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The potential role of an expert computer system to augment the opportunistic detection of individuals with familial hypercholesterolaemia from a community laboratory ☆,☆☆,★

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ABSTRACT

Background: Familial hypercholesterolaemia (FH) is the most common monogenic cause of premature atherosclerotic cardiovascular disease (CVD). However, most individuals with FH remain undiagnosed. We sought to determine if an expert system (ES) at a community laboratory could identify information relevant for estimating an individual's likelihood of FH using the Dutch Lipid Clinic Network criteria (DLCNC).
Methods: An ES (RippleDown®) retrospectively analysed laboratory results and clinical details on the current and previous lipid requests from a community laboratory in Western Australia, over 12 months.
Results: 84,823 individuals had ≥1 LDL-cholesterol request with data available on 84,083 (99.1%). Clinical details were provided on 71,282 (84.8%) individuals' current or previous requests. History relevant to the DLCNC was present in 883 (1.1%) individuals, with premature CVD and non-cardiac vascular disease present in 177 and 64 individuals, respectively. Statin therapy was reported in 5118 individuals; 112 individuals with a current LDL-cholesterol of <6.5 mmol/L had a previous LDL-cholesterol of ≥6.5 mmol/L.
Conclusions: The ES was able to identify information that increased the likelihood of FH in 5471 cases. The ability to detect individuals with premature CVD and to classify them based on their highest LDL-cholesterol may augment FH detection, although further investigation is required to confirm this.

1. Introduction

Familial hypercholesterolaemia (FH) is a co-dominantly inherited condition characterised by elevated low density lipoprotein cholesterol (LDL)-cholesterol, tendon xanthomata and premature atherosclerotic cardiovascular disease (CVD). However, despite FH fulfilling the World Health Organization's disease screening criteria, the majority of individuals with FH are currently undiagnosed [1–4]. Community laboratories performing large volumes of lipid profiles are well placed to perform opportunistic FH screening [5]. This may be achieved by highlighting to the requesting doctor that individuals found to have very elevated LDL-cholesterol concentrations are at risk of FH [6,7]. It has been previously shown that general practitioners prefer interpretative comments to highlight when an individual is at risk of FH [8], and value advice outside the remit of pathology when advising on further patient management [9–11].

The considerable overlap in the distributions of LDL-cholesterol concentration between individuals with FH and the general population adversely affects the sensitivity and specificity of any LDL-cholesterol based screening approach [12]. Furthermore, a significant number of individuals with undiagnosed FH are already on lipid lowering medications, with their measured LDL-cholesterol lower than their off-treatment genetically determined level [13,14].

The Dutch Lipid Clinic Network Criteria (DLCNC) incorporates clinical information such as a personal or family history of heart disease as well as LDL-cholesterol concentration to determine the likelihood of

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FH [15]. A family history of myocardial infarction has been shown to be an important predictor of FH which is independent of LDL-cholesterol [16]. Therefore, screening protocols incorporating clinical details as well as LDL-cholesterol concentration may improve FH detection rates.

Interpretative commenting occurs in the majority of laboratories in the United Kingdom, often with computer assistance for lipid profiles [17]. However, the computer systems are generally not expert systems (ES) with most laboratories relying upon conventional rule-based technologies, which tend to generically classify data. More sophisticated ES have the potential to more specifically classify patients' laboratory data. An ES approach to interpretative commenting tends to be more 'patient-specific', rather than the more limited 'results-specific' [18] approach of many conventional computer systems. The ES may achieve this by identifying and integrating additional information including current and/or previous laboratory results along with clinical details provided on request forms.

We sought to determine if an ES based at a community laboratory could identify additional laboratory or clinical information relevant for estimating an individual's likelihood of FH using the DLCNC.

2. Methods

A retrospective analysis was performed on a cohort of patients who had lipid profiles requested from St John of God Pathology, a private community laboratory in Western Australia, between the 1st of May 2010 and the 30th of April 2011. All serum LDL-cholesterol requests were included, with no exclusion criteria. If an individual had more than one LDL-cholesterol performed during this period, the most recent result was selected as the 'current' LDL-cholesterol.

The ES, RippleDown® (Pacific Knowledge Systems, Sydney, Australia), was used to retrospectively search a database consisting of laboratory results and the clinical details provided on the lipid request forms of the current as well as previous requests for each individual from the 1st of January 2008 until the 30th of April 2011. St John of God Pathology routinely employs this ES to assist appending interpretative comments to lipid profiles. RippleDown® uses ripple-down rules technology to acquire and use knowledge [19] to provide an interpretation of the results incorporating analyte concentrations and clinical information provided by the requesting medical practitioner. The clinical notes from the request are transcribed into the laboratory information system manually during the registration process.

The ES was able to identify clinical details relevant to the DLCNC by searching for keywords or phrases in the clinical history provided by the requesting medical practitioner. The chemical pathologist created lists of key words, phrases and rule-based and contextual modifiers, in the ES for the conditions of interest (e.g. CVD, diabetes mellitus and statin therapy) by manually reviewing the clinical histories in free text form from a cohort of previous cases. Large numbers of textual case histories are reviewed to create lists and modifiers specific to the condition of interest e.g. the list for CVD consists of 158 words or phrases.

The ES then exported the list of individuals with CVD to Microsoft Excel 2003 for further manual analysis. The DLCNC definition of premature ischaemic heart disease (IHD) was used; males <55 and females <60 years of age [15]. Other non-cardiac vascular disease included all other atherosclerotic vascular disease defined as premature also using the DLCNC age criteria. We also sought information on family history relevant to the DLCNC, specifically, a lipid disorder, CVD and non-cardiac vascular disease using the same methods.

To determine the ES ability to identify individuals who were likely to have LDL-cholesterol concentrations higher than their currently measured LDL-cholesterol due to lipid lowering therapy, the clinical details were searched for phrases matching the list defining HMG-CoA reductase inhibitors (statins). Individuals were categorised by LDL-cholesterol concentration as described in the DLCNC using the result obtained during the selection period. The ES was then used to search for individuals on statin therapy, who would have moved to another DLCNC category if the statin therapy resulted in an absolute LDL-cholesterol reduction of 1.0 or 1.7 mmol/L, given that the dose and specific statin were often unknown. The 1.0 mmol/L LDL-cholesterol reduction was a conservative population estimate based on an average of the proportional reductions in LDL-cholesterol seen in the West of Scotland Coronary Prevention Study [20] representing primary prevention, and the Heart Protection Study [21] representing secondary prevention, which were applied to the mean LDL-cholesterol of 3.1 mmol/L from this population [5]. The second absolute reduction used was 1.7 mmol/L, derived from the 4S study [22].

Total cholesterol, triglyceride and high density lipoprotein (HDL)-cholesterol analyses were performed with enzymatic, colorimetric assays using Siemens reagents on a Siemens Dimension RXL chemistry analyser (Siemens Healthcare Diagnostics, Tarrytown NY, USA). LDL-cholesterol was calculated according to the Friedewald equation [23]. Data were described as the absolute number and percentage.

3. Results

There were 99,467 LDL-cholesterol requests on 84,823 individuals during the 12 month selection period. The demographics of this cohort have been described previously [5]. The average age was 56 ± 15 years; 51.3% were females. A potential secondary cause of elevated LDL-cholesterol (hypothyroidism, mixed hyperlipidaemia, cholestasis or nephrotic syndrome) was present in 8.3% of cases [5]. Data were available for analysis by the ES on 84,083 (99.1%) individuals. A history was provided on the lipid request from the selection period in 55,463 (66.0%) individuals, and on an additional 15,819 individuals on review of their previous requests. Thus, a total of 71,282 (84.8%) individuals had some clinical details provided between the 1st of January 2008 and the 30th of April 2011. A clinical history potentially useful for calculating the DLCNC was present in 883 (1.1%) individuals, of whom 709 had an LDL-cholesterol <4.0 mmol/L (Table 1). There were 444 children aged <18 included in this dataset; 43 had an LDL-cholesterol of ≥3.5 mmol/L, 18 an LDL-cholesterol of ≥4.0 mmol/L and two had an LDL-cholesterol of ≥ 5.0 mmol/L.

A history of IHD was found in 1425 individuals; 1073 males and 352 females. Premature IHD was present in 125 males and 52 females, with 115 (92%) and 47 (90%), respectively, having a current LDL-cholesterol of <4.0 mmol/L. A history of non-cardiac vascular disease was demonstrated in 404 individuals (229 males and 175 females). Premature non-cardiac disease was present in 24 males and 40 females, 18 (75%) and 35 (88%) of whom had a current LDL-cholesterol of <4.0 mmol/L, respectively. In total, the ES identified 241 individuals with premature vascular disease, of whom 215 (89%) had an LDL-cholesterol of <4.0 mmol/L.

Statin therapy was identified in 5118 individuals. Assuming that statin therapy resulted in a 1.0 mmol/L reduction in LDL-cholesterol, the pre-statin DLCNC LDL-cholesterol category would have increased in 1257 individuals (Table 2). However, if statin therapy resulted in a 1.7 mmol/L reduction in LDL-cholesterol, the pre-statin DLCNC LDL-cholesterol category would have increased in 2012 individuals. Reviewing previous LDL-cholesterol concentrations from the 1st of January 2008 for individuals with a selection period LDL-cholesterol of <6.5 mmol/L, 112 individuals with a maximum LDL-cholesterol of ≥6.5 mmol/L were identified.

The ES was able to identify a condition that increases the likelihood of FH e.g. history of premature vascular disease, previously higher LDL-cholesterol, or current statin therapy in 5471 cases.

4. Discussion

This is the first study to show that an ES may have a role in the detection of FH. The ES was able to identify a significant number of individuals at a higher risk of FH than predicted from their current LDL-cholesterol; 89% of the individuals identified with premature vascular disease had an LDL-cholesterol of <4.0 mmol/L. The ability to