Evidence map for tools that assist with lipid management and identification of Familial Hypercholesterolaemia (FH)

Carried out on behalf of the Eastern AHSN (Academic Health Science Network)

by Solutions for Public Health

August 2022

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Background and methods

Eastern AHSN (Academic Health Science Network) commissioned this high-level evidence map to identify the volume and type of published evidence available about the effectiveness of tools that assist in lipid management and familial hypercholesterolaemia (FH) identification. A formal quality appraisal of the evidence was not conducted. Searches for UK studies published since 1st January 2012 were conducted on 7th June 2022 on the electronic databases Cochrane Library, Embase, Medline and TRIP database.

Results

The volume of evidence identified was low and no controlled studies comparing different tools or strategies were identified.

A systematic review by Silva et al (2021), searched for studies assessing the effectiveness of interventions to systematically identify FH in primary care. Two of the three studies included in this systematic review were UK studies. One uncontrolled before and after study (Green et al 2016) used an FH Audit Tool to identify and tag patients with high cholesterol for further assessment. A second uncontrolled before and after study (Weng et al 2018) conducted an automated search of electronic health records to identify patients for further assessment but did not name a specific tool[1].

Other studies included in the evidence map were Qureshi et al (2021a), which contrasted the performance of the FAMCAT algorithms (FAMCAT 1 and FAMCAT 2) against established case-finding criteria to detect FH cases, and a companion study by Jones et al (2022) which considered the cost effectiveness of these approaches. A further study by Ingoe et al (2021) evaluated two search strategies for identifying FH cases, the first based on the FAMCAT algorithm and the second based on the CDRC Composite algorithm.

- The study by Qureshi et al (2021) concluded that the FAMCAT 2 algorithm performed better than the FAMCAT 1 algorithm and other case finding strategies in terms of the accuracy of the tools or strategies to identify FH cases. No equivalent figures were identified for the accuracy of other tools.
- Three studies provided information on the numbers of possible or confirmed FH cases identified through the use of the tools or strategies described (Ingoe et al 2021, Green et al 2016, Qureshi et al 2016).
- One study (Weng et al 2018) provided evidence about clinical outcomes following the use of a strategy to detect patients with high lipid levels. This reported an increase in the tests performed, collection of information on family history, diagnoses of secondary causes of hypercholesterolaemia and prescriptions for statins.

[1] Green et al (2016) and Weng et al (2018) were also separately included in the evidence map, along with a study by Qureshi et al (2016) which describes the same study reported in Weng et al (2018)

- There were no studies reporting results relating to any longer term impact of detecting and managing patients with high lipid levels, such as control of lipid levels or cardiovascular disease events.
- No evidence was identified about the acceptability or uptake of tools by healthcare staff.

Discussion and conclusions

In conclusion, the evidence map identified two types of studies. The first type considered the different algorithms that can be used to identify patients who might be at risk of FH. These encompassed consideration of the accuracy of the different tools (e.g. sensitivity and specificity), which are as important as practical issues in using the tools in healthcare settings and whether they result in higher FH diagnosis and treatment rates. The second type of study considered whether using a tool, or a tool plus patient review, increases the number of FH patients identified and/or improves lipid management, compared to standard practice in the time period before the tool was applied.

The systematic review concluded that there was evidence to support the clinical value of searching primary care electronic records to identify patients with FH. However, they concluded that there was insufficient evidence to determine the most effective method of identifying FH. The individual studies identified for this evidence map provide additional support for the ability of tools and systems to identify patients with FH and the cost effectiveness of this approach but are unlikely to provide sufficient evidence to allow any robust conclusions to be drawn about the best approach to use. The studies identified provided little evidence relating to the effectiveness of tools in improving lipid management.

1 Background

This high-level evidence map was commissioned by Eastern AHSN (Academic Health Science Network) to identify published evidence relating to any tools that assist in lipid management and FH identification. The evidence map addresses the following questions:

1. Which tools have been evaluated for assisting with lipid management and FH identification?
2. What is the volume and type of evidence available for the effectiveness of these tools?
3. What are the overall findings in relation to effectiveness? (at a high-level, without critical appraisal)
4. What are the limitations and gaps in the evidence in terms of type, size and relevance of studies?

The detailed PICOS[2] framework used to guide the searches and the selection of studies of interest is provided as Appendix 1.

2 Methods

Searches for UK studies published since 1st January 2012 were conducted on 7th June 2022 on the electronic databases Cochrane Library, Embase, Medline and TRIP database. The Medline search strategy is provided as Appendix 2.

The search results were initially sifted by an information scientist for potential relevance. Case reports, conference abstracts, trial registrations, preprints, commentary, non-systematic reviews and individual studies clearly conducted outside the UK were excluded at this stage. The titles and abstracts of the remaining studies were reviewed by one reviewer with quality assurance by a second senior reviewer. Studies clearly ineligible were excluded. Full papers for studies that met the inclusion criteria, or where there was any uncertainty, were ordered and reviewed by one reviewer. The decisions made about the final selection of studies for inclusion in the evidence map were quality assured by the second senior reviewer. Any disagreements or uncertainty about exclusion were discussed and a consensus reached. The reference lists of the systematic reviews identified were reviewed to check for additional potential studies.

Studies that met the inclusion criteria are summarised below. A formal quality appraisal of the evidence was not required, given the remit of the evidence map.

[2] Population, Intervention, Comparator, Outcome, Studies

3 Search results

The searches returned 859 unique studies. Seventy-one studies met the criteria for more detailed consideration by the review team. All references were reviewed at abstract level, with full texts ordered where needed to clarify whether a paper met the inclusion criteria.

Reasons for exclusion based on review of the title and abstract included:

- Papers about the management of people with a condition such as diabetes, chronic kidney disease, chronic heart failure or atrial fibrillation, rather than specifically about detecting or managing people with high lipid levels
- Papers about the effectiveness of a service or system rather than a tool
- Studies about the development or testing of an algorithm, rather than about using it in clinical practice
- Studies about interventions to address inappropriate prescribing or adherence to guidance rather than tools to support management
- Studies about the effectiveness of a specific treatment
- A review of guidance relating to lipid monitoring.

Twenty-eight papers met the criteria for further consideration. These papers were reviewed at full text to confirm their eligibility for inclusion. An additional seven studies, identified through their inclusion in systematic reviews, were also considered.

Additional reasons for exclusion after review of the full text included:

- Systematic reviews where none of the included studies met the criteria for this map
- Systematic reviews with a very broad population and no separate reporting of results for the population of interest
- Studies about tools to improve glycaemic control in people with diabetes
- Studies about the different ways of measuring cholesterol
- Database studies, not about the use of a tool in clinical practice
- Studies about strategies to identify cases that do not involve the use of tools in practice
- Non-UK studies.

The seven studies meeting the inclusion criteria are summarised in Table 1 below. A further ten reviews or studies that did not fully meet the inclusion criteria, but may be of interest, are summarised in the narrative after the discussion of the included studies. A glossary of the key tools, interventions and comparators described in the studies is provided as Appendix 3.

Table 1: Studies evaluating tools for assisting with lipid management and FH identification

Abbreviations are listed below the table. See glossary (Appendix 3) for further details of the tools/ interventions described.

Study reference and type	Study aim	Study population, size and context	Tool/ system	Intervention(s)/ comparator(s)	Key results	Author's conclusion
Silva et al (2021) Systematic review (search date not stated in main paper) The systematic review did not identify any RCTs for inclusion. Three non-randomised (uncontrolled before and after) studies met their inclusion criteria	To assess the effectiveness of interventions to systematically identify FH in primary care	Adults (>17 years) 3 included studies: 1. UK (n=290,000) (Green et al 2016) 2. UK (n=118) (Weng et al 2018) 3. Australia (n=96) Primary care See individual studies below for further details of the 2 UK studies	Electronic (on-screen) prompts in electronic health records to identify FH (in the included studies)	**Intervention vs comparator in the 3 included studies** 1. Computer based reminder message and FH nurse advisor case review vs baseline prevalence of FH cases (see Green et al 2016 below for further detail) 2. Computer-based reminder message and postal invitations for assessment vs baseline prevalence of FH cases (see Weng et al 2018 below for further detail) 3. Interpretive comments added to lipid results vs usual care (i.e. no comments) (this Australian study is out of scope for this evidence map)	The systematic review reported: • Improvements in the number of people identified with definitive FH, although these were generally small (<0.2% to ~2%) • Improvements in the number of people with possible FH identified, although this varied between studies (<0.1% to 25%) • Varied impact on cholesterol level; lipid-lowering treatment generally increased; one study reported an increase in referral to specialist services See individual studies below for results of the UK studies	The review authors concluded that there was insufficient evidence to determine the most effective method of identifying FH in non-specialist settings

Study reference and type	Study aim	Study population, size and context	Tool/ system	Intervention(s)/ comparator(s)	Key results	Author's conclusion
Ingoe et al (2021) Evaluation of tool deployment	To proactively identify patients at high risk of FH using an integrated, optimised FH search tool within GP IT systems and establishment of a nurse-led FH genetic testing outreach service	General population registered with UK GP practices 9 UK general practices (n=94,444) Primary care	FH identification algorithms	**Interventions** Searches based on the FAMCAT and CDRC Composite FH algorithms Desktop screening was conducted by a FH nurse specialist to exclude patients with hypercholesterolaemia due to other causes or who were otherwise unsuitable for further testing (e.g. no longer registered)	**Tool development**: • The study initially used a system incorporating the FAMCAT algorithm (search 1). After review of data from 4 practices they concluded this system was classifying large numbers of cases as very high risk of FH who were not eligible for FH genetic testing on review • A modified algorithm was developed - the CDRC Composite (search 2) (see Glossary for further details) **Search 1 (FAMCAT)** • 5 GP practices (n=45,123) • 103 patients already had a diagnosis of FH or were already undergoing testing • 303 identified as very high risk of FH (303/45,123 = 0.67%) • 43 invited for further assessment (after desktop screening) (43/303 = 14%) • 21 attended assessment clinic • 12 eligible for genetic testing • 3 tested positive. Confirmed FH (n=1); variant of unknown significance (n=2) (3/303 = 0.99%)	The study authors concluded that an optimised FH identification pathway, based on NICE CG71 recommendations for systematic searching of electronic health records can be deployed successfully in primary care NB: This study was not designed as a comparison of the FAMCAT and CDRC algorithms

Study reference and type	Study aim	Study population, size and context	Tool/ system	Intervention(s)/ comparator(s)	Key results	Author's conclusion
					Search 2 (CDRC)[3] • 5 GP practices (n=49,321) • 69 patients already had a diagnosis of FH or were already undergoing testing • 269 identified as very high risk of FH • (269/49,321 = 0.55%) • 70 invited for further assessment (after desktop screening) (70/269 = 26%) • 53 attended assessment clinic[4] • 52 eligible for genetic testing • 23 tested positive. Confirmed FH (n=21); variant of unknown significance (n=2) (23/269 = 8.6%)	
Qureshi et al (2021a) Prospective validation study	To compare the performance of the FAMCAT algorithms against established case-finding criteria	General adult population (≥18 years old) with a figure for cholesterol level documented in their electronic	FH identification algorithms	**Interventions** FH detection algorithms: • FAMCAT 1 • FAMCAT 2 • DLCN score ≥6	*Detection rates (DR), sensitivity (Sens) and specificity (Spec)[7] (with 95%CI) for the different algorithms/ case finding strategies (based on the study population who had received genetic testing):*	The study authors concluded that FAMCAT 2 performs better than other case-finding criteria to detect genetically

[3] There is a small discrepancy in the numbers provided in different sections (text, table and flow chart) of the paper (a difference of one patient in the numbers invited for screening, tested and testing positive). The figures from the flow chart and text are reported here

[4] Improved patient information was developed for the second phase (search 2) due to the low attendance for further assessment during the first phase (search 1)

[7] The sensitivity is the proportion of people with the disease who are 'positive' using the algorithm/ case-finding criteria. The specificity is the proportion of people without the disease who are 'negative' using the algorithm/ case-finding criteria

Study reference and type	Study aim	Study population, size and context	Tool/ system	Intervention(s)/ comparator(s)	Key results	Author's conclusion

		health record and no previous FH diagnosis
		
		• 14 UK general practices (n=193,589)
		• Recruited to study: n=336
		• Genetic test conducted: n=283[5]
		• Full clinical data available from electronic health record: n=260
		• Confirmed FH (n=16) or variant of unknown significance (n=10)[6]
		
		Primary care
				• NICE recommended cholesterol threshold
				• Simon-Broome criteria
					• FAMCAT 1
					  • DR: 27.8% (12.5 to 50.9)
					  • Sens: 31.2% (11.0 to 58.7)
					  • Spec: 94.7% (91.1 to 97.1)
					• FAMCAT 2
					  • DR: 45.8% (27.9 to 64.9)
					  • Sens: 68.8% (41.3 to 89.0)
					  • Spec: 94.7% (91.1 to 97.1)
					• DLCN
					  • DR: 35.3% (17.3 to 58.7)
					  • Sens: 37.5% (15.2 to 64.6)
					  • Spec: 95.5% (92.1 to 97.7)
					• NICE
					  • DR: 28.0% (14.3 to 47.6)
					  • Sens: 43.8% (19.8 to 70.1)
					  • Spec: 92.6% (88.6 to 95.6)
					• Simon-Broome
					  • DR: 11.3% (6 to 20)
					  • Sens: 56.3% (29.9 to 80.2)
					  • Spec: 70.9% (64.8 to 76.5)
					
					A further publication (Qureshi et al 2021b[8]) confirmed that all 26 patients with positive genetic test results were recommended for referral and 19 (73%) attended
						confirmed FH with no prior clinical review required for case finding

[5] Participants were invited for genetic testing if identified by the practice administrator to have FAMCAT probability of FH above 0.002
[6] This figure is reported as 9 or 10 in different papers relating to this study
[8] Qureshi et al 2021b described the genetic and lipid profile of patients found to be at increased risk of FH and with positive genetic test results. However, it does not provide any further data on the effectiveness of the FAMCAT algorithm in comparison to usual care or the use of another tool

Study reference and type	Study aim	Study population, size and context	Tool/ system	Intervention(s)/ comparator(s)	Key results	Author's conclusion
					specialist assessment	
Jones et al (2022) Cost effectiveness study	To determine the cost effectiveness of case-finding strategies for screening of electronic health records to identify patients at risk of FH	A hypothetical cohort of 4,500 adult patients with a mean age of 56 years (using the profile of patients who took part in the study by Qureshi et al (2021b) Primary care	FH identification algorithms	**Interventions** FH detection algorithms: • FAMCAT 1 • FAMCAT 2 • DLCN score • Cholesterol screening (as recommended by NICE) • Simon-Broome criteria	• FAMCAT 2 dominated (i.e. was cheaper and more effective) than cholesterol screening, DLCN and FAMCAT 1. This was because FAMCAT 2 required fewer genetic tests to identify one monogenic FH case • FAMCAT 2 did not dominate the Simon-Broome criteria because the Simon-Broome criteria yielded the greatest number of FH cases, but at a higher total cost per patient as more genetic tests were required to find one FH patient Data for this analysis was taken from Qureshi et al (2021b). Healthcare costs were calculated from an NHS England perspective over a 12 week time horizon	The study authors concluded that using electronic criteria to screen patients' electronic health records is a highly cost effective approach for identifying FH index cases within primary care
Green et al (2016) Evaluation with a before and after design	To introduce and evaluate a systematic informatics-based audit of electronic medical records to improve the identification of	Adults with elevated total cholesterol (>7.5 mmol/L) or LDL cholesterol (>4.9 mmol/L); Children (<16 years) with elevated total cholesterol (>6.7	FH identification algorithm	**Interventions** FH audit tool that identified patients diagnosed with FH or possible FH and electronically tagged patients with high cholesterol for further	Diagnosed or possible FH prevalence: • Baseline: 0.13% • After the 2 year 'electronic tagging' phase: 0.22% (99 additional cases) • During the 9 month nurse-led programme: 0.28% (334	The study authors concluded that their interventions increased the detection of FH. They also concluded that opportunistic identification of

Study reference and type	Study aim	Study population, size and context	Tool/ system	Intervention(s)/ comparator(s)	Key results	Author's conclusion
	patients with FH, followed by a nurse-led clinic to screen more intensively for new FH index cases	mmol/L) or LDL cholesterol (>4.0 mmol/L) • 56 eligible GP practices within one CCG (n=~290,000) • 53 practices participated in the audit • 47 practices participated in the nurse-led programme • Baseline population: n=262,030 • 2-year audit population: n=199,346 • Nurse-led programme population: n=281,55 Primary care		assessment A 9 month intensive nurse-led clinic (introduced after a 2-year period of electronic tagging) to screen more intensively for new FH index cases	additional cases) Prevalence of patients 'at risk and unscreened': • Baseline: 0.59% (n=1,553) • After the 2 year 'electronic tagging' phase: 0.58% (n not stated) • During the 9 month nurse-led programme: 0.14% (n=398)	patients with specific computer reminders had little impact on the number of patients identified as at risk and unscreened. However, the two-stage process including the nurse-led programme increased the proportion of patients diagnosed with FH
Qureshi et al (2016) Weng et al	To assess the feasibility of improving the identification of FH	Patients (aged ≥18 years) with elevated cholesterol (>7.5 mmol/L) without an	Automated search of electronic health records	**Interventions** GPs and practice nurses initially received a 1 hour educational session on	**Detection of FH:** • Of the 127 who completed the family history questionnaire, 86 (of 802 (10.7%)) received the	The study authors concluded that the intervention was feasible in GP

Study reference and type	Study aim	Study population, size and context	Tool/ system	Intervention(s)/ comparator(s)	Key results	Author's conclusion
(2018) Feasibility of intervention study NB: These 2 publications are about the same study. Results relating to the detection of FH are taken from Qureshi et al. Clinical outcome data are taken from Weng et al	in primary care	existing confirmed diagnosis of FH • 6 UK GP practices (n=45,033) • Eligible for the study: n=831 • Received the postal invitation: n=802 • Invited opportunistically: n=207 • Recruited and completed family history questionnaire: n=127 (15.3%) Primary care		case identification and assessment of FH Computer reminders to invite for further assessment in opportunistic consultations Universal postal invitation to eligible patients not yet invited opportunistically Identified patients were given a study pack (opportunistically or in the postal invite) with a form for an updated blood test (if required) and a family history questionnaire	postal invitation and 41 (of 207 (19.8%)) were recruited opportunistically • 125 were eligible for further assessment • 32 patients had a possible diagnosis of FH (32/125 = 25.6%) • 14 patients were seen by a GP (others declined or did not reply) • 9 patients were referred to a lipid specialist • 7 patients had a specialist assessment • 2 patients had confirmed FH and 5 had possible FH (7/831 = 0.84%) **Clinical outcomes** N=118[9] unless otherwise stated The results reported are the increase in the proportion of patients receiving the test/ assessment/ intervention stated between the 6 months before and after the extraction of baseline data (absolute difference (95%CI)): • Repeat cholesterol test: +75.4% (66.9 to 82.3) • Prescribed any statins (n=32[10]): +18.8% (8.9 to 35.3)	practices, identified patients for targeted assessment for FH and showed promise for the management of possible FH. They also concluded that the 6 month follow-up period was too short to collect complete outcome data

[9] Patients who consented to further assessment whose medical records could be accessed (seven patients had left the GP practice during the study period)

Study reference and type	Study aim	Study population, size and context	Tool/ system	Intervention(s)/ comparator(s)	Key results	Author's conclusion
					• Prescribed high potency statins (n=32): +9.4% (3.2 to 24.2) • Diagnosed with secondary cause of hypercholesterolaemia: +7.7% (4.1 to 13.9) • Any family history of CHD assessed: +35.6% (27.0 to 44.2) • Complete family history of CHD assessed: +6.8% (3.5 to 12.8) • TSH assessed: +12.7% (6.7 to 18.7) • HbA1c assessed: +10.1% (5.9 to 16.9) • Serum creatine assessed: +8.5% (4.7 to 14.9) • Liver function tests: +6.8% (3.5 to 12.8) • Arcus senilis or xanthelasma diagnosed: +6.0% (2.9 to 11.7) The increase from pre-intervention to post-intervention was statistically significant for all the above outcomes ($p<0.05$) For the 32 patients diagnosed with possible FH, there was no statistically significant improvement for:	

[10] Patients with a possible diagnosis of FH

Study reference and type	Study aim	Study population, size and context	Tool/ system	Intervention(s)/ comparator(s)	Key results	Author's conclusion
					• Total cholesterol (mean difference (95%CI) mmol/L): -0.16 (-0.78 to 0.46) • LDL cholesterol: (mean difference (95%CI) mmol/L): -0.12 (95%CI -0.81 to 0.57) • Given dietary or weight management advice: 3.1% (0.01 to 15.7) • Given smoking cessation advice: 0% (0 to 10.7)	

Abbreviations:
CDRC: Clinical Digital Resource Collaborative; CHD: Coronary heart disease; CI: Confidence interval; DLCN: Dutch Lipid Clinical Network; DR: Detection rate; FAMCAT: Familial hypercholesterolaemia Case Ascertainment Tool; FH: Familial hypercholesterolaemia; GP: General practitioner; Hb: Haemoglobin; IT: Information technology; L: Litre; LDL: Low density lipoprotein; mmol: Millimoles; NICE: National Institute for Health and Care Excellence; RCT: Randomised controlled trial; Sens: Sensitivity; Spec: Specificity; TC: Total cholesterol; TSH: Thyroid stimulating hormone

4 Discussion and conclusions

The tools used in the included studies were FAMCAT 1, FAMCAT 2, the CDRC Composite tool and the FH Audit Tool. Some of the included studies referred to automated searches of electronic health records without describing a named tool for this process. No studies were identified for the other tools of interest specified in the PICO, namely Ardens lists, UCLP frameworks, Eclipse live or AlinIQ Digital Health Solutions.

The volume of evidence identified was low and no controlled studies comparing different tools or strategies were identified. A systematic review by Silva et al (2021), searched for studies assessing the effectiveness of interventions to systematically identify FH in primary care. This systematic review did not identify any RCTs but did identify three uncontrolled before and after studies, about the use of electronic (on screen) prompts in electronic health records to identify FH. Two of these three studies (Green et al 2016, Weng et al 2018) were set in the UK and were also separately included in this evidence map, along with a study by Qureshi et al (2016) which describes the same study reported in Weng et al (2018). One of these studies (Green et al 2016) used an FH Audit Tool to identify and tag patients with high cholesterol for further assessment. The study published in Qureshi et al (2016) and Weng et al (2018) conducted an automated search of electronic health records to identify patients for further assessment but did not name a specific tool.

A further three, recently published, studies that were not included in the systematic review were also identified and included in this evidence map. These comprised a study by Qureshi et al (2021a), which contrasted the performance of the FAMCAT algorithms (FAMCAT 1 and FAMCAT 2) against established case-finding criteria to detect FH cases, and a companion study by Jones et al (2022) which considered the cost effectiveness of these approaches. The third study by Ingoe et al (2021) evaluated two search strategies for identifying FH cases, the first based on the FAMCAT algorithm and the second based on the CDRC Composite algorithm.

The study by Qureshi et al (2021) concluded that the FAMCAT 2 algorithm performed better than the FAMCAT 1 algorithm and other case finding strategies in terms of the accuracy of the tools or strategies to identify FH cases. No equivalent figures were identified for the accuracy of other tools, although in the study by Ingoe et al (2021) the initial search strategy based on the FAMCAT algorithm was modified due to a concern that the initial search was classifying large numbers of cases as very high risk of FH who were not eligible for FH genetic testing on review.

Three studies provided information on the numbers of possible or confirmed FH cases identified through the use of the tools or strategies described (Ingoe et al 2021, Green et al 2016, Qureshi et al 2016). These numbers partially reflect the ability of the tools or strategies to identify the patients who need further assessment but also reflect subsequent activities taken by practices to review cases, invite patients to assessments and refer patients for

genetic tests. The number of confirmed tests also reflects the proportion of patients who take up the offer of further assessment.

Only one study provided any evidence about clinical outcomes following the use of a strategy to detect patients with high lipid levels. This reported an increase in the tests performed, collection of information on family history, diagnoses of secondary causes of hypercholesterolaemia and prescriptions for statins. No statistically significant improvement in cholesterol levels were observed, but the duration of the study may not have been sufficient for this to be assessed. There were no studies reporting results relating to any longer term impact of detecting and managing patients with high lipid levels, such as control of lipid levels or cardiovascular disease events.

No evidence was identified about the acceptability or uptake of tools by healthcare staff, although GP practices did participate in the included studies.

In conclusion, the evidence map identified two types of studies. The first type considered the different algorithms that can be used to identify patients who might be at risk of FH. These encompassed consideration of the accuracy of the different tools (e.g. sensitivity and specificity), which are as important as practical issues in using the tools in healthcare settings and whether they result in higher FH diagnosis and treatment rates. The second type of study considered whether using a tool, or a tool plus patient review, increases the number of FH patients identified and/or improves lipid management, compared to standard practice in the time period before the tool was applied.

The systematic review concluded that there was evidence to support the clinical value of searching primary care electronic records to identify patients with FH. However, they concluded that there was insufficient evidence to determine the most effective method of identifying FH. The individual studies identified for this evidence map provide additional support for the ability of tools and systems to identify patients with FH and the cost effectiveness of this approach but are unlikely to provide sufficient evidence to allow any robust conclusions to be drawn about the best approach to use. The studies identified provided little evidence relating to the effectiveness of tools in improving lipid management.

5 Additional studies identified by the searches

During the production of the evidence map several studies were identified that did not meet the criteria for inclusion in the map but are briefly described here in case they are of interest. These related to adherence to treatment, the management of patients with a diagnosed condition such as diabetes or who were receiving antipsychotic medications for chronic mental health problems, case finding for cardiovascular risk and medication reviews. The context of these studies was more about tools to support patient or healthcare professionals' compliance with advice or guidance (not specifically lipid management guidance) rather than tools for clinicians to aid the identification or management of patients with high lipid levels. It should be noted that our searches were not intended to identify studies of this nature so

these studies do not necessarily represent the best available evidence in this area. However, they provide an additional perspective on ways to improve lipid management.

Adherence to treatment:

- A systematic review by van Driel et al (2016) and a meta-analysis by Deichmann et al (2016) both assessed the effectiveness of interventions aimed at improving adherence to lipid lowering drugs. These studies covered a range of different types of interventions with some related to automated systems or decision support systems. Only one UK study of potential relevance to tools to assist lipid management was included in these reviews. This UK RCT by Wald et al (2014) (cited in van Driel et al 2016) compared text messages sent using an automated computer programme to no text reminders in 303 patients who had been prescribed blood pressure and/ or lipid-lowering medication. They reported an improvement in adherence to medication with text reminders.

Management of patients with other conditions that may result in increased lipid levels:

- A systematic review by Melamed et al (2019) considered interventions to improve metabolic risk screening in patients taking antipsychotic medications. The aim of the included studies was to assess whether patients received physical health screening, such as blood pressure, body mass index, blood glucose and lipids. Two of the UK studies included in this review described the use of an audit tool to identify whether patients had received screening; an audit tool for NHS Trusts or other healthcare organisations developed by the Prescribing Observatory for Mental Health (described in Barnes et al 2015) and a 5 Boroughs Partnership Comprehensive Physical Health Assessment tool (described in Latoo et al 2015). However, these tools were about identifying whether patients at risk of physical health issues had received screening to monitor their physical health rather than about identifying or managing patients with high lipid levels.
- Willis et al (2020) conducted an RCT set in UK primary care. This assessed the effectiveness of an electronic prompt to identify patients with type 2 diabetes with a cardiovascular risk factor above a target range and a treatment algorithm to manage patients. The primary outcome was about adherence to best-practice cardiovascular risk factor targets around blood pressure and cholesterol level.

Case finding for cardiovascular risk:

- A systematic review by Sparrow et al (2019) searched for studies on interventions aimed at increasing statin-prescribing rates in adults without a history of cardiovascular disease. Only one UK study was included in this review (Hemming et al 2016). This study used software to search for and identify untreated high-risk patients from electronic patient records. The Framingham risk equation was used to estimate 10-year cardiovascular disease risk with missing blood pressure or cholesterol values replaced with averages for similar patients. The primary outcome of this study was the proportion of high risk patients who were prescribed antihypertensives or statins, which increased with the intervention compared to the previous time period.

Medication reviews:

- A systematic review by Ahumada-Canale et al (2019) appraised economic evaluations of pharmacist-led medication reviews in patients with cardiovascular risk factors, specifically hypertension, type 2 diabetes or dyslipidaemia. This review concluded that there was evidence supporting the cost-effectiveness of pharmacist-led medication review.

6 References

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7 Appendix 1 – PICOS framework

P – Population and Indication	Patients in the UK who need lipid management or screening for FH identification. i.e. people with high lipid levels (e.g. high cholesterol)
I – Intervention	Tools or systems used in healthcare settings in the UK that aim to assist with lipid management and/or FH identification. Excluding general cardiovascular prevention tools that do not include lipid measurements, such as online heart health tools that do not include blood tests. [Included tools may, for example, be questionnaires, checklists, templates, reminders, prompts, electronic health record integrated systems, etc. Examples are the CDRC precision lipid management tool, Ardens lists, UCLP frameworks, Eclipse Live, FAMCAT and FAMCAT 2, AlinIQ Digital Health Solutions, Tools specific to System One, EMIS]
C – Comparator(s)	• No tool / usual practice • A different tool used in healthcare settings in UK that aims to assist with lipid management and/or FH identification. If no comparator study identified, studies without a comparator will be considered.
O – Outcomes	*Key outcomes of effectiveness:* • Rates of suspected FH identification and referral to secondary care • Control of lipid levels • Lipid-related prescribing rates • Cardiovascular disease events e.g. myocardial infarctions, strokes, transient ischaemic attacks, deaths • Acceptability of the tool to healthcare staff • Uptake of the tool by healthcare staff • Cost-effectiveness
Inclusion criteria	
Study design	Peer reviewed published studies listed on Medline, Embase or Cochrane databases. In order of priority: • Systematic reviews • Randomised controlled trials • Controlled trials • Comparative studies Qualitative studies would be in scope for acceptability outcome. If no higher-level evidence is found, inclusion of non-comparative studies will be considered. The highest level evidence for each included tool was prioritised.
Language	English
Patients	UK
Age	All ages
Date limits	2012-2022
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, prepublication prints, grey literature and guidelines
Study design	Individual patient case reports, resource utilisation studies

8 Appendix 2 – Medline search strategy

1	exp Dyslipidemias/
2	lipids/ or exp lipoproteins, hdl/ or lipoproteins, idl/ or exp lipoproteins, ldl/ or exp lipoproteins, vldl/
3	(dyslipid* or hyperlipid* or hypercholesterol* or hyperlipoprotein*).ti,ab,kf.
4	(lipid* or cholesterol or hdl or ldl or triglyceride? or lipoprotein? or apolipoprotein?).ti,ab,kf.
5	exp Hypolipidemic Agents/
6	((lipid lowering or hypolipid?emic or antilip* or anti-lip* or anticholester?emic or anti-cholester?emic) adj2 (therap* or agent? or drug?)).ti,ab,kf.
7	(statin? or hist or pcsk9i or ezetimibe).ti,ab,kf.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	(reminder? or prompt* or tool* or checklist? or template? or alert* or framework? or pathway? or incentiv* or decision support).ti,ab,kf.
10	(opportunistic* adj2 (monitor* or management or check* or screen* or track* or identif*)).ti,ab,kf.
11	(lipid? adj2 (monitor* or management or check* or screen* or track* or identif*)).ti,ab,kf.
12	((fh or famil* hypercholesterol* or hyperlipoprotein?emia?) adj5 (monitor* or management or check* or screen* or track* or identif*)).ti,ab,kf.
13	9 or 10 or 11 or 12
14	exp Medical Records Systems, Computerized/
15	(((electronic or computer* or patient or medical or health) adj3 record?) or epr or ehr or emr).ti,ab,kf.
16	(emis or s1 or "system 1" or "system one").ti,ab,kf.
17	14 or 15 or 16
18	13 and 17
19	Decision Support Systems, Clinical/
20	Reminder Systems/
21	Alert Fatigue, Health Personnel/
22	((clinical or computer* or automat* or electronic or online or web* or system?) adj2 (reminder? or prompt* or tool* or checklist? or template? or alert* or framework? or pathway? or incentiv* or decision support)).ti,ab,kf.
23	(famcat* or familial hypercholesterol* ascertainment tool or uclp* or innovation agency or cdrc or clinical digital resource collaborative or arden or eclipse live or eclipselive or aliniq or digital health solution*).ti,ab,kf.
24	18 or 19 or 20 or 21 or 22 or 23
25	8 and 24
26	exp United Kingdom/
27	(national health service* or nhs*).ti,ab,in.
28	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.
29	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.
30	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.
31	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.
32	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or

	"londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.
33	(bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachuse tts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.
34	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp oceania/) not (exp great britain/ or europe/)
36	34 not 35
37	25 and 36
38	limit 37 to (english language and yr="2012 -Current")
39	limit 25 to ((meta analysis or "systematic review") or "reviews (maximizes specificity)")
40	limit 39 to (english language and yr="2012 -Current")
41	38 or 40

9 Appendix 3 – Glossary

The Simon-Broome criteria
The Simon-Broome criteria variables are total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C), family history of premature chronic heart disease (CHD) and/ or hypercholesterolaemia and clinical signs of FH (Qureshi et al 2021a).

The Dutch Lipid Clinical Network (DLCN) criteria
A points-based system with points awarded on the basis of symptoms, cholesterol levels, family history of illness and/ or DNA test. The DLCN criteria variables are LDL-C, clinical history of coronary heart, cerebrovascular and peripheral vascular disease, family history, and clinical signs of FH (Jones et al 2022, Qureshi et al 2021a).

NICE screening threshold criteria
The NICE recommended criteria are individuals who are younger than 30 years old with a total cholesterol concentration greater than 7.5 mmol/L or 30 years or older with a total cholesterol concentration of 9.0 mmol/L (Jones et al 2022).

The FAMCAT tool
The FAMCAT tool is a case-finding tool to identify patients eligible for further assessment, specialist referral and genetic testing for possible FH. It searches the available data in patients' electronic health records to identify those with highest likelihood of FH (Qureshi et al 2021a).

The original FAMCAT 1 algorithm includes nine diagnostic indicators, stratified by gender. These are TC or LDL-C, age during cholesterol measurement, triglycerides, lipid-lowering drug usage, family history of FH, family history of CHD, family history of raised cholesterol, diabetes and chronic kidney disease. A later version of the algorithm (FAMCAT 2) added a tenth indicator, coded personal history of premature CHD. In FAMCAT-2 the regression equations with TC, LDL-cholesterol, triglycerides and age were re-estimated as continuous variables to improve its calibration (Qureshi et al 2021a).

Clinical Digital Resource Collaborative (CDRC) Composite tool
In the study by Ingoe et al (2021) they initially developed a search system that incorporated the FAMCAT algorithm, based on the Simon-Broome diagnostic criteria. This identified clinical and laboratory data associated with FH from primary care records including highest TC, LDL-C, triglyceride levels, previous history of CHD, family history of myocardial infarction, previous FH diagnosis and elevated cholesterol levels. After initial use of this system they concluded that it was classifying very large numbers of cases as 'very high risk of FH' that were not eligible for FH genetic testing according to the local criteria based on DLCN score.

A modified algorithm was developed in collaboration with the CDRC, known as the CDRC Composite. This search system was based on a combination of:

- NICE recommended TC thresholds for FH identification on primary care searches (CG71), modified to include corresponding raised LDL and non-HDL cholesterol thresholds and with an adjustment based on fasting triglyceride levels to help exclude patients with other causes of hypercholesteremia
- A virtual, estimated DLCN score based on information available in the primary care electronic record.

The FH Audit Tool

The FH Audit Tool was based on NICE recommendations (CG71) and the Simon-Broome criteria. A Read Code for patients with possible FH was sought from the NHS and added. The FH Audit Tool initially prompted healthcare staff to consider a diagnosis of definite or possible FH. However, a Read Code for probable FH was also requested and added and the FH Audit Tool was enhanced to include the DLCN score (Green et al 2016).

The nurse-led programme that formed the second part of the study by Green et al used the Simon-Broome criteria and the DLCN criteria to classify definite, probable and possible FH. The nurse reviewed the list of 'at risk and unscreened' patients to identify any missing clinical or non-clinical parameters in patient records that prevented a calculation of DLCN score.