Evaluation of the performance of Dutch Lipid Clinic Network score in an Italian FH population: The LIPIGEN study

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Background and aims: Familial hypercholesterolaemia (FH) is an inherited disorder characterized by high levels of blood cholesterol from birth and premature coronary heart disease. Thus, the identification of FH patients is crucial to prevent or delay the onset of cardiovascular events, and the availability of a tool helping with the diagnosis in the setting of general medicine is essential to improve FH patient identification.

Methods: This study evaluated the performance of the Dutch Lipid Clinic Network (DLCN) score in FH patients enrolled in the LIPIGEN study, an Italian integrated network aimed at improving the identification of patients with genetic dyslipidaemias, including FH.

Results: The DLCN score was applied on a sample of 1377 adults (mean age 42.9 ± 14.2 years) with genetic dyslipidaemia, including FH. This study evaluated the performance of the Dutch Lipid Clinic Network (DLCN) score in FH patients enrolled in the LIPIGEN study, an Italian integrated network aimed at improving the identification of patients with genetic dyslipidaemias, including FH.

Conclusions: Although the DLCN score is a useful tool for physicians in the diagnosis of FH, it may be limited by the complexity to retrieve all the essential information, suggesting a crucial role of the clinical judgement in the identification of FH subjects.

1. Introduction

Familial hypercholesterolaemia (FH) is a monogenic disorder characterized by increased LDL cholesterol (LDL-C) levels from birth and increased risk of early coronary heart disease (CHD) [1]. The early identification of FH subjects is therefore essential to reduce the burden of cholesterol and prevent or at least delay the occurrence of cardiovascular events. The early initiation of lipid-lowering therapies in these subjects will reduce morbidity and mortality for premature CHD, and will also have an economical return. Unfortunately, FH is an underdiagnosed condition and, as a consequence, commonly undertreated until the occurrence of the first cardiovascular event [1].

The diagnosis of FH may be achieved either by targeted screening, aimed at identifying FH cases among hypercholesterolemic subjects with personal or family history of premature CHD or hypercholesterolemia, or, in alternative, by cascade screening (including genetic testing), aimed at identifying first- and second-degree family members of a subject diagnosed with FH. The targeted screening approach is cost-effective, but entails the risk of missing 30–60% of affected patients; the cascade screening approach guarantees a higher detection rate, although a considerable risk of missing affected individuals is still present. These observations have prompted some of the recent guidelines to recommend a strategy of universal lipid screening of
2. Materials and methods

TransPortDisordersItalianGEneticNetwork)network[6],addressingthequestion
score in patients with genetic diagnosis of FH enrolled in the LIPIGEN (LIpid
pact on the diagnosis rate. (e.g., age groups, mild phenotypes) and how much missing information may im-
diagnostic scores may efficiently apply to different countries or subpopulations
soon aspossible. However, it is not clear whether the performance of the available
FH patient identification and to start the appropriate pharmacological therapy as
specialized in the management of lipid metabolism diseases) is crucial to improve
tendon xanthomas [5] (Supplementary table 1). The availability of a tool that
based cascade screening may be preferable.

FH is clinically diagnosed on the basis of clinical characteristics and laboratory
parameters; criteria to identify FH subjects include the MEDPED (Make Early
Diagnosis to Prevent Early Deaths) score [3] and the Simon Broome criteria [4],
based on the LDL-C values and the family clinical history, and the Dutch Lipid
Clinic Network (DLCN) score, which also includes physical characteristics such as
tendon xanthomas [5] (Supplementary table 1). The availability of a tool that
 guides diagnosis in the setting of general medicine (or for health professionals not
specialized in the management of lipid metabolism diseases) is crucial to improve
FH patient identification and to start the appropriate pharmacological therapy as
soon as possible. However, it is not clear whether the performance of the available
diagnostic scores may efficiently apply to different countries or subpopulations
(e.g., age groups, mild phenotypes) and how much missing information may im-
 pact on the diagnosis rate.

In the present study, we aimed at evaluating the performance of the DLCN score in patients with genetic diagnosis of FH enrolled in the LIPIGEN (Lipid
TransPort Disorders Italian GEnetic Network) network [6], addressing the question
whether missing information may affect the identification of FH subjects.

2. Materials and methods

The LIPIGEN is an integrated network aimed at improving the identification of
patients with genetic dyslipidaemics, including FH, in Italy [6]. The LIPIGEN-FH
study, an observational, multicenter, retrospective and prospective study started in
2012 [6], collects data on FH patients followed by lipid clinics all over Italy as part of
the normal clinical practice. Available information includes demographic and clinical
data (age, gender, personal and family history of hypercholesterolemia or premature
cardiovascular or cerebrovascular events, data from physical examination), pharma-
ocological therapies and biochemical data. After the visit by a specialized physician,
patients with clinical suspect of primary hypercholesterolemia are referred for genetic
testing of the appropriate candidate genes. The decision to address a subject to the
 genetic testing may be based either on the application of the clinical score or on the
decision of the lipid specialist, supported by anomalies in her/his lipid profile or by
the presence of a familial history of premature cardiovascular disease (even in the
absence of individual increased LDL-C levels, as for example in children). The iden-
tification of a causative mutation in a patient is then followed by the cascade
screening of family members to identify new cases of FH, who undergo genetic testing
if FH is clinically suspected.

To test the performance of the DLCN score, the analysis was carried out in all
mutation-positive patients (as established by genetic test performed in different
laboratories), aged 18 years or more, who underwent clinical evaluation and had
available information on LDL-C levels. The population used for this analysis
included both FH index cases and the FH relatives identified by cascade screening.
The DLCN score performance was evaluated also as a function of the number and
type of missing parameters. In the absence of available pre-therapy LDL-C values
(as a part of the DLCN score), they were estimated from the actual levels adjusting
by correction factors which consider the type and dose of current lipid-lowering
therapy [7]. As sensitivity analysis, the performance of the DLCN score was evalu-
ated also in a smaller sample of patients (N = 343) with clinical suspect of FH
who have been genetic tested by a centralized laboratory searching for a broad
range of possible mutations of several candidates genes. For exploratory purposes,
the DLCN score was applied also on patients aged less than 18 years, in whom the
algorithm has not been validated.

Continuous variables are presented as mean ± SD, whereas categorical vari-
ables are presented as cases (n) and percentage rate (%). To define the sensitivity of
the DLCN score, the Bayes’ theorem was applied on the subsample.

3. Results

A total of 1377 mutation-positive adult patients has been included in the
present analysis. Supplementary table 2 provides the general characteristics of
these subjects. The number of men and women in the sample was comparable
(48.6% vs 51.3% respectively), mean BMI value was 25.5 (± 4.4) Kg/m²,
meanglucoselevelwas90.1(±18.2)mg/dL.MeanLDL-C, HDL-C, TG levels
were 285.5 (±95.0) mg/dL, 52.8 (±14.3) mg/dL, and 121.4 (±67.4) mg/
dL, respectively. Among the subjects included in the analysis, 44.2% were not
on statin therapy.

When applied to this population with positive genetic test, the DLCN score
classified as probable FH (score 6–8) 28.5% and as definite FH (score ≥ 9)
37.9% of subjects; 66.4% had thus a DLCN score ≥ 6 and defined as potential
FH (Fig. 1). Similar results were observed when the DLCN score was applied to
the subgroup who underwent the genetic testing in a centralized laboratory

Fig. 1. DLCN score in the mutation-positive group of the LIPIGEN Study.
The diagnosis was unlikely for 29.2% and definitive for only 7.5% of children. One major limit in the application of the DLCN score could not classify all of them as definite FH. Overall, less than half of subjects were classified as definite FH (37.9%).

As for many FH subjects the pre-treatment LDL-C levels were not available, we evaluated whether the use of estimated pre-treatment LDL-C levels (adjusting by correction factors considering the type and dose of current lipid-lowering therapy) might affect the DLCN score. Patients on statin therapy (representing 44.2% of the whole studied population) were grouped based on the availability of their pre-treatment LDL-C levels [10]. In our study, we found that, in the group with estimated pre-statin LDL-C levels, a higher percentage of subjects had values > 325 mg/dL, which, by conferring the highest score for this category (Supplementary table 1), translated into a higher percentage of subjects categorized as definite FH compared with the group having measured pre-statin LDL-C levels.

It is possible that the DLCN score needs adaptations when applied to populations other than the original one. Even more, clinicians should remember that this tool has not been developed for the paediatric population. Indeed, from all these considerations, it is evident that a timely diagnosis of FH is crucial to start immediately with a pharmacological approach integrated with lifestyle modifications, in order to reduce the overall cardiovascular risk of FH patients, thus gaining time free of cardiovascular events. Therefore, the availability of diagnostic tools that can be widely and easily used by physicians may represent a relevant opportunity for the identification of high cardiovascular risk patients.

Finally, when the DLCN score was applied in the mutation-positive paediatric population, it is possible that the DLCN score needs adaptations when applied to populations other than the original one. Even more, clinicians should remember that this tool has not been developed for the paediatric population. Indeed, from all these considerations, it is evident that a timely diagnosis of FH is crucial to start immediately with a pharmacological approach integrated with lifestyle modifications, in order to reduce the overall cardiovascular risk of FH patients, thus gaining time free of cardiovascular events. Therefore, the availability of diagnostic tools that can be widely and easily used by physicians may represent a relevant opportunity for the identification of high cardiovascular risk patients.


discussion
Due to the high burden of cholesterol from birth, patients with FH have a significantly increased risk of developing atherosclerosis early in the life and may experience premature coronary heart disease. Thus, these patients need to be aggressively and promptly treated to reduce their cardiovascular risk. Despite this awareness, FH is largely underdiagnosed in most countries [1] and frequently the diagnosis of FH is done following a casual biochemical evaluation of LDL-C levels or after the occurrence of a premature cardiovascular event. In addition, in most cases FH is undertreated, as reported in a study showing that only 48% of FH subjects receive statins [8], and frequently the dose of statin provided is not adequate to reduce their plasma LDL-C to the levels recommended by current guidelines [1,9]; finally, statin therapy is often introduced too late in life.

From all these considerations, it is evident that a timely diagnosis of FH is crucial to start immediately with a pharmacological approach integrated with lifestyle modifications, in order to reduce the overall cardiovascular risk of FH patients, thus gaining time free of cardiovascular events. Therefore, the availability of diagnostic tools that can be widely and easily used by physicians may represent a relevant opportunity for the identification of high cardiovascular risk patients.

From our analysis, it is clear that, despite the subjects had a positive genetic test which defined their FH condition, the “a posteriori” application of the DLCN score could not classify all of them as definite FH. Overall, less than half of subjects were classified as definite FH (37.9%).

Due to its structure, one major limit in the application of the DLCN score is the fact that it derives not only from objective information (biochemical evaluation of LDL-C levels and physical examination), but also from the personal and family cardiovascular history, which may be more difficult to be unbiased. The weight of missing information in the determination of the final score is not clear. However, the lack of one or more parameters which are part of the algorithm may reduce the final score and may lead to the attribution of an incorrect FH category. This may be of particular relevance for those subjects having a DLCN score of 5 and one or more missing data, as they might increase their score in the presence of further positive information and thus be shifted to the probable or even definite FH category.

Among subjects with at least 1 missing data, those lacking information on the personal clinical history or physical examination were more likely to be categorized in the “possible FH” group (54.6% and 40.4%, respectively). In the setting of a new diagnosis, this could lead to an underestimation of the individual risk to have FH, and thus may increase the general practitioner not to investigate further this possibility and therefore the subject would not be directed to the genetic test. Indeed, although the genetic test to detect an underlying molecular defect in an index FH patient is costly, it allows early diagnosis, even in childhood, when it is carried out once in a lifetime. In addition, the FH genetic diagnosis provides a cost-effective tool for cascade testing of the FH index case relatives and to prevent premature CHD. As a consequence, also the therapeutic strategy adopted might be inadequate to treat this type of patient. Based on these considerations, it is evident that the appropriate diagnosis can have a relevant clinical impact.

Another critical issue concerns the LDL-C levels, as the score should be applied using pre-therapy values, while many of the available LDL-C level values are obtained post-statin therapy, and thus need to be adjusted based on the drug type and dose. However, this could lead to an overestimation of the pre-treatment LDL-C levels [10].

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Table 1

<table>
<thead>
<tr>
<th>Number of missing information</th>
<th>Frequency</th>
<th>Percentages</th>
<th>Cumulative percentages</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>779</td>
<td>56.57</td>
<td>56.57</td>
</tr>
<tr>
<td>1</td>
<td>209</td>
<td>15.18</td>
<td>71.75</td>
</tr>
<tr>
<td>2</td>
<td>185</td>
<td>13.44</td>
<td>85.19</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>4.87</td>
<td>90.05</td>
</tr>
<tr>
<td>≥4</td>
<td>137</td>
<td>9.95</td>
<td>100.00</td>
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Table 2

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Missing (%)</th>
</tr>
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<tbody>
<tr>
<td>First-degree relative with known premature CHD</td>
<td>11.62</td>
</tr>
<tr>
<td>First-degree relative with known LDL cholesterol &gt; 95th percentile</td>
<td>12.85</td>
</tr>
<tr>
<td>First-degree relative with tendon xanthoma and/or corneal arcus</td>
<td>34.57</td>
</tr>
<tr>
<td>Child(ren) &lt; 18 years with LDL cholesterol &gt; 95th percentile</td>
<td>25.78</td>
</tr>
<tr>
<td>Subject has premature CHD</td>
<td>9.08</td>
</tr>
<tr>
<td>Subject has premature cerebral or peripheral vascular disease</td>
<td>10.17</td>
</tr>
<tr>
<td>Tendon xanthoma</td>
<td>5.37</td>
</tr>
<tr>
<td>Corneal arcus in a person &lt; 45 years</td>
<td>11.62</td>
</tr>
</tbody>
</table>

(29.2% and 34.9%, respectively). The presence of variants of uncertain clinical significance was 11.0% (DLCN score ≥ 9), 21.3% (DLCN score 6–8), 31.3% (DLCN score 3–5), and 45.5% (DLCN score 0–2) (Supplementary table 3). The Bayes theorem showed that the sensitivity of DLCN test is 0.33.

Overall, in our sample, only 56.6% of patients had all the information required to calculate the DLCN score through the 8 criteria besides LDL-cholesterol, and about 10.0% had 4 or more missing data (Table 1). In particular, among subjects with a DLCN score of 5 (9.2%), just below the threshold of the possible diagnosis, about 46.0% had at least one missing criteria information.

About 34.6% of patients had no information on the presence of tendon xanthoma and/or corneal arcus in first-degree relatives and 11.6% and 12.9% had not information on positive history of premature coronary heart disease (CHD) or hypercholesterolemia in first-degree relatives, respectively. The information on premature CHD or on cerebral/peripheral vascular disease was missing in 9.1% and 10.2% of the subjects, respectively (Table 2). The nature of missing information had a differential impact on the ability of the DLCN score to identify FH patients. Thus, the lack of information related to the family clinical history did not modify the rate of patient identification compared with that of subjects without missing data (Table 3); in contrast, the lack of information concerning the physical signs typical of FH or the personal history of cardio/cerebrovascular events strongly reduced the percentage of subjects classified as definite FH (Table 3).

As for many FH subjects the pre-treatment LDL-C levels were not available, we evaluated whether the use of estimated pre-treatment LDL-C levels (adjusting by correction factors considering the type and dose of current lipid-lowering therapy) might affect the DLCN score. Patients on statin therapy (representing 44.2% of the whole studied population) were grouped based on the availability of their pre-treatment LDL-C levels or not (65.2% and 34.8% of the on-statin therapy group, respectively) and compared with subjects not on statin therapy. Within the first subgroup, 26.2% had pre-treatment LDL-C levels > 325 mg/dL (Table 4), in line with what observed in patients not on statin treatment (22.0%); in contrast, 39.6% of subjects with estimated pre-treatment LDL-C value had LDL-C levels > 325 mg/dL (Table 4). This translated into different percentages of patients classified as probable or definite FH by the DLCN score (≥ 6) (Table 4).

Finally, when the DLCN score was applied in the mutation-positive paediatric population (18 years) in whom the algorithm has not been validated, the diagnosis was unlikely for 29.2% and definitive for only 7.5% of children.
Table 3
DLCN score by missing information.

<table>
<thead>
<tr>
<th>Number of missing</th>
<th>DLCN score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unlikely (0–2)</td>
</tr>
<tr>
<td>0 missing</td>
<td>5.01%</td>
</tr>
<tr>
<td>At least 1 missing in Group 1 (family history)</td>
<td>5.89%</td>
</tr>
<tr>
<td>At least 1 missing in Group 2 (clinical history)</td>
<td>9.79%</td>
</tr>
<tr>
<td>At least 1 missing in Group 3 (physical examination)</td>
<td>9.04%</td>
</tr>
</tbody>
</table>

*Group reference Supplementary table 1.

Table 4
LDL-C levels and DLCN score in the mutation-positive sample based on sources of LDL-C levels.

<table>
<thead>
<tr>
<th>LDL-C levels</th>
<th>Total FH population 1377</th>
<th>Not on statin (N = 768)</th>
<th>On statin treatment, with known pre-treatment LDL-C levels (N = 397)</th>
<th>On statin treatment, with estimated pre-treatment LDL-C levels (N = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 155 mg/dL</td>
<td>2.47%</td>
<td>2.60%</td>
<td>1.26%</td>
<td>4.25%</td>
</tr>
<tr>
<td>155–190 mg/dL</td>
<td>7.42%</td>
<td>7.42%</td>
<td>6.30%</td>
<td>3.30%</td>
</tr>
<tr>
<td>191–250 mg/dL</td>
<td>28.40%</td>
<td>28.91%</td>
<td>31.74%</td>
<td>20.28%</td>
</tr>
<tr>
<td>251–325 mg/dL</td>
<td>39.06%</td>
<td>39.06%</td>
<td>34.51%</td>
<td>32.55%</td>
</tr>
<tr>
<td>&gt; 325 mg/dL</td>
<td>22.01%</td>
<td>22.01%</td>
<td>26.20%</td>
<td>39.62%</td>
</tr>
<tr>
<td>DLCN score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite &gt; 8</td>
<td>37.91%</td>
<td>33.46%</td>
<td>32.75%</td>
<td>37.53%</td>
</tr>
<tr>
<td>Probable 6-8</td>
<td>28.47%</td>
<td>27.47%</td>
<td>30.98%</td>
<td>27.36%</td>
</tr>
<tr>
<td>Possible 3-5</td>
<td>28.32%</td>
<td>31.90%</td>
<td>28.72%</td>
<td>14.62%</td>
</tr>
<tr>
<td>Unlikely &lt; 3</td>
<td>5.30%</td>
<td>7.16%</td>
<td>2.77%</td>
<td>3.30%</td>
</tr>
</tbody>
</table>

off for LDL-C levels in this specific group [11].

From this analysis, it appears obvious that the correct application of the DLCN score requires that all the information included in the algorithm must be solicited by the physician during the patient visit, to avoid a misclassification and address the right subject to the genetic testing. It is worth noting, however, that the less severe phenotypes may not be classified as definite FH, and on the other hand, a polygenic form of hypercholesterolemia might be not recognized during a genetic testing. We cannot exclude that the low performance of the DLCN score observed in our study could be related to the extension of the genetic analysis to the young relatives of the index patients, in which the suspect of the disease was suggested basically by lipid levels and by the presence of the mutation in the family. This identifies a group of subjects for whom opportunistic screening based on clinical algorithms would be ineffective, highlighting the decisive role of cascade screening.

Although the DLCN score is undoubtedly a very useful tool for the physician in the diagnosis of FH, in daily practice it could be limited by difficulty in finding information; moreover, it failed to identify a third of the subjects with genetic diagnosis of FH. Even if an update of this tool and its validation in individual national contexts would be warranted, physicians should be aware that it is just a support tool and must rely on their clinical judgment.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

MC, EO, and ALC were responsible for the study concept and design. EO did the analysis. MC and ALC contributed to the data analysis and interpretation of the results. MC and AP drafted the manuscript and all authors critically revised for important intellectual content and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at [10.1016/j.atherosclerosis.2018.08.013](https://doi.org/10.1016/j.atherosclerosis.2018.08.013).

References


