University of Sheffield

Evidence Map: Screening for inherited cardiac conditions

Protocol

Produced by: Sheffield Evidence Network for Screening Synthesis (SENSS)

Produced for: UK National Screening Committee (UK NSC)

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Plain Language Summary

Inherited cardiac conditions (ICCs) are heart conditions that are caused by a genetic mutation. These mutations can run in families, and can be passed on from parents to children. These conditions can cause problems with the heart muscles (cardiomyopathies) or with the electrical signals that make the heart beat rhythmically (channelopathies). They can cause heart attacks and sudden cardiac death, sometimes in young adults, but also in people at older ages. They can also cause symptoms such as light headedness, fainting, palpitations, shortness of breath, fatigue, chest pain and sometimes swelling ankles, feet, legs or stomach.

A person may be tested for ICCs if they have symptoms of the disease and a diagnosis of a cardiac condition. There are genetic tests, and clinical tests such as electrocardiograms (to measure the electrical signals), imaging tests such as ultrasound and magnetic resonance imaging (MRI) to look at the heart, and other tests which look at how the heart responds to exercise and certain drugs. Genetic tests do not always pick up mutations as not all mutations that cause ICCs are currently known. If a person has a genetic mutation, they may not get the condition. The proportion of people with the mutation who get the condition is known as penetrance. Equally, some patients with a genetic mutation may not get symptoms until they are older.

If the person is diagnosed with an ICC by clinical tests with or without a genetic confirmation, family members (brothers, sisters, mothers, fathers, children) could be offered testing as part of their care. However, there is no formal national screening programme in place. If a genetic cause was identified in the first family member who was tested (known as the index case or proband), relatives may be tested genetically to see if they have the same mutation. Not all relatives will have inherited the condition. However, if no genetic mutation was identified in the proband, family members can be monitored every few years with tests such as electrocardiograms, imaging tests, exercise tests and drug tests to see if they have developed the condition. If the condition is caught early, there are treatments such as implantable cardioverter defibrillators (which can shock the

heart back into a correct rhythm and prevent a heart attack), medication and lifestyle changes that can help prevent symptoms and death.

In the UK, genetic testing and screening is offered to family members of those who have a genetically confirmed ICC, but there may be differences in the way the tests are done across the country, and the systems used to manage screening may not always be well developed.

This evidence map focusses on genetic testing, and aims to summarise how much and what type of research evidence is available relating to the penetrance of the genetic mutations, how accurate the genetic tests are, and what impact they have on people's health in the long term. It will also look for clinical guidelines from the UK and other countries. This will support the National Screening Committee in determining the appropriate next steps for the topic in the evidence review process.

Brief background

Inherited cardiac conditions (ICCs), also called inherited heart conditions, are genetically inherited conditions that run in families.(1) Although the epidemiological data remains incomplete, it is estimated that the total prevalence of ICCs is approximately 340,000 in the UK.(2) ICCs are among the common causes of sudden cardiac death (SCD) among young people,(3) and can cause cardiac events throughout the life course. The most common ICCs are cardiomyopathies and channelopathies.

Cardiomyopathies affect heart muscle function. The most common cardiomyopathies include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and arrhythmogenic cardiomyopathy (ACM). HCM occurs when the heart muscle thickens abnormally, making it stiff and less effective at pumping blood. DCM involves the enlargement of the left ventricle, causing the heart's muscle wall to stretch and thin, which weakens its ability to pump blood. In ACM, heart muscle cells fail to adhere properly, which weakens the heart wall, and reduces the heart's ability to pump blood. Global overall prevalence is estimated to be 1 in 500 for HCM, 1 in 250 to 1 in 400 for DCM, and 1 in 2000 to 1 in 5000 for ACM.(4) However, these values may be underestimated.

Channelopathies affect ion channels in the membrane of the cells of the heart, disrupting electrical signalling and leading to abnormal heart rhythms.(5) Among the most common channelopathies

is Long QT syndrome (estimated prevalence 1:2000-1:2500)(6, 7) where the heart recharge rate between beats in prolonged, due to aberrant repolarization of the heart. Other less common channelopathies include Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, (CPVT) progressive cardiac conduction defect (PCCD) and short QT syndrome. Brugada syndrome (estimated prevalence 1:2000)(8) is caused by mutations in genes which primarily code for sodium, potassium and calcium channels or the proteins associated with them.(5) It can cause dangerously fast heart rhythms or irregular heartbeats which can lead to sudden cardiac death. The other inherited channelopathies are either rarer (CPVT) or less well studied (PCCD, Short QT).

Across ICCs, the causative genetic mutation may only be identified in a proportion of patients. For example, a recent systematic review found that the pooled detection rate (based on the identification of a pathogenic or likely pathogenic mutation) for HCM (one of the most studied conditions) was 42% (95% confidence interval (CI) 38% to 45%) in adults and 56% (95% CI 45% to 67%) in paediatric cohorts.(9) Another review notes most cardiomyopathies and arrhythmias are caused by monoallelic variants in single genes, but that penetrance (the likelihood that having a pathogenic variant (genotype) will result in clinical disease (phenotype)) is variable and often age-related.(10)

Symptoms vary by condition, and include light headedness or fainting, palpitations, shortness of breath, fatigue, chest pain, and sometimes swelling ankles, feet, legs or stomach; however, others do not have any symptoms. In advanced disease, people present with heart failure, stroke due to undiagnosed atrial fibrillation, and SCD. Most of the ICCs are brought to attention when one family member has ICCs, or there is family history of cardiac arrests or diagnosis of angina or a heart attack at a young age.

There are effective interventions that can alter outcomes when the disease is picked up at an early stage. Implantable cardioverter defibrillators are fitted to prevent sudden cardiac death in individuals judged to be at high risk. Medications and lifestyle changes are given to prevent arrhythmia before the onset of symptoms in long QT syndrome. Heart failure therapies are used in left ventricular impairment to slow the decline in cardiac function, with those at risk of heart failure undergoing more intensive surveillance. Anticoagulation is provided to patients with atrial fibrillation at risk of cardioembolic complications. In the advanced phase, cardiac transplantation

and mechanical circulatory support are deployed. In late-stage disease, severe pulmonary hypertension ensues, precluding intervention and treatment is palliative.

As these conditions are inheritable, guidelines in some countries recommend familial screening/cascade screening (e.g., American Heart Association(11); Journal of the American College of Cardiology(12); European Society of Cardiology(13); Japanese Circulatory Society).(14) This type of screening usually involves testing the index case (also known as the proband, the first member of a family to be suspected of a genetic condition) using a gene panel test (i.e., testing multiple genes at once). The panel may include the genes most robustly associated with the phenotype, and may be widened if no causative variant is identified. If a pathogenic variant is identified, family members can then be identified using targeted genetic testing for the individual mutation at a low cost. The classification of variants changes over time, and a variant of uncertain significance (VUS) can later be upgraded to pathogenic or likely pathogenic or downgraded to a non-pathogenic status. This information should be used to update diagnoses. Where no disease-causative variant is identified, family members and probands are monitored clinically using tests such as electrocardiogram, cardiac ultrasound, magnetic resonance imaging, drug provocation test, and exercise tolerance test. Where there is no evidence of the condition, investigations are repeated in childhood and adulthood since ICCs can develop clinically later in life.

In the UK, NHS England has published a national service specification for ICCs, which outlines the clinical care pathway for patients with ICCs and those with a first-degree relative affected by these conditions.(2) The document defines the service model and guidance for diagnosis and treatment of affected individuals and their family members. This service specification describes genetic cascade screening for first degree relatives of those with a genetically confirmed ICC. It also mandates specialised ICCs services to investigate suspected cases. Individuals diagnosed with any of the following conditions, or those with a first-degree relative affected, will be able to access the ICCs service; this will include the next of kin in cases of SCD:

- arrhythmia syndromes: including long QT syndrome, short QT syndrome, Brugada syndrome, CPVT
- cardiomyopathies: including HCM, DCM, arrhythmogenic right ventricular cardiomyopathy (ARVC)
- inherited arteriopathies
- muscular dystrophies

However, this is not a national screening programme, and uniformity of practice between centres performing testing in the UK is thought to be lacking, and the systems used to manage screening may not meet standards described in the UK NSC manual.

Rationale

A proposal for 'targeted screening for ICCs through genetic testing' was received during the National Screening Committee's (NSC's) 2024 'Open Call for New Topics'. The NSC has not previously considered this topic. However, a review of screening for cardiac conditions associated with sudden cardiac death (SCD) in the young was completed in 2019 and was not recommended by the NSC.[1] An update of SCD is currently underway.

Aims

The aim of this evidence map is to provide an overview of the volume and type of evidence that is available relating to genetic penetrance, screening tests, the effectiveness of screening, and any guidelines on genetic cascade screening. The review questions are as follows:

1. What is the volume and type of evidence available on the penetrance of mutations associated with ICCs?
2. What is the volume and type of the evidence available on the accuracy of genetic tests in detecting ICCs?
3. What is the volume and type of evidence evaluating the effectiveness of genetic cascade screening in family members of people with a genetically confirmed ICC?
4. Are any guidelines on targeted screening for ICCs available in the UK and / or other high-income countries?

[1] This was because there were uncertainties in how many young people each year were affected by sudden cardiac death; it was unclear whether tests could accurately detect heart conditions in young people without symptoms; and no studies were identified which met the inclusion criteria for whether screening young people reduced the risk of SCD.

Methods

Scoping searches indicated a potentially very large return if search terms were kept broad (e.g., for question 2 the estimated total for all years and all study designs was 68,000 hits). This is largely because the scope is broad, including multiple conditions and multiple tests. The inclusion criteria and review strategy have therefore been devised to reduce the screening burden and prioritise records of highest relevance.

Focussing on the five main conditions: The review will focus on the five most prevalent and/or studied conditions, namely: HCM, DCM, ACM, long QT syndrome, Brugada syndrome.

Date limit: Although this topic has not been reviewed by the NSC previously, in the first instance data from the previous 10 years will be identified since genetic testing changes over time with respect to known variants and test methodologies. If insufficient data are found from this time period, searches may be extended back by another 10 years.

Focus on systematic reviews: Systematic reviews will be sought in the first instance, and primary studies sought from the search date of the most recent identified systematic review for questions 1-3. However, brief scoping searches indicate there may be no systematic reviews for some aspects of some of the questions.

Include most recent guidelines: For question 4, only the most recent clinical guideline from any given group (e.g., American heart Association; European Heart Rhythm Association) will be included.

Prioritise studies from the UK: For all questions, studies from the UK will be prioritised. Where UK evidence is limited, studies from other countries (especially those of high-income) can be reported, particularly 1) Northwest Europe; 2) other G7 countries (Canada, France, Germany, Italy, Japan, the United States); and 3) the EEA (27 EU member countries plus Iceland, Liechtenstein, Norway and Switzerland) as well as Australia, New Zealand and China.

Conference abstracts: conference abstracts will not be sought or included in the review.

Focus on major genes: for questions 1 and 2, primary studies will only be included if they include a major gene responsible for the condition (see Table and Appendix for details). Systematic reviews of studies of any relevant genes will be included.

Focus on larger studies: for questions 1 and 2, primary studies will only be included if they are of a certain size. See Table for details. Systematic reviews of studies of any size will be included.

Other pragmatic approaches to study selection: If the volume of eligible studies is high, the NSC will be consulted regarding whether other criteria could be used to prioritise relevant studies.

Phased approach: In phase 1, searches for systematic reviews (questions 1-3) and guidelines (question 4) will be run. Results from phase 1 will be discussed with the NSC during a "checkpoint" to determine which activities are required in phase 2. In phase 2, additional searches for primary studies published since the most recent systematic reviews for questions 1-3 could be conducted, or for the last 10 years if no systematic review was found for a given condition. If these searches are large, it may be necessary to further focus search strategies and/or inclusion criteria, or elongate timelines. The NSC would be consulted in this instance.

Search strategy

Following approval, the strategy below will be run as presented on Ovid MEDLINE and translated for EMBASE.

We anticipate considerable overlap between the evidence for the four questions, so the searches for all four questions will be run at the same time. However, due to the large number of results for questions 2 and 3 (on the accuracy and effectiveness of genetic screening, respectively) we propose to conduct an initial search for review level evidence, followed by a targeted search for primary studies to fill the remaining gaps.

While the search strategy below does not explicitly seek to identify guidelines (as required by question 4), we anticipate that the searches for questions 1-3 will retrieve many of those relevant to the population of interest. However, we also note Farrah & Kaunelis's findings that "repositories of clinical practice guidelines, such as TRIP and ECRI

Guidelines Trust, can be a more efficient method of identifying guidelines compared with bibliographic databases such as PubMed".2[3]

Therefore, we propose an additional guideline search using the two grey literature sources they recommend (TRIP Database and ECRI Guidelines Trust). These searches will be based on lines 1-5 (population terms) only, in order to find guidelines related to the diagnosis or management of ICCs.

Ovid MEDLINE(R) ALL <1946 to May 29, 2025>
1 exp Cardiomyopathies/ 119785
2 Channelopathies/ 942
3 exp Cardiomyopathy, Hypertrophic/ or Cardiomyopathy, Dilated/ or exp Long QT Syndrome/ or Brugada Syndrome/ 48261
4 (hypertrophic cardiomyopathy or HCM or dilated cardiomyopathy or DCM or (arrhythmogenic adj3 cardiomyopathy) or ACM or long QT syndrome or LQTS or Brugada* syndrome).mp. 68524
5 ((inherit* or hereditary) and (cardiac condition* or heart condition* or cardiomyopath* or channelopath* or arrhythm*)).mp. 8721
6 1 or 2 or 3 or 4 or 5 162039
7 penetrance/ 2634
8 penetrance.mp. 16159
9 6 and (7 or 8) 887
10 limit 9 to english language 852
11 meta analysis.mp,pt. or review.pt. or search?.tw. 3956774
12 10 and 11 229
13 10 not 11 623
14 exp Mass Screening/ or (screen* or diagnos* or test*).mp. 10943380
15 (((gene* or pathogen*) adj3 (screen* or test* or sequen* or panel* or mutation* or variant*)) or (sanger sequen* or Polymerase chain reaction or PCR or allele or SNP array* or array comparative genomic hybridi#ation or ACGH or Multiplex ligation dependent probe application or MLPA or next generation sequen* or high throughput sequen* or whole exome sequenc* or whole genome sequen* or targeted sequen* or targeted gene capture or variant interpretation)).mp. 1765962
16 6 and 14 and 15 8842
17 6 and 11 and 14 and 15 1751
18 limit 17 to english language 1591
19 (at risk or hereditary or inherited or inheritable or family history or family member* or family screening or familial or close relati* or first degree relati* or 1st degree relati* or parent* or

[3] In response to "Lunny et al. Validation of five search filters for retrieval of clinical practice guidelines produced low precision" Farrah, Kelly et al. Journal of Clinical Epidemiology, Volume 121, 114 – 116

mother* or father* or brother* or sister* or sibling* or ancestr* or pedigree or cascade).mp. 1867547

20	(proband* or index case*).mp.	39077
21	6 and 14 and 15 and (19 or 20)	4708
22	21 not 17	3618
23	**limit 22 to english language**	**3453**

Inclusion criteria

Inclusion criteria for all four questions are provided below.

Table: Inclusion criteria for evidence map for Inherited cardiac conditions

Item	Q1: penetrance of mutations associated with ICCs	Q2: Accuracy of genetic tests in detecting ICCs	Q3: Effectiveness of genetic cascade screening in family members of people with a genetic diagnosis of an ICC	Q4: Guidelines on targeted screening for ICCs
Priority studies	Include systematic reviews of studies of any size in any gene related to the 5 priority ICCs. Include primary studies in major gene(s) related to the 5 priority ICCs, where sample size is ≥10 patients AND ≥3 families. Exclude all case reports (defined as ≤3 people)	Include systematic reviews of studies of any size in any gene related to the 5 priority ICCs. Include primary studies in major gene(s) where there are either i)≥10 probands in studies of index cases or ii) ≥3 families in studies of cascade screening of family members. Exclude all case reports (defined as ≤3 people)	Studies comparing outcomes in patients identified through cascade screening compared to those who were not identified through screening. No limits on sample size or genes will be placed initially.	Guidelines on targeted screening for ICCs especially in UK and other high-income countries.
Safety netting We will exclude but label whilst screening any studies that meet the above criteria but are: • Post mortem studies (label: post-mortem) • Pre-natal or post-natal studies (label: pre- or peri-natal)				

• Studies in specific conditions (label: specific conditions) where cardiomyopathy or channelopathy is not the primary presenting symptom e.g., Fabry disease, Sengers syndrome • Studies in major genes with 3-9 patients or <3 families • We will also tag studies for which the full text is required and return to these if we have insufficient studies where data could be obtained from the abstract.				
Population	People of any age selected on the basis of having a genetically confirmed ICC **Exclude:** studies of patients with a clinical diagnosis only, or which are at risk of over-selecting patients with a clinical diagnosis	i) index cases / probands - individuals clinically diagnosed with an ICC and / or ii) cascade screening - family members of those with a genetically confirmed ICC	Family members of index cases/probands with a genetically confirmed ICC	i) index cases / probands - individuals clinically diagnosed with an ICC and / or ii) cascade screening - family members of those with a genetically confirmed ICC
Index test/Intervention		Genetic tests and genetic testing strategies ***i)Index cases/probands:*** at least one of the major genes implicated in the clinical disease subtype should be included in the test.*** ***ii) Cascade screening in family members:*** most usually the specific variant found in the proband should be included in the test	Genetic cascade screening	Genetic cascade screening We will also note if included guidelines cover non-genetic cascade screening, diagnosis and management.

Exposure (Q1) or Target condition (Q2-4)	Individuals with pathogenic or likely pathogenic genetic variants/ mutations* associated with • hypertrophic cardiomyopathy (HCM) • dilated cardiomyopathy • arrhythmogenic cardiomyopathy • long QT syndrome • Brugada syndrome **Exclude:** Studies in single genes or variants will be excluded unless the study is a systematic review or the gene/variant is a major gene for that condition***	Relevant pathogenic or likely pathogenic genetic variants / mutations* of: • hypertrophic cardiomyopathy (HCM) • dilated cardiomyopathy • arrhythmogenic cardiomyopathy • long QT syndrome • Brugada syndrome **Exclude:** Studies in single genes or variants will be excluded unless the study is a systematic review or the gene/variant is a major gene for that condition ***	Pathogenic or likely pathogenic genetic variants / mutations* of: • hypertrophic cardiomyopathy (HCM) • dilated cardiomyopathy arrhythmogenic cardiomyopathy • long QT syndrome • Brugada syndrome	• hypertrophic cardiomyopathy (HCM) • dilated cardiomyopathy arrhythmogenic cardiomyopathy • long QT syndrome • Brugada syndrome
Comparator or Reference Standard	None or any reported in the study	Clinical investigation, e.g., electrocardiogram, cardiac ultrasound, magnetic resonance imaging, drug provocation test, and exercise tolerance test. Any other reported in the study.	Usual care / no screening / patients presenting clinically	N/A

Outcomes	• Proportion with a clinical diagnosis of ICC • Cumulative penetrance estimates • Any other penetrance metric	• Sensitivity and Specificity • Positive and negative predictive values • Likelihood ratios • Area under the curve • Any other test accuracy/validity outcomes e.g., detection rate, diagnostic yield	Any reported benefits and harms of cascade screening, for example: Clinical outcomes: • Premature mortality reduction • Cardiac events • Other clinical outcomes relevant to ICCs, e.g., quality of life Harms: • Anxiety • Overtreatment • Pathway attrition • Reproduction issues	N/A
Study designs	• Systematic reviews of studies of any size • Cohort studies ≥10 participants and ≥3 families • Cross-sectional studies ≥10 participants and ≥3 families • other study designs with a consecutive or	Systematic reviews of studies of any size that meet the following criteria • Studies with a single-gate recruitment strategy, ideally consecutively recruited or randomly assigned	• Randomised controlled trials • Quasi-experimental studies • Cohort studies If unavailable, other study designs should be reported Qualitative study designs will be excluded	Any national and/or international guidelines/recommendations on targeted screening for ICCs

	randomly assigned recruitment strategy **Exclude:** Studies with <10 participants or <3 families.	• If unavailable, other study designs such as case-control (two-gate) studies, or studies recruiting only clinically confirmed cases • If unavailable, note whether analytical validity studies were found **Exclude (**unless reporting sensitivity and specificity)**:** ***i) Index case/proband:*** Primary studies with n<10 unrelated probands (i.e., case studies and case series) ***ii) Cascade screening in family members:*** Primary studies with <3 families		
Limits and prioritisation	• Limit to o English language o last 10 years (extend to 20 if insufficient evidence) • Prioritise to o Studies with a focus on the 5 ICCs named, rather than a focus on a specific condition that also causes an ICC, e.g., Fabry disease, Sengers disease. NB, some LQTS have specific			

	names: ankyrin-B syndrome; Andersen-Tawil syndrome type 1; Timothy syndrome, but as these are not major genes in LQTS they will be excluded. o Systematic reviews (update with subsequently published primary studies) o UK studies ▯ If unavailable, high-income countries and/or countries with similar healthcare systems and demographics may be prioritised** o Other criteria (to be discussed with NSC) if required to further prioritise studies

ICC – inherited cardiac condition; N/A, not applicable; Q – question.

*** Exclusion criteria:** Studies will be excluded if the conditions being studied are not all (100%) cardiomyopathies or channelopathies, e.g., if the study also focuses on congenital heart disease or familial hypercholesterolaemia, except where a subgroup of relevant patients (100% inherited cardiomyopathies or channelopathies) are reported. Studies are eligible for inclusion if the conditions being studied includes a proportion with inheritable cardiomyopathies or channelopathies other than the 5 listed in the scope, e.g. catecholaminergic polymorphic ventricular tachycardia (CPVT) or progressive cardiac conduction defect (PCCD),but will be excluded where the population is 100% another ICC, for pragmatic reasons (e.g., restrictive cardiomyopathy).** Where UK evidence is limited, studies from other countries (especially those of high-income) can be reported, particularly 1) Northwest Europe; 2) other G7 countries (Canada, France, Germany, Italy, Japan, the United States); and 3) the EEA (27 EU member countries plus Iceland, Liechtenstein, Norway and Switzerland) as well as Australia, New Zealand and China. *** major genes are listed in the Appendix.

Screening of Titles and Abstracts

Titles and abstracts will be screened for relevance by the reviewer team. The first 100 references for each search (or the search as a whole if the search results are merged) will be screened by all reviewers, then checked for consistency of inclusion decisions in order to align interpretation of the inclusion criteria. If agreement is low then this process will be repeated until agreement is high. The remaining titles and abstracts will each be screened by a single reviewer (within a team of two to four reviewers). All included references will be checked for inclusion by a second reviewer.

Full texts will only be obtained and consulted where insufficient information is available from the abstract to either assess eligibility, or extract data (consistent with the NIHR-NSC Evidence Map Process Document). In cases where there is uncertainty about inclusion, a second reviewer will be consulted or the UK NSC Evidence Team asked for advice.

Data Extraction

Data will be extracted from abstracts where possible. Full texts will only be checked where necessary to clarify unclear information from the abstract (consistent with the NIHR-NSC Evidence Map Process Document).

Data will be extracted by one reviewer and numerical data checked by a second reviewer.

Data extraction will focus on the following essential information for each study (as in Appendix 2 of the UK NSC Evidence Map template, and with reference to the PICOS for each question):

- Study type
- Objectives of the study
- Components of the study (e.g. PICO)
- Outcomes reported and brief results on these outcomes
- Conclusions of the study.

Depending on the number of studies, data will either be extracted directly into the UK NSC Evidence Map template Appendix 2 (structured summary per study), or be extracted initially into an Excel table for ease of extraction and to ensure consistency across studies, then into a word table for presentation in the appendices. The table columns will relate to the data extraction items listed above.

Quality assessment

No formal quality assessment will be conducted (consistent with the NIHR-NSC Evidence Map Process Document). Any obvious quality issues evident from the data available in the abstracts will be highlighted through the narrative review of the studies.

Reporting

The evidence map will be constructed in accordance with the UK NSC Evidence Map template. This will include:

- Summary section and brief recommendations regarding further work
- Background and objectives
- Aims and research questions
- Search methods and search results with PRISMA flow charts
- Summary of findings per question
- Conclusions
- Recommendations regarding further work
- Appendix 1 with details of search strategies and inclusion criteria
- Appendix 2 with structured summary of each included study, or a summary table if the number of studies is large
- References.

Outputs

The main output will be a report for the UK NSC as described above. We are happy to discuss further publication and dissemination activities with the UK NSC.

Project team

The project team will include:

- Project lead: Sue Harnan
- Systematic reviewers: Sue Harnan, Jo Leaviss. Beauty Igein, Yashwini Chandrawat
- Information specialist: Mark Clowes
- Statistical advice if required (for study interpretation): Sarah Ren.

The three systematic reviewers will undertake regular meetings and checks to ensure consistency of understanding and processes.

Timelines

Timelines for the evidence map are provided in the table below. There is some uncertainty regarding the timelines, since the evidence maps are likely to be large and may involve significant numbers of primary studies if there are no published systematic reviews for aspects of the questions, e.g., systematic reviews are found for HCM but not for DCM. The SENSS team will endeavour to keep to the timelines outlined, but should the number of studies identified put the timelines at risk, the SENSS team will discuss this with the NSC. The SENSS team note that the Adult Reference Group on 11th October 2025 would require papers by 6th October 2025.

Table 6: Timelines for evidence map for Inherited Cardiac Conditions

Task	**Timepoint**	**Date**
Initial meeting	**Start**	**28 April 2025**
Additional start-up meeting to discuss search strategy	Week 2	8 May 2025
Draft search strategy shared with NSC	Week 3	12 May 2025
Protocol to UK NSC Evidence Team for feedback	**Week 5**	**28 May 2025**
Search strategies and protocol agreed with UK NSC Evidence Team*	Middle of Week 6	3 June 2025

Phase 1 – Q1-4 (Systematic reviews (Q1-3) and guidelines(Q4))		
Literature searches	End of Week 6	6 June 2025
Sifting titles/abstracts and selection of includable studies	End of Week 8	20 June 2025
Data extraction and production of structured abstracts/table of included studies	End of Week 10	4 July 2025
Phase 2 – Primary studies		
Checkpoint: Meet with NSC to discuss available evidence and next steps	Early Week 11	7-8th July 2025
Search strategy sent to NSC	End of Week 11	11th July 2025
Literature searches	Week 12	18th July
Sifting titles/abstracts and selection of includable studies	End of Week 14	1st August 2025
Data extraction and production of structured abstracts/table of included studies	End of Week 16	15th August 2025
Draft evidence map	**End of Week 18**	**29 August 2025**
Feedback from UK NSC Evidence Team	End of Week 20	12 September 2025
Updated evidence map	**End of Week 22**	**26 September 2025**
Feedback from Reference Group	tbc	tbc
Updated evidence map	tbc	tbc
UK NSC Meeting	tbc	tbc
Updated evidence map	tbc	tbc
* usually the protocol and search strategy would be delivered concurrently, but due to annual leave the protocol will precede the search strategy		

Acknowledgements & disclaimer

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Appendix

Major Genes for each of the main 5 conditions

Two or three recent studies (expert reviews or primary studies) were consulted for each condition. Major genes were those with highest prevalence in any one condition. Sometimes this data was missing, and it may be necessary to make decisions about studies on these genes once screening has taken place.

Cardiomyopathy

Condition	Causative genes
Hypertrophic Cardiomyopathy (16, 17)	**Major genes**

	MYBPC3 (40%–50%) MYH7 (35%–40%) TNNT2 (7%–15%) TNNI3 (5%) TPM1 (3%) MYL2 (1%-2%) MYL3 (1%) ACTC1 (1%) **Other genes** TNNC1 ACTN2 ALPK3 FHOD3 CSRP3 TRIM63 FLNC FHL1 PLN JPH2
Dilated Cardiomyopathy (18, 19)	**Major genes** TTN (10-25%) LMNA (2-6%) FLNC (2%) TNNT2 (1-6%) MYH7 (1-5%) DSP (1-3%) BAG3 (1-2%) DES (1-2%) RBM20 (1-2%) SCNA5 (1-2%) **Other genes** TNNC1 (<1%) PLN (<1%) TTR VCL ACTC1 TPM1 NEXN
Arrhythmogenic Cardiomyopathy(20-22)	**Major genes** PKP2 (80%)

	Other genes, unclear if any are also major (exclude and label) DSP DSC2 DES DSG2 JUP TMEM43 PLN PLN

Channelopathy

Condition	**Causative genes**
Brugada syndrome(23, 24)	**Major genes** SCN5A (20-30%) SCN10A (5-17%) **Other genes** Sodium channel current: HEY2 PKP2 GPD1-L RANGRF SLMAP SCN1B SCN2B SCN3B SCN4A KCNE3 Calcium channel current: ACNA1C CACNB2B CACNA2D1 TRPM4 Potassium channel current: CNE3 KCNJ8 KCND3 KCNE5 ABCC9

	HCN4 SCN1B
Long QT syndrome(25) ● LQT1-16 ● JLNS1 ● JLNS2	**Major genes** KCNQ1 (40-55%) KCNH2 (30-45%) SCN5A (5-10%) **Other genes** ANK2 KCNE1 KCNE2 KCNJ2 CACNA1C CAV3 SCN4B AKAP9 SNTA1 KCNJ5 CALM1-3