Diagnosis, treatment and opportunities

Genetic cascade screening for familial hypercholesterolaemia in Switzerland

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Introduction

Familial hypercholesterolaemia (FH) is a genetic disorder associated with an increased risk of early-onset cardiovascular events [1]. As the prevalence of the disorder is estimated to be 1/200 in the European general population, about 40,000 Swiss subjects may have FH. Among them, it is estimated that only 15% are diagnosed [2]. Actually, many patients with FH are only diagnosed at the time of hospitalisation for a cardiovascular event [3]. Even when diagnosed at a young age, many patients with FH are not using lipid-lowering drugs to decrease their cardiovascular risk [4]. This mini-review aims to describe current knowledge about diagnosis and treatment of FH, as well as to discuss opportunities to use genetic testing for family cascade screening in Switzerland.

Clinical familial hypercholesterolaemia

In order to facilitate the diagnosis of FH, the American Heart Association (AHA) has defined FH based on two clinical criteria, without the need to perform a genetic test. A clinical FH is established when both low-density lipoprotein cholesterol (LDL-c) >4.9 mmol/l and a family or personal history of premature cardiovascular disease are present [5]. Premature cardiovascular disease is defined as occurring below 55 years of age for men and below 60 for women. At least two separate LDL-c measurements should be nade to confirm the diagnosis. Alternatively, FH can also be defined as LDL-c >4.9 mmol/l and a family history of very high LDL-c levels. The AHA clinical definition is similar to the "possible FH" category of the Dutch Lipid Clinic Network score, endorsed by the European guidelines on dyslipidaemia [6]. The Dutch Lipid Clinic Network score is based on a set of clinical and biological criteria such as family history of premature cardiovascular disease in first-degree relatives, personal cardiovascular disease history, untreated LDL-c levels and physical signs such as the presence of tendon xanthomata or arcus cornealis prior to the age of 45 years.

Cardiovascular risk of familial hypercholesterolaemia

Clinical FH is associated with an increased life-long risk of a cardiovascular event. Based on six large epidemiological cohort studies from the US with up to 30 years of follow up and more than 65,000 adults without cardiovascular disease, Perak et al. have demonstrated that the life-long cardiovascular risk of men and women with clinical FH was 2- to 3-fold higher than among men and women with LDL-c values below 3.4 mmol/l, independently of the age category [7]. Among patients with premature acute coronary syndrome in Switzerland, we reported that those with LDL-c of 5 mmol/l or above at hospital admission had also a 2- to 3-fold higher risk of recurrent cardiovascular event within the year after discharge, compared with patients without clinical FH [8].

Lipid lowering drugs for familial hypercholesterolaemia

In Switzerland, the health authorities (Swissmedic) have authorised five different lipid-lowering drugs to be used in patients with clinical FH: (1) statins, (2) ezetimibe, (3) monoclonal antibody PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (evolocumab or alirocumab), (4) small interfering RNA PCSK9 inhibitor (inclisiran) and (5) bempedoic acid (table 1). Monoclonal antibody PCSK9 inhibitors have reimbursement limitations by health insurances. Inclisiran and bempedoic acid are currently being evaluated by the Swiss Federal Office of Public Health to be registered in the specialities list at the time of writing this review. The evidence that lipid-lowering

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Table 1: Lipid-lowering drugs indicated for patients with familial hypercholesterolaemia in Switzerland.

Year	Name	Efficacy to lower LDL-cholesterol	Indications in secondary prevention	Indications in primary prevention	Route	Side effects	Cost per year
1987	High-intensity statins, such as rosuvastatin 20 mg or atorvastatin 40 mg	40–50%	Yes	Intermediate–high CVD risk, Familial hypercholesterolaemia	Oral, daily	Myalgias (5–10%)	CHF 280
2001	Ezetimibe 10 mg	20%	Yes	Intermediate–high CVD risk, Familial hypercholesterolaemia	Oral, daily	Myalgias (2–3%)	CHF 310
2016	Monoclonal antibody PCSK9 inhibitors evolocumab 140 mg or alirocumab 150 mg	50–60%	Yes	Familial hypercholesterolaemia	S/c, 2x/month	Injection site erythema (5–10%)	CHF 5200
2021	Small interfering RNA PCSK9 inhibitors Inclisiran 284 mg	50–60%	Yes	Familial hypercholesterolaemia	S/c, 2x/year	Injection site reaction (2–4%)	Unknown
2021	Bempedoic acid 180 mg	20%	Yes	Familial hypercholesterolaemia	Oral, 1 daily	Increase uric acid levels with risk of gout	Unknown

CVD: cardiovascular disease; LDL: low density lipoprotein; PCSK9: proprotein convertase subtilisin/kexin type 9; S/c: subcutaneous

drugs reduced cardiovascular risk among patients with clinical FH remains mainly indirect. In patients with clinical FH, no designed phase III randomised controlled trial comparing incidence of cardiovascular outcomes has been ever published. However, much indirect evidence exists. Randomised controlled trials testing lipid-lowering drugs vs placebo have demonstrated a consistent benefit in reducing cardiovascular events even among patients with lower LDL-c levels than patients with clinical FH [9]. Observational evidence from a cascade screening registry of patients with genetic FH also demonstrated that untreated patients with FH had higher life-long cardiovascular risk than their siblings who had earlier access to lipid-lowering drugs [10].

Monogenic familial hypercholesterolaemia

Heterozygous genetic FH or heterozygous monogenic FH is defined as the presence of a pathogenic variant in one of three main genes: *LDLR*, *APOB*, and *PCSK9* [11]. The positive monogenic test result is found in about 40% of patient with untreated LDL-c levels >6.5 mmol/l. When the genetic test is negative, patients with clinical FH have probably a polygenic cause of the disease. A total cholesterol cut-off of 8 mmol/l has been chosen by European guidelines on dyslipidaemia to recommend genetic testing [6]. However, this genetic testing is rarely performed in Switzerland because the procedure is not currently reimbursed by health insurers.

Importance of genetic testing

There are at least three reasons why genetic testing can improve clinical care of patients with FH. First, patients with both the monogenic pathogenic variant and the clinical definition of FH carry a substantial increased risk of cardiovasular disease compared with patients in whom only the phenotype is found [12]. This information may help to better target high-intensity lipid-lowering treatment or combinations of drugs. Second, adherence to a healthy lifestyle or lipid-lowering drugs may be improved when patients are aware of their genetic status. Finally, by conducting family cascade screening, genetic testing may improve the detection yield of patients with FH. The transmission mode of the pathogenic variant for FH is autosomal dominant. Therefore, each first-degree family member of an index case with the pathogenic variant has a 50% probability of being also affected, independently of sex or LDL-c levels.

Cascade genetic testing for familial hypercholesterolaemia

Once an index case with a pathogenic variant has been identified, cascade family screening involves several rounds of screening across the entire family. First-degree relatives of an index case in whom a pathogenic variant has been identified are screened, and so on. When the family genetic mutation is not identified, cascade screening stops for first-degree relatives of this individual. The aim of performing several cycles

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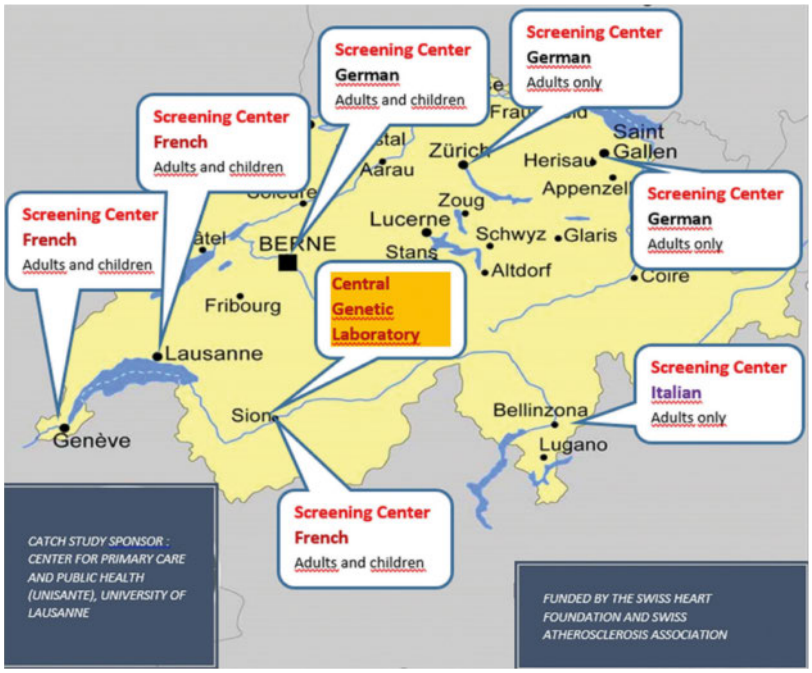

Figure 1: French, German and Italian Swiss centres participating in the CATCH study.

of cascade screening is to identify all family members with the disease.

Ethical concerns for cascade screening

Because FH increases the life-long cardiovascular risk and can be effectively treated with lipid-lowering drugs and appropriate diet, physicians should ideally inform relatives of an index case of their potential cardiovascular risk and their options to reduce it. However, legal protection to guarantee privacy of data do not authorise physicans to directly contact at-risk relatives of an index case. Alternatively, the index case can be counselled to inform his relatives about the risk of FH. However this process can be limited in some families. Even if family communication is effective, there might be reluctance of relatives to contact unknown healthcare professionals. In Switzerland, to be ethically acceptable, the procedure for contacting a relative should respect individual autonomy and privacy. Therefore, it should only be initiated by the index case. Additionally, a relative can be directly contacted only when information about willingness to be contacted was obtained by the relative, and not by the index case.

Implementation of genetic cascade screening in Switzerland

In Switzerland, the implementation of a multicentre genetic cascade screening programme for FH has never been tested. Particularly, it is unknown what would be the best method to contact at-risk relatives to improve the yield of FH detection. Furthermore, the transmission rate of the polygenic form of the disease within families has been poorly studied. Therefore, we designed a multicentre open-label randomised controlled trial across Switzerland to test whether a cascade screening programme for monogenic or clinical FH, in comparisonwith usual care, will increase the detection rate of FH within families: the CATCH study [13]. At the time of writing this review (October 2021) the CATCH study is still including index cases and their relatives in the French, German and Italian part of Switzerland (fig. 1).

The CATCH study

The CATCH study offers genetic testing for patients with severe hypercholesterolaemia and a familial or personal history of early-onset CVD with a Dutch Lipid Clinic Network score (DLNC) ≥6 points. Patients are separated into two groups before randomisation based on the result of the genetic test, either positive for a mongenic mutation in one of the three genes causing FH (monogenic FH group), or negative for the monogenic mutation (polygenic FH group). The presence or absence of a monogenic mutation in the index case will determine the screening test used for cascade screening of relatives, either with a genetic or with a lipid test.

Intervention

Each index case will be counselled to contact their first-degree relatives. In the intervention arm, the index case will be additionally supported to contact relatives with the help of prepared email or SMS to be sent from an internet platform dedicated to the study. Relatives can then click on a link embedded in the message and provide consent to be contacted by one of the participating centres in Switzerland. In the control arm or "usual care arm", the index case will also be encouraged to initiate contact with their first-degree relatives contact, but without the support of the internet platform.

Outcomes

The primary outcome is the difference in the yield of detection of FH between arms (fig. 2). The detection rate is the number of test performed/number of contactable relatives. Secondary endpoints include the transmission rate of phenotype and genotype into families, as well as the change in the use of lipid-lowering drug and change in LDL-cholesterol levels assessed 6 months after receipt of the results of the genetic test.

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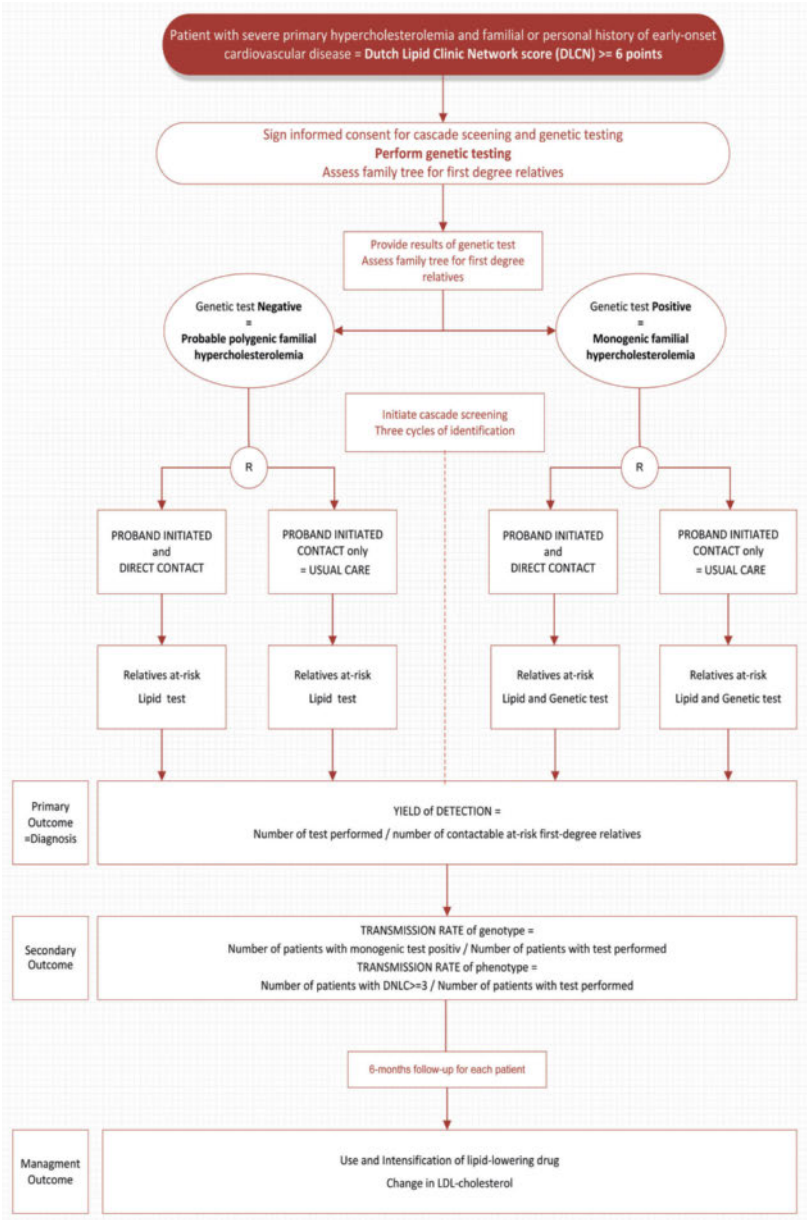

Figure 2: Design and outcomes of the CATCH study.

Genetic database for familial hypercholesterolaemia

When the genetic test is performed in an index case or in a relative, the DNA extracted from an EDTA blood tube is stored at –80°C in a centralised biobank in Switzerland. The biobank is registered in Europe and Switzerland with defined governance and quality control [14, 15]. The DNA biobank can be linked to clinical data collected within the CATCH study, including family trees, allowing future identification of new genetic patterns associated with elevated cholesterol levels.

Conclusions

The clinical diagnosis of FH can be confirmed with a genetic test within the frame of the Swiss CATCH study, which also allow cascade genetic testing of all relatives of an index case. The CATCH study will provide new information about the performance of current mobile information technology to conduct family cascade screening. Designed as an implementation study in clinical practice, the CATCH study will also provide needed evidence of the utility of genetic information for the clinical management of FH.

Key points

- The diagnosis of familial hypercholesterolaemia (FH) is mainly based on clinical criteria.
- The clinical diagnosis of FH can be confirmed with a genetic test to assess the presence of a pathogenic variant in one of three main genes: *LDLR, APOB*, and *PCSK9*.
- Although genetic testing provides important diagnosis and prognosis information, more evidence is needed to confirm the effectiveness of implementing genetic testing in the clinic.
- The Swiss CATCH implementation study will provide new evidence regarding public health, societal and clinical effectiveness of genetic cascade screening for FH.

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References
The full list of references is included in the online version of the article at https://cardiovascmed.ch/article/doi/CVM.2022.w10123.