A response bias is thus possible in this cohort.

CONCLUSIONS

We developed expert-based family criteria that can be used in the general population to assess whether an individual has a potentially increased risk of CVD due to genetic and/or familial factors and would qualify for consultation with the GP. Five family criteria were consented to being associated with increased risk of CVD and showed substantial diagnostic accuracy for use in first-degree relatives. We plan to incorporate these family criteria in a digital tool to allow easy risk assessment by laypeople.

DATA AVAILABILITY

Data generated as part of this study are available from the corresponding author on reasonable request. Data from the Lifelines Biobank is available at Lifelines (www.lifelines.nl).

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AUTHOR CONTRIBUTIONS

IC conceived the project. TD and LMvdH led the data collection and analysis. TD and IC wrote the first draft. LMvdH, JPvT, CvdW, IMvL, and IC made substantial revisions to the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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COMPETING INTERESTS

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ETHICAL APPROVAL

The Medical Ethical Review Board of the University Medical Center Groningen evaluated the study design and decided that the Medical Research Involving Medical Subjects Act (WMO) does not apply to this study (METc 2020/551).

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Imke Christiaans.

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