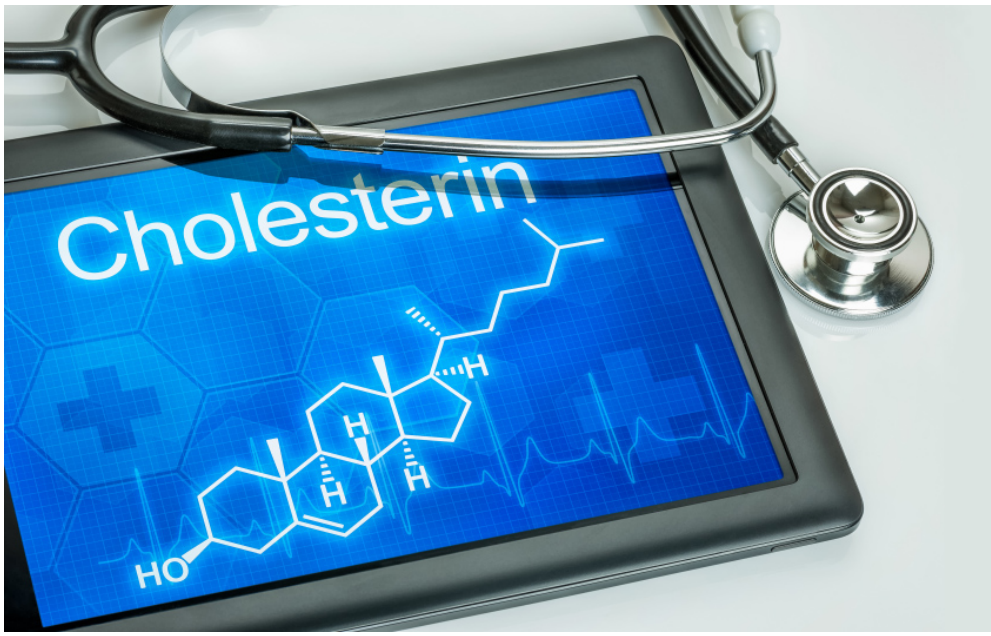
HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Genetic Testing in the Context of Familial Hypercholesterolaemia Management



Organisational and ethical implications (part 1), and economic aspects (part 2)

Final Report

AIHTA Project report No.: 130 | ISSN: 1993-0488 | ISSN-online: 1993-0496

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Genetic Testing in the Context of Familial Hypercholesterolaemia Management

Organisational and ethical implications (part 1), and economic aspects (part 2)

Vienna, November 2020

Project Team

Project leader: Melanie Walter, PhD Eu-MSc BSc (part 1), Christoph Strohmaier, Bakk. rer.soc.oec. (part 2)

Authors: Melanie Walter, PhD Eu-MSc BSc, Christoph Strohmaier, Bakk. rer.soc.oec.

Project Support

External Review: OÄ Dr. med. Anja Vogt, Medizinische Klinik und Poliklinik IV, Klinikum der Universität München
Univ.-Prof. Dr. Andreas Sönnichsen, Abteilung für Allgemeinmedizin und Familienmedizin, Zentrum für Public Health, Medizinische Universität Wien

Internal Review: Dr. rer.soc.oec. Ingrid Zechmeister-Koss, MA

Correspondence: Melanie Walter, melanie.walter@aihta.at
Christoph Strohmaier, christoph.strohmaier@aihta.at

Cover photo: © Zerbor – stock.adobe.com

This report should be referenced as follows:

Strohmaier, C. and Walter, M., Genetic Testing in the Context of Familial Hypercholesterolaemia Management: Organisational and Ethical Implications, and Economic Aspects. AIHTA Project report No.: 130, 2020. Vienna: HTA Austria – Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the HTA Austria – AIHTA GmbH is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the HTA Austria – AIHTA GmbH.

CONTENT INFORMATION

Publisher:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Garnisongasse 7/Top 20 | 1090 Vienna – Austria
https://www.aihta.at/

Responsible for content
Priv.-Doz. Dr. phil. Claudia Wild, CEO

AIHTA Project reports do not appear on a regular basis and serve to publicize the research results of the Austrian Institute for Health Technology Assessment.

AIHTA Project reports appear in small print runs and are available through the document server
http://eprints.aihta.at/view/types/hta_report.html

AIHTA Project report No.: 130

ISSN 1993-0488

ISSN online 1993-0496

Content

List of Figures

List of Tables

List of Abbreviations

AAS ..... Austrian Atherosclerosis Society
ACVD..... Artheriosclerotic cardiovascular disease
AHA ..... American Heart Association
ACC..... American College of Cardiology
AKH ..... Allgemeines Krankenhaus Wien/Vienna General Hospital
AM..... Allgemeinmedizin, Allgemeinmediziner*innen/general practioner(s)
ApoB..... Apolipoprotein B
APS..... Arbeitsgemeinschaft für Pädiatrische Stoffwechselstörungen in der Deutschen Gesellschaft für Kinderheilkunde und Jugendmedizin/Working group for paediatric metabolic disorders in the German Society for Paediatrics and Youth Medicine
BIA ..... Budget impact analysis
CAD ..... Coronary artery disease
CCS ..... Canadian Cardiovascular Society
CCU ..... Coronay care unit
CE..... Cost-Effectivness
CEA..... Cost-Effectiveness analysis
CHD..... Coronary heart disease
CI..... Confidence interval, if not further specified: 95%
CV..... Cardiovascular
CVD ..... Cardiovascular disease
DGFF..... Deutsche Gesellschaft zur Bekämpfung von Fettstoffwechselstörungen und ihren Folgeerkrankungen/German Society for Combating Lipometabolic Disorders and their Consequences
DGPK ..... Deutsche Gesellschaft für pädiatrische Kardiologie/German Society of Pediatric Cardiology
DKG..... Deutsche Gesellschaft für Kardiologie/German Society of Cardiology
DLCN ..... Dutch Lipid Clinic Network criteria
DMP..... Disease/disorder management programme
EAS..... European Artheriosclerotic Society
ESC ..... European Society of Cardiology
FA.....Facharzt, Fachärztin/specialist
FÄ.....Fachärzte/specialists
FH .....Familial hypercholesterolaemia
GC .....Genetic counselling
GDx.....Genetic diagnostics
ges.ök.....gesundheitsökonomisch
GP.....General practioner
GTG .....Gentechnikgesetz/Act of Genetic Engineering
HbA1c .....Hämoglobin A1c
HDL-C.....High density lipoprotein-cholesterol
HE .....Health economic(s)
HeFH .....Heterozygous familial hypercholesterolaemia
HoFH.....Homozygous familial hypercholesterolaemia
IFHF .....International Familial Hypercholesterolaemia Foundation
IHD .....Ischemic heart disease
IP .....Indexpatient*in(nen)/index patient(s)
KH.....Krankenhaus/hospital
klin .....klinisch/clinical
KUK.....Kepler Universitätsklinikum
LDLR.....Low density lipoprotein receptor
LDLRAP1 ...Low density lipoprotein receptor adaptor protein 1
LDL-C .....Low density lipoprotein-cholesterol
LKH .....Landeskrankenhaus/state hospital
LLD .....Lipid lowering drug
LLT.....Lipid lowering treatment/therapy
MAB-G.....Medizinisches Assistenzberufs-Gesetz/Regulation for the medial assisstent profession
MGT.....Molecular genetic test
MI.....Myocardial infarction
NA .....Not available/not applicable
NICE.....National Institute for Health and Clinical Excellence
NLA .....National Lipis Association
ÖSG.....Österreichischer Strukturplan Gesundheit/Austrian Structural Plan for Healthcare
Pat. .....Patient*in(nen)/patient(s)

PCSK9..... Proprotein convertase subtilisin/kexin type 9
PCSK9i ..... Proprotein convertase subtilisin/kexin type 9-inhibitor
PHE..... Public Health England
RIA..... Resource impact analysis
SB ..... Simon-Broome Diagnostic criteria
SP ..... Specialist
TC .....Total cholesterol
UK.....United Kingdom
USA.....United States of America
v .....von/of
VU .....Vorsorgeuntersuchung/voluntary preventive medical check-up
VUS .....Variants of unknown clinical significance

Executive Summary

Introduction

zunehmender Einsatz von molekulargenetischer Diagnostik (GDx)

Molecular genetic diagnostic (GDx) is an increasingly important instrument in the so-called personalised medicine or precision health care and its utilisation is expected to rise further in the near future. It allows forming individual risk-based strata and thus personalised preventive and therapeutic decisions. Further, extended clinical use of GDx can contribute to more efficient case identification, especially of at-risk family members, but requires a structured and controlled implementation in the health care system.

familiäre Hypercholesterinämie als Beispiel für systematischen Einsatz von GDx

In the course of the discovery of functional gene sequences causing familial hypercholesterolaemia (FH), GDx has also become more important in endocrinology and cardiovascular medicine, particularly as triage mechanism for risk stratification in the prevention of arteriosclerosis and coronary heart diseases.

Ziel: Darstellung der Komplexität von GDX im Rahmen systematischer Teststrategien

Against this background, organisational-regulatory questions as well as ethical aspects of the implementation of a systematic test strategy including GDx, but also far-reaching economic effects, have to be considered. The aim of this report is to illustrate the general complexity of such diagnostic tests and systematic test strategies by using the example of FH, and to emphasise which implications have to be considered beyond effectiveness and safety.

5 Forschungsfragen hinsichtlich organisatorischer, ethischer und ökonomischer Aspekte

Five research questions, concerning (inter-)national guidance on FH test strategies and diagnostic processes, the current Austrian FH situation, ethical and regulatory aspects of (predictive) genetic testing, as well as budget and resource implications of an FH management strategy including molecular genetic testing in the Austrian context, were addressed.

Methods

Handsuche nach relevanter Literatur

für die österreichische Situation zusätzliche Experten-Interviews

Ressourcenfolgen-Analyse

The overview of recommended or implemented (inter-)national FH test strategies (Europe, Australia, Canada, Belgium, Germany, Slovenia, Switzerland, UK, USA) and the ethical aspects of (predictive) genetic testing are based on an iterative manual literature search. To answer questions concerning Austrian-specific organisational aspects expert interviews were conducted. For the question regarding the economic implications, a resource impact analysis (RIA), based on international evidence, was carried out. The resource impact calculations were based on identifying FH cases through an active systematic search in primary care data *(Vorsorgeuntersuchung)* and through cascade screening of first, second and third degree relatives including GDx. The identified FH cases were then assigned costs and volumes of a lipid-lowering therapy (LLT).

Results

mehrere charakteristische Komponenten von FH-Teststrategien

Amongst others, we identified the method for detection of so-called FH index patients, the clinical criteria indicating a diagnosis and the recommended diagnostic tool for assessment, implementation of GDx, and recommendations concerning cascade screening, genetic counselling, registries, and awareness programmes, as important components of the included (inter-)national FH test strategies.

GDx als Diagnosetool nach klinischer Diagnose in opportunistischen und systematischen Behandlungsansätzen

Detection and diagnosis of index patients comprise opportunistic approaches or organised systematic screenings in non-specialized (primary care-led) or specialized (secondary care-led) settings. Integrated in them, use of GDx is most often recommended only after a clinical FH diagnosis, by applying scores from clinical instruments assessing phenotype and family history (e.g. DLCN score), has been made. In the course of cascade screening of at-risk family members, GDx is partly recommended or included in existing strategies.

in Österreich systematische Ermittlung von Indexpatient*innen weder formell empfohlen noch umgesetzt; verschiedene Diagnosepfade

In Austria, systematic FH index case identification is currently neither formally recommended nor implemented. Patients are, in daily practice, either identified in a hospital-based setting following a premature or repeated cardiovascular event, in primary care during an unrelated clinical consultation by a GP, or when persons contact the Austrian patient organisation (FHchol) on their own initiative. Cascade screening of at-risk family members is systematically integrated in a FH registry project, but the assessment is most often solely based on clinical criteria. Prior and post molecular genetic testing for FH, genetic counselling is obligatory in Austria and has to be conducted by specialists for medical genetics or professionals from FH-related medical fields. GDx for FH-associated pathogenic variants is reimbursed in Austria, but exact numbers of the frequency of molecular genetic tests for FH are not available publicly.

verpflichtende genetische Beratung

Autonomie, Informed Consent, Privatsphäre als zentrale ethische Aspekte

The ethical discussion highlighted especially issues concerning autonomy, informed consent and privacy, which are to be addressed during the process of genetic counselling. As a (molecular genetic) diagnosis has also impact on at-risk family members (cascade screening), there is an increased risk for intrafamilial conflicts, e.g. on disclosure of test results.

Basisfallanalyse ergab Ressourcen folgen von rund 17,5 Mio. €; GDx als größter Kostenanteil; und zahlreiche weitere Kostenkomponenten

The results of the base case analysis in the resource impact analysis showed an overall resource impact of € 17.5 million for one year with GDx (including genetic counselling) as the main cost-driver. Besides GDx costs there are a number of other cost components to be taken into account when implementing an organised FH-screening approach, e.g. costs for clinical tasks prior to GDx, costs for active case finding, costs for LLT etc.)

tatsächliche Prävalenz hat signifikanten Einfluss auf die Gesamtkosten

Kostenverschiebung durch verschiedene Prävalenzannahmen

The resource specific consequences are dependent on a number of factors, including probabilities of an index case to agree to cascade testing, uptake rates, the likelihood that the identified people actually have FH and diagnostic performance of clinical assessment instruments. One factor, which particularly influences the economic consequences, is the prevalence of FH in the total population. Depending on the assumed prevalence, the total costs ranged from ~€ 9.8 (prevalence 1:500) million to € 21.3 million (prevalence 1:200). Further, with decreasing prevalence, there seems to be a relative shift from costs of GDx (including counselling) to active case finding.

Conclusion

wesentliche Entscheidung: opportunistisch vs. organisiertes Screening

The results demonstrate that before introducing GDx on a broader scale, it has to be clearly defined which role the test should play within the overall diagnostic and management processes of the disease in question. In the case of FH, key decisions to make are, whether it should be part of an organised or opportunistic screening approach, at which level of care the different steps should take place, and which professional groups to involve in which step.

koordinierte Implementierung ist wesentlich

The analysis of the current Austrian situation has shown that if this is neglected, diffusion into the health care system will be uncoordinated, resulting in very different diagnostic and care processes in which access to care is mainly dependent on initiatives of single providers or medical professionals.

es bestehen zahlreiche organisatorische Herausforderungen

Regardless of which approach to choose, implementing GDx results in a number of organisational challenges, such as defining practice steps and personnel to identify the index patients, providing enough and well-educated genetic counsellors and linking them logistically to the clinical and laboratory processes around the testing. Further, medical doctors trained in standardised clinical assessment, as well as communication activities in order to raise awareness and health literacy on the topic in public, need to be installed.

Investition in professionelle genetische Beratung essentiell

Investing in professional and well-trained genetic counsellors seems to be paramount, as the numerous ethical questions we identified require sensitive communication with patients and their relatives. In particular, skills for transparent and non-directive communication need to be developed.

österreichspezifische (Kosten-)Effektivitäts-Studien und robuste Prävalenzzahlen sind nötig

However, introducing GDx in such an organised way can result in substantial costs that go considerably beyond the cost of the actual test itself. Hence, before implementing, a thorough effectiveness and cost-effectiveness analysis should be undertaken in order to identify the most effective and cost-effective strategy for Austria. This will require more robust prevalence data in the first place.

Zusammenfassung

Einleitung

molekulargenetische Diagnostik (GDx) in der personalisierten Medizin von steigender Relevanz

Funktion: (Companion) Diagnostik, Prognostik

Die molekulargenetische Diagnostik (GDx) ist ein zunehmend wichtiges Instrument in der so genannten personalisierten Medizin oder Präzisionsgesundheitsfürsorge. Diese Bereiche werden stark von neuen Diagnostika und Therapeutika bestimmt, welche die Unterscheidung einzelner Patient*innen mit ähnlichen klinischen Bedingungen möglich machen soll, um damit personalisierte therapeutische und präventive Entscheidungen zu treffen. Es ist zu erwarten, dass die Nutzung in naher Zukunft weiter zunehmen wird. Darüber hinaus kann der erweiterte klinische Einsatz von GDx zu einer effizienteren Fallidentifizierung beitragen, insbesondere beim Kaskadenscreening von Familienmitgliedern mit erhöhtem Risiko.

Beispiel FH: GDx als Instrument zur Risiko-Stratifizierung in der Prävention von kardiovaskulären Erkrankungen

Im Zuge der Entdeckung funktioneller Gensequenzen, die familiäre Hypercholesterinämie (FH) verursachen (LDLR, ApoB, PCSK9), hat GDx auch in der Endokrinologie und der inneren Medizin an Bedeutung gewonnen, insbesondere als Triage-Mechanismus zur Risiko-Stratifizierung bei der Prävention von Arteriosklerose und koronaren Herzerkrankungen. Die FH ist eine vererbbare Störung des Lipidstoffwechsels, welche das Risiko von (arteriosklerotischen-)kardiovaskulären Ereignissen, auch schon in jungen Jahren, stark erhöht. Derzeit ist in Österreich für die Diagnose eine molekulargenetische Bestätigung des Vorliegens einer Mutation auf den FH-assoziierten Genen nicht zwingend erforderlich. Eine Ausweitung der molekulargenetischen Testung kann, neben der definitiven Diagnose, zu effektiveren Kaskadentests gefährdeter Verwandter, der Einleitung von Therapien schon in früheren Jahren als auch generell zu verbesserten und effizienteren therapeutischen Entscheidungen verhelfen.

GDx-Implementierung wirft einige Fragen auf

Allerdings sind bei und vor der Implementierung einer systematischen FH-Managementstrategie mit integrierter GDx sowohl organisatorisch-regulatorische Fragen als auch ethische Aspekte zu beleuchten. Des Weiteren gilt es auch, weitreichende ökonomische Auswirkungen zu berücksichtigen. Ziel des vorliegenden Berichts ist es, die generelle Komplexität solcher diagnostischen Tests und systematischer Teststrategien am Beispiel der FH zu verdeutlichen und Implikationen, welche über die Wirksamkeit und Sicherheit hinausgehen, hervorzuheben.

Folgende fünf Forschungsfragen werden im Bericht adressiert:

5 Forschungsfragen hinsichtlich organisatorischer, ethischer und ökonomischer Aspekte

1. Welche Teststrategien und Diagnoseverfahren zur Diagnose von FH werden von (inter-)nationalen Richtlinien und medizinischen Fachgesellschaften empfohlen?
2. Wie wird eine FH in Österreich diagnostiziert und wie ist die aktuelle Teststrategie aufgebaut?
3. Könnte die derzeitige FH-Teststrategie in Österreich verbessert werden und welche organisatorischen Schritte sind dafür notwendig?
4. Welche ethischen und regulatorischen Aspekte sind bei der (prädiktiven) molekulargenetischen Diagnostik mit besonderer Betonung auf FH und einem Kaskadenscreening zu berücksichtigen?
5. Wo fallen bei einer systematischen FH-Management-Strategie inklusive GDx Kosten an und welche ressourcenspezifischen Folgen sind für den österreichischen Kontext zu erwarten?

Methoden

Der Überblick über empfohlene bzw. umgesetzte (inter-)nationale FH- Teststrategien (Europa, Australien, Kanada, Belgien, Deutschland, Slowenien, Schweiz, UK, USA) basierte auf einer iterativen manuellen Literatursuche. Zur Beantwortung der Fragen zur österreichischen Situation und österreichspezifischen organisatorischen Aspekten wurden Experteninterviews durchgeführt. Ethische Aspekte (prädiktiver) genetischer Diagnostik wurden anhand des Hofmann'schen Fragenkatalogs aus manuell gesuchter Literatur identifiziert.

Methoden: iterative manuelle Handsuche, Hofmann'scher Ethik-Fragenkatalog, Experteninterviews

Zur Abschätzung der ökonomischen Implikationen wurde eine Ressourcenfolgenanalyse (RIA) aus der Perspektive der öffentlichen Kostenträger für einen 1-jährigen Zeithorizont auf Basis des FH-Modells des National Institute for Health and Care Excellence (NICE), durchgeführt. Dazu war eine Schätzung der epidemiologischen Dimension erforderlich. Als FH-Screening-Strategie zur Identifikation der Indexpatient*innen wurde eine systematische Suche in den Primärversorgungsdaten/-akten der österreichischen Vorsorgeuntersuchung gewählt, gefolgt von einem Kaskadenscreening von Verwandten einschließlich GDx und anschließender Behandlung mit lipidsenkender Therapie (LLT). Sämtlichen Prozessschritten wurden Kosten zugeordnet, denen österreichische Preise, Tarife und Kollektivverträge zugrunde liegen. In einer Sensitivitätsanalyse wurden Unsicherheit bezüglich der Prävalenz getestet.

ökonomische Folgen mit Ressourcenfolgen-Analyse geschätzt

Basis: Screening von Primärversorgungsdaten

Zuordnung von Kosten zu gesamten Screening- und Behandlungsprozess

Ergebnisse

(Inter-)nationale FH Testrategien

Als wichtige charakteristische Bestandteile von FH-Teststrategien wurden u. a. die Methode zur Detektion sogenannter FH-Indexpatient*innen, die klinischen Kriterien, die auf eine Diagnose hindeuten, das empfohlene diagnostische Instrument zur Beurteilung einer FH, der Einsatz von GDx sowie Empfehlungen zu Kaskadenscreening, genetischer Beratung, Registern und Awareness-Programmen identifiziert.

FH-Teststrategien bestehen aus mehreren Komponenten

Das Identifizieren und Diagnostizieren von Indexpatient*innen umfasst opportunistische Ansätze oder organisierte systematische Screenings in nichtspezialisierten (primärversorgungsorientierten) oder spezialisierten Settings. In beiden Settings wird der Einsatz von GDx meist erst nach einer klinischen FH-Diagnose empfohlen, welche meist anhand standardisierter Instrumente (z. B. DLCN-Score) gestellt werden. Im Rahmen des Kaskadenscreenings von Familienmitgliedern mit FH-Risiko wird GDx teilweise empfohlen, aber meistens sollte vorher die jeweilige familiäre FH-Mutation des/der Index-Patient*in bereits bekannt sein.

GDx als Diagnosetool nach klinischer Diagnose in opportunistischen und systematischen Behandlungsansätzen

FH in Österreich

In Österreich wird die systematische FH-Indexfallermittlung derzeit weder formell empfohlen noch umgesetzt. Patient*innen werden entweder im Krankenhaus nach einem vorzeitigen oder wiederholten kardiovaskulären Ereignis, in der Primärversorgung während einer nicht interventionsassoziierten hausärztlichen Sprechstunde oder nach selbst initiierter Kontaktaufnahme mit der österreichischen Patient*innenorganisation (FHchol) identifiziert. Das Kaskadenscreening von Familienmitgliedern ist systematisch in ein FH-Registerprojekt integriert. Die Diagnosestellung erfolgt jedoch meist ausschließlich nach klinischen Kriterien.

systematische Ermittlung von Indexpatient*innen wird in AT derzeit weder formell empfohlen noch umgesetzt; Kaskadenscreening nur im Zuge eines FH-Registerprojekts

GDx für FH wird öffentlich bezahlt, genetische Beratung ist verpflichtend

Vor und nach der molekulargenetischen Untersuchung für FH ist eine genetische Beratung in Österreich obligatorisch und muss von Fachärzt*innen für medizinische Genetik oder Expert*innen aus FH-spezifischen medizinischen Bereichen durchgeführt werden. GDx für FH-assoziierte pathogene Varianten wird in Österreich rückvergütet, genaue Zahlen über die Anwendung molekulargenetischer Untersuchungen für FH sind jedoch nicht vorhanden.

Ethische Aspekte

Autonomie, Informed Consent, Privatsphäre als zentrale ethische Aspekte

In der Diskussion der ethischen Aspekte wurden insbesondere Fragen der Autonomie, des Rechts auf Selbstbestimmung (Informed Consent) und des Schutzes der Privatsphäre hervorgehoben, welche eine besondere Verantwortung für die genetische Beratung mit sich bringen. Da eine (molekulargenetische) Diagnose auch Auswirkungen auf Familienmitglieder hat (Kaskadenscreening), besteht ein erhöhtes Risiko für innerfamiliäre Konflikte, z. B. bei der Offenlegung von Testergebnissen.

Ressourcenfolgenanalyse

Epidemiologie

mit Primärversorungsdaten-Screening rund 5.000 Patient*innen identifizier- und behandelbar

Die epidemiologische Schätzung ergab, dass unter der Annahme einer FH-Prävalenz von 1:250 (Basisfall) mit dem gewählten Screening-Ansatz in Österreich rund 5.000 FH-Patient*innen (810 neue Indexfälle + 1.178 alte/bereits diagnostizierte Indexfälle + 1.215 Verwandte neuer Indexfälle und 1.767 Verwandte alter/bereits diagnostizierte Indexfälle) identifiziert und mit nachfolgender LLT behandelt werden könnten.

Ressourcenfolgen und Verteilung der geschätzten Kosten

Basisfallanalyse: Ressourcenfolgen von ~€ 17,5 Millionen; molekulargenetische Diagnostik inkl. genetische Beratung machen ~3/4 der Gesamtkosten aus

In der Basisfallanalyse wurden für das gesamte Screening- und Behandlungsprogramm Ressourcenfolgen von ~€ 17,5 Millionen (Mio.) errechnet. Der größte Kostenanteil im Behandlungsprozess entfällt mit mehr als ¾ der Gesamtkosten (~€ 13,5 Mio. €) auf den molekulargenetischen Test einschließlich genetischer Beratung, wobei Letztere lediglich 7,4 % der GDx-Kosten (~€ 1 Mio.) ausmachen. Daneben sind eine Reihe weiterer Kostenkomponenten zu berücksichtigen (z. B. Kosten für die Identifizierung der Index-Patient*innen, Kosten für medikamentöse Therapie).

Sensitivitätsanalyse

unterschiedliche Prävalenzzahlen, um Unsicherheit darzustellen

Niedrigere (1:500) und höhere (1:200) Prävalenzzahlen resultieren in niedrigeren (2.488) bzw. höheren (6.213) identifizierten und zu behandelnden Patient*innen. In der Folge variieren die geschätzten Ressourcenfolgen zwischen ~€ 9,8 und ~€ 21,3 Mio. Die Ressourcenfolgen sind zusätzlich von weiteren Faktoren abhängig (z. B. von der diagnostischen Genauigkeit der klinischen Diagnostik-Tools, welche in weiterer Folge die genetisch bestätigten FH-Diagnosen determinieren, von den bereits diagnostizierten und in Behandlung befindlichen FH-Patient*innen, von der durchschnittlichen Anzahl betroffener Angehöriger oder die Teilnahmerate/Compliance).

Diskussion

Ausgehend von den Ergebnissen, sind von den Entscheidungsträgern eine Reihe an Themen und offenen Fragen zu adressieren:

Fragen, die es bei einer Umsetzung zu beachten gilt

- Wissenslücke in der **(Kosten-)Effektivität** systematischer FH-Teststrategien im österreichischen Kontext, mögliche **Interessenkonflikte** bei Ersteller*innen von Leitlinien und Wirksamkeitsstudien können die Empfehlungen und Evidenz beeinflussen
- Wissenslücke zu tatsächlicher **FH-Prävalenz**
- Entscheidung bezüglich eines organisierten oder opportunistischen FH **Screening-Ansatzes** und der **Rolle des GDx** in einem solchen
- Definition und **Klärung der Verantwortlichkeiten** auf Personalebene und bezüglich involvierter med. Bereiche
- Ruf nach systematischeren Ansätzen für LDL-C-Messungen in der **Primärversorgung**
- Überarbeitung des österreichischen **Konzepts der genetischen Beratung** und Möglichkeiten der Personalentwicklung
- GDx in organisierten Screening-Programmen derzeit in **gesetzlichen Reglungen** nicht explizit adressiert
- Umfassende begleitende **Forschungsaktivitäten**
- Steigerung der **FH-Awareness** bei Gesundheitsdienstleistern, Patienten und der allgemeinen Bevölkerung
- Adäquate **Refundierung einer professionellen genetischen Beratung,** welche deren Komplexität und Verantwortung widerspiegelt und Kontrastierung mit derzeitigem Tarif

GDx-Kosten als Hauptkostentreiber, Tarif für genetische Beratung gering

Prävalenz hat einen maßgeblichen Einfluss

neben GDx-Kosten gibt es noch eine Reihe weitere Kostenkomponenten

Hinsichtlich der Ressourcenfolgenanalyse scheint der größte Kostenfaktor zwar der molekulargenetische Test zu sein, allerdings sind eine Reihe weiterer Kostenkomponenten zu berücksichtigen. Insgesamt lassen sich die tatsächlichen Ressourcenfolgen nur grob abschätzen, da sie von zahlreichen schwer einschätzbaren Faktoren abhängen. Ein wesentlicher Unsicherheitsfaktor ist die tatsächliche Prävalenz. Ein weiterer ist die individuelle Entscheidung der Patient*innen (z. B. Zustimmung der Indexpatient*innen zum Kaskadenscreening, Teilnahmeraten), die jedoch aus ethischer Sicht unbedingt zu befürworten ist. Zusätzliche sind ökonomische Implikationen aufgrund von Investitionen in Personal (insbesondere Berater*innen) und deren Ausbildung/Training, notwendige Forschung, Evaluation und Monitoring zu berücksichtigen.

Limitationen

Die zentralen Limitationen sind:

keine explizite Berücksichtigung der Wirksamkeit, Sicherheit und Kosten-Effektivität

- aufgrund des Fokus auf ethische, organisatorische und ressourcespezifische Aspekte kann keine Aussage über die (Kosten)-Effektivität der diversen Screening-Strategien getroffen werden

keine explizite systematische Suche

- durch die Einschränkung auf deutsch- und englischsprachige Literatur, bestimmte Länder und Handsuche kam kein expliziter systematischer Suchansatz zur Anwendung

kein ausführlicher moralischer Diskurs

- die Information zur österreichischen Situation basiert aufgrund fehlender Publikationen primär auf dem Wissen dreier Expert*innen
- von einem umfangreichen moralischen Diskurs im Rahmen der ethischen Implikationen wurde abgesehen

Darstellung „nur" eines speziellen FH-Management-Modells

- Die Ressourcenfolgenanalyse beschränkt sich auf ein ausgewähltes Screening-Modell, da für Österreich bis dato kein definiertes Modell existiert

zahlreiche Annahmen, Vereinfachungen,

- Im Ressourcenmodell wurden zahlreiche Vereinfachungen vorgenommen und Annahmen getroffen
- Die Berücksichtigung der LLT einschließlich der Medikation für nur ein Jahr scheint relative Kostenvergleiche zwischen den Behandlungskomponenten zu verzerren.

nur Variation der Prävalenz

- die Sensitivitätsanalyse wurde auf einen Parameter (Prävalenz) beschränkt; weitere Sensitivitätsanalysen wären empfehlenswert (z. B. Compliance, durchschnittliche Anzahl von Verwandten pro Indexfall)

kein Kosten-Offset (keine Einsparungen von Ressourcen)

- potenzielle Kosteneinsparungen (z. B. durch verhinderte kardiovaskuläre Ereignisse) wurden nicht berücksichtigt

Conclusio

klare Zuordnung der Rolle von GDx innerhalb des FH-Management-Prozesses

Vor einer Einführung von GDx im größeren Maßstab ist klar zu definieren, welche Rolle das Testen innerhalb des gesamten Diagnose- und Managementprozesses der betreffenden Krankheit spielen soll. Im Falle von FH ist eine Schlüsselentscheidung zu treffen, ob dies im Zuge eines organisierten oder opportunistischen Screening-Ansatzes geschehen soll bzw. welcher der verschiedenen Ansätze konkret verfolgt werden soll.

Diffusion in das Gesundheitssystem ist abhängig von einer koordinierten Implementierung

Die österreichische Situationsanalyse zeigt, dass es bei ungesteuerter Diffusion von GDx zu unterschiedlichen Diagnose- und Versorgungsprozessen und dementsprechend uneinheitlicher Versorgung der Patient*innen kommt. Eine erfolgreiche Implementierung erfordert – unabhängig vom gewählten Modell – die Spezifikation jedes Prozessschrittes inklusive Verantwortlichkeiten, Ausbau von Personalkapazitäten und Professionalisierung, sowie begleitende Öffentlichkeitsarbeit und Monitoring. Aus ethischer Sicht ist besonders die genetische Beratung relevant, da die komplexen Entscheidungen, die Patient*innen zu treffen haben, professionelle Unterstützung erfordern.

robust Prävalenzzahlen sind notwendig

Die damit verbundenen Kosten gehen jedenfalls über die Kosten des eigentlichen Tests hinaus, weshalb eine (Kosten)-Effektivitätsanalyse unterschiedlicher Screening-Alternativen einer allfälligen Entscheidung vorangehen sollte. Jedenfalls sind robustere Prävalenzdaten nötig.

1 Introduction

molekulargenetische Tests in der personalisierten Medizin

The so-called personalised medicine or precision health care are domains that gradually take roots in the medical field influencing the decisions and behaviour of clinicians, the pharmaceutical industry, patients, payers, decision makers, and the functioning of the health system in general. These fields are strongly driven by new diagnostics and therapeutics, which – based on biomarkers, genetic, phenotypic or psychosocial characteristics – distinguish an individual patient from other patients with similar clinical conditions and thus form risk-based strata [1]. Molecular genetic tests are an increasingly important instrument of diagnostics, on the one hand for the definitive diagnosis of a disease and on the other hand as a prerequisite (companion diagnostics) for therapy with specifically effective drugs (prognostics). Often, however, the focus is not only on the genetic constitution of the affected patients themselves, but also on the resulting consequences for their offspring and relatives (prediction). In oncology and neurology, molecular genetic diagnostic, prognostic as well as predictive tests have been established for years and are widely used.

Funktion: (Companion) Diagnostik, Prognostik

Implikationen und Konsequenzen nicht nur für Patient*in, sondern auch Angehörige

Beispiel FH: GDx als Instrument zur Triage und Risikostratifizierung in der Prävention von kardiovaskulären Erkrankungen

Due to the discovery of functional gene sequences related to familial hypercholesterolemia (FH), molecular genetic testing is becoming increasingly important in cardiovascular medicine, particularly as a triage mechanism for risk stratification in the prevention of arteriosclerosis and cardiovascular diseases. In addition to a definitive diagnosis, an expansion of molecular genetic testing may help to more effective cascade tests of relatives at risk, the initiation of therapies in earlier years as well as to improved and more efficient therapeutic decisions in general (e.g. a decision on the use of PCSK9 inhibitors) [2].

Aufarbeitung der Komplexität organisierter Teststrategien mit integrierter GDx

Against this background, organisational-regulatory questions as well as ethical aspects of the implementation of a systematic test-strategy including molecular genetic diagnostics, but also far-reaching economic effects, have to be considered. We aim to illustrate the general complexity of such diagnostic tests and systematic test strategies, by using the example of FH, and to emphasise which implications have to be considered beyond effectiveness and safety.

2 Background

2.1 Clinical applications of genetic testing

Anwendung molekulargenetischer Tests in der Klinik: Diagnostik, Prognostik, therapeutische Entscheidungen (Companion Diagnostics)

Clinical genetic testing refers to diagnostic methods that can provide information about individual genes, the genome, i.e. the entire genetic make-up of an individual, or various gene products. Genetic information can be of considerable importance for preventive health care, for therapeutic decisions, for individual life planning and especially for reproductive decisions. Often not only the patients themselves, but also their partners or family members are affected [3]. Consequently, the range of clinical applications of genetic analyses is very wide and they are also performed at different times during a patient's life. Molecular genetic diagnostics (GDx) are applied in clinical routine for i.a. diagnosing a disease, predicting disease risk (e.g. Huntington's disease), or determining carrier status of an individual. GDx is also becoming more and more important in therapeutic decisions. Thus, within the framework of pharmacogenetic testing, GDx is used to guide drug dosing or drug avoidance in individuals with variants that affect drug metabolism or toxicities (companion diagnostics) [4]. In oncology and neurology, molecular genetic diagnostic, prognostic, as well as predictive tests have been established for years and are widely used. More recently, they have also become increasingly important for risk stratification in the prevention of arteriosclerosis and cardiovascular diseases (CVD).

2.2 Familial hypercholesterolaemia

häufigste autosomal-dominante monogene Störung

stark erhöhtes Risiko für ACVD

FH is the most common autosomal dominant monogenetic disorder worldwide. Due to lifelong exposure to elevated low-density lipoprotein cholesterol (LDL-C) levels the risk of premature CVDs especially coronary/ischemic heart diseases (CHD/IHD) is considerably increased in affected individuals. Not identified and therefore not appropriately treated male individuals are at a 50% risk for a fatal or nonfatal coronary event by 50 years of age and untreated female individuals are at a 30% risk by 60 years of age [2].

homozygote vs. heterozygote FH

geschätzte Prävalenz HeFH: 1:500 bis 1:200

A distinction can be made between heterozygous FH, in which a pathogenic mutation of an FH-associated gene is only present on one allele, and the clinically far more severe homozygous FH, with pathogenic mutations on both alleles. The overall prevalence of heterozygous FH (in the following referred to as FH, if not further specified) is estimated at 1:500 to 1:200 by many international reviews and national studies [2]. In a recent meta-analysis of 11 million subjects the worldwide, FH prevalence amongst the general population was estimated at 1:313 (0.32% [CI: 0.26, 0.39]) and among subjects with arteriosclerotic CHD 1:31 (3.2% (95% [CI: 2.2, 4.3]) respectively 1:15 (6.7% [CI: 4.9, 8.7]) among subjects with premature arteriosclerotic CHD. In patients with severe hypercholesterolaemia (LDL-C ≥190 mg/dl) 1:14 (7.2% [CI: 4.6, 10.8]) individuals were diagnosed with FH [5].

klinisches Bild: stark erhöhte LDL-C Blutwerte

Folgen: erhöhtes Risiko für Arteriosklerose und CVD bereits in jungen Jahren

The clinical presentation of undiagnosed FH patients shows symptoms or signs of atherosclerotic CVD (e.g. angina or arteriosclerotic lesions) or adverse atherosclerotic CVD events (e.g. myocardial infarction, sclerosis of aortic valve, and sudden cardiac death) already in early age. A marker for arteriosclerotic CVD is the coronary artery calcification that can be identified in heterozygous FH patients already at age 11 to 23 [6]. Pathophysiological atherosclerosis is characterised by inflammatory and disrupted metabolic processes, which result in endothelial dysfunction, plaque formation and plaque complications. The importance of LDL-C for endothelial and monocyte function in the pathophysiology of atherosclerosis was demonstrated in-vitro and animal model studies [7]. Untreated FH patients often, especially increased over age, demonstrate further clinical symptoms. The excess LDL-C is sometimes deposited in the arteries as atheroma and in the tendons and skin, mainly in elbows, hands and Achilles tendons, as xanthomata, and around the eyes, as xanthelasma. Additionally, arcus corneae, corneal lipid deposits, are proven symptoms of FH [6, 8].

homozygote FH: Prävalenz 1:300,000

Homozygous FH (HoFH) is a much rarer genetic condition concerning one out of 300.000 individuals in the general population and generally manifest in childhood [6]. Undiagnosed homozygous FH results in premature, atherosclerotic cardiovascular disease and death before age 20 in many cases [2].

2.2.1 Genetics

Aufarbeitung der Komplexität organisierter Teststrategien mit integrierter GDx

The spectrum and severity of the clinical phenotype of a hypercholesterolaemia depend in parts on the underlying range of the pathogenic variant [2]. Heterozygous FH is usually caused by a functional mutation variant at one allele of the 3 primary genes associated with FH: the low-density lipoprotein receptor gene (*LDLR*), the proprotein convertase subtilisin/kexin 9 gene (*PCSK9*), and the apolipoprotein B gene (*ApoB*). The clinical syndrome of HoFH is caused by a bi-allelic pathogenic variant of one of the FH genes, generally the LDLR gene. The compound heterozygous genotype, with a different pathogenic variant at each allele of one of the FH genes, and the double heterozygous genotype, with a pathogenic variant at one allele of one FH gene and one allele of a different FH gene, result in a more severe heterozygous FH phenotype [6].

häufigste Mutationen in LDLR-, PCSK9- oder ApoB-Gen

führen zu unterschiedlichen Störungen des LDL-C Metabolismus

In general, decreased LDLR activity is resulting in increased LDL-C plasma levels. LDLR pathogenic variants, which are the most common, are defects of the gene that encodes for the ApoB/E (LDL) receptor itself, resulting in reduced (or fully stopped) clearance of LDL-C from the blood circulation. More than 1,000 different single nucleotide polymorphisms, frameshifts, or non-sense mutations in the LDLR gene are known, resulting in different phenotypic severity [2, 6]. The PCSK9 gene encodes for a same named serine protease which is secreted by the liver. This enzyme binds extracellularly to the LDLR, after which the resulting PCSK9-LDLR complex is internalised into the cell. If a LDLR is bound to PCSK9, it is prevented from recycling to the cell surface and undergoes destruction inside liver cells. Gain-of-function mutations in PCSK9 genes result in increased level of PCSK9 enzymes in the plasma that lead to fewer LDL receptors and therefore less clearance of LDL-C. In contrast, the more common loss-of-function mutations in the PCSK9 gene are associated with reductions of both LDL-C and risk of ischemic heart disease because of an increased recycling of LDLR [6]. A defective ApoB gene is associated with impaired binding of LDL-C particles to

the specific ApoB/E (LDL) receptor. In contrast to LDLR functional mutations, where the function of the receptor itself is affected, the defect is localised at the ApoB ligand on the LDL-C particle. This results in a two- to threefold reduced clearance of LDL-C and increased plasma levels [6].

funktionelle Mutationen im LDLR-Gen am häufigsten (85-90 %)

Functional mutations in the LDLR gene are the most common, representing 85% to 90% of all genetically positive tested FH patients, whereas gain-of function mutation in the PCSK9 gene account for 2% to 4%. The least common mutations of these 3 genes are detected in the ApoB gene (1% to 2%) [6].

nur 60-80 % aller Pat. mit definitiver klin. Diagnose auch genetisch pos. (Hauptgene)

Nevertheless, in only ~60% to 80% of patients diagnosed with "definite" FH and in only ~21% to 44% of patients with "possible" FH according to clinical diagnostic criteria (see section 2.2.2), a pathogenic variant in 1 of the 3 main FH-causing genes can be identified [2].

kein Ausschluss der Diagnose bei neg. GDx: unbekannte Mutation oder polygene FH

If a patient shows the clinical phenotype of FH but no functional genetic mutation could be found, a FH diagnosis should not be excluded and the patient should be considered as having either a still unknown mutation or instead should be diagnosed with severe polygenic hypercholesterolaemia. Here a combination of minor effects of multiple individual variants leads to significantly elevated LDL-C. These minor effects still can cumulate in LDL-C levels within the same range as the major single genes associated with heterozygous FH [6].

bei Nachweis einer funktionellen Mutation und erhöhtem LDL-C Risiko für arteriosklerotische CVD um Faktor 3.3 erhöht

In a large scales meta-analysis it was shown, that if a monogenetic cause can be proven, the risk of arteriosclerotic CHD is substantially increased even if levels of LDL-C are lower. Patients with LDL-C >190 mg/dl and a proven mutation in one of the three main genes associated with monogenic FH had a 3.3-fold higher risk for CHD than patients with LDL >190 mg/dl without a detectable pathogenic variant [9].

Prinzip der lebenslangen kumulativen LDL-C-Belastung

This increased risk despite identical LDL-C levels can probably be attributed to the fact that mutation positive patients already have significantly increased cholesterol levels as children and adolescents [8, 9], resulting in adult FH patients with high levels of LDL-C since birth. Adults with high LDL-C levels not due to FH are exposed to high levels of LDL-C for a shorter duration of time and thus are at lower risk of premature arteriosclerotic CHD [6]. This is called the principle of lifelong LDL-C load or the cumulative lifetime burden of LDL-C.

2.2.2 Diagnostics

Diagnose meist klinisch/phänotypisch

In most cases, FH is diagnosed on the basis of clinical phenotypic characteristics, but molecular genetic diagnostics are applied more and more. Depending on the corresponding guidelines, clinical criteria to initially suspect FH in an individual are:

häufige Kriterien: erhöhtes LDL-C im Blut, Patienten-geschichte zu CVD, familiär gehäufte frühzeitige CVDs, äußere physische Symptome

- Elevated blood cholesterol levels in fasting lipid profiles, especially LDL-C (≥190 mg/dL) but also total cholesterol (TC)
- Personal history of CVD, especially CHD and arteriosclerotic events
- Family history of premature CVD events, tendon xanthomata and elevated cholesterol levels
- Physical symptoms like tendon xanthomata or corneal arcus [6]

Ausschluss sekundärer Hypercholesterinämie

In order to be able to suspect an FH from elevated blood cholesterol values, the individual must have a primary hypercholesterolaemia. For this purpose, all secondary causes of hypercholesterolaemia must first be excluded. It has to be assured that there is no other primary disease that can cause hypercholesterolaemia, such as cholestatic liver disease, nephrotic syndrome, chronic renal disease, or hypothyroidism [6, 7]. Beside primary diseases, increased LDL-C blood values can be due to medications, as well as lifestyle decisions, e.g. eating habits and physical activity [6]. Still, it has to be noted, that increased LDL-C levels caused by FH are unlikely to be influenced by lifestyle decisions.

LDL-C kann als direkter Laborwert bestimmt werden, aber meist indirekt über Friedewald-Formel

In clinical routine, LDL-C of a fasting patient can be determined directly after ultracentrifugation of the blood sample. But most often, because it is more simple and cheaper, it is calculated indirectly using the *Friedewald formula* (although less reliable), which includes measures of TC, HDL-C, and triglycerides [10]:

LDL-C (mg/dL) = TC (mg/dL) – HDL-C (mg/dL) – (Triglycerides (mg/dL) x 0.2)[1]

nach erstem Verdacht der FH folgt klinische Diagnose anhand standardisierter Punktscores

Following a first suspicion and after exclusion of secondary causes, standardized clinical tools should be used for final diagnosis. The most common tool is the Dutch Lipid Clinic Network criteria (DLCN, Table 2-1, see section 5.1.2) [12, 13]. This score assigns points based on LDL-C levels, personal history of premature CVD, family history of premature CVD, or high cholesterol levels in a first-degree relative, and personal physical examination findings (tendinous xanthomata or corneal arcus). *Premature* is here defined as a CVD event prior to 55 years of age in men and prior to 60 years of age in women. Depending on the estimated point score a patient is either diagnosed with definite FH (DLCN >8), probable FH (DLCN 6-8), possible FH (DLCN 3-5), or unlikely to have FH (DLCN <3). Detection of a functional mutation in the LDLR, ApoB or PCSK9 gene, which is another criterion in the DLCN tool, scores the patient immediately as a definite FH diagnosis.

DLCN Punktscore am verbreitetsten (definitive, wahrscheinliche, mögliche, unwahrscheinliche FH)

Table 2-1: Dutch Lipid Clinics Network criteria for familial hypercholesterolaemia [12, 13]

Dutch Lipid Clinic Network Criteria for Familial Hypercholesterolaemia	
Criteria	**Point**
Family History	
First-degree relative with known premature* coronary and vascular disease OR First-degree relative with known LDL-C level above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged less than 18 years with LDL-C level above the 95th percentile	2
Clinical History	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
Physical Examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4

[1] mg/dL cholesterol = mmol/L × 38.7; mg/dL triglyceride = mmol/L × 88.6, [11]

Dutch Lipid Clinic Network Criteria for Familial Hypercholesterolaemia	
Cholesterol levels mg/dL (mmol/L)	
LDL-C ≥330 mg/dL (≥8.5)	8
LDL-C 250 – 329 mg/dL (6.5 – 8.4)	5
LDL-C 190 – 249 mg/dL (5.0 – 6.4)	3
LDL-C 155 – 189 mg/dL (4.0 – 4.9)	1
DNA Analysis	
Functional mutation in the LDLR, ApoB or PCSK9 gene	8
Diagnosis (diagnosis is based on the total number of points obtained)	
Definite familial hypercholesterolaemia	>8
Probable familial hypercholesterolaemia	6-8
Possible familial hypercholesterolaemia	3-5
Unlikely familial hypercholesterolaemia	<3

* *Premature = < 55 years in men; < 60 years in women*

Abbreviations: ApoB – apolipoprotein B, LDL-C – low density lipoprotein cholesterol, LDLR –low density lipoprotein receptor, PCSK9 – proprotein convertase subtilisin/kexin 9

Simon Broome Punktescore, besser geeignet für die Diagnose von Kindern, weil weniger Gewicht auf LDL-C

Another tool often recommended and used for clinical diagnosis in the United Kingdom (UK) are the Simon-Broome Diagnostic criteria (SB) (Table 2-2)[14, 15]. Similar to the DLCN criteria, diagnosis is based on personal or a family member's blood cholesterol (TC), personal and family history of CVD, physiological symptoms in the patient or family members, and also the detection of a pathogenic variant of the associated genes. Diagnosis distinguishes between definite or possible FH in the SB score. Compared to the DLCN score, the SB score puts less weight on blood cholesterol findings and more on family history. Therefore the SB score is deemed better eligible for diagnosing FH in children, as blood cholesterol findings are often not suspiciously elevated in younger years [2].

Table 2-2: Simon-Broome Diagnostic Criteria for Familial Hypercholesterolaemia [14]

Simon-Broome Diagnostic Criteria for Familial Hypercholesterolaemia	
Point	**Criteria**
1	Total cholesterol levels >290 mg/dL (7.5 mmol/L) or LDL-C >190 mg/dL (4.9 mmol/L) in adults Total cholesterol levels >260 mg/dL (6.7 mmol/L) or LDL-C >155 mg/dL (4.0 mmol/L)
2	Tendon xanthomas in the patient or tendon xanthomas in a first or second degree relative
3	DNA-based evidence of an LDL-receptor mutation, familial defective ApoB, or a PCSK9 mutation
4	Family history of myocardial infarction before age 50 years in a second degree relative or before age 60 years in a first degree relative
5	Family history of elevated total cholesterol >290 mg/dL (7.5 mmol/L) in an adult first or second-degree relative Family history of elevated total cholesterol >260 mg/dL (6.7 mmol/L) in a child, brother, or sister 16 years or younger
Diagnosis	
Definite familial hypercholesterolaemia = 1+2 or 3	
Possible familial hypercholesterolaemia = 1+4 or 5	

Abbreviations: ApoB – apolipoprotein B, LDLR – low density lipoprotein receptor, PCSK9 – proprotein convertase subtilisin kexin 9

MEDPED Kriterien, nur Gesamtcholesterin wird betrachtet

Already in 1993, the "Make Early Diagnoses Prevent Early Deaths Program" (MEDPED) diagnostic criteria for FH were established in the United States of America (USA; Table 2-3) [16]. These criteria are solely based on TC findings exceeding age specific cut-off points and are additionally stratified by the confirmed cases of FH in the family of the individual to diagnose. If FH is not diagnosed in the family, the cut-off point is as per *general population*.

weitere nationale diagnostische Scores

In addition to these three most frequently used diagnostic scores, there are other national tools established such as the FH Canada score [17, 18] and the Japanese FH criteria [19].

Table 2-3: "Make Early Diagnoses Prevent Early Deaths Program" (MEDPED) diagnostic criteria for familial hypercholesterolaemia [16]

US MEDPED Diagnostic Criteria for Familial Hypercholesterolaemia*				
FH is diagnosed if total cholesterol exceeds these cut-off points in mg/dL (mmol/L)				
Age (years)	First degree relative with FH	Second degree relative with FH	Third degree relative with FH	General population
<20	220 (5.7)	230 (5.9)	240 (6.2)	270 (7.0)
20-29	240 (6.2)	250 (6.5)	260 (6.7)	290 (7.5)
30-39	270 (7.0)	280 (7.2)	290 (7.5)	340 (8.8)
≥40	290 (7.5)	300 (7.8)	310 (8.0)	360 (9.3)

* *"The total cholesterol cut-off points for FH is dependent upon the confirmed cases of FH in the family, if FH is not diagnosed in the family, then the cut point for diagnosis is as per general population".*

Abbreviations: FH – familial hypercholesterolaemia

Diagnose auch über molekulargenetischen Test möglich

In addition to clinical diagnostic, confirmation of FH can be sought via a molecular genetic test (GDx), testing for a pathogenic variant. The following potential benefits have been outlined [2]:

Vorteile: ermöglicht Prognose und Risiko-Stratifizierung, gezieltere genetische Beratung, frühe Behandlung von Kindern verbessert, Therapie-Entscheidungen

- GDx provides prognostic and risk stratification information due to the impact of different pathogenic variants on clinical presentation and CVD risk
- GDx allows for precision during genetic counselling, which should be offered pre- and post-testing
- GDx has value to the paediatric patient population with FH, as it allows for early treatment in childhood even if LDL-C is not yet significantly increased
- GDx has implications for therapeutic choices in FH, e.g. patients with a gain-of-function mutation in the PCSK9 gene are particularly responsive to PCSK9 inhibitors (PCSK9i; see section 2.2.3)

dennoch: Diagnose meist nur über klinische Scores

Still, most cases of FH are diagnosed using clinical criteria and the above presented scores.

2.2.3 Treatment

vorderstes Ziel: LDL-C im Blut senken zur Primär- oder Sekundärprävention

Lowering LDL-C values, to prevent first-time or reoccurring CVD events, is the primary goal of treatment in FH patients. Whether for primary or secondary prevention, therapy is always based on specific threshold values to which the LDL-C of the patient should be reduced. The current guideline of the European Society of Cardiology (ESC) together with the European Atherosclerosis Society (EAS) from 2019 [20] recommends the following therapy goals for FH patients:

ESC/EAS Guideline definiert genaue Therapieziele zur Reduktion von LDL-C

- FH patients with ACVD or in primary prevention with another major risk factor are at very high risk treatment to achieve a ≥50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended.
- In the absence of ACVD or another major risk factor, patients with FH are categorized as high-risk, and LDL-C goals are a ≥50% reduction of LDL-C from baseline and an LDL-C <1.8 mmol/L (<70 mg/dL).
- Children with FH should be educated to adopt a proper diet and treated with a statin from 8-10 years of age. Goals for treatment should be LDL-C <3.5 mmol/L (<135 mg/dL) at >10 years of age.

LDL-C Zielwerte von FH Pat. meist durch Lebensstil-Modifikationen nicht erreichbar

In general, the therapy of hypercholesterolaemia always includes an adoption of healthy lifestyle as a first step. Based on a special counselling, dietary modification, physical activity, and weight loss in obese individuals should be achieved. In the case of FH, however, the above-mentioned target values are usually not achieved by these lifestyle adaptions and LDL-C lowering drug therapy should be initiated as soon as possible after a diagnosis has been made [21].

initiale medikamentöse Therapie: Statine, bei nicht erreichen der Zielwerte zusätzlich Ezetimibe

Initial drug therapy includes a maximally tolerated statin therapy, based on broad evidence for the LDL-C lowering effect of statins in patients with and without FH [8]. It has also been shown that initiation of an early statin drug therapy can reduce the risk of CHD in FH patients to that of the general population [22]. Still, in many FH patients LDL-C target values are not reached despite maximum statin therapy, a combination therapy with ezetimibe is recommended as next therapy step. High-dose statins combined with ezetimibe can reduce LDL-C in FH patients by 60% to 70% on average [8, 20].

hoch-Risiko Pat. bei nicht erreichen der Zielwerte: PCSK9-Inhibitoren

For third-line therapy, the ESC/EAS 2019 guideline recommends a therapy with PCSK9i in very-high-risk FH patients, if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe [20]. PCSK9i can reduce LDL-C by another 50-60% in addition to statin therapy. Mainly because of the higher price of PCSK9i compared to statins, drug therapy with PCSK9i is mainly intended for FH patients in secondary prevention or in patients showing statin intolerance [8]. The exact indications for reimbursement vary from country to country.

HoFH: zusätzlich Lomitapide und Lipid-Apharese

For HoFH, Lomitapide is indicated but mostly lipoprotein apheresis remains the therapy of choice to improve long-term survival.

2.2.4 Screening

FH-Screening: frühe Diagnose ermöglicht Therapie und steigert Prävention

As early diagnosis and medical management with LLDs beginning in childhood have high potential to reduce the risk of atherosclerosis and CVD events in patients with FH to that of individuals without FH, early identification of patients is of major importance, both for the individual and for public health. Based on this, screening for FH is recommended by a variety of guidelines [11, 23-25].

WHO-Definition

The World Health Organisation (WHO) defines screening as follows:

> *"Screening is defined as the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population. A screening programme must include all the core components in the screening process from inviting the target population to accessing effective treatment for individuals diagnosed with disease" [26].*

Ziel v. Screening: wahrscheinlich Betroffene von wahrscheinlich nicht Betroffenen unterscheiden

Accordingly, a screening programme includes testing of apparently healthy, symptom-free people to detect a risk factor or a pre-existing, undetected disease, i.e. people who are screened either have no symptoms/signs of the disease they are screened for or have not yet noticed it. The purpose of screening is to distinguish between those who are *likely to be affected* and those who are *unlikely to be affected*. The aim of screening is either to reduce an individual's risk for a particular disease or to provide information about the risk, even if the risk itself cannot be changed by the screening [27, 28].

WHO-Kriterien sollen für Screening-Programme erfüllt sein

In 1968 the WHO published ten criteria that a screening programme should fulfil [29]. In the revised and adapted form by Anderman et al. 2008 [30], many of these criteria apply to FH screening:

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.

opportunistisches vs. systematisches (universell vs. selektiv) Screening

Raffle and Gray distinguish between different screening strategies: it can be a test opportunistically offered to an individual or it can be a test systematically offered to an entire population. This systematically organised screening can be either universally population-based or based on selective criteria [27]. The two screening variants are also recommended and applied for the diagnosis of FH. In addition, the FH test strategies also distinguish between primary care based screening (non-specialised setting) and screening in a secondary or even tertiary care setting (specialised setting) [31].

The so-called cascade screening, in which family members are step-wise screened starting from an initial patient (index patient), plays a very special role in the diagnostic process of FH.

Kaskadenscreening von Familienmitgliedern

2.2.5 Economic background

Generally, a model of care for FH needs to cover and answer questions on the following three components:

- The specific context the index patient identification is conducted such as searching via primary health care records,
- the embedding of a certain screening or diagnostic programme such as cascade screening in the specific identification strategy context, and
- the specific lipid-lowering therapy (LLT) or treatment strategy with lipid-lowering medications.

Versorgungsmodell FH besteht aus 3 Komponenten: Identifizierung von Indexpatient*innen (IP), Screening-/Diagnose-Strategie, und Behandlungsstrategie bzw. lipidsenkende Therapie (LLT)

All of these considerations can result in different costs and resources needed depending on the specification of procedures within. Additionally, different strategies can result in different cost-effectiveness levels and thus, more or less efficient ways to use limited resources.

According to the existing health economic (HE) evaluation literature in the FH context, cascade screening of family members of a known index case has been identified as a cost-effective strategy – preferably carried out by a lipid clinic and including molecular genetic testing of the index case as recommended by the National Institute for Health and Clinical Excellence (NICE) [32-35]. The NICE recommendations on cascade testing strategies in the preceding NICE evidence guideline (CG71) from 2008 were also based on an accompanied systematic review of HE evaluations [36-40]. Of two alternative cascade testing strategies the strategy based on molecular genetic testing was cost-effective compared to the lipid-based cascade screening.

gesundheitsökonomische (ges.ök.) Literatur: Kaskadenscreening von Verwandten ist kosteneffektiv

There is some recent evidence available that identifying index patients using primary health care records, a clinical assessment using the SB criteria before molecular genetic testing, and a cascade screening strategy, testing the relatives of both current and new index cases is cost-effective [41-46]. Furthermore, it was found that primary care case identification using the DLCN criteria had a 43% probability of being the most cost-effective strategy. The increase in molecular genetic testing was the main cost driver, accounting for around 50% of short-term costs (without LLT).

Identifizierung von IP durch primäre Gesundheitsdaten/-akten scheint kosteneffektiv zu sein

On the contrary, secondary case identification of people with early myocardial infarction (MI) was unlikely to be cost-effective. Furthermore, primary case identification was also cost-effective compared with a broader treatment strategy with lipid-lowering therapy regardless of their FH status and without genetic testing [41].

Identifikation von sekundären Fällen weniger kosten-effektiv

One important conclusion from the current cost-effectiveness literature is that an effective index patient identification process (early identification by a systematic approach) has major impacts on further steps in FH management and also affects the degree of cost-effectiveness. Not only identified cases benefit from identification but also their relatives, both current and potential. This seems an effective strategy given that adults with a definite FH mutation have at least three times the risk of a CV event as those without FH. Hence, in cost-effectiveness terms, this makes systematic screening interventions more attractive, because it is likely to represent a relatively inexpensive, targeted

Literatur: effektive Identifizierung von IP hat Auswirkungen auf die weiteren Schritte und auch den Grad der Kosten-Effektivität

and effective approach compared to alternatives [47]. If the subsequent cascade screening leaves too many cases undetected or implementation in an existing healthcare system is difficult, then only other approaches such as universal screening of children or broad based LLT seem to be an alternative, which may be more expensive [33, 47].

Verallgemeinerbarkeit/ Übertragbarkeit von Kosten-Effektivitäts-Studien/Ergebnissen auf unterschiedliche Kontexte ist aufgrund der Parameter-Unsicherheit in den Studien begrenzt

However, the transferability and generalisability of cost-effectiveness results is limited due to different health care system characteristics and unit costs. Additionally, cost-effectiveness analysis (CEA) of care models – not to confuse with single care subtasks or treatments in care models – are mostly conducted by a modelling approach which combines cost-effectiveness evidence of single sub-treatments including many assumptions. Furthermore, cost-effectiveness studies often use "no screening" as a comparator, which does not reflect the reality in some health care systems, and therefore likely overestimates the effect. Therefore, existing cost-effectiveness (CE) modelling studies and systematic reviews of HE evaluations of models of care are often associated with a lot of uncertainty and need to be interpreted with caution within the Austrian context. They can, however, be used to give a rationale for strategies in the subsequent hypothetical resource impact analysis (section 5.5) and to understand the most important economic questions regarding FH treatment measures.

3 Project Aim and research questions

3.1 Project aim

This report provides an overview of the current internationally recommended and implemented test strategies to identify patients with FH in order to diagnose them at an early age and reduce the risk of premature CVDs by rapid initiation of LLT. Special focus is given on the strategy to identify and diagnose FH index patients, subsequent cascade screening of at-risk family members, and the utilisation of (predictive) molecular genetic diagnostics as a triage mechanism in prevention of arteriosclerosis and CVD. Related organisational and regulatory aspects, as well as questions of ethics in genetic molecular diagnostics will be highlighted

organisatorische, ethische, regulative Aspekte molekulargenetischer Diagnostik am Beispiel FH

In addition to the overview of organisational characteristics and the ethical analysis, a resource impact analysis aiming to roughly quantify economic implications for a hypothetical FH screening and treatment model of care including molecular genetic testing in the Austrian population is carried out. This is done by depicting a hypothetical FH management programme including the respective patient flow on the basis of epidemiological data, discussing relevant treatment tasks and quantifying respective costs including a sensitivity analysis.

Ressourcen- bzw. Budgetfolgenanalyse zur Quantifizierung ökonomischer Implikationen

Overall, we aim to illustrate the general complexity of such diagnostic tests and systematic test strategies, as well as demonstrating potential financial implication by using the example of FH.

Komplexität systematischer Teststrategien mit integrierter GDx

It is not the aim of this report to analyse benefits, risks or cost-effectiveness of molecular genetic testing in general and of FH screening (including GDx) and treatment in particular.

nicht: Wirksamkeit und Nutzen, Kosten-effektivität

3.2 Research questions

1. Which test strategies and diagnostic processes for diagnosis of FH are recommended by (inter-)national guidelines and medical associations?

   (inter-)nationale Teststrategien
2. How is FH diagnosed in Austria and how is the current testing strategy structured?

   österreichische Situation
3. Could the current FH test strategy in Austria be improved and what organisational steps are necessary to achieve this?

   Ansätze zur Weiterentwicklung
4. Which ethical and regulatory aspects have to be considered in (predictive) molecular genetic diagnostics with a special emphasis on FH and cascade screening?

   ethische Aspekte (prädiktiver) Gendiagnostik
5. What are the economic implications of a systematic FH management strategy including molecular genetic testing for the Austrian population and what resource impact can be expected?

   ökonomische Implikationen und Ressourcen-Folgen

4 Methods

This assessment is limited to the clinical picture of heterozygous FH. There are guidelines and recommendations for the diagnosis and management of homozygous FH available as well, but these are not considered here.

Fokus auf heterozygoter FH

4.1 International and national FH test strategies

4.1.1 Literature search

For the synthesis of possible FH test strategies and identification of their characterizing components, we conducted an iterative hand search for (inter-)national guidelines, recommendations, position statements, consensus papers, scientific publications, or other FH test strategies-related publications, as well as for sources on country-specific implementations of the guidelines and recommendations on FH diagnostics. In the following, the term *guidance* will be used for the variety of these types of information sources. The focus was solely on the identification of actual applied or recommended FH test strategies.

Handsuche nach (inter-)nationalen Empfehlungen und Teststrategien

At first, we searched in the Guidelines International Network (G-I-N) Library and in the Trip-Database for relevant literature (search terms in appendix Table 9-1), followed by a search on web pages of official public health institutions, HTA/EbM institutions, (inter-)national expert societies, scientific societies, and patients' organisations. A detailed list can be found in appendix Table 9-2.

Suche in Datenbanken (GIN, Trip), Seiten von Fachgesellschaften und Pat.-Organisationen

In addition to international recommendations on the process of FH diagnostics and test strategies, nine countries were selected for a more detailed description and comparison of its components and different organisational approaches. Following selection criteria were defined for this, at least one of which had to apply:

Kriterien für Auswahl nationaler Teststrategien:

Appropriate countries should

- have systematic (e.g. universal) screening in use or recommended,
- provide sufficient and detailed information on the national FH test strategy or diagnostic procedure,
- have a comparably developed health system to Austria, and
- provide relevant literature and information in English or German language between the years 2011 and 2020.

systematisches Screening implementiert, Informationen publiziert, mit Ö vergleichbar, Literatur in deutsch oder englisch

Based on these characteristics we selected Germany, Switzerland, Belgium, Slovenia, the United Kingdom, the United States of America, Canada, and Australia, New Zealand and Oceania (Australasia) for a detailed country comparison.

AUS, BE, CA, CH, D, SL, UK, USA

This synthesis does not aim to completely cover the existing literature, the goal is rather to identify different recommended or implemented strategies and diagnostic processes. In the following, the term *national* does not necessarily describe an official FH test strategy organised by the government, but can also refer to recommendations of expert societies and individual projects initiated by them

keine systematische Erfassung der gesamt verfügbaren Literatur

4.1.2 Data extraction

Komponenten der Datenextraktion:

Adapted to the guidelines from UK [15, 23] and Australasia [48], which provided a detailed structure of their test strategies, we identified 9 components characterizing FH test strategies:

IP, klinische Diagnostik und Kriterien, involvierte medizinische Dienste, molekulargenetische Diagnostik, Kaskadenscreening, genetische Beratung, Register, Aufklärung und Bildung, Therapie

- Detection of index-cases
- Criteria for diagnosis and tool for assessment
- FH service providers
- Molecular genetic testing
- Cascade screening
- Genetic counselling
- Registry
- Awareness and education
- Lipid-lowering treatment

A particular focus was on the differences in the case finding procedure and screening methods, i.e. how index patients are identified.

Datenextraktionstabelle in Anhang

The information retrieved from the selected (inter-)national literature (see Appendix Table 9-2) were systematically extracted into a comprehensive data extraction table (see Appendix Table 9-3). When extracting the components of the test strategies, we made no distinction between formal recommendations from guidelines or position papers, and actually applied national procedures. The focus was solely on identifying different components and approaches.

keine Evaluierung von Wirksamkeit und Nutzen der Strategien

An evaluation of the effectiveness and the benefit of the respective test strategy or the diagnostic test was not conducted as this was beyond the scope of this project.

4.2 FH in Austria – Current test strategy and diagnostic processes

Beschreibung der österreichischen FH Teststrategie: Literatursuche und Experteninterviews

The narrative description of the current FH test strategy and diagnostic process in Austria is based on published literature and legislative texts, as well as on expert interviews. Its content structure is based on the components of the FH test strategies identified in Q1.

4.2.1 Literature search

Handsuche in Google und Fach-spezifischen Quellen, Gentechnikgesetz

An iterative hand search was conducted to identify published information on FH in Austria. Starting with a Google search, we scanned for the terms *Familial Hypercholesterol** (resp. *Familiäre Hypercholesterinämie*) and *Austria* (resp. *Österreich*). We then checked Austria-specific sources like national expert societies and patients organisations, for guidelines, policy documents, or any FH related information. Further we identified the law code and legislative texts on genetic testing in Austria as relevant.

4.2.2 Expert interviews

Experteninterviews zum diagnostischen Vorgehen in Ö

In order to gain a better overview of the actual FH test strategy and diagnostic processes in Austria, to receive more detailed background information, and to identify possible future perspectives, we conducted expert interviews.

klinische Experten aus Humangenetik, Labormedizin, AM

Since a major focus of this assessment is the molecular genetic diagnostics of the FH, we decided to interview clinical experts in human genetics, laboratory medicine, and general medicine.

persönlich und telefonisch, Audiomitschnitt extrahiert

The interviews were conducted on 07.07.2020 (by phone), 08.07.2020 (in person), and 27.7.2020 (by phone). After given consent, they were audio recorded, but not transcribed. Excerpts of the descriptions and information about the Austrian FH test strategy were extracted, paraphrased, and presented in combination with information derived from literature in a narrative form.

strukturierte Befragung

The expert interviews, personal and by phone, were semi-structured, based on a predefined guidance. In Appendix 9.2.1 the set of topics and questions is provided. Results were fed back to the experts for corrections.

4.3 FH in Austria – Opportunities for improvement and organisational requirements

organisatorische Aspekte

Organisational aspects include the interactions that arise from a diagnostic method, in this case molecular genetic testing for FH, on the organisation of the health care system.

mögliche Verbesserungsänsätze identifiziert durch Experteninterviews, Vergleich mit int. Teststrategien, organisatorische Konsequenzen

In addition to the current test strategy and diagnostic processes of FH in Austria (see section 5.2), the experts were also asked how this process could be improved and how the test strategy should ideally be (target state) with regard to index case finding, diagnostic procedure, GDx, cascade screening, etc. The aspects identified from the experts are compared with test strategies in other countries and international guidelines and missing information was added if provided (see section 5.1). Organisational implications are narratively summarized and associated organisational consequences are highlighted.

4.4 Ethical and regulatory aspects of genetic testing for FH

ethische und regulatorische Aspekte (prädiktiver) Gendiagnostik:

Fürsorge (Benefizienz), Schadensvermeidung (Non-Malefizienz), Autonomie, Gerechtigkeit

The analysis of ethical and regulatory aspects of GDx for FH was based on the Hofmann's simplified catalogue of questions [49], which addresses the following moral aspects for the use of the health technology of interest:

- *Beneficence:* Health care professionals should act in the best interest of their patient
- *Non-maleficence* (including aspects of *vulnerability* and *stigmatisation* of certain patient and stakeholder groups): Health care professionals (or the technology of interest) should not harm the patient
- *Autonomy and respect for persons:* Patients should have the right to refuse or choose their treatment and give autonomous informed consent

- *Justice*: Concerns the equitable distribution of health resources, including the decision of who gets the respective treatment or has access to the technology of interest [50]

pragmatischer Ansatz

This method does not claim to be exclusive or comprehensive and is merely intended to provide a pragmatic framework for the discussion of relevant moral aspects [51].

Literatursuche spezifisch zu molekulargenetischer Diagnostik bei FH

Within the scope of an orienting search, the (ethics-related) databases Belit, EthxWeb, MEDLINE, and Scopus were searched for relevant literature using the keywords listed in Appendix Table 9-1. In addition, the studies included in the description of test strategies (see section 5.1) and the status quo of Austria (see section 5.2), as well as interest-dependent information sources such as the websites of interest groups were used.

Extraktion ethischer Aspekte zu Zielpopulation, Krankheit, Intervention und Stakeholdern

Based on the above described Socratic approach by Hofmann [49], we identified ethics-relevant aspects related to the target group including FH index patients and family members, the disease, stakeholders, as well as the intervention at stake (Table 4-1). They are described in a narrative overview and a detailed extraction table of all aspects is provided in Appendix Table 9-8.

Table 4-1: Technology, intended use of the technology and comparator for the ethical analysis of molecular genetic testing for FH

Technology	Molecular genetic diagnosis of FH (mutations in FH-associated genes (LDLR, ApoB, PCSK9))

Intended use of the technology	**Target condition:** Heterozygous FH
	Target population:
	■ Patients with clinically and/or genetically diagnosed FH
	■ Patients with
	  ■ primary hypercholesterolaemia and suspected FH
	  ■ primary hypercholesterolaemia and diagnostically confirmed coronary artery disease and/or peripheral arterial disease and/or cerebral arterial disease
	  ■ suspected FH
	■ Family/relatives of the above patient groups

Comparator	Standard clinical diagnosis of FH including assessment of lipid profile, personal history of ACVD, family history of ACVD, other related clinical symptoms

Abbreviations: ACVD – arteriosclerotic cardiovascular disease, ApoB – apolipoprotein B, FH – familial hypercholesterolaemia, LDLR – low density lipoprotein receptor, PCSK9 – proprotein convertase subtilisin/kexin 9

4.5 Resource impact

4.5.1 Foundations and definitions

Ressourcenfolgenanalysen (RIA) werden bei der Implementierung von neuen Interventionen, Leitlinien oder bei Kostenerstattungsentscheidungen eingesetzt

A resource or budget impact analysis (RIA or BIA) evaluates the direct financial impact that arises when a new health technology is reimbursed or introduced, a guideline is implemented, or when the use of an existing health technology in a health care system is changed – typically in the short-to-medium term [52]. RIA are mainly used for budget and resource planning and are therefore increasingly required by health planners when implementing screening strategies, disease or disorder management programmes (DMP) on a population level or by reimbursement authorities as part of a reimbursement decision. A RIA can be a complement to a comprehensive HE evaluation such as a CEA or a separate analysis [53, 54].

The analysis includes, for example, financing flows and follow-up costs for the potential proportion of patients who will receive the new or altered service or resource means that are used to disseminate the service in the health care system. Follow-up costs or revenues include implementation or legal enforcement costs (e.g. personnel costs, administrative costs) and nominal costs (transfer payments, tangible or intangible services provided by a public body to individuals, groups of individuals or other public bodies and institutions) that arise when a new legislative measure is introduced. Costs incurred with regard to initial investment, expansion, supplementary or replacement investments for new legislative measures are generally not taken into account when calculating financial effects. The resource impact approach is concerned exclusively with public costs for a limited time horizon, whereas a decision on efficient resource allocation based on CEAs requires a comparison of costs in relation to benefits (e.g. life years gained, quality adjusted life years) for a possibly longer time horizon and from an often broader societal perspective. Thus, while HE evaluations focus on efficiency (effectiveness in relation to costs), the resource impact analysis is primarily concerned with the affordability of a new technology or programme, although both types of studies are based on similar data content or methodological requirements.

Folgekosten und Finanzierungsflüsse werden dabei berücksichtigt (unmittelbare Interventionskosten, Personalkosten, administrative Kosten etc.)

Fokus von RIA: Finanzierbarkeit und nicht Effizienz

While an Austrian-specific cost-effectiveness analysis is beyond the scope of this study (see section 3.1), international economic evaluations were utilised as a reference point defining the hypothetical screening and subsequent strategy and identifying relevant cost parameters. For the calculations, the resource impact report on the management and identification of FH by the NICE served as an underlying economic framework for Austrian-specific calculations [41]. However, some adaptations were made, since the NICE model does not include increases in administrative and practice staff workload in primary care and it also presents treatment steps in a highly aggregated form, which was deemed inappropriate for our own purpose.

internationale ges.ök. Evaluationen als Referenz für die Berechnungen bzw. Adaptierung des NICE-Modells für AT

Overall, the resource impact calculation requires three broad steps to be undertaken in order to depict the patient flow of the respective FH management strategy and associated costs:

3 notwendige Kalkulationsschritte:

1. Identifying and/or estimating the epidemiological dimensions of the relevant (sub-)population(s);
2. defining and costing a systematic strategy including respective tasks to detect index patients and to identify affected relatives;
3. defining and costing the DMP[2] for identified cases, which in particular includes a lipid-lowering therapy (LLT).

Epidemiologie und Subpopulation,

Identifikations-Strategie von IP und Verwandten,

und Behandlungsstrategie

4.5.2 Epidemiology

The data basis for the calculations of epidemiological dimensions were epidemiological and demographical data from Austrian-specific sources. Population statistics from Statistik Austria were used to define the base population [55]. As overall population size we used the demographic data for the population ≥18 years. This age group was chosen because it corresponds to the age group of the Austrian preventive medical check-up (*Vorsorgeuntersuchung*/VU)

Datenbasis: Bevölkerung ≥18 (Statistik Austria) mit verfügbaren VU-Daten

[2] Even though there is no uniform definition for the term disease management, it is rather appropriate to use the term disorder management programme for FH treatment rather than disease management programme as it is used in the context of diabetes.

which we have defined as a source for identifying index cases. According to the Austrian social security for 40% of the population VU records are available [56] (details see section 4.5.3).

Diagnose- und Prävalenzzahlen von der AAS und internationale Zahlen für weitere Parameter

FH prevalence numbers, data on people diagnosed and identified were taken from the position paper of the Austrian Atherosclerosis Society (AAS) and applied to the VU population for which health care records/VU records are available [57]. However, due to the lack of precise data and some general data gaps on subpopulations required for the calculation, international data sources such as specificity and sensitivity of DLCN criteria were used in addition. This information set has been extrapolated for Austria in parts and matched with the available data [33]. The detailed sources for each parameter are presented in the result section in overview tables (section 5.5 in Table 5-5, Table 5-6 and Table 5-7).

relevante Subpopulationen bei einer FH-Management-Strategie

Relevant subpopulations that we considered in the selected FH management strategy are:

- People with a current diagnosis of FH (old/existing index cases)
- Relatives of people with a current diagnosis
- People newly identified (new index patients)
- Relatives of people newly identified
- People who have experienced an early cardio vascular event (e.g. MI)/new index cases in secondary care
- Relatives of new index cases in secondary care

4.5.3 FH management strategy

Modellannahmen auf Basis internationaler (ges.ök.) Evidenz

Since a wide range of possible FH management programmes (different index patient identification, screening programmes and opportunistic treatment) with different cost-effectiveness levels are available and an Austrian model has not been defined so far, we selected the following FH management strategy as an example for the resource impact calculation based on cost-effectiveness evidence and strategies followed in other countries (see section 4.5.1 and 5.1):

Identifikation von IP: systematisches Screening von Gesundheitsakten der VU

As a strategy to identify index patients we chose the primary care records screening approach. One source for screening health records in Austria would be the electronic patient record system (*Elektronische Gesundheitsakte*/ELGA), since ELGA is already in use in all public hospitals, outpatient clinics, physicians in private practice in primary care, nursing homes and pharmacies. However, due to the lacking data availability for the ambulatory sector and other uncertainties related to this strategy (e.g. legal requirements) we assumed that the VU records would be used as a starting point for screening.

erhobene Lipidwerte bei der VU: Gesamtcholesterin (GesChol), HDL-C, GesChol/HDL-C-Quotient, TGC

The consultation of VU records may offer a target specific approach for FH management and is conducted locally at a low-threshold. As part of the health-checks, the GP in cooperation with a laboratory assesses lipid values (LDL-C indirectly via Friedewald formula) and screens for general hypercholesterolaemia (TC/HDL-C quotient) and hypertriglyceridemia [58]. The GP has to document these records in a separate documentation paper (*Befundblatt*). Cholesterol data available at the GP level is used for identifying new index patients and already treated FH (old/existing index cases), the latter additionally serving as index cases for cascade screening. We assumed that the core task of active case finding through search of practice database is done by practice assistants at the GP-level.

Personen mit GesChol ≥310 mg/dL werden eingeladen

FH index patients should be identified among other criteria according to a TC level ≥8 mmol/L (≥310 mg/dL) and without treatment in an adult or adult family member in the VU records. People fulfilling these criteria will be invited by the GP assistant for a preliminary assessment in primary care.

einleitende Untersuchung und mögliche Überweisung an eine/n FA

At this intermediate step the uptake rate plays a crucial role. It depends on the compliance by the invited person, but also whether the invitation process initiated by the respective GP and practice assistant was frictionless. The subsequent preliminary examination consists of an assessment of phenotypical predictors of FH including family history potentially including a DLCN assessment, blood sampling at a medico-chemical laboratory and a preparation of a report for referral to a specialist.

Beurteilung auf Basis von DLCN-Kriterien uns sonstigen Unterlagen des/der Pat.

After referral, we assumed that the specialist conducts an assessment of potential or definite FH via DLCN criteria (DLCN>5), if this was not already conducted by the GP. The assessment task at the specialist includes the evaluation of DLCN criteria and/or the evaluation of the prepared report by the GP, discussion of findings and clarification of further steps. This evaluation step is either conducted by a lipid specialist in a specialist-led setting or can be carried out at the GP level. For the costing we assumed no difference in unit costs in either setting.

genetischer Test bzw. Sequenzierung: NGS (LDLR, ApoB, PCSK9, LDLRAP1)

Regarding the method applied in genetic testing we assumed that genetic sequencing by next generation sequencing (NGS) of mutations in relevant genes (LDLR, ApoB, PCSK9 and in several cases LDLRAP1[3]) is undertaken both in index patients and in their relatives.

Kaskadenscreening von biologischen Verwandten

Cascade screening using DNA testing in our model is carried out to identify affected first- and second- and, when possible, third-degree biological relatives of people with a genetic diagnosis of FH. According to NICE the Quality Standard for FH we restricted cascade screening to monogenic FH index cases only [33]. FH has an autosomal dominant pattern of inheritance. Therefore, it is assumed that siblings and children of people with FH have a 50% risk of inheriting FH [33]. For simplification this risk is assumed for all family members of people with a confirmed diagnosis of FH [59].

Genetische Beratung

In addition, genetic counselling which is mandatory in Austria before and after a DNA test (if people agree to be tested) was included in the costing.

lipidsenkende Therapie: „High-potential" Statine und/oder Ezetimibe

keine Berücksichtigung von PCSK9-Hemmern

It is assumed that all identified people with FH will be prescribed LLT. Generally, statins can be categorised into low, medium and high intensity depending on how much they reduce LDL concentrations. In most of the cases high potential statins lower LDL concentrations by more than 40% [20, 60]. In our model we assumed treatment with a high-potential statin (Atorvastatin 80mg or Rosuvastatin 40mg), ezetimibe[4] (10mg) or a combination of the two. We are aware that in daily practice LLT-approaches are more complex (e.g. patients have different LDL-C levels and different treatment intensities are needed for achieving the targeted LDL-C level reduction, statin therapy can be contraindicated and ezetimibe monotherapy is used instead) but it would go beyond the scope of this assessment to model all different treatment strategies.

[3] Mutations in the low-density lipoprotein receptor adapter protein 1 (LDLRAP1) lead to LDLR malfunctions that is associated with FH. According to our requested source LDLRAP1 is also sequenced in the course of GDx for FH. Therefore, the gene is also included in the cost calculations.

[4] In some cases, ezetimibe is used as a monotherapy for primary hypercholesterolemia/ FH, because a statin is unsuitable or is not tolerated.

Darstellung der LLT- und Medikationsosten nur für 1 Jahr

Fokus liegt auf den (prädiktiv) diagnostischen Komponenten

It needs to be emphasised that when we are talking about a life-long disorder such as FH, the inclusion of LLT costs for just one year seems to distort the distribution of the costs. Medication (and monitoring) costs are recurring for approximately 50 or 60 years after diagnosis. If we would calculate costs for 50 or 60 years, the initial costs of active case finding, cascade screening and GDx would be a smaller in relative terms. Nevertheless, the depiction of the LLT costs in the section 5.5.3 and section 5.5.4 was carried out in this way on the one hand due to the assumed time horizon of one year for the resource impact analysis. On the other hand, the focus of the resource analysis was rather on the (predictive) diagnostic component of FH. Hence, the inclusion of LLT including monitoring for just one year can be seen as a further diagnostic step towards a correct LLT therapy considering the response for the individual. FH patients need to be correctly adjusted to their right therapy and some patients may be non-responders to the initial LLT that would demand further considerations.

Finally, a small proportion of people may be eligible for PCSK9i [20, 33]. However, PCSK9i are only publicly funded for secondary prevention which we do not address in our analysis. PCSK9i treatment is therefore excluded from our analysis.

Annahme Compliance-/ Teilnahmerate: 100 %

All uptake or compliance rates of the respective treatment steps except for the preliminary clinical assessment were assumed to be 100%. Whether this assumption is realistic for the Austrian context is not quite clear. However, from a public funding agency perspective (social security) this would constitute the most resource intensive setting with regard to the uptake rate.

LLT für alle identifizierten FH-Fälle

We are aware that some of the people identified via the systematic search are already prescribed LLT medication for high cholesterol (old/existing index cases). Assuming that this is a low proportion and being aware of the proportionally low costs of statins, we ignored this fact in our model and calculated LLT treatment costs for all patients identified.

keine Berücksichtigung von sekundären Fällen bei der Identifizierung und Behandlung von Indexpatient*innen

Although, to a certain degree, FH is prevalent in people that already experienced an MI event (~2% had a pathogenic variant in the main gene – LDLR – causing FH) or in people with coronary artery diseases such as stable or unstable angina, our resource calculation did not consider secondary care case identification. The rational for this decision is: Firstly, the estimates of FH prevalence within secondary care are quite heterogeneous depending on the study population data or data bases consulted with very low (pathology databases, lipid clinics/registries) or moderate to low evidence quality (coronary units) [33]. Furthermore, in the hospital discharge statistics, only discharged cases but not persons are shown. Thus, a person who has visited a hospital several times in the course of a calendar year due to a cardiovascular disease (even for the same diagnosis) will appear several times in the statistics. This would have distorted our estimations of prevalence. For simplification, it is assumed that FH cases in this population including their relatives are already in treatment in some form of a cascade screening. These costs are already incurred and so no "new" costs would incur for secondary care cases.

Fokus auf monogene FH

Furthermore, only monogenic FH cases were considered in the calculations. Details and justification for neglecting secondary cases and homozygous FH in the calculations are given in section 5.5.1 discussing epidemiology of FH and patient flow.

4.5.4 Perspective

Kosten aus der Perspektive des öffentlichen Gesundheitswesens

The cost calculation was conducted from the perspective of public funding agencies (social security). This means that neither private costs (e.g. deductibles) nor indirect costs (productivity losses) were taken into account. The public costs are shown as a total amount in €. This means that there is no differentiation of the expected costs (savings) for individual public funding agencies.

4.5.5 Prices, tariffs and unit costs

für Preise, Tarife und Kosten wurden mehrere Informationsquellen herangezogen: Tarife für AM/FÄ, DMP Diabetes, Labortarife, Spezialtarife (BVAEB, Salzburg)

For the derivation of unit costs for FH associated services, multiple sources were consulted. In general, the Austrian health care sector is quite fragmented with respect to the service provision and the financial structure. There is no uniform Austrian-wide tariff catalogue source for single services or lump sum tariffs for same service bundles that are provided across federal states and across health care sectors (inpatient and ambulatory sectors). However, the situation with regard to availability of tariff information and standardised tariffs has improved over the last years. For contracted GPs and specialists, specific treatment programmes such as the DMP for diabetes (*Therapie aktiv*) and laboratory services, uniform tariffs are available. For some services, however, special tariff catalogues were consulted (insurance institution for public servants, railroads and mining (BVAEB) and a specific tariff catalogue for Salzburg). Flat-rate payments per quarter (*Fallpauschale*) for GPs and specialists were also included in the calculations.

Kollektivverträge gemäß MAB-G

The costs for searching of index cases in VU patient records by GP assistants, subsequent assessment of TC levels, writing and sending of invitational letters (administrative task) are based on the tariff and regulation for the medical assistant profession (MAB-G). These costs would additionally accrue to the "normal" service supply mandate (*Versorgungsauftrag*) as a result of implementing the systematic search.

Abrechnungstarife für molekulargenetisches Testen: Hanusch Krankenhaus, Wien

No official tariff was available on costs and services connected to molecular genetic testing and genetic counselling. Treatments and unit costs for a representative FH patient are therefore based on an expert interview at the human genetics centre of the Hanusch hospital, Vienna [61].

Preise für Medikation und Therapie aus dem Erstattungskodex

Prices for medication and LLT respectively were derived from the reimbursement code (*Erstattungskodex*) of the main association of the Austrian health insurance institutions and from tariffs for service bundles of the DMP for diabetes [62].

Medikationskosten: gewichteter Durchschnitt von Atorvastatin, Rosuvastatin und Ezetimib je nach Verschreibung und Anwendung

For the costs of LLT medication a weighted average of the costs of atorvastatin, rosuvastatin and ezetimibe depending on the prescription and utilisation was calculated. Since no specific data on the utilisation and distribution of high intensity statins was available, data from the NICE model was used for approximation in Austria. Since some patients take ezetimibe alone, and some take a prescribed combination of the two, the proportion prescribed that was used in the calculations does not sum to 100% [33, 41]. In addition to the lipid lowering therapy, care and monitoring steps or so-called follow-up care tasks were included. Necessary monitoring parameters for blood sampling are taken from the ESC/EAS guideline [20].

Tarife für Leistungen von weiteren Gesundheitsberufen

Furthermore, measures and tariffs for services of various health care professions were utilised from tariffs of the social insurance and wages of collective labour agreements. If necessary, they were supplemented with international tariffs.

4.5.6 Time horizon

Zeithorizont: 1 Jahr für die Identifikation von IP und den assoziierten Leistungen

LLT-Kosten können linear über das Basisjahr extrapoliert werden

The cost calculations for the index patient identification and the screening steps were made in a static manner, i.e. on the basis of the epidemiological parameters, the number of affected people (identified index patients and potentially affected relatives) were calculated for one year (base year). Hence, it is assumed that the relevant population affected by FH is constant over the costed horizon and no significant changes with regard to the FH prevalence in the population occurs. The cost calculations for the LLT were also conducted for a short-term time horizon of one year. It can be assumed that costs of lipid-lowering medications and monitoring steps beyond the budget year can be linearly extrapolated.

4.5.7 Discounting

keine Diskontierung

Due to the short time horizon, costs were not discounted.

4.5.8 Sensitivity analysis

Sensitivitätsanalyse: Variation der FH-Prävalenz

Resource and cost calculations are highly dependent on epidemiological data and also on the population that can be identified for treatment. Therefore, sensitivity analysis was conducted with respect to the prevalence of FH due to the high degree of uncertainty of the prevalence in general and for the Austrian context in particular. Specifically, the base case prevalence of 1:250 was varied to 1:500 and 1:200 respectively.

5 Results

5.1 International and national FH test strategies

(inter-)nationale Leitlinien, Empfehlungen und Implementierungen. Inkludierte Literatur: 2 International, 2 AUS, 2 BEL, 2 KA, 4 DE, 1 SL, 1 CH, 2 UK, 2 USA

Appendix Table 9-2 provides an overview of guidelines, recommendations, position statements, consensus papers, scientific publications, general FH test strategies-related publications, as well as for sources on country-specific implementations of the guidelines and recommendations on FH test strategies and diagnostic procedures that were taken into account according to a predefined selection (see section 4.1.1). We included 2 international guidelines [11, 20], 2 documents from Australia, New Zealand, and Oceania [48, 63], 2 Documents from Belgium [24, 64], 2 from Canada [17, 18], 4 from Germany [10, 60, 65, 66], 1 from Slovenia [67], 1 from Switzerland [68], 2 from UK [15, 23], and 2 documents describing national guidance for FH from the USA [25, 69].

9 zentrale Komponenten von FH-Teststrategien

Based on this international and national guidance we identified nine different central components that characterize possible FH test strategies: detection of index case/type of screening program (Table 5-1), clinical diagnosis and assessment, FH service providers, molecular genetic testing, cascade screening, genetic counselling, awareness and education of FH professionals, patients and population, registry, and lipid lowering treatment. A detailed country-wise description of the FH test strategy features is provided as extraction table (Appendix Table 9-3).

5.1.1 Detection of index-case: type of screening and setting

Identifikation von IP: opportunistisches vs. organisiertes Vorgehen

The method of identifying index patients is crucial for each test strategy, it should not be mistaken for the method of cascade screening later described in section 5.1.2. Test strategies for the diagnosis of FH may include an opportunistic approach or an organised systematic screening. Both variants for identifying index patients are described in the (inter)national literature or are practically implemented in different countries. In addition to the type of screening, a distinction of test strategies can also be made in the clinical setting of the initial diagnosis: the specialised setting, e.g. hospital based setting, and the non-specialised setting, e.g. primary care GPs. In the course of our literature search only the following three combinations could be found:

allgemeinmedizinischer vs. spezialisierter Bereich

- Opportunistic screening in non-specialised setting
- Opportunistic screening in specialised setting
- Systematic screening in non-specialised setting

In the following, the identified approaches to index case finding are described in more detail, as well as the respective clinical criteria to initially suspect FH.

meist Teststrategie nicht für FH selbst sondern für allg. Fettstoffwechselstörungen

It should also be noted that in most guidance, the test strategy or screening program is not explicitly designed for FH, but the goal is to find general dyslipidaemias or hyperlipidaemias. FH is indirectly screened as a consequence of the general lipid screening.

Opportunistic screening

opportunistische Identifikation von IPs Teil jeder Teststrategie

Incidental opportunistic identification of FH index cases is part of every (inter-)national test strategy identified in this assessment. Some countries' FH index case identification, even exclusively rely on or recommend non-organised opportunistic methods [20, 24, 48, 68].

Opportunistic screening non-specialised setting

opportunistischer FH-Erstverdacht während anderer medizinischer Untersuchung durch den AM

In their Cochrane protocol Qureshi *et al.* 2018 [70] describe the opportunistic screening in non-specialised setting for detection of FH index cases as follows: assessment of FH during an unrelated clinical consultation, assessment of FH as part of a routine health check or health screen, and assessment of FH when an individual raises concerns about their cholesterol or family history of heart disease.

rezente europäische Leitlinie empfiehlt IP-Identifikation anahnd klin. Kriterien im spezialisierten und nicht-spezialisierten Bereich

In the recent European guideline by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) [20] FH index patients should be identified according to the following criteria:

- TC ≥8 mmol/L (≥310 mg/dL) without treatment in an adult or adult family member (or >95th percentile by age and gender for country);
- Premature CHD in the patient or a family member;
- Tendon xanthomas in the patient or a family member; or
- Sudden premature cardiac death in a family member

This should be applied in non-specialised as well as specialised settings.

Deutschland

For opportunistic search of adult index patients, German guidance recommends the ESC/EAS guideline [20, 60]. FH in children should be considered in those who have a positive family history of CVD or high levels of cholesterol or xanthomas. Diagnosis should be assessed at pre-school age with regard to plasma lipid levels. Targeted diagnosis should generally be carried out in the 2nd year of life at the earliest, because before that no therapeutic consequences are drawn [10].

Schweiz

In Switzerland, a FH diagnosis should be considered for patients (or if this applies to 1st degree relatives) with: TC ≥8.0 mmol/L (310 mg/dL) or

- LDL-C ≥5.0 mmol/L (194 mg/dL) or
- Premature atherosclerosis (especially CHD) or
- Tendon xanthomas or arcus cornealis <45 years old

Opportunistic diagnosis of FH in children should be considered if premature atherosclerosis (especially CHD) and/or pronounced hypercholesterolaemia in the family, or TC or LDL-C >95th percentile (by age and sex) is given [68].

UK

Also the UK guidance [15, 23] provides information on when an opportunistic assessment for FH in adults should be taken into consideration:

- TC level greater than 7.5 mmol/L (289 mg/dL) and/or
- personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative).

Opportunistic screening specialised setting

oft keine explizite Abgrenzung zu nicht-spezialisiert

In the opportunistic screening in specialised setting, most often the diagnosis of index patients is similar or the same as in the opportunistic screening in non-specialised setting or not further specified [18, 20, 23, 25, 60, 64, 67, 68].

Australien und Belgien: opportunistische IP-Identifikation unter hospitalisierten CVD-Pat.

Exceptions are Australasia and Belgium, which both specify in their national guidance an opportunistic search for people who have been admitted to hospital with premature myocardial infarction or other CVD events (adults). In Australasia FH patients should be sought amongst patients aged less than 60 years with CVD presenting to coronary care, stroke, cardiothoracic and vascular units, as well as amongst similar patients attending cardiac rehabilitation programs [48].

And in Belgium patients undergoing acute CV events with

- LDL-C level (LDL-C) above 190 mg/dL without treatment, or above 130 mg/dL on LLD(s) in a blood sampling performed as soon as possible after admission (not necessarily in the fasting state); and
- age of onset of the acute coronary syndrome (ACS) or any other atherosclerotic disease before 65 years

should be suspected as possible FH patients [24].

Systematic screening

Systematic screening non-specialised setting

Empfehlungen und nationale Umsetzung von systematischem Screening im nicht-spezialisierten Bereich

According to Qureshi et al. [70] systematic screening approaches could include: prospective population screening, retrospective searches of health records, proactive computer-generated reminders, case-finding by health care practitioners and review of patient records, and pathology laboratories reporting back clinicians about patients who might have FH. Some of them were also described in the included (inter-)national guidance.

Kanada: universelles Screening bei Erwachsenen nach erhöhten Lipidwerten

For example in Canada, where a universal screening of adults is recommended, lipid levels for Canadian men 40 years of age and older and women 50 years of age or older (or postmenopausal), or earlier if other ACVD risk factors are present, should be assessed [18, 71].

USA: universelles Screening bei Kindern und Erwachsenen empfohlen

Another approach for a population based universal screening in the non-specialised setting is recommended in the included US literature where all individuals should be screened by the age of 20 by primary healthcare providers (or relevant specialists) [25]. FH should be suspected and further clinically assessed when untreated fasting LDL-C or non-HDL-C levels are at or above the following:

- adults (>20 years): LDL-C >190 mg/dL (4.9 mmol/L) or non-HDL-C >220 mg/dL (5.7 mmol/L);
- children, adolescents and young adults (<20 years): LDL-C>160 mg/dL (4.2 mmol/L) or non-HDL-C >190 mg/dL (4.9 mmol/L);

Additionally, the presence of

- family history of high cholesterol and heart disease in first-degree relatives should be collected;
- tendon xanthomas at any age, arcus corneae in a patient under age 45, tuberous xanthomas or xanthelasma in a patient under age 20 to 25

should be assessed.

The cholesterol screening should be considered beginning at age 2 for children with a family history of premature cardiovascular disease or elevated cholesterol.

Slowenien: universelles Screening bei Kindern zur Einschulungsuntersuchung

Particularly noteworthy is the method implemented in Slovenia for the identification of FH index patients: Here a universal screening for hypercholesterolaemia in children is not only recommended but also implemented in actual daily practice since 1995. Pre-school children (5- or 6-year old) will be assessed for TC at their programmed visit at the primary care paediatricians, followed by genetic FH screening in suspected children at tertiary care level (lipid clinic at the UCH Ljubljana)[67].

UK: systematisches Screening Pat.-Akten durch AM

In the UK, GP records are systematically searched for high cholesterol measurements for identification of possible FH patients. Persons younger than 30 years, with TC >7.5 mmol/L (289 mg/dL) and those 30 years or older, with TC >9.0 mmol/L (347 mg/dL) are suspected and should therefore be assessed against FH diagnostic criteria [15, 23].

Deutschland: in Register integriertes Screening von Pat.-Akten teilnehmender AM, FÄ und Lipidambulanzen

A similar approach is implemented in the CareHigh Registry project in germany, where participating physicians are urged to screen their patients' records for suspicious findings [66]:

- LDL-C >190 mg/dL (4.9 mmol/L) without lipid lowering therapy (LDL values with lipid lowering therapy are corrected for drug and dose);
- TC >290 mg/dL (7.5 mmol/L);
- tendon xanthomas;
- family history of hypercholesterolaemia;
- family history of myocardial infarction before the age of 50 in grandparents, uncles, aunts or before the age of 60 in parents, siblings or children;
- family history of FH in a first or second degree relative

Systematic screening specialised setting

kein systematisch organisiertes Screening im spezialisierten Bereich

Considering the literature included, we could not identify a test strategy with systematic screening in a specialised setting.

Table 5-1: Detection of FH index case/type of screening recommended or described in (inter-)national literature including criteria to suspect FH if given.

	Opportunistic screening		Systematic screening
Country	**Non-specialised setting**	**Specialised setting**	**Non-specialised setting**
Europe	✓ (Criteria: TC >8 mmol/L (>310 mg/dL) without treatment in an adult or adult family member (or >95th percentile by age and gender for country); premature CHD in the patient or a family member; Tendon xanthomas in the patient or a family member; sudden premature cardiac death in a family member)	✓ (same as non-specialised)	-
International	**Adults** and **children** in primary care, based on age- and gender-specific plasma LDL-C levels	**Adults** with premature CVD, primarily coronary heart disease and a personal and/or family history of hypercholesterolaemia	**Universal children and adolescents:** age- and gender-specific plasma LDL-C levels should be considered prior to age 20 years and ideally before puberty
Australia, New Zealand, Oceania	✓	Patients aged less than 60 years with CVD presenting to coronary care, stroke, cardiothoracic and vascular units, as well as amongst similar patients attending cardiac rehabilitation programs	-
Belgium	✓	**Adults** admitted to hospital with premature CVD event (LDL-C above 190 mg/dL without treatment, or above 130 mg/dL on LLD(s) in a blood sampling performed as soon as possible after admission (not necessarily in the fasting state); and age of onset of the (A)CVD before 65 years)	-
Canada	✓	✓	**Universal:** Lipid levels for men 40 years of age and older and women 50 years of age or older, or earlier if other ACVD risk factors are present
Germany	✓ (**Adults:** according to European guideline; **children:** generally diagnose >2 years of age, positive family history of CVD should be assessed at pre-school age with regard to plasma lipid levels)	✓	**Registry:** participating physicians screen their patients records (LDL cholesterol >190 mg/dL (4.9 mmol/L) without lipid lowering therapy (LDL values with lipid lowering therapy are corrected for drug and dose); TC >290 mg/dL (7.5 mmol/L)); Tendon xanthomas: family history of hypercholesterolaemia; family history of myocardial infarction before the age of 50 in grandparents, uncles, aunts or before the age of 60 in parents, siblings or children; first and second degree relatives of FH patients)
Slovenia	✓	✓	**Universal children:** lipid profile for pre-school children (5- or 6-year old) at programmed visit at primary care paediatricians, family history, followed by genetic screening in tertiary care

	Opportunistic screening		Systematic screening
Country	**Non-specialised setting**	**Specialised setting**	**Non-specialised setting**
Switzerland	**Adults:** patient (or 1st degree relative): TC ≥8.0 mmol/L (310 mg/dL); or LDL-C ≥5.0 mmol/L (194 mg/dL); or premature atherosclerosis (especially CHD); or Tendon xanthomas or Arcus cornealis <45 years old), **Children:** premature atherosclerosis (especially CHD) and/or pronounced hypercholesterolaemia in the family; or known FH with one parent (cascade screening); or TC or LDL-C >95th percentile (by age and sex), or in case of suspicion of HeFH, clarification of children of both sexes from 5 years of age; in case of suspicion of HoFH (both parents affected by FH, presence of xanthomas) clarification as early as possible	✓ (same as non-specialised)	-
UK	**Adults:** TC >7.5 mmol/L (289 mg/dL) and/or a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative)	✓ (same as non-specialised)	**GP records:** search of for high cholesterol measurements: <30 years, with TC >7.5 mmol/L (289 mg/dL) and ≥30 years, with TC >9.0 mmol/L (347 mg/dL)
USA	✓	✓	**Universal:** primary healthcare providers and relevant specialists, when untreated fasting LDL-C or non-HDL-C levels are at or above the following: Adults (>20 years): LDL-C >190 mg/dL (4.9 mmol/L) or non-HDL-C >220 mg/dL (5.7 mmol/L); Children, adolescents and young adults (<20 years): LDL-C>160 mg/dL (4.2 mmol/L) or non-HDL-C >190 mg/dL (4.9 mmol/L); family history of high cholesterol and heart disease in first-degree relatives should be collected; Cholesterol screening should be considered beginning at age 2 for children with a family history of premature cardiovascular disease or elevated cholesterol, all individuals should be screened by age 20; Tendon xanthomas at any age, Arcus corneae in a patient under age 45, Tuberous xanthomas or xanthelasma in a patient under age 20 to 25

Systematic screening for FH in a specialized setting was not described in any document.

- No information given, ✓Yes, but no further details or according to European guideline [20]

Abbreviations: ACVD – arteriosclerotic cardiovascular disease, CCU – coronary care unit, CHD – coronary heart disease, CVD – cardiovascular disease, DLCN – Dutch Lipid Clinic Network criteria, FH – familial hypercholesterolaemia, GDx – genetic diagnostic, GP – general practitioner, HDL-C – high density lipoprotein cholesterol, HoFH – homozygous familial hypercholesterolaemia, LDL-C – low density lipoprotein cholesterol, LLD – lipid lowering drug, PCSK9i – proprotein convertase subtilisin/kexin 9 inhibitor, SB – Simon Broome diagnostic criteria, TC – total cholesterol, UK – United Kingdom, USA – United States of America

5.1.2 Other components of FH test strategies

weitere charakteristische Komponenten von Teststrategien

Besides the type of screening for detection of FH index cases, there are also other components in which FH test strategies may differ (Appendix Table 9-3). As not all (inter-)national guidance provide sufficient and detailed information on each component, the following descriptions are restricted to most of the comprehensive guidance.

Type of Assessment (clinical tool for diagnosis)

meist wird FH klinisch/phänotypisch diagnostiziert

In case of suspicion and first signs of FH (e.g. due to the criteria described in section 5.1.1) a specific diagnostic procedure must follow. In general, prior to any assessment specific to FH, all secondary causes for hypercholesterolaemia should first be ruled out [11]. As described earlier (see section 2.2.2), there are several diagnostic tools and scores established to diagnose FH based on blood cholesterol, personal and family anamnesis, other clinical symptoms, e.g. tendon xanthomas or arcus corneae. While some of the scores may include a molecular genetic test (DLCN point score), the diagnosis of FH can be solely based on the clinical components of these scores. The molecular genetic diagnosis is, beside in the context of cascade screening, most often not necessary and only utilised if the phenotypic findings are insufficient for a definite diagnosis of the index case.

DLCN Punktescore häufige Empfehlung

The most commonly used or recommended diagnostic score for FH diagnosis in adults is the DLCN point score. It is recommended by the European guideline [20], the Australasian model of care [48], the German guidance [60], and by the Swiss guideline [68].

Kanada: DLCN, SB und nationale Falldefinition. UK: DLCN, SB

Canadian and UK documents recommend the use of either DLCN point score or SB score. In Canada, additionally the national FH Canada case definition may be used for diagnosis [17, 18].

USA: MEDPED, SB, DLCN

In the US guideline, the MEDPED, SB, or DLCN scores are recommended [25, 69].

Belgien: DLCN, schrittweiser Prozess

In the opportunistic case finding procedure in the hospital setting in Belgium, there is a multi-step process for FH diagnosis implemented [24]. After the first step of index case identification in the CCU, patients undergo a more precise diagnosis of FH, which takes place after the hospital stay and includes optional genetic confirmation:

- 1st step (in hospital):
  LDL-C >190 mg/dL (4.9 mmol/L) without treatment, or
  >130 mg/dL (3.4 mmol/L) on LLD(s); onset of CVD <65 years;
- 2nd step (after hospital):
  DLCN point score assessment (incl. genetic testing if DLCN >5)

Kinder: adaptierte diagnostische Kriterien

For children, most of the documents recommend adapted diagnostic criteria for the initial diagnosis of FH:

Australien: alters- und geschlechtsspezifische Grenzwerte für Kinder

In Australasia age- and gender-specific plasma LDL-C concentration thresholds should be used for phenotypic diagnosis of FH in children, whereby LDL-C ≥5.0 mmol/L (194 mg/dL) indicates highly probable/definite FH. Two fasting lipid profiles are recommended [48].

In Belgium, the following process is defined for FH diagnosis in children [64]:

- 1st step: LDL-C levels (when suspicious for FH: TC, TG, HDL-C),
- 2nd step: lipid profile (+ biochemical analysis and Lipoprotein-A);
- 3rd step: repeated lipid profile after 2 to 3 months of diet
- Final diagnosis: after confirmation of FH in one of the parents

Slowenien: 2-stufig, TC, dann GDx

In Slovenia, where a universal screening for FH in pre-school children is implemented, the diagnostic procedure is divided into two steps: after the first assessment for suspicious TC blood values, assessed during pre-school examination by paediatrician, for the final diagnosis a molecular genetic confirmation is obligatory [67].

Schweiz: kritische LDL-C Grenzwerte für Kinder

The Swiss guideline defines the following diagnostic criteria for a high probability for FH in children [68]:

- LDL-C ≥5.0 mmol/L (194 mg/dL) with two determinations after three months diet, or
- LDL-C ≥4.0 mmol/L (154 mg/dL) and premature CHD in close relatives and/or high cholesterol in one parent, or
- LDL-C ≥3.5 mmol/L (135 mg/dL) and genetically diagnosed FH in one parent

Molecular genetic diagnostic

Empfehlungen für GDx meist zur Bestätigung der Diagnose und Kaskadenscreening

As summarised in section 2.2.2, the rationale for molecular genetic testing for FH comprises a wide range of arguments. Nevertheless, the (inter-)national guidance on when FH should be tested genetically for is mainly limited to confirmation of clinical diagnosis and initiation of cascade screening.

europäische Leitlinie

In the European ESC/EAS guideline GDx is recommended to confirm the clinical diagnosis, if possible [20]. Further guidance is not provided.

internationale Leitlinie empfiehlt GDx für alle IP und bei Kaskadenscreening

Similarly, the international guideline by the IFHF [11] recommends GDx if possible and outlines that it should be considered to confirm the diagnosis and that it should ideally be offered to all index cases who have a clinical diagnosis of FH. However, when the clinical diagnosis is unlikely, GDx needs not be carried out. Further, it is recommended in cascade screening and should be conducted by fully accredited laboratories. In children, a GDx is only recommended after a pathogenic variant has been identified in a parent or first degree relative or as a first step, in cases where parents or first-degree relatives are unknown or deceased.

Australien: GDx für alle mit phänotypischer FH empfohlen, darf nur in akkreditierten Labors durchgeführt werden

According to the Australasia model of care GDx should be

- offered to all index cases who have a phenotypic diagnosis of FH, and
- must be carried out in an accredited laboratory, and
- if the genetic testing protocol does not detect a mutation, the laboratory report should include a caveat that the result does not exclude FH due to undetected mutations or mutations in untested genes, particularly if the clinical phenotype is strongly suggestive of FH [48].

Belgien: GDx zur Bestätigung der Diagnose (Erstattung an DLCN gebunden)

The Belgian literature states that GDx should be conducted for confirmation of diagnosis and it is reimbursed if the DLCN point score is greater than 5 [24]. The same applies for children, who should be referred to a specialist for genetic testing, but there is no need to visit a genetic centre. FH GDx is provided by the National Institute of Health and may be prescribed by any clinician [64].

GDx for FH is currently not available in most of the provinces of Canada. If available, it should be provided to complement a diagnosis of FH and enable cascade screening. The decision to request genetic screening should be made by the treating physician after discussion with the patient [18].

Kanada: zur Bestätigung der Diagnose und im Kaskadenscreening

Within the framework of the German registry, the treating physician decides if a GDx should be offered to an included patient [66]. GDx should be carried out in an accredited laboratory using standardised methods that test for specific mutations and/or by an exon-by-exon sequencing [10].

Deutschland: akkreditierte Labore

In contrast to previous approaches to GDx, in Slovenia it is not only advisable to confirm an uncertain FH diagnosis by GDx, but GDx is a fixed part in the framework of universal screening of pre-school children and is carried out centrally at the University Children's Hospital in Ljubljana [67].

Slowenien: obligatorisch bei universellem Kinder-Screening

The Swiss guidance recommends GDx to confirm the diagnosis, if a DLCN >5 is estimated. In cascade screening, testing all 1st-degree relatives is recommended. Children should be tested even with only moderate hypercholesterolaemia, if one parent had premature CHD [68].

Schweiz: nur empfohlen, wenn DLCN >5

Similarly, in the UK it is advised that referral to a FH specialist service for GDx should depend on whether the clinical diagnostic scores in the SB or DLCN tool are >5. GDx is funded when performed in official genomic laboratory hubs [15, 23].

UK: nur empfohlen, wenn DLCN >5

In the US GDx is generally not recommended for diagnosis or clinical management of FH but may be useful when the diagnosis is uncertain [25, 69].

USA: keine generelle Empfehlung für GDx

FH service providers and care pathways

A large variety of medical service providers are included in the model of care for FH. Some guidelines and position papers even describe the optimal care pathway and how patients should be referred in the FH diagnostic and treatment process.

sehr diverse Empfehlungen zu involvierten med. Diensten

The IFHF international guideline recommends different care pathways for FH according to country-specific and local needs. The included specialist services should be multidisciplinary based and should be linked to primary care. Specialists involved should include experts in cardiology, paediatrics, genetics, imaging techniques, transfusion medicine, nursing, dietetics, psychology, pharmacy, and pathology laboratory services. In post-diagnose management it is recommended that patients who respond well to LLT should be managed in primary care, with the option of annual specialist review, and patients, whose treatment is more complex should be managed principally in specialist centres [11].

International: national individuelles Pat.-Management empfohlen, multidisziplinär

According to the Australasian test strategy, all patients with possible-to-definite FH should be referred to a lipid clinic for more detailed assessment and initiating of cascade screening. They further provide a detailed list of all FH service providers, included in the FH model of care [48]:

Australien: umfangreiche Auflistung involvierter med. Dienste

- clinical liaison
- medical laboratory services
- specialised laboratory for genetic testing
- clinical genetics, family and genetic counselling
- specialist nurses and allied health support
- administrative, secretarial and IT services

- specialised adult-paediatric service: family clinics
- structured clinical management program
- specialist and primary care physicians, physicians-in-training
- influencers and stakeholders
- audit and research program: registry, clinical and basic science, clinical trials, epidemiology and health economics
- structured education program
- patient and family support groups
- cardiac and imaging facilities

Belgien: Primär- und Sekundärversorgung

Belgian documents recommend to manage FH patients diagnosed in a Belgian CCU in-house by cardiologists and afterwards by outpatient FH specialists [24]. For children, diagnosis and management are recommended to take place in the primary care setting by GPs and in FH specialist setting including lipid clinics [64].

Deutschland: Primär- und Sekundär-versorgung, FH Study Nurses (Register)

In Germany, FH patients are managed in primary care but also in specialist-led settings. FH specialist study nurses are involved in the recruitment and implementation of cascade screening within the framework of the registry [66].

Slowenien: Kinder-FA oder AM, bei klinischer Diagnose Überweisung an Lipidklinik

The first part of the universal screening program in pre-school children in Slovenia is taking place in primary care, where GPs assess lipid levels and family history of hypercholesterolaemia and premature CVDs. In case of a positive clinical diagnosis of FH or suspected FH, the children are referred directly to the lipid clinic at the UCH Ljubljana, which belongs to the tertiary care level [67].

UK: Primär- und Sekundärversorgung, eigene FH Study Nurses

UK guidance recommend to diagnose and manage FH patients in a specialist-led setting, primary care-led setting, or within regional dual care models. There are also many FH specialist study nurses involved in the model of care. GDx should be provided by specialists for FH or by genetic services, e.g. regional genomic laboratory hubs [15, 23].

USA: Pat.-Management in Primär- und Sekundärversorgung

Guidance from the USA advises to manage FH patients in primary care and in secondary care by lipid specialists. Primary care should be responsible for screening and diagnosis [25].

Cascade screening

Ausgehend von IP werden schrittweise Verwandte untersucht

In cascade screening, 1st and 2nd degree (sometimes 3rd degree) at-risk family members of a diagnosed FH index patient are examined and, if necessary, a primary preventive therapy is started [8]. If the index patient is a child, one speaks of so-called reversed cascade screening, in which the parents and other family members are screened starting from the affected child.

ESC/EAS: empfohlen, am besten durch Lipidzentren

The current ESC/EAS guideline recommends cascade screening for FH and that it is best performed by a lipid clinic [20], but does not provide any further organisational aspects.

International: Angehörige sollten nur durch IP informiert werden, Koordination durch zentrales FH-Zentrum, nicht durch AM (besonders bei GDx),

The international IFHF guideline, on the other hand, specifies cascade screening more detailed and provides recommendation on the operational processes. Thus, notification of at-risk relatives should generally not be carried out without the consent of the index case. Relatives should only be directly notified of their risk without consent of the index case, if there is specific legislative provision for breach of confidentiality in the relevant jurisdiction. In general, for family disclosure a proactive approach that respects the principles of

privacy, justice and autonomy is required. Cascade Screening should ideally be co-ordinated by a dedicated centre and should not be carried out in primary care without central co-ordination, particularly if employing GDx. Still it should be carried out using both, a phenotypic and genotypic strategy. The utilisation of GDx is recommended as it makes cascade screening more cost-effective, if employed to screen family members after the mutation is identified in the index case. If GDx is not available, a phenotypic strategy alone should be used. Initially it should be carried out as a priority in 1st-degree relatives and then extended to 2nd- and 3rd-degree relatives [11].

wenn GDx nicht verfügbar nur phänotypisches Kaskadenscreening

The recommendation that cascade screening should take place in a specialised setting is also given by the Australasian guideline. It should ideally be carried out as a collaboration between lipid disorders and clinical genetics services, yet also involve close communication and liaison with primary care physicians. Further, it should employ a user-friendly family based data management system. At-risk relatives should not be notified without the consent of the index case. If no consent/assent for the at-risk relative for genetic testing is obtained, clinical testing for FH should be offered [48, 63].

Australien: sollte von FH-Spezialist*innen durchgeführt werden, Angehörige sollten nur durch IP informiert werden

Concerning cascade screening initiated by diagnosis of an index case in the CCU setting, the Belgian guidance recommends the assessment of routine lipids and the MEDPED criteria, and if necessary GDx for confirmation [24]. In families where FH has been identified or suspected (clinical/genetic criteria), in a family with a history of premature CVD (males <55 years of age, females <65 years of age), or if one parent has primary hypercholesterolaemia, children should be included in cascade screening once they are two years of age [64].

Belgien: Kaskadenscreening klinisch, nur zur Bestätigung GDx empfohlen

According to Canadian documents, lipid profiles in cascade screening are recommended. Additionally, protocols should be implemented at the local, provincial, and national level and cascade screening should be offered to first-degree relatives of patients with FH. GDx should be performed when available [17, 18].

Kanada: bei Angehörigen 1. Grades anhand von Lipidprofilen, GDx nur wenn verfügbar

In the framework of the German CaRe-High registry, cascade screening is conducted in a systematically organised form. Included patients are asked to inform relatives and the registry about the possible FH diagnosis. If the relatives give consent, they are contacted by the study nurse to be included into the registry. At-risk family members will, however, not be contacted directly, thus accounting for German privacy regulations [66]. Measuring lipid values is advised in all children (≥2 years of age) who have at least one parent with confirmed hereditary hypercholesterolaemia (premature CVD in relatives of 1st- and 2nd-degree before the age of 55 in men or 65 in women, or pronounced hyperlipidaemia in parents or other 1st-degree relatives). The use of GDx for diagnosis is recommended, if a pathogenic variant has already been identified in a parent or 1st-degree relative. In addition, reverse cascade screening, i.e. screening of adults if a child is diagnosed with FH, is recommended. If a child or adolescent is diagnosed with hyperlipidaemia which is not caused by another disease, 1st-degree relatives should also be examined for the presence of primary genetic hyperlipidaemia via targeted anamnesis and fasting blood collection from parents and siblings [10].

Deutschland: im Register systematisch organisiert, klinisch, GDx empfohlen, wenn familiäre Mutation bekannt ist

The Slovenian strategy of universal screening for FH in children includes reverse cascade screening, too. Here, genetic testing of family members is implemented [67].

Slowenien: rückwärts-Kaskadenscreening ausgehend von Kind

Schweiz: zumindest klinisch, optimal GDx

According to the Swiss guidance, cascade screening should be conducted in children, siblings, nieces and nephews of all affected FH index patients by at least examining the lipid status, risk factors, and ideally gene mutation [68].

UK: GDx (wenn IP gen. positiv)

The UK guidance states that all affected 1st- and 2nd- and, when possible, 3rd-degree biological relatives of people with a genetic diagnosis of FH should undergo GDx for FH. Systematic cascade testing in children is indicated if FH is confirmed in a relative [15, 23].

USA: klinisch, auch rückwärts-Kaskadenscreening

In the USA, cascade screening is recommended on the basis of lipid levels in all 1st-degree relatives of diagnosed FH patients [25]. In addition reverse cascade screening is recommended starting with children and adolescents with moderate or severe hypercholesterolaemia, by testing cholesterol of 1st-, 2nd-, and when possible, 3rd-degree family members [69].

Genetic counselling

genetische Beratung für IP und besonders bei Kaskaden-screening von Bedeutung

As FH index patients and their families require focused education regarding the heritable nature of FH, the risk to family members, the necessity of cascade screening, and the availability of genetic testing, FH diagnosis and management are often accompanied by a counselling process. This happens mostly in the case of a planned molecular genetic diagnosis but can also take place alongside clinical assessment. Genetic counselling is most often conducted by specialised health care professionals with training in both, medical genetics and psychosocial counselling [72].

Inhalte der genetischen Beratung:

According to Sturm et al. 2018 [2] and Sturm 2014 [72] genetic counselling for individuals who may have FH, should in a pre-test setting include implications and considerations like

individuelle und familiäre Risikoanalyse, Bedeutung des Ergebnisses für Familienangehörige, Präventions- und Therapiemöglichkeiten, Einverständniserklärung, psycho-soziale Beratung, etc.

- performance of risk assessment utilizing medical and family history information,
- discussion of mode of inheritance and recurrence risk to family members,
- disclosure and documentation of genetic testing results,
- facilitation of family-based care and cascade screening,
- discussion of screening, prevention, and medical management options in conjunction with the managing physician,
- discussion of reproductive options,
- provision of written documentation of medical, genetic, and counselling information to referring health care providers and patients,
- provision of psychosocial counselling,
- provision of education and resources from national organisations and advocacy groups, and
- discussion of available research study options, e.g. enrolling of patients in registries.

ESC/EAS: keine explizite Empfehlung zu genetischer Beratung

The current European guideline of the ESC/EAS does not mention any recommendations for counselling at all [20]. The international IFHF guideline recommends that pre-testing counselling should be offered to at risk family members of an index patient prior to any form of testing, in both molecular genetics and clinical diagnostics [11].

A similar approach is proposed by the Australasian guidelines, which also recommend the offer of pre-testing counselling to all at risk family members of the index patients prior to clinical or genetic testing [48, 63]. For children with suspected FH, genetic counselling should be provided at the time the affected parent receives the genetic results confirming the diagnosis of FH [48].

Australien: sowohl vor GDx, aber auch schon vor klinischer Diagnose

In Germany, genetic counselling is recommended pre- and post-genetic diagnosis [10, 66], similarly to the UK, where genetic counselling should be conducted by healthcare professionals with expertise in FH [15, 23].

Deutschland und UK: vor und nach GDx empfohlen

In the Slovenian universal screening programme for children, genetic counselling post-GDx is obligatory [67].

Slowenien: nach GDx verpflichtend (Kinder)

According to the Canadian guidance, genetic counselling should be provided if available [17, 18]. Similarly, the Belgium guidance on FH in children only mentions that psychological support and family counselling is occasionally required [64].

Belgien und Kanada: empfohlen, wenn verfügbar

The guidelines from Switzerland and the USA do not provide any advice on genetic counselling [25, 68, 69].

Schweiz und USA: keine Empfehlung zu genetischer Beratung

Awareness and education

For the early diagnosis of the FH, a high awareness of the healthcare professionals to first clinical signs of FH is indispensable. Additionally, the general population, including possible at-risk individuals, need to be aware of the possibility of an FH. Information and education campaigns can improve the awareness among healthcare professionals and the potentially affected patients. For this purpose, different approaches are recommended or already in place in each country.

frühzeitige Diagnose nur durch Bewusstsein für FH bei med. Personal, Pat., Bevölkerung und Entscheidungsträgern möglich

The international guideline by the IFHF for example defines to establish support groups of patients and families as a major priority for enhancing public, government and health care provider awareness, as well as the total quality of care of FH [11]. Health care professionals who are managing patients with FH, like physicians, nurses and allied health staff should be qualified in CV prevention and the services should establish partnerships with academic and professional organisations to enhance teaching, training and research [11].

Support groups are established in many countries in the form of FH patient organisations, as in Germany (CholCo e.V., https://cholco.org/) and the UK (Heart UK, https://www.heartuk.org.uk/). At the European level, the European FH Patient Network (FH Europe, https://fheurope.org/) offers support and information for patients and health care professionals.

Spezielle FH Pat.-Organisationen in vielen Ländern

According to the UK guidelines, healthcare professionals should be aware of the latest guidance on data protection when undertaking cascade testing and should offer people with FH and their families written advice and information about patient support groups [23].

The US guidance recommends to increase public awareness of FH to promote early diagnosis of FH and the prevention and treatment of CHD by a variety of methods. Additionally, healthcare providers' awareness may be increased through education at all levels, through partnering with professional organisations and through local, national and international health agencies. They also refer to the responsibility of other stakeholders, such as health systems, hospitals, pharmacy benefits management organisations, and insurance companies to contribute to patient and provider education on FH. Not least,

governmental agencies and other policymakers at local, state, national and international levels may be engaged in efforts to screen and treat FH [25].

Registry

internationale Empfehlung für FH-Register

Registries for FH patients and families aid the co-ordination of national cascade screening and reporting of FH. The IFHF guideline recommends establishing a FH registry of patients and families for clinical, research and audit purposes [11] and many countries already have implemented a national registry.

national implementiert in Australien, Kanada, Slowenien, Deutschland, UK

Nationwide registries are established in Australia in the form of a web-based registry in over 30 sites [48], in Canada (FH Canada registry)[17, 18], Slovenia [67], and in the USA (CASCADE FH registry) [69]. In Germany, where the CARE-High Registry project is implemented, participating physicians are instructed to screen their patient records for suspicious LDL-C values and for patients with increased CVD incidence in their family history [66]. In the UK, a nationwide registry for adults as well as a paediatric registry are implemented [15, 23].

Lipid lowering treatment

generelle Empfehlung: hochdosierte Statine bei Erwachsenen

Early onset of LLT in FH patients is a prerequisite to reduce the risk of arteriosclerosis and premature CVD (see section 2.2.3). All international as well as national guidelines recommend high intensity statin therapy of adults at first stage.

bei nicht-Erreichen der LDL-C Zielwerte: zusätzlich Ezetimibe empfohlen

If the treatment targets of LDL-C are not achieved with statins alone, many guidelines recommend in a next step the additional use of ezetimibe [11, 20, 24, 48][17, 18, 25, 60, 68, 69]. In the UK, ezetimibe is recommended as monotherapy when statins are contraindicated or not tolerated [15, 23].

bei hoch-risiko Pat.: PCSK9i

If the treatment goal is not achieved on maximal tolerated statin plus ezetimibe, PCSK9i are recommended in very-high risk FH patients[5] by the ESC/EAS guideline [20]. Consideration of PCSK9i is also recommended by Belgian [24], Canadian [17, 18], Swiss [68], and USA [25, 69] guidance if the first and second line treatment does not achieve target values.

Kinder: meist frühzeitige Einleitung einer Statin-Therapie (altersabhängig)

For children affected with FH, statins are recommended by the German and Slovenian guidance [10, 67]. The Canadian guideline states that statin therapy should be considered usually between 8 and 10 years of age [17, 18]. This is similar to the Belgian guidance, which advises statins as first line drugs, usually after 10 years of age, if LDL-C levels remain above 5 mmol/L (190 mg/dL), or above 4 mmol/L (160 mg/dL) in the presence of a causative mutation, a family history of early cardiovascular disease or severe risk factors [64]. Swiss children with FH should be treated in first stage with statins, which are approved from 8 years onwards, and in second stage with ezetimibe (approved from 10 years onwards) and phytosterols/stanols (nutraceuticals, from 6 years onwards).

[5] FH patients with ACVD or who have another major risk factor [20]

PCSK9 inhibitors

Repatha® und Praluent® mit EMA-Zulassung

The PCSK9 inhibitors Repatha® (active substance Evolocumab) [73] and Praluent® (active substance Alirocumab) [74] have been approved by the European Medicines Agency (EMA) in 2015.

beide bedingt indiziert bei Pat. mit primärer Hypercholesterinämie (HeFH und nicht-familiär) und als Sekundärprävention nach CVD

According to the EMA, Praluent® and Repatha® are indicated for LLT in adults with

- primary hypercholesterolaemia (heterozygous FH and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
  - in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
  - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated
- established ACVD to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:
  - in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,
  - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated

Repatha zusätzlich für HoFH indiziert

Repatha is in addition approved for LLT of HoFH in adults and adolescents aged 12 years and over in combination with other lipid-lowering therapies.

national unterschiedliche Erstattungsregelungen

In Appendix Table 9-5 regulatory status, reimbursement, indications as approved or reimbursed, and special health service providers for PCSK9i are listed. All countries considered in this assessment have a national approval and some also reimburse PCSK9i with conditional indications for primary prevention in FH patients and secondary prevention in patients with clinical ACVD, similar to those of the EMA [75-87].

Australien und Belgien: Erstattung von DLCN abhängig

In Australia and Belgium, reimbursement of PCSK9i for FH patients is in addition to the above listed conditions subject to a defined DLCN value in clinical diagnosis [78, 88, 89] or even a molecular genetic diagnosis [88].

Erstverordnung meist nur durch FÄ

In Australia, prescription and according reimbursement is limited to specialist physicians [88]. This is similar to Germany, where either a specialist for internal medicine and cardiology, for internal medicine and nephrology, for internal medicine, endocrinology and diabetology, for internal medicine and angiology or specialists working at outpatient clinics for lipid metabolism disorders needs to initiate and monitor PCSK9i therapy. Further prescription is possible by all medical specialists, e.g. general practitioners [75]. Likewise, in Switzerland diagnosis, initial prescription, and regular check-ups must be carried out by a medical specialist in angiology, diabetology/endocrinology, cardiology, nephrology, neurology, or by qualified hypercholesterolemia experts [76, 77].

5.2 FH in Austria – Current test strategy and diagnostic processes

5.2.1 Prevalence in Austria

FH-Prävalenz in Ö geschätzt 1:200 bis 1:250

To date, there is no specific data on the prevalence of FH in Austria available. Experts [90, 91] estimate the prevalence to be similar to the data from European literature [2]: 1:250 to 1:200 (but also to 1:500). So, probably around 40,000 people in Austria may be affected, of whom only a small number are diagnosed and therefore receive preventive therapy (10-15%) [57].

5.2.2 Detection of index cases

kein systematisches Screening nach FH IP in Ö

Currently there is no systematic screening or organised test strategy to identify FH index cases in place in Austria, neither in a specialised nor in a non-specialised setting. According to experts, index patients are identified via 3 possible diagnostic routes: (1) the FH diagnosis is made in a specialised hospital-based setting in CCUs (or stroke units, vascular units, etc.) after a CV event, (2) attentive GPs detect suspicious lipid levels in patients, or (3) the patients refer themselves to the GP [90-92].

häufig Diagnose im KH nach kardiovaskulärem Event

In daily practice index patients are often identified in the hospital-based setting. Particularly in the case of early cardiovascular events, the suspicion that the cause could be FH suggests itself. Due to an increased sensitivity of the specialists working in the CCUs, patients with suspected FH are more quickly referred to lipid specialists, often in-house. The definitive diagnosis is then made in these lipid centres [91]. According to section 5.1.1 this represents an opportunistic specialised index case finding approach.

definitive Diagnose auch durch AM, aber schon bei Verdacht meist Weiterleitung an FÄ

In addition to identification in the specialised setting, index patients are also commonly diagnosed by GPs. Many GPs clinically assess patients for FH themselves but often, if there is a first suspicion, they are also directly referred to specialists or lipid clinics for a definitive diagnosis. Diagnosis of FH in the primary care setting takes place often during other unrelated or routine clinical consultations and are mostly random findings. The number of patients who are identified in the non-specialist setting, no matter if first suspicion or confirmed diagnosis, strongly depends on the awareness for FH of the respective GP [91].

Lipidprofil (nur TC, HDL-C) im Rahmen der Vorsorgeuntersuchung

derzeit keine standardisierte Überprüfung des LDL-C Blutwertes, wird dennoch häufig erfasst

The Austrian *Vorsorgeuntersuchung* (VU), a voluntary preventive medical checkup, offers all persons from the age of 18 years with residence in Austria an annual extensive medical examination program [56]. As part of this screening and consultation programme, lipid values are assessed and a screening for general hypercholesterolaemia (TC/HDL-C quotient) and hypertriglyceridemia is currently routinely conducted in adults ≥18 years every 3 years (age 18-40 years) or every 2 years (age >40 years) [58]. By now, measuring LDL-C is not explicitly recommended but still very often additionally done by the GP in the course of the VU. Usually, the LDL-C value is not provided in the standard laboratory lipid profile of the VU and must be requested if required. The tariff catalogue for laboratory diagnostics lists the service items “direct measurement of the LDL-C value” and “indirect measurement via the Friedewald formula”. However, many family doctors request the indirect LDL-C value from the laboratory via the Friedewald formula or calculate it themselves [92].

Österreichischer Patientenbericht: allg. Hypercholesterinämie meist durch AM diagnostiziert

According to the 2015 *Österreichischer Patientenbericht* on hypercholesterolaemia [93], in which 402 patients with hypercholesterolaemia (not FH) were interviewed, 48.6% were diagnosed by their GP, 22.7% by an extramural specialist, 18.7% by a specialist in a hospital and 9.9% in a hospital outpatient clinic. When asked whether the physician checked if the hypercholesterolaemia could be due to FH (or other primary hypercholesterolaemia), only 31.4% answered YES.

Pat. wenden sich selbständig an Pat.-Organisation

Awareness-raising campaigns by expert societies (e.g. Austrian Atherosclerosis Society) and patient organisations (FHchol Austria), which can draw the attention of patients with an increased incidence of premature CVDs in their families to the FH's clinical picture, play an important role in the index case identification. Therefore, it is also possible that patients themselves suspect that they could suffer from FH and contact the organisations independently, which refers them to their GPs or lipid specialists [91].

Kinder werden meist über Kaskadenscreening identifiziert

Children are often identified as FH patients by cascade screening but also as index patients in opportunistic settings (see section 5.2.7) [91]. An exemption is the regional pilot study on universal screening in pre-school children conducted 2017 in Vienna, the so-called FH Kids Austria study [94]. Here, all children should be screened as part of the compulsory pre-school examination by school physicians. The first screening step was based on a questionnaire for the school physician and also for each parent, available in different languages. If the questionnaire was positive for suspicion of FH, the pre-school child and its siblings were screened for blood cholesterol. Cholesterol screening was defined as positive when non-HDL-C ≥160 mg/dL (4.2 mmol/l) and/or LDL-C ≥130 mg/dL (3.4 mmol/L) was measured. Then, all positive screened children were invited to follow the standardised FH program at the outpatient clinic of obesity, lipometabolic disorder and nutritional medicine at the Medical University of Vienna.

Wiener Studie: 14 Kinder wurden auf FH diagnostiziert

In total, 133 pre-school children were tested for blood cholesterol from whom nine were positive. Further four siblings could be identified with positive cholesterol tests. Five children were genetically confirmed for FH.

As a limitation of the study, the response rate to the questionnaires was stated: only 35% of all children in Vienna who had their school enrolment examination were assessed via the questionnaires. Possible reasons for that were: school doctors had no sufficient time resources, little experience with studies, parents refused study participation, and despite multilingual study documents language difficulties seemed to be the main factor [94].

3 Hauptwege der FH Diagnose:

im KH nach CVD, opportunistisch durch AM, Eigeninitiative und Verdacht durch Pat. selbst

In summary, there are 3 main scenarios in Austria in which FH index patients are first identified, all of them opportunistic:

- in a hospital based setting (CCU, stroke unit, etc.), after a premature or repeated CV event,
- in primary care during an unrelated clinical consultation by a GP,
- or persons contact patient organisations on their own initiative, due to concerns about their cholesterol or family history of heart disease, and are forwarded from there to GPs and medical FH services.

5.2.3 FH service providers and patient flow

Grafik zu FH Pat.-Fluss

The current FH patient flow in Austria was derived with the help of the experts and is presented in simplified form in Figure 5-1.

If FH is initially suspected on the basis of clinical criteria, the hospital CCU (after a CV event) or the GP usually refer the patient to a metabolism specialist in extramural setting or to an ambulatory lipid centre. Here a first or repeated assessment according to diagnostic criteria (see section 5.2.4) as well as a more detailed evaluation of the patient takes place. In some cases, for confirmation of the clinical diagnosis (see section 5.2.5) or initiation of an effective cascade screening of the patient's family (see section 5.2.7) molecular genetic tests are initiated. They are conducted at human genetics centres or medical genetics laboratories [2, 90, 91]. Prior and post molecular genetic testing genetic counselling is obligatory (see section 5.2.6) [95]. In addition to referring the patient to a lipid specialist, it is also possible for the GP to make the FH diagnosis himself/herself and to keep the management in a non-specialist setting. The GP may also refer the patient directly to genetic analysis if required [90, 92]. If FH causing mutation is identified, cascade screening of family members is initiated, mostly by the lipid specialist. Independent of whether or not the diagnosis is genetically confirmed, each patient is reported to the national FH Registry, if the lipid specialist is part of the registry project (see section 5.2.8). The post-diagnosis management (see section 5.2.10) then usually continues to take place in the lipid centre or at a specialist in an extramural setting. However, it can also take place in primary care by the GP [92], whereby the GP frequently refers the patient to a lipid specialist if the diagnosis of FH is confirmed and intense LLT is required [90].

5.2.4 Clinical diagnosis and assessment

Erwachsene: klinische Diagnose mit DLCN Punktescores

It has been stated that the diagnosis FH is made too often solely on the basis of lipid findings (LDL-C or TC) in the general population [20]. In Austria, a standardised clinical diagnosis of FH is based on the ESC/EAS guideline [20] and should be carried out in adults using the DLCN point score. This, in addition to the LDL-C values, takes into account the family history, the personal CVD history, a clinical examination of visual manifestations of FH (tendon xanthomas and arcus lipoides), and an optional molecular genetic test (see section 5.2.5).

Kinder: klinische Diagnose mit modifiziertem SB Score

For children, other diagnostic criteria or diagnostic scores with less weight on the LDL-C and TC blood values is recommended. In Austria, a modified score (according to SB score) is used to clinically diagnose children (<19 years old) [94, 96].

5.2.5 Molecular genetic testing

molekulargenetische Diagnose bei IP zur Bestätigung der Diagnose und zur Einleitung des Kaskadenscreenings

In all the above-mentioned approaches for index case finding in Austria, both those actually used and those under consideration, patients are primarily identified on the basis of their LDL-C blood value and not at first by a molecular genetic test. Molecular genetic diagnosis of the FH serves on the one hand to confirm the diagnosis in case of uncertain clinical findings and on the other hand to initiate an efficient cascade screening of the family, and it's the latter which is most often applied [90, 91].

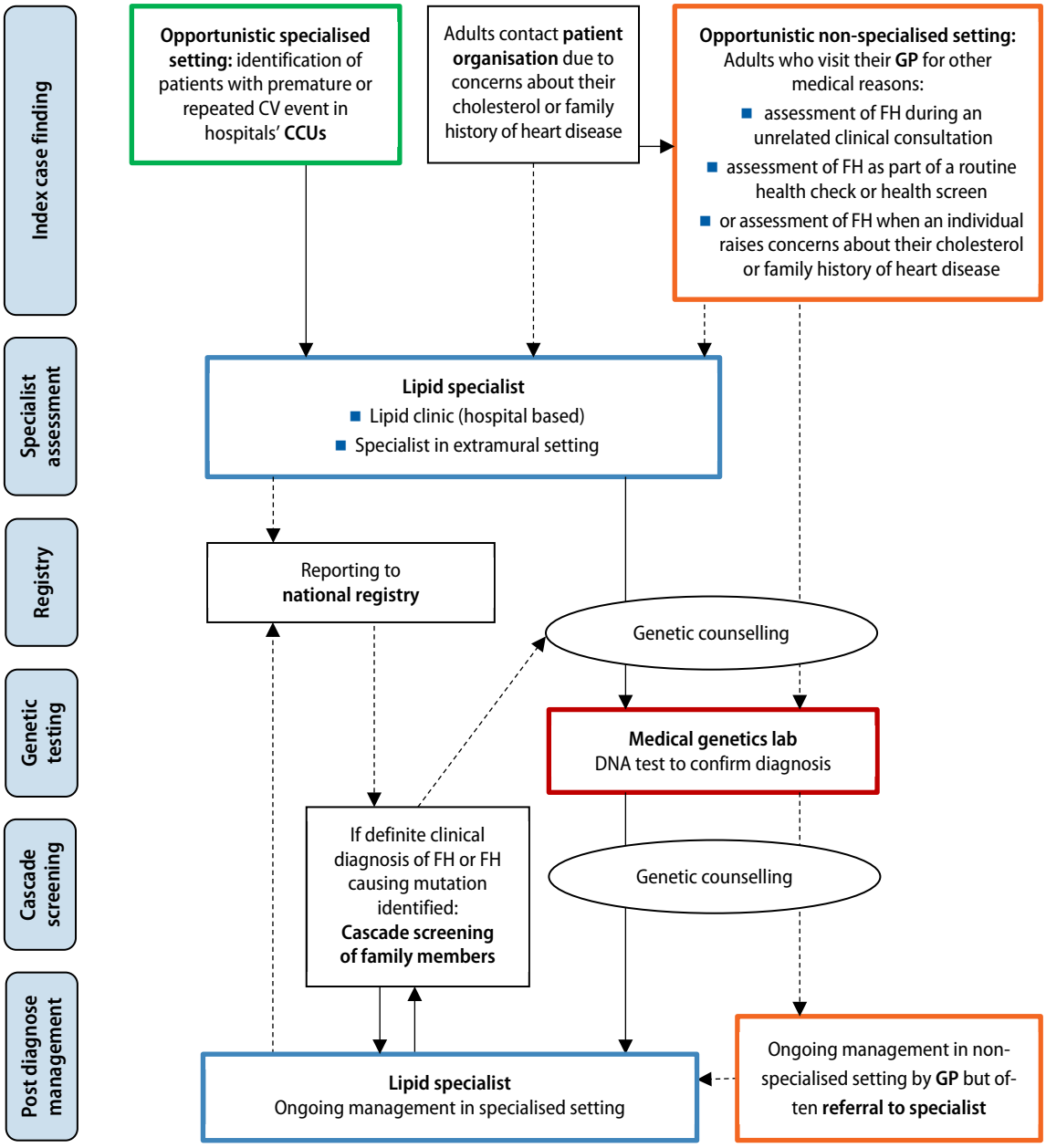


Figure 5-1: Simplified pathway of the current Austrian Familial Hypercholesterolemia (FH) patient flow and the main medical service providers: hospital-based coronary care units (CCU; green), general practitioner in primary care (GP; orange), medical genetics laboratory (red), and lipid specialists (blue). Continuous arrows indicate most common paths, dashed arrows less common or not obligatory ones.

In general, genetic testing of humans is regulated in Austria within the framework of the Austrian Gene Technology Act (Gentechnikgesetz, GTG) [95]. According to the classification of genetic analysis in humans for medical purposes (§ 65 Abs 1 GTG), FH is categorized as type 3: *Type 3 serves the determination of a predisposition for a disease, in particular the disposition for a potential future onset of a genetically based disease or the determination of a carrier status, for which, due to new scientific knowledge and technical progress a prevention or therapy is possible.* Thus, a personal consent is obligatory and genetic counselling is necessary before and after the genetic examination (§ 69 GTG, see section 5.2.6).

Gentechnikgesetz: reguliert genetische Untersuchungen am Menschen
GDx für FH: zwingende genetische Beratung, gilt als Verwandtenuntersuchung

Furthermore, relatives' examinations are classified as type 3 analyses (*Verwandtenuntersuchungen*, § 65 Abs 1 GTG and § 70 GTG) [95].

Österreichischer Strukturplan Gesundheit 2017 definiert 6 überregionale Zentren für Medizinische Genetik

Resource and coverage planning for GDx in general is organised within the framework of the Austrian Structural Plan for Healthcare 2017 (Österreichischer Strukturplan Gesundheit, ÖSG) [97]. The centres for medical genetics defined here are classified as special centres with supra-regional care planning (*Spezialzentren mit überregionaler Versorgungsplanung*). Their task is diagnosis, medical genetic counselling and adequate psychological assistance for persons with hereditary increased risk of disease. Accredited medical-genetic laboratories require approval in accordance with the GTG (§ 68, § 68a GTG).

There are currently 6 such centres at the following locations:

- KUK Linz, MC IV
- Salzburg LKH
- Graz LKH
- Innsbruck LKH
- Vienna AKH
- Hanusch KH

private Labors benötigen Bewilligung zur Rückfinanzierung

Molecular genetic diagnostic of FH is usually performed by those centres. If GDx is done in a private institution, approval for reimbursement must be sought [90].

GDx an 3 Universitätsnahen Zentren individuell finanziert

The 3 centres Graz LKH, Innsbruck LKH, and Vienna AKH are university institutes and are conceptually located close to the hospitals. Here, GDx is financed by individual contracts and agreements with the social insurance. The medical genetic centres KUK Linz and Salzburg LKH are state institutions and therefore GDx is financed via the outpatient clinic in the hospital department [90]. GDx performed by the Hanusch KH, which is an institution of the social insurance, is also financed directly by the latter.

komplexe, nicht einheitliche Finanzierungsstrukturen der Zentren

The funding structures for GDx in Austria are complex and it cannot be excluded that there are other situations where the genetic diagnosis is not reimbursed. Furthermore, the official tariffs for the processes steps of molecular genetic analyses are not publicly available.

Entscheidung über GDx abhängig von Vorgehen des regionalen Lipidzentrums und behandelndem Arzt

However, whether a (suspected) FH patient is referred for GDx also depends on the lipid centre or the GP where he or she is treated. For example, in the centres in Vienna and Innsbruck, all (suspected) cases of FH will by referred to GDx, whereas in Graz more selective referral is carried out [91].

Zahlen zur Anwendung von GDx bei FH nicht verfügbar, in Innsbruck ca. 50-80 Analysen jährlich

Exact numbers of the frequency of molecular genetic tests for FH diagnostics are not available, but exemplary at the Institute of Human Genetics of the Medical University of Innsbruck (Innsbruck LKH) about 50-80 analyses are performed annually [90].

genaue molekulargenetische Methode abhängig von spezifischer Fragestellung

IP: Panel-Sequenzierung oder Sequenzierung des gesamten Exoms

The molecular genetic method used to diagnose FH depends on whether the genetic basis of the index patient needs to be clarified (exploratory approach), or whether the specific mutation of the index patient is already known and the analysis is conducted within the framework of cascade screening. In the genetic analysis of the index patient, panel sequencing is most often used, in which only the genes for the disease pattern of interest are sequenced and examined for pathogenic mutations. When testing for FH-associated mutations, other dyslipidaemia-associated genes are usually checked, too [90]. The Institute of Medical Genetics of the Medical University of Vienna (Vienna AKH), for example, sequences a list of 25 different genes (including the 5

most important FH genes) when a genetic analysis for FH is requested [98]. As an alternative method, the entire exome[6] of the patient can be sequenced and then specifically searched for mutations in the gene sections of interest. Although this method is more expensive than panel sequencing, it also allows for follow-up examinations of genes that were not in demand during the primary genetic analysis [90].

Kaskadenscreening: gezielte Suche nach bekannter familiärer FH-Mutation

If a genetic follow-up examination of family members is requested, the genetic basis of the family including the FH causing mutation should already be known. This means that for GDx within the framework of cascade screening, it is not necessary to analyse the entire exome or the entire gene panel of a disease pattern, but it is sufficient to search specifically for the specific FH mutation. This procedure is therefore cheaper and is also generally applied in Austria [90].

nur bei 60 % aller genetischer Analysen von IP wird eine pathogene Mutation nachgewiesen

Approximately in 60% of the index patients with a phenotypic probable FH (DLCN >5) genetic mutation in the 5 most important genes (and mainly in the FH-associated genes LDLR, Apo B, and PCSK9) can be found. The remaining 40% would be diagnosed as molecularly genetic negative for FH, although there could be other monogenic variations causing hereditary hypercholesterolaemia. Often, there are follow-up genetic analyses initiated to detect them in a second step [91].

5.2.6 Genetic counselling

GTG und Gentechnikbuch regulieren genetische Beratung, Datenschutz, Einverständ-niserklärung

The Austrian GTG regulates issues like data protection, informed consent, the inclusion of patient's relatives, and genetic counselling [95]. In addition to these legislative regulations, further directive is provided in the Austrian Book of Gene Technology. It is published by an Advisory Board on Gene Technology and has soft-law character [99, 100].

Typ 3 Genanalyse: genetische Beratung vor und nach Test zwingend erforderlich

As GDx of FH is on the one hand used for a confirmation of diagnosis in the index patient but on the other hand, in the case of cascade screening for family members, as a predictive analysis, it is classified as Type 3 genetic analysis according to the GTG (§ 65 Abs 1 GTG) [95] and therefore genetic counselling prior and post testing is obligatory.

Kapitel 2 des Gentechnikbuches beschreibt Vorgehen bei genetischer Beratung:

In chapter 2 of the Austrian Book of Gene Technology the requirements for genetic counselling are described in more detail and 6 guidelines for genetic counselling are defined [101]. The guidelines are summarised in the report *Qualitätsstandard "Humangenetische Beratung und Diagnostik"* [102] as follows:

1. Comprehensive information basis for decisions by those seeking advice
2. The consultation includes a concrete definition of the question and goal, the patient's own and family history, the evaluation of findings, information on the disease in question, information on preventive/therapeutic options, information on genetic testing (nature, scope, significance and possible sources of error) and information on the possible implications for life and family planning.
3. The consultation also includes:
   - The objective, comprehensive discussion of all examination results and medical facts and the explanation of possible medical, social and psychological consequences (non-directive)

[6] All exons of an organism, i.e. all sections that potentially encode proteins.

- If serious physical, psychological and social consequences are to be expected, a psychotherapist shall be directly involved in the counselling at the personal request of the person seeking advice or at the suggestion of the counsellor. If necessary, the advisability of psychotherapeutic counselling – and in the case of social consequences also the advisability of counselling by a social worker – must be pointed out in writing. Reference can also be made to other counselling facilities and/or self-help groups

4. Right to know and not to know; a comprehensible letter to document the consultation; confidentiality obligations; information about communications (physician – therapist)
5. Proof of qualifications:
   - Qualification in the field of medical genetics (specialist for medical genetics)
   - Specialist advice on genetic diseases is provided by specialist of the special medical field concerned. In special cases the cooperation of both medical fields is desired.
   - Regular participation in relevant further training courses in accordance with the Occupation Act, which also includes proof of skills in non-directive counselling
6. For additional psychotherapeutic counselling, psychotherapists licensed under the Psychotherapy Act with a corresponding additional qualification in the field of medical genetics must be consulted.

genetische Beratung nur durch FA für medizinische Genetik oder FA des jeweiligen med. Gebietes

It has been emphasized that genetic counselling may only be carried out by specialists in medical genetics or specialists from the respective medical field of the disease/genetic disposition to be investigated (for FH e.g. endocrinologists, cardiologists, paediatricians, etc.) and that regular participation in relevant training sessions, which also includes the proof of skills in non-directive counselling, is mandatory [101].

standardisiertes und Qualitäts-gesichertes Vorgehen

The organisational and structural requirements for a standardised and quality assured medical genetic counselling are summarized in Table 5-2. The table is taken from the report *Qualitätsstandard "Humangenetische Beratung und Diagnostik"* and refers only to the genetic counselling by a medical genetic specialist and not to the specialist counselling of the individual medical field of the disease pattern or genetic disposition of interest [102].

postgradueller Masterstudiengang

The first German-speaking (postgraduate) Master's programme for genetic and genomic counselling was introduced at the Medical University of Innsbruck in 2019 (www.gencouns.at)[103].

Table 5-2: Requirements for a standardised and quality-assured medical genetic counselling by a medical genetic specialist. This table does NOT apply to specialist counselling for the respective medical field and genetic diseases. Taken from Qualitätsstandard "Humangenetische Beratung und Diagnostik" der Zielsteuerung Gesundheit [102].

Scope	Consultation by the specialist for medical genetics
Target group	■ Healthy persons with suspected genetic modifications ■ Individuals with known genetic modifications to predict the risk of developing a genetic disease(s) or to assess the risk of genetic diseases in their offspring ■ Relatives of persons with genetic changes/genetic diseases ■ Patients/symptom carriers with suspected genetic modifications

Guiding principles	■ Addresses the needs and concerns of the person seeking advice ■ Is not directive – remains open-ended ■ Is generally understandable ■ Respects and protects human dignity ■ Refers to the generally recognised state of the art in science and technology
Fields	■ diagnostic ■ predictive ■ pre/postnatal

Aim/Contents	Consultation before genetic examination:
	■ Specification of the expectations of the genetic examination (motivation, scope, goal, possible later consequences)
	■ Assistance in decision-making for or against the genetic investigation ("informed decision")
	■ Clarification regarding knowledge – not knowing for a self-determined decision
	■ Reasonable reflection period until the investigation date
	Consultation after genetic examination:
	■ Clear communication of the result of the investigation
	  ■ taking into account the previously agreed conditions/patient preferences
	  ■ in close cooperation with relevant medical specialists
	  ■ on the basis of an individual risk concept (explanation of disease risks in relation to risks of exogenous factors)
	■ Explanation of the relevance for future life
	■ Support for self-determined decisions
	■ Information regarding offers for further support

Setting	■ Centres for medical genetics, associated facilities, secondary care ■ Forms of consultation: Genetic consultation hour, if necessary external consultation
Qualifications	Specialist for medical genetics

5.2.7 Cascade screening

in nat. Register implementiert

For FH cascade screening, family members of a prior diagnosed index patient are examined in order to provide (early) treatment if necessary. This is systematically organised in Austria within the FH registry (see section 5.2.8) and is proactively promoted [91, 104].

meist über klinische Diagnose, genetische Beratung auch beim Kaskadenscreening Pflicht

Currently, measuring cholesterol levels, i.e. a clinical assessment, is the gold standard for FH diagnosis in first and second degree relatives in Austria. However, experts state, that if the causal pathogenic mutation of the index patient is known, GDx should be performed in relatives in addition to the clinical examination [91]. Here, only the specific gene mutation of the index patient is searched for [90, 91]. Also in cascade screening, genetic counselling must always take place before and after GDx (§ 65 Abs 1 GTG and § 70 GTG) [95].

Kontaktaufnahme zu Angehörigen nur durch IP

In Austria, only the index patient may contact family members concerning hereditary diseases prior detailed counselling. During the counselling session the patient needs to be informed about implications of the notification for the patient himself/herself. Also addressing implications of notifying the family members should be standard in any case – regardless whether the diagnostics are planned clinically or genetically [92].

auch außerhalb des Registers

Clinical and genetic FH cascade screening is also provided and done outside the organised framework of the registry but which patients are offered it depends on the initiative of the involved physician [92].

geschätzt 3 zusätzliche Diagnosen durch Kaskadenscreening

Similar to international experience, the rule of thumb in Austria is that in a well-established diagnostic programme, cascade screening can identify 3 additional affected persons [91].

5.2.8 Registry

ESC/EAS Guideline empfiehlt nationale Register zu FH, in Ö teilweise implementiert

As recommended by the recent ESC/EAS guideline [20] and implemented by many other European countries [23, 66], there is also a FH registry project set up in Austria. It is financially supported Austrian Atherosclerosis Society, Tyrolean Science Funds, the Austrian Heart Fund (Österreichischer Herzfonds, www.herzfonds.at) and industry [105].

2015 als Pilotprojekt in Wien, Graz und Innsbruck gestartet

It was initiated in 2015 by the Austrian Atherosclerosis Society (AAS) in close cooperation with the Austrian patients' organisation FHchol Austria with the aim of recording all persons affected with FH throughout Austria. Further project goals were [57]:

Projektziele

- survey of the care and treatment status of patients with FH in Vienna, Innsbruck and Graz, designed as pilot study
- assessment of the effectiveness of an early detection programme for the detection of FH in the population by means of cascade screening (1st and 2nd degree relatives of the index patient)
- special focus on affected children in whom the diagnosis of FH is unnecessarily delayed due to the lack of regular blood tests
- survey of the acceptance of systematic screening outside the oncological field among physicians and patients
- establishment of a registry with index patients already known or newly identified within the scope of the project, which will serve as a basis for a national registry for FH patients.

The registry "*Fass dir ein Herz" Screening und Register für Familiäre Hypercholesterinämie* started as a pilot project in the cities and university hospitals of Vienna, Graz, and Innsbruck, but was subsequently expanded to more cities and regions. Today only the cities and areas of Linz and Salzburg, as well as Carinthia are not covered in the registry by the local lipid centres [91].

Einschlusskriterien

In the initial project description from 2015 inclusion criteria for index patients were defined as follows [57]:

- persons in whom LDL-C of 190 mg/dL (4.9 mmol/L) or more (for children 155 mg/dl) and/or TC of 290 mg/dL or more (for children 230 mg/dl) is documented without LLT (in patients who already receive treatment with statins and for whom previous values without treatment are not known, the previous value should be concluded on the basis of the statin used and the dose; for patients receiving other lipid-lowering drugs, a reduction of LDL-C by 15% with fibrate therapy and by 10% with the administration of an exchanger resin should be assumed);
- DLCN point score or SB score must be available in adults over 18 years of age and children respectively; or
- persons with a positive family history of tendon xanthomas, family history of hypercholesterolaemia, or myocardial infarction before the age of 50 in grandparents, uncles, aunts, or before the age of 60 for parents, siblings, or children.

Ausschlusskriterien

Excluded from participation were persons who

- refuse to give written consent to participate;
- have an obvious and clinically demonstrated impairment of their cognitive functions;
- are unable to understand the purpose of the project;
- have been diagnosed with decompensated acute psychiatric illness;
- are acutely ill; or
- have undergone surgery within the last three months.

Angehörige 1. und 2. Grades miteingeschlossen

After the inclusion of appropriate index patients in the register, the respective family members are assessed. All first and second degree relatives of patients with FH, regardless of age and sex, are included. Exclusion criteria for relatives are the same as for index patients.

Einverständniserklärung

Then, based on the information given in the description of the pilot project [57], all potential participants are informed about the objectives and process of the project in written and oral form. Withdrawal of participation and consent is possible at any time [57].

Untersuchungsprogram: klinische Kriterien

The subsequent examination program consists of clinical documentation, laboratory diagnostics and GDx. Clinical documentation includes risk factors such as smoking status, family history of CVD, diabetes mellitus, dietary habits, physical activity, medications, other diseases, and previous surgeries. During the subsequent clinical examination, blood pressure, ankle-arm index, height, weight, abdominal girth, body mass index, and ultrasound of carotid arteries are measured. If possible, a family tree of the patients is drawn.

umfangreiche Labordiagnose

For laboratory diagnostics the parameters TC, LDL-C, HDL-C, Lp(a), ApoAI, ApoB, AST, creatine kinase, ALT, alkaline phosphatase, GGT, hs-CRP, fasting glucose, uric acid, HbA1c, urea, bilirubin, creatinine enzymatic, TSH, eGFR and albumin in urine are measured [105].

eingeschlossene Pat. sollen auch über GDx diagnostiziert werden

Additionally, all FH patients included in the registry should undergo GDx for mutations on the FH-associated genes LDLR, ApoB, und PCSK9. For the pilot project, GDx was carried out at the Department for Laboratory Medicine at the Medical University of Vienna, at the Institute of Human Genetics at the Medical University of Innsbruck and at the Institute for Human Genetics at the Medical University of Graz [57].

elektronische Fragebogen für Erhebung der Pat.-Daten

All data are collected and evaluated with two electronic questionnaires which are entered by study nurses into the AskiMed [106] data entry platform provided by the Medical University Innsbruck.

Data protection is secured by pseudonymisation and hosting the database on an external server. Further, if a patient withdraws his or her consent to participate in the registry, his or her data are deleted.

nationale Ausweitung des Pilotprojektes

The entire procedure described here is based on the initial report on the pilot project [57] but will be continued in the now nationwide extended form of the registry.

Ziel Pilotprojekt: Diagnose von 4000 FH-Pat.

According to the initial project report, there should be 4000 potential FH patients in the three starting cities (assumed prevalence 1:500) and the goal was to identify half of these patients by means of an organised cascade screening, to examine them biochemically and clinically, to introduce an appropriate, standardised treatment as well as to lay the structural foundation for a follow-up with regard to long-term complications [57, 104].

Derzeit 800 Pat. in Register inkludiert

As of 17. December 2017, an interim and activity report of the AAS reported the performance figures listed in Table 5-3. In total, the registry included 460 FH patients up to that date [105]. At present, more than 800 FH patients have been integrated into the registry. A scientific data evaluation is in progress and a publication is planned [91].

Table 5-3: Patients included in the Austrian FH registry per centre and clinical department as of 17. December 2018 [105]

Centre and clinical department	Number
AKH Lipidambulanz Endokrinologie	37
AKH Lipidambulanz Kardiologie	4
AKH Pädiatrie	85
Feldkirch Kinderklinik	3
Krankenanstalt Rudolfstiftung	2
Medizinische Universität Innsbruck Innere Medizin	156
Medizinische Universität Innsbruck Kinderklinik	1
Medizinische Universität Graz	94
Österr. Akad. Institut für Ernährungsmedizin	55
Universitätsklinikum Krems	14
Wilhelminenspital Kardiologie	2
Total	**460**

5.2.9 Education and awareness

Pat.-Organisation: FHchol Austria

Medizinische Fachgesellschaft: AAS

A large part of the education and awareness campaigns for medical staff as well as the general population are initiated and supported in Austria by the AAS and the national FH patient organisation FHchol Austria (www.fhchol.at) [107]. Besides the organisation of seminars for patients or medical staff, dissemination at (specialist) conferences, media-effective public relations work is carried out in the form of articles in health magazines and TV reports etc., all in close cooperation with the FH registry of the AAS (see section 5.2.8) [57, 105]. Regular meetings for patients and family members as well as the annual patient meetings with expert lectures are to promote the exchange of experiences of those affected. Besides providing information for patients and medical staff, international cooperation and networking activities are on the agenda of FHchol Austria [107].

5.2.10 Post-diagnosis management

Pat.-Management meist durch Lipidkliniken aber auch (bei unkomplizierten Fällen) durch AM

After diagnosis, most FH patients are managed in specialised lipid clinics. Still, a large proportion of the patients, especially those with less pathogenic FH-variants where a reduction of LDL-C is easier to achieve, are monitored by their GPs. In general, therapy goals and treatment of FH patients in Austria should be based on the ESC/EAS guideline [91] (see section 5.1.2).

PCSK9 inhibitors

Rückerstattung nur bei Sekundärprävention

In Austria PCSK9i are solely reimbursed for secondary prevention. FH is not specified as an indication in the positive list (*Erstattungscodex*) [108].

The indication and criteria for reimbursement of PCSK9i are:

Indikationen und Kriterien laut Erstattungskodex

In primary hypercholesterolaemia for secondary prevention following an acute atherosclerotic ischemic cardiovascular event in patients with diagnostically confirmed coronary artery disease and/or peripheral arterial occlusive disease and/or cerebral arterial occlusive disease ...

... if an additional reduction of LDL-C is medically necessary due to the very high cardiovascular risk

and

... if a professional nutritional consultation is carried out, the arterial blood pressure is controlled and the blood sugar is adjusted to an HbA1c of less than 8%, as well as a tobacco smoke abstinence is aimed at,

and

... if an LDL-C value of less than 100 mg/dL (2.6 mmol/L) cannot be achieved for at least 3 months with the maximum tolerated dose of an intensified LDL-C-lowering therapy with Atorvastatin or Rosuvastatin, in each case in combination with Ezetimib (or Ezetimib with or without Colesevelam for statin intolerance), or if these treatments are contraindicated.

Kontrolle der Therapie

The *Erstattungscodex* stipulates that PCSK9 antibody therapy may only be continued if ...

... in a laboratory control 2-3 months after the start of treatment, the LDL-C has decreased by at least 40% compared to the initial value under the maximum intensified lipid-lowering therapy or an LDL-C value of less than 70 mg/dL (1.8 mmol/L) was reached.

Erstmalige Verschreibung nur durch definierte Erstverordnungszentren

Furthermore, PCSK9i may initially only be prescribed in so-called *Erstverordnungszentren*. These have been specified by the Umbrella Association of Austrian Social Security Institutions (Dachverband der Österreichischen Sozialversicherungsträger) and include nationwide 33 departments and units in specialist hospital centres as well as district hospitals as of 30. January 2020: Vienna 6, Lower Austria 5, Burgenland 1, Upper Austria 5, Salzburg 3, Tyrol 4, Vorarlberg 3, Styria 4, and Carinthia 2.

5.3 FH in Austria – Opportunities for improvement and organisational requirements

Ableitung von Ansätzen zur Weiterentwicklung des österreichischen FH-Diagnoseprozesses

In section 5.2 the current test strategy and diagnostic processes of FH in Austria are described, i.a. on the basis of expert interviews. In addition to this, the experts were also asked how this process could be improved with regard to index case finding, diagnostic procedure, GDx, cascade screening, etc. The aspects identified here are compared below with the test strategies in other countries and the international guidance (see section 5.1) and the organisational implications are narratively summarized.

5.3.1 Prevalence in Austria

Erhebung der tatsächlichen österreichischen FH-Prävalenz

Currently, the data on FH prevalence in Austria are based on averaged international estimates of 1:250 to 1:200 (but also to 1:500) [20]. These values are supported by a recent international meta-study. This study also reports prevalence numbers on national levels, which differ within Europe. For example, the prevalence of FH in Finland, Hungary and Italy is given as 1:1000 to 1:500, in Germany, the Netherlands and the UK as 1:332 to 1:250, and Denmark and Spain showed prevalence values of 1:249 to 1:250 [5]. A national prevalence study could be useful to obtain exact data on the FH situation in Austria. Further, the question should not only be asked what is the overall prevalence in the Austrian population on basis of individual patients, but also how many families are affected by FH [90].

5.3.2 Detection of index case

Standardisierte LDL-C Erhebung bei VU als systematisches Screening auf FH

With regard to the identification of FH index patients, the experts mentioned several approaches that may improve the identification. One example was to establish a more systematic approach for screening lipid values during the annual VU. According to expert opinion, measuring and evaluating LDL-C on a regular basis is for sure desirable, but it would be already sufficient if every adult got a lipid profile with LDL-C measurement at least once in his life [92]. The last revision of the VU was in 2005 and a new scientific revision was commissioned in order to restructure the programme according to current scientific findings in 2020 [58]. In the course of this revision, a panel of experts also discussed the structure and organisation of the aforementioned screening for lipid metabolic disorders and issued the following recommendation:

Überarbeitung: Empfehlung zur Erhebung von LDL-C bei VU

> *All adults should be screened for lipid metabolic disorders by means of serum lipid determination (total cholesterol, triglycerides, LDL, HDL) every 5 years. For persons with increased risk, the screening interval should be differentiated and individually determined by the screening physician (strong recommendation with moderate quality of evidence (strong consensus, expert agreement >95%) [58].*

Form des systematischen universellen Screenings

Based on the classification earlier (see section 5.1.1), this could be classified as a systematic non-specialised index case finding approach, in detail a universal population based screening. However, experts pointed out that whether an FH patient is diagnosed during a GP consultation relies still strongly on the awareness of the disease among the respective physicians. Even with a standardised procedure additional effort is needed to create awareness under which conditions it makes sense to diagnose an FH or to search for a possible FH more precisely [92]. This approach is partly comparable to the Canadian recommendation on universal screening for lipid levels in adults (men ≥40 years of age, women ≥50 years of age, or earlier if other ACVD risk factors are present), but the Canadian document does not provide information on the time interval in which screening should be conducted [17, 18]. The interval suggested for Austria may therefore differ from that in other countries.

Diagnose abhängig von FH-Sensibilisierung des behandelnden Arztes

Automatische Notiz auf Blutbefund falls LDL-C erhöht

Another approach mentioned by one of the experts is that suspicious LDL-C blood levels could automatically be marked in the laboratory findings with a short note like "Familial hypercholesterolaemia should be assessed". This would simultaneously result in raising awareness on a possible FH in patients who could then actively address this topic with their GPs. This automatic notification could be implemented as part of the VU as well as for all serum lipid profiles with LDL-C measurement in general [91].

Kinder werden meist nur über Kaskadenscreening identifiziert

Regionale Studie zu universellem Screening bei Wiener Schulkindern

Children are almost exclusively diagnosed in the framework of cascade screening and in a few cases opportunistically as index patients in Austria (see section 5.2.7) [91]. Some guidance recommend universal population-based screening for children [11, 25, 69]. In Slovenia for example lipid profiles for preschool children (5- or 6-year old) at programmed visit at primary care paediatricians, are routinely assessed. If additionally a positive family history of CVD is identified, genetic screening in tertiary care follows [67]. If this is to be implemented in Austria, the regional pilot study (see section 5.2.2) may be a starting point.

Forschungsprojekt: Wie kann GDx massentauglicher gemacht werden, Blutspender*innen

Another quite different approach represents an upcoming research project at the Medical University of Innsbruck, which covers the question of how GDx can be made more suitable for the general population in Austria, with a special focus on FH. The LDL-C values as well as the genetic status for FH-associated mutations of blood donors will be assessed. For this purpose, new genetic methods will be applied, e.g. a ligand assay preceding the actual sequencing. This is also a possible strategy for the identification of index patients [90].

Zusammenfassung möglicher Strategien zur IP-Identifizierung

In summary, the following systematic screening approaches for identifying FH index patients could be identified from the expert interviews and existing activities in Austria:

- universal screening for LDL-C blood values in adults (>18 years) as part of the existing *Vorsorgeuntersuchung*,
- written notes of a possible FH in all suspicious and elevated LDL-C laboratory reports,
- universal screening for cholesterol in children during the compulsory pre-school examination,
- or systematic testing for LDL-C blood values and genetic status in blood donors.

5.3.3 Molecular genetic testing

Weiterentwicklung genetischer Methoden bringt Änderung von Handlungschritten im Diagnose-Prozess, Ziel: gemeinsames nationales Vorgehen

Regardless whether to confirm the diagnosis of the index patient as well as on a larger scale in cascade screening, GDx is increasingly in use in Austria. Due to the constant further development and progress of molecular genetic methods, the Austrian operational steps in GDx for FH have naturally developed further [91]. In this respect, a joint (national) approach is considered to be of general importance in order to standardise the procedure alongside the questions "who is to be molecularly genetically tested, under what conditions" and "who is referring to the testing"? Experts recommended a general mandatory interconnection of specialised lipid centres [90].

molekulargenetisches Screening ist im GTG nicht explizit adressiert (Vgl. zu D)

When implementing organised genetic screening programmes, e.g. universal screening in children as performed in Slovenia [67] or in cascade screening based on GDx, it is advantageous if the preconditions for performing them are clearly defined and implemented in a legal framework. In the *Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes* by the Council of Europe the need for regulation of genetic screening is addressed [109]. In contrast to, for example, Germany [110], the Austrian GTG [95] and the *Qualitätsstandard "Humangenetische Beratung und Diagnostik"* [102] do not yet specifically address molecular genetic diagnostics within the framework of organised screening programmes (e.g. screening for FH index cases or cascade screening). Even though these programmes are not included, (national) screening approaches need to be handled differently from "normal" individual molecular genetic diagnostics. According to experts, addressing molecular genetic screening in the GTG is a great challenge, but very desirable [90].

5.3.4 Genetic counselling

Ausweitung von GDx hat Folgen auf Situation der genetischen Beratung

An extended utilisation of GDx for the diagnosis of FH index patients has implications on genetic counselling, which in Austria must take place before and after a molecular genetic analysis for FH-associated pathogenic variants [95]. Experts have raised a number of counselling issues which need to be considered in an extended systematic FH diagnosis.

erhöhter Bedarf an Personal für genetische Beratung bei Ausweitung, Profession Genetische/r Beratungsassistent*in in anderen Ländern etabliert

In general, due to the rapid development of genetic diagnostic methods, there is an increasing demand for qualified professionals who are able to explain the background, goals, methods, results, and consequences of genetic testing in the context of individual medical problems [103]. In some countries, especially in the Anglo-Saxon region, the profession of a genetic counsellor in form of a non-medical profession already exists for this purpose. Here, the genetic counsellor is seen as a communication specialist [90]. In Germany this job profile (*Genetische/r Beratungsassistent*in*) has recently been submitted for accreditation by the German Society for Human Genetics and the professional association of German human geneticists [90, 111]. It is, however, important to bear in mind that the tasks of genetic counselling assistants described here still must be performed under the responsibility and supervision of a medical specialist educated in human genetics [111].

genetische Beratung nur durch FÄ oder auch durch anderes ausgebildetes Fachpersonal möglich?

Austrian experts suggest a more explicit debate on how genetic counselling should be optimally organised and whether it should be solely carried out by medical specialists [90, 92]. Up to now, the question what trained genetic counsellors are allowed to do at all or to what extent they are allowed to work

independently is not clarified. In the UK for example counsellors are most often integrated in the Centres for Medical Genetics [90]. The first German-speaking (postgraduate) Master's programme for genetic and genomic counselling which was introduced at the Medical University of Innsbruck in 2019 (www.gencouns.at)[103], may be a valuable source for moving the discussion forward and qualifying experts.

GTG: Beratung und Einwilligung nicht klar genug getrennt

Additionally, genetic counselling is a difficult concept in the GTG because there is no clear separation between the terms counselling, education, and consent. Experts would appreciate a more precise definition [90].

Beratung sollte auch bei rein klinischer FH Diagnose angeboten werden

Furthermore, it was also stated by an expert that counselling should not only take place in connection with the actual genetic analysis, but should also be taken into consideration within a clinical assessment for hereditary diseases. Therefore, FH basic counselling on the personal, social, and ethical implications of a diagnosis, should be offered both, the index patient and his/her relatives. This type of counselling and advice may also be provided at the primary care level [92].

5.3.5 Cascade screening

Einsatz von GDx im Kaskadenscreening oft empfohlen, aber auch erhöhter Bedarf an genetischer Beratung als Folge

In Austria, the measurement of cholesterol levels, i.e. a clinical assessment, is currently the gold standard for FH diagnosis in first and second degree relatives, but GDx is increasingly used in cascade screening. Here, genetic counselling must take place before and after GDx, too (§ 65 Abs 1 GTG and § 70 GTG) [95]. Although most (inter-)national guidelines and position papers recommend cascade screening of family members using clinical diagnostic scores complemented with GDx, there is also guidance recommending it primarily based on GDx, like in the UK [15, 23] and in Slovenia [67]. An extension of GDx would increase the organisational effort and personnel capacities concerning the genetic counselling [90, 92].

5.3.6 Education and awareness

Bewusstsein für FH bei Medizinern, (potentiellen) Pat. und Bevölkerung soll verbessert werden

A point particularly emphasised by the experts was that the awareness and education of physicians and other health care professionals, as well as patients, regarding the clinical signs and diagnosis of the FH should be increased [90-92]. As GPs they are often the first point of contact with patients with hypercholesterolaemia [93], their awareness for increased blood cholesterol and its connection to FH is of particular importance.

Beispiel Belgien: Informationskampagne in kardiovaskulären Einheiten in KHs

An example of how to increase awareness in intramural setting is the Belgian campaign. Here, for example, a poster was produced with information on criteria for a diagnosis of FH. This poster is displayed in all CCUs throughout the country and is intended to remind medical practitioners to consider the possibility of an FH whenever a patient with CV event is admitted [24].

Beispiel Slowenien: universelles Screening-Programm wird im Medizin-Studium behandelt

Another example is Slovenia, where the universal screening program is promoted by including education about it into the medical school curriculum and in paediatric residencies. It is further regularly presented at workshops and symposia to health care professionals [67, 112].

5.4 Ethical and regulatory aspects of genetic testing for FH

In the following ethical and regulatory aspects of predictive molecular genetic testing in general and in particular for diagnosis of FH index patients (non-predictive) and family-based cascade screening (predictive) are described.

5.4.1 General ethical aspects and risks of predictive genetic testing

prädiktive Gentests: präsymptomatisches vs. Suszeptibilitäts-Testen

Predictive genetic tests are defined as tests that are performed on healthy or apparently healthy (asymptomatic) individuals to identify their risk for developing a disease of interest in the future [113]. They can be divided into two types: pre-symptomatic tests and susceptibility tests. Pre-symptomatic tests are used to identify healthy individuals that are very likely (almost certainly 100%) to develop a devastating and debilitating disease in the future, which at this time have no treatment or cure, e.g. Huntington's disease. Whereas susceptibility testing involves searching for pathogenic mutations that confer a higher risk for developing disease, e.g. BRCA1/2-genes for breast cancer [113]. A positive test result of the latter type does not mean that the disease will inevitably occur or remain absent. The diseases concerned can be multifactorial, mono- or polygenic, treatment is mostly available, and the severity of the phenotypic symptoms is highly variable, as it is the case for FH. Therefore, ethical issues concerning pre-symptomatic and susceptibility testing are not quite the same. Whereas in pre-symptomatic testing the questions "Are we better off knowing our fate?" and "what are the psychological costs for those tested?" play a major role, susceptibility testing goes along with issues of the complexity of test interpretation, education and counselling for those at risk [113].

Hauptaspekte:

Although susceptibility testing provides the opportunity to identify a predisposition to a treatable disease at an early stage, predictive genetic testing methods are also associated with risks. The World Health Organisation [114] and the German Reference Centre for Ethics in Life Sciences (*Deutsches Referenzzentrum für Ethik in den Biowissenschaften*) [115] defined the main aspects and risks in the ethical evaluation of predictive genetic tests in general as follows:

Recht auf Selbstbestimmung

- *Violation of the right to informational self-determination*
  As genetic tests and data can affect core areas of an individual's personality, every individual is entitled the right to choose between the "right to know" as well as a "right not to know" about their own genetic constitution. Problems may arise in cases where one person's right not to know collides with another person's right to know resulting in intra-familial conflicts [115].

intra-familiäre Konflikte

- *Intra-familial conflicts*
  Testing an individual for genetic constitutions contains always information about the biological relatives, which can lead to special conflict situations within families. A positive test result can be used to draw conclusions about the genetic constitution of a biological relative. For example, if a person has a grandfather with Huntington's disease and tests positive, it is then clear that the corresponding parent also has the genetic mutation causing the disease. This collides massively with the right to informational self-determination of the biological relative

[115]. Another ethical issue concerns undisclosed familial relationships, e.g. no biological relationship because of adoption or unclear paternity.

- *Confidentiality* **Vertraulichkeit**
  In addition to the right of informational self-determination, the aspect of confidentiality is also closely connected to intra-familial conflicts when it comes to predictive genetic information. As genetic tests give information on an individual's inherent risk for disease and disability, their predictive power makes genetic testing particularly liable for misuse. Especially in the context of health care insurance and employment the knowledge of genetic dispositions needs to be handled confidential. Misuse can be socially debilitating and may have severe socio-economic consequences. Confidentiality of test results needs to be ensured and legislation permitting only selective access to this information has to be established [114].
- *Genetic discrimination and stigmatisation* **Diskriminierung und Stigma**
  Non-confidential handling of genetic information can lead to genetic discrimination and stigmatisation of not only the tested individual but also the whole family. Concerning predictive genetic information, there is the risk that a positive tested individual may be considered as a "healthy invalid". This means that healthy individuals are made patients even though they have no symptoms. They are often perceived as sick and hence treated accordingly [114, 115].
- *Psychological strains due to positive test results* **Psychologische Folgen positiver Testergebnisse**
  If the predictive genetic test reveals that a person has a disease causing mutation, it can lead to considerable psychological strains for the affected person. These strains can be increased by the complexity associated with genetic test results: especially when a disease has a low penetrance or is highly variable in its expression and symptoms, the question of an appropriate approach and an optimal treatment may be difficult [115].
- *Risk of "geneticising" the living world* **Risiko der „Genetisierung" der Lebenswelt**
  "Geneticising" refers to a process in which differences between individuals are reduced to their genetic status. Diseases and behaviour are increasingly understood to be determined solely by genetics. This results in the problem of genetic determinism, which states that a person is completely pre-defined by his or her genes [115].

5.4.2 Specific ethical and regulatory aspects of molecular genetic testing for FH

spezieller Fokus auf ethische Aspekte bei FH: GDx bei IP und Kaskadenscreening

Based on the above mentioned general aspects of predictive genetic testing, the following special focus is on GDx of FH. Molecular genetic diagnostics of FH is used on the one hand to confirm diagnosis in index patients. On the other hand, the detection of a pathogenic mutation on FH-associated genes also has immediate and direct effects on family members, some of whom do not yet show symptoms phenotypically/clinically, and therefore GDx in FH can be characterized as predictive testing. In this assessment we focus on both, ethical aspects of diagnostic testing of the index-patient and the consequences of predictive testing as part of the family-based cascade screening.

According to the Socratic approach checklist [49], we identified ethics-relevant aspects related to the target group, including FH index patients and family members, the disease, the stakeholders, as well as the intervention at stake. A detailed extraction table of the ethical aspects is provided in Appendix Table 9-8.

Ethical issues concerning the target patient population

Aspekte betreffend FH-Pat.

Since this descriptive ethical analysis not only includes the diagnosis of the FH index patient, but also molecular genetic diagnosis as part of the cascade screening, the target patient population refers to the index patient and the corresponding at-risk family members.

Beneficience

Benefizienz

The ethical principal beneficence in context to the target patient population is strongly dependent on the disease burden of interest. FH is the most common autosomal dominant monogenetic disorder worldwide. This dyslipidaemia is causing premature CVD due to lifelong elevation of plasma levels of LDL-C [20]. Especially the risk of coronary/ischemic heart diseases (CHD/IHD) is considerably increased in affected individuals as described in section 2.2.

Screening zur Prävention gegen Arteriosklerose und CVDs

Screening for FH patients is an important issue in primary prevention of arteriosclerosis and CVDs. Early diagnosis and initiation of appropriate treatment can reduce the risk for ACVDs amongst individuals with definite or probable FH, whose risk is otherwise at least 10-fold increased, compared to non-affected individuals [20]. This was also shown in a Danish study, which compared patients with FH versus non-FH patients, on events of fatal and non-fatal CAD. Odds ratios for CAD were 10.3 ([CI: 7.8, 13.8]) in subjects treated with LLT and 13.2 [CI: 10.0, 17.4]) in subjects not treated with LLT [116].

lebenslange Kumulation von LDL-C

The concept of cumulative cholesterol burden illustrates the importance of early diagnosis of FH and initiation of medical management in childhood with statins and other LLTs [2, 20]. For this reason screening for FH is recommended by many medical guidelines, including universal screening of children [67], as well as systematic approaches in primary care to identify FH index cases [15, 23].

Kaskadenscreening als mächtiges Tool zur frühen Diagnose und rechtzeitigen Einleitung präventiver Maßnahmen

Systematic tracing of at-risk family members after identifying FH index patients via screening is, due to the hereditary aetiology of the disorder, a powerful tool for early diagnosis, as the average age at which relatives with FH are diagnosed is lower than those of index patients at diagnosis [2]. If positively tested family members start LLT early, this has the potential to reduce their risk of atherosclerosis to that of individuals without FH. Furthermore, cascade screening using GDx seems to be of high personal utility for family members being tested negative for the known familial mutation. This is because they are unlikely to have FH and are therefore relieved by the knowledge of having little risk to pass the familial pathogenic variant to their offspring [2].

Non-maleficence

Non-Malefizienz, Schadensvermeidung

Besides the beneficial aspects of the diagnosis of FH, arguments concerning non-maleficence, i.e. that patients should not be harmed, must also be considered. One aspect of non-maleficence is that there is some evidence that adverse psychological impact of GDx is suggested to be minimal and it is not perceived as anxiety provoking [2]. Further, it is stated in Sturm et al. 2018 [2] that molecular genetic diagnosis could provide reassurance to patients that their dietary and lifestyle habits were not the primary cause of their condition.

Psychologische Folgen der FH Diagnose werden als gering eingeschätzt

Concerning the diagnosis of FH in general, independent from the mode of diagnosis, Agård et al. 2005 [117] reported in their study, that some interviewed FH patients reported concerns related to their LLT and feelings of

guilt when not complying with treatment recommendations. Though, none of them expressed sustained emotional distress or would have preferred to not know the FH diagnosis. It is further reported that their awareness of FH did not appear to have had substantial impact on their way of life, besides from being more attentive to diet, and that interviewed patients, who did not suffer from any other diseases, even generally regarded themselves as healthy.

Unwarranted reassurance from false-negative test results during diagnosis will be discussed later in this chapter, when it comes to the benefit/harm balance of the intervention.

Vulnerability

Kinder als besonders vulnerable Pat.-Gruppe

As universal screening at pre-school examinations and cascade screening aim to identify FH patients at a very young age (childhood), the target patient populations represents a vulnerable group.

If LLT is initiated early enough, the cumulative LDL-C burden can be lowered to an extent comparable to that of non-affected individuals. Parents should be aware, that If FH is left untreated in their child, it will be at higher risk of coronary events compared to an adult because of the cumulative burden of elevated LDL-C levels [2].

Verantwortung des Gesundheitssystems Eltern über FH und Diagnose aufzuklären, Konflikt der Selbstbestimmung der Kinder

This means, on the one hand, that there is a certain responsibility of the health care system towards the children, that parents are informed about FH and the possible consequences of molecular genetic and clinical diagnosis. On the other hand, there is also a potential conflict with other ethical aspects, especially that of the autonomy and self-determined decision of the person. If parents decide that children should be screened, or that children should be tested in cascade screening, they automatically deprive the more vulnerable person (the child) of the right to not know (see ethical aspect below).

Eltern haben unterschiedliche Einstellungen zu Diagnose ihrer Kinder

In a small study from the UK, parents responses to neonatal screening for FH were assessed [118]. They showed, that according to perceptions of the underlying cause of the positive test result, the reactions of the parents were different. Some parents perceived the diagnostic test as a procedure detecting elevated cholesterol in their children. In this case it was perceived as less threatening, as FH was classified as a familiar, dietary in origin, and controllable disorder. Others saw the test as detecting a genetic problem in their child. In those cases, the condition was perceived as uncontrollable and, hence, more threatening [118].

Test wird von Eltern als wenig invasiv wahrgenommen

Nevertheless, it is stated, that parental attitudes towards genetic testing in children are still affirmative. This may be influenced by the fact, that testing can be accomplished via readily accessible and low invasive sample types, including saliva and buccal swabs [2].

Autonomy, privacy and respect for persons

Autonomie, Recht auf Selbstbestimmung und Privatsphäre sollen im Rahmen der genetischen Beratung thematisiert werden

As described in the general ethical aspects of predictive genetic testing (see section 5.4.1), GDx and resulting data can affect the core areas of an individual's personality and privacy [115]. This is also the case with the molecular genetic testing of FH. The final decision to conduct GDx is left to the patient. The patient decides whether he/she wants to know about his/her genetic status, or whether he/she is exercising his/her right to not know about his/her own genetic constitution. In Austria, the process of genetic counselling (see section 5.2.6) includes a conversation about personal consequences for the patient, including information on preventive and therapeutic options, in-

formation on the process of genetic testing and information on the possible implications for life and family planning in addition to informative medical aspects of the genetic disposition to be investigated. This process is intended to help patients decide whether they want to exercise their right to know or not to know and to be aware of the consequences of the GDx findings for their own privacy and that of their family.

Concerning cascade screening for FH, there is potential for intra-familial conflicts, particularly in the area of disclosure of the results and possible risks to family members and the following privacy concerns.

Intra-familial conflicts

FH-Diagnose kann intra-familiäre Konflikte auslösen

Due to the genetic aetiology of the disorder, a diagnosis of FH has direct implications on at-risk family members. Therefore, the procedure of cascade screening is prone to affect family dynamics and relationships, which may result in intra-familial conflicts.

IP sollten Angehörige informieren, nicht nur bei genetischer Diagnose

In general, FH patients should receive recommendations to inform and warn at-risk relatives about their risk for FH [2]. The disclosure of an FH diagnosis to family members should not only be considered if the diagnosis is based on molecular genetics, but also if the diagnosis is based on phenotypic and clinical criteria. The impact and significance of an FH diagnosis on family members can be discussed with the patient for each type of diagnosis [92].

vielfältige Gründe für Offenlegung oder Zurückhaltung der Diagnose

The reasons for disclosure and non-disclosure of the diagnosis can be wide-ranging. Some FH index patients may experience difficulties in communicating their GDx results to at-risk family members, and may experience a loss of privacy in doing so [2]. Additionally, there may be concerns to violate the privacy of the relatives if disclosing the potential risk of having FH. It is also stated by index patients that they hesitated to disclose to their relatives out of respect for the autonomy of their relatives. Index patients were worried that relatives may feel under pressure to get tested out of responsibility to the family [76].

Verletzung der Privatsphäre der Angehörigen bei Offenlegung

The argument of not violating privacy is also important when it comes to the question on who in the family should be informed about the possible risk of an FH. Van Nieuwenhoff et al. [119] reported that index patients generally alerted their first-degree relatives of the genetic risk. Mostly because they felt morally obliged to do so or because they were advised to do so by a health professional. More distant relatives seem to be alerted rather rarely due to insufficient risk knowledge or fear of being perceived as interfering in their relative's affairs [119]. 'Out of the blue' contacting of family members who live at a distance and who may not be in regular contact with the index patient may raise medical and ethical problems, particularly when such individuals decide not to be tested [120]. Further, non-disclosure or delayed disclosure could be due to risk awareness reasons such as a limited risk perception and low self-efficacy expectations regarding disclosure competence [119].

Schuldgefühl der Eltern gegenüber den Kindern

Furthermore, an FH diagnosis can also lead to parents feeling guilty about passing their pathogenic variant to their children. Sturm et al. 2018 [2] describe that it may be helpful to emphasize the benefits provided by this information. One of it is to initiate early and sufficient LLT which will effectively reduce the child's risk of CVD to that of the general population.

Schuldgefühle bei nicht-Diagnose

Finally, family members who test negative for the familial pathogenic variant may experience a so-called survival guilt [2].

Ethical issues concerning the disorder

Ethical issues concerning the metabolic disorder FH include issues related to diagnosis, prejudice and stigma.

Aspekte betreffend FH und möglicher Folgen

Diagnosis

Concerning diagnosis of FH based on phenotypical criteria, there is indication that the classical clinical presentation of FH has changed over time [2]. From the USA, decreased average LDL-C levels across the population in general are reported. This could be due to decreased saturated fat intake and increased use of statins [121]. If only the lipid level in the blood is considered for diagnosis, this makes it more difficult to distinguish individuals affected by FH from individuals not affected by FH. Another difficulty in clinical diagnosis arises from the possibly overlapping LDL-C values in the blood of individuals affected by common hypercholesterolaemia, caused by secondary disorders or environmental factors, in contrast to individuals affected by the monogenetic FH (causing primary hypercholesterolaemia).

Diagnose: typische LDL-C Level haben sich über Jahrzehnte geändert

It should also be considered that diagnosis solely based on lipid values, especially in children, may result in over-diagnosis. This represents a potential harm as most children with elevated lipid levels would not develop a clinically relevant lipid metabolism disorder or premature CVD [122]. This calls for the need to additionally assess the family history of hypercholesterolaemia and premature CVDs.

mögliche Überdiagnose: nicht alle Kinder mit erhöhtem LDL-C erleiden CVD

Another aspect to mention concerning the diagnosis of FH is the potential underutilisation of GDx. Data from the United States national FH registry (CASCADE FH) indicates that genetic testing is reported in only 3.9% of individuals in the registry with a clinical diagnosis [2].

Geringe Anwendung von GDx

On the other hand, there is also potential for medicalisation in FH patients due to overuse of LLDs without supporting patients first to reduce blood lipids with lifestyle changes, like smoking, dietary habits, or physical activity even if we know that the targeted LDL-C value is often only achieved by a high intensity statin therapy [20].

Gefahr der Medikalisierung

Discrimination, prejudice and stigma

Besides potential social and psychological consequences, like stigmatisation and discrimination within the community [114], knowledge about the genetic constitution of an FH patient can also have far-reaching consequences for insurances and employment. Individuals with a genetic diagnosis of FH but which are actually healthy (i.e. mild hypercholesterolaemia, but no CAD) may be denied life assurance or health assurance [120]. Especially in the course of cascade screening, FH patients are diagnosed at a younger age and often do not have increased blood cholesterol, nor did they have a CVD event [2]. In Austria, possible genetic discrimination in this context is addressed with a legislative regulatory model. The GTG regulates the prohibition of the collection and use of data from genetic tests for certain purposes by employers and insurance companies:

(genetische) Diagnose kann Einfluss auf Versicherungen und Arbeitgeber haben

> *Employers and insurers including authorised representatives and co-workers thereof are prohibited to collect, to demand, to accept or else to make use of results from genetic tests of their employees, job applicants or insurees or insurance canvassers. This prohibition also covers the demand for delivery and the acceptance of body substances for genetic test purposes (§ 67 Abs 1 GTG) [95].*

GTG reguliert Verbot der Verwendung von genetischer Information für bestimmte Zwecke

Nevertheless, individuals requesting life, health, or disability insurances are most often asked for information about their own health and that of their relatives. Individuals may also have a medical check-up including a measurement of blood cholesterol, and thus FH may be identified anyway [120]. Homsma et al. 2008 even suggest that insurance applicants with FH should be accepted at normal rates if LDL-C levels are <4.0 mmol/L (154 mg/dL), in the absence of additional risk factors [123].

Ethical issues concerning the intervention, comparators, and stakeholders

Aspekte betreffend GDx und klinische Diagnose, Stakeholder

The group of stakeholders do not include family members of the FH index patient, as they are in the context of cascade screening part of the target population themselves.

Autonomy, consent and confidentialitiy

genetische Beratung als Schlüsselelement

Genetic counsellors are particularly important stakeholders in the context of an ethical analysis of the molecular genetic diagnostic of FH and family cascade screening. In contrast to pre-symptomatic GDx, where because of the fatality, the psychological part of genetic counselling is of great importance, genetic counselling in susceptibility GDx has a main focus on the complexity of risk stratification [113].

Pat. und Angehörigen soll genaue Risikoabschätzung ermöglicht werden

A major goal of genetic counselling during the diagnostic process of FH is to enable patients and their relatives to make an accurate estimate of his/her risk for arteriosclerosis and CVD (risk stratification), to make them aware of the psychological impact of the diagnosis, and to explain benefits and risks of LLT [120].

unabhängige voll-informierte Einverständniserklärung der Pat.

The ability of the patient, family members, or a particular child to give full 'informed consent' is of importance in GDx and cascade screening. However, the genetic counsellor has a powerful role in that she/he still needs to decide which information is relevant for the patient to make an informed and autonomous decision without overburdening the patient. Through the selection of information he/she is in charge of the patient's autonomy [124].

In a survey among Austrian medical professionals, various aspects were named, which reveal particular ethical and professional challenges faced in relation to genetic counselling. Although this study refers to genetic counselling in general, the identified aspects can also be extrapolated to the example of the GDx of FH. In Table 5-4 16 domains of possible ethical/professional challenges are listed [125]. Organisational constraints were frequently mentioned as challenges encountered. Organisational constraints comprise i.e. language barriers or a lack of written information material, and too much time-effort for non-medical organisational tasks, which is also related to the domain of time constraints. Lack of experience, lack of training as a psychotherapist, or limited cooperation between institutes, and attaining/maintaining proficiency are also named challenges [99]. Further, another stated challenge was to be up-to-date to information about rapidly advancing genetics [99].

GTG: genetische Beratung muss nicht-direktiv sein

The non-directiveness of genetic counselling prescribed by the Austrian GTG [95] was not mentioned by the medical professionals as an ethical and professional challenge. Non-directiveness was instead even regarded as a major principle for genetic counselling in Austria. According to this, it seems that medical professionals mostly have internalised this principle [99].

Table 5-4: Description of 16 domains of ethical/professional challenges faced in relation to genetic counselling [125]. On the survey the Resource Allocation domain was divided into three items: time restrictions, financial restrictions, and organisational restrictions; and the Emotional Responses domain was divided into two items: patient emotional reactions, and own emotional reactions.

Domain name	Definition
Informed consent	What information is most relevant? Does a patient decide voluntarily?
Withholding information	Professional wonders whether to withhold a specific piece of information because patient does not want to know or would not be able to understand; testing uncovered unanticipated information; or the duty of re-contacting patients
Facing uncertainty	Information is limited in meaning or usefulness for a particular patient or family
Resource allocation	Constraints in service provision due to time, financial, and/or organisational restrictions
Value conflicts	Disagreements among professional, patients, family members, society about what to do, based on personal or professional values
Directiveness/non-directiveness	Patient wants to be told what to do or professional believes patient should make certain decisions
Determining the primary patient	To whom does the professional's primary obligation lie when family members or others are involved?
Professional identity issues	Professional questions nature or extent of her or his professional role
Emotional responses	Struggling with patient or own emotional reactions
Diversity issues	Differences in expectations, norms, practices due to culture, ethnicity, socioeconomic level, religion
Confidentiality	How much information should the professional share with whom?
Attaining/maintaining proficiency	Difficulty keeping up with genetic knowledge, tests, resources
Professional misconduct	Patient is exploited by other health care professionals (e.g. researchers)
Discrimination	Potential threat to insurance and/or employment due to genetic status
Colleague error	Due to unintentional mistakes by other healthcare professionals, remediation measures are required
Documentation	Patient requests certain information be left out of the medical record, or be recorded in a certain way

Niederlande: Screening mit systematischer Benachrichtigung der Angehörigen wurde eingestellt

In the Netherlands, a nationally organised cascade screening programme and expert lead active approach of disclosure was in place until 2014. The possible paternalism of this proactive and direct approach was mentioned as one drawback in Dutch policy documents. Furthermore, it was stressed that patients should be enabled to seek healthcare autonomously and that privacy of at-risk relatives was seen as potentially at odds. Furthermore, the right not to know may be trespassed by active direct contacting by health care professionals [119, 126].

Best interest

Bestes Interesse und Vertraulichkeit

Confidentiality and best interest principles are not only of special importance in the context of genetic counselling but also in the general clinical care of FH patients.

zusätzliche genetische Diagnose hat kaum Einfluss auf klinisches Vorgehen

On the one hand, Will et al. 2010 [127] report that medical professionals appear to be aware of and interested in the genetic component of FH and the possibility of GDx, but this nevertheless has not a major impact on daily clinical work and LDL-C levels are still seen as the key factor to diagnose FH.

dennoch: unterschiedliche genetische Mutationen können Therapie-Entscheidungen beeinflussen

On the other hand, Sturm et al. 2018 [2] emphasize that GDx results may influence therapeutic choices, particularly in patients with severe HeFH or HoFH. The value of genetic testing for precision medicine in lipid treatment is currently being studied and further research is needed to evaluate how information from GDx can improve medication adherence and outcomes for patients with FH. However, it must be noted that not always a detectable pathogenic variant can be identified in patients and that these patients need of course still be treated to the full extent and not be denied medication on the basis of a genetic test [2].

Einleitung von Kaskadenscreening wahrscheinlicher nach GDx

GDx may not only confirm the clinical diagnosis of the index patient but may also have impact on the willingness of medical professionals to test relatives [120]. GDx allows for more unequivocal results at least for the confirmation of the familial pathogenic variant.

Justice and equity

gerechter Zugang zu GDx: Kosten werden in Ö von Sozialversicherung übernommen

Regarding equal access to a technology, GDx is often associated with cost issues. In some countries, individuals may want to undergo GDx, but the costs or the lack of insurance coverage may limit ability to obtain testing [2]. In Austria, GDx for FH is reimbursed by the social insurance and testing is therefore not associated with private costs for the patient. Access to the technology is therefore not restricted for economic reasons. Furthermore, due to technological development, costs of genetic analyses continuously decrease over time [2]. Even highly complex molecular technologies like exome sequencing are state-of-the-art by now and are commonly used for diagnosis of FH. As part of cascade screening, GDx is considerably cheaper, since only site-specific testing for the known FH-associated mutation of the index patient has to be performed [2].

Bewusstsein für FH bei med. personal und Pat.

Another aspect that could limit the equal access to molecular genetic diagnostic of FH is related to health literacy of health care professionals as well as patients themselves. Awareness and education concerning FH as a possible reason for hypercholesterolemia and premature CVD is essential in identifying index patients and initiating cascade screening. In Austria, one of the three main scenarios to identify FH index patients is, that persons contact patient organisations on their own initiative and are then forwarded to GPs and medical FH services. So proper health literacy may support equal access to GDx for FH.

Benefit-harm ratio of the intervention at stake

The list of benefits of GDx for the diagnosis of index patients and for cascade screening seems to be very long, but there are also potential harms for the patients.

GDx ermöglicht präzisere Prognose und Risikoabschätzung für den Pat.

For the index patient, GDx provides prognostic information and the ability to perform refined risk stratification [2]. In general, the prevalence of an FH-associated pathogenic variant in adults with LDL-C levels ≥190 mg/dL and no personal or family history data is only around 2%. Hence, not every patient with suspicious elevated blood cholesterol will have FH. When concerning patients with acute coronary syndrome, ≤65 years of age, and with LDL-C levels ≥160 mg/dL (4.2 mmol/l) the prevalence of genetically confirmed FH is raised to ~9% [2] which leaves still a much higher percentage of people who do not have FH.

Since diagnosing FH is complex based on lipid profiles alone (due to the overlap in LDL-C levels, caused by the accumulation with age, between individuals with and without an FH pathogenic variant), the advantage of GDx is to distinguish FH patients from those with elevated cholesterol levels due to other reasons. Furthermore, GDx has the advantage to diagnose patients with pathogenic variants who generally do not meet clinical diagnostic criteria based on blood cholesterol, clinical and physical features, or family history [2].

GDx ermöglicht eindeutigere Unterscheidung zwischen Pat. mit FH und genereller/anderer Hypercholesterinämie

Besides the personal benefits for the FH index patient, GDx has a large impact on the implementation and success of cascade screening. It is likely that increasing the use of GDx to identify index patients will lead to identifying a higher number of patients with FH per family. In a Czech database study it was shown, that in families with a known pathogenic variant, the number of patients with FH per family is on average 1.77, whereas in families without this information it is just 1.18 [2].

GDx erhöht Erfolg des Kaskadenscreenings

The proof of a pathogenic variant in the index case allows for targeted, site-specific cascade testing in at-risk family members. This results in helpful information for family members on whether they are affected from the family specific mutation or not [2].

Not testing for pathogenic variants in a FH index patient can result in misclassification of compound FH (2 different mutations) for severe HeFH. This can have negative implications on family members, because accurate identification of all at risk relatives is not possible, if it is not known that both sides of the family are at risk [2].

Regarding harms, it needs to be pointed out that FH genetic testing is not 100% sensitive or specific. Of patients clinically diagnosed with “definite” FH (e.g. DLCN ≥8), a pathogenic variant in 1 of the 3 main FH-causing genes can be identified in only ~60% to 80%. In patients clinically diagnosed with “probable” FH (e.g. DLCN 6-8) ~21% to 44% are proven to have one of these FH-associated mutations. However, a negative genetic test result in a patient with phenotypical FH, as defined by clinical criteria, does not exclude the existence of FH. The negative molecular genetic test result may be due to technical limitations, the presence of polygenic causes, or the presence of mutations in yet to-be identified genes [2]. Insufficient education and information regarding the test results could lead to a false reassurance for the patient that he/she is not affected by FH.

GDx bietet keine 100 %-ige Sensitivität und Spezifität, FH bei neg. GDx nicht ausschließbar

Another point to bear in mind when diagnosing FH on the basis of genetic mutations is the importance of variant interpretation, as some of the variants show unknown significance in the clinical manifestation of FH. For example, in a recently updated LDLR variant database, 7% of them are currently still classified as variants of unknown significance [2].

nicht alle genetischen Varianten haben signifikanten Einfluss auf LDL-C im Blut

Finally, it should be mentioned that despite the evidence of a risk-associated mutation, their influence is highly modifiable by the co-inheritance of other genetic factors and the presence of environmental factors. This can complicate the ACVD risk stratification based on genetic testing [120].

Effekt der genetischen Mutation auf LDL-C kann durch andere Faktoren beeinflusst sein

Benefit-harm ratio of the comparator

As described above, a major disadvantage of the diagnosis based solely on clinical features and LDL-C measurement is that LDL-C levels in FH and non-FH relatives may overlap, especially in adults. Therefore, diagnosis of FH based solely on LDL-C levels may potentially harm patients due to possible over- as well as underdiagnosis [2].

rein klinische Diagnose birgt Gefahr der Unter- als auch Überdiagnose

falscher Stopp des Kaskadenscreenings

Furthermore, cascade screening based on LDL-C could incorrectly stop at family members who are below a pre-defined threshold, although they still carry the causal pathogenic variant [2].

passend definierte LDL-C Schwellenwerte

Thresholds and cut-offs for clinical diagnosis to consider GDx is another important issue. Since the prevalence of pathogenic variants and LDL-C blood values may differ among countries, races and ethnic backgrounds [2], attention needs to be paid to have a well-defined threshold.

maskierte bzw. unbekannte Familiengeschichte problematisch bei diagnostischen Scores

Furthermore, a diagnosis of FH solely based on clinical criteria can have limitations due to the limited clinical sensitivity for identifying a family history of CVD which is part of every diagnostic criteria and score for FH, like DLCN and SB. Limitations can arise because of reduced LDL-C penetrance, for example if affected relatives already receive LLT, which can "mask" the hypercholesterolaemia and CHD phenotype. Furthermore it is limited due to reduced clinical sensitivity or specificity of self-reported family history, or because reliable family history information may simply be unavailable [1]. In the course of the universal lipid screening for pre-school children in Slovenia, in only 41% of molecular genetically diagnosed children, a family history of CVD was given [67].

eingeschränkte klinische Diagnose bei Kindern

In general, exclusively basing FH diagnosis on clinical criteria reaches its limits in children. DLCN criteria for example are not valid in children which means that the diagnosis relies on family history and serial fasting plasma LDL-C measurements. Only the SB criteria are suitable and can be applied to children <16 years of age, using adapted lower TC and LDL-C cut points, in the presence of tendon xanthoma or positive family history [2].

5.5 Resource impact analysis

5.5.1 Epidemiology and patient flow

Epidemiologie und Patient*innenfluss in den einzelnen Behandlungsschritten

In the following paragraphs the results of the calculations for the various subpopulations are described. The following Tables (Table 5-5, Table 5-6, Table 5-7) show the parameters used to calculate the patient flow. The Table 5-8 summarises the sizes of relevant populations for each step of the patient flow. Patient numbers were always rounded up to the next higher natural number. A number has been assigned to each parameter in order to comprehend where they were used in the course of the calculations.

Population with a current diagnosis

Prävalenz: 1:500-1:200, d. h. 14.700-36.790 Personen ≥18 mit potentieller FH

In Austria 7,358,443 people ≥18 years are living. The exact number of people affected by FH is not known. If we assume a prevalence of 1:500 to 1:200, proposed by experts and the literature, approximately 14,700 to 36,790 people in Austria will potentially have the disorder (17,800 to 44,500 people in the whole population) [5, 8].

nur ein kleiner Teil der Leute sind explizit als FH-Fälle identifiziert und in Behandlung (ca. 10 % in AT)

Several sources show that only a small fraction of people with FH are diagnosed and treated. The proportions vary widely in the literature and in Austrian estimates. While on a global scale, literature states a proportion of <1% for the majority of countries, data from the Netherland suggest a proportion of 71% [13]. Austrian estimates are around 10-15% [57], corresponding to

figures from Switzerland (13%) or the UK (12%) [13]. This is in contrast to another Austrian source, which assumes a proportion of 1%. Based on this diverging figures we assume in our model that a maximum proportion of 10% of people affected by FH (~14,700 to 36,790) are currently diagnosed and treated in Austria, which corresponds to 1,470 to 3,680 people in treatment. People identified through the register are not considered further in our calculations of people diagnosed and treated (old/existing index cases).

Table 5-5: Epidemiology assumptions and parameters for Austria

#	Parameter	Analysis	Amount		Sources
	Epidemiology				
	Population statistics/Prevalence to calculate number of people with a current clinical diagnosis (old/existing index cases) and potential new index cases				
1	Population in Austria, age ≥18 years (and total population)		7,358,443 (8,901,064)		Population statistics 01/01/2020, population 18 years or older, Statistik Austria (2020) [55]
2	Proportion of the affected/identified population with a current clinical FH diagnosis that are in treatment for FH	B	10%		FH identified in <10% using DLCNC or SBC, Lee et al. (2019); It is estimated that far <10% of those affected in Austria are diagnosed and treated, Hanauer-Mader (2017); Proportion of people diagnosed and treated ~10-15%, AAS (2015) [57, 107, 128]
3	Prevalence of monogenic FH in the general population	B	0.3%	1:250	Prevalences assumed in the ESC Guideline and also assumed as an epidemiological working hypothesis for Austria, ESC (2020), Krychtiuk and Speidl (2017) [8, 20]
3′		S	0.5%	1:200	
3″		S	0.2%	1:500	

Abbreviations: B – Base case analysis/assumption, DLCN – Dutch Lipid Clinical Network Criteria, S – Sensitivity Analysis, SBC – Simon and Broome Criteria

FH management and treatment pathway

Index patient identification

Kalkulation auf Basis von potentiellen FH-Fällen, die realitätsnah identifiziert werden können

Cost calculations and determination of index patients based on people potentially having FH from the total population (i.e. 1:250 of 7,358,443 or 8,901,064) are not adequate, because index patients need to be identified as a first step to assure a realistic and viable calculation. As we described in the method section 4.5, we chose to base our calculation on the strategy to identify index cases by systematically searching for them in primary care records (documentation of health-checks).

Datenverfügbarkeit VU: ~40 % der österreichischen Bevölkerung ≥18 (~2.943.378 Personen)

According to the Austrian social security, for 40% of the population ≥18 years VU data and hence primary health care records including TC, HDL-C, indirect LDL-C and triglyceride respectively are available. Therefore, approximately 2,943,378 people could be addressed by a systematic search, applying a specific threshold for total cholesterol (ESC/EAS guideline: TC level ≥8 mmol/L or ≥310 mg/dL without treatment in an adult or adult family member; NICE threshold: ≥7.5 mmol/L (≥290 mg/dL).

~0,4 % (1:250) haben potentiell eine FH

We assumed that 0.4% (1:250) of the total number of 2,943,378 people will be identified as having potentially FH and will subsequently be invited for an assessment. This is based on the following rationale: The NICE assumes that 0.51% of people will be identified as having possible FH and invited for an assessment. If a prevalence of 1:250 (0.4%) is assumed within the Austrian VU population (our base case assumption), then the prevalence value of 0.4% is almost approaching the value of 0.51% [33].

Einladung für eine einleitende Untersuchung: 11.774 Personen

Consequently, the absolute number of persons identified as potentially having FH or already having an FH diagnosis via this process corresponds to 11,774 persons. In our model, these 11,774 people are assumed to be invited for a preliminary assessment in primary care.

Table 5-6: Parameters for the calculations – identification of new index cases

#	Parameter	Analysis	Amount	Source
	Identification of index patients and FH screening management			
	People identified by search of preventive medical care check-up records (new index cases)			
4	Availability of data in preventive medical checkup (VU) records/primary health care records to enable search for FH criteria	B	40% (~2,943,378)	"40% of the Austrian population can be addressed by the preventive medical checkup (Vorsorgeuntersuchung – VU)", Social Security Austria and former Main Association of Social Security Institutions and annual report (2020) [56]
4′	Number of people identified by primary health care data base with a potential diagnosis of FH/without a current diagnosis of FH and invited for a preliminary examination by the GP	B	10,596	Own calculations based on the assumed parameters #1, #2, #3, #4: (Relevant population * Availability of data * Prevalence) – (Relevant population * People with a current diagnosis (possible or definite))
5	Uptake of a preliminary clinical assessment of phenotypical predictors of FH incl. family history by the GP in people identified by primary health care data base search	B	26.40%	Proportion and absolute number of at risk people identified for further assessment/molecular genetic testing, Kirke et al. (2015) [129]
			15.26%	Joint Probability of detection of hypercholesterolaemia by a GP and detection of a FH, Patientenbericht: Hypercholesterinämie (2015) [93]
6	Prevalence of FH among people who were assessed/people that actually have FH	B	33.33%	Austrian FH registry: If FH is clinically suspected, the diagnosis can be confirmed in about one third of those examined, AAS/FHchol (2015) [57]
			28.00%	NICE: FH – identification and management – evidence review, NICE (2019), Futema (2015) [33, 130]
7	Sensitivity of clinical assessment for FH (DLCNC probable and definite)	B	86.80%	NICE: FH – identification and management – evidence review, NICE (2019) [33]
7′	Specificity of clinical assessment for FH (DLCNC probable and definite)	B	45.70%	NICE: FH – identification and management – evidence review, NICE (2019) [33]
8	Proportion of people with an FH diagnosis who are offered cascade testing for their relatives	B	100%	Assumption: Full uptake

Abbreviations: AAS – Austrian Atherosclerosis Society, B – Base case analysis/assumption, DLCN – Dutch Lipid Clinical Network Criteria, FHchol – Patient organization for familial hypercholesterolaemia Austria, NICE – National Institute for Health and Care Excellence

Abzug von bereits diagnostizierten FH-Fällen („alte" IP) → 10.596 potentielle neue IP ohne FH-Diagnose

To differentiate between potential new index cases and already diagnosed ones, FH patients that are already diagnosed and in treatment (so-called old/existing index patients) need to be subtracted from the total number of 11,774 persons. If we assume that 10% of the 11,774 identified persons are already diagnosed and treated for FH (see previous paragraphs), this amounts to 1,178 people (prevalence of 1:250 * VU population * 10%), leaving 10,596 people without a current potential diagnosis of FH who could be identified by database search and are invited for a preliminary examination.

2.798 potentielle neue IP (26,4 %) folgen der Einladung

Based on international evidence, we assume that 26.4% (2,798) follow the invitation for a preliminary GP examination and receive a referral to a specialist [129]. The preliminary examination consists of an assessment of phenotypical predictors of FH including family history potentially including a DLCN assessment, blood sampling at a medico-chemical laboratory and a preparation of a report for referral to a specialist.

For the old/existing index cases (1,178) it is assumed that the uptake rate for invitation for a referral consultation is 100%, because they are partially aware of the disorder and potential implications. For simplification we neglect that a proportion of these 1,178 people's relatives could already have been identified by a form of cascade screening and diagnosed with FH [33].

1.178 „alte" IP (100 %) kommen der Einladung nach

In total, 3,976 people are invited and referred – 2,798 receive a preliminary examination and referral, and 1,178 receive a briefing of further steps and a referral to a specialist (e.g. established lipid specialist or lipid clinic).

Insgesamt werden 3.976 eingeladen und zur/zum FÄ überwiesen

For estimating the final number of positive FH diagnoses (clinical diagnosis confirmed by DNA testing), diagnostic accuracy of clinical diagnosis (e.g. specificity of 45.7% and sensitivity of 86.6% of the DLCN criteria) needs to be taken into account [33]. Based on the NICE value of 28% and FHchol/AAS value of 33.33% of assessed patients actually having FH [57], we assume that a priori 33.33% of patients fulfilling clinical criteria actually have FH confirmed by GDx. This seems reasonable also because of the fact that in patients diagnosed with definite FH according to clinical diagnostic criteria, a pathogenic variant in 1 of the 3 main FH-causing genes can be identified in only ~60% to 80%, in "possible" FH only ~21% to 44% [2]. In our model this results in an absolute number of 933 people.

diagnostische Richtigkeit (Accuracy) des DLCN Scores muss berücksichtigt werden

a priori:
bei 933 Personen wird ein klinischer Verdacht durch GDx zu bestätigen sein

Taking these 933 people and the performance measures of the DLCN criteria into account, positive clinical diagnoses for FH amounts to ~1,823 people (~65.14% of 2,798) who will be referred to a DNA test and subsequently receive a DNA test (true positives plus false positives). Approximately 975 (34.86% of 2,798) people receive a negative clinical diagnoses for FH. These people will not receive a DNA test and will be treated in line with the existing lipid management guidance (true negatives plus false negatives).

1.823 Personen mit positiver klinischen Diagnose → bekommen einen DNA-Test

In the course of the GDx step, it is important to consider whether all patients referred to a DNA test factually take the test and agree by informed consent (full uptake). To simplify the analysis, a GDx uptake rate of 100% is assumed meaning that all identified and referred are offered a test and agree to the test. For the molecular genetic test the assumption of perfect sensitivity and specificity (perfect diagnostic accuracy) is made. Additionally, we do not consider the potential impact of variants of unknown clinical significance (VUS), because VUS occur only in around 5% of molecular genetic tests and compared to the clinical diagnosis, false positives are ruled out after molecular genetic testing [33].

GDx: 100 % Aufnahmerate, perfekte Sensitivität und Spezifizität, keine VUS

Of the 1,823 people referred to DNA test, ~44.43% or ~810 people have a positive predictive diagnosis. This number is approximately 86.82% of the assumed 933 patients fulfilling clinical criteria and actually having FH confirmed by GDx a priori. Therefore, the 810 persons are the people who – based on DLCN criteria – will be clinically diagnosed with FH and will factually have a mutation in at least one of the relevant genes (DNA positive). Approximately 1,012 people (~55.57%) will have a negative predictive diagnosis. These are people who – based on DLCNC – will be clinically diagnosed with FH but will not have a detectable mutation (DNA negative).

810 Personen haben eine positive prädiktive FH-Diagnose durch GDx

Cascade screening

The number of eligible people for cascade screening consists of index cases that were newly identified by the systematic identification strategy confirmed by all intermediate steps including DNA testing (~810 new index cases) and the number of people with an existing FH diagnosis that were referred to a lipid specialist after a briefing by the GP (1,178 old/existing index cases).

810 neue IP und 1.178 „alte" IP geeignet für ein Kaskadenscreening

durchschnittliche Anzahl an Verwandten pro IP in AT: 3 Personen

According to the AAS, the average number of relatives per index case (new index and old/existing index cases) offered testing is about 3 people (NICE model: 2.2). That means each person with a FH diagnosis will have on average 3 relatives, who will also be offered testing [57]. Like in the case of index patients, a DNA uptake rate of 100% is assumed for the relatives. Some of the relatives may have already been identified by some form of a cascade screening and in addition, instead of a direct application of GDx, a potential FH case could be ruled out based on an initial clinical assessment via DLCN at first making GDx obsolete. However, for simplification reasons and complying with mentioned guidelines and the NICE model, both cases are neglected as already stated above. Furthermore, 3 relatives per index case seems rather a conservative lower limit [33].

insgesamt 5.964 Verwandte, wobei nur auf die bekannte Mutation getestet wird → 50 % der Verwandten haben die Mutation

In sum 5,964 relatives are offered a test and actually tested (2,430 relatives of new index cases and 3,534 relatives of old/existing index cases). Only the known mutation of the family member with a confirmed diagnosis of FH is tested. If we assume that 50% of relatives have the mutation (genetic inheritance), the number of relatives who are identified with FH through DNA testing amounts to 2,982 people [33, 41, 59].

Table 5-7: Parameters for the calculations – relatives of index patients

#	Parameter	Analysis	Amount	Source
	Identification of index patients and FH screening management			
	Relatives of new index cases and old/existing index cases identified by cascade screening			
9	Average number of relatives per person diagnosed with FH/invited for testing	B	3	FHchol: The ratio between index patients and examined relatives is about 1 plus 3, i.e. for every index patient examined there are about 3 examined relatives, AAS/FHchol (2015) [57]
10	Uptake of DNA testing among relatives of people with a new and confirmed diagnosis of FH	B	100%	Assumption: Full uptake and consent by relatives
10′	Uptake of DNA testing among relatives of people with an existing FH diagnosis	B	100%	Assumption: Full uptake and consent by relatives
11	Relatives who have a FH diagnosis confirmed by DNA testing	B	50%	50% of family members of people with a confirmed diagnosis of FH will have the mutation, Hadfield (2009) [59]
12	Number of relatives who agree to cascade testing	B	100%	Assumption: Full uptake

Abbreviations: AAS – Austrian Atherosclerosis Society, B – Base case analysis/assumption, FHchol – Patient organization for familial hypercholesterolaemia Austria

Disorder management: Lipid-Lowering Therapy

insgesamt können 4.970 Personen für eine LLT identifiziert werden

As a result of the active case finding and cascade testing, in total 4,970 people (810 new index cases + 1,178 old/existing index cases + 1,215 relatives of new index cases and 1,767 relatives of old/existing index cases) could be identified for receiving LLT. Table 5-8 summarises the patient flow and parameters on the various sub-populations used for calculating the resource impact in the following section (5.2.2).

Table 5-8: Patient flow and relevant population in the respective screening and treatment steps

Treatment steps and respective population	#	Value	Number of people
Epidemiology			
Adult population in Austria (≥18 years)	1	7,358,443	7,358,443
Estimated number of current FH patients in Austria (diagnosed and treated for FH) in absolute numbers of the VU population	2 + 3 + 4	0.016%	1,178
Systematic/active case finding and cascade screening **Active case finding through primary care data**			
Availability of data (primary care records/VU data) to enable search for FH criteria/proportion of the population for which preventive care records are available	4	40.00%	2,943,378
Proportion of adult population and absolute number identified by active case finding through search of practice database and invited for a clinical assessment/clarification talk	3	0.40%	11,774
People with a current diagnosis of FH invited receiving a clarification talk and referral to a specialist (e.g. established lipid specialist or lipid clinic)	2 + 3 + 4	0.016%	1,178
People identified by database search without a current diagnosis of FH and invited for a preliminary examination of phenotypical predictors of FH incl. family history by the GP			10,596
Uptake of a preliminary clinical assessment using DLCN criteria in people identified by primary care database search, receiving an examination of phenotypical predictors of FH incl. family history by the GP to rule out clear cases of (homozygous) FH and referral to a specialist (e.g. established lipid specialist or lipid clinic)	5	26.40%	2,798
Estimated actual prevalence of FH among people who were assessed (from the literature)	6	33.33%	933
Sensitivity of clinical assessment for FH (DLCN score probable and definite)	7	86.80%	
Specificity of clinical assessment for FH (DLCN score probable and definite)	7′	45.70%	
Positive clinical diagnoses for FH (these people will be referred to a DNA test and actually receive a DNA test – true positives plus false positives = 933 * 86.8% + (2.798-933) * (100%-45.7%)		65.14%	1,822.54
Negative clinical diagnoses for FH (these people will not receive a DNA test and will be treated in line with the existing lipid management guidance – true negatives plus false negatives) = (2.798-933) * 45.7% + 933 * (100%-86.8%)		34.86%	975.46
Positive predictive diagnoses/Factual true positive diagnoses – these are people who based on DLCN criteria will be clinically diagnosed with FH and will actually have one of the mutations (DNA positive) = 933 * 86.8%		44.43%	809.84
Negative predictive diagnoses/Factual false positive diagnoses – these are people who based on DLCN criteria will be clinically diagnosed with FH but will not have the mutation (DNA negative) = 1,822.54 – 809.84		55.57%	1,012.70
Cascade screening			
Number of index cases identified (new index cases)			810
Number of people with an existing FH diagnosis (old/existing index cases)			1,178
Proportion of people with FH who are offered cascade testing for their relatives (new index cases) and absolute number	8	100.00%	810
Proportion of people with FH who are offered cascade testing for their relatives (old/existing index cases) and absolute number	8	100.00%	1,178
Average number of relatives per index case offered testing (new index cases)	9	3	2,430
Average number of relatives per index case offered testing (old/existing index cases)	9	3	3,534
Uptake of DNA testing among relatives of people with a new FH diagnosis	10	100%	2,430
Uptake of DNA testing among relatives of people with an old/existing FH diagnosis	10′	100%	3,534
Number of relatives who are identified with FH through DNA testing (new index cases)		50%	1,215
Number of relatives who are identified with FH through DNA testing (old/existing index cases)		50%	1,767
Number of relatives who are identified with FH through DNA testing (in total)	11	50%	2,982

Treatment steps and respective population	#	Value	Number of people
Lipid-lowering therapy (LLT)			
Number of people with an existing FH diagnosis (old/existing index cases) prescribed LLT			1,178
People diagnosed with familial hypercholesterolemia as a result of active case finding (number of new index cases identified) and prescribed LLT			810
People prescribed LLT for FH as a result of cascade testing (number of relatives who are identified with FH through DNA testing)			2,982
Total people prescribed lipid-lowering therapy as a result of the active case finding and cascade testing (new index cases + old/existing index cases + relatives of new and old/existing index cases)			**4,970**

Abbreviations: DLCN – Dutch Lipid Clinical Network, GP – General practitioner, LLT – Lipid-lowering therapy, VU – Primary care check-up/Vorsorgeuntersuchung

5.5.2 Unit costs and volumes

Einzelkosten sowie Leistungsmengen wurden den Behandlungsschritten und den Subpopulationen zugewiesen

Based on the entire process from systematic case finding until LLT (described in section 4.5.2) we assigned unit costs as well as information on the required volumes for each step. In summary, the cost of active case finding of new and old/existing index patients, cost of genetic testing of new index cases, costs of their relatives and relatives of old/existing index cases, administrative and staffing costs involved during the whole FH management phase are taken into account.

The results are summarised in Table 5-9 to Table 5-12, which provide detailed information on main care tasks and subtasks, costs per unit in €, units needed, unit costs per person in €, as well as source and item number in the respective tariff catalogue.

Kosten für die aktive Suche in VU-Akten können nur grob geschätzt werden

Costs for active case finding can only be roughly approximated, because every assistant at a contracted GP has to review the VU records (VU records are not equally distributed across contracted GPs and consequently different working loads are faced by GP assistants and GPs). We assumed one minute per brief review of a VU patient record and 10 minutes per invitation latter at an average wage of € 0.69 per minute.

Kosten der klinischen Erstuntersuchung, Überweisung, Blutabnahme und Auswertung

In summary, the expected costs for a clinical examination of phenotypical predictors of FH incl. family history by GP and/or referral to specialist amount to € 52.51 for new index cases and € 32.51 for old/existing index cases. The unit costs for blood sampling including TC, LDL-C indirect and direct, TRZ and Lp(a)[7] and the flat-rate payment have been estimated at € 34.55. For the clinical assessment via DLCNC, unit cost of € 75.27 were estimated.

Einzelkosten der GDx inkl. Blutabnahme, genetischer Beratung und weiteren Leistungen

Concerning costs for molecular genetic testing, costs for index patients are higher (€ 1,740) than for their relatives (€ 1,560) because for the latter, only a sequencing of the known gene has to be carried out. These costs include a number of tasks which are required in the course of molecular genetic testing (consultation to plan genetic testing, arrangement of the DNA test, taking a blood sample and sending it to DNA service, and notification of index patients). According to the available information, costs for genetic counselling are estimated at € 120. The molecular genetic test (MGT/DNA test) and genetic counselling (GC) are summarised under the term GDx in the calculations.

[7] According to the EAS/ESC guideline (2020) it is recommended that measurement of Lp(a) should be considered at least once in each person's lifetime especially for people at risk for developing ASCVD. At which level (GP or specialist) this value is collected does not matter for the calculations.

Table 5-9: Tariffs and prices of systematic case finding and cascade screening in Austria 1

Main Task and subtasks	Cost per Unit	Units needed	Unit cost	Source	Item number
Systematic/active case finding and cascade screening					
Active case finding					
Active case finding through primary care database search and information gathering by the general practicioner (GP) practice assistant (administrative task)					
Search for index cases in the prevention medical checkup/patient records by GP assistant: Assessing the records for total cholesterol levels (non-face-to-face-task)	41.47 / 60 min	1 min	0.69	Collective Agreements for medical practice assisstant according to MAB-G (Average hourly wage across Austrian federal states) (2018-2020)	-
Invitation of the patients identified by GP practice assistant (non-face-to-face-task: standardised invitational letter)	41.47 / 60 min	10 min	6.91	Collective Agreements for medical practice assisstant according to MAB-G (Average hourly wage across Austrian federal states) (2018-2020)	-
Clinical examination of phenotypical predictors of FH incl. family history by GP and/or referal to specialist (e.g. established lipid specialist or lipid clinic)					
Flat-rate payment GP per quarter	18.74 / 1 x	1 x	18.74	Tariff for contracted GPs (individual contract) (2019)	1.
Examination of phenotypical predictors of FH incl. family history by the GP to rule out clear cases of (homozygous) FH, possible cases (DLCNC ≤ 6) and referral to a specialist (e.g. established lipid specialist or lipid clinic)	20 / 1 x	1 x	20	Fee regulation general contract Salzburg (Honorartarif zum Gesamtvertrag Salzburg): Supplement for a detailed first medical history (2020)	048
Preparation of a report for referral to a specialist (e.g. established lipid specialist or lipid clinic)	13.77 / 1 x	1 x	13.77	Fee regulation for GPs and specialist physicians (SP) of the insurance institution for public servants, railroads and mining (BVAEB): Medical coordination activities by the treating physican (2019)	J1
Expected unit costs			**52.51**		
Blood sampling at a medico-chemical laboratory for determination of the serum lipids (lipid profile)					
Flat-rate payment specialist (SP) per quarter	18.74 / 1 x	1 x	18.74	Tariff for contracted SP (individual contract) (2019)	1.
Blood collection from the vein for a blood count	3.07 / 1 x	1 x	3.07	Tariff for contract specialists for medical and chemical laboratory diagnostics (individual contract)	01.01
Total-Cholesterol	0.92 / 1 x	1 x	0.92		05.13
HDL-Cholesterol (+LDL-C via Friedewald formula is included)	1.37 / 1 x	1 x	1.37		05.14
LDL-Cholesterol (direct)	1.83 / 1 x	1 x	1.83		05.50
Triglyceride	0.95 / 1 x	1 x	0.95		05.12
Lipoprotein a (Lpa)	7.67 / 1 x	1 x	7.67		06.20
Expected unit costs			**34.55**		

Table 5-10: Tariffs and prices of systematic case finding and cascade screening in Austria 2

Main tasks and subtasks	Cost per unit	Units needed	Unit cost	Source	Item number
Assessment of potential or definite FH via Dutch Lipid Clinical Network Score (DLCNS) and discussion of findings					
Flat-rate payment SP per quarter	18.74 / 1 x	1 x	18.74	Tariff for contracted SP (individual contract) (2019)	1.
Conduct, evaluation of DLCNS and discussion of findings/consultation/ examination/clarification of further steps by GP or specialist (e.g. established lipid specialist or lipid clinic)	56.53 / 1 x	1 x	56.53	DMP "Therapie aktiv" (Ta) – Initial care within the scope of Ta (is paid once when a person is admitted to Ta, the date of performance is the date noted on the documentation form) (2020)	96
Expected unit costs			**75.27**		
Molecular genetic testing and diagnosis (new index cases): tasks from admission to diagnosis except genetic counsellling					
Base tariff of genetic test	1,500 / 1 x	1 x	1,500	Information provided by Prim. Univ. Prof. Dr. med. Gökhan Uyanik from the centre of medical genetics, Hanusch hospital, Vienna (2020)	-
Sequencing: amount per gene (ApoB, LDLR, PCSK9, LDLRAP1)	60 / 1 x	4 x	240		-
Expected unit costs			**1,740**		
Cost of genetic counselling (pre and/or post testing)					
Genetic counselling after genetic testing, discussion of cascade testing (family tree etc.) and offer cascade testing regardless of acceptance/uptake (contact all indentified relatives): new index cases and all relatives	120 / 1 x ~8h	1 x	120	Information provided by Prim. Univ. Prof. Dr. med. Gökhan Uyanik from the centre of medical genetics, Hanusch hospital, Vienna (2020)	-
General counselling, discussion of cascade testing (family tree etc.) and offer cascade testing regardless of acceptance/uptake (contact all indentified relatives): old/existing index cases	120 / 1 x	0.5 x	60		
Cascade screening of relatives					
Molecular genetic testing and diagnosis (relatives of new and old/existing index cases): tasks from admission to diagnosis except genetic counsellling					
Base tariff of genetic test	1,500 / 1 x	1 x	1,500	Information provided by Prim. Univ. Prof. Dr. med. Gökhan Uyanik from the centre of medical genetics, Hanusch hospital, Vienna (2020)	-
Sequencing: only known/relevant gene	60 / 1 x	1 x	60		-
Expected unit costs			**1,560**		

Table 5-11: Tariffs and prices for lipid-lowering therapy

Main task and subtasks	Cost per unit	Units needed	Unit cost	Source	Item number
Lipid-lowering therapy (LLT)					
LLT steps excluding medication costs					
Care and monitoring steps in the first year					
Initiation of LLT including explanation of conduct, provision of information on lipid lowering diet and life style modifications (e.g. smoking) by GP or specialist (e.g. established lipid specialist or lipid clinic)	56.53 / 1 x	1 x	56.53	DMP "Therapie aktiv" (Ta) – Initial care within the scope of Ta (is paid once when a person is admitted to Ta, the date of performance is the date noted on the documentation form) (2020)	96
Response to LLT within the FH management/treatment programme after 6-8 weeks	29.86 / 1 x	1	29.86	DMP "Therapie aktiv" (Ta) – Further treatment in the course of Ta (2020)	97
Subsequent follow-up monitoring after 6-12 months and feedback consultation	43.73 / 1 x	1 x	43.73	DMP "Therapie aktiv" (Ta) – Feedback conversation in the course of Ta (2020)	97a
Expected unit costs			**130.12**		
Blood sampling at a medico-chemical laboratory for blood sampling, determination of the serum lipids and relevant parameters for monitoring					
Blood collection from the vein for a blood count	3.07 / 1 x	1 x	3.07	Tariff for contract specialists for medical and chemical laboratory diagnostics (individual contract)	01.01
Total-Cholesterol	0.92 / 1 x	1 x	0.92		05.13
HDL-Cholesterol (+LDL-C via Friedewald formula)	1.37 / 1 x	1 x	1.37		05.14
LDL-Cholesterol (direct)	1.83 / 1 x	1 x	1.83		05.50
Triglyceride	0.95 / 1 x	1 x	0.95		05.12
ALAT (GPT/ALT)	0.92 / 1 x	1 x	0.92		
Creatin kinase (CK) (at baseline/before statin therapy)	1.52 / 1 x	1 x	1.52		05.21
HbA1/HbA1c (before and during statin therapy, because high statin doses are potentially related to an increased frequency of DM)	3.67 / 1 x	2 x	7.34		05.03
Expected unit costs			**17,92**		
Medications					
Atorvastatin 80mg	8.40 / 1 x	1 x	8.40	Reimbursement code of the social security (Erstattungskodex – EKO) (2020)	
Rosuvastatin 40mg	6.64 / 1 x	1 x	6.64		
Ezetimibe 10mg	10.21 / 1 x	1 x	10.21		

Table 5-12: Medication prices – Expected unit costs (weighted average)

LLT medication					
Dose	**Cost per pack**	**Doses per pack**	**Cost per dose**	**Annual cost**	**% prescribed**
Atorvastatin 80mg	8.40	30	0.28	102.24	70.00%
Rosuvastatin 40mg	6.64	30	0.22	80.81	15.00%
Ezetimibe 10mg	10.21	30	0.34	124.27	40.00%
Expected unit costs (weighted average)					**133.40**

Abbreviations: DLCNC – Dutch Lipid Clinical Network Criteria, DMP – Disease management programme, GP – General practitioner, LLT – Lipid-lowering therapy, MAB-G – Medizinische Assistenzberufe-Gesetz, mg – Milligram, min – minute, SP – specialist, Tu – Therapie aktiv, VU – Primary care check-up/Vorsorgeuntersuchung

Einzelkosten der LLT und assoziierte Folgekosten

Regarding LLT, unit cost for care and monitoring steps in the course of LLT account for € 130.12 for the 1-year horizon. The unit costs for blood sampling for LLT amount to € 17.92. Here, a flat-rate payment is not considered, because flat-rate payments were already considered at the GP, specialist, and laboratory before and can only be billed once every quarter from a contracted party. Expected unit cost (weighted average) for LLT-medication for one year amounts to € 133.40.

5.5.3 Resource impact

Kosten werden nach Subpopulationen aufgeschlüsselt, Kosten für die Medikation und die aktive systematische Suche werden getrennt dargestellt

In the following the resource impact of index patient identification, cascade screening and LLT for one year is depicted. To estimate the resource impact, the various costs incurred by conducted treatments and subtasks excluding medication costs are assigned to the specific subpopulations defined in section 5.5.1 (new index cases, relatives of new index cases, old/existing index cases, relatives of old/existing index cases). Expected unit costs for single steps in the process from Table 5-9 to Table 5-12 are multiplied with the number of people that undergo each respective treatment. Costs of the systematic search strategy and medication costs for the identified FH patients are shown separately. Table 5-13 presents an overview of the results.

Active case finding

Kosten für die aktive systematische Suche: ~€ 2,11 Mio.

For active case finding in the VU records, in sum approximately € 2.11 million are estimated. Of this amount, approximately € 2.03 million (~94%) are estimated for the search in the VU records and assessment of TC levels by the GP assistant. For the invitation letters for patients identified by GP practice assistants ~€ 81,400 are calculated (10 minutes per patient times the average wage).

New index cases

„neue" IP: ~€ 454.200 für klinische Leistungen ohne GDx, LLT und Medikation

Clinical tasks prior to GDx (excluding molecular genetic testing and associated tasks, genetic counselling, LLT steps, and medication for new index cases) amount to ~€ 454,200. Of this amount ~€ 146,900 (~33%) are estimated for preliminary examination of phenotypical predictors of FH including family history by the GP and referral to a specialist (e.g. established lipid specialist or lipid clinic), ~€ 96,700 (~21%) arise for blood collection to determine a lipid profile (TC, HDL-C + LDL-C via Friedewald formu-

la[8], direct LDL-C, triglyceride, Lipoprotein a [Lpa] – tariffs for blood collection and clinical parameters in Table 5-9), and € 210,600 (~46%) are estimated for an assessment of probable or definite FH via DLCNC and a discussion of findings.

For molecular genetic testing of new index patients and genetic counselling in total € 3.39 million are estimated. A large amount of these costs – € 3.17 million (~93,5%) – are costs of genetic testing itself consisting of all associated tasks from admission to the diagnosis, excluding genetic counselling. Genetic counselling is estimated to incur costs of about € 218,800 (~6.5% of total GDx amount).

~€ 3,39 Mio. für GDx (davon ca. 6,5 % für genetische Beratung)

The costs for LLT monitoring steps excluding medication costs are estimated to be approximately ~€ 119.900 and are split into costs for general care, monitoring in the first year (~€ 105,400 [~88%]), and costs for blood sampling, determination of the serum lipids and relevant parameters for monitoring (~€ 14,500 [~12%]).

~€ 119.900 für LLT-Monitoring-Kosten

In total cost of € 3.96 million are estimated accruing for new index patients.

gesamt ~€ 3,96 Mio.

Relatives of new index cases

For relatives of new index cases € 4.08 million are estimated for molecular genetic testing and genetic counselling (€ 3.79 million [~93%] for the test and € 291,600 [~7%] for genetic counselling).

Verwandte von „neuen" IP: ~€ 4,08 Mio. für GDx

LLT excluding medication costs amounts to approximately € 179,900. For care and monitoring costs in the first year ~€ 158,100 (87.5%) and for blood sampling and relevant parameters ~€ 21,800 (~12.5%) have been estimated.

LLT ohne Medikationskosten: ~€ 179.900

In total, costs of ~€ 4.26 million are estimated accruing for relatives of new index patients.

gesamt ~€ 4,26 Mio.

Old/existing index cases

Old/existing index cases induce referral cost and genetic counselling cost for one session in order to discuss relevant aspects with regard to contacting relatives. For referral to a specialist, ~€ 38,300 have been estimated and for genetic counselling ~€ 70,680 are costed. For LLT excluding medications, € 174,400 are estimated (care and monitoring: € 153,300 [~88%], blood sampling and determination of relevant parameters: ~€ 21,100 [~12%]).

„Alte" IP: ~€ 38.300 für Überweisung, ~€ 70.680 für genetische Beratung und ~€ 174.400 für LLT

In sum costs of ~€ 283,400 arise for old/existing cases.

gesamt ~€ 283.400

Relatives of old/existing index cases

Relatives of old/existing index cases also undergo a molecular genetic test including genetic counselling. The estimated costs amount to € 5.94 million of which ~€ 5.51 million (~93%) are for the test itself and ~€ 424,100 (~7%) for counselling. Further cost with respect to LLT are ~€ 230,000 for care and monitoring in the first year and for blood sampling including the relevant parameters ~€ 31,700 are estimated.

Verwandte von „alten" IP: ~€ 5,94 Mio. für GDx, ~€ 261.600 für LLT ohne Medikationskosten

In total ~€ 6.20 million are estimated for this subpopulation.

gesamt ~€ 6,20 Mio.

[8] LDL-C via Friedewald formula is included in the HDL-C tariff position.

Medication costs for all identified FH patients

Medikationskosten gesamt: ~€ 663.000

In sum ~€ 663,000 of medication costs arising for one year are estimated. These are the costs for 4,970 identified FH patients and can be viewed as recurrent costs that arise each year.

Total costs

Gesamtkosten für alle Behandlungsschritte und Leistungen: ~€ 17,5 Mio.

In total ~€ 17.5 million are estimated for all treatments and subtasks for the specific subpopulation (new index cases, relatives of new index cases, old/existing index cases, relatives of old/existing index cases), for costs derived from the active systematic search in VU records up to medication costs for the identified FH patients.

Table 5-13: Total costs per subpopulation, costs of care tasks and total costs

Subpopulation and care tasks	Unit costs	Number of people	Total costs per care task	Total costs per costing block	Total costs per sub-population/other tasks
Active case finding through VU/primary care database search and Information gathering (for all patients identified by search):				**2,115,562.73**	**2,115,562.73**
Search for index cases in VU records/assessing the records for TC levels (non-face-to-face-task by GP assistant)	0.69	2,943,378	2,034,191.69		
Invitation of the patients identified by GP practice assistant (non-face-to-face-task, invitational letter)	6.91	11,774	81,371.04		
New index cases					**3,964,899.85**
Clinical tasks (prior GDx/excl. MGT/GC)				454,207.45	
Preliminary examination of phenotypical predictors of FH incl. family history by the GP and referral to a specialist (e.g. established lipid specialist or lipid clinic)	52.51	2,798	146,931.09		
Blood sampling at a medico-chemical laboratory and determination of the serum lipids (lipid profile)	34.55	2,798	96,670.90		
Assessment of probable or definite FH via DLCNC and discussion of findings	75.27	2,798	210,605.46		
GDx – Molecular genetic testing (MGT) and genetic counselling (GC)				3,390,780.00	
Molecular genetic testing and diagnosis: tasks from admission to diagnosis except genetic counsellling	1,740	1,823	3,172,020.00		
Cost of genetic counselling (pre and post testing)	120	1,823	218,760.00		
LLT steps excluding medication costs				119,912,40	
Care and monitoring in the first year	130.12	810	105,397.20		
Blood sampling, determination of the serum lipids and relevant parameters for monitoring	17,92	810	14 515,20		
Relatives of new index cases					**4,262,268.60**
GDx – Molecular genetic testing (MGT) and genetic counselling (GC)				4,082,400.00	
Molecular genetic testing and diagnosis: tasks from admission to diagnosis except genetic counsellling	1,560	2,430	3,790,800.00		
Cost of genetic counselling (pre and post testing)	120	2,430	291,600.00		
LLT steps excluding medication costs				179,868.60	
Care and monitoring in the first year	130.12	1,215	158,095.80		
Blood sampling, determination of the serum lipids and relevant parameters for monitoring	17,92	1,215	21,772.80		
Old/Existing index cases					**283,371.32**
Clinical tasks (prior GDx/excl. MGT/GC)				38,300.20	
Referral to specialist (e.g. established specialist or lipid clinic)	32.51	1,178	38,300.20		
GDx – Molecular genetic testing (MGT) and genetic counselling (GC)				70,680.00	
General counselling, discussion of cascade testing (family tree etc.) and offer cascade testing regardless of acceptance/uptake (contact all indentified relatives)	60	1,178	70,680.00		

Subpopulation and care tasks	Unit costs	Number of people	Total costs per care task	Total costs per costing block	Total costs per sub-population/other tasks
LLT steps excluding medication costs				174,391.12	
Care and monitoring in the first year	130.12	1,768	153,281.36		
Blood sampling, determination of the serum lipids and relevant parameters for monitoring	17,92	1,768	21,109.76		
Relatives of old/existing index cases					**6,198,706.68**
GDx – Molecular genetic testing (MGT) and genetic counselling (GC)				5,937,120.00	
Molecular genetic testing and diagnosis: tasks from admission to diagnosis except genetic counsellling	1,560	3,534	5,513,040.00		
Cost of genetic counselling (pre and post testing)	120	3,534	424,080.00		
LLT steps excluding medication costs				261,586.68	
Care and monitoring in the first year	130.12	1,767	229,922.04		
Blood sampling, determination of the serum lipids and relevant parameters for monitoring	17,92	1,767	31,664.64		
Medication costs for all identified FH patients				**662,982.91**	**662,982.91**
Medication costs for all identified FH patients for the first year (new index cases + old/existing index cases + relatives of new and old/existing index cases)	133.40	4,970	662,982.91		
In total			**17,487,792.09**	**17,487,792.09**	**17,487,792.09**

Abbreviations: DLCNC – Dutch Lipid Clinical Network Criteria, GP – General practitioner, LLT – Lipid-lowering therapy, VU – Primary care check-up/Vorsorgeuntersuchung

5.5.4 Distribution of estimated costs

Kostenverteilung auf Subpopulation, Suche und Medikation (1) bzw. Behandlungsschritte (2)

In the previous section it has been shown that different costs arise for different tasks, treatment steps and subpopulations. To get a better picture of costs for the various treatment/costing blocks and subpopulations, graphical distributions of the costs are presented. At first (1), costs are broken down into subpopulations, costs for searching in VU records (active case finding) and LLT costs for medication for 1 year. In addition, costs of the active case finding and medication are allocated to the subpopulations depending on the subpopulation size. As a second step (2), costs are depicted regarding the respective treatment tasks. The respective numbers can be found in Table 5-14 for (1) and in Table 5-15 for (2).

Table 5-14: Total costs and costs with respect to subpopulation and other costs (active case finding, medication)

Care task/subpopulation	Cost amount	%	Other costs (allocated)	%	Cost amount plus other costs	%	FH cases	%
Active case finding	2,115,562.73	12,10%	-					
New index cases	3,964,899.85	22,67%	452,841.44	16.30%	4,417,741.30	25.26%	810	16.30%
Relatives of new index cases	4,262,268.60	24,37%	679,262.16	24.45%	4,941,530.76	28.26%	1,215	24.45%
Old/existing index cases	283,371.32	1,62%	658,576.81	23.70%	941,948.13	5.39%	1,178	23.70%
Relatives of old/existing index cases	6,198,706.68	35,45%	987,865.22	35.55%	7,186,571.90	41.09%	1,767	35.55%
Medication costs for all identified FH patients	662,982.91	3,79%	-					
Total	**17,487,792.09**		**2,778,545.64**		**17,487,792.09**		**4,970**	**100%**

höchster Kostenanteil fällt auf Verwandte von „alten" IP, Kosten „neue" IP ≈ Kosten Verwandte „neue" IP

Figure 5-2 shows the distribution of costs with respect to the subpopulations, active case finding and medication. The highest cost share with 35.45% (~€ 6.2 million) falls on relatives of old/existing index cases. New index cases and their relatives share almost the same proportion with 22.67% (€ 3.96 million) and 24.37% (€ 4.26 million) of total cost respectively. The lowest costs are incurred by old/existing index cases with ~€ 282,300 (1.61%). Active case finding and medication for one year account for 12.1% (~€ 2.1) and 3.79% (~€ 660,000) of total costs respectively.

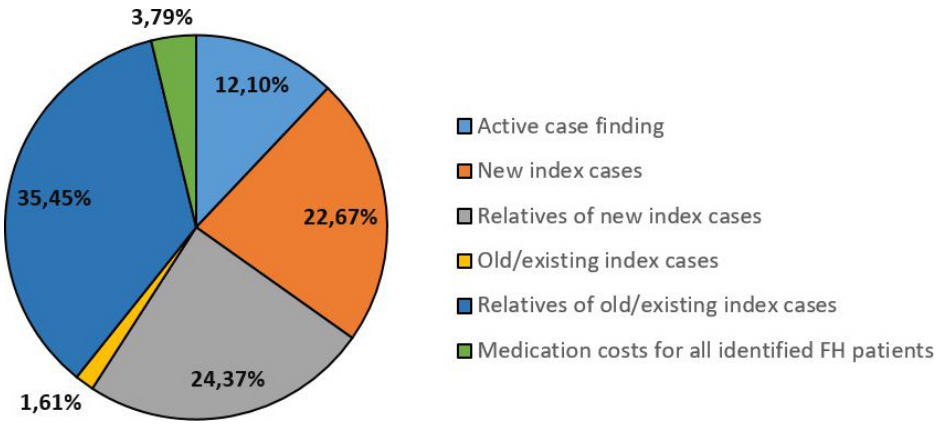


Figure 5-2: Proportion of costs with respect to subpopulation, active case finding and medication

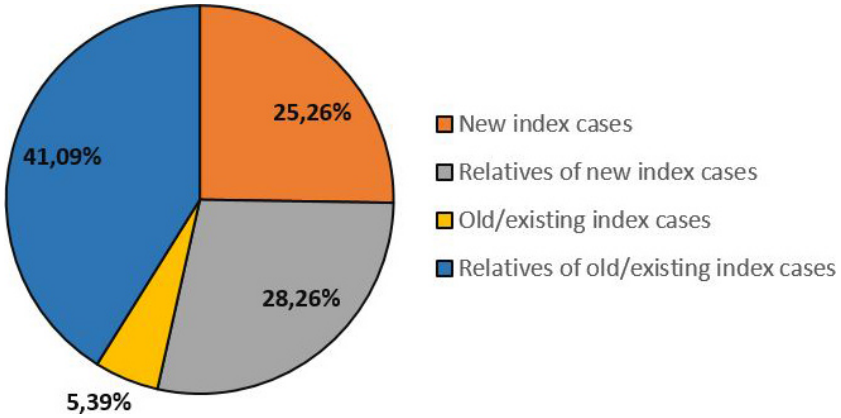


Figure 5-3: Proportion of costs with respect to subpopulation (costs for active case finding and medication allocated to subpopulation)

Allokation der Medikations- und Suchkosten auf die Subpopulationen

Figure 5-3 shows the distribution of costs after costs for active case finding and medication costs have been allocated to the subpopulations according to population size. Like before, relatives of old/existing index cases cause the largest share of total costs, accounting for 2/5 of the total costs with ~€ 7.2 million (41.09%). New index cases and their relatives share again almost the same proportion 25.26% (~€ 4.4) and 28.26% (~€ 4.9 million) respectively. The proportion accrued by old/existing index cases amounts to 5.39% of total cost (~€ 1 million).

Aufschlüsselung in 5 Leistungskategorien

To identify which steps in the process account for which proportion of costs, costs are broken down into 5 categories (treatment tasks): searching in VU records/active case finding, clinical treatment steps without molecular genetic testing (prior to GDx), molecular genetic testing including genetic counselling, LLT steps and medication costs (Figure 5-4).

Table 5-15: Costs and cost composition with respect to treatment task

Treatment task	New index cases	Relatives of new index cases	Old/existing index cases	Relatives of old/ existing index cases	Total	%
FH cases indentified in subpopulation	810	1,215	1,178	1,767	4,970	
% of all identified FH cases	16.30%	24.45%	23.70%	35.55%	100%	
Active case finding	344,789.90	517,184.85	501,435.19	752,152.78	2,115,562.73	12.10%
Clinical tasks prior to GDx	454,207.45	–	38,300.20	–	492,507.65	2.82%
MGT and GC (GDx)	3,390,780.00	4,082,400.00	70,680.00	5,937,120.00	13,480,980.00	77,09%
MGT excl. GC	3,172,020.00	3,790,800.00		5,513,040.00	12,475,860.00	71.34%
GC	218,760.00	291,600.00	70,680.00	424,080.00	1,005,120.00	5.75%
LLT steps excluding medication costs	119,912.40	179,868.60	174,391.12	261,586.68	735,758.80	4.21%
Medication costs for all identified FH patients	108,051.54	162,077.31	157,141.62	235,712.44	662,982.91	3.79%
Total	**4,417,741.30**	**4,941,530.76**	**941,948.13**	**7,186,571.90**	**17,487,792.09**	**100%**

Abbreviations: GC – Genetic counselling, GDx – genetic diagnostic/testing (molecular genetic test and counselling), LLT – Lipid-lowering therapy MGT – molecular genetic test

Figure 5-4 shows the proportions of the costs disaggregated by treatment tasks. Molecular genetic testing including genetic counselling accounts by far for the largest share of the total costs with more than ¾ of total costs (€ 13.5 million). Of these total costs for GDx, 7.5% (~€ 1 million) accrues for genetic counselling, while the genetic test including associated tasks account for more than 90% of the total GDx costs. Costs of genetic counselling account for 5.75% of overall total costs. Among the other treatment services is due to the active search in patient records with 12.10% of total costs. LLT steps including medication costs account for 8% (4.21%+3.79%) of total costs. The smallest share with 2.82% of total costs accrues for other clinical tasks excluding molecular genetic testing and counselling.

größter Kostenanteil (~77 %) mit ~€ 13,5 Mio. fällt auf GDx, Kosten der genetischen Beratung ~5,75 % der Gesamtkosten, Anteil für aktives systematisches Suchen nach IP beträgt ~12 %

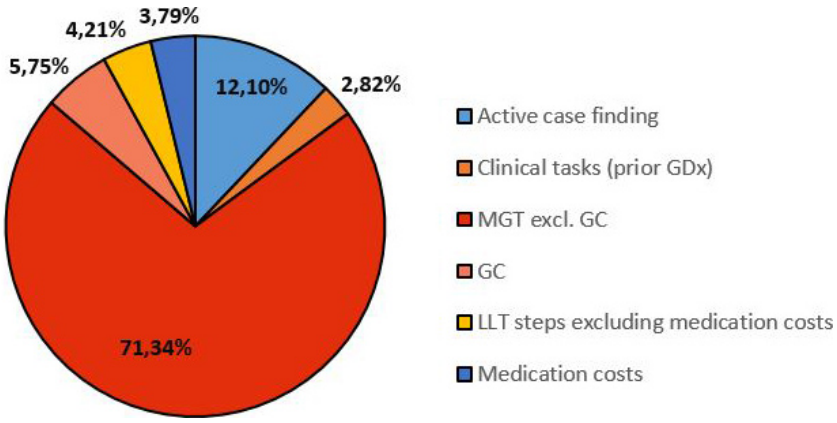


Figure 5-4: Proportion of costs of total costs with respect to treatment task

5.5.5 Sensitivity analysis

As it has been mentioned in several passages throughout the report, the general prevalence of FH is related to a high degree of uncertainty. In particular, no exact Austria-specific prevalence data could be identified in the literature and only general numbers from the international context varying from 1:500 (lower bound) to 1:200 (higher bound) are available. Sensitivity analyses with respect to different prevalence numbers is necessary to account for uncertainties, to consider the dependence of resources needed on epidemiological realities and also to correctly display subpopulations in the calculations.

allgemeine Prävalenz von FH ist mit einem hohen Maß an Unsicherheit verbunden; für AT keine spezifische Prävalenz

Table 5-16 demonstrates the impact of different prevalence assumptions on the number of people identified. If we assume lower and higher prevalence numbers than in our base case (1:500, 1:200), the number of identified people declines to 2,488 or rises to 6,213 respectively (the minor differences in the relative numbers are due to rounding).

Variation der Prävalenz: 1:500 bis 1:200

Table 5-16: Sensitivity analysis – Number of people identified depending on the prevalence (subpopulations)

Parameter text	No. of people	%	No. of people	%	No. of people	%
Sensitivity Analysis: Prevalence	1:500		1:250		1:200	
Old/existing index cases	589	23.67%	1,178	23.70%	1,472	23.69%
Number of new index cases identified	406	16.32%	810	16.30%	1,013	16.30%
Relatives identified of old/existing index cases	884	35.53%	1767	35.55%	2,208	35.54%
Relatives identified of new index cases	609	24.48%	1215	24.45%	1,520	24.46%
Total people prescribed lipid-lowering therapy as a result of active case finding and cascade testing	**2,488**		**4,970**		**6,213**	

Kostenintervall: ~€ 9,8 (1:500) bis ~€ 21,3 Mio. (1:200)

The variation of prevalence in the FH care model has an impact on the composition of total costs, but also on absolute costs. The total cost interval starts at ~€ 9.8 million for a prevalence of 1:500 and goes to ~€ 21.3 million for a prevalence of 1:200 (Table 5-17).

Table 5-17: Sensitivity analysis – Total costs with respect to treatment task

Prevalence	Treatment task	New index cases	Relatives of new index cases	Old/existing index cases	Relatives of old/existing index cases	Total	%
Sensitivity analysis: Costs with respect to treatment task							
1:500	Active case finding	338,585	507,878	491,199	737,215	2,074,877	21.24%
	Clinical tasks (prior GDx/excl. MGT/GC)	227,104	–	19,150	–	246,254	2.52%
	MGT and GC	1,696,320	2,046,240	35,340	2,968,560	6,746,460	69.07%
	MGT excl. GC	1,586,880	1,900,080	–	2,756,520.00	6,243,480	63.92%
	GC	109,440	146,160	35,340	212,040.00	502,980	5.15%
	LLT steps excluding medication costs	60,104	90,156	87,196	130,867	368,324	3.75%
	Medication costs	54,159	81,239	78,571	117,923	331,892	3.40%
	Total	**2,376,272**	**2,725,513**	**711,455**	**3,954,565**	**9,767,806**	
1:250	Active case finding	344,790	517,185	501,435	752,153	2,115,563	12.10%
	Clinical tasks (prior GDx/excl. MGT/GC)	454,207	–	38,300	–	492,508	2.82%
	MGT and GC	3,390,780	4,082,400	70,680	5,937,120	13,480,980	77.09%
	MGT excl. GC	3,172,020	3,790,800	–	5,513,040	12,475,860	71.34%
	GC	218,760	291,600	70,680	424,080	1,005,120	5.75%
	LLT steps excluding medication costs	119,912	179,869	174,391	261,587	735,759	4.21%
	Medication costs	108,052	162,077	157,142	235,712	662,983	3.79%
	Total	**4,417,741**	**4,941,531**	**941,948**	**7,186,572**	**17,487,792**	
1:200	Active case finding	348,249	522,545	506,043	759,065	2,135,902	10.00%
	Clinical tasks (prior GDx/excl. MGT/GC)	567,678	–	47,859	–	615,537	2.88%
	MGT and GC	4,237,080	5,105,520	88,320	7,418,880	16,849,800	78.92%
	MGT excl. GC	3,963,720	4,740,840	–	6,888,960	15,593,520	73.04%
	GC	273,360	364,680	88,320	529,920	1,256,280	5.88%
	LLT steps excluding medication costs	149,965	225,021	217,915	326,872	919,773	4.31%
	Medication costs	135,131	202,763	196,360	294,540	828,795	3.88%
	Total	**5,438,102**	**6,055,849**	**1,056,498**	**8,799,358**	**21,349,807**	

Abbreviations: GC = genetic counselling, MGT = molecular genetic testing, LLT = lipid-lowering therapy

Kostenanteil von aktiv systematischer Suche: 21,24 % (1:500) bis ~10 % (1:200), Kostenanteil von GDx nimmt mit Prävalenz zu

The absolute costs for active case finding range from ~€ 2 million (1:500) to € 2.1 million (1:200) respectively. The cost share of active case finding is highest for a prevalence of 1:500 (21.24%), decreasing to 10% of total costs for a prevalence of 1:200. Similar to the base case analysis, the costs for molecular genetic testing and genetic counselling still account for the largest proportion of the total costs in the sensitivity analyses. The higher the prevalence, the higher the proportion of GDx costs within total costs, which ranges from 69.07% (1:500) to 78.92% (1:200). Within the costs for GDx, 5.15% to 5.89% (~€ 503,000 to € 1.3 million) respectively accrue for genetic counselling. The cost proportions of the other tasks remain almost the same in the different prevalence scenarios (Figure 5-5). However, a higher prevalence results in higher absolute costs for the different tasks due to an increasing number of patients identified by active case finding (Table 5-16 and Table 5-17).

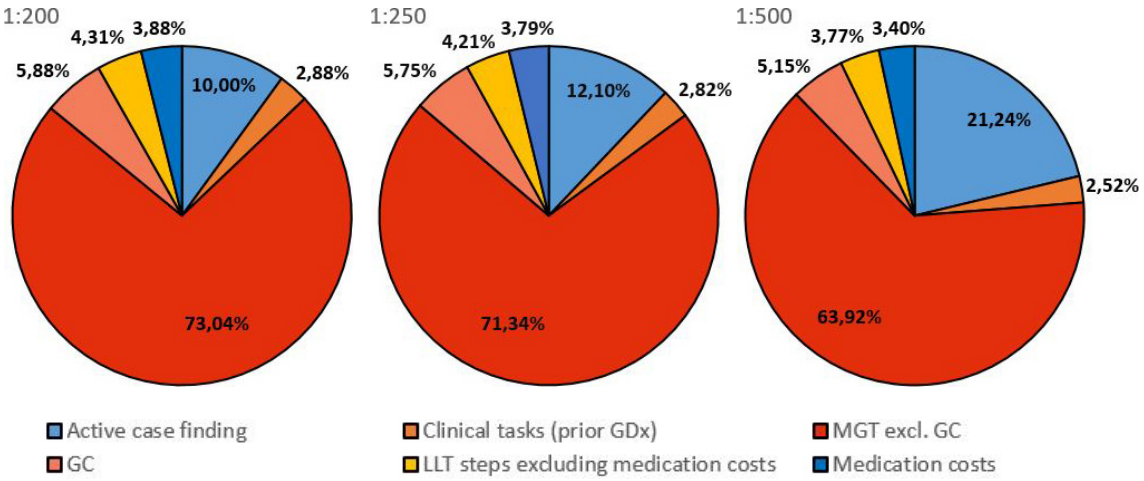


Figure 5-5: Sensitivity analysis – Proportion of costs with respect to treatment tasks for different prevalence numbers

relative Verschiebung des Kostenanteils zwischen GDx und aktiver Suche

As demonstrated in Table 5-18, with decreasing prevalence there is a relative shift from costs of GDx (molecular genetic testing and counselling) to active case finding. On the contrary, cost distribution with regard to the subpopulations, active case finding and LLT medication did not change significantly in relative terms. Only the absolute values increased as discussed above.

Table 5-18: Sensitivity analysis – Costs with respect to subpopulation, medication and active case finding

Prevalence	Parameter text	Cost amount	%	Costs of other tasks (allocated)	%	Cost amount total	%
Sensitivity analysis: Costs with respect to subpopulation, active case finding and medication							
1:500	Active case finding	2,074,877	21.24%				
	New index cases	1,983,528	20.31%	392,744	16.32%	2,376,272	24.33%
	Relatives of new index cases	2,136,396	21.87%	589,117	24.48%	2,725,513	27.90%
	Old/existing index cases	141,686	1.45%	569,770	23.67%	711,455	7.28%
	Relatives of old/existing index cases	3,099,427	31.73%	855,138	35.53%	3,954,565	40.49%
	Medication costs	331,892	3.40%				
	Total	**9,767,806**	**100%**	**2,406,769**	**100%**	**9,767,806**	**100%**
1:250	Active case finding	2,115,563	12.10%				
	New index cases	3,964,900	22.67%	452,841	16.30%	4,417,741	25.26%
	Relatives of new index cases	4,262,269	24.37%	679,262	24.45%	4,941,531	28.26%
	Old/existing index cases	283,371	1.62%	658,577	23.70%	941,948	5.39%
	Relatives of old/existing index cases	6,198,707	35.45%	987,865	35.55%	7,186,572	41.09%
	Medication costs	662,983	3.79%				
	Total	**17,487,792**	**100%**	**2,778,546**	**100%**	**17,487,792**	**100%**
1:200	Active case finding	2,135,902	10.00%				
	New index cases	4,954,723	23.21%	483,380	16.30%	5,438,102	25.47%
	Relatives of new index cases	5,330,541	24.97%	725,308	24.46%	6,055,849	28.36%
	Old/existing index cases	354,094	1.66%	702,404	23.69%	1,056,498	4.95%
	Relatives of old/existing index cases	7,745,752	36.28%	1,053,606	35.54%	8,799,358	41.22%
	Medication costs	828,795	3.88%				
	Total	**21,349 807**	**100%**	**2,964,697**	**100%**	**21,349,807**	**100%**

6 Discussion

FH als Beispiel einer systematischen Teststrategie mit GDx

The aim of this report is to provide an example for issues to be considered by decision makers when implementing molecular genetic diagnostics (GDx) as part of a systematic diagnostic procedure that are beyond benefits, safety and cost-effectiveness. We selected GDx for familial hypercholesterolaemia (FH) as our case study and summarised the currently recommended test strategies for identifying patients with FH with a specific focus on the role of molecular genetic testing. Furthermore, we aimed to derive organisational and economic implications for Austria and to present core ethical considerations that will have to be taken into account in the course of implementing a test strategy in general and GDx in particular.

In the following, the results are summarised and discussed, and methodical limitations are described.

International and national FH test strategies

FH is a widespread monogenic lipid metabolism disorder based on an autosomal dominant inheritance. Based on the concept of cumulative lifelong cholesterol-burden, early diagnosis of FH may have a number of benefits. It enables the initiation of therapeutic measures and cascade screening of at-risk family members.

Beschreibung der Teststrategie: Europäische und internationale Guideline, Australien, Belgien, Deutschland, Kanada, Slowenien, Schweiz, UK, USA

Two international guidelines (European Society of Cardiology/European Arteriosclerosis Society (ESC/EAS), International FH Foundation (IFHF)) and eight national approaches for FH test strategies (Australasia, Belgium, Canada, Germany, Slovenia, Switzerland, United Kingdom (UK), United States of America (USA)) were described by means of type of detection of index-cases, criteria for diagnosis and tool for assessment, FH service providers, implemented molecular genetic testing, cascade screening, genetic counselling, availability of a registry, awareness and education programmes, and recommended lipid-lowering therapy (LLT).

empfohlene oder implementierte IP-Teststrategie: opportunistisch vs. systematisches Screening im spezialisierten oder nicht-spezialisierten Bereich

Recommended or already implemented test strategies for the diagnosis of FH index patients include opportunistic approaches or organised systematic screening in non-specialized (primary care-led) or specialized (secondary care-led) settings. Incidental opportunistic identification of FH index cases (e.g. as part of a routine health check) is part of every (inter-)national test strategy identified in this assessment [18, 20, 23, 25, 60, 64, 67, 68]. Systematic screening for FH includes recommendations for prospective universal population-based screening of adults [17, 18, 25, 69] and children [11, 67], and retrospective searches of patient records by general practitioners (GPs) as implemented in the United Kingdom (UK) [15, 23] or in the national registry in Germany [66]. In most guidance the program is not explicitly designed for FH, but the goal is to find general dyslipidaemias or hyperlipidaemias. FH is indirectly screened as a consequence of the general lipid screening.

GDx meist nur nach erfolgter klinischer FH-Diagnose empfohlen, kann abhängig von DLCN sein

Molecular genetic testing of index patients is mainly recommended only after a clinical FH diagnosis by applying scores from clinical instruments assessing phenotype and family history (e.g. DLCN score in Australasia, Switzerland, UK). The restricted use of GDx may partly be because some of the guidance included in our analysis is already several years old (but is nevertheless repeatedly referenced and in use), while GDx has undergone further development since then.

genetische Beratung oft empfohlen bzw. verpflichtend

FH diagnosis and management is often accompanied by a counselling process, mostly in the case of a planned molecular genetic diagnosis but also in the context of clinical assessment. However, detailed contents and organisational aspects regarding counselling are hardly provided.

Management von Pat. meist in Spezialzentren, Primärversorgung soll eingebunden sein

In the overall model of care for FH, a large variety of medical service providers are included. We identified a primary-care led approach of diagnosis and management of FH patients and a specialist-led approach, whereby most guidelines recommend final diagnosis and ongoing management of FH patients in specialised lipid clinics. However, the role of the primary care sector seems to become increasingly important [31].

Kaskadenscreening von Familienangehörigen oft implementiert, meist klinisch, GDx nur wenn Mutation schon bekannt ist

In cascade screening, 1st and 2nd degree (sometimes 3rd degree) at-risk family members of a diagnosed FH index patient are examined and, if necessary, a primary preventive therapy is started [8]. Additionally, reversed cascade screening can be done if the index patient is a child and the parents and other family members are screened subsequently. Like most other guidance, the recent ESC/EAS guideline recommends cascade screening for FH best performed by a lipid clinic [20]. It can be based on the assessment of clinical criteria for FH or if the specific pathogenic variation of the family is known, on molecular genetic diagnosis. Cascade screening is often systematically organised in the framework of national FH registries, like in Germany, Canada and the UK.

Pat.-Organisationen unterstützen Sensibilisierung des med. Personals, der Pat. und der Bevölkerung

Comprehensive guidance on how to improve awareness and education of health service providers, patients and the general population is rarely provided, although the need for a general health literacy for FH is often mentioned. Often, especially for (possible) FH patients and their family members, reference is made to patient organisations and their special responsibility in raising awareness and providing support.

viele FH-Register, Gerüst für Kaskadenscreening

Registry projects of FH patients and families aid the co-ordination of cascade screening and reporting of FH. The IFHF guideline recommends establishing an FH registry of patients and families for clinical, research and audit purposes [11] and in many countries such projects are already implemented, as in Australia, Canada, Slovenia, UK, USA, and Germany.

FH diagnosis and mangement in Austria

derzeit in Ö kein systematisches Vorgehen zur FH IP-Identifizierung

In Austria, systematic FH index case identification is currently neither formally recommended nor implemented. FH index patients are, in daily practice, either identified in CCUs in a hospital based setting, after a premature or repeated CV event, in primary care during an unrelated clinical consultation by a GP, or when persons contact the national patient organisation (FHchol) on their own initiative.

organisiertes Kaskadenscreening im Register-Projekt

An exception to this is the systematic cascade screening of at-risk family members within the scope of the registry project (initiated by the Austrian Arteriosclerosis Society, the patient's organisation FHchol and co-funded by the pharmaceutical industry). However, only patients and family members who are managed in or by participating lipid centres, extramural specialists, or GPs, are included and recorded.

Management oft in Lipidzentren (auch AM), GDx nur mit genetischer Beratung vorher und nachher

Most often, suspected FH patients are referred to a metabolism specialist in extramural settings or to an ambulatory lipid centre for a more detailed diagnosis and management. In some cases, GDx is undertaken by a human genetics centre or medical genetics laboratory to confirm the clinical diagnosis or to initiate cascade screening. Prior and post molecular genetic testing, ge-

netic counselling is obligatory in Austria, and has to be conducted by a specialist of the respective medical field or a specialist for medical genetics. In some cases, patients are diagnosed and managed solely in the primary care setting by their GP, especially those that respond well to lipid lowering drugs.

Zahlen zu Anwendung von GDx für FH in Ö nicht verfügbar

GDx for FH-associated pathogenic variants is reimbursed in Austria, if commissioned by a practitioner and conducted in a centre for medical genetics. Exact numbers of the frequency of molecular genetic tests for FH are not available publicly.

Ethical aspects of genetic testing for FH

nicht nur IP selbst betroffen, sondern auch Auswirkungen auf Familienangehörige

In the discussion of the ethical aspects of GDx for FH, not only the diagnostic method itself needs to be considered, but also the ethical implications in relation to the overall screening programmes, especially cascade screening. Particular attention needs to be paid to the fact that molecular genetic analysis within the FH-context is not only used to confirm a clinical diagnosis, but also for the early detection of phenotypically non-conspicuous individuals in the form of predictive susceptibility testing.

keine Anzeichen für negative psychologische Auswirkungen von GDx, Kinder als besonders vulnerable Pat.-Gruppe

FH is a common lipid metabolism disorder which, if left untreated, increases the risk of premature arteriosclerosis and CVDs. Early diagnosis and screening of individuals who are not clinically apparent allows early initiation of LLT and may prevent secondary damage as part of primary prevention. Further, there is indication that the molecular genetic diagnosis of FH has low adverse psychological impact on the patient and serves rather as reassurance that the primary causes of the hypercholesterolemia are not dietary and lifestyle habits. However, as especially cascade screening aims to identify patients at a very young age, the target patient population includes the paediatric population, which is particularly in need of protection.

GDx bedarf besonderem Schutz der Autonomie und Privatsphäre des Pat.

genetische Beratung von großer Bedeutung auch für Aufklärung und Einverständniserklärung

Potential für intra-familiäre Konflikte, z. B. bei Offenlegung der Testergebnisse

Molecular genetic tests and analyses on humans are intrusions into core areas of an individual's personality and privacy. In order to be able to make an autonomous decision and to ensure that the patient is able to correctly classify the consequences of a genetic diagnosis for himself and his family, he/she needs extensive and detailed consultation in the context of genetic counselling before he/she undergoes GDx. In the context of genetic counselling, the impact of detecting a pathogenic variant and the consequences, non-detection, as well as potential consequences of a genetic diagnosis on the patient's family relationships, need to be discussed in particular. The latter is important, since intra-family conflicts could occur in the context of cascade screening, especially when it comes to disclosure of the risk for FH to relatives. Disclosure of an FH diagnosis to at risk-family members may affect the patient's privacy itself, but the patient may also feel guilty for interrupting the privacy of the family members by announcing a potential risk. Consequently, not only the index patient's privacy and autonomy but also that of family members need to be addressed. Well-trained genetic counsellors are needed to be able to adequately communicate all of this to patients and family members.

klin. Diagnose kann auch zu intra-familiären Konflikten führen

However, the potential for intra-family conflicts exists not only when the FH is diagnosed by molecular genetics, but also with the classical diagnosis of the patient based on clinical criteria. Therefore, this ethical aspect cannot be attributed solely to molecular genetic testing.

Gefahr der Medikalisierung

Due to decrease saturated fat intake and increased use of statins, the classical clinical presentation of FH seems to have changed over time, and therefore it could become more difficult to distinguish between FH-affected and FH-non-affected patients solely based on blood lipids. Further, underutilisation of GDx in FH diagnosis can result in medicalisation, due to the overuse of lipid lowering drugs (LLDs). On the other hand, it needs to be emphasised that not all patients with FH automatically develop arteriosclerosis or CVD events.

in Ö Verwendung von gen. Information für Versicherungen und Arbeitgeber verboten

A diagnosis of FH may also result in discrimination, prejudice and stigma, in form of social and psychological consequences. However, in Austria discrimination by insurances and employment because of GDx is addressed in the GTG, which prohibits the collection and use of data from genetic tests for these purposes.

eventuell sind Kliniker bei bekannter Mutation gewillter Kaskaden-screening einzuleiten

Although LLT will be initiated in an index patient regardless of molecular genetic confirmation, an available molecular genetic analysis may increase the willingness of medical professionals to carry out testing in relatives [120], as GDx allows for more unequivocal results at least for the confirmation of the familial pathogenic variant.

gerechter Zugang zu GDx

Regarding justice and equity, in Austria GDx is reimbursed if indicated by a clinician and therefore there is no explicit barrier to access, but still, the lack of health literacy concerning FH in health care professionals and patients can limit access indirectly.

GDx ermöglicht präzisere Risikoabschätzung

neg. GDx bedeutet nicht automatisch keine FH

One of the main benefits of diagnosing FH using GDx in addition to clinical criteria (e.g. LDL-C and family history of premature CVDs) is that it provides prognostic information and the ability to perform refined risk stratification. It further allows to distinguish between patients with hereditary caused hypercholesterolemia and those with hypercholesterolemia due to other reasons (non FH related). When implemented in cascade screening, GDx increases the number of patients with FH identified per family in contrast to cascade screening solely based on clinical criteria. Nevertheless, a negative result of GDx (i.e. no pathogenic variant was identified) does not necessarily mean, that the patient has no FH. Not least, even a risk-associated mutation does not automatically lead to a disease since co-inheritance of other genetic factors and environmental factors have a strong influence as well.

Organisational and economic implications for Austria

Based on the results from the international guidance, the Austrian situation, the ethical concerns and the resource impact example, the following organisational, economic, and broader implementation issues need to be addressed by decision makers:

Österreich-spezifische Kosten-Effektivitätsanalyse

- *Knowledge gap in (cost-)effectiveness of systematic FH test strategies in the Austrian context*
  In general, international and national guidelines and position papers seem to be very much in favour of a systematic FH screening approach (partly including GDx) for diagnosing FH index patients and cascade screening. However, since this report did not analyse the evidence on effectiveness and safety for patients, it is unclear whether the benefits outweigh the harm and which of the international strategy would be most beneficial and cost-effective in Austria. Recommendations on the effectiveness and evidence level of individual treatment measures or entire FH screening strategies in specific FH guidelines must be viewed

with a critical eye, especially in the light of possible conflicts of interest of the authors of those guidelines and in studies based on it [131, 132]. The international cost-effectiveness studies presented in the background section are not directly transferable to the Austrian context and partly lack rigour regarding quality. Thus, before any decision on implementing a systematic screening approach is made, the comparative effectiveness of different strategies needs to be assessed. The knowledge gap in cost-effectiveness evidence can be met in form of an up-to-date systematic health economic evaluations (HEE) and cost-effective (CE) model for the Austria-specific context with sufficient comparators. According to the position paper of the Austrian FH register from 2015, a modelling study in cooperation with the Tiroler Privatuniversität (UMIT) is in preparation [57]. In the context of this, a decision needs to be made whether reducing FH-related morbidity and mortality is defined as a clear health policy goal.

- *Clarifying professional and service level responsibilities*
  While most guidelines recommend diagnosis and ongoing management of FH patients in specialised lipid clinics, the first steps in the Austrian diagnostic strategy are less clear. A well-defined process and clear responsibilities will have to be defined. Questions to be discussed are for example whether every FH patient diagnosed in primary care by a GP has to be referred to a lipid specialist, or whether further treatment in primary care with an effective therapy and a well-adjusted LDL-C value is reasonable, whether a lipid specialist is necessary if the FH can be controlled with statins, etc. Potential conflicts between different professional groups and medical specialists are to be expected and need to be actively dealt with.

Definition von präzisen Prozessen, verantwortlichem Personal und beteiligten med. Diensten notwendig

- *Systematic approaches for LDL-C measurements in primary care*
  An organisational implication from installing a more systematic approach is to implement systematic LDL-C measurements in primary care. Since there are different approaches to do this, a decision on which one to follow is required on a central level. Approaches which were suggested may be to install the systematic assessment of LDL-C values in the annual *Vorsorgeuntersuchung (VU)* and/or automatic notifications on lab reports, if blood cholesterol is suspiciously increased. This requires an adaptation of the electronic report template.

  Other options should be considered as well. One strategy may be to use the electronic health record (ELGA) for screening purpose. ELGA to date does not provide full coverage of patient data for the ambulatory sector and on lipid values for primary care in particular, but may so in future. However, ethical, data protection, legal, effectiveness and economic issues need to be taken into account if this approach is considered further.

systematisches Vorgehen für LDL-C Messungen in der Primärversorgung

- *Revision of the Austrian concept of genetic counselling and human resource development*
  Since GDx is expected to be increasingly used (regardless of whether within opportunistic or organised screening), there seems to be a need for evaluating and probably revising the current regulation of genetic counselling. In particular, requirements for the specialized occupational groups which are officially allowed to provide genetic counselling need to be specified in more detail. As a consequence, staff and training capacities in genetic counselling will have to be increased. This is particularly apparent in the light of the results in the ethical

vermehrter Einsatz von GDx führt zu erhöhtem Bedarf an genetischer Beratung: Überarbeitung des derzeitigen Konzeptes

analysis which has demonstrated the important role of counselling in different steps of the screening process and the challenges counsellors face, e.g. on how to explain information in order to allow informed decision, avoid family-conflict etc.

Einsatz von GDx in organisierten Screening-Programmen bedarf rechtlicher Regelungen

- *Legal regulation of GDx in organised screening programs*
  If GDx is established within the framework of an organised screening programme, but also within the framework of targeted cascade screening, the legal regulations and quality standards need to be revised (e.g. similarly to those in Germany) and genetic screening needs to be precisely defined and discussed.

Umfangreiche Begleitstudien, z. B. FH-Prävalenz in Ö

- *Comprehensive accompanying research activities*
  It has been clearly shown that there is a lack of robust data on FH prevalence in Austria. This does not only make it difficult to estimate the true burden of disease, but also to do precise planning including calculating the budget impact for different screening and testing strategies. As demonstrated by our resource impact calculation example, uncertainties of such calculations are high. Filling this knowledge gap requires research resources to do a comprehensive prevalence study.

  Furthermore, within an organised screening, an evaluation and monitoring concept needs to be defined. In that context the role of the existing registry within evaluation and monitoring needs to be reflected on and possibly newly defined. Resources for an ongoing monitoring need to be ensured.

stärkere Sensibilisierung für FH von med. Personal, Pat. und der Bevölkerung

- *Strengthening of FH awareness in health service providers, patients, and the general population*
  If the reduction of FH-related premature morbidity and mortality is defined as a policy goal by decision makers, there is a need to actively raise awareness among professionals and patients. This will require investing in and organising training of medical staff, e.g. in medical school, but also increasing knowledge and health literacy on FH and screening/prevention options in the general population. Patient organisations may play a role here, however, their other funding (often from pharma-industry) needs to be born in mind to minimise conflict of interest and guarantee objective information activities.

molekulargenetisches Testen als Kostentreiber mit ca. 71 % (größer als im NICE-Modell mit 50 %)

To get a first impression of the potential resource impact of implementing a more systematic FH screening including GDx, we calculated budgetary consequences for one selected approach, which is to identify index patients via primary health care record screening. The results of the base case analysis showed an overall resource impact of € 17.5 million for one year. Molecular genetic testing including genetic counselling (GDx) has been identified as the main cost-driver, accounting for a proportion of approximately ¾ of total costs. The largest share is due to the test and associated task itself (without genetic counselling). With a proportion of ~71%, this share is even higher than in the NICE resource impact model (50%) [33].

Tarif für genetische Beratung sehr gering in Relation zum Aufwand/zur Komplexität

In contrast to the costs for the actual test, costs for genetic counselling accounted for a rather small proportion of GDx costs (7.4%) and overall total costs respectively (5.75%). This is due to the current tariff. It needs to be critically revised, whether this tariff (€ 120 for 7-8 hours) reflects the importance of professional counselling in the overall process and the complexity of this task, as outlined earlier in the ethical considerations.

besonders die Prävalenz, aber auch andere Faktoren haben Auswirkungen auf die Kosten(zusammensetzung) (Kostenintervall: ~€ 9,8 bis ~€ 21,3 Mio.)

The budgetary consequences are dependent on a number of factors, including probabilities of an index case to agree to cascade testing, uptake rates, the likelihood that the identified people actually have FH and diagnostic performance of clinical assessment instruments. As demonstrated in the sensitivity analysis, one factor which particularly influences the economic consequences, is the prevalence of FH in the total population. Since we do not have robust prevalence data in Austria, this lack of information causes considerable uncertainty in the resource impact calculation. Depending on the assumed prevalence, the total costs ranged from ~€ 9.8 million to € 21.3 million.

mit steigender Prävalenz steigt der Kostenanteil von GDx an den Gesamtkosten

Another result of the sensitivity analysis is that the share of GDx costs within total costs increases with a higher prevalence ranging from a share of 69.07% (1:500) to 78.92% (1:200). This is because the larger number of index cases identified result in a larger number of identified relatives (average number of relatives with a potential FH per index case is 3).

relative Kostenverschiebung mit fallender Prävalenz von GDx (variable Kosten) zu aktiver Suche (fixe Kosten)

Furthermore, with decreasing prevalence, there seems to be a relative shift from costs of GDx (molecular genetic test and counselling) to active case finding. This can be explained by the "nature" of the medical record searching costs. Searching VU records is a fixed cost component of the total costs, whereas the other costs, e.g. GDx costs, are variable components which depend on the number patients identified (which in turn is dependent on prevalence).

neben den Kosten für GDx fallen noch Kosten für weitere Komponenten an

Although the most expensive component of the analysed strategy seems to be the molecular genetic test and GDx respectively, the results demonstrate that there are a number of other cost components to be taken into account when implementing an organised FH-screening approach. Further resource consequences that have not been addressed in the resource impact calculation may arise from investing in personnel (especially counsellors) and education/training. Additionally, resources for research, evaluation and monitoring need to be considered.

Limitations

keine Evaluierung von (Kosten-)Effektivität und Sicherheit

This report focused on organisational, ethical and economic issues, while the evidence on effectiveness, safety and cost-effectiveness was not considered. Therefore, this report does not allow conclusions on most effective and safe or cost-efficient test strategies for diagnosing FH.

keine systematische Literatursuche nach (inter-)nationalen FH Teststrategien

vordefinierte Auswahl relevanter Länder

The description of possible test and management strategies is based on an iterative hand search for official guidelines and scientific papers, and not on a systematic literature search with a comprehensive search strategy. Further guidelines may therefore be available. However, the manual search strategy is justified, since the aim was to identify the variety in screening and treatment strategies rather than a comprehensive review of guidelines. We also restricted the selection of documents to a predefined set of countries, plus recent international guidelines. Furthermore, due to language barriers, only sources in English and German could be included. Although the identified literature usually provides precise criteria for the identification and diagnosis of FH patients, a precise description of organisational implications and how the respective test strategy should be implemented in practice is mostly missing. There is currently no European guideline that specifically refers to the diagnostic procedure and test strategy of FH. Information on this is part of the current ESC/EAS Guideline "*Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk*" [20].

kaum publizierte Information zu FH-Situation in Ö

In order to describe the current FH test strategy in Austria, published literature and expert interviews were taken into account. However, only very limited and partly outdated published information on the diagnostic approach of FH could be identified, therefore a large part of the description is based on the personal knowledge of experts. Due to resource constraints, it was not possible to do a systematic primary data collection and the number of interviews was limited to 3 experts.

relevante ethischer Aspekte aufgezeigt, aber kein ausführlicher moralischer Diskurs, keine systematische Literatursuche

The analysis of ethical aspects of the GDx of FH, especially within the framework of the family-based cascade screening, was based on the Hofmann's simplified catalogue of questions [49], a Socratic approach. The focus here was on highlighting the spectrum of ethically relevant arguments but not on discussing them and morally classifying them in a value system. In contrast to the project protocol, we limited the ethical analysis to literature that was identified by an orienting hand search, already used in the scoping process, or included in answering other study questions of this report. This was because the aim was to identify the variety of potential ethical considerations but not the entire literature on ethical dimensions.

einige Limitation hinsichtlich der RIA

Regarding the resource impact calculation, a number of limitations exist. Firstly, while a wide range of possible FH management programmes with different cost-effectiveness results exist, this report addresses one selected model, because it is unclear to date which screening model would be relevant for Austria.

Kalkulationen basieren auf zahlreichen Annahmen hinsichtlich der Prävalenz, der FH-Patient*innen in Behandlung, der Compliance etc.

Secondly, numerous assumptions had to be made in order to operationalise the care pathway of the present model. Prevalence data of FH in the literature is associated with a high level of uncertainty and is not available for all health care contexts. In addition, the specific number of people treated with a clear FH diagnosis is also uncertain. Further assumptions made are the full uptake of molecular genetic tests, the proportion of people with FH who are offered cascade testing for their relatives, and that there are 3 relatives per index patient affected on average. Whether these are representative for the Austrian population is uncertain. However, a 100% uptake rate of GDx would constitute the most resource intensive setting with regard to the uptake rate.

speziell die Compliance bei der Erstuntersuchung ist unklar

For Austria there are no specific compliance numbers with regard to the invitation and initial detection. Based on international evidence, we assume that 26.4% follow the invitation for a preliminary GP examination and receive a referral to a specialist [129]. Whether this uptake rate is valid for the Austrian context is not clear.

Crossover wurde nicht berücksichtigt

Furthermore, crossover was not considered. Hence, the initial search in VU records may identify relatives of already diagnosed index cases who have already been cascade tested, and vice versa.

Darstellung der LLT- und Medikationsosten nur für 1 Jahr

Medication and monitoring tasks in the course of a LLT for a life-long disorder such as FH constitute yearly recurring tasks. Hence, consideration of LLT including medication for just one year seems to distort relative comparisons of costs between the treatment tasks/components. As mentioned above, if we would calculate costs for 50 or 60 years, the initial costs of active case finding, cascade screening and GDx would be a smaller in relative terms. However, a time horizon of 50 to 60 years would demand the inclusion of the effectiveness domain and benefits of all associated interventions including discounting, and would additionally demand for costing further individual therapeutic steps that is beyond the scope of the report.

LLT wurde homogenisiert, gewichtete Kosten für die Medikation wurden berechnet, Extrapolation der Inanspruchnahme

Additionally, LLT in the current calculation is homogenised. However, as it has been mentioned in the method section 4.5.3 in reality FH patients may be quite heterogeneous and require different LLT approaches. For the price of LLT medication, a weighted average of the costs of atorvastatin, rosuvastatin and ezetimibe depending on the prescription and utilisation was calculated. Unfortunately, no specific data for Austria on the utilisation and distribution of high intensity statins was available to this date. Hence, data from the NICE model served as approximation for the normal prescription practice in Austria.

herangezogene Tarife und Preise sind möglicherweise für den FH-Kontext nur bedingt verwendbar

Assumptions have also been made regarding prices and tariffs. Due to the absence of FH-specific tariff data, for some cost categories (clinical assessment with the DLCN criteria, examination of phenotypical predictors, preparation of a report for referral etc.) data had to be taken from specific tariff catalogues such as tariffs from the disease order management programme diabetes, tariff catalogue of the insurance institution for public servants, railroads and mining [BVAEB], and a specific tariff catalogue for Salzburg. These sources are partly limited in terms of generalisability/transferability for the FH context. Flat-rate payments were considered at the GP, specialist, and laboratory level for all patients and can only be billed once every quarter from a contracted party. Whether patients may already have seen the physician at the respective level in the quarter of the calculation period is neglected.

Kosten der aktiv systematischen Suche konnten nur approximiert werden

Costs for the search of index patients can only be roughly approximated. Reasons are manifold, e.g. the number of patients and therefore VU records that need to be processed are not equally distributed across contracted GPs and consequently different working loads are faced by GP assistants and GPs. For tariffs of molecular genetic testing and associated treatments only one provider was contacted.

Sensitivitätsanalyse beschränkt sich nur auf die Prävalenz

Sensitivity analysis in this report is restricted to varying one parameter only (prevalence). If resource impact estimates are used for implementation considerations, further sensitivity analyses are recommended. Parameter to be included in sensitivity analysis are for example uptake rate of a preliminary clinical assessment of potential new index cases, tariffs and billing data for the molecular genetic test, proportion of the affected population with a current clinical FH diagnosis that are in treatment for FH or average number of relatives per index case offered and accepting testing.

keine Berücksichtigung von sekundären FH-Fällen

Although, to a certain degree FH is prevalent in people that already experienced a MI event or in people with coronary artery diseases such as angina pectoris, these secondary care FH cases are not considered in the calculations. However, reasons for this decision were presented earlier (section 4.5.3).

ein Kostenausgleich (Cost-Offset) wurde nicht gemacht

Finally, cost-offsets are not considered. Hence, potentially arising resource savings or potential benefits such as (monetary valued) benefits due to preventing premature cardiovascular diseases are subject matter for future research in the course of cost-effectiveness studies.

7 Conclusio

organisatorische, ethische und ökonomische Implikationen

Molecular genetic testing has played an increasingly important role in several disease areas and its utilisation is expected to rise further in the near future. This report has addressed ethical, organisational and economic issues to be considered when implementing GDx into a health care system in a structured and governed way. We have illustrated this by using the example of GDx in the context of familial hypercholesterolaemia.

Definition der Rolle von GDx innerhalb des Teststrategie, klare Zuordnung von Verantwortlichkeiten

The results demonstrate that before introducing GDx, it has to be clearly defined which role the test should play within the overall diagnostic and management processes of the disease in question. In the case of FH, a key decision to make is whether it should be part of an organised or opportunistic screening approach, which of the different organised approaches that are suggested in international guidance (whether to identify index patients in children or adults, which method to use for identification, etc.) to choose and at which level of care the different steps should take place.

unkoordiniertes Vorgehen kann zu ungleichem Zugang führen

The Austrian situation analysis has shown that if this is neglected, diffusion into the health care system will be uncoordinated, resulting in very different diagnostic and care processes in which access to care is mainly dependent on initiatives of single providers or medical doctors. Consequently, patients' access to care is unequal. Furthermore, it is unclear whether core quality criteria (e.g. professional genetic counselling) are fulfilled.

systematische Implementierung bringt eine Reihe organisatorischer Herausforderungen mit sich

Regardless of which approach to choose, implementing GDx results in a number of organisational challenges, such as defining practice steps and personnel to identify the index patients, providing enough and well-educated genetic counsellors and linking them logistically to the clinical and laboratory processes around the testing. Furthermore, medical doctors need to be trained in standardised clinical assessment, and communication activities need to take place in order to raise awareness and health literacy on the topic in public, and a monitoring system needs to be installed. Some of these tasks may also require revising existing legal regulations.

gut ausgebildete genetische Berater*innen

The way forward to deal with the numerous ethical questions that arise is to guarantee transparent and non-directive communication with patients and their relatives. Therefore, investing in professional and well-trained counsellors seems to be paramount.

Österreich-spezifische Kosten-Effektivitätsanalyse

However, introducing GDx in such an organised way results in substantial costs that go considerably beyond the cost of the actual test itself. Hence, before implementing, a thorough effectiveness and cost-effectiveness analysis should be undertaken in order to identify the most effective and cost-effective strategy for Austria. This will require more robust prevalence data in the first place.

8 Literature

[1] Jameson J. L. and Longo D. L. Precision Medicine – Personalized, Problematic, and Promising. New England Journal of Medicine. 2015;372(23):2229-2234. DOI: 10.1056/NEJMsb1503104.

[2] Sturm A. C., Knowles J. W., Gidding S. S., Ahmad Z. S., Ahmed C. D., Ballantyne C. M., et al. Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel. J Am Coll Cardiol. 2018;72(6):662-680. DOI: 10.1016/j.jacc.2018.05.044.

[3] Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF). S2k-Leitlinie Humangenetische Diagnostik und Genetische Beratung. medizinische genetik. 2018;30(4):469-522. DOI: 10.1007/s11825-018-0223-1.

[4] Raby B. A., Kohlmann W. and Hartzfeld D. Genetic testing. 2020 [updated 14.06.2020; cited 10.10.2020]. Available from: https://www.uptodate.com/contents/genetic-testing?search=genetic%20testing&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H990910167.

[5] Beheshti S. O., Madsen C. M., Varbo A. and Nordestgaard B. G. Worldwide Prevalence of Familial Hypercholesterolemia. Journal of the American College of Cardiology. 2020;75(20):2553. DOI: 10.1016/j.jacc.2020.03.057.

[6] Rosenson R. S. and Durrington P. Familial hypercholesterolemia in adults: Overview. 2020 [updated 01.07.2020; cited 13.09.2020]. Available from: https://www.uptodate.com/contents/familial-hypercholesterolemia-in-adults-overview?search=familial%20hypercholesterol&topicRef=122013&source=see_link.

[7] Beier C., Nonhoff D., Løge I., Eriksson M., Cooper J. and Vaaler S. Hyperlipidämie. 2019 [cited 03.04.2019]. Available from: https://deximed.de/home/b/endokrinologie-stoffwechsel/krankheiten/uebergewicht-und-fettstoffwechselstoerungen/hyperlipidaemie/#diagnostik.

[8] Krychtiuk K. and Speidl W. Familial Hypercholesterolaemia – Epidemiology, Diagnostics and Therapy Austrian Journal of Cardiology. 2017;7-8:153-159.

[9] Khera A. V., Won H. H., Peloso G. M., Lawson K. S., Bartz T. M., Deng X., et al. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. J Am Coll Cardiol. 2016;67(22):2578-2589. Epub 2016/04/07. DOI: 10.1016/j.jacc.2016.03.520.

[10] Chourdakis M., Buderus S., Dokoupil K., Oberhoffer R., Schwab K. O., Wolf M., et al. S2k-Leitlinien zur Diagnostik und Therapie von Hyperlipidämien bei Kindern und Jugendlichen. 2015 [cited 13.09.2020]. Available from: https://www.awmf.org/uploads/tx_szleitlinien/027-068l_s2k_Hyperlipid%C3%A4mien_Kinder_Jugendliche_2016-02.pdf.

[11] Watts G. F., Gidding S., Wierzbicki A. S., Toth P. P., Alonso R., Brown W. V., et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. Int J Cardiol. 2014;171(3):309-325. DOI: 10.1016/j.ijcard.2013.11.025.

[12] Austin M. A., Hutter C. M., Zimmern R. L. and Humphries S. E. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol. 2004;160(5):407-420. Epub 2004/08/24. DOI: 10.1093/aje/kwh236.

[13] Nordestgaard B. G., Chapman M. J., Humphries S. E., Ginsberg H. N., Masana L., Descamps O. S., et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34(45):3478-3490a. Epub 2013/08/21. DOI: 10.1093/eurheartj/eht273.

[14] Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. Bmj. 1991;303(6807):893-896. Epub 1991/10/12. DOI: 10.1136/bmj.303.6807.893.

[15] National Institute for Health and Care Excellence (NICE). Familial hypercholesterolaemia: identification and management. 2019.

[16] Williams R. R., Hunt S. C., Schumacher M. C., Hegele R. A., Leppert M. F., Ludwig E. H., et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. Am J Cardiol. 1993;72(2):171-176. Epub 1993/07/15. DOI: 10.1016/0002-9149(93)90155-6.

[17] Anderson T. J., Gregoire J., Pearson G. J., Barry A. R., Couture P., Dawes M., et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol. 2016;32(11):1263-1282. DOI: 10.1016/j.cjca.2016.07.510.

[18] Brunham L. R., Ruel I., Aljenedil S., Riviere J. B., Baass A., Tu J. V., et al. Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia: Update 2018. Can J Cardiol. 2018;34(12):1553-1563. DOI: 10.1016/j.cjca.2018.09.005.

[19] Tanaka N., Teramoto T. and Yokoyama S. Application of the Japanese Guidelines for the Diagnosis of Familial Hypercholesterolemia in General Practice: It is to be Validated in International Harmonization. Journal of atherosclerosis and thrombosis. 2019;26(1):93-98. Epub 2018/11/27. DOI: 10.5551/jat.46979.

[20] Mach F., Baigent C., Catapano A. L., Koskinas K. C., Casula M., Badimon L., et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-188. DOI: 10.1093/eurheartj/ehz455.

[21] Rosenson R. S. and Durrington P. Familial hypercholesterolemia in adults: Treatment. 2020 [updated 14.09.2020; cited 16.09.2020]. Available from: https://www.uptodate.com/contents/familial-hypercholesterolemia-in-adults-overview?search=familial%20hypercholesterol&topicRef=122013&source=see_link.

[22] Versmissen J., Oosterveer D. M., Yazdanpanah M., Defesche J. C., Basart D. C., Liem A. H., et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. Bmj. 2008;337:a2423. Epub 2008/11/13. DOI: 10.1136/bmj.a2423.

[23] Public Health England (PHE). Familial Hypercholesterolaemia: Implementing a systems approach to detection and management. 2018 [cited 13.09.2020]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/731873/familial_hypercholesterolaemia_implementation_guide.pdf.

[24] Descamps O. S., Van Caenegem O., Hermans M. P., Balligand J. L., Beauloye C., Bondue A., et al. A Belgian consensus strategy to identify familial hypercholesterolaemia in the coronary care unit and its subsequent cascade screening and treatment: BEL-FaHST (The BELgium Familial Hypercholesterolaemia STrategy). Atherosclerosis. 2018;277:369-376. Epub 2018/10/03. DOI: 10.1016/j.atherosclerosis.2018.05.037.

[25] Goldberg A. C., Hopkins P. N., Toth P. P., Ballantyne C. M., Rader D. J., Robinson J. G., et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3 Suppl):S1-8. DOI: 10.1016/j.jacl.2011.04.003.

[26] World Health Organization (WHO). Screening. 2020 [cited 13.09.2020]. Available from: https://www.who.int/cancer/prevention/diagnosis-screening/screening/en/.

[27] Raffle A., Mackie A. and Gray M. Screening: Evidence and practice. 2 ed: Oxford University Press; 2019.

[28] Reinsperger I., Winkler R. and Piso B. Eltern-Kind-Vorsorge neu Teil IX: Empfehlungen aus evidenzbasierten Leitlinien für Screenings von Schwangeren und Kindern (0–6 Jahre). Wien: Ludwig Boltzmann Institut für Health Technology Assessment, 2013.

[29] World Health Organisation (WHO). Principles and practice of screening for disease. The Journal of the Royal College of General Practitioners. 1968;16(4):318-318.

[30] Andermann A., Blancquaert I., Beauchamp S. and Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bull World Health Organ. 2008;86(4):317-319. Epub 2008/04/29. DOI: 10.2471/blt.07.050112.

[31] Brett T., Qureshi N., Gidding S. and Watts G. F. Screening for familial hypercholesterolaemia in primary care: Time for general practice to play its part. Atherosclerosis. 2018;277:399-406. Epub 2018/10/03. DOI: 10.1016/j.atherosclerosis.2018.08.019.

[32] Mach F., Baigent C., Catapano A. L., Koskinas K. C., Casula M., Badimon L., et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2019;41(1):111-188. DOI: 10.1093/eurheartj/ehz455.

[33] National Institute for Health and Care Excellence (NICE). Familial hypercholesterolaemia: identification and management: Evidence reviews for case-finding, diagnosis and statin monotherapy. 2019 [cited 29/07/2020]. Available from: https://www.nice.org.uk/guidance/cg71/evidence/evidence-reviews-for-casefinding-diagnosis-and-statin-monotherapy-pdf-4660992685.

[34] National Institute for Health and Care Excellence (NICE). National Institute for Health and Care Excellence: Clinical Guidelines – Familial hypercholesterolaemia: identification and management. London: National Institute for Health and Care Excellence (UK) Copyright © NICE 2019.; 2019.

[35] Pears R., Griffin M., Futema M. and Humphries S. E. Improving the cost-effectiveness equation of cascade testing for familial hypercholesterolaemia. Current opinion in lipidology. 2015;26(3):162-168. DOI: 10.1097/MOL.0000000000000173.

[36] National Collaborating Centre for Primary Care and National Institute for Health and Clinical Excellence (NICE). National Institute for Health and Clinical Excellence: Guidance – Identification and Management of Familial Hypercholesterolaemia (FH). London: Royal College of General Practitioners (UK) Copyright © 2008, Royal College of General Practitioners.; 2008.

[37] Marks D., Thorogood M., Neil H. A., Wonderling D. and Humphries S. E. Comparing costs and benefits over a 10 year period of strategies for familial hypercholesterolaemia screening. J Public Health Med. 2003;25(1):47-52. Epub 2003/04/03. DOI: 10.1093/pubmed/fdg010.

[38] Marks D., Wonderling D., Thorogood M., Lambert H., Humphries S. E. and Neil H. A. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. Bmj. 2002;324(7349):1303. Epub 2002/06/01. DOI: 10.1136/bmj.324.7349.1303.

[39] Marang-van de Mheen P. J., ten Asbroek A. H., Bonneux L., Bonsel G. J. and Klazinga N. S. Cost-effectiveness of a family and DNA based screening programme on familial hypercholesterolaemia in The Netherlands. Eur Heart J. 2002;23(24):1922-1930. Epub 2002/12/11. DOI: 10.1053/euhj.2002.3281.

[40] Wonderling D., Umans-Eckenhausen M. A., Marks D., Defesche J. C., Kastelein J. J. and Thorogood M. Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands. Semin Vasc Med. 2004;4(1):97-104. Epub 2004/06/17. DOI: 10.1055/s-2004-822992.

[41] National Institute for Health and Care Excellence (NICE). Resource impact report: Familial hypercholesterolaemia: identification and management (CG71). 2017 [cited 29/07/2020]. Available from: https://www.nice.org.uk/guidance/cg71/resources/resource-impact-report-pdf-4660987501.

[42] Nherera L., Marks D., Minhas R., Thorogood M. and Humphries S. E. Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart. 2011;97(14):1175-1181. Epub 2011/06/21. DOI: 10.1136/hrt.2010.213975.

[43] Chen C. X. and Hay J. W. Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. Int J Cardiol. 2015;181:417-424. Epub 2015/01/09. DOI: 10.1016/j.ijcard.2014.12.070.

[44] Kerr M., Pears R., Miedzybrodzka Z., Haralambos K., Cather M., Watson M., et al. Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK. Eur Heart J. 2017;38(23):1832-1839. Epub 2017/04/08. DOI: 10.1093/eurheartj/ehx111.

[45] Ademi Z., Watts G. F., Pang J., Sijbrands E. J., van Bockxmeer F. M., O'Leary P., et al. Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. J Clin Lipidol. 2014;8(4):390-400. Epub 2014/08/12. DOI: 10.1016/j.jacl.2014.05.008.

[46] National Collaborating Centre for Primary Care. NICE Clinical Guideline 71 – Familial Hypercholesterolaemia, appendix E, health economic modelling. 2008.

[47] Wiegman A., Gidding S. S., Watts G. F., Chapman M. J., Ginsberg H. N., Cuchel M., et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015;36(36):2425-2437. Epub 2015/05/27. DOI: 10.1093/eurheartj/ehv157.

[48] Watts G. F., Sullivan D. R., Poplawski N., van Bockxmeer F., Hamilton-Craig I., Clifton P. M., et al. Familial hypercholesterolaemia: a model of care for Australasia. Atheroscler Suppl. 2011;12(2):221-263. DOI: 10.1016/j.atherosclerosissup.2011.06.001.

[49] Hofmann B., Droste S., Oortwijn W., Cleemput I. and Sacchini D. Harmonization of ethics in health technology assessment: a revision of the Socratic approach. Int J Technol Assess Health Care. 2014;30(1):3-9. DOI: 10.1017/S0266462313000688.

[50] Gillon R. Medical ethics: four principles plus attention to scope. Bmj. 1994;309(6948):184. DOI: 10.1136/bmj.309.6948.184.

[51] Lühmann D. and Raspe H. Ethik im Health Technology Assessment – Anspruch und Umsetzung. Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen. 2008;102(2):69-76. DOI: 10.1016/j.zefq.2008.02.003.

[52] Garattini L. and van de Vooren K. Budget impact analysis in economic evaluation: a proposal for a clearer definition. The European Journal of Health Economics. 2011;12(6):499. DOI: 10.1007/s10198-011-0348-5.

[53] Mauskopf J. A., Sullivan S. D., Annemans L., Caro J., Mullins C. D., Nuijten M., et al. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices – budget impact analysis. Value Health. 2007;10(5):336-347. Epub 2007/09/25. DOI: 10.1111/j.1524-4733.2007.00187.x.

[54] Sullivan S. D., Mauskopf J. A., Augustovski F., Jaime Caro J., Lee K. M., Minchin M., et al. Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value in Health. 2014;17(1):5-14. DOI: https://doi.org/10.1016/j.jval.2013.08.2291.

[55] Statistik Austria. Statistik des Bevölkerungsstandes – Bevölkerung am 1.1.2020 nach Alter und Bundesland. 2020 [cited 01/10/2020]. Available from: http://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/bevoelkerung/bevoelkerungsstruktur/bevoelkerung_nach_alter_geschlecht/index.html.

[56] Main Association of Social Security Institutions (Dachverband der Sozialversicherungsträger). Vorsorgeuntersuchung. 2020 [cited 29/07/2020]. Available from: https://www.sozialversicherung.at/cdscontent/?contentid=10007.844026.

[57] Österreichische Atherosklerosegesellschaft e.V. (AAS). Erstellung eines gesamtösterreichischen Registers zur Erfassung der Familiären Hypercholesterinämie – Pilotprojekt Wien, Innsbruck, Graz. 2015 [cited 27/07/2020]. Available from: https://www.aas.at.

[58] Sommer I., Titscher V., Teufer B., Klerings I., Nußbaumer-Streit B., Szelag M., et al. Evidenzbasierte Empfehlungen zur Überarbeitung der österreichischen Vorsorgeuntersuchung. Wiener Medizinische Wochenschrift. 2019;169(13):339-349. DOI: 10.1007/s10354-019-0699-6.

[59] Hadfield S. G., Horara S., Starr B. J., Yazdgerdi S., Marks D., Bhatnagar D., et al. Family tracing to identify patients with Familial Hypercholesterolaemia: the second Audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. Annals of Clinical Biochemistry. 2009;46(1):24-32. DOI: 10.1258/acb.2008.008094.

[60] Deutsche Gesellschaft für Kardiologie (DGK). ESC/EAS Pocket Guidelines: Diagnostik und Therapie der Dyslipidämien. 2020 [cited 13.09.2020]. Available from: https://leitlinien.dgk.org/2020/pocket-leitlinie-diagnostik-und-therapie-der-dyslipidaemien-version-2019/.

[61] Hanusch Krankenhaus Wien – Zentrum für Humangenetik (Prim. Univ. Prof. Dr. med. Gökhan Uyanik). Abrechnungstariffe und Behandlungsabläufe familiäre Hypercholesterinämie (FH), 29.09. 2020.

[62] Österreichische Gesundheitskasse (ÖGK). DMP Therapie aktiv – Tarif Allgemeinmedizin/Allgemeine Fachärztinnen/-ärzte Einzelvertrag. 2020 [cited 30.09.2020]. Available from: https://www.gesundheitskasse.at/cdscontent/load?contentid=10008.735138&version=1587642973, https://www.gesundheitskasse.at/cdscontent/load?contentid=10008.735142&version=1587643360.

[63] Cardiac Society of Australia and New Zealand (CSAN). Diagnosis and Management of Familial Hypercholesterolaemia – Position Statement. 2016 [cited 13.09.2020]. Available from: https://www.csanz.edu.au/wp-content/uploads/2017/07/Familial-Hypercholesterolaemia_ratified_-25-Nov-2016.pdf.

[64] Descamps O. S., Tenoutasse S., Stephenne X., Gies I., Beauloye V., Lebrethon M. C., et al. Management of familial hypercholesterolemia in children and young adults: consensus paper developed by a panel of lipidologists, cardiologists, paediatricians, nutritionists, gastroenterologists, general practitioners and a patient organization. Atherosclerosis. 2011;218(2):272-280. Epub 2011/07/19. DOI: 10.1016/j.atherosclerosis.2011.06.016.

[65] Schulze-Bahr E., Klaassen S., Abdul-Khaliq H. and Schunkert H. Gendiagnostik bei kardiovaskulären Erkrankungen. Der Kardiologe. 2015;9(3):213-243. DOI: 10.1007/s12181-014-0636-2.

[66] Schmidt N., Grammer T., Gouni-Berthold I., Julius U., Kassner U., Klose G., et al. CaRe high – Cascade screening and registry for high cholesterol in Germany. Atheroscler Suppl. 2017;30:72-76. Epub 2017/11/04. DOI: 10.1016/j.atherosclerosissup.2017.05.015.

[67] Groselj U., Kovac J., Sustar U., Mlinaric M., Fras Z., Podkrajsek K. T., et al. Universal screening for familial hypercholesterolemia in children: The Slovenian model and literature review. Atherosclerosis. 2018;277:383-391. DOI: 10.1016/j.atherosclerosis.2018.06.858.

[68] Arbeitsgruppe Lipide und Atherosklerose (AGLA). Pocketguide: Statin-Intoleranz, Familiäre Hyperlipidämien. 2019.

[69] Grundy Scott M., Stone Neil J., Bailey Alison L., Beam C., Birtcher Kim K., Blumenthal Roger S., et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1082-e1143. DOI: 10.1161/CIR.0000000000000625.

[70] Qureshi N., Weng S. F., Tranter J. A., Da Silva M. L., Kai J. and Leonardi-Bee J. Strategies for identifying familial hypercholesterolaemia in non-specialist clinical settings. Cochrane Database of Systematic Reviews. 2018. DOI: 10.1002/14651858.Cd012985.

[71] Genest J., Hegele R. A., Bergeron J., Brophy J., Carpentier A., Couture P., et al. Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia. Canadian Journal of Cardiology. 2014;30(12):1471-1481. DOI: https://doi.org/10.1016/j.cjca.2014.09.028.

[72] Sturm A. C. The Role of Genetic Counselors for Patients with Familial Hypercholesterolemia. Current Genetic Medicine Reports. 2014;2(2):68-74. DOI: 10.1007/s40142-014-0036-8.

[73] European Medicines Agency (EMA). Repatha. 2020 [cited 20.09.2020]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/repatha.

[74] European Medicines Agency (EMA). Praluent. 2020 [cited 20.09.2020]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/praluent#authorisation-details-section.

[75] Gemeinsamer Bundesauschuss (G-BA). Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage III – Übersicht über Verordnungseinschränkungen und -ausschlüsse: Evolocumab. 2016 [cited 20.09.2020]. Available from: https://www.g-ba.de/downloads/39-261-2600/2016-06-02_AM-RL-III_Evolocumab_BAnz.pdf.

[76] Bundesamt für Gesundheit (BAG). Spezialitätenlise. 2020 [cited 20.09.2020]. Available from: http://www.spezialitätenliste.ch/ShowPreparations.aspx.

[77] Swiss Medical Forum. Neue Studien und die Situation in der Schweiz im Jahr 2017: PCSK9-Inhibitoren 2017 [cited 20.09.2020]. Available from: https://medicalforum.ch/article/doi/smf.2017.03102.

[78] Vallejo-Vaz A. J., De Marco M., Stevens C. A. T., Akram A., Freiberger T., Hovingh G. K., et al. Overview of the current status of familial hypercholesterolaemia care in over 60 countries – The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Atherosclerosis. 2018;277:234-255. Epub 2018/10/03. DOI: 10.1016/j.atherosclerosis.2018.08.051.

[79] National Institute for Health and Care Excellence (NICE). Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. 2016 [cited 20.09.2020]. Available from: https://www.nice.org.uk/guidance/ta393.

[80] National Institute for Health and Care Excellence (NICE). Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. 2016 [cited 20.09.2020]. Available from: https://www.nice.org.uk/guidance/ta394.

[81] Datapharm. Electronic Medicines Compendium. 2020 [cited 20.09.2020]. Available from: https://www.medicines.org.uk/emc/product/8093/smpc.

[82] US Food and Drug Administration (FDA). HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use PRALUENT safely and effectively. 2017 [cited 20.09.2020]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125559s002lbl.pdf.

[83] US Food and Drug Administration (FDA). HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use REPATHA® safely and effectively. 2017 [cited 20.09.2020]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125522s014lbl.pdf.

[84] Health Canada – Drug Product Database. Praluent, Product information. 2020 [cited 20.09.2020]. Available from: https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=94029.

[85] Health Canada – Drug Product Database. Repatha, Product information. 2020 [cited 20.09.2020]. Available from: https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=93132.

[86] Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH Canadian Drug Expert CommitteeRecommendation – Repatha. 2017 [cited 20.09.2020]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0515_Repatha_Resubmission_complete_Nov_24_17.pdf.

[87] Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH Canadian Drug Expert CommitteeRecommendation – Praluent. 2016 [cited 20.09.2020]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0469_complete_Praluent_Jul-20-16.pdf.

[88] Pharmaceutical Benefits Scheme (PBS). Evolocumab. 2020 [cited 20.09.2020]. Available from: https://www.pbs.gov.au/medicine/item/10958R.

[89] De Fays C., Persu A., Beauloye C., Balligand J. L., Wallemacq C., Rietzschel E., et al. One-year experience with monoclonal antibodies against PCSK9 in belgian patients with familial hypercholesterolemia. Atherosclerosis. 2018;275:e99-e100. DOI: 10.1016/j.atherosclerosis.2018.06.272.

[90] Expert 1. Expert interview – Testing for Familial Hypercholesterolemia in Austria, 07.07.2020 2020.

[91] Expert 2. Expert interview – Testing for Familial Hypercholesterolemia in Austria, 08.07.2020 2020.

[92] Expert 3. Expert interview – Testing for Familial Hypercholesterolemia in Austria, 27.7.2020 2020.

[93] PERI Consulting GmbH. Österreichischer Patientenbericht – Ergebnisbericht Hypercholesterinämie 2015. 2015 [cited 06/07/2020]. Available from: http://patientenbericht.at/files/Hypercholesteirna%CC%88mie_Ergebnisbericht.pdf.

[94] Kreissl A., Walleczek N., Espina P. R., Hallwirth U. and Greber-Platzer S. Selective screening for familial hypercholesterolemia in Austrian children – first year results. BMC Pediatr. 2019;19(1):208. Epub 2019/06/27. DOI: 10.1186/s12887-019-1586-4.

[95] GTG. GTG, Gentechnikgesetz – Bundesgesetz, mit dem Arbeiten mit gentechnisch veränderten Organismen, das Freisetzen und Inverkehrbringen von gentechnisch veränderten Organismen und die Anwendung von Genanalyse und Gentherapie am Menschen geregelt werden 2020.

[96] Ramaswami U., Futema M., Bogsrud M. P., Holven K. B., Roeters van Lennep J., Wiegman A., et al. Comparison of the characteristics at diagnosis and treatment of children with heterozygous familial hypercholesterolaemia (FH) from eight European countries. Atherosclerosis. 2020;292:178-187. Epub 2019/12/07. DOI: 10.1016/j.atherosclerosis.2019.11.012.

[97] Gesundheit Österreich GmbH (GÖG). Österreichischer Strukturplan Gesundheit 2017 inklusive Großgeräteplan gemäß Beschluss der Bundes-Zielsteuerungskommission vom 27. Septmeber 2019. 2019.

[98] Medizinische Universität Wien. Auftrag zur DNA-Diagnostik. 2020 [cited 10/10/2020]. Available from: https://www.meduniwien.ac.at/hp/fileadmin/med-genetik/Eaddm.pdf.

[99] Gschmeidler B. and Flatscher-Thoeni M. Ethical and Professional Challenges of Genetic Counseling – the Case of Austria. Journal of Genetic Counseling. 2013;22(6):741-752. DOI: 10.1007/s10897-013-9610-6.

[100] Gentechnikommission. Erstes Kapitel – Kriterienkatalog, Anforderungen an Veranlassung und Durchführung einer Genetischen Analyse. Gentechnikbuch: Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz; 2008.

[101] Gentechnikommission. Zweites Kapitel – Leitlinien für die Genetische Beratung. Gentechnikbuch: Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz; 2002.

[102] Zielsteuerung-Gesundheit. Qualitätsstandard „Humangenetische Beratung und Diagnostik". 2015 [cited 05.08.2020]. Available from: http://www.oegh.at/images/stories/oegh2017/qualitatsstandard_humangenetik_122015.pdf.

[103] Medizinische Universität Innsbruck. Genetisches und Genomisches CounsellingUniversitätslehrgang – Master of Science (MSc). 2019 [cited 10/10/2020]. Available from: https://www.i-med.ac.at/gencouns/documents/ULG_v-NEU_-ENDVERSION.pdf.

[104] Dieplinger H. and Hanauer-Mader G. Fass dir ein Herz: Österreichweites Register- und Screeningprojekt für Familiäre Hypercholesterinämie. Austrian Journal of Cardiology. 2017;7-8:163-165.

[105] Österreichische Atherosklerosegesellschaft e.V. (AAS). Bericht 04/2018 über die Initiative der AAS zur Etablierung eines gesamtösterreichischen Registers zur Erfassung der Familiären Hypercholesterinämie (FH) und weitere in diesem Zusammenhang stehende Aktivitäten. 2018 [cited 16/07/2020]. Available from: http://www.herzfonds.at/laufende-projekte.html.

[106] Medizinische Universität Innsbruck. Askimed. 2020 [cited 13.09.2020]. Available from: https://www.askimed.com/.

[107] Hanauer-Mader G. FHchol Austria: Patientenorganisation für Patienten mit Familiärer Hypercholesterinämie oder verwandten genetisch bedingten Stoffwechselstörungen. Austrian Journal of Cardiology. 2017;7-8:160-162.

[108] Dachverband der Sozialversicherungsträger. Erstattungskodex- EKO Stand 1. Jänner 2020 Wien: Hauptverband der österreichischen Sozialversicherungsträger. 2020.

[109] Council of Europe. Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes. 2008 [cited 13.09.2020]. Available from: https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/203.

[110] Bundesministerium für Gesundheit. Gesetz über genetische Untersuchungen bei Menschen (Gendiagnostikgesetz – GenDG). 2019.

[111] Deutsche Gesellschaft für Humangenetik e.V. (GfH). Darstellung des Gesundheitsberufs Genetischer „Beratungsassistent/in" für das Gesamtkonzept zur Neuordnung und Stärkung der Ausbildung der Gesundheitsfachberufe – GfH-BVDH-Stellungnahme vom 12.7.2019. 2019.

[112] Wilemon K. A., Patel J., Aguilar-Salinas C., Ahmed C. D., Alkhnifsawi M., Almahmeed W., et al. Reducing the Clinical and Public Health Burden of Familial Hypercholesterolemia: A Global Call to Action. JAMA Cardiol. 2020;5(2):217-229. Epub 2020/01/03. DOI: 10.1001/jamacardio.2019.5173.

[113] Quaid K. A. Ethical Issues in Genetic Testing. 2016 [cited 27/08/2020]. Available from: https://www.genome.gov/Multimedia/Slides/WGT/Quaid.pdf.

[114] World Health Organization (WHO). Human Genomics in Global Health – Genetic testing. 2020 [cited 27/08/2020]. Available from: https://www.who.int/genomics/elsi/gentesting/en/.

[115] Deutsches Referenzzentrum für Ethik in den Biowissenschaften (DRZE). Predictive Genetic Testing – Ethical aspects. 2020 [cited 07.09.2020]. Available from: http://www.drze.de/in-focus/predictive-genetic-testing/ethical-aspects.

[116] Wong B., Kruse G., Kutikova L., Ray K. K., Mata P. and Bruckert E. Cardiovascular Disease Risk Associated With Familial Hypercholesterolemia: A Systematic Review of the Literature. Clinical Therapeutics. 2016;38(7):1696-1709. DOI: 10.1016/j.clinthera.2016.05.006.

[117] Agård A., Bolmsjö I. A., Hermerén G. and Wahlström J. Familial hypercholesterolemia: ethical, practical and psychological problems from the perspective of patients. Patient Educ Couns. 2005;57(2):162-167. Epub 2005/05/25. DOI: 10.1016/j.pec.2004.05.010.

[118] Senior V., Marteau T. M. and Peters T. J. Will genetic testing for predisposition for disease result in fatalism? A qualitative study of parents responses to neonatal screening for familial hypercholesterolaemia. Social Science & Medicine. 1999;48(12):1857-1860. DOI: https://doi.org/10.1016/S0277-9536(99)00099-4.

[119] van den Nieuwenhoff H. W. P., Mesters I., Gielen C. and de Vries N. K. Family communication regarding inherited high cholesterol: Why and how do patients disclose genetic risk? Social Science & Medicine. 2007;65(5):1025-1037. DOI: https://doi.org/10.1016/j.socscimed.2007.04.008.

[120] Humphries S. E., Galton D. and Nicholls P. Genetic testing for familial hypercholesterolaemia: practical and ethical issues. Qjm. 1997;90(3):169-181. Epub 1997/03/01. DOI: 10.1093/qjmed/90.3.169.

[121] Kindt I., Mata P. and Knowles J. W. The role of registries and genetic databases in familial hypercholesterolemia. Current opinion in lipidology. 2017;28(2):152-160. Epub 2017/02/09. DOI: 10.1097/mol.0000000000000398.

[122] US Preventive Services Task Force (USPSTF). Final Recommendation Statement – Lipid Disorders in Children and Adolescents: Screening. 2016 [cited 13.09.2020]. Available from: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/lipid-disorders-in-children-screening.

[123] Homsma S. J., Huijgen R., Middeldorp S., Sijbrands E. J. and Kastelein J. J. Molecular screening for familial hypercholesterolaemia: consequences for life and disability insurance. Eur J Hum Genet. 2008;16(1):14-17. Epub 2007/10/25. DOI: 10.1038/sj.ejhg.5201940.

[124] Rantanen E., Hietala M., Kristoffersson U., Nippert I., Schmidtke J., Sequeiros J., et al. What is ideal genetic counselling? A survey of current international guidelines. Eur J Hum Genet. 2008;16(4):445-452. Epub 2008/01/17. DOI: 10.1038/sj.ejhg.5201983.

[125] Veach P. M., Bartels D. M. and LeRoy B. S. Ethical and professional challenges posed by patients with genetic concerns: a report of focus group discussions with genetic counselors, physicians, and nurses. J Genet Couns. 2001;10(2):97-119. Epub 2002/01/05. DOI: 10.1023/a:1009487513618.

[126] van El C. G., Baccolini V., Piko P. and Cornel M. C. Stakeholder Views on Active Cascade Screening for Familial Hypercholesterolemia. Healthcare (Basel). 2018;6(3). Epub 2018/09/12. DOI: 10.3390/healthcare6030108.

[127] Will C. M., Armstrong D. and Marteau T. M. Genetic unexceptionalism: Clinician accounts of genetic testing for familial hypercholesterolaemia. Social Science & Medicine. 2010;71(5):910-917. DOI: https://doi.org/10.1016/j.socscimed.2010.05.018.

[128] Lee C., Rivera-Valerio M., Bangash H., Prokop L. and Kullo I. J. New Case Detection by Cascade Testing in Familial Hypercholesterolemia. Circulation: Genomic and Precision Medicine. 2019;12(11):e002723. DOI: doi:10.1161/CIRCGEN.119.002723.

[129] Kirke A. B., Barbour R. A., Burrows S., Bell D. A., Vickery A. W., Emery J., et al. Systematic Detection of Familial Hypercholesterolaemia in Primary Health Care: A Community Based Prospective Study of Three Methods. Heart, Lung and Circulation. 2015;24(3):250-256. DOI: 10.1016/j.hlc.2014.09.011.

[130] Futema M., Talmud P. J., Shah S., Whittall R., Howard P., Cooper J. A., et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. The Lancet. 2013;381(9874):1293-1301. DOI: 10.1016/S0140-6736(12)62127-8.

[131] Arznei-Telegramm (a-t). Neue europäische Leitlinie zur Cholesterinsenkung ... So niedrig wie möglich? a-t. 2019;50: 89-91.

[132] Der Arzneimittelbrief (AMB). Neue europäische „Leitlinie“ zur Lipidsenkung: As low as possible? AMB. 2019;53, 73.

[133] Akioyamen L. E., Genest J., Shan S. D., Reel R. L., Albaum J. M., Chu A., et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open. 2017;7(9):e016461. DOI: 10.1136/bmjopen-2017-016461.

9 Appendix

9.1 International and national FH test strategies

9.1.1 Search terms for hand and orienting literature search

Table 9-1: Search terms for hand and exploratory literature search in English and German

Search term	(Optionally) Linked with
English terms	
familial hypercholesterol*	genetic
hypercholesterol*	screening
familial	
hyperlipid*	
lipid*	
dyslipid*	
German terms	
Familiäre Hypercholesterinämie	geneti*
Familiär*	Screening
Hypercholesterinämie	
Hyperlipidämie	
Hyperlipoproteinämie	
Dyslipidämie	
Lipid*	

***** *indicates that also the plural was used in the search*

9.1.2 Included (inter-)national literature

Table 9-2: Overview of included international and national guidance on FH test strategies.

Guideline/position-paper/scientific publication	Year	Country	Organisation (Abbreviation)	Source
Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk	2019	Europe	European Society of Cardiology, European Atherosclerosis Society (ESC/EAS)	[20]
Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation	2014	International	International FH Foundation (IFHF)	[11]
Diagnosis and Management of Familial Hypercholesterolaemia– Position Statement	2016	Australia, New Zealand	The Cardiac Society of Australia and New Zealand (CSAN)	[63]
Familial hypercholesterolaemia: A model of care for Australasia	2011	Australia, New Zealand, Oceania	FH Australasia Network (FHAN)	[48]
Management of familial hypercholesterolemia in children and young adults: Consensus paper developed by a panel of lipidologists, cardiologists, paediatricians, nutritionists, gastroentero-logists, general practitioners and a patient organization	2011	Belgium	NA (Descamps et al.)	[64]
A Belgian consensus strategy to identify familial hypercholesterolaemia in the coronary care unit and its subsequent cascade screening and treatment: BEL-FaHST	2018	Belgium	Belgian Society of Cardiology, Belgian Atherosclerosis Society, Royal Belgian Society of Laboratory Medicine (BSC/BAS/BLC/RBSLM)	[24]
Position Statement on Familial Hypercholesterolemia: Update 2018	2018	Canada	Canadian Cardiovascular Society (CCS)	[18]
Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk in adults	2016	Canada	Canadian Cardiovascular Society (CCS)	[17]
Gendiagnostik bei kardiovaskulären Erkrankungen	2015	Germany	Deutsche Gesellschaft für Kardiologie, Deutsche Gesellschaft für pädiatrische Kardiologie (DGK/DGPK)	[65]
Pocket-Leitlinie: Diagnostik und Therapie der Dyslipidämien	2019	Germany	Deutsche Gesellschaft für Kardiologie (DGK)	[60]
S2k -Leitlinien zur Diagnostik und Therapie von Hyperlipidämien bei Kindern und Jugendlichen	2015	Germany	Arbeitsgemeinschaft für Pädiatrische Stoffwechselstörungen in der Deutschen Gesellschaft für Kinderheilkunde und Jugendmedizin (APS)	[10]
CaRe high – Cascade screening and registry for high cholesterol in Germany	2017	Germany	Schmidt et al.	[66]
Universal screening for familial hypercholesterolemia in children: The Slovenian model and literature review	2018	Slovenia	NA (Groselj et al.)	[67]
Pocketguide: Statin-Intoleranz, Familiäre Hyperlipidämien	2018	Switzerland	Arbeitsgruppe Lipide und Atherosklerose (Schweizer Gesellschaft für Karidologie) (AGLA)	[68]
Familial Hypercholesterolaemia: Implementing a systems approach to detection and management	2018	UK	Public Health England (PHE)	[23]
Familial Hypercholesterolaemia: Identification and mangement	2019	UK	National Institute for health and Care Excellence (NICE)	[15]
Familial Hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients	2011	USA	National Lipid Association (NLA)	[25]
Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines	2019	USA	American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines (AHA/ACC)	[69]

9.1.3 Other components of the (inter-)national FH test strategies

Table 9-3: Summarized overview of other characteristic components of the (inter-)national FH test strategies (part 1).

Country	Europe (ESC/EAS [20])	International (IFHF[11])	Australia, New Zealand, Oceania (CCS [48], FHAN [63])	Belgium (Decamps [64], BSC/BAS/BLC/RBSLM [24])	Canada (CCS [17, 18])
Criteria to suspect FH and tool for diagnosis	> 18 years TC > 310 mg/dL (8.1 mmol/L) premature CHD in case or family member Xanthoma in case or family member Sudden cardiac death in family member Tool: DLCN	Two fasting measures of plasma LDL-cholesterol Patients aged less than 60 years with CVD Family history of hypercholesterolaemia and premature CVD (age < 60 years) Patients with tendon xanthomata and premature arcus cornealis Tools (country-specific): DLCN, SB, MEDPED, Japanese FH criteria Children: Age-, gender- and country -specific plasma LDL-C concentration thresholds, two fasting LDL-C values are recommended High probability of FH: LDL-C ≥ 5.0 mmol/L (absence of a positive parental history of hypercholesterolemia or premature CHD) LDL-C ≥ 4.0 mmol/L (presence of a positive parental history of hypercholesterolemia or premature CHD)	Adults: DLCN Children: Age- and gender-specific plasma LDL-cholesterol concentration thresholds should be used to make the phenotypic diagnosis of FH, an LDL-cholesterol ≥5.0 mmol/L (194 mg/dL) indicating highly probable/definite FH; two fasting lipid pro-files are recommended	CCU: 1st (in hospital): LDL-C >190 mg/dL (4.9 mmol/L) without treatment, or >130 mg/dL (3.4 mmol/L) on LLD(s); onset of CVD <65 years; 2nd (after hospital): DLCN (incl. genetic testing if DLCN >5) Children: 1st: LDL-C levels (when suspicious for FH: TC, TG, HDL-C), 2nd: lipid profile (+ biochemical analysis and Lipoprotein-A); 3rd: lipid profile after 2 to 3 months of diet Final diagnosis of FH: Confirm vertical transmission (collect cholesterol data of the relatives), Confirm HeFH in one of the parents (includes genetic testing, if needed), LDL-C > 3.5 mmol/L (>135 mg/dL) in the suspected child. NB: if LDL-C < 3.5 mmol/L (<135 mg/dL), repeat the LDL-C measure-ment one year later (<5% HeFH), Confirm by genetic test (LDL-receptor; ApoB)	Men ≥40 years, women ≥ 50 years LDL-C >5 mmol/L (194 mg/dL) (≥ 40 years), LDL-C ≥ 4.5 mmol/L (173 mg/dL) (18-39 years); ≥ 4.0 mmol/L (154 mg/dL) (<18 years), earlier if other ACVD risk factors are present Fasting or non-fasting lipid profile and the LDL-C calculated with the Friedewald formula Tool: FH Canada (national case definition), DLCN, SB
GDx	Recommended if DLCN score ≥6, and in cases with xanthomas and/or hypercholesterolaemia plus premature CHD, in cascade screening, if possible	Recommended, if possible; should be considered to confirm the diagnosis, in cascade screening Fully accredited laboratory should be used; should ideally be offered to all 'index cases' who have a phenotypic diagnosis of FH; when the phenotypic diagnosis is unlikely, genetic testing of the 'index case' need not be carried out Children: only after a pathogenic variant has been identified in a parent or first degree relative; initially when parents or first degree relatives are unknown or deceased, or as an accepted screening practice in certain countries, such as the Netherlands	Should be offered to all index cases who have a phenotypic diagnosis, must be carried out in an accredited laboratory, If the genetic testing protocol does not detect a mutation, the laboratory report should include a caveat that the result does not exclude FH due to undetected mutations or mutations in untested genes, particularly if the clinical phenotype is strongly suggestive of FH	For confirmation of diagnosis, reimbursement if DLCN > 5, reimbursed by National Institute of Health Children: for confirmation of diagnosis, referral to specialist for genetic testing, no need to visit genetic centre, covered by National Institute of Health, may be prescribed by any clinician	When available, to complement a diagnosis of FH and enable cascade screening; Decision to request genetic screening should be made by the treating physician after discussion with the patient, currently not available in most provinces
FH service providers/ referral	-	■ Care pathways for FH should be developed for country-specific and local needs ■ Specialist services should be multidisciplinary based and integrated with primary care ■ Specialist care of FH should ideally be supported by cardiology, paediatric, genetic, imaging, transfusion medicine, nursing, dietetic, psychology, pharmacy and pathology laboratory services.	All patients with possible-to-definite FH should be referred to a lipid disorders clinic for more detailed assessment and institution of cascade screening FH service providers: – Clinical Liaison ■ Medical Laboratory Services ■ Specialised Laboratory for Genetic Testing	CCU: cardiologists in hospitals, outpatient FH specialists Children: GPs, FH specialists (including lipid clinics)	-

Country	Europe (ESC/EAS [20])	International (IFHF[11])	Australia, New Zealand, Oceania (CCS [48], FHAN [63])	Belgium (Decamps [64], BSC/BAS/BLC/RBSLM [24])	Canada (CCS [17, 18])
FH service providers/ referral *(continuation)*		■ Low complexity patients should be managed in primary care, with the option of annual specialist review ■ Higher complexity patients should be managed principally in specialist centres.	■ Clinical Genetics, Family & Genetic Counselling ■ Specialist Nurses & Allied Health Support ■ Administrative, Secretarial & IT Services ■ Specialised Adult-Paediatric Service: Family Clinics ■ Structured Clinical Management Program ■ Specialist & Primary Care Physicians, Physicians-in-training ■ Influencers & Stakeholders ■ Audit & Research Program: Registry, Clinical & basic Science, Clinical trials, Epidemiology & Health Economics ■ Structured Education Program ■ Patient & Family Support Groups ■ Cardiac & Imaging Facilities		
Cascade screening	Recommended, best performed by lipid clinic	■ Notification of relatives at risk of FH should generally not be carried out without the consent of the index case ■ Relatives should only be directly notified of their risk without consent of the index case if there is specific legislative provision for breach of confidentiality in the relevant jurisdiction ■ A proactive approach that respects the principles of privacy, justice and autonomy is required ■ should ideally be co-ordinated by a dedicated centre and should not be carried out in primary care without central co-ordination, particularly if employing DNA testing ■ should be carried out using both a phenotypic and genotypic strategy, but if DNA testing is not available a phenotypic strategy alone should be used ■ should initially be carried out as a priority in first-degree relatives and then extended to second- and third-degree relatives ■ DNA testing makes cascade screening more cost-effective and should be employed to screen family members after the mutation is identified in the index case Children with suspected heterozygous FH should be screened between the ages of 5 and 10 years; age at screening should be similar in boys and girls	Recommended Notification of relatives at risk of FH should not be instituted without the consent of the index case Should ideally be carried out as a for-mal collaborative process between lipid disorders and clinical genetics services. It should also involve close communication and liaison with primary care physicians and employ a user-friendly family based data management system If no consent/assent for genetic testing is obtained phenotypic testing for FH should be offered	CCU: assessment of routine lipids (MEDPED criteria), genetic testing for confirmation Children: after the age of 2 years: In a family where HeFH has been identified or suspect-d (clinical/genetic criteria), in a family with a history of premature cardiovascular disease (<55 (M), <65 (W)), if one parent has primary hypercholesterolaemia	Lipid profile, protocols be implemented at the local, provincial, and national level in Canada and offered to first-degree relatives of patients with FH

Country	Europe (ESC/EAS [20])	International (IFHF[11])	Australia, New Zealand, Oceania (CCS [48], FHAN [63])	Belgium (Decamps [64], BSC/BAS/BLC/RBSLM [24])	Canada (CCS [17, 18])
Genetic counselling	-	Pre-testing counselling should be offered to at risk family members of an index case prior to any form of testing	Pre-testing counselling should be offered to at risk family members of an index case prior to phenotypic or genetic testing Children: Genetic counselling including discussion of the implications of DNA testing in children should be provided at the time the parent receives the genetic results confirming the diagnosis	Children: psychological support and family counselling occasionally required	Should be provided when available
Registry	-	A registry of patients and families should be established for clinical, research and audit purposes	Web-based registry in over 30 sites across Australia	Planned	FH Canada registry
Education/ Awareness	-	Patients: A support group of patients and families should be established as a major priority for enhancing public, government and health care provider awareness, as well as the total quality of care of FH Health care professionals: Medical, nursing and allied health staff managing patients with FH should be accredited in cardiovascular prevention; services should establish partnerships with academic and professional organisations to enhance teaching, training and research	Patients organisation (FH Australasia Network, plus local patient support)	-	-
Lipid-lowering treatment	High intensity statin combined with Ezetimibe and/or Resins PCSK9i are recommended in very-high risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe	Fat-modified, heart-healthy diet and statin therapy with or without ezetimibe	High intensity statin optionally combined with Ezetimibe	CCU: High intensity statin, if the patient is al-ready on low- or moderate-intensity statin, a shift to a high-intensity statin must be considered, combination of statin with Ezetimibe should be considered, PCSK9i should be considered Children: statins as first line drugs, should usually be started after 10 years if LDL-C re-main above 5 mmol/L (190 mg/dL), or above 4 mmol/L (160 mg/dL) in the presence of a causative mutation, a family history of early CVD or severe risk factors	Statins as the primary line of therapy Ezetimibe as second-line agent PCSK9i if needed Children: statin therapy be considered usually between 8 and 10 years of age

Table 9-4: Summarized overview of other characteristic components of the (inter-)national FH test (part 2)

Country	Germany (DGK [60], DGK/DGPK [65], Schmidt 2017[66], APS [10])	Slovenia (Groselj et al. [67])	Switzerland (AGLA [68])	UK (NICE [23], PHE [15])	USA (NLA [25], AHA/ACC [69])
Criteria to suspect FH and tool for diagnosis	According to ESC/EAS guideline Registry: LDL cholesterol > 190 mg/dL (4.9 mmol/L) without lipid lowering therapy (LDL values with lipid lowering therapy are corrected for drug and dose Total cholesterol > 290 mg/dL (7.5 mmol/L) Tendon xanthomas Family history of hypercholesterolaemia Family history of myocardial infarction before the age of 50 in grandparents, uncles, aunts or before the age of 60 in parents, siblings or children First and second degree relatives of FH patients Tool: DLCN Children: lipid profile, TC	Children: TC >5 mmol/L (194 mg/dL) Family history Tool: -	If for the person or a 1st degree relative the following is true: TC ≥8.0 mmol/L (310 mg/dL) or LDL-C ≥5.0 mmol/L (194 mg/dL) or premature atherosclerosis (especially CHD) or Tendon xanthomas or Arcus cornealis <45 years old Tool: DLCN Children: High probability for FH at: LDL-C ≥5.0 mmol/L (194 mg/dL) with two determinations after three months diet or LDL-C ≥4.0 mmol/L (154 mg/dL) and premature CHD in close relatives and/or high cholesterol in one parent, or LDL-C ≥3.5 mmol/L (135 mg/dL) and genetically diagnosed FH in one parent	> 16 years TC > 290 mg/dL (7.5 mmol/L) LDL-C > 190 mg/dL (4.9 mmol/L) Personal or family history of PCHD (before age 60 years) Tool: SB, DLCN	> 20 years LDL-C > 190 mg/dL (4.9 mmol/L) Non-HDL-C > 220 mg/dL (5.7 mmol/L) Tool: MEDPED, DLCN, SB Children: Fasting lipid levels (age <20 years): LDL-C >160 mg/dL (4.2 mmol/L) or non-HDL-C >190 mg/dL (4.9 mmol/L)
GDx	Physician decides if a genetic analysis should be offered to the patient Registry: results of GDx are documented Children: should be carried out in an accredited laboratory using standardised methods that are tested for specific mutations and/or by exon-by-exon sequencing search	Children: obligatory if TC positive for FH, genetic test is reimbursed	Genetic test if DLCN >5, to confirm the diagnosis, if 1st-degree relatives were diagnosed with genetic defects in the cascade screening, in children, even with only moderate hypercholesterolaemia, if one parent died/fell ill prematurely from CHD, no reimbursement (status 2017)	Referral to an FH specialist service for DNA testing if Simon Broome criteria for possible or definite FH, DLCN score > 5, funded when performed in official genomic laboratory hubs, in cascade screening	Not needed for diagnosis or clinical management but may be useful when the diagnosis is uncertain
FH service providers/ referral	Specialist-led, primary care-led, FH specialist study nurses	Children: Primary care level, tertiary care level	-	Specialist-led, primary care-led, dual care models, many FH specialist study nurses GDx: Specialist FH or genetic service, genomic laboratory hubs (GLH), providing tests as set out in the National Genomic Test directory, reimbursed if done by GLH	Primary care, lipid specialist Primary care clinicians should be responsible or screening and diagnosis
Cascade screening	Organised and supported by CaRe-High registry Registry: patient is asked to inform relatives about possible FH diagnosis and the study. If the relative gives his consent, he is contacted by the study nurse to be included into the registry. Relatives will not be contacted directly, thus accounting for German privacy regulations.	Reverse cascade screening, genetic testing of family members	Based on the index case; testing of children, siblings, nieces and nephews of all affected feature carriers Examinations: at least lipid status, risk factors, ideally gene mutation, no reimbursement (status 2017)	Genetic testing of all affected first- and second- and, when possible, third-degree biological relatives of people with a genetic diagnosis of FH Children: systematic cascade testing indicated due to confirmed diagnosis in relative	Cascade screening involves testing lipid levels in all first-degree relatives of diagnosed FH patients Children and adolescents found to have moderate or severe hypercholesterolaemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolaemia.

Country	Germany (DGK [60], DGK/DGPK [65], Schmidt 2017[66], APS [10])	Slovenia (Groselj et al. [67])	Switzerland (AGLA [68])	UK (NICE [23], PHE [15])	USA (NLA [25], AHA/ACC [69])
Cascade screening *(continuation)*	Children: After diagnosis of hyperlipidaemia in a child or adolescent who is not classified as secondary consequence of an underlying disease, should also 1st degree relatives be examined for the presence of primary genetic hyperlipidaemia (targeted anamnesis and fasting blood collection from parents and siblings). In all children who have at least one parent with confirmed hypercholesterolaemia, a determination of the lipid values should be carried out.				
Genetic counselling	Pre-/post genetic diagnosis	Children: post genetic diagnosis	-	Pre-/post genetic diagnosis Healthcare professional with expertise in FH	-
Registry	Nationwide CaRe-High registry	National registry	-	Nationwide, for co-ordination of cascade screening	CASCADE FH Registry
Education/ Awareness	DGFF: advanced training (certified lipidologist), certification of specialised lipid clinics and lipid centres, information of physicians and general public via website, educational activities, and information materials to improve diagnostic and treatment. Registry: aims to intensify communication within the medical community Patients organisation (CholCo e.V.)	-	Patients organisation	Healthcare professionals should be aware of the latest guidance on data protection when undertaking cascade testing and should offer people with FH and their families written advice and information about patient support groups	Public and provider awareness: To promote early diagnosis of FH and the prevention, and treatment of CHD, public awareness of FH needs to be increased by a variety of methods Health care provider awareness needs to be increased through education at all levels and in multiple specialties, through partnering with professional organisations and through local, national and international health agencies. Responsibility for education: Health systems, hospitals, pharmacy benefits management organisations, and insurance companies should contribute to patient and provider education Governmental agencies and other policymakers at local, state, national and international levels should be engaged in efforts to screen and treat FH

Country	Germany (DGK [60], DGK/DGPK [65], Schmidt 2017[66], APS [10])	Slovenia (Groselj et al. [67])	Switzerland (AGLA [68])	UK (NICE [23], PHE [15])	USA (NLA [25], AHA/ACC [69])
Lipid-lowering treatment	According to ESC/EAS guideline Children: Statins, ezetimibe	Statins	1st stage: Highly intensity statin in maximum tolerable dose; if the target values are not reached, additional ezetimibe. 2nd stage: If the target values are not reached with statins/ezetimibe: consider PSCK9i Children: 1st stage: statins (approval from 8 years) 2nd stage: Ezetimibe (approval from 10 years), hytosterols/stanols (nutraceuticals, from 6 years)	High intensity statin Ezetimibe combined with statin when LDL-C is not controlled with high intensity statin Ezetimibe in monotherapy when statins are contraindicated or not tolerated	High intensity statin Consider to add Ezetimibe and resins Patients 30–75 years with FH and with on-treatment LDL-C ≥100 mg/dL (2.6 mmol/L) despite maximally tolerated statin and ezetimibe therapy, consider PCSK9i

- No information given

Abbreviations: *ACVD – arteriosclerotic cardiovascular disease, AGLA – Arbeitsgruppe Lipide und Atherosklerose in der Schweizer Gesellschaft für Karidologie, AHA/ACC – American Heart Association Task Force on Clinical Practice Guidelines, American College of Cardiology, APS – Arbeitsgemeinschaft für Pädiatrische Stoffwechselstörungen in der Deutschen Gesellschaft für Kinderheilkunde und Jugendmedizin, BSC/BAS/BLC/RBSLM – Belgian Society of Cardiology, Belgian Atherosclerosis Society, Royal Belgian Society of Laboratory Medicine, CCS – Canadian Cardiovascular Society, CCU – coronary care unit, CHD – coronary heart disease, CSAN – The Cardiac Society of Australia and New Zealand, CVD – cardiovascular disease, DGFF – Deutsche Gesellschaft zur Bekämpfung von Fettstoffwechselstörungen und ihren Folgeerkrankungen (lipid-Liga) e.V., DGK – Deutsche Gesellschaft für Kardiologie, DGPK – Deutsche Gesellschaft für pädiatrische Kardiologie, DLCN – Dutch Lipid Clinic Network diagnostic criteria, ESC/EAS – European Society of Cardiology, European Atherosclerosis Society, FH – familial hypercholesterolaemia, FHAN – Familial Hypercholesterolaemia Australasia Network, GDx – genetic diagnostic, GP – general practitioner, HDL-C – High density lipoprotein cholesterol, IFHF – International FH Foundation, LDL-C – Low density lipoprotein cholesterol, NICE – National Institute for health and Care Excellence, NLA – National Lipid Association, PCSK9i – proprotein convertase subtilisin kexin 9 inhibitor, PHE – Public Health England, SB – Simon Broome diagnostic criteria, TC – Total cholesterol, UK – United Kingdom, USA – United States of America*

9.1.4 PCSK9 inhibitors – FH-specific reimbursement criteria

Table 9-5: PCSK9 inhibitors – FH-specific reimbursement criteria according to EMA and selected countries (part 1).

PCSK9i	EU	Australia	Belgium
Product (Substance)	Praluent® (Alirocumab) Repatha® (Evolocumab)	Praluent® (Alirocumab) Repatha® (Evolocumab)	Praluent® (Alirocumab) Repatha® (Evolocumab)
Regulatory status	Approved	Approved	Approved
Reimbursement	not applicable	yes, Repatha conditional	yes, conditional
Indications as approved	Praluent: in adults with Primary hypercholesterolaemia (HeFH and non-familial) or mixed dyslipidaemia, as an adjunct to diet: ■ in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, ■ alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated Established ACVD to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors: ■ in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or, ■ alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated Repatha: in adults with Primary hypercholesterolaemia (HeFH and non-familial) or mixed dyslipidaemia, as an adjunct to diet: ■ in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, ■ alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. Established ACVD (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors: ■ in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or, ■ alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated in adults and adolescents aged 12 years and over with HoFH in combination with other lipid-lowering therapies	Praluent: in adults with Primary (HeFH or non-familial) hypercholesterolaemia as an adjunct to diet and exercise to reduce LDL-C in patients with moderate to very high cardiovascular risk: ■ in combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with maximum tolerated dose of a statin; ■ alone or in combination with other lipid lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated who are unable to reach LDL-C goals. Prevention of CV events to reduce the risk of cardiovascular events (myocardial infarction, stroke, unstable angina requiring hospitalisation) in adults with established cardiovascular disease, in combination with optimally dosed statins and/or other lipid-lowering therapies Repatha: in adults with CV events (myocardial infarction, stroke and coronary revascularisation) in combination with an optimally dosed statin and/or other lipid-lowering therapies Primary Hypercholesterolaemia (including HeFH and non-familial hypercholesterolaemia) to reduce LDL-C: ■ in combination with a statin or statin with other lipid lowering therapies, or ■ alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant in adults and adolescents aged 12 years and over with HoFH in combination with other lipid-lowering therapies	-

PCSK9i	EU	Australia	Belgium
Indications for reimbursement	not applicable	Repatha: Familial homozygous hypercholesterolaemia, initial treatment Criteria: ■ treatment must be in conjunction with dietary therapy and exercise, AND ■ condition must have been confirmed by genetic testing; OR ■ condition must have been confirmed by a DLCN score ≥ 7, AND ■ patient must have an LDL-C level in excess of 2.6 mmol/l, AND ■ patient must have been treated with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) according to the TGA-approved Product Information or the maximum tolerated dose of atorvastatin or rosuvastatin for at least 12 consecutive weeks in conjunction with dietary therapy and exercise; OR ■ patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; OR ■ patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information. qualifying LDL-C level following at least 12 consecutive weeks of treatment with a statin (unless treatment with a statin is contraindicated or following completion of statin trials as described in these prescriber instructions in the event of clinically important adverse events) must be stated at the time of application, documented in the patient's medical records and must be no more than 8 weeks old	FH reimbursement criteria: ■ DLCN>8 and LDL-C >130mg/dL or ■ LDL-C >100mg/dL if a history of acute coronary syndrome present
Health service provider	not applicable	specialist physician for reimbursement	-

Table 9-6: PCSK9 inhibitors – FH-specific reimbursement criteria according to EMA and selected countries (part 2).

PCSK9i	Canada	Germany	Slovenia
Product (Substance)	Praluent® (Alirocumab) Repatha® (Evolocumab)	Repatha® (Evolocumab) (Praluent® (Alirocumab) currently no market approval due to patent infringement)	Praluent® (Alirocumab) Repatha® (Evolocumab)
Regulatory status	Approved	Approved	Approved
Reimbursement	yes, conditional	yes, conditional	yes, conditional
Indications as approved	-	-	-
Indications for reimbursement	Recommendation for reimbursement: Praluent: in adults with HeFH as an adjunct to diet and maximally tolerated statin therapy who require additional LDL-C, if the following clinical criteria and condition met: ■ Patient has a confirmed diagnosis of HeFH ■ Patient is unable to reach the target LDL-C level specified in current guidelines ■ Patient is currently receiving optimally tolerated standard of care (maximally tolerated statins (MTS) with or without ezetimibe) Clinical ACVD as an adjunct to diet and maximally tolerated statin therapy in adult patients at high risk for CV events, who require additional lowering of LDL-C, if the following clinical criteria and condition are met: ■ Patient is unable to reach the target LDL-C level specified in current guidelines ■ Patient is currently receiving optimally tolerated standard of care Repatha: in adults who require additional lowering of LDL-C with HeFH Clinical ACVD as an adjunct to diet and maximally tolerated statin therapy	Repatha: cannot be prescribed as long as it is associated with additional costs compared to a therapy with other lipid-lowering agents (statins, fibrates, anion exchangers, cholesterol absorption inhibitors). This does not apply to patients with HoFH in which drug and dietary options for lipid reduction have been exhausted, or HeFH or non-familial hypercholesterolaemia or mixed dyslipidaemia in therapy-refractory courses in which, in principle, despite maximum dietary and drug lipid-lowering therapy documented over a period of 12 months (statins and/or other lipid-lowering drugs with statin contraindication), the LDL-C value cannot be sufficiently reduced and it is therefore assumed that there is an indication for LDL apheresis. Only patients with confirmed vascular disease (coronary heart disease, cerebrovascular manifestation, PAC) and other risk factors for cardiovascular events (e.g. diabetes mellitus, renal function GFR below 60 ml/min) are eligible for this treatment, as well as patients with confirmed familial heterozygous hypercholesterolemia, taking into account the overall risk of familial exposure.	FH in adults with LDL-C >5.0 mmol/L, >4.0mmol/L or >3.6mmol/L in primary prevention, secondary prevention or progressive CVD, respectively, on maximal statin/ezetimibe (or with documented statin intolerance)
Health service provider	-	Initiation and monitoring of the therapy by specialist for internal medicine and cardiology, for specialist for internal medicine and nephrology, for internal medicine and endocrinology and diabetology, for internal medicine and angiology or by specialists working at outpatient clinics for lipid metabolism disorders Further prescriptions by all medical specialists, e.g. general practitioners	-

Table 9-7: PCSK9 inhibitors – FH-specific reimbursement criteria according to EMA and selected countries (part 3).

PCSK9i	Switzerland	UK	USA
Product (Substance)	Praluent® (Alirocumab) Repatha® (Evolocumab)	Praluent® (Alirocumab) Repatha® (Evolocumab)	Praluent® (Alirocumab) Repatha® (Evolocumab)
Regulatory status	Approved	Approved	Approved
Reimbursement	yes, conditional	yes, conditional	-
Indications as approved		-	Praluent: in adults with HeFH as an adjunct to diet and maximally tolerated statin therapy Clinical ACVD, who require additional lowering of LDL-C Repatha: in adults with Established CVD to reduce the risk of myocardial infarction, stroke, and coronary revascularization Primary hyperlipidemia (including HeFH) as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), to reduce LDL-C in patients with HoFH as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) who require additional lowering of LDL-C
Indications for reimbursement	Praluent: in adults in conjunction with a diet and in addition to a maximum tolerated dose of an intensified LDL-C-lowering therapy for the treatment of the following conditions Severe HeFH with LDL-C > 5 mmol/l in primary prevention or with LDL-C > 4.5 mmol/l with at least one of the following additional risk factors: diabetes mellitus, elevated lipoprotein(a) > 50 mg/dL, severe arterial hypertension or premature clinically manifest familial ACVD (<55 years in men, <60 years in women) Clinical ACVD in secondary prevention and an LDL-C >3.5 mmol/l, and/or progressive clinical ACVD (repeated acute coronary syndrome, myocardial infarction, stroke, or unplanned repeated coronary revascularisation within 5 years after the first cardiovascular event) with an LDL-C > 2. 6 mmol/l Praluent is only reimbursed if an additional LDL-C reduction is medically necessary due to the very high cardiovascular risk, i.e. ■ if the above-mentioned LDL-C values cannot be achieved for at least 3 months with the maximum tolerated dose of an intensified LDL-C-lowering therapy with at least two different statins with or without Ezetimib (or Ezetimib with or without further lipid-lowering agents in the case of statin intolerance) and	Praluent: adults with Primary hypercholesterolaemia (HeFH and non-familial) or mixed dyslipidaemia, as an adjunct to diet: ■ in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, ■ alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. Established ACVD (myocardial infarction, stroke or peripheral arterial disease) to reduce CV risk by lowering LDL-C levels, as an adjunct to correction of other risk factors: ■ in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or, ■ alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated	-

PCSK9i	Switzerland	UK	USA
Indications for reimbursement *(continuation)*	■ if the arterial blood pressure is controlled and ■ if the blood sugar is set to an HbA1c less than 7.5% and ■ if the aim is to abstain from nicotine. An intolerance to statins is deemed to be proven if ■ therapy trials with several statins for myalgia or ■ an increase in creatinine kinase to at least five times the upper normal value, or ■ if a severe hepatopathy has occurred as a result of a statin Treatment may only be continued if, in a control 6 months after the start of treatment, the LDL-C has fallen by at least 40% compared with the initial value under the maximum intensified lipid-lowering therapy or if an LDL-C value of less than 1.8 mmol/l has been reached. Repatha: in adults to accompany a diet and in addition to a maximum tolerable statin dose with or without other lipid-lowering therapies Severe HeFH Clinical ACVD in adults and adolescents aged 12 years and older with HoFH who require additional LDL-C lowering	Repatha: in adults with Primary hypercholesterolaemia (HeFH and non-familial) or mixed dyslipidaemia, as an adjunct to diet: ■ in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, ■ alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated Established ACVD (myocardial infarction, stroke or peripheral arterial disease) to reduce CV risk by lowering LDL-C levels, as an adjunct to correction of other risk factors: ■ in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or, ■ alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated in adults and adolescents aged 12 years and over HoFH in combination with other lipid-lowering therapies	
Health service provider	Diagnosis and initial prescription as well as regular check-ups must be carried out by a medical specialist in angiology, diabetology/endocrinology, cardiology, nephrology, neurology, or by qualified hypercholesterolemia experts	-	-

Abbreviations: ACVD – arteriosclerotic cardiovascular disease, CHD – coronary heart disease,, CVD – cardiovascular disease, FH – familial hypercholesterolaemia, HeFH – heterozygous familial hypercholesterolaemia, HoFH – homozygous familial hypercholesterolaemia, LDL-C – low density lipoprotein cholesterol, LLT – lipid-lowering treatment

9.2 FH in Austria – Current test strategy and diagnostic processes

9.2.1 Guidance for expert interviews

- *Prevalence in Austria:*

  What is the prevalence of FH in Austria?
  Are there regional differences in the diagnosis of frequency of FH within Austria?

- *Diagnosis of index patients:*

  Who diagnoses of the index patient (GP/specialist/special clinic)?

- *Patient flow*:

  How is FH patient flow characterized in general (first diagnosis/referral to a special clinic/therapy/ further procedure)? Which (medical) services and actors are involved in the FH diagnosis process?

- *Molecular genetic diagnosis*:

  How is the molecular genetic diagnosis of the FH carried out? Which medical services are involved? Which changes in the requirements for personnel, material and organisation of the service provision (structure) would bring an intensified molecular genetic diagnosis with it? Which molecular methods are used? Are all clinical (suspected) cases examined by molecular genetics? If not, why? What is the proportion of diagnoses confirmed by molecular genetics in all FH diagnoses? How many molecular genetic tests for FH are done in Austria each year?

- *Genetic counselling*:

  How is genetic counselling integrated in the current diagnosis of FH in Austria?
  At what time point does it take place? Who carries out genetic counselling?
  How could genetic counselling be made mass-compatible in Austria?

- *Cascade screening*:

  How is cascade screening of relatives of FH index patients organised in Austria?
  Which medical services are involved? How are relatives contacted?
  Are there differences in the diagnostic methods between index and follow-up patients?
  How many family members are diagnosed based on 1 index patient?

- *Registry:*

  How far is the Austrian FH Register implemented? What is the current status?

- *Post-diagnosis management*:

  How are FH patients in Austria stratified regarding their ACVD risk?

- *Awareness and education:*

  What is the awareness of the FH in Austria? Among the medical profession?
  Among the general population? Are there information campaigns? To whom are they addressed?

- *Personal comments:*

  How could the identification/finding of FH index patients in Austria be improved/more efficient?
  What do you think is missing? What options for systematic screening are possible? What would be the organisational requirements/challenges for a more systematic patient identification?
  Do results of genetic test influence decisions of insurance companies, employers etc.?

9.3 Ethical and regulatory aspects

9.3.1 FH specific ethical and regulatory aspects

Table 9-8: Identified ethical aspects concerning molecular genetic testing for FH for diagnostic (and predictive) purposes in general and special aspects concerning cascade screening

Overarching question	Group	Ethical aspect	Citation
What are the morally relevant issues related to the disease and the patient/patient group?	P	Dimension of the disease burden that is relevant in this assessment	*"FH is a common codominant monogenic dyslipidaemia causing premature CVD due to lifelong elevation of plasma levels of LDL-C. If left untreated, men and women with HeFH typically develop early CAD before the ages of 55 and 60 years respectively." [20]*
			"The pooled prevalence of FH from 19 studies including 2 458 456 unique individuals was 0.40% (95% CI 0.29% to 0.52%) which corresponds to a frequency of 1 in 250 individuals." [133]
			"While FH affects males and females equally, regional and age-specific variations exist in FH frequency." [133]
	P	Prevention of damage and treatment of FH	*"An individual with FH has a very high relative risk care of developing premature CAD (>9-fold higher)" [120]*
			"The risk of CHD among individuals with definite or probable HeFH is estimated to be increased at least 10-fold. However, early diagnosis and appropriate treatment can dramatically reduce the risk for CAD." [20]
			"... the Danish study revealed a low bias in each of the 4 selection bias criteria and 2 attrition risk criteria. Fatal and nonfatal CVD events were collected in the study. Comparing patients with FH versus non-FH patients, the odds ratios for coronary artery disease were 10.3 (95% CI, 7.8–13.8) and 13.2 (95% CI, 10.0–17.4) in subjects treated and not treated with lipid-lowering therapy, respectively. These ratios fall within the ranges of ratios reported in other studies but are generally higher than the ratios from registries and clinics, in which intensive specialized management is available." [116]
			"The concept of cumulative cholesterol burden illustrates the importance of early treatment. Treatment should be initiated with high-intensity statin therapy, in most cases in combination with ezetimibe." [20]
			Early diagnosis and medical management beginning in childhood with statins and other LLTs have the potential to reduce the incidence of atherosclerosis in patients with FH to that of individuals without FH" [2]
			"FH genetic testing provides prognostic information and the ability to perform refined risk stratification. Within the Myocardial Infarction Genetics Consortium case control cohort populations, the risk for CAD was higher in FH pathogenic variant carriers compared with non-carriers at any LDL-C value" [2]
	CS	Paediatric population	*"If left untreated, children with FH will be at higher risk of coronary events as adults because of the cumulative burden of elevated LDL-C levels, with many experiencing their first cardiovascular event at a young age." ... "Depending on the age of initiating statin therapy, the cumulative LDL-C burden can be lowered to an extent that the LDL-C burden in the patient may be comparable to a non-affected individual." [2]*
			"responses to screening seemed to vary according to perceptions of the underlying cause of the positive screening test result. When parents perceived the test as detecting raised cholesterol the condition was perceived as familiar, dietary in origin, controllable and less threatening. When the test was seen as detecting a genetic problem, the condition was perceived as uncontrollable and, hence, more threatening."[118]
			"Research has shown favourable parental attitudes towards genetic testing in children, and testing can be accomplished via readily accessible sample types, including saliva and buccal swabs" [2]
	P	Personal utilisation psychological impact	*"Data suggest that a DNA-based diagnosis of FH seems to have minimal adverse psychological impact, and genetic testing for FH is not perceived as anxiety provoking." [2]*
			"... interviews have shown that receiving a molecular diagnosis of FH could provide reassurance to patients that diet and lifestyle factors were not the primary cause of their condition." [2]

Overarching question	Group	Ethical aspect	Citation
			"Some interviewees reported concerns related to their medication and feelings of guilt when not complying with treatment recommendations. However, none of the respondents expressed sustained emotional distress or would have preferred to be ignorant of their diagnosis. Apart from being more observant about food intake, their awareness of FH did not appear to have had a substantial impact on their way of life. In fact, those who did not suffer from any other diseases generally regarded themselves as healthy." [117]
	P	The role of screening	Screening for FH index patients and cascade screening of at-risk relatives is recommended by many medical guidelines (see section 5.1).
	CS	Vulnerability	As cascade screening aims to identify FH patients at a very young age (childhood), the target populations represents a vulnerable group
	CS	Cascade screening can reduce the average age of diagnosis	*"Cascade testing can also reduce the average age at which relatives with FH are diagnosed compared with the age of diagnosis for index patients." [2]*
	D	The "classic" FH clinical presentation has changed over time	*"... secular trends in the United States including decreased saturated fat intake and increased use of statins have led to decreases in average LDL-C levels across the population in general" [121]*
			"The "classic" FH clinical presentation has changed over time due to statin treatment and potentially due to decreased saturated fat intake" [2]
What are the ethical, social, cultural, legal, and religious challenges related to the health technology?	CS	Disclosure – Contacting family members for cascade screening	*"... contacting members of the family who are at 50% risk or less of being heterozygous for FH, but who live at a distance, who may not be in a regular contact with the nuclear family, and do not live in the same health district. Contacting such individuals 'out of the blue' raises medical and ethical problems, particularly when such individuals decline testing." [120]*
			"IPs revealed that they generally alerted their first-degree relatives of the genetic risk because they felt morally obliged to do so or because they were advised to do so by a health professional. However, IPs rarely alerted their more distant relatives due to insufficient risk knowledge or fear of being perceived as interfering in their relative's affairs." [119]
			"Furthermore, many IPs stated that they would not seek to persuade a relative to undergo testing out of respect for their autonomy."[119]
	CS	Expert lead active approach of disclosure. The example of the stopped Dutch programme	*"Policy documents mentioned paternalism as a drawback of the previous proactive and direct approach, stressing that patients should be responsible to seek healthcare autonomously. However, respondents held various opinions whether this objection was important enough to ban such direct approaches, given the otherwise substantial health gain. In weighing pros and cons, ideas of patient autonomy play an important role, such as in policy, though the ways forward envisaged by the interviewed stakeholders, based on such notions, varied."[126]*
			"However, the findings did suggest that less direct methods were used for persuasion. An example would be stressing the severity of the condition. Consequently, the self-reported disclosures were incomplete and unbalanced. Typically, IPs provided information regarding the threat of inherited high cholesterol without furnishing information on means of coping with the risk. As IPs want and need professional support to help them disclose this information to their relatives…"[119]
	CS	Reasons for disclosure	*"The IPs' reasons for disclosure varied from simple compliance with a professional's advice to more complex moral, social and emotional motivations. IPs revealed that many factors were influenced by familial, institutional and communal contexts." [119]*
	CS	Reasons for non-disclosure or delayed disclosure	*"Reasons for non-disclosure or delaying disclosure varied. They included risk awareness reasons such as a limited risk perception, low self-efficacy expectations regarding disclosure competence, and moral and social reasons. These reasons were also influenced by familial, institutional, policy and community contexts." [119]*
			"First-degree relatives were alerted more often than more distant relatives, possibly due to: (a) unawareness of the distant relatives' risk; (b) a perception that disclosing to distant relatives was interfering; and (c) a perception of a higher moral duty towards relatives that were close and more frequently contacted. Yet, regarding relatives of the same degree, some were alerted more often than others. These differences can be explained by IPs' preferences in emotional support seeking, the responsibility to protect certain relatives from the psychological harm of knowing, expected rejection of the information, and also by the frequency of contact." [119]
	I/CS	Misclassification of severe HeFH and compound FH has implications on family members.	*"... without genetic testing, these FH probands with 2 mutations may be misclassified as having severe HeFH, and this misclassification could have negative consequences for the proper identification of all at risk relatives if it is not known that both sides of the family are at risk due to the presence of 2 mutations in the proband." [2]*

Overarching question	Group	Ethical aspect	Citation
	CS	Disclosure	*"Cascade testing: FH probands should receive a recommendation to warn at-risk relatives about their risk for FH." [2]*
	CS	Disclosure – Privacy	*"Privacy: individuals with FH may experience difficulty in communicating their genetic testing results to at-risk relatives, and may experience a loss of privacy in doing so." [2]*
			"Privacy was seen as potentially at odds with direct contacting of family members, while also trespassing the right not to know was mentioned." [126]
	CS	Intra-familial conflicts – Parental guilt	*"Parental guilt: parents may experience feelings of guilt related to passing their pathogenic variant(s) to children; in this situation, it may be helpful to emphasize the benefits provided by this information in children because early and sufficient lipid-lowering therapy will effectively reduce the risk of heart disease to that of the general population." [2]*
	CS	Intra-familial conflicts – Survival guilt	*"Survival guilt: individuals in the family who test negative for the familial pathogenic variant may experience feelings of guilt; however, it is important to explain that early and sufficient lipid-lowering therapy in family members with the familial pathogenic variant will effectively reduce the risk of heart disease to that of those without the pathogenic variant." [2]*
	CS	Family members who test negative for the known variant will be relieved by the knowledge of being unaffected and having no risk to pass the familial pathogenic variant to their offspring	*"Cascade genetic testing also identifies those relatives who did not inherit the familial pathogenic variant and therefore are highly unlikely to have FH (unless inherited from the unrelated parent). This outcome is of high personal utility, as relatives who test negative will be relieved by the knowledge of being unaffected and having no risk to pass the familial pathogenic variant to their offspring." [2]*
	S	Costs of genetic testing	*"Individuals may want to undergo genetic testing, but the cost and/or lack of insurance coverage may limit ability to obtain testing." [2]*
			"Costs continue to decrease over time, due in part to the use of next-generation sequencing (NGS) technologies." [2]
			"Site-specific genetic testing for the known pathogenic variant(s) in at-risk relatives (cascade genetic testing) is performed at a considerably lower cost." [2]
What are the moral challenges with structural changes related to the health technology?	D	Underutilisation	*"Although genetic testing has the potential to improve diagnosis and provide prognostic data and accurate risk assessment, data from the CASCADE FH (Cascade Screening for Awareness and Detection of FH) Registry indicate that FH genetic testing is underutilized for patients in the United States, with genetic testing reported in 3.9% of individuals in the registry with a clinical diagnosis." [2]*
	D	Overmedicalisation	Overlap of typical LDL-C ranges of common hypercholesterolaemia and HeFH
What are the moral issues related to the characteristics of the health technology?	I	FH genetic testing is not completely sensitive or specific	*"For those designated according to clinical diagnostic criteria as "definite" FH, a pathogenic variant in 1 of the 3 known FH-causing genes can be identified in ~60% to 80%; in "possible" FH, the yield is lower (~21% to 44%)" ... "genetical sensitivities ranging from ~60% to 95%. Therefore, a negative genetic test result in a patient with an FH phenotype as defined by using clinical criteria does not exclude a diagnosis of FH. Negative genetic test results may be due to technical limitations and/or the presence of mutations in yet to-be identified genes." [2]*
	I	Mutation variant interpretation is of paramount importance, there a variants that show unknown significance	*"Accurate variant interpretation is of paramount importance in the application of clinical genetic testing" … The LDLR variant database includes variant classification information based on the 2013 published guidelines from the Association for Clinical Genetic Science. In this recently updated LDLR variant database, 7% of variants are currently classified as variants of unknown significance" [2]*
	I	GDx aids diagnosis of patients with pathogenic variants who do not meet clinical diagnostic criteria	*"... the ability to distinguish those with FH from those with elevated cholesterol levels due to other reasons is complicated by an overlap in LDL-C levels between individuals with and without an FH pathogenic variant. Discrimination based on LDL-C levels is best in youth, but because LDL-C rises with age, overlap increases between those with an FH pathogenic variant and those without. Genetic testing can help distinguish these 2 groups of individuals." [2]*
			"Genetic testing aids FH diagnosis by identifying those with pathogenic variants who do not meet diagnostic criteria based on lipid levels, clinical and physical features, and/or family history." [2]
	I	Challenges in ACVD risk stratification based on genetic testing	*"... the effects of all these risk-associated mutations will be highly modifiable by the co-inheritance of other genetic factors and the presence of environmental factors, for example which may result in marked obesity, high blood pressure, insulin resistance, etc." [120]*

Overarching question	Group	Ethical aspect	Citation
	I	Prevalence of FH pathogenic variant in clinical diagnosed patients	*"The prevalence of FH pathogenic variants in adults with LDL-C levels ≥190 mg/dL and no additional clinical or family history data is ~2% (7,36). Therefore, not every patient with LDL-C levels ≥190 mg/dL should be considered to have FH. However, the prevalence of genetically confirmed FH in patients with acute coronary syndrome who are ≤65 years of age and with LDL-C levels ≥160 mg/dL is ~9%" [2]*
	I	GDx increases the number of patients with FH identified per family.	*"Moreover, knowledge of the pathogenic variant in the family increases the number of patients with FH identified per family. This concept is supported by findings from the Czech national database: in families with a known causal pathogenic variant, the number of patients with FH per family is on average 1.77, whereas in families without this information it is 1.18" [2]*
	I	Identification of a pathogenic variant, or variants, in the FH proband allows for targeted, site-specific cascade genetic testing in at-risk relatives	*"Identification of a pathogenic variant, or variants, in the FH proband allows for targeted, site-specific cascade genetic testing in at-risk relatives, with very high sensitivity and specificity. This approach can provide unambiguous results for relatives with and without FH." [2]*
	C	LDL-C cut-off may differ among countries, races and ethnic backgrounds	*"It is important to note that the LDL-C cut points used to offer or consider FH genetic testing may differ among countries, as well as between individuals of different races and ethnic backgrounds." [2]*
	S/I	Willingness of clinicians to initiate cascade screening	*"The availability of DNA tests will not only confirm the clinical diagnosis for the patient, but may have a major impact on the willingness of clinicians to carry out testing in relatives, since unequivocal results can now be obtained." [120]*
	C/CS	LDL-C levels in FH and non-FH relatives overlap	*"Cascade testing can be performed by using analysis of LDL-C levels alone, but this approach has sensitivity and specificity issues. LDL-C levels in FH and non-FH relatives overlap considerably, especially in adults. A substantial number of relatives who inherit the causal pathogenic variant have some degree of reduced penetrance" and LDL-C levels that, although usually elevated, would not qualify them for a clinical diagnosis of FH. In some cases, individuals with genetically proven FH also carry genetic variation associated with lower LDL-C levels." [2]*
	C/CS	Cascade screening based on LDL-C could stop due to inappropriate thresholds	*"If only LDL-C levels are used for cascade screening, and are below a pre-defined threshold, the screening cascade is at risk of stopping at family members who carry the causal pathogenic variant. DNA testing, however, yields unambiguous cascade testing results for at-risk relatives." [2]*
	C	Limitations to the clinical sensitivity of a family history	*"There are also limitations to the clinical sensitivity of a family history of cardiovascular disease, which is part of all published diagnostic criteria for FH. These limitations can be due to several reasons, including reduced penetrance, affected relatives receiving LLT (thereby masking" the hypercholesterolaemia and coronary heart disease phenotype), the reduced clinical sensitivity and/or specificity of self-reported family history, as well as the simple unavailability of reliable family history information. Only 41% of children with a molecularly confirmed FH diagnosis in a Slovenian national universal lipid screening program had a family history of cardiovascular disease." [2]*
	C	Limitations of clinical diagnosis in children	*"In the absence of molecular genetic testing, there are limitations to diagnosing FH in children, as the DLCNC are not valid in children; thus, the diagnosis relies on family history and serial fasting plasma LDL-C measurements. The Simon Broome diagnostic criteria can be applied to children <16 years of age, using lower total cholesterol and LDL-C cut points, in the setting of tendon xanthoma or positive family history." [2]*
What are the moral issues related to stakeholders?	S	Therapeutic choices/decisions	*Particularly in patients with severe HeFH or HoFH, molecular genetic test results may influence therapeutic choices." [2]*
			"It must be emphasized that because not all patients with phenotypic FH have identifiable pathogenic variants, these medications should not be denied to patients with the clinical diagnosis of FH in whom detectable pathogenic variants cannot be detected." [2]
			"Understanding the value of genetic testing for precision medicine in lipid treatment is currently being studied. Having the capability to guide pharmacological therapies and improving our understanding of gene–gene and gene–environment interactions may affect patient outcomes. Further research is needed to evaluate how information from genetic testing can improve medication adherence and outcomes for patients with FH." [2]
			"For those with FH, recommended medical management can be initiated, and it has been well documented that identifying affected relatives by using cascade genetic testing has significant therapeutic consequences, as reviewed by Leren et al. Specifically, in the Netherlands, the proportion of adult affected relatives receiving LLT increased from 39% at the time of genetic testing to 93% 1 year after, and in affected but previously untreated adult relatives, a 23% reduction in total serum cholesterol level was observed 1 year after testing." [2]

Overarching question	Group	Ethical aspect	Citation
	S	Genetic discrimination for life, health, and disability insurances	*"Active identification by DNA testing has social implications such as difficulties in obtaining life and disability insurance."... "Risk assessment should be based on phenotype, that is, lipoprotein profile and the presence of classical cardiovascular risk, instead of the LDL receptor gene mutation. Applicants with FH should be accepted at normal rates if LDL-c levels are <4.0 mmol/L, in the absence of additional risk factors." [123]*
			"... healthy individuals with a genetic diagnosis of FH (i.e. hypercholesterolaemia, but no CAD) being denied life assurance or health assurance." [120]
			…individuals requesting such insurance are usually asked for information about their own health and that of their relatives, and the individuals may also have a medical check-up including a measurement of plasma cholesterol, and thus an individual with FH may be identified anyway." [120]
	S	Genetic counselling and informed consent	*"The domains informed consent and withholding information are related to each other as they both deal with informing the patient. The professional has to decide which information is relevant for the patient to make an informed and autonomous decision while not being overburdened. The counselling professional has to make sure not to be directive and is through the selection of information in charge of the patient's autonomy. This relates to Rantanen et al.'s (2008) [124] observation about contradictory aspects in the guidelines. They described that due to information selection for the needs of each patient the information would not be objective and decision making could be directed in some way"[124]." [99]*
	S	Medical professionals and non-directiveness– in general, not FH specific, Austria	*"Non-directiveness is seen as a major principle for genetic counseling in Austria, and it seems that medical professionals mostly have internalized this principle as they do not declare it as a frequent challenge." [99]*
	S	Medical professionals and maintaining experts – in general, not FH specific, Austria	*"A challenge experienced frequently both by medical and psychosocial professionals was maintaining proficiency. Information about genetics is rapidly advancing and difficulties in keeping up with the knowledge about genetics were a prevalent challenge. For the physicians one explaining factor might be that nearly all of the respondents did not have medical genetics as their first medical specialization. Furthermore, keeping up with medical knowledge is time consuming and nearly half of the respondents experience time constraints frequently. This might be influencing maintaining proficiency as well." [99]*
	S	Medical professionals and organisational constraints – in general, not FH specific, Austria	*"Further challenges frequently encountered by medical professionals were organizational constraints such as language barriers or a lack of written information material. But the challenges subsumed in this domain are broad-ranging. The answers in this study varied from too much time-effort for non-medical organizational tasks to lack of experience, lack of training as a psychotherapist or deficient cooperation between institutes. These challenges can be related to other domains as for example time constraints and attaining/maintaining proficiency. "[99]*
	S	Goal of genetic counselling	*"Genetic testing in the FH proband affords the ability to provide precise and accurate recurrence risk information during genetic counseling and informs the correct approach to family cascade genetic testing." [2]*
	S	Genetic counselling and informed consent	*"... ability of the individual, family group, or a particular child to give fully 'informed consent'. This is critically on being able to make an accurate estimate of (i) the risk of CAD in the identified individuals, (ii) the psychological impact of the diagnosis, and (iii) the benefits of treatment." [120]*
	S	GDx is not having a major impact on clinical work	*"Though these professionals appear aware of and interested in the genetic component of the condition, and DNA testing is underway in at least some centres, their accounts suggest that the genetic test is not having a major impact on clinical work. Instead we find that professionals report that they generally rely on other information when making a diagnosis, especially cholesterol levels understood as a key risk factor, while the results of DNA tests, if used, come late in a much longer series of clinical investigations, judgements and interventions. In addition to elaborating professional views of genetic testing, the research provides a way of understanding other studies that describe lay people as not necessarily privileging genetic explanations of familial hypercholesterolaemia." [127]*

Group: C – Comparator (clinical/phenotypical diagnosis), CS – cascade screening (at-risk family members), D – disease (FH), I – Intervenion (GDx), P – patient, S – stakeholder (clinicians, genetic counselors)

***Abbreviations:** ACVD – arteriosclerotic cardiovascular disease, CHD – coronary heart disease, CI – confidence interval, CVD – cardiovascular disease, DLCNC – Dutch Lipid Clinic Network diagnostic criteria, FH – familial hypercholesterolaemia, GDx – genetic diagnostic, GP – general practitioner, HeFH – heterozygous familial hypercholesterolaemia, IP – index patient, LDL-C – Low density lipoprotein cholesterol, LLT – lipid-lowering treatment*

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH