HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Genetic Testing in Austria

Part B: Carrier Screening for Selected Genetic Conditions

Final report

AIHTA Project Report No.: 176b | ISSN: 1993-0488 | ISSN-online: 1993-0496

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Part B: Carrier Screening for Selected Genetic Conditions

Vienna, March 2026

Project Team

Project leader: Gregor Goetz Dr.PH

Authors: Beyzanur Yoldas
Aline Dragosits, MA, PhD
Gregor Goetz, Dr.PH

Project Support

Systematic literature search: Tarquin Mittermayr, MA

External Review: Johannes Zschocke, Univ.-Prof. Dr. med. PhD (Medizinische Universität Innsbruck)
Chantal Babb de Villiers, PhD Senior Policy Analyst (PHG Foundation)
Sophia Petschnak, Prim. Dr.in med. univ., MSc. WIGEV

Internal Review: Sabine Geiger-Gritsch, Dr. scient. med., Mag. sc. hum., Mag. Pharm

Human genetic working group: We would like to thank Reinhard Jeindl and Alba Colicchia for their support during this project through regular meetings and valuable exchanges.

Generative AI (Claude 3.5 Sonnet, Gemini 2.5 Flash, Perplexity) was used to assist with several tasks such as drafting and formatting. The authors remain fully responsible for all content.

Correspondence: Gregor Goetz, gregor.goetz@aihta.at

Cover photo: @ AI-generated – ChatGPT.com

This report should be referenced as follows:

Yoldas, B. Dragosits, A. Goetz, G. Genetic testing in Austria. Part B: Carrier Screening for Selected Genetic Conditions. AIHTA Project Report No.: 176b; 2026. 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).

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IMPRINT

Publisher:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Josefstädter Straße 39 | 1080 Vienna – Austria
https://www.aihta.at/

Responsible for content:
Dr. rer. soc. oec. Ingrid Zechmeister-Koss, MA, managing director

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AIHTA Project Report No.: 176b

ISSN 1993-0488 | ISSN online 1993-0496

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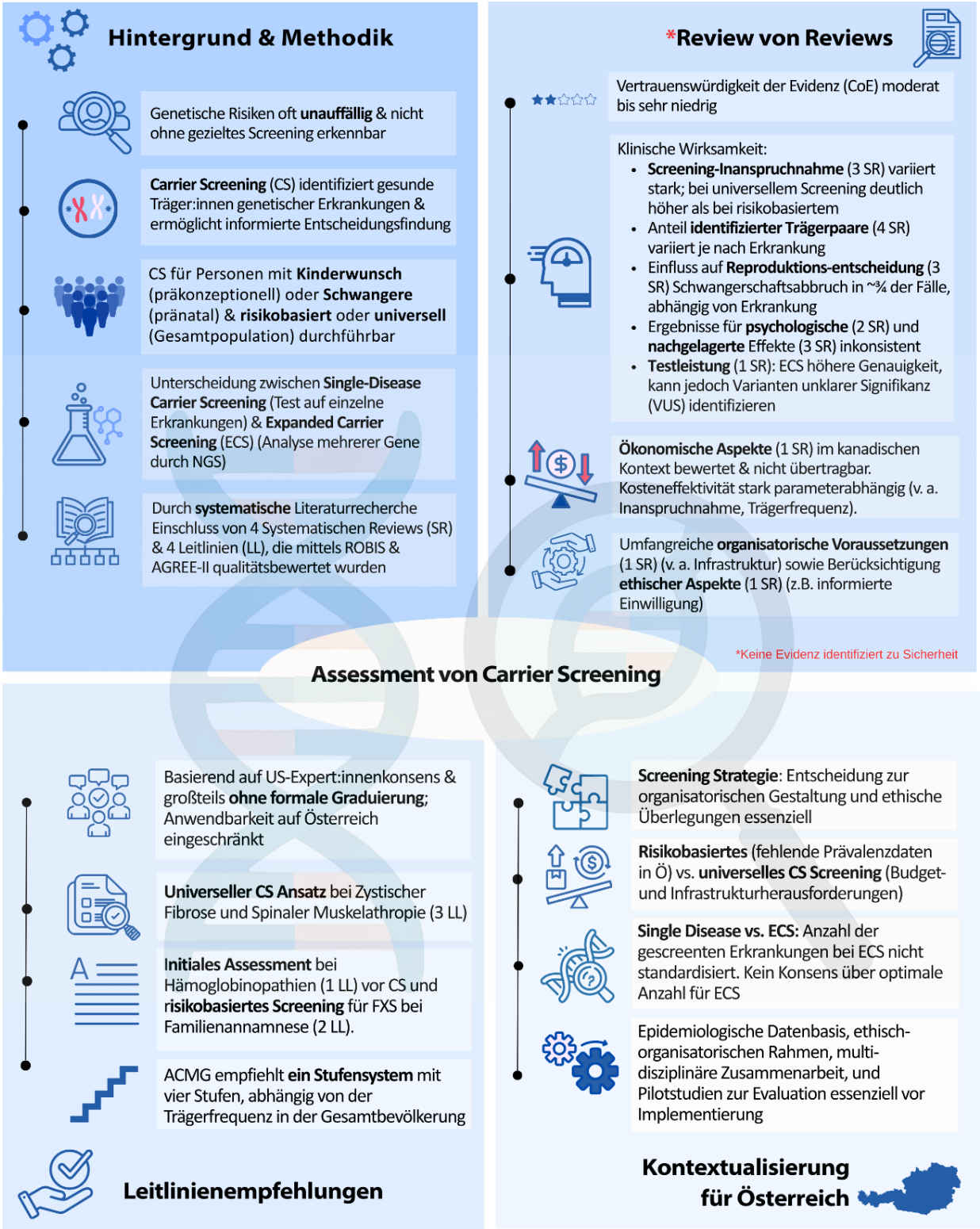
List of abbreviations

ACMG ..... American College of Medical Genetics and Genomics
ACOG ..... American College of Obstetricians and Gynecologists
AGREE-II ..... Appraisal of Guidelines for Research & Evaluation II
AIHTA ..... Austrian Institute for Health Technology Assessment
AMSTAR 2 ..... A Measurement Tool to Assess Systematic Reviews, version 2
AR ..... Autosomal recessive
CE mark ..... Conformité Européenne (European conformity)
CENTRAL ..... Cochrane Central Register of Controlled Trials
CF ..... Cystic Fibrosis
CFTR ..... Cystic Fibrosis Transmembrane Conductance Regulator
CINAHL ..... Cumulative Index to Nursing and Allied Health Literature
CLIA ..... Clinical Laboratory Improvement Amendments
CoE ..... Certainty of Evidence
CVS ..... Chorionic Villus Sampling
ECO ..... Economic
ECS ..... Expanded Carrier Screening
EFF/SAF ..... Effectiveness/Safety
ETH ..... Ethical
EUnetHTA ..... European Network for Health Technology Assessment
FMR1 ..... Fragile Mental Retardation-1 (Gene associated with Fragile X Syndrome)
FSH ..... Follicle-Stimulating Hormone
FXS ..... Fragile X Syndrome

GoR .....Grade of Recommendation
GRADE.....Grading of Recommendations Assessment, Development, and Evaluation
GTG.....Gentechnikgesetz (Genetic Testing Act)
HRCs.....High-Risk Couples
HTA .....Health Technology Assessment
HQO.....Health Quality Ontario
HQO HTA .....Health Quality Ontario Health Technology Assessment
ICER .....Incremental Cost-Effectiveness Ratio
ICUR.....Incremental Cost-Utility Ratio
IVDR.....In Vitro Diagnostic Regulation
IVF .....In Vitro Fertilization
JBI .....Joanna Briggs Institute
LDTs.....Laboratory-Developed Tests
LILACS .....Latin American and Caribbean Health Science Information Database
LoE.....Level of Evidence
MLPA.....Multiplex Ligation-dependent Probe Amplification
NGS.....Next-Generation Sequencing
NHS EED .....National Health Service Economic Evaluation Database
NICE.....National Institute for Health and Care Excellence
NR.....Not Reported
NSGC.....National Society of Genetic Counselors
ORG .....Organisational
OSF .....Open Science Framework
PCR.....Polymerase Chain Reaction
PICO .....Population, Intervention, Comparison, and Outcome Framework
PFS.....Progression-Free Survival
PGT.....Pre-Implantation Genetic Testing
PND .....Prenatal Diagnosis
PRISMA.....Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCPA .....Royal College of Pathologists of Australasia
RCS .....Reproductive carrier screening
RoB.....Risk of Bias
ROBIS.....Risk of Bias in Systematic Reviews tool
RoBANS.....Risk of Bias Assessment tool for Non-randomised Studies
SCD.....Sickle Cell Disease
SMA .....Spinal Muscular Atrophy
SMN1 .....Survival of motor neuron 1 (Gene associated with Spinal Muscular Atrophy)
SNP .....Single Nucleotide Polymorphism
SR.....Systematic Review
TECH.....Technology (HTA Core Model Domain)
TOP.....Termination Of Pregnancy
UK.....United Kingdom
US/USA .....United States/United States of America
VUS .....Variants of Uncertain Significance
WES .....Whole Exome Sequencing
WGS.....Whole Genome Sequencing
XL .....X-linked

Visual Abstract



Abkürzungen: ACMG…American College of Medical Genetics and Genomics; AGREE II…Appraisal of Guidelines for Research & Evaluation II; CoE…Certainty of Evidence; CS…Carrier Screening; ECS…Expanded Carier Screening; LL…Leitlinie; ROBIS…Risk of Bias in Systematic Reviews tool; SR…Systematischer Review; US…United States; v.a...vor allem

Executive Summary

Introduction

Carrier screening is a screening strategy designed to identify asymptomatic individuals who carry pathogenic variants for autosomal recessive and X-linked hereditary conditions. This assessment evaluated the clinical effectiveness, safety, economic, organisational, and ethical aspects of different carrier screening strategies: universal versus risk-based approaches and single-disease panels versus expanded carrier screening (ECS). The target population comprised reproductive-age individuals and pregnant women.

Methods

We employed a review-of-reviews approach to synthesise systematic reviews and health technology assessments published between June 2020 and March 2025. Systematic literature searches were conducted in five databases (Medline, Embase, Cochrane Library, Epistemonikos, INAHTA). International guideline recommendations were additionally identified and synthesised. The European Network for Health Technology Assessment (EUnetHTA) Core Model framework structured the assessment across four outcome domains: clinical effectiveness and safety, economic, organisational, and ethical aspects. Evidence was synthesised narratively, with certainty of evidence assessed using GRADE methodology where available.

Results

Four systematic reviews were identified, synthesising 11 to 107 primary studies. The included systematic reviews predominantly comprised observational studies with one randomised controlled trial identified but also for example health economic evaluations, studies on ethical or organisational aspects and model studies.

Clinical Effectiveness and Safety: Identified evidence indicated that carrier screening identifies at-risk couples (0-25% depending on condition and population, moderate certainty) and supports informed reproductive decision-making. Screening uptake varied substantially (4.7-99.5%) depending on strategy and setting. Among at-risk pregnancies, prenatal diagnosis uptake was 64.4% and pregnancy termination rate was 71.4% among pregnancies confirmed to be affected within the prenatal diagnosis. ECS demonstrated superior test performance compared to single-disease panels. Psychological impacts remained uncertain with very low certainty of evidence. Downstream impacts including cascade testing rates were inconsistently reported.

Economic, Organisational, and Ethical Aspects: Economic evaluations were limited and context-specific to the Canadian healthcare setting; universal screening with standard panels may be cost-effective, though highly sensitive to carrier frequency and uptake. Implementation required substantial investment in genetic counselling capacity and infrastructure. Key ethical considerations included respect for autonomy, informed decision-making, and privacy protection.

Guideline Recommendations: Identified guidelines recommended universal screening for Cystic Fibrosis and Spinal Muscular Atrophy, with variable recommendations for expanded panels and risk-based screening for Fragile X syndrome. Applicability of guidelines to the Austrian setting is limited.

Discussion and conclusion

Carrier screening can identify at-risk couples and support informed reproductive decisions. No formal carrier screening programme exists in Austria, and international guideline recommendations are not applicable to the Austrian healthcare context. Responsible implementation requires consideration of Austrian epidemiological data, ethical frameworks, substantial organisational capacity, and multidisciplinary collaboration.

Zusammenfassung

Einleitung

Dieser Bericht ist Teil eines umfassenden AIHTA Genetik-Projekts. Ziel dieses Assessments ist die Bewertung der klinischen Wirksamkeit und Sicherheit von Carrier Screening und hier insbesondere von Expanded Carrier Screening (ECS).

Beschreibung Krankheitsbilder und Vererbungsmuster

Seltene Erkrankungen, definiert als Erkrankungen mit einer Prävalenz von weniger als fünf Fällen pro 10.000 Personen, sind überwiegend genetischen Ursprungs. Zystische Fibrose (CF), Spinale Muskelatrophie (SMA), Hämoglobinopathien (Sichelzellerkrankung, Thalassämie) und Fragiles-X-Syndrom (FXS) sind genetische Erkrankungen mit schwerwiegenden gesundheitlichen Komplikationen und reduzierter Lebenserwartung. In Österreich werden jährlich etwa 25 Kinder mit CF geboren, SMA tritt bei circa 1 von 10.000 Neugeborenen auf. Die Trägerrate für Hämoglobinopathien beträgt etwa 0,2 %. Für FXS liegen keine österreichischen Daten vor.

Paare mit erhöhtem Risiko sind Paare, bei denen beide Partner jeweils pathogene Varianten desselben Gens tragen. In diesem Fall besteht für deren Nachkommen ein erhöhtes Erkrankungsrisiko. Das Vorliegen eines genetischen Risikos kann bekannt sein (z. B. aufgrund der Familienanamnese), häufig bleibt das Risiko jedoch unauffällig und kann ohne gezieltes Screening nicht identifiziert werden.

Autosomal-rezessive Vererbung (CF, SMA, Hämoglobinopathien): Bei Paaren mit erhöhtem Risiko besteht pro Schwangerschaft ein 25 %-iges Risiko für ein betroffenes Kind, ein 50 %-iges Risiko für ein Kind als Träger und ein 25 %-iges Risiko für ein nicht betroffenes, nicht-Träger-Kind. Etwa 1-2 % der Paare in der Allgemeinbevölkerung sind Paare mit erhöhtem Risiko.

X-chromosomale Vererbung (FXS): Bei Trägerinnen besteht pro Schwangerschaft ein 25 %-iges Risiko für einen betroffenen Sohn, 25 % für einen nicht betroffenen Sohn, 25 % für eine Träger-Tochter (meist mild und manchmal variabel betroffen) und 25 % für eine nicht betroffene Tochter.

Beschreibung der genetischen Tests

Carrier Screening ist ein genetisches Screening zur Identifikation von Anlageträgerschaften bei gesunden Träger:innen pathogener Genvarianten, welche an Nachkommen weitergegeben werden können. Das Ziel von Carrier Screening ist es, informierte reproduktive Entscheidungen zu unterstützen.

Carrier Screening Strategien variieren hinsichtlich Methodik, Panel-Größe, Detektionstechniken und klinischer Anwendung. Für dieses Assessment werden folgende Carrier Screening Strategien für CF, SMA, Hämoglobinopathien und FXS für Personen mit Kinderwunsch (präkonzeptionell) oder Schwangeren (pränatal) betrachtet:

- *Single-Disease Carrier Screening:* genetische Teststrategie, die auf die Identifikation von Träger:innen einer einzelnen genetischen Erkrankung abzielt,
- *Expanded Carrier Screening:* Screening-Strategie, die aktuell meist massiv-parallele Hochdurchsatz-Multi-target-DNA -Sequenzierungstechnologie nutzt, üblicherweise bekannt als Next-Generation Sequencing (NGS). Die Technologie umfasst weitreichende genetische Test-Panels zur simultanen Analyse multipler Gene. Alternativ können mehrere Gene auch mit einer günstigen Array-Technologie simultan analysiert werden.

Methoden

Die Assessment-Elemente des European Network for Health Technology Assessment (EUnetHTA) Core Model® bildeten die Grundlage für die Berichtsstruktur. Für das Assessment wurde eine systematische Literatursuche in fünf Datenbanken (Medline via Ovid, Embase, Cochrane Library, Epistemonikos, INAHTA) für den Zeitraum Juni 2020 bis März 2025 durchgeführt. Ergänzt wurde diese Suche um eine manuelle Recherche in Leitliniendatenbanken (NICE, Trip medical database, GIN, AWMF). Eingeschlossen wurden Health Technology Assessment (HTA)-Berichte, systematische Reviews und evidenzbasierte Leitlinien. Insgesamt wurden 514 Studien gescreent.

Die Studienselektion erfolgte durch zwei unabhängige Reviewer:innen, bei Uneinigkeit wurde eine dritte Person hinzugezogen. Das Verzerrungsrisiko wurde mittels ROBIS (Risk of Bias in Systematic Reviews)-Tool für systematische Reviews und AGREE-II (Appraisal of Guidelines for Research and Evaluation) Checkliste für Leitlinien bewertet.

Ergebnisse

Verfügbare Evidenz

Nach der systematischen Literatursuche wurden insgesamt vier systematische Reviews, darunter ein HTA-Bericht mit 107 Primärstudien, eingeschlossen.

Die eingeschlossenen systematischen Reviews basieren auf Primärstudien zur klinischen Wirksamkeit von präkonzeptionellen Carrier Screening und Expanded Carrier Screening vor oder während einer Schwangerschaft. Die Größe der Panels variierte stark, von Single-Disease bis über 400 Gene. Ein systematischer Review beschränkte sich auf Carrier Screening für das Krankheitsbild Zystische Fibrose, während der HTA-Bericht auf Carrier Screening vor allem, aber nicht ausschließlich für die Indikationen Zystische Fibrose, Spinale Muskelathropie, Fragiles-X-Syndrom und Hämoglobinopathien fokussierte. Der HTA-Bericht war der einzige Review, der zusätzlich ökonomische und organisatorische Domänen sowie ethische Aspekte basierend auf dem kanadischen Kontext adressierte.

Für die Leitliniensynopse wurden US-amerikanische Leitlinienempfehlungen von vier Organisationen, American College of Obstetricians and Gynecologists (ACOG), American College of Medical Genetics and Genomics (ACMG), National Society of Genetic Councelors (NSGC) and Carelon zu Carrier Screening und Expanded Carrier Screening identifiziert.

Ergebnisse Review von Reviews

Zur Bewertung der Wirksamkeit von Carrier Screening wurden Screening-Inanspruchnahme, Anteil identifizierter Paare mit erhöhtem Risiko, psychologische Effekte, nachgelagerte Auswirkungen, sowie Testgenauigkeit bewertet. Die Vertrauenswürdigkeit der Evidenz (Englisch: Certainty of Evidence/CoE) für diese Endpunkte wurde mit moderat bis sehr niedrig eingestuft.

- *Screening Inanspruchnahme (3 Reviews; sehr niedrige CoE):* Die Inanspruchnahme variierte erheblich zwischen den Studien innerhalb der Reviews (4,7 bis 99,5 %). Universelles Screening zeigte deutlich höhere Raten (68-71 %) als risikobasiertes Screening (4,7-5 %), mit höchster Inanspruchnahme im Rahmen einer künstlichen Befruchtung (Invitro Fertilisation, IVF) und bei schrittweisem Screening.
- *Anteil identifizierter Paare mit erhöhtem Risiko (4 Reviews; moderate CoE):* Der Anteil variierte je nach Erkrankung: CF 0-5 %, SMA etwa 1 %, Hämoglobinopathien bis 25 % der gescreenten Paare.
- *Einfluss auf Reproduktionsentscheidungen (3 Reviews; moderate CoE):* Bei einem positiven Screeningergebnis wurde die Entscheidung für eine prenatale Diagnostik sowie das anschließende Schwangerschaftsmanagement von der Art und dem Schweregrad der Erkrankung beeinflusst.
- *Psychologische Auswirkungen (2 Reviews; sehr niedrige CoE):* Die Ergebnisse waren inkonsistent. Schwangere ohne Vor-Test-Beratung äußerten häufig Verwirrung über Bedeutung und Konsequenzen positiver Befunde.

- *Nachgelagerte Auswirkungen (3 Reviews; sehr niedrige CoE):* Die Ergebnisse waren inkonsistent.
- *Testgenauigkeit:* dieser Endpunkt wurde nur in einem HTA-Bericht berücksichtigt. Expanded Carrier Screening Panels zeigten überlegene Testgenauigkeit bei der Identifikation von Paaren mit erhöhtem Risiko im Vergleich zu Single-Disease Panels. ECS-Panels können jedoch Varianten unklarer Signifikanz (VUS) identifizieren, was jedoch in keiner der Studien berichtet wurde.

Ökonomische Aspekte wurden nur in einem HTA-Bericht bewertet, wobei die Analysen aufgrund des kanadischen Kontexts nicht auf das österreichische Setting übertragbar sind. Die Kosteneffektivität war dabei stark parameterabhängig, insbesondere von Inanspruchnahme und Trägerfrequenz.

Die Implementierung von Carrier-Screening-Programmen erfordert substanzielle organisatorische Voraussetzungen, insbesondere genetische Beratungskapazitäten, sowie Infrastruktur und optimierte Arbeitsabläufe. Zentrale ethische Überlegungen müssen in die Organisation einfließen und genetische Beratung ist dabei essenziell, um ethische Prinzipien wie Patient:innenautonomie, informierte Einwilligung sowie gerechten Zugang zu gewährleisten.

Ergebnisse Leitliniensynopse

Gemäß Appraisal of Guidelines for Research and Evaluation (AGREE) II sind alle Leitlinien empfehlenswert, zwei mit Modifikationen (ACOG, ACMG). Alle zeigen methodische Limitationen bei Evidenzreview und -synthese. Die Anwendbarkeit auf Österreich ist stark eingeschränkt, da alle Empfehlungen von US-Expert:innen stammen. Nur NSGC graduierte Evidenz und Empfehlungsstärke; die Mehrheit der Empfehlungen ist konsensbasiert ohne formale Graduierung.

Screening Strategie: NSGC empfiehlt ECS als Alternative zu ethnizitätsbasiertem Screening (konditionale Empfehlung, niedrige-moderate Evidenz). Carelon und ACOG empfehlen universelles krankheitsspezifisches Screening (CF, SMA, Hämoglobinopathien universell; FXS nur bei Familienanamnese). Beide schlagen zusätzliches Screening bei spezifischen Kriterien vor (Familienanamnese, ethnischer Hintergrund). Expanded Carrier Screening nur bei spezifischen Kriterien (höheres Risiko aufgrund einer Familienanamnese). ACMG empfiehlt ein Stufensystem mit vier Stufen: Bei einer AR- und XL-Frequenz ≥1/200 (Stufe 3) soll Expanded Carrier Screening universell angeboten werden; Stufe 4 nur bei Konsanguinität/Anamnese.

Grundsätzlich empfehlen drei Leitlinien einen universellen Carrier Screening Ansatz für CF und SMA. Für Hämoglobinopathien schlägt ACOG initiales Assessment vor. Risikobasiertes FXS-Screening bei Familienanamnese wird von zwei Empfehlungen vorgeschlagen. ACMG folgt einer anderen Vorgehensweise und schlägt ein Stufen-System vor: häufigere Erkrankungen werden universell gescreent, seltenere nur bei Konsanguinität/Anamnese. ECS wird empfohlen, wenn bestimmte Kriterien erfüllt sind (risikobasiert). NSGC fokussiert ausschließlich auf ECS als Option und empfiehlt es konditional als Alternative zu ethnizitätsbasiertem Screening.

Diskussion

Kontextualisierung für Österreich

Dieses Pilot-Assessment basiert auf einem Review-of-Reviews und Leitliniensynopse-Ansatz, welcher bei der Bewertung genetischer Testverfahren unterstützen kann. Dabei wurden für den österreichischen Kontext mehrere Kernherausforderungen identifiziert:

Leitlinienanwendbarkeit: Die identifizierten Leitlinien variieren stark und sind nicht direkt auf das österreichische Setting anwendbar, obwohl einige Prinzipien als Orientierung dienen könnten.

Screening Strategie: Die Auswahl einer angemessenen Screening Strategie ist entscheidend für eine verantwortungsvolle Implementierung von Carrier Screening. Dabei müssen Entscheidungen zur organisatorischen Gestaltung sowie ethische Überlegungen einfließen.

- Organisation von Carrier Screening:
  - Bei Familienplanung (präkonzeptionell) oder Schwangerschaft (pränatal)
  - Nur die Mutter, oder bei einem positiven Test auch den Partner (stufenweise) oder in bestimmten Settings beide (simultan)
  - Risikobasiert (z. B. aufgrund der Zugehörigkeit zu einer ethnischen Gruppe, die eine erhöhte Prävalenz aufweist oder bei bekanntem Risiko) vs. universell (alle Erwachsenen mit Kinderwunsch)
  - Single-Disease Carrier Screening vs. Expanded Carrier Screening
- Ethische Überlegungen zu Carrier Screening:
  - Deklaration des Primärzwecks
  - Priorisierung schwerer frühkindlicher Manifestationen (solide Evidenzbasis)
  - Informierte Einwilligung nach professioneller und ausführlicher Aufklärung
  - Servicequalität

Risikobasiertes vs. universelles Carrier Screening: In Österreich wäre ein risikobasierter Ansatz aufgrund fehlender etablierter Prävalenzdaten für spezifische Gruppen herausfordernd, während universelles Screening substanzielle Budget- und Infrastrukturherausforderungen mit sich bringen kann. Historisch basierte Carrier Screening auf einer risikobasierten Strategie, die jedoch signifikante Nachteile aufweist: Sie identifiziert viele Träger:innen nicht, da die meisten mit diesen Erkrankungen geborenen Kinder keine bekannte Familienanamnese haben.

Single-Disease vs. Expanded Carrier Screening: Umfassende genetische Test-Panels zur simultanen Analyse multipler Gene, welche bei Expanded Carrier Screening eingesetzt werden, werden zunehmend günstiger. Die Ergebnisse eines HTA-Berichts zeigen, dass Single-Disease-Carrier-Screening kurzfristig am kosteneffektivsten ist, während Langzeitmodelle darauf hinweisen, dass universelles Screening potenziell kostensparend sein kann. Bei Expanded Carrier Screening ist die Anzahl der gescreenten Erkrankungen nicht standardisiert und reicht von einigen Dutzend bis über hundert. Es besteht kein Konsens über die optimale Anzahl und Auswahl von Erkrankungen für Screening Panels.

Gesellschaftliche und ethische Aspekte: Mit Routinisierung und Medikalisierung der Schwangerschaft sowie dem Angebotsdruck von Carrier Screening kann ein gesellschaftliches Klima für „perfekte Kinder“ genährt werden. Stigmatisierung und Diskriminierung von Personen, die entweder betroffen sind oder die sich gegen die Carrier-Screening-Optionen entscheiden, könnten weitere negative soziale Aspekte darstellen. Pilot-Implementierungsstudien sind vor breiter Implementierung erforderlich, um potenzielle unvorhergesehene Konsequenzen zu antizipieren.

Limitationen des Assessments

Das vorliegende Assessment sollte im Kontext seiner Limitationen betrachtet werden. Es wurde ein Review-of-Reviews-Ansatz verwendet, anstatt eines De-novo-systematischen Reviews. Die Literaturrecherche wurde auf englisch- und deutschsprachige Publikationen beschränkt, wodurch potenziell relevante Publikationen in anderen Sprachen ausgeschlossen wurden. Es wurde keine dezidierte systematische Suche für Artikel zu ökonomischen, sozialen, rechtlichen oder organisatorischen Aspekten im Zusammenhang mit der Implementierung von Carrier Screening durchgeführt. Qualitative Reviews, von denen einige verfügbar sind und sich auf Barrieren und Facilitatoren für Carrier Screening konzentrieren, wurden ebenfalls nicht einbezogen. Für das österreichische Setting wurden weder primäre Datenerhebung noch Kosteneffektivitätsmodellierung verschiedener Screening-Panels oder Stakeholder-Konsultationen mit Patient:innen, Leistungserbringern oder genetischen Berater:innen durchgeführt.

Schlussfolgerung

Dieser Bericht dient als Überblick zur Wirksamkeit, Sicherheit und zu Empfehlungen für Carrier Screening. Die vorliegende Evidenz zeigt mit moderater Sicherheit, dass Carrier Screening für CF, SMA, FXS und Hämoglobinopathien Paare mit erhöhtem Risiko identifizieren und informierte reproduktive Entscheidungen unterstützen kann. Die Evidenz zu psychologischen Auswirkungen bleibt sehr unsicher.

Es besteht erhebliche Unsicherheit darüber, ob und wie eine Carrier-Screening-Strategie für Österreich optimal gestaltet und implementiert werden sollte. Keine der identifizierten internationalen Leitlinienempfehlungen ist direkt auf österreichische Verhältnisse anwendbar, obwohl einzelne Konzepte – wie ein Stufen-System (z. B. Euler-Diagramm zur Konzeptualisierung überlappender Erkrankungs-Stufen) – als Orientierung zur Strukturierung der Auswahl von Erkrankungen dienen könnten. Die Auswahl sollte an bestimmte Kriterien wie z. B. Krankheitslast geknüpft sein und erfordert Kollaboration zwischen verschiedenen Expert:innen.

Bei Überlegungen zur Implementierung von Carrier Screening in Österreich müssen ethische, rechtliche, technische, organisatorische und soziale Aspekte berücksichtigt werden. Ein multidisziplinäres Steuerungskomitee mit relevanten Expert:innen ist dabei essenziell. Darüber hinaus erfordert eine erfolgreiche Implementierung den Aufbau adäquater Testinfrastruktur sowie entsprechende Ausbildungsprogramme für die beteiligten Disziplinen. Genetische Beratung spielt eine zentrale Rolle bei der Wahrung ethischer Prinzipien wie Patientenautonomie, informierter Entscheidungsfindung und gerechtem Zugang zu den Leistungen und muss entsprechend ausgestaltet werden.

Pilotimplementierungsstudien werden empfohlen, um unvorhergesehene Konsequenzen zu identifizieren sowie Kontext- und Machbarkeitsanalysen verschiedener Screening-Strategien im österreichischen Gesundheitssystem zu evaluieren.

1 Background

This review is part of a comprehensive Austrian Institute for Health Technology Assessment (AIHTA) project on genetic testing, with a particular focus on sequencing technologies. The purpose of this report is to assess the clinical effectiveness and safety of carrier screening, along with its economic and organisational aspects. This topic was prioritised by Austrian decision makers, based on findings from a scoping review and results from a stakeholder workshop (see part A [1]). The following chapter provides background on the genetic disorders of interest and context on carrier screening approaches.

Genetik Projekt 2025 – Teil B: Bewertung der Evidenz von Carrier Screening

1.1 Overview of the disease and current clinical practice

Overview and classification of genetic disorders

Orphan or rare diseases, defined as conditions with a prevalence of fewer than five cases per 10,000 individuals, are predominantly of genetic origin [2]. Cystic Fibrosis (CF), Spinal Muscular Atrophy (SMA), certain Hemoglobinopathies, including sickle cell disease (SCD) and Thalassemia, as well as the Fragile X Syndrome (FXS), are examples of genetic disorders associated with serious and chronic health complications and reduced life expectancy. Although these diseases are individually rare, collectively they can cause morbidity and mortality in infants and children and are amongst the most common inherited conditions in Europe [3].

seltene Erkrankungen überwiegend genetischen Ursprungs

In Austria, around 25 children are born with CF annually [4], while SMA occurs in roughly one out of every 10,000 newborns [5]. The number of individuals living with Hemoglobinopathies is relatively small in Austria; However, the carrier rate for SCD and Thalassemia was estimated to be around 0.2% in 2021 in Europe. It has to be noticed that migration to Europe has changed the distribution of haemoglobin disorders, leading to an increase in carriers and affected patients across the European Union [6]. Reliable epidemiological data for FXS in Austria is not available; however, worldwide the prevalence in the general population is estimated to be 1:5,000-7,000 in men and 1:4,000-6,000 in women [7].

z. B. Zystische Fibrose (CF), Spinale Muskelatrophie (SMA), Hämoglobinopathien, Fragiles-X-Syndrom (FXS)

CF, SMA and various Hemoglobinopathies, including SCD and Thalassemia, are **autosomal recessive** (AR) genetic disorders of inheritance, meaning that for a child to be affected by an AR condition, it must inherit one pathogenic gene variant from each parent [3]. When both parents are carriers for the same AR condition (an "at-risk couple"), there is a one in 25% chance with each pregnancy that the child will be affected [3]. Specifically, for each pregnancy, the risks are:

CF und SMA als autosomal-rezessive Erbkrankheiten; bei Paaren mit erhöhtem Risiko besteht ein 25-prozentiges Risiko für erkranktes Kind

- A 25% (one in four) chance that the child will be affected by the condition
- A 50% (one in two) chance that the child will be an unaffected carrier (just like the parents)
- A 25% (one in four) chance that the child will be unaffected and not a carrier [3, 8]

CF, SMA und Hämoglobinopathien durch spezifische Genvarianten verursacht

In total there are currently approximately 8,000 entries for described AR phenotypes and around 17,000 entries for described AR genes in the Online Mendelian Inheritance in Man (OMIM) database [9]. CF is caused by pathogenic variants in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, affecting mucus, sweat and digestive enzyme production and is one of the most common autosomal recessive conditions [3, 10]. SMA, which is caused by pathogenic variants of the Survival of motor neuron 1 (SMN1) gene, results in motor neuron degeneration and can lead to muscle weakness and infant mortality [11]. Hemoglobinopathies are inherited blood disorders that impair the haemoglobin function [6] and for some Hemoglobinopathies like sickle cell disease there is an increased risk of miscarriages and stillbirths [12].

FXS als X-chromosomal-dominante Erbkrankheit; Männer häufiger und schwerer erkrankt als Frauen

FXS, on the other hand, is inherited through an **X-Linked (XL)** dominant pattern and is passed down on the X chromosome [3]. Because males (XY) have only one X chromosome, they are typically affected more often and more severely than females (XX), who have a second, usually unaffected, X chromosome. OMIM currently counts around 500 entries for described XL phenotypes and approximately 800 entries for described genes [9].

If a mother is asymptomatic carrier for an XL condition (like FXS), her risk estimates for each pregnancy are:

- A 25% (one in four) chance of having an affected son
- A 25% (one in four) chance of having an unaffected son
- A 25% (one in four) chance of having a carrier daughter (who is typically unaffected or may have milder symptoms)
- A 25% (one in four) chance of having an unaffected, non-carrier daughter [13]

Table 1-1 provides an overview of the inheritance patterns, the carrier frequencies and treatment options for the mentioned genetic disorders. The specific disorders were selected by decision makers; yet, these conditions are exemplary and do not restrict carrier screening to this selection alone.

Table 1-1: Overview of selected genetic disorders

Disease	Explanation	Inheritance (AR/XL)	Carrier Frequency	Treatment Availability[1]
Cystic Fibrosis (CF)	CF, the most common autosomal recessive condition among individuals of Northern European ancestry, is caused by CFTR gene variants, affecting mucus, sweat, and digestive enzyme production [3, 10]	AR	1 in 25 among Northern Europeans, a group typically including populations from the UK, Ireland, Germany, the Netherlands, and the Scandinavian countries [14]	Treatment focuses on symptom management and prevention of complications, including infection control, airway clearance, and nutritional support. CFTR modulators (e.g., ivacaftor and elexacaftor/ tezacaftor/ivacaftor) are approved for eligible patients, and surgical interventions may be required for certain complications.
Spinal Muscular Atrophy (SMA)	SMA, caused by SMN1 gene variants, results in motor neuron degeneration, leading to muscle weakness and, in severe cases like Type 1 (the most severe form with onset in infancy, causing profound weakness and respiratory failure), infant mortality if untreated, with a life expectancy under two years without treatment [11]	AR	Carrier frequency ranges from approximately 1 in 40 to 1 in 70 across different European population groups [11]	SMA therapies include Nusinersen (enhances SMN2 splicing), Onasemnogene abeparvovec (gene replacement for children under 2), and Risdiplam (SMN2 splicing modulator for patients ≥2 months). Supportive management includes physical therapy, assistive devices, and respiratory support.

Disease	Explanation	Inheritance (AR/XL)	Carrier Frequency	Treatment Availability[1]
Hemoglobino-pathies	Hemoglobinopathies like sickle cell disease and Thalassemia, which impair haemoglobin function, are among the most common inherited diseases worldwide.	AR	These conditions are rare in Northern Europeans but rising due to migration [6, 15]	Treatment varies by severity. Severe cases (e.g., Hb Bart's, β-Thalassemia major) often require transfusions, folic acid, and iron chelation. Additionally, gene therapies such as Casgevy (CRISPR/Cas9-based) and Lyfgenia offer potentially curative options for sickle cell disease and β-Thalassemia in eligible patients.
Fragile X Syndrome (FXS)	FXS, linked to CGG repeat expansions in the FMR1 gene, is the most common inherited cause of intellectual disability and contributes to autism spectrum disorders. [3]	XL	Approximately one in 250 females and one in 800 males are carriers in the UK [16]	No disease-specific therapy is available. Management focuses on supportive measures, including individualized education, behavioural interventions, early developmental support, and environmental stability.

Abbreviations: AR … Autosomal Recessive; CF … Cystic Fibrosis; CFTR … Cystic Fibrosis Transmembrane Conductance Regulator; CGG … Cytosine–Guanine–Guanine; CRISPR-Cas9 … Clustered Regularly Interspaced Short Palindromic Repeats – CRISPR Associated Protein 9; FMR1 … Fragile X Messenger Ribonucleoprotein 1; FXS … Fragile X Syndrome; SMA … Spinal Muscular Atrophy; SMN1 … Survival Motor Neuron 1; SMN2 … Survival Motor Neuron 2;
UK … United Kingdom; XL … X-linked

Note:

[1] *This information is taken from the Ontario Health, ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES, Carrier Screening Programs for Cystic Fibrosis, Fragile X Syndrome, Hemoglobinopathies and Thalassemia, and Spinal Muscular Atrophy [3]*

AR- und XL-Erkrankungen verursachen ca. 20 % der Säuglingssterblichkeit; Träger meist asymptomatisch und ohne Familienanamnese

AR and XL conditions account for approximately 20% of infant deaths and 10% of paediatric hospitalisations [17]. As described, individuals who are carriers of these conditions are typically healthy and asymptomatic, yet they can pass on a pathogenic gene variant to their children. Most carriers are unaware of this risk, as they often have no family history of genetic diseases. For AR, for example, it is estimated that 1-2% of couples in the general population are "at-risk couples" for this condition, putting them at a high risk of having a child with a genetic condition [18]. The presence of a genetic risk may be known (e.g. due to family history). In many cases, the risk remains unrecognised and cannot be identified without carrier screening [3]. The focus of this report is on the latter.

Target population

Zielpopulation: Individuen und Paare vor oder während Schwangerschaft

In this report, the target population is defined as pregnant women (prenatal) or individuals and couples who are planning pregnancy (preconception). The precise size of the target population is difficult to quantify. However, according to data from Statistics Austria, approximately 77,000 live births occur annually [19], representing a rough indicator. The preconception population is more difficult to quantify as it depends on individual reproductive intentions and the timing of screening access.

Current Clinical Management in Austria

Derzeit kein routinemässiges Carrier Screening in Austria

There is currently no universal carrier screening for AR and XL conditions, especially for CF, SMA, Hemoglobinopathies, and FXS in Austria. Carrier screening is occasionally provided within the private healthcare sector and primarily in the reproductive care setting [20].

Carrier risk assessment should be distinguished from carrier screening. When one partner is already known to be a carrier of a specific genetic condition, carrier testing will be publicly offered to the other partner as part of genetic counselling and the costs for this analyis is covered by the public health system, according to a personal communication with a clinical expert [20].

Gezielte Testung bei bekanntem Anlageträgerstatus

Newborn screening should be distinguished from carrier screening. Identification of a genetic condition in an affected child can implicitly provide carrier status information of the parents but also uncover carrier status information for specific conditions [3, 18]. Screening for inherited metabolic and endocrine disorders, including CF, is included within the national newborn screening program, which was introduced in the late 1960s [21]. According to information of an Austrian expert, newborn screening through genetic testing is in priniciple prohibited by Austrian law (GTG) but in 2021 molecular genetic screening for the diagnosis of SMA was introduced in Austria in 2021 on a research basis [20].

Neugeborenen-Screening (CF, SMA) kann indirekt Träger-Status von Neugeborenen und Eltern aufdecken

1.2 Features of the intervention

Carrier Screening

Carrier screening is a genetic test designed to identify whether an individual is a carrier – healthy, asymptomatic individuals who can pass on a pathogenic gene variant to their offspring – of a gene variant that can cause a genetic hereditary condition [3, 22]. Carrier screening in individuals and couples who are planning pregnancy (preconception) or are currently pregnant (prenatal) aims to identify reproductive risks and enables informed reproductive decision-making regarding prenatal diagnosis, assisted reproduction with preimplantation genetic testing, or pregnancy management [23, 24]. Carrier screening for couples may be performed either simultaneously or sequentially, with the second partner tested only if the first partner is detected as a carrier [18].

Carrier Screening zielt auf Identifikation asymptomatischer Träger ab, um informierte Reproduktions-entscheidungen zu ermöglichen

Carrier screening is typically performed using a blood sample, though other tissues or bodily fluids may be used depending on the testing method [3]. So, the strategies can vary in their methodologies but also in the panel sizes (a defined set of genes), detection techniques and clinical applications.

Testung mittels Blutprobe, Strategien unterscheiden sich in Methodik, Panel-Größe und Nachweistechniken

Carrier Screening varies regarding their **detection techniques**, the specific laboratory methodology, employed to identify deviations from a reference genetic sequence. An *assay* is a procedure or test used to measure the presence or activity of a specific substance, whereas an *array* is an organized arrangement of many assays on a single surface for simultaneous analysis [23].

A *targeted molecular* test is an assay specifically designed to detect a predefined set of known pathogenic mutations or hotspots [24]. *Massive parallel/high-throughput sequencing technologies* allow for the simultaneous sequencing of millions of DNA fragments, significantly increasing data output and efficiency. *Next-Generation Sequencing* (NGS) is a high-throughput DNA sequencing technology that enables the rapid analysis of large gene panels or whole exomes [23].

For the purpose of this assessment, carrier screening for conditions such as CF, SMA, Hemoglobinopathies and FXS is considered as the technology of interest. The specific disorders were selected by decision makers; yet, these

conditions are exemplary and do not restrict carrier screening to this selection alone. The focus lies on the following strategies:

Expanded Carrier Screening

- Universal screening with Expanded Carrier Screening (ECS) multi-target Next-Generation Sequencing (NGS) panels, sometimes supplemented by specific tests
- Risk-based screening with ECS

Single-Disease Carrier Screening

- Universal screening with single-disease panels (targeted molecular tests per disease)
- Risk-based screening with single-disease panels

Expanded Carrier Screening (ECS) für multiple Gene vs. Single-Disease für Einzelerkrankungen, universell oder risikobasiert durchführbar

Expanded Carrier Screening (ECS) is a screening strategy that either utilises massive parallel sequencing, a high-throughput, multi-target DNA sequencing technology, commonly known as NGS, or microarray-based platforms (which are glass or silicon chips used to detect known mutations or sequence variations efficiently), to simultaneously analyse multiple genes or variants associated with autosomal recessive (AR) and X-linked (XL) genetic disorders. ECS encompasses comprehensive genetic testing panels that assess the carrier status for hundreds of inherited conditions in asymptomatic individuals or couples who are planning reproduction [3].

ECS nutzt Next-Generation Sequencing (NGS), analysiert simultan multiple Gene für einige bis hunderte AR- und XL-Anlagen

Single-disease carrier screening, or carrier screening, is a genetic testing strategy that targets on identifying carriers of a single genetic disorder, typically frequent in the population, and associated with significant morbidity and reduced life expectancy, by using targeted molecular tests for specific single diseases [3, 18].

Single-Disease Carrier Screening testet gezielt auf einzelne genetische Anlagen

Advances in molecular testing methodologies, particularly NGS, have facilitated a move from single-disease screening toward ECS. ECS allows for the simultaneous assessment of carrier status for AR and XL conditions. Compared to single-disease carrier screening, ECS offers increased sensitivity and specificity, alongside its capacity to provide couples with more comprehensive genetic information, to inform family planning decisions [25]. ECS is anticipated to detect a broader spectrum of pathogenic variants across many genes, thereby identifying at-risk couples that might be missed by single-disease panels [26].

ECS detektiert breiteres Variantenspektrum als Single-Disease-Screening

The distinguishing features of these carrier screening strategies are further described in Table 1-2.

Table 1-2: Features of carrier screening strategies [18, 27]

	Expanded Carrier Screening (ECS) Panels	Single-Disease Carrier Screening Panels
Panel Size/Coverage*	A few to a hundred conditions	Single or a few conditions
Detection Method	Multi-target NGS panels, allele-specific DNA arrays	NGS, PCR, Southern blot, allele-specific assays
Clinical Application	Universal or risk-based screening	Universal or risk-based screening

Abbreviations: DNA … Deoxyribonucleic acid; ECS … Expanded Carrier Screening; NGS … Next-Generation Sequencing; PCR … Polymerase Chain Reaction

Note:

** there is no clear cut-off between ECS and single-disease carrier screening panels in terms of amount of genes/conditions [27]*

unterschiedliche Carrier-Screening-Ansätze weltweit, in Europa v. a. risikobasiert und privat finanziert

Globally, carrier screening is organised in different ways. Some countries focus on individuals at increased risk due to ethnic background, while others adopt a more universal carrier screening approach [3, 18]. Many countries, like for example those in the Mediterranean (for Thalassemia) and Israel and Australia (for CF), have implemented screening programs for relatively common genetic disorders which are common in the respective population [3, 18]. A recent survey on the current practice of carrier screening among healthcare professionals in medically assisted reproductive practices in Europe shows that single-disease carrier screening was reported as most frequently used (66%). ECS has not been widely adopted in Europe and is mainly used in specific settings, such as In Vitro Fertilisation (IVF) [28]. Depending on the legal frameworks in the respective countries, the primary options for action are the offering of prenatal genetic diagnosis, but also alternatives such as egg or sperm donation, reconsidering the desire to have children, adoption, or acceptance of a potentially affected child. Until now, such offerings in Europe have primarily been available in private healthcare and are therefore only accessible to couples who utilise the services of a private provider and can afford the costs of the examination [29].

Costs

ECS-Kosten in Europa: € 150-€ 2.500 je nach Panel-Umfang

ECS costs can vary per country and strategy used. According to a recent survey in Europe, the reported prices per test vary from €150 to €800 for a small ECS panel, and €400 to €2,500 for ECS using whole exome sequencing [28].

Clinical implementation and resources

genetische Beratung, Optionen: In-vitro Fertilisation vor bzw. pränatale Diagnostik während Schwangerschaft

Conversations about carrier screening usually begin in a primary care or maternal care setting [3]. Carrier screening generally begins with counselling about the type, accuracy and limitations of the testing method during a preconception or prenatal visit [10]. Couples found to be at risk are referred for post-test genetic counselling, where reproductive options are discussed, including IVF with pre-implantation genetic testing (PGT), use of donor gametes, adoption, or prenatal diagnosis using invasive procedures like chorionic villus sampling (CVS) or amniocentesis [30].

Steigender Bedarf an qualifizierten genetischen Berater:innen

Carrier screening program implementation requires a multidisciplinary team, including, for instance, molecular medical geneticists and certified genetic counsellors, gynaecologists, as well as laboratory and bioinformatics specialists and technicians, all operating under the legal framework in Austria, which is defined as the Genetic Engineering Act (Gentechnikgesetz). As genetic testing possibilities continue to expand rapidly, the demand for qualified professionals to provide genetic counselling is also increasing. Many countries have therefore established the profession of genetic counsellors, who are academically trained non-physician professionals who provide the genetic counselling in a medical genetic setting; legal amendment in Austria is pending [29].

NGS-Panels potenziell effizienter, erfordern aber Infrastruktur-Investitionen

Technically, NGS panels are often used due to their potentially broader coverage and efficiency [18]. The choice of genetic test, including NGS panels, is determined by general recommendation or the specific clinical indication. Establishing such programs requires investment in sequencing platforms, bioinformatics infrastructure, laboratory automation, personnel training, and sustainable financing through public or insurance reimbursement [18].

Testing infrastructure and regulatory status

sechs genetische Zentren für Medizinische Genetik in Österreich definiert im ÖSG,

According to expert information, genetic testing in Austria is provided by six medical specialised genetic centres (Zentren für Medizinische Genetik, ZMG) specified in the Austrian health structure plan (Österreichischer Strukturplan Gesundheit), as well as other institutions [20]. Genetic testing in Austria is regulated by the Genetic Testing Act (GTG, Gentechnikgesetz), introduced in 1994 and updated in 2005; a major update of the GTG is pending [20, 29]. The GTG outlines the legal framework for genetic testing, prioritising patient protection and preventing data misuse. It classifies different types of tests, specifies authorisation requirements, mandates that both genetic testing and counselling (Genetische Beratung) must be conducted by qualified medical doctors, requires explicit informed consent, and prohibits employers and insurers from accessing or using genetic data, thus protecting individuals from genetic discrimination [29, 31]. According to expert information, screening tests without individual genetic counselling are currently not permitted, although they have been introduced with justification as a non-consented research project for SMA neonatal screening [20]. Hence, there is no regulation that allows genetic screening under defined conditions. Carrier screening in Austria is not implemented as genetic testing laboratories must be authorised and individual genetic counselling is mandatory before and after testing [29, 32]. Furthermore, no national guideline currently exists for carrier screening.

Gentechnikgesetz (GTG) regelt Testung und Beratung durch qualifizierte Ärzt:innen

EU-Regulierung erlaubt In-house-Tests ohne CE-Kennzeichnung, Validierung durch lokale Labore

Under the EU's In Vitro Diagnostic Regulation (IVDR 2017/746), which has replaced the previous IVD Directive, there are stricter requirements for manufacturers to obtain a Conformité Européenne (CE) mark for their tests. However, a significant portion of genetic testing, especially several high-throughput sequencing panels, are used as validated "in-house-tests" or Laboratory-Developed Tests (LDTs). This is necessary as there are often no CE marked assays available on the market [33]. This includes clinical validation for these LDTs and is indeed performed locally by Austrian clinicians and geneticists. It is a rigorous process to ensure the test accurately and reliably detects and interprets the genetic variants it targets within the specific patient population. This ISO 15189-based "in-house exemption" under the IVDR has been achieved by most ZMGs in Austria. It allows for flexibility and innovation but places further responsibility for the test's performance and safety on the respective diagnostic institution and the clinicians who use it [33].

Carrier Screening platforms

Illumina und Thermo Fisher Scientific als Hauptanbieter, nutzen Mikroarray-Plattformen für bis zu 600 Gene

llumina Inc. and Thermo Fisher Scientific Inc. are among the major companies operating in the carrier screening market. Illumina Technologies [34] utilise both sequencing-based and microarray platforms, including the Infinium Global Diversity Array systems. The technology employs BeadChip microarray technology with high-density Single Nucleotide Polymorphism (SNP) coverage and targeted variant detection across hundreds of genes associated with inherited disorders. Thermo Fisher Scientific [35] offers carrier screening arrays covering variants across 600 genes, but has not been accredited for diagnostic use in Austria.

Reimbursement status in Austria

Carrier Screening is currently not publicly reimbursed and not offered routinely within the public healthcare sector. However, referral or facilitation can be provided upon request (privately for example within IVF) or when clinically indicated (Carrier risk assessment if there is a known family history) [20].

Potential Harms

potenzielle Risiken: u. a. Varianten unklarer Signifikanz (VUS), Konsequenzen von falsch-positiven/negativen Resultaten

Potential harms include any adverse events and consequences from false-positive/false-negative tests. NGS-based analyses panels raise important risks regarding more tested carrier conditions and greater sequencing depth: A key challenge is the detection of variant of uncertain significance (VUS) – genetic changes whose clinical significance has not been definitively determined [36]. ECS panels may identify VUS, which can contribute to clinical uncertainty.

According to clinical expert information there are different technological trade-offs, depending on the detection technique:

- *Targeted Panels (e.g. Genotyping/PCR):* Avoid VUS by testing only known pathogenic variants, but at the cost of missing rare or population-specific pathogenic variants if they are not purposefully included in the panel
- *NGS (Sequencing):* Detects almost all variants, increasing the sensitivity for rare pathogenic mutations but significantly increasing the VUS rate

Detecting VUS via NGS contributes to a 'learning health system'. Over time, these VUS can be reclassified, improving the diagnostic yield for the local population, which is the great benefit compared to targeted panels [20]. However, VUS create uncertainty in genetic counselling and may cause anxiety without providing actionable information; they are generally not reported in genetic screening tests. Further potential harms include any adverse events and consequences.

Currently, no organised carrier screening programme exists in Austria. Accordingly, the aim of the following report is to assess the clinical effectiveness and safety of carrier screening, along with its economic, organisational and ethical aspects and to discuss those findings within the Austrian context.

2 Scope of assessment

2.1 Research questions

Forschungsfragen zur Evidenz unterschiedlicher Screeningstrategien sowie ökonomischen, organisatorischen und ethischen Aspekten und Leitlinienempfehlungen

During this report, the following research questions will be answered:

- What is the comparative effectiveness and safety of different carrier screening strategies (universal vs. risk-based; single-disease panels vs. Expanded Carrier Screening (ECS); NGS-based[1] screening vs. no screening)?
- What organisational, economic, and ethical implications of these molecular tests are reported in identified Health Technology Assessment (HTA) reports and systematic reviews?
- What do current evidence-based clinical practice guidelines recommend regarding carrier screening strategies with a specific focus on the role of expanded carrier screening using high-throughput sequencing?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 2-1.

Table 2-1: Inclusion criteria

Population	Individuals considering pregnancy or who are pregnant
Intervention	Carrier screening with a primary focus on Cystic Fibrosis (CF), Fragile X Syndrome (FXS), Hemoglobinopathies and Thalassemia, and Spinal Muscular Atrophy (SMA), with a focus on: ■ Universal Screening with single-disease panels: Targeted molecular tests for each condition individually (e.g., specific CFTR mutation analysis, FMR1 PCR/Southern blot, globin gene analysis, SMN1 deletion/duplication testing). ■ Universal Screening with Expanded Carrier Screening (ECS) Panels: Multi-target NGS panels for all conditions, potentially supplemented by specific tests (e.g., Southern blot for FXS, MLPA for SMA) for certain variant types. ■ Risk-Based Screening with single-disease panels: As in intervention 1 but offered based on specific risk factors. ■ Risk-Based Screening with Expanded Carrier Screening (ECS) Panels: As in intervention 2 but offered based on specific risk factors.
Control	No screening or other testing/screening approaches (including direct comparisons with embryo, fetus, or child screening, or other carrier screening methods).* Head-to-head comparison of screening strategies (main interest: standard panels versus ECS [e.g., multi-target NGS])

[1] Although Array-based or other methods can also be used in ECS, this report focused primarily on high-throughput sequencing in ECS, as this is the most common technique.

Outcomes	Clinical effectiveness: ■ Clinical utility (e.g., screening uptake, uptake of pre-implantation or prenatal diagnosis, choices regarding pregnancy continuation or termination, proportion of affected births) ■ Patient relevant outcomes (e.g. downstream impacts, including rates and effects of cascade testing of family members) ■ Clinical validity as linked evidence (sensitivity, specificity, predictive values, likelihood rations) and concordance (i.e., agreement) Safety: any adverse events and consequences from false-positive/false-negative test results Organisational, economic, and ethical implications (according to EUnetHTA Core Model); e.g., practical implementation of data management, informed consent, personal autonomy, implementation aspects and economic considerations[1]. Evidence-based guideline recommendations with regard to any of the mentioned aspects, e.g., test criteria when targeted NGS panels are used and in which circumstances more resource-intensive tests (e.g., WES/WGS) are recommended (LoE, GoR) *Rationale:* Appropriate outcomes have been informed by recent reviews, EUnetHTA guidelines and clinical expert input
Study design	Systematic reviews, HTA reports, reviews with modelling studies (e.g., benefit-harm; if available) Evidence-based clinical guidelines from professional organisations for synopsis of recommendations
Setting	Review of reviews: no restriction Guideline synopsis: countries from the Global North[2]
Language	English, German
Publication Period	From 6/2020 until 03/2025

Abbreviations: CF … Cystic Fibrosis; CFTR … Cystic Fibrosis Transmembrane Conductance Regulator; ECS … Expanded Carrier Screening; EUnetHTA … European Network for Health Technology Assessment; FMR1 … Fragile Mental Retardation 1; FXS … Fragile X Syndrome; GoR … Grade of Recommendation; HTA … Health Technology Assessment; LoE … Level of Evidence; MLPA … Multiplex Ligation-dependent Probe Amplification; NGS … Next-Generation Sequencing;
PCR … Polymerase Chain Reaction; SMA … Spinal Muscular Atrophy; SMN … Survival of motor neuron 1; WES … Whole Exome Sequencing; WGS … Whole Genome Sequencing

Notes:

** The current control relevant for Austria is 'no organised screening'.*
However, we didn't restrict the inclusion criteria to this control.

[1] No cost-effectiveness analysis will be performed.
Yet, results will be narratively described if cost-effectiveness analyses were performed within an identified HTA report.

[2] Evidence-based guideline recommendations will be considered with attention to their geographical applicability and resource context.

3 Methods

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® were used to guide the reporting structure and were customised to the specific objectives of the report [37].

EUnetHTA Core Model® als Grundlage für Berichtsstruktur

3.1 Systematic literature search

The systematic literature search was conducted from July 21st-25th, 2025, in the following databases:

systematische Literatursuche in 5 Datenbanken

- Medline via Ovid
- Embase
- The Cochrane Library
- Epistemonikos
- International HTA Database (INAHTA)

The systematic search was limited to articles published from 6/2020 until 03/2025 and to systematic reviews (including meta-analyses), Health Technology Assessment (HTA) reports and guidelines. After deduplication, overall, 514 citations were included for abstract screening. The specific search strategy employed can be found in the Appendix.

Insgesamt 514 Publikationen identifiziert

Furthermore, the following databases were manually searched to identify current evidence-based guidelines:

- National Institute for Health and Care Excellence (NICE)
- Trip medical database
- Guidelines International Network (GIN)
- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)

By hand-search, an additional three records were found, resulting in a total of 514 screened hits.

3.2 Flow chart of study selection

Literaturauswahl

Overall, 609 hits were identified. After deduplication, 514 references were screened by two independent researchers (GG and BY), and in case of disagreement, a third researcher was involved to resolve the differences. The selection process is displayed in Figure 3-1.

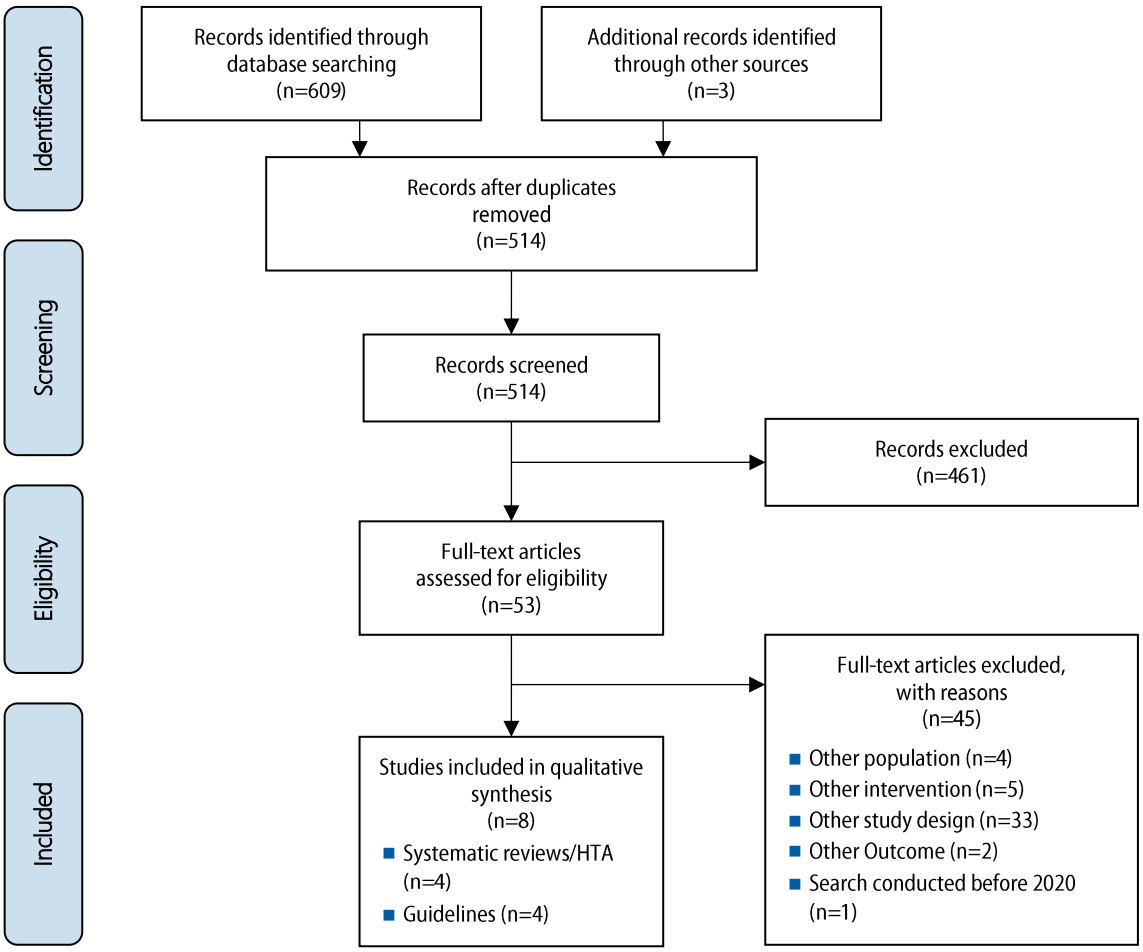


Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.3 Data extraction and risk of bias

Vier-Augen-Prinzip bei allen Arbeitsschritten

We used single-data extraction with verification by a second reviewer. For included systematic reviews and HTA reports, data extraction focused on review methodology, study characteristics, test specifications (including genetic sequencing techniques), reference standards, and clinical outcomes as detailed Table A-1 in the Appendix.

Leitlinienempfehlungen mit Evidenzgrad extrahiert

From the included guidelines, we extracted evidence-based recommendations relevant to our Population, Intervention, Comparison, and Outcome (PICO) question, including recommendation strength and certainty of evidence as described in Table A-2 in the Appendix.

Qualitätsbewertung durch 2 unabhängige Autor:innen

Risk of bias (RoB) for the four included reviews [3, 10, 17, 30] was assessed using the Risk of Bias in Systematic Reviews tool (ROBIS) [38] for systematic reviews and the Appraisal of Guidelines for Research and Evaluation (AGREE) II checklist [39] for clinical guidelines, as detailed in Table A-3 in the Appendix. Of these, three reviews [3, 10, 17] were rated as having a low risk of bias, while one review [3, 10, 17] was rated as unclear RoB.

3.4 Evidence synthesis

narrative Synthese der Ergebnisse

A narrative synthesis of findings from systematic reviews and HTA reports was conducted. Guideline recommendations were synthesised to identify areas of consensus and divergence across different guidelines. If necessary, monetary values were converted into € using the exchange rates from the Austrian National Bank as of 17.10.25 [40].

3.5 Contextualisation for Austria

External Austrian experts were asked to provide input on Austrian relevant aspects (e.g., organisational aspects) in written format, next to formal peer-review of the report. Based on this input, a specific subsection in the discussion was dedicated for both discussing applicability of evidence and guideline recommendations to Austria and summarising further implementation aspects for Austria.

4 Results: Systematic reviews/Health Technology Assessments

Ergebnisse systematischer Reviews zu Carrier Screening

The following chapter presents results from systematic reviews and Health Technology Assessment (HTA) reports examining carrier screening with a focus on Cystic Fibrosis (CF), Spinal Muscular Atrophy (SMA), Hemoglobinopathies as well as Fragile X Syndrome (FXS), following the Population, Intervention, Comparison, and Outcome (PICO) framework.

4.1 Included systematic reviews/Health Technology Assessments

4 SRs/HTAs inkludiert

For the evaluation of carrier screening with a focus on CF, SMA, Hemoglobinopathies, and FXS, four reports were included:

- *Health Quality Ontario (HQO) 2023 [3]:* A comprehensive health technology assessment evaluating clinical effectiveness, safety, cost-effectiveness, budget impact, organisational aspects, and ethical considerations of carrier screening (universal vs. risk-based; single-disease panels vs. Expanded Carrier Screening (ECS)) for CF, SMA, Hemoglobinopathies, and FXS.
- *Ramdaney et al. 2022 [30]:* A systematic review assessing clinical utility, psychosocial impact, and provider perspectives on ECS in the US population.
- *Banzi et al. 2023 [10]:* A systematic review as part of a health technology assessment evaluating effectiveness, organisational features, and economic aspects of population-based CF carrier screening in reproductive-age adults using the EUnetHTA Core Model [37].
- *Wang et al. 2023 [17]:* A systematic review and meta-analysis assessing the clinical utility of reproductive carrier screening for preconception and pregnant couples, including outcomes on identified high-risk couples and reproductive decision-making.

Throughout this report, Ramdaney et al. [30], Wang et al. [17] and Banzi et al. [10] are referred to as systematic reviews (SR) using their respective citation numbers, whilst the HTA from Health Quality Ontario [3] is referred to as 'HQO HTA' to reflect its broader scope. The term 'review' is used as an umbrella term for any included document.

Characteristics of included reviews/Health Technology Assessments

systematische Suchen 1990-2022

The systematic searches of the included reviews were conducted, ranging from 1990 to 2022, with some reviews having defined a filter for the last 10 years in their systematic search [3, 10, 17, 30]. The included reviews evaluate the clinical effectiveness, utility, economic aspects, and patient/provider perspectives of carrier screening with a focus on CF, SMA, Hemoglobinopathies and FXS.

klinische Wirksamkeit basierend auf 4 SRs/HTAs, überwiegend Beobachtungsstudien, 1 RCT identifiziert

The clinical effectiveness was evaluated based on the evidence reported in all four included SRs/HTAs, which predominantly identified SR, observational studies and one RCT. One SR [30] included 36 primary studies, which were predominantly observational (n=30) alongside one RCT and five in-silico studies. Another SR [10] included 71 publications, while HQO HTA [3] identified 107 studies assessing clinical effectiveness, health economics, and ethical aspects. One further SR [17] included eleven studies, separated into quantitative (n=10; randomised controlled trials, prospective cohort studies, etc.) and qualitative (n=1) analyses (Interviews, focus groups, etc.). The breakdown of these studies is as follows: Clinical Effectiveness and Safety (n=107; mixed methods including randomised controlled trials, observational studies, and systematic reviews), Health Economic evaluations (n=21; cost-effectiveness analyses, cost-utility analyses, etc.), and ethical or organisational aspects (n=29; Qualitative studies, policy analyses, etc.). The geographic scope of the included studies differed significantly. One SR [30] focused exclusively on the United States of America (USA). Another SR [10] included studies from Australia, the Netherlands and the United Kingdom (UK). Two reviews [3, 17] had a broad international scope, including studies from Africa, Asia, Europe, North America, and Oceania.

Population: Individuen mit Kinderwunsch oder während Schwangerschaft

The reviews predominantly included individuals and couples who were considering a pregnancy or who were pregnant [3, 17], only one SR [10] had a broader focus and also included other adults of reproductive age. Another SR did not clearly describe the scope of the target population [30], but also described provider and test-outcomes. One SR [10] solely focused on carrier screening for CF, and the HQO HTA [3] assessed carrier screening for CF, SMA, Hemoglobinopathies, and FXS. The remaining reviews [17, 30] focused on multiple genetic conditions (including the conditions in the scope of this report). Further characteristics concerning the type of screening, carrier screening strategy and included study designs of the reviews are presented in Table 4-1 and detailed study characteristics and outcomes of the SR and HTA are outlined in Table A-1 in the Appendix [10].

Interventions and comparators: the reviews included population-based and reproductive carrier screening programmes – single-disease or expanded – for autosomal (AR) and X linked (XL) conditions. The interventions varied by conditions included, testing modality and timing and programme delivery. The included reviews [3, 10, 17, 30] showed a wide range of comparators such as no screening, minimal or alternative screening strategies.

Table 4-1: Type of screening, indication, carrier screening strategy and included study designs of the reviews

Name, year	Type of screening	Screening approach	Indication	Carriers Screening strategy	Included study designs
HQO HTA, 2023 [3]	ECS, minimal guideline	Individual, couple	CF, SMA, Hemoglobinopathies, FXS and multiple genetic conditions	Universal and risk-based	RCTs, SRs, comparative and non-comparative
Ramdaney, 2022 [30]	ECS, Minimal guidelines	Individual, couple	Multiple genetic conditions	universial	Observational, in silico RCT
Banzi, 2023 [10]	n.a	Individual, couple	CF	universal	SRs, overviews, Primary studies, any design
Wang 2023 [17]	ECS, massive parallel sequencing (NGS), genomic sequencing	Individual, couple	Multiple genetic conditions	universial	SR, Primary studies

Abbreviations: CF … Cystic Fibrosis; ECS…Expanded Carrier Screening; HTA … Health Technology Assessment; n.a … not available; RCT … Randomised Controlled Trial; SR … Systematic Review;

Selected outcome domains

Endpunkte in 4 Reviews:

In accordance with the PICO framework, the relevant outcomes were grouped into four key domains: effectiveness/safety (EFF/SAF), economic (ECO), organisational (ORG), and ethical (ETH) aspects (see Table 4-2).

alle Reviews bewerteten klinische Wirksamkeit und Sicherheit

All the included reports evaluated the clinical effectiveness and safety of different screening strategies [3, 10, 17, 30]. Most reviews primarily included observational studies, while two also incorporated randomised controlled trials (RCTs) [3, 30], with the number of included studies ranging from 11 [17] to 107 [3].

ökonomische Aspekte in einem Review

Economic (ECO) considerations were also assessed in one of the four reviews, where the HQO HTA [3] report also performed a cost-effectiveness, cost-utility and budget-impact analysis. The organisational (ORG) and ethical (ETH) domains were also only reported in one study, the HQO HTA [3], which identified 29 studies covering "Ethical or organisational aspects." This was the only review to provide a comprehensive assessment across all four domains. An overview of the outcome domains of the included reviews is provided in Table 4-2. The specific findings for each of these outcomes will be described in detail in the following parts.

Table 4-2: Overview of included systematic reviews and outcome domains.

Name, year	EFF/SAF	ECO	ORG	ETH
HQO HTA, 2023 [3]	X	X	X	X
Ramdaney, 2022 [30]	X			
Banzi, 2023 [10]	X			
Wang 2023 [17]	X			

Abbreviations: EFF/SAF … effectiveness and safety domain, ECO … economical domain, ETH … ethical domain, HQO HTA … Health Quality Ontario Health Technology Assessment, ORG … organisational domain.

Carrier screening methods assessed

Vergleiche verschiedener Strategien: universell vs. risikobasiert, ECS vs. Single-Disease, vs. kein Screening

The included reviews compared various carrier screening strategies. The HQO HTA [3] provided comprehensive direct comparisons: universal vs. risk-based screening for all four conditions, and ECS vs. single-disease panels. One review [17] synthesised evidence on multi-condition screening ranging from three to 176 conditions. Another review [30] assessed ECS (broad panels) compared to minimal guideline-based screening in US populations. One review [10] evaluated population-based CF screening programs. All reviews included comparisons to no screening.

präkonzeptionell und pränatal

Screening was assessed at preconception and prenatal timepoints, using sequential or concurrent partner testing approaches [10, 17, 30]. Screening strategies varied by setting, invitation method, and population characteristics.

Panel size and composition

Panel-Größen stark variabel: von Einzelerkrankungen bis über 400 Erkrankungen (ECS)

Panel sizes varied substantially in all included reviews: single-disease panels (one to four conditions), small ECS panels (three to ten conditions), medium ECS panels (eleven to 100 conditions), and large ECS panels (101 to 400+ conditions). The HQO HTA [3] focused on the four conditions of interest (CF, SMA, Hemoglobinopathies, FXS). Another SR [10] solely focused on CF, while

two reviews [17, 30] included studies with broader ECS panels, often without specifying all conditions. The term "expanded carrier screening (ECS)" was used inconsistently, referring to panels ranging from three to over 400 conditions, and most included reviews did not group the ECS strategies according to the number of tested conditions.

Molecular testing methods

Testmethoden selten berichtet

The molecular testing method was rarely reported in the included reviews. However, Next-Generation Sequencing (NGS)-based gene panel sequencing was the predominant method for ECS. Single-disease panels used targeted genotyping (PCR, allele-specific assays).

Risk of Bias (RoB) assessment and methodological quality

RoB aller Primärstudien von Reviews bewertet, verschiedene Tools je nach Studiendesign

The Risk of Bias (RoB) of included reviews was rated to be low in three reviews [3, 10, 17] [30] and unclear in another review [30]. The RoB [38] of the included primary studies was critically appraised by all included reviews. The HQO HTA [3] utilised the Cochrane Risk of Bias tool [41] for RCTs and the ROBANS (Risk of Bias Assessment tool for Non-randomised Studies) [42] tool for RoB assessment of primary studies. the RoB of included observational studies ranged from low to high. High RoB was identified in the areas of confounding variables (51/96 studies), incomplete outcome data (50/96 studies), selection of participants (41/96 studies), and selective outcome reporting (31/96 studies). Conversely, low RoB was identified in intervention measurement or blinding of outcome assessment (0/96 studies for both domains).

One SR [10] focusing on Cystic Fibrosis carrier screening used the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews, version 2) [43] checklist to assess methodological quality and the Newcastle-Ottawa Scale for comparative cohort studies [44]. Specific RoB ratings were not reported. Another SR [30] assessed the methodological quality using different tools depending on the study design: the Newcastle-Ottawa Scale [44] for cohort studies, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist [45] for case series, and the Cochrane Risk of Bias 2.0 [3] for RCT. The majority of which were rated as having a high risk of bias (rated as 'serious/poor' or 'very serious/very poor'). Predominant concerns included reporting bias, small sample sizes, and a lack of generalisability, without providing further domain-specific breakdowns of the assessment. Another review [17] assessed its included studies using the AXIS [46] critical appraisal tool for cross-sectional studies and the NICE (National Institute for Health and Care Excellence) qualitative studies appraisal checklist, finding the overall risk of bias to be low to medium [47]. Five and six out of eleven included studies were rated as having low or moderate RoB, respectively.

Synthesis

verschiedene Synthesemethoden: Meta-Analysen, Mixed-Methods oder narrative Synthese je nach Evidenz

For data synthesis, the reviewed studies employed diverse methodologies. One SR [17] conducted a comprehensive quantitative analysis, which included a meta-analysis of proportions and meta-regression analyses. They pooled data using a random-effects model (DerSimonian-Laird) to calculate overall estimates for key outcomes. Similarly, one SR [30] utilised a mixed-methods approach, performing a random-effects meta-analysis for the specific outcome of ECS uptake while applying a narrative synthesis for non-quantitative data

or quantitative data unsuitable for meta-analysis. In contrast, other reviews focused exclusively on qualitative synthesis. The HQO HTA [3] performed a qualitative analysis, presenting their findings in a narrative summary and further applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [48] tool to evaluate the certainty of the body of evidence. This variation highlights that the choice of synthesis strategy was tailored to the nature of the available evidence and the specific objectives of each review.

Funding

Finanzierung der Primärstudien nicht systematisch berichtet

Funding for the included reviews came from a diverse range of governmental and non-profit organisations. Governmental support was provided by the Ontario Ministry of Health for the HQO HTA [3], and the Australian Government's Medical Research Future Fund [17]. Support from professional and non-profit bodies included support by a grant from the Italian Cystic Fibrosis Research Foundation for the review of an HTA [10] and funding from the National Society of Genetic Counselors (NSGC) for another SR [30]. The funding sources of the individual primary studies included in these SR and HTA were not systematically reported across the reviews.

4.2 Clinical effectiveness and safety

klinische Wirksamkeitsendpunkte: z. B. Screening-Inanspruchnahme, identifizierte Risiko-Paare, Einfluss auf Reproduktions-entscheidungen

The following clinical effectiveness outcomes were considered within the following report:

- Clinical utility
- Patient-relevant outcomes and
- Clinical validity (test performance).

For clinical utility and patient-relevant outcomes, the included reviews captured the following endpoints:

- *Screening Uptake ([3, 10, 30]):* This refers to the rate of participation in carrier screening. Participation can include only the primary person tested or also their partner.
- *Proportion of At-Risk Couples ([3, 10, 17, 30]):* This endpoint can be measured as the proportion of couples identified through carrier screening as being at an increased risk of having a child affected by the condition.
- *Reproductive Decision-Making Impact ([3, 17, 30]):* This endpoint assesses the influence carrier screening results have on current or future reproductive choices. The most reported decisions involved choosing subsequent prenatal diagnostic testing and In Vitro Fertilisation (IVF) or deciding on pregnancy termination based on the screening results.
- *Psychological Impact ([3, 17]):* This refers to the potential psychological effects, especially the level of anxiety when undergoing carrier screening (or not) and receiving the test results.
- *Downstream Impact ([3, 10, 30]):* These are consequences that arise following the screening test results or the decisions made based on them. Examples include complications from subsequent diagnostic

tests, rates of cascade testing for other family members, and the impact of finding variants of uncertain significance or Fragile X premutation carriers.

Test Performance (clinical validity) was captured by one report [3]: This endpoint relates to the diagnostic accuracy of the screening tests, specifically their sensitivity (detection rate) and specificity. While test performance was excluded as an outcome measure in the clinical review, these characteristics were used as key input parameters for the economic models.

keine Sicherheitsendpunkte erfasst

None of the included reports captured *safety endpoints*, such as in their assessments, although psychological impact may also be regarded as a potential safety endpoint.

The results of the endpoints will be described narratively with reference to the included reviews and the certainty of evidence, if reported by the included reviews.

Screening Uptake

variable Inanspruchnahme in 3 Reviews

Screening uptake was reported in three reviews [3, 10, 30] in various ways, indicating variability in uptake rates, which varied substantially by setting, invitation method, and population characteristics

universelles Screening: 68-71 % Uptake, risikobasiert: 4,7-5 %

Very low certainty evidence from 45 observational studies was found by the HQO HTA [3] for this endpoint. This review found that universal preconception carrier screening had a higher uptake rate (71% ± 7%) compared to risk-based preconception screening (5% ± 0.5%). Similarly, the HQO HTA reported that universal prenatal screening demonstrated a pooled uptake rate of 68%, whilst risk-based prenatal screening was estimated with an uptake of 4.7% (±0.5%). The reporting of the uptake rate also varied across the studies, with some reporting only rates for pregnant individuals (range from 10%-100%) and others including at-risk couples (20%-90%). Overall, the GRADE certainty was rated as very low for the screening uptake in the HQO HTA [3], and the fact that the screening uptake was calculated from inputs of various studies, potentially limiting comparability.

in IVF-Setting und bei schrittweiser Testung bis 100 %

Another review found low certainty evidence [30] that the ECS uptake rate ranged from 8.6% to 99.5% across five included observational studies and different study populations. An analysis of these studies revealed notable differences between screening in the preconception and prenatal periods, with the highest acceptance identified in IVF clients (74.5%).

Another SR [10] compared the uptake of different screening strategies. Based on 40 primary studies, 6 modelling studies and three reviews, high heterogeneity of screening uptake was found. The screening uptake ranged from 4% to 100% across included studies. Primary care had lower inconsistent uptake (4% to 75%). In the preconception primary care setting it was (75% to 91%) and in the antenatal/hospital setting, screening uptake across studies ranged from 59% to 100%. Yet, the highest uptake was found when applying a stepwise approach (i.e., inviting and testing the pregnant individual first and if the first person is found to be a carrier, inviting the second person). In the preconceptional setting, the screening uptake varied between individuals (17% to 42%) and couples (3% to 75%) and in the prenatal phase between couples (76% to 89%) and a stepwise approach (82% to 100%). Hence, high variability of uptake was found with regard to different modalities between different approaches and modalities of invitation and testing.

Proportion of At-Risk Couples

Anteil identifizierter Risiko-Paare in 3 Reviews berichtet

The proportion of couples identified as at-risk (i.e., both partners are carriers for the same autosomal recessive condition) was reported in three reviews [3, 17, 30]. The reported rates vary significantly based on the specific conditions screened, the testing methodology, and the prevalence of conditions within the study population.

stark variabel je nach getesteten Erkrankungen und Population

The HQO HTA [3] found moderate certainty of evidence (93 observational studies) indicating that the proportion of screened couples identified as at-risk ranges from 0-5% for Cystic Fibrosis (CF), approximately 1% for Spinal Muscular Atrophy (SMA), 3% for Fragile X Syndrome (FXS) and reached as high as 25% for Hemoglobinopathies. The GRADE certainty was moderate for the proportion of at-risk couples and for reproductive decision-making impact. Another SR [30] found eight observational studies with a range of at-risk couples identified of 0.1% to 16.9%. The SR further found high variability across studies with regard to specific populations, conditions/genes/mutations tested, as well as the panels utilised.[2] Lastly, one SR [17] included five observational studies, which screened for 3 to 176 conditions, indicating a range between 1 and 24 high-risk couples identified if 1,000 individuals are screened.

Reproductive Decision-Making Impact

etwa zwei Drittel nutzen pränatale Diagnostik,

Schwangerschafts-abbruchrate bei Betroffenen rund drei Viertel

The impact on reproductive decision-making was reported in four reviews [3, 10, 17, 30]. The HQO HTA [3] found evidence from 59 observational studies (moderate certainty of evidence). The probability of undergoing PND given positive result was estimated to be 95% (standard error/SE: 9.5%). Furthermore, the probability of assisted reproductive technologies was 79% (SE: 0.4) for IVF or Pre-Implantation Genetic Testing (PGT) and 16% (SE: 0.3) for other choices including adoption or no future pregnancy. Termination rates vary by condition, estimated at 80% (SE 0.03) for CF, 67% (SE 0.04) for SMA, and 29% (SE 0.04) for FXS and Hemoglobinopathies. Further, the findings for Hemoglobinopathy showed that decisions for PND and subsequent pregnancy management, including Termination Of Pregnancy (TOP) were influenced by the type and severity of this condition [3].

Another review [17] found a pooled uptake rate of 64.4% (95% CI: 36.4-92.3) for prenatal diagnosis (PND) and 63.1% (95% CI: 53.8-72.5) for IVF with PGT. Among pregnancies confirmed to be affected within the PND, the pooled TOP rate is 71.4% (95% CI: 052.4-90.4) [17].

Another review [10] found one study reporting that 91% of the couples with a one-in-four risk of a child with CF opted for PND and in eight cases, where the fetus was found to be affected, couples chose to terminate.

Similarly, another review [17], despite limited certainty due to the included studies' low-to-medium risk of bias and heterogeneity potentially affecting the reliability of pooled estimates, synthesised findings from 10 quantitative and 1 qualitative study. The review provided a detailed overview of reproductive decisions for preconception and pregnant couples. When at-risk couples were identified during the preconception phase, most of them would undergo IVF in addition to PND. For at risk couples identified during pregnancy, two studies separated by disease severity. Between 39% to 55% of pregnant

[2] The SR further included modelling studies that equally found high variability in dependence of the factors such as

at risk couples would undergo PND, whereas it is 0% to 29% for moderate conditions. In case these PND revealed an affected pregnancy, the TOP rate further varied by disease severity. It was between 50% to 100% for profound disease severity, 45% to 50% for sever and 25% for moderate conditions [30].

Another SR [30] found two studies in the prenatal setting. In one study, where the ECS screened for 176 conditions, 56 (37%) of the at risk couples chose a PND. In this cohort, 8 out of 20 affected pregnancies were terminated (40%). In another study, where the ECS screened conditions were unspecified, 33% choose PND which resulted in three affected pregnancies and two of them were terminated.

Psychological Impact

psychologische Auswirkungen inkonsistent: teils Angstreduktion, teils negative Emotionen wie Wut und Bedauern

Psychological impact was reported in two reviews [3, 17]. The HQO HTA [3] found very low certainty and inconclusive evidence (8 observational studies). Although some studies included in the HQO HTA found a reduction in anxiety, and some other studies also report negative emotions such as anger and regret, only few studies employed standardised assessment methods. A review [17] with limited-certainty evidence indicates that carrier screening may increase anxiety, especially when it identifies at-risk couples for conditions that are mild or treatable. Additionally, pregnant women who discovered they were carriers without receiving pre-test counselling frequently expressed confusion about the meaning and consequences of a positive result.

Downstream Impact

nachgelagerte Effekte: inkonsistente Ergebnisse

Out of all the reviews considered, a total of two report on downstream impact [3, 10]. The HQO HTA [3], based on 12 observational studies with a very low certainty of evidence, found that the results on fetal loss were inconsistent. Three studies included in the HQO HTA [3] reported no cases of fetal loss, while two studies reported spontaneous fetal loss associated with prenatal diagnosis (one study found a 1.1% rate, with 3 losses in 269 cases), for example through membrane rupture. With regard to cascade screening, five of the included studies noted it as either offered or completed. The other SR [10] included an observational study from Italy revealing that implementing a carrier screening program led to a 15% annual reduction in the birth prevalence of Cystic Fibrosis (CF) in a particular Italian region. In contrast, a neighbouring region without such a program experienced only a 1% annual decline in CF birth prevalence.

Test Performance

ECS mit überlegener Testgenauigkeit, ...

Only one review included information on test performance, although the certainty of evidence was not formally assessed for this endpoint [3]. For CF, SMA, Hemoglobinopathies and FXS, the sensitivity and specificity of standard (single-disease) panels ranged from 90% to 95.7% and 99% to 99.3%, respectively. In contrast, the HQO HTA found a sensitivity of 99.88% and a specificity of 99.99% of an expanded (multiple-diseases) NGS panel.

... aber Risiko der Identifikation von Varianten unklarer Signifikanz

The HQO HTA [3] further noted that ECS panels may identify Variants of Uncertain Significance (VUS), which can contribute to clinical uncertainty. Yet, the VUS rate is hard to quantify in clinical studies and was, hence, not reported in any identified studies.

Safety

None of the studies included in the reviews addressed safety endpoints.

4.3 Economic aspects

Economic aspects of carrier screening were addressed in the HQO HTA [3].

ökonomische Aspekte nur in HQO HTA bewertet

Characteristics of the economic evaluations and models

The HQO HTA [3] followed a three-step approach. First, a systematic search for relevant economic literature was conducted to assess the cost-effectiveness of population-based preconception and prenatal genetic carrier screening for CF, SMA, Hemoglobinopathies and FXS and found 21 studies which fulfilled the inclusion criteria. Of the 21 included studies, two were SR of economic studies and 19 were primary economic evaluations. Some analysed multiple-disease carrier screening, and others single-disease carrier screening. The HQO HTA [3] further conducted a cost-effectiveness, a cost-utility as well as a budget impact analysis for universal and risk-based carriers screening for the conditions CF, SMA, Hemoglobinopathies and FXS. The cost-effectiveness analysis evaluated short-term costs and clinical outcomes related to screening and events during pregnancy (e.g. probability of at-risk pregnancy, probability of false negative, chance of having an affected birth). The incremental cost-effectiveness ratio (ICER) was expressed as additional cost per additional unit of health outcome (e.g. additional cost per at-risk pregnancy identified or per affected birth) [3]. The cost-utility analysis followed a long-term perspective and focused on Quality-Adjusted Life Years (QALY) per couple tested and total direct medical costs per couple tested over lifetime, starting at 0 years in the newborn and 20 years in the parent utility perspective and together estimated the incremental cost-utility ratio (ICUR) [3]. The budget impact analysis estimated the budget impact for publicly funded universal or risk-based carrier screening for people who are considering a pregnancy (preconception) or who are pregnant (prenatal) over a time period of five years, for both single-disease carrier screening (standard panel) and ECS (multi-disease panel).

HQO HTA: 21 ökonomische Evaluationen identifiziert; zusätzlich eigene Kosteneffektivitäts-, Kosten-Nutzwert- und Budget-Impact-Analysen

Results

The HQO HTA [3] included a systematic review of cost-effectiveness evaluations with mixed results. Some studies indicated that compared to risk based or no screening, population-based preconception and prenatal CS for CF, SMA, Hemoglobinopathies and FXS could be cost-effective. This finding needs to be considered within the context of the limitations outlined.

Kosteneffektivität in kanadischem Setting:

The cost-effectiveness and cost-utility analyses of preconception and prenatal carrier screening in the HQO HTA [3] report are specific to the Canadian healthcare context, reflecting the country's unique infrastructure, funding model, and healthcare priorities. The key findings include[3] the following:

- **Cost-Effectiveness of Universal carrier screening:** Universal preconception and prenatal carrier screening with single-disease panels for all conditions was assessed as cost-effective in identifying at-risk preg-

Kosteneffektivität stark parameterabhängig, ICER variiert je nach Uptake und Trägerfrequenz erheblich

[3] Note: Based on the current market data for October 17, 2025: The exchange rate is 1 EUR = 1.1601 USD

nancies, with Incremental Cost-Effectiveness Ratios (ICERs) of approximately €25,000 per additional at-risk pregnancy identified and €317,200-€372,400 per cases where reproductive options could be performed. By health condition, universal carrier screening with single-disease panels was cost-effective for CF, SMA and Hemoglobinopathies, whereas for FXS, risk-based screening with the standard panel was assessed as the dominant strategy. However, the ICER is highly sensitive to several parameters (e.g. at a 20% uptake in carrier screening, the ICER would be 1.6 times higher than in the reference case or a ten times higher carrier frequency in CF or SMA would result in an ICER of €316,981) [3].

- **Cost Comparison of Universal and Risk-Based Programs:** Over a five-year period, the cost of universal carrier screening using the standard panel ranged from €179.3 (preconception carrier screening) – €110.3 (prenatal carrier screening) million and for universal carrier screening using a multi-disease panel ranged from €423,2 (preconception carrier screening) – €262.9 (prenatal carrier screening) million for CF, SMA, Hemoglobinopathies and FXS. This was significantly higher than risk-based screening programs, which were estimated at €1.03 (preconception carrier screening) – €0.68 (prenatal carrier screening) million for standard panels and €2.33 (preconception carrier screening) – €1.47 (prenatal carrier screening) for multi-disease panels.
- **Potential for Long-Term Cost Savings:** Analysis indicated that universal preconception and prenatal carrier screening can lead to a small change in QALYs and could result in long-term savings by preventing affected births and reducing treatment-related expenses [3].

Limitations

identifizierte ökonomische Evaluationen heterogen mit methodischen Qualitätsproblemen, Generalisierbarkeit stark eingeschränkt

The HQO HTA [3] found that most studies in the systematic review of economic evaluations were heterogeneous regarding model structure, population, outcomes, and inputs, with potentially serious or very serious methodological quality issues. These limitations hindered the generalizability and transferability of results. To address this, the authors conducted cost-effectiveness, cost-utility, and budget impact analyses from a Canadian healthcare perspective [3]. The main limitations involved assumptions about clinical parameters and practices due to data gaps. Sensitivity analyses showed that the results were highly dependent on key parameters (e.g., screening uptake, carrier frequency). Similarly, the budget impact analysis relied on estimated parameters, with outcomes sensitive to factors such as target population size and partner testing rates.

4.4 Organisational aspects

organisatorische Aspekte in einem HTA: Implementierung erfordert Investitionen in Fachpersonal, Schulungen und optimierte Arbeitsabläufe

Organisational aspects were considered in one included HTA report [3]. The implementation of carrier screening programs was found to experience substantial organisational challenges, particularly in the areas of human resources, infrastructure, and clinical workflows [3]. Carrier screening requires investments in building a specialised workforce, providing improved training programs, and streamlining workflows [3]. The HQO HTA [3] found that feasibility and scalability of ECS programs depend on key factors such as effective program management, the implementation of standardised pre-test counselling protocols, and the strategic allocation of organisational resources. Without resolving these systemic barriers, carrier screening initiatives may struggle with inefficiencies, reducing their capacity to deliver the desired clinical and psychological benefits.

4.5 Ethical aspects

ethische Aspekte in 1 HTA (22 Patient:innen-Interviews): Schwangerschaftsabbruch, Autonomie/informierte Entscheidung, Datenschutz

The HQO HTA [3] identified aspects relating to ethics and equity through qualitative interviews of 22 patients. The main themes identified related to general ethical aspects of **termination of pregnancy**, **autonomy and informed decision making** and **privacy concerns**.

- **Termination of pregnancy** was acknowledged as an ethical concern by many participants, but it was also highlighted that carrier screening can also be valuable for adults to support a child, not exclusively to terminate pregnancy.
- **Autonomy and informed decision-making** was mentioned insofar as the persons involved in carrier screening may not understand the limitations of the approach and the implications of a test result, and language barriers and issues relating to access may impose barriers in informed decision-making.
- **Privacy** was further highlighted by one participant, with potential concerns that carrier testing may inadvertently identify parentage in some situations.

identifizierte Themen nicht erschöpfend

The identified themes in the HQO HTA are not exhaustive, and general ethical aspects are critical in any implementation of such screening strategies. Furthermore, some aspects, such as anxiety as a potential psychological impact, indirectly cover ethical aspects, which are described in chapter 4.2.

5 Results: guideline recommendations and committee opinions from professional societies

internationale Leitlinien und Stellungnahmen inkludiert

In the absence of formal evidence-based recommendations in the European setting, we included both guideline recommendations and committee opinions from international professional societies in the context of carrier screening for several common inherited conditions. This chapter presents an overview of these, specifically addressing carrier screening for Cystic Fibrosis (CF), Spinal Muscular Atrophy (SMA), Hemoglobinopathies and Fragile X Syndrome (FXS).

5.1 Included guidelines

vorwiegend US-amerikanische Leitlinien identifiziert

For the role of carrier screening for CF, SMA, Hemoglobinopathies and FXS, guideline recommendations and committee opinions from the following US-based organisations were included.

- *American College of Obstetricians and Gynaecologists (ACOG) 2017 Committee Opinion (reaffirmed in 2020) [24]:* an opinion which outlines the evidence base for different carrier screening (ethnic-specific, panethnic, expanded) strategies
- *American College of Medical Genetics and Genomics (ACMG) 2021 [23]:* a practice resource on screening for autosomal recessive (AR) and X-linked (XL) conditions during pregnancy and preconception for different carrier screening strategies
- [American] *National Society of Genetic Counsellors (NSGC) 2022 [49]:* a practice guideline on screening for AR and XL conditions, focusing on Expanded Carrier Screening (ECS) for reproductive risk assessment
- *Carelon Clinical Appropriateness Guidelines 2025 [50]:* an appropriateness guideline on carrier screening for AR and XL conditions

Throughout this report, the term guideline covers guideline recommendations and committee opinions.

Methodological quality of included guidelines

Leitlinien mit fehlender Übertragbarkeit auf österreichischen Kontext

According to the AGREE II [39] assessment, all of the included guidelines for carrier screening are recommended for use, although two are recommended with modifications [23, 24]. The NSGC [49], ACOG [24], and ACMG [50] guidelines showed strong stakeholder involvement. Overall, each included guideline demonstrated some methodological limitations – particularly in the depth of their evidence review and synthesis – which should be carefully considered when interpreting their recommendations. The applicability of recommendations to the Austrian context is limited as all guidelines were developed by US experts, they are most relevant to clinical practice in the United States and not to the Austrian context. The AGREE II rating can be found in Table A-3.

Recommendation classification systems of included guidelines

heterogene Empfehlungssysteme, nur NSGC nutzt GRADE-Framework

The included guidelines use different recommendation systems. ACOG [24] presented as consensus statements developed by the Committee on Genetics to reflect emerging clinical and scientific advances; ACMG [23] publishes a practice resource that does not grade recommendation strength; instead, it defines a tiered panel scope by carrier frequency. NSGC [49] uses the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework; under GRADE, certainty of evidence ranges from high (⊕⊕⊕⊕) to very low (⊕⊖⊖⊖). Carelon [50] does not use a specific recommendation classification system like others. Instead, Carelon develops its own "Clinical Appropriateness Guidelines". These guidelines aim to establish "objective and evidence-based criteria" to determine whether services are medically necessary.

5.2 Guideline synopsis

konsensbasierte Empfehlungen meist ungraduiert, nach Zielpopulation und Ansatz strukturiert

The synthesis solely includes consensus-based recommendations, where the majority lack a formal appraisal of the quality, strength and consistency of the available evidence [23, 24, 50]. However, to reflect the increasing inclusion of screening guidance in the clinical context, the synopsis considers these recommendations. Before presenting the indication-specific recommendations for CF, SMA, Hemoglobinopathies and FXS, the guideline positions are summarised under the following key headings:

- Target population
- Carrier screening approach
- Risk-based or condition-specific carrier screening

Summaries of the carrier screening recommendations from the respective guidelines – including those specific for CF, SMA, Hemoglobinopathies and FXS – are presented in Table 5-1. Verbatim guideline recommendations are provided in Table A-2 in the Appendix.

Target population

Zielpopulation: Schwangere und Partner:innen mit Kinderwunsch

The target population is relatively homogeneous across the recommendations as all of the guidelines address pregnant individuals, individuals who are considering reproduction, as well as their reproductive partners [23, 24, 49, 50].

Carrier screening approach

Empfehlungen variieren: von ethnisch-spezifisch bis ECS, 1 Leitlinie empfiehlt abgestuftes System nach Trägerfrequenz

The recommended screening approach varies across the recommendations. ACOG [24] recommends ethnic-specific, pan-ethnic, and expanded carrier screening as acceptable strategies for both pre-pregnancy and prenatal carrier screening. NSGC [49] specifically recommends ECS as an alternative to the ethnicity-based carrier screening, describing it as a conditional recommendation, which should consider the balance of benefit and harm of ECS and the underlying low and moderate evidence certainty. Carelon [50] recommends condition-specific carrier screening. ECS is only recommended if certain criteria are met, for example, a higher risk due to family history. The same applies to condition-specific requirements. ACMG [23] recommends using a

tiered screening system for specifying carrier screening and selecting specific genes/conditions to be included in carrier screening (see Figure 5-1). For example, Tier 1 follows an ethnic and population neutral approach for CF, SMA and risked based screening, whereas 'higher' Tiers consider a lower carrier frequency. ACMG recommends a Tier 3 screening and does not recommend a routine offering of Tier 4 panels (only in certain cases like second cousins or closer).

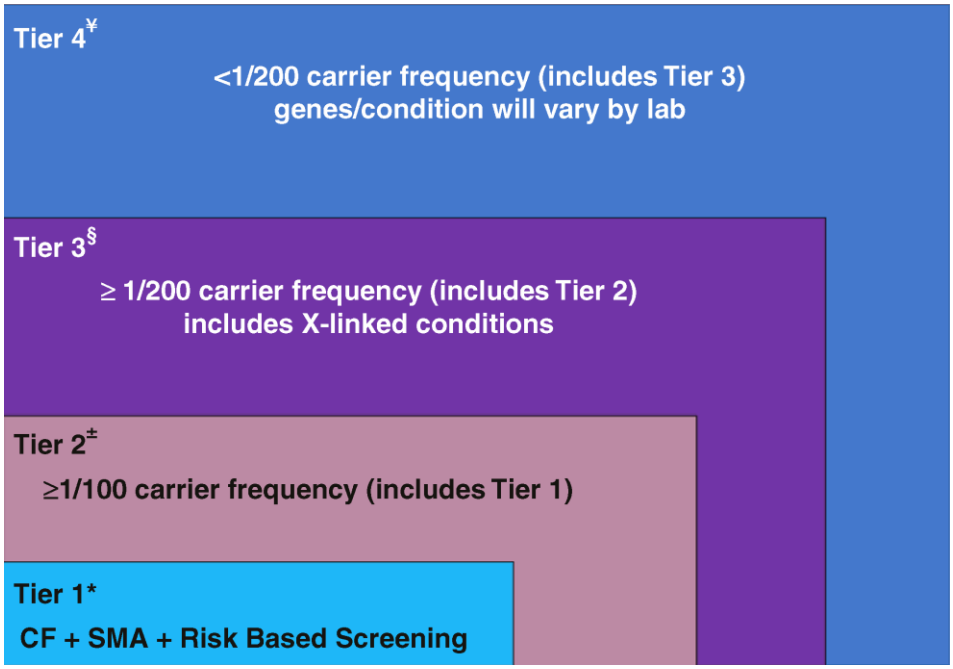


Figure 5-1: The Euler diagram shows an overlapping tiered approach to carrier screening [23]

Risk-based or condition-specific carrier screening

überwiegend universelles Screening für CF/SMA empfohlen, FXS risikobasiert, ACMG mit abgestuftem System

Two guidelines [24, 50] propose condition-specific screening for all patients considering pregnancy or already pregnant, as carrier screening for CF, SMA, and Hemoglobinopathies is recommended. Further, both recommend Fragile X premutation carrier screening for women with a family history of FXS disorders, intellectual disability suggestive of Fragile X Syndrome, unexplained ovarian insufficiency or failure, or elevated follicle-stimulating hormone (FSH) levels prior to age 40. Both recommendations [24, 50] propose additional screening as medically necessary if certain criteria are met. This mainly includes the patient's specific family history or ethnic background. For individuals with a known familial genetic mutation, identifying the specific mutation may be of much higher relevance than general carrier screening.

No recommendations were identified, providing context-independent mutations that should be selected for carrier screening.

Summary of the recommendations for carrier screening

Overall, three guidelines [23, 24, 50] are following a broad approach by assessing carrier screening for pregnant individuals, individuals who are considering reproduction and their reproductive partners. Two of those [24, 50] recommend following a universal carrier screening approach for CF and SMA. For Hemoglobinopathies, one recommendation suggests an initial assessment, including a complete blood count to evaluate the risk [24]. Risk-based screening for FXS in women with a family history is suggested by two recommendations [24, 50]. One guideline, the ACMG [23], proposes a tiered approach where screening for more prevalent conditions with higher carrier frequencies is universally offered, while screening for less frequent mutations is reserved for cases with known consanguinity or relevant family/personal medical history.

ECS bedingt empfohlen, Evidenzgraduierung meist fehlend

ECS is recommended as medically necessary if certain criteria are fulfilled (risk-based). One recommendation [49] solely focused on ECS as an option and concluded that it is conditionally recommended as an alternative to ethnicity-based carrier screening, depending on its balance of benefits and harms. However, this recommendation was the only one which graded the level of evidence and grade of recommendation, as the majority of the included guideline recommendations [23, 24, 50] did not report the level of evidence, nor the grade of recommendation (see Table 5-1).

Table 5-1: Overview of guideline recommendations for carrier screening

	Carrier screening recommendation		Explanation	Grade of recommendation	Level of evidence
	Risk based	Universal			
NSGC [49] (2022)	(?)	(?)	Uncertain as the recommendation considers ECS as alternative to ethnicity-based carrier screening	Conditional	Low–moderate
ACOG [24] (2017/2020)	(✓)	(✓)	Universal: CF, SMA, Hemoglobinopathies Risk based: ECS panel disease criteria Fragile X with family history	Not stated	Not stated
ACMG [23] (2021)	(✓)	(✓)	Universal: Tier 3 (AR + XL genes, ≥1/200 freq Risk based: Tier 4 if consanguinity/history	Not stated	Not stated
Carelon [50] (2025)	(✓)	(✓)	Universal: CF, SMA, Hemoglobinopathies Risk based: ECS panel disease criteria Fragile X with family history	Not stated	Not stated

Abbreviations: (✓) … yes; (X) … no; (?) … uncertain; ACMG … American College of Medical Genetics and Genomics; ACOG … American College of Obstetricians and Gynecologists; AR … autosomal recessive; CF … Cystic Fibrosis;
ECS … Expanded carrier screening; NSGC … National Society of Genetic Counselors; SMA … Spinal Muscular Atrophy; XL … X-linked condition; XL … X-linked

6 Discussion

Summary of Findings

Evidenz überwiegend aus Beobachtungsstudien, niedrige bis moderate Vertrauenswürdigkeit der Evidenz

This assessment synthesised evidence from three systematic reviews [10, 17, 30] and one Health Technology Assessment (HTA) report [3] and provided an overview of guideline recommendations of four clinical practice guidelines [23, 24, 49, 50] comparing different carrier screening to no screening with a focus on Cystic Fibrosis (CF), Spinal Muscular Atrophy (SMA), Hemoglobinopathies and Fragile X Syndrome (FXS). The evidence base consisted predominantly of observational studies with moderate to very low certainty (as assessed by one HTA report). The main results can be summarised as follows:

Screening identifiziert Risiko-Paare und beeinflusst Entscheidungen, psychologische Effekte unklar

Clinical effectiveness: All included reviews addressed clinical effectiveness [3, 10, 17, 30]. The Health Quality Ontario Health Technology Assessment (HQO HTA) [3] synthesised over 100 observational studies with Grading of Recommendations Assessment, Development, and Evaluation (GRADE) certainty ratings and found that carrier screening for CF, SMA, Hemoglobinopathies and FXS would:

- Likely identify couples with an increased risk of having an affected pregnancy
- Likely impact reproductive decision-making, whether to continue with an affected pregnancy, and
- May decrease anxiety among pregnant people, although the certainty of evidence is very low.

nachgelagerte Auswirkungen unklar, hochvariable Inanspruchnahme

Further, inconsistent results were found for the potential downstream impact of carrier screening (very low certainty of evidence). The other three reviews [10, 17, 30] did not use GRADE but found similar results. Further, the screening uptake was found to be highly variable (4.7-99.5%).

ECS zeigt überlegene Testgenauigkeit gegenüber Standard-Panels

Test performance: The HQO HTA [3] reported on test performance and found evidence indicating that expanded carrier screening (ECS) using Next-Generation Sequencing (NGS) reaches higher sensitivity and specificity when compared to carrier screening with single-disease panels.

gesundheitsökonomische Analysen nicht auf Österreich übertragbar, hochsensitiv gegenüber Trägerfrequenz und Inanspruchnahme

Economic aspects: The HQO HTA [3] considered economic aspects, with numerous identified cost-effectiveness analyses with varying methodologies and results. Although some studies suggest that population-based carrier screening may be cost-effective, none were applicable to the Austrian healthcare context. The most comprehensive cost-effectiveness analysis conducted for the Canadian context estimated that universal screening with standard single-disease panels for selected conditions may be the most cost-effective carrier screening option, though cost-effectiveness ratios require cautious interpretation due to uncertain willingness-to-pay thresholds. Cost-effectiveness is highly sensitive to methodological details, number of screened diseases, carrier frequency and uptake. Long-term analyses show potential cost savings with screening, particularly when accounting for expensive novel therapies [3]. The economic aspects need to be interpreted with caution, as none of the economic analyses were conducted for the Austrian healthcare context. However, there is a difference if ECS is performed by massive parallel sequencing technology or array-based technology. While array-based methods are generally cheaper, they may be less sensitive than massive parallel sequencing approaches.

Organisational and ethical aspects: The HQO HTA report [3] addressed *organisational considerations*. Resources, infrastructure, and workforce constraints, especially in the context of genetic counselling capacity, were, among others, identified as significant organisational barriers in the Canadian healthcare context. Termination of pregnancy, autonomy, informed decision making and privacy were identified by the same HQO HTA report as important *ethical aspects* to be considered in any carrier screening strategy [3]. These issues are also highly relevant in Austria.

Beratungskapazität als organisatorische Barriere, zentrale ethische Aspekte identifiziert

The main screening strategies assessed included universal approaches versus risk-based approaches. Advanced genetic testing technologies, such as NGS-based gene panels, play a key role in expanding the scope of detection beyond single conditions or traditional ethnicity-based panels [3].

Screening-Strategien: universell oder risikobasiert

Guideline recommendations on expanded carrier screening applicable to Austria are lacking; no formal population-wide carrier screening programme has been established nationally, and most available international guidelines recommend varied approaches. The American College of Medical Genetics and Genomics (ACMG) [23] proposes a tiered framework for carrier screening, which guides the inclusion of specific genes based on carrier frequency. ACMG [23] recommends offering Tier 3 screening to all individuals planning a pregnancy or who are currently pregnant. Tier 3 is defined as screening for conditions with a carrier frequency of ≥1/200. Similarly, the American College of Obstetricians and Gynaecologists (ACOG) [24] finds pan-ethnic and ECS acceptable strategies and recommends universal screening for CF, SMA, and Hemoglobinopathies, but reserves FXS screening for those with risk factors. ACOG [24] also suggests criteria for conditions on expanded panels, such as a carrier frequency of 1 in 100 or greater and excludes adult-onset conditions. Carelon [50] deems universal screening medically necessary for CF, SMA, and Hemoglobinopathies, but restricts ECS to individuals with specific risk factors (e.g., high-risk ancestry, consanguinity, or lack of family history access).

fehlende österreichische Leitlinien, internationale Empfehlungen heterogen, meist universell für CF/SMA

Contextualisation for Austria

Kontextualisierung

This assessment was part of a comprehensive AIHTA project on genetic testing for human health and focused on informing Austrian decision-makers about carrier screening strategies. Several key challenges were identified:

Guideline Applicability: International guidelines on expanded carrier screening vary widely, are mostly from a North American perspective, and are generally not directly applicable to the Austrian setting, where no formalised screening program currently exists. Yet, based on expert input, international guidelines provide a good foundation, especially the Euler framework highlighted in the ACMG guideline, for reflecting and developing an Austrian evidence-based guideline.

fehlende Übertragbarkeit der Leitlininen

Screening Strategy Focus: Selecting the appropriate screening strategy – including the organisation of testing (e.g., preconception vs. prenatal, stepwise vs. couple, expanded vs. single-disease, universal vs. risk-based), counselling approaches, and ethical considerations – is crucial for successful implementation [3, 23, 49]. Aligning with European recommendations, the responsible ECS implementation relies on legal compliance, public education, data protection, and continuous quality management [36], which cover the following aspects according to Henneman et al. (2016) [18] and information from a clinical expert [20]:

Screening-Strategie entscheidend: Zeitpunkt, Testumfang, Beratung, verantwortungsvolle Implementierung nach europäischen Kriterien (12 Aspekte)

1. Carrier screening should primarily inform people about genetic risks to future children and support autonomous reproductive choices.
2. Expanded carrier screening should focus on severe childhood-onset disorders and use tests with high clinical validity and proven clinical utility.
3. A solid, continually updated evidence base is required before and during expanded carrier screening programs.
4. Carrier screening should ideally be offered before pregnancy to maximize reproductive options and minimize emotional stress.
5. Program success should be measured by how well it supports informed reproductive decision-making, not by reducing affected births.
6. Comprehensive information, counselling, and psychosocial support must be provided, including explanations of risks, options, and limitations.
7. Consent processes must clearly explain the purpose and implications of multi-condition screening without overwhelming couples with excessive detail.
8. Participation must be voluntary, informed, and equitable, giving people enough time and information to decide.
9. Genetic testing and counselling should be delivered by accredited services and properly trained professionals.
10. Couples should be assured of continued high-quality care regardless of their choices, and screening should not justify reduced care for affected children.
11. Health professionals and the public need better education and open dialogue about the benefits and limitations of carrier screening.
12. Governments should actively guide responsible implementation, quality control, evaluation, equity, and oversight of both public and commercial genetic testing services.

keine Standards für Panel-Auswahl

Furthermore, there is debate and no uniform approach to implement ECS or deciding which conditions to include on screening panels. Commercial panels often test for conditions which may not be recommended for routine screening by professional societies [31]. However, for a condition to be included on a screening panel, two criteria are essential: the current understanding of the disease progression and reliable availability of validated testing modalities regarding sensitivity, specificity and predictive values. Furthermore, a critical appraisal of the advantages and disadvantages of ECS for the target population is essential [18].

ECS-Panels variabel (Dutzende bis über 100 Erkrankungen), optimale Panel-Zusammensetzung unklar

Expanded vs Single Carrier Screening: ECS using NGS is increasingly affordable, making it a feasible alternative to single-disease panels (e.g., CF, SMA) [30]. However, the HQO HTA [3] found single-disease panels (CF, SMA, Hemoglobinopathies, FXS) most cost-effective in the short term. Although the primary analysis remains robust, the underlying cost assumptions may have shifted since the initial data collection. Long-term models suggest universal screening may be cost-saving. ECS becomes more beneficial when test costs are low or treatment costs are high.

The quantity of conditions screened for by ECS is not standardised, ranging from several dozen to over one hundred. This variability in panel composition, along with the optimal criteria for condition selection, remains a subject of ongoing clinical investigation and policy deliberation [36]. A pan-ethnic approach can detect at-risk couples who might be missed by traditional risk-based methods. However, the optimal number and selection of conditions to

include in screening panels remains debated [24]. The key challenges of ECS will not only be to decide which conditions should be selected for screening but also which pathogenic variants will be reported as well as the availability and decision upon the best infrastructure to analyse large-scale sequencing data [20].

Trend zu universellem Screening international, Umsetzung in Österreich herausfordernd

Risk-based vs. universal Carrier screening: Major guidelines are increasingly advocating for universal (pan-ethnic) screening to ensure equity and address inaccuracies in self-reported ancestry. The ACMG recommends universal Tier 3 screening, while ACOG supports universal screening for CF, SMA, and Hemoglobinopathies. However, risk-based screening remains advised for certain conditions (e.g., ACOG for FXS) or as a prerequisite for accessing expanded panels under some guidelines (e.g., Carelon). Universal screening programs have a higher short-term budget impact but detect more carriers. whereas risk-based programs are less costly but risk missing high-risk couples (HRCs) in the general population. In Austria, adopting a risk-based approach would be difficult due to the lack of established prevalence data for specific groups, while universal screening faces substantial budget, infrastructure and legal challenges. Due to the latter, an Austrian expert hereby perceived a universal screening approach especially difficult to implement. Hence, further consultations in steering committees with Austrian experts is needed to reflect on feasible approaches for Austria.

historisch setzten manche Länder auf risikobasierte ethnische Screeningstrategien: problematisch und ungenau

Historically, carrier screening relied on a risk-based strategy in countries that had implemented such screening strategies, focusing on individuals with a membership in specific ethnic groups perceived to have a higher prevalence of certain disorders [3]. This approach, however, has proven to have significant drawbacks. Crucially, it fails to identify many carriers, as it misses the majority of relevant diseases. most children born with these disorders have no known family history [23]. Furthermore, the reliance on ethnic targeting is increasingly problematic in modern, pan-ethnic populations [3]. Self-reported ancestry can often be inaccurate, and growing rates of mixed ancestry make it difficult to reliably predict genetic risk based on background alone [30]. While this traditional model did lead to single-disease screening for conditions like Tay-Sachs disease and Hemoglobinopathies in specific populations [23], its fundamental limitations highlight the shortcomings of an ethnicity-based framework.

ECS Panel-Größe stark variabel, ACMG bietet Auswahlhilfe

Sequencing Technologies Utilised and Number of Mutations: The literature did not specify which sequencing platforms were implemented, but it is likely that ECS relies primarily on NGS gene panel sequencing methodologies. The number of mutations or genes screened varies widely, from four conditions to over 2,000 genes [17]. The Euler diagram highlighted in the ACMG [23] guideline may hereby be a practical toolkit for determining the exact selection of diseases or conditions to be included in a screening panel. However, there is a difference if ECS is performed by NGS or array-based technology. While array-based methods are generally cheaper, they may be less sensitive than NGS [20].

begrenzte Übertragbarkeit der Evidenz

Evidence Applicability: the direct transferability of the findings may be limited due to heterogeneity among the included reviews and the presence of methodological limitations in the included studies, as reflected in the GRADE assessment in HQO HTA [3].

australische Leitlinie zu Single-Disease-Screening, empfiehlt sequenzielles Testen und Verweisung bei Paaren mit erhöhtem Risiko

One Australian guideline [51] on reproductive genetic carrier screening was excluded as the scope of the guideline did not extend to screening for large panels of genes (expanded carrier screening). Nonetheless, some of the recommendations may be relevant for the implementation of such tests. The Royal College of Pathologists of Australasia (RCPA) [51] states that carrier screening may be undertaken using either a sequential or concurrent model. The sequential approach, which underpins Australian Medicare item numbers, involves screening the female partner first, with male partner testing performed only if the female is identified as a carrier. Referral to a clinical genetics service is recommended when both partners are carriers for CF or SMA, or when the female partner carries a FXS premutation. The guideline further specifies that CF screening should target variants associated with severe childhood-onset disease and exclude reporting of variants of uncertain significance; FXS screening should recognise the different reproductive and health implications of the disease in both sexes; and SMA testing should detect single-copy deletions of SMN1 exon 7.

gesellschaftliche und ethische Implikationen von ECS: Prävention von Stigmatisierung und Diskriminierung

With the increase of ECS, including hundreds of mutations, there may not only rise questions with regard to clinical utility alone, but societal and ethical issues worth noting: With routinisation, medicalisation of pregnancy and a supply push of carrier screening, a societal climate for "perfect children" may be nourished [52]. Stigmatisation and discrimination against those people who are either affected or decide against carrier screening options could also have further implications and could, in theory, be negative social aspects. [52] Suffice it to say that pilot implementation studies are also needed before widespread implementation to anticipate potential unforeseen consequences.

Based on input from the external experts, the same organisational aspects are relevant for Austria, highlighting the following:

- *Infrastructure:* Establishing a robust bioinformatics infrastructure for processing genomic data and managing the reporting of pathogenic variants.
- *Regulatory Framework:* Revising the Austrian Gene Technology Act (GTG) to establish a formal Screening Commission and define reporting standards.
- *Counseling Capacity:* Addressing the consultation bottleneck by officially recognizing Genetic Counsellors and utilising the existing (but underused) legal right of the medical specialist (in this context: gynecologists) to provide genetic counseling within their field.
- *Education & Training:* Promoting low-threshold training for gynecologists and expanding the Austrian Medical Chamber's Genetics Diploma to distribute the counseling load beyond human geneticists.
- *Consultation Workflow:* Evaluating whether comprehensive pre-test counseling is realistic for all participants or if resources should focus on post-test counseling for positive findings.
- *Specialised Centers:* Utilising existing technical expertise at established national locations.
- In addition, the current Austrian gene technology law (GTG) prohibits genetic screening without formal genetic counselling by a competent doctor, which may need to be a medical geneticist if diseases from different specialties are included in the screening program.

Costs of Carrier screening and genetic conditions

variable Kosten je nach Panel-Umfang und Ansatz; Beratung und Infrastruktur

Carrier screening costs vary by strategy: single-disease panels versus ECS panels, and universal versus risk-based population approaches. Declining panel costs have made ECS increasingly accessible, though total program costs must account for genetic counselling, follow-up testing, and infrastructure. Available economic evaluations are briefly presented in Chapter 4.

Behandlungskosten erheblich

In contrast, families of affected individuals face extensive lifelong challenges, including managing daily medical routines, frequent hospital visits, and the psychosocial impacts of these conditions, such as anxiety and depression [3]. Lifetime care costs for individuals with CF are substantial. For example, a 2007 study estimated these costs to be approximately one-third of the expense of implementing a population-wide screening program [3]. Innovative treatments, while beneficial, are costly – CF modulator therapies can cost approximately €258,060 annually, and SMA gene therapies up to approximately €609,000 in the first year and €305,000 annually thereafter[4] [53, 54].

Limitations of the report

Limitationen: Review-of-Reviews statt De-novo-Synthese, Sprachrestriktion, keine österreichischen Primärdaten oder Stakeholder-Konsultation

First, a review-of-reviews approach was employed to synthesise existing systematic reviews and health technology assessments, rather than conducting a *de novo* systematic review of primary studies on clinical utility or patient-reported outcomes. Second, the literature search was restricted to English and German publications, potentially excluding relevant publications published in other languages. Third, no dedicated systematic search for articles on economic, ethical, legal, organisational and social aspects related to carrier screening implementation was conducted. We also did not include qualitative reviews, of which some are available, focusing on barriers and facilitators to carrier screening [55]. Furthermore, no primary data collection, cost-effectiveness modelling of different screening panels (e.g., expanded vs. single-disease), or stakeholder consultation (with patients, providers, or genetic counsellors) was performed for Austrian settings. Fourth, the synopsis of carrier screening guidelines included informal text passages alongside formally graded recommendations. To mitigate concerns, formal recommendations and these explanatory text passages were transparently distinguished throughout the synthesis. Fifth, we focused on carrier screening in individuals without consanguinity. There are reports that we have excluded, focusing solely on genetic risk assessment in known carriers [56].

Conclusion

moderate Evidenz für Risiko-Identifizierung und Entscheidungs-unterstützung

Current available evidence suggests that carrier screening for Cystic Fibrosis, Spinal Muscular Atrophy, Hemoglobinopathies and Fragile X Syndrome can identify at-risk couples and support informed reproductive decisions. The certainty of evidence for this conclusion is moderate, while the certainty surrounding psychological impacts remains very low.

Evidenzlücken etwa bei psychologischen Effekten und optimale Strategie für Österreich unklar

There is uncertainty about whether and how a carrier screening strategy should be best designed and implemented in the Austrian healthcare context. None of the identified guideline recommendations are applicable to the Austrian setting, although some of the identified topics may provide relevant guiding principles when designing and implementing carrier screening in Austria.

[4] Based on the current market data for October 17, 2025: The exchange rate is 1 EUR = 1.1601 USD

US-Leitlinien nicht übertragbar, aber konzeptionelle Frameworks als Orientierungshilfe für Panel-Zusammenstellung

Some conceptual frameworks employed within identified guidelines – such as the Euler diagram, which conceptualises carrier screening as overlapping tiers of conditions – may be useful for structuring the selection of diseases or conditions to be included in a screening panel. This selection should rely on multi-criteria considerations, such as sound Austrian epidemiological data and disease severity and requires collaboration between different experts, such as medical geneticists and reproductive medicine specialists.

ethische, rechtliche, organisatorische und soziale Aspekte zentral

Our report highlights the need to consider ethical, legal, organisational and social aspects when considering implementing carrier screening in Austria. A multidisciplinary steering committee is hereby required, comprising relevant experts.

Beratung sichert ethische Prinzipien, Infrastruktur und Schulungen notwendig

These include, for instance, genetic counselling, which is crucial to uphold sound ethical principles, including respect for patient autonomy, informed consent, and equitable access to services. Expert input highlighted that there should be reflection whether new professions need to be established or whether competencies of existing professions need to be expanded. Furthermore, organisational, technical and human-resource capacities, such as adequate testing infrastructure and training programmes for involved professionals, must be established to ensure the successful deployment of the screening strategy.

wissenschaftliche Begleitevaluation erforderlich

From an HTA perspective, an ideal future approach would involve complementing the conceptualisation of carrier screening strategies which would be ideally accompanied by a decision analytic model such as health economic evaluation or quantitative benefit harm analysis. Hence, the development and broader application of relevant epidemiological data sources and modelling approaches would therefore represent an important area for future work in Austria.

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Carrier screening results from systematic reviews and Health Technology Assessment reports

Author, year	HQO HTA, 2023 [3]	Ramdaney, 2022 [30]	Banzi, 2023[10]	Wang, 2023[17]
Study Design	Full HTA	SR	SR as part of an HTA	SR
Study aim(s)	To evaluate safety, effectiveness, cost-effectiveness, budget impact, and patient perspectives of carrier screening for CF, FXS, Hemoglobinopathies/Thalassemia, and SMA in preconception and prenatal settings.	To assess the evidence on expanded carrier screening in the USA population, focusing on clinical utility, psychosocial impact, and ethical considerations.	To evaluate the effectiveness and optimal organisation of population-based CF carrier screening in reproductive-age adults.	This study aimed to assess the clinical utility of RCS and synthesize outcomes in a meta-analysis.
Population	Eligibility for screening extends to all prospective parents and gamete donors, regardless of risk level, during the preconception or prenatal stages (including IVF).	Parents in the USA, including any individual who is pregnant or planning a pregnancy.	General population screening (Adults ≥16 y)	Adult couples or individual members of adult couples who were either planning a pregnancy (preconception) or were in the early stages of pregnancy.
Intervention	Risk-based or universal carrier screening programs for pathogenic variants of CF, FXS, Hemoglobinopathies and thalassemia, or SMA. This includes various testing approaches related to timing, simultaneous or sequential testing, analytic methods, and methods of result disclosure.	ECS for AR or XL disorders.	Population-based CF carrier screening programs offered to adults of reproductive age in the general population.	RCS to identify at-risk couples whose offspring are at risk of an autosomal recessive and/or X-linked condition.
Control	No testing, a different test or screening approach (head-to-head comparisons), or no comparison.	Minimal guideline-based carrier screening for the same types of disorders.	Different approaches to invitation and testing (e.g., settings, target population, invitation methods), as well as a comparison of screening versus no screening.	The review did not limit the options for comparators, such as no screening.
Outcomes	Screening uptake rate Proportion of at-risk couples Impact on reproductive decision-making Proportion of affected children born Psychological impact of testing and results Downstream impacts based on test results Impact of results of VUS Rates and impacts of cascade testing of family members	Screening uptake Yield of identified at-risk couples Influence on reproductive decision-making, and levels of anxiety Provider preferences for one type of screening over the other Perceived barriers to offering the tests, and the amount of time spent on counseling.	Attitude towards screening Uptake of screening Changes in CF incidence	Clinical Utility Intervention outcomes relating to identified HRCs by RCS (such as the number of identified HRCs and genetic counselling). Outcomes relating to the impact of screening results on reproductive choice/decision (such as rates of choosing prenatal diagnosis, termination, and IVF with PGT) Affected children are born with conditions.
Study design	English-language full-text publications RCTs, Systematic reviews, Comparative and noncomparative Nonrandomized studies	RCTs Observational studies In silico studies using modeled data	SRs Reviews and overview of reviews Any primary study (no restriction) Any studies on different modalities and organisational features of screening were included.	SRs Reviews and overview of reviews Any primary study.

Author, year	HQO HTA, 2023 [3]	Ramdaney, 2022 [30]	Banzi, 2023[10]	Wang, 2023[17]
Exclusion Criteria	Animal and in vitro studies, nonsystematic reviews, narrative reviews, abstracts, editorials, letters, case reports, and commentaries.	Articles published before 2003, non-English, small case reports/series (N ≤ 10), non-USA populations, and conference abstracts.	Studies assessing carrier status only in populations with a known risk of CF (e.g., persons with a partner who is a carrier or a family history of CF), narrative reviews, editorials, and commentaries.	Excluded were letters, editorials, case studies, non-peer-reviewed articles, non-human research, autosomal dominant conditions, cancer screenings, single-condition carrier screenings, non-English papers, pre-1990 publications, studies unrelated to preconception or pregnancy, and those lacking outcomes on reproductive decisions.
Number of Included Studies	n=107 Clinical Effectiveness and Safety (n=107) Health Economic evaluations (n=21) Ethical or organisational aspects (n=29)	n=36 RCT (n=1) Observational studies (n=30) In-silico studies (n=5)	n=71 publications, corresponding to Reviews (n=3) Cohort studies (n=11 comparative, n=29 single-arm) Model studies (n=6)	n=11 Quantitative analysis (n=10) Qualitative analysis (n=1)
Timeframe of Search	01/2005-04/2021	2004-2021	01/1992-03/2022	1990-2020
Countries of Included studies	Africa (n=1) Asia (n=10) Europe (n=7) North America (n=3) Oceania (n=1)	USA	Australia Europe North America	Asia (n=1) Europe (n=2) North America (n=7) Oceania (n=1)
Settings of Included Studies	Antenatal clinics, infertility clinics, obstetric or family practices, hospitals, and community health centers.	Prenatal or preconception settings. (urban, private hospital-based prenatal center and research settings)	Primary care, public high schools, obstetric clinics and maternal hospitals, and regional public health systems.	Genetic center, laboratory, infertility clinic, reproductive practice, outpatient clinic.
Funding	Ontario Ministry of Health.	NSGC	The Fondazione per la Ricerca sulla Fibrosi Cistica Onlus	Australian Government's Medical Research Future Fund
Databases/ Sources Searched	Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Health Technology Assessment (HTA) Database (CRD), National Health Service Economic Evaluation Database (NHS EED), International HTA Database	Embase, Pubmed (MEDLINE), and Scopus	MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Latin American and Caribbean Health Science information database (LILACS)	Embase, OVID Medline, OVID PsycINFO, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index of Nursing and Allied Health Literature (CINAHL), Current Controlled Trials in the meta Register of National Institutes of Health database (clinicaltrials.gov)
Total number of Patients	NR	NR	NR	337-270,000 for the quantitative analyses and 17 for the qualitative study
Type of Index Test	NGS, MLPA, PCR, and Southern blot analysis.	NR	CFTR molecular carrier testing (platform/analytic method not specified)	Expanded carrier screening panels
Type of Reference Standard	NR	NR	NR	NR
Type of Genetic Testing	(E)CS	ECS	Single gene test (~80% of studies) ECS (~20% of studies)	Next generation sequencing and genomic sequencing.

Author, year	HQO HTA, 2023 [3]	Ramdaney, 2022 [30]	Banzi, 2023[10]	Wang, 2023[17]
Screening Uptake	No comparative evidence for sceening uptake and carrier detection (universal vs. risk based) Universal Preconception: 71% (±7%) uptake by both partners. Risk-based Preconception: 5% (±0.5%) uptake by both partners. Universal Prenatal: 68% (±6.8%) uptake by both partners Risk-based Prenatal: 4.7% (±0.5%) uptake by both partners. Carrier Detection Ratio (Universal vs. Risk-based): 14.2 (45 observational studies; very Low CoE)	8.6-99.5% (5 observational studies) Preconception vs. Prenatal: 68.7% uptake preconception vs. 35.1% prenatal (1 retrospective review). Highest Acceptance: Preconception IVF clients, 74.5%. Decline Reasons (General Population): 50% declined ECS → no family history, low perceived risk, results not influencing decisions 66% declined ECS (preconception, research setting) → lack of time, lack of interest, not wanting information	Intervention uptake varied widely (4%-100%). It was highest in antenatal/hospital settings (59%-100%) and prenatal programs (75%-91%), showing the value of integrating into maternity care. Primary care had lower, inconsistent uptake (4%-75%). Mail invitations performed poorly (4%-12%), while on-site recruitment achieved higher but variable uptake (23.5%-70%).	NR
Proportion of at-risk couples	0%-5% for CF to up to 25% for Hemoglobinopathies, 3% for FXS, and 1% for SMA (93 observational studies, Moderate CoE)	At-risk couples (observational): 0.1%-16.9% (8 observational studies) At-risk couples (in silico models): highly variable and in dependence of genetic mutations and setting Comparative yield: 6 studies → guideline-based (CF + SMA) screening would have missed ≥881 of 966 at-risk couples detected by ECS	NR	The screening programs led to the identification of one to 24 HRCs per 1,000 screened individuals.
Reproductive decision making impact	Probability of undergoing PND given positive result: 95% (±9.5) Probability of assisted reproductive technologies: IVF/PGT-M: 79% (±0.4) Probability of other than IVF/PGT-M choice, including adoption, or no future pregnancy: 16% (±0.3%) Probability of voluntary termination of pregnancy (TOP): 80% (±0.3) for CF, 67% (±0.4) for SMA, 29% (±0.4) for FXS/Hemoglobinopathies (59 observational studies; moderate CoE)	Prenatal acceptance: 61% Prenatal decline: 37.5% Study data (prenatal, n=154 at-risk couples): 56 (37%) chose prenatal diagnosis; of 20 affected pregnancies, 8 (40%) terminated	Measured uptake for prenatal diagnosis among at-risk couples was reported in only 1 study: 91% (20/22) chose prenatal diagnosis, and 8 couples terminated pregnancies with affected fetuses Other studies included report only participant intentions or attitudes regarding reproductive decisions (e.g., whether individuals would opt for prenatal diagnosis or pregnancy termination if found at risk).	PND Rate: Among pregnant HRCs, the pooled rate for undergoing PND was 64.4%. Termination Rate: Among affected pregnancies (diagnosed as carrying the condition), the pooled rate for elective pregnancy termination was 71.4%. IVF with PGT Rate: Among preconception HRCs (before pregnancy), the pooled rate for choosing in-vitro fertilization (IVF) with Preimplantation Genetic Testing (PGT) was 63.1%.
Psychological impact	Limited evidence on psychological impact with few studies using validated instruments Some studies indicate a reduction in anxiety, and some studies also report negative emotions like anger or regret, particularly if they learn of a genetic link to a pre-existing condition like infertility. (8 observational studies; very Low CoE)	NR	NR	Screening for many conditions may increase anxiety in couples. This is because more at risk couples are identified, even for conditions that may be mild or treatable. Pregnant women who were carriers but did not receive pretest counseling were sometimes confused about the meaning of a positive screening result.

Author, year	HQO HTA, 2023 [3]	Ramdaney, 2022 [30]	Banzi, 2023[10]	Wang, 2023[17]
Downstream impact	*Fetal loss:* inconsistent evidence; no fetal loss in 3 studies and 3/269 (1.1%) spontaneous fetal loss due to PND Cascade Screening: Cascade Screening offered or completed in 5 studies. (12 observational studies; very Low CoE)	NR	One study conducted in Italy suggested an association between carrier screening and a decrease in the incidence of CF. In one region wher carrier screening was offered, there was a 15% annual decrease in the birth prevalence of CF (estimated birth prevalence from 1/2,730 to 1/14,200), whereas in an area where screening was not offered, the decrease was 1% annually (estimated birth prevalence from 1/3,589 to 1/3,870).	NR
Test Performance	SEN/SPEC Standard Panel: 0.90 to 0.957/0.99 to 0.993 SEN/SPEC ECS: 0.9988/0.9999	NR	NR	NR
Safety	NR	NR	NR	NR
Health Economic aspects (method and results)	21 economic studies (two systematic reviews, 19 original economic evaluations, 2005-2021) Four reviews Four cost-effectiveness analyses showed that, in the short term, all carrier screening strategies were associated with higher costs than no screening but also detected more at-risk pregnancies. Universal screening with standard panels was the most cost-effective strategy. The incremental cost-effectiveness ratio (ICER) compared to no screening was approximately €25,089 per additional at-risk pregnancy detected and €317,004 per affected birth averted. Universal screening with standard panels was also the most cost-effective strategy. The corresponding ICERs were about €25,652 per additional at-risk pregnancy detected and €372,218 per affected birth averted. Publicly funding a universal program was estimated to cost an additional €179.3 million to €423.2 million. Publicly funding a risk-based program was estimated to cost an additional €0.69 million to €2.59 million over the same period. When the long-term treatment costs for the screened conditions were considered, the total additional costs for universal programs decreased, and risk-based programs could result in cost savings.	NR	NR	NR

Author, year	HQO HTA, 2023 [3]	Ramdaney, 2022 [30]	Banzi, 2023[10]	Wang, 2023[17]
Organizational aspects	Substantial challenges related to human resources Limitations in infrastructure capacity Disruptions and inefficiencies in clinical workflows Need for investment in a specialised carrier screening workforce Requirement for improved and expanded training programs Need to streamline and optimise clinical workflows	NR	NR	NR
Ethical aspects	Ethical aspects identified within patient engagement (qualitative interview, n=22):	NR	NR	NR

Abbreviations: CENTRAL … Cochrane Central Register of Controlled Trials; CF … Cystic Fibrosis; CFTR … Cystic Fibrosis Transmembrane Conductance Regulator; CINAHL … Cumulative Index to Nursing and Allied Health Literature; CoE … Certainty of Evidence; ECS … Expanded Carrier Screening; EUnetHTA … European Network for Health Technology Assessment;
FXS … Fragile X Syndrome; HRCs … High-Risk Couples; HTA … Health Technology Assessment; ICER … Incremental Cost-Effectiveness Ratio; IVF … In Vitro Fertilization; LILACS … Latin American and Caribbean Health Science Information Database; MLPA … Multiplex Ligation-Probe Amplification; NGS … Next-Generation Sequencing; NHS EED … National Health Service Economic Evaluation Database; n … number; NR … Not Reported; NSGC … National Society of Genetic Counselors; PCR … Polymerase Chain Reaction; PGT … Preimplantation Genetic Testing; PND … Prenatal Diagnosis; QALY … Quality-Adjusted Life Year; RCTs … Randomized Controlled Trials; RCS … Reproductive Carrier Screening; SEN/SPEC … Sensitivity/Specificity; SMA … Spinal Muscular Atrophy; SR … Systematic Review; TOP … Termination of Pregnancy; UK … United Kingdom; US … United States; USA … United States of America;
VUS … Variants of Uncertain Significance; y … year

Table A-2: Guideline recommendations

Guideline	Date of issue	Country/ies to which applicable	Recommendation (verbatim)	Specific testing recommendation	Type, evidence quality, strength of recommendation
NSGC [49]	Accepted: 23 December 2022	USA	Expanded carrier screening (ECS) presents an ethnicity-based carrier screening alternative which does not rely on race-öbased medicine; therefore, ECS should be offered to all who are currently pregnant, considering pregnancy, or might otherwise biologically contribute to pregnancy.	ECS should be made available to all individuals considering reproduction and all pregnant reproductive pairs as an alternative to ethnicity-based screening.	Type: Conditional Recommendation Evidence certainty: Low and moderate certainty in the evidence
			Sequencing assays for ECS are recommended to achieve the goal of equitable testing and care. The risk of mild variant identification through sequencing is preferable to the risk of variant non-identification through genotyping.	Utilization of sequencing assays is recommended over genotyping to achieve equitable test performance and mitigate the risk of variant non-identification (false negatives) in diverse populations.	Type: Conditional Recommendation Evidence certainty: Low and moderate certainty in the evidence
			If VUS reporting should become a standard feature in ECS panels for all genes included on the panel, counseling on VUSs will need to be included in the informed consent process. At present, we do not recommend the routine inclusion of VUSs on ECS reports.	Routine inclusion of Variants of Uncertain Significance (VUSs) on ECS reports is not recommended at present.	Type: Conditional Recommendation Evidence certainty: Low and moderate certainty in the evidence
			Patients should be counseled that a consecutive testing strategy for ECS will delay receipt of final results when compared to simultaneous	Simultaneous testing of the reproductive pair is the ideal and preferred strategy over consecutive testing	Type: Conditional Recommendation

Guideline	Date of issue	Country/ies to which applicable	Recommendation (verbatim)	Specific testing recommendation	Type, evidence quality, strength of recommendation
			testing, and therefore, simultaneous ECS is ideal, especially in the context of pregnancy.	to avoid delays in comprehensive risk assessment, particularly during pregnancy.	Evidence certainty: Low and moderate certainty in the evidence
Carelon [50]	Last Review Date: July 16, 2024 Effective Date: March 23, 2025	USA	Standard carrier screening *Cystic fibrosis and Spinal Muscular Atrophy* Standard screening for Cystic Fibrosis (CFTR testing) and Spinal Muscular Atrophy (SMN1 testing) using accepted gene variant sets is considered medically necessary in the following scenarios: ■ All pregnant individuals ■ An individual considering pregnancy *Hemoglobinopathies* Standard screening for Hemoglobinopathies (HBA1/HBA2 and HBB testing) using Hemoglobin electrophoresis or molecular genetic testing is considered medically necessary in the following scenarios IF no prior testing results (Hemoglobin electrophoresis and/or HBA1/HBA2 and HBB gene analysis) are available for interpretation: ■ All pregnant individuals ■ An individual considering pregnancy	Standard Carrier Screening ■ Cystic Fibrosis (CF) & Spinal Muscular Atrophy (SMA): Medically necessary for all pregnant individuals or those considering pregnancy. ■ Hemoglobinopathies: Medically necessary for all pregnant individuals or those considering pregnancy, if no prior test results are available	Type: Consensus-Based Recommendations Evidence certainty: Not formally assessed
			Fragile X premutation carrier testing is considered medically necessary in EITHER of the following scenarios: ■ Women with a family history of Fragile X-related disorders or intellectual disability suggestive of Fragile X Syndrome who are pregnant or considering pregnancy ■ Women with unexplained ovarian insufficiency or failure, or an elevated follicle-stimulating hormone (FSH) level prior to age 40	Fragile X premutation carrier testing is considered medically necessary in either of the following scenarios: ■ Women with a family history of Fragile X-related disorders or intellectual disability suggestive of Fragile X Syndrome who are pregnant or considering pregnancy. ■ Women with unexplained ovarian insufficiency or failure, or an elevated follicle-stimulating hormone (FSH) level prior to age 40	Type: Consensus-Based Recommendations Evidence certainty: Not formally assessed
			Expanded Carrier Screening Multigene carrier testing is considered medically necessary if all of the following are met: At least one of the following: ■ Individual or partner has ancestry at increased risk for certain conditions (e.g., Ashkenazi Jewish, Finnish, French Canadian), excluding cystic fibrosis, SMA, and Hemoglobinopathies ■ Individual or partner lacks access to biological family history (e.g., adoption, reproductive donor) ■ Individual and partner are known or suspected to be consanguineous Conditions on the panel have a carrier frequency ≥1/100 (lower allowed for consanguineous couples) Genetic disorders have gene-disease clinical validity and pathogenic variants cause significant morbidity/mortality	Expanded carrier screening is considered medically necessary if at least one of the following patient criteria is met: ■ The individual or partner has ancestry with increased risk for certain conditions (e.g., Ashkenazi Jewish, Finnish), excluding CF, SMA, and Hemoglobinopathies. ■ The individual or partner lacks access to biological family history (e.g., adoption, reproductive donor). ■ The individual and partner are known or suspected to be consanguineous.	Type: Consensus-Based Recommendations Evidence certainty/Grade of recommendation: Not formally assessed

Guideline	Date of issue	Country/ies to which applicable	Recommendation (verbatim)	Specific testing recommendation	Type, evidence quality, strength of recommendation
			Test has high sensitivity and specificity for clinical decision-making		
ACOG [24]	Issued/ Published: March 2017 Reaffirmed: 2020	USA	*General Screening Strategies and Provider Approach* Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening. Each obstetrician-gynecologist or other health care provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy. After counselling, a patient may decline any or all carrier screening.	Healthcare practices should recognize ethnic-specific, pan-ethnic, and expanded carrier screening as valid strategies in pre-pregnancy and prenatal care. Each practitioner is encouraged to establish a standardized screening approach that is consistently offered and discussed with every patient, ideally before pregnancy.	Type: Consensus-Based Recommendations Evidence certainty/Grade of recommendation: Not formally assessed
			All patients who are considering pregnancy or are already pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for cystic fibrosis and Spinal Muscular Atrophy, as well as a complete blood count and screening for Thalassemias and Hemoglobinopathies.	All individuals considering pregnancy or who are already pregnant – regardless of ethnicity – should be offered carrier screening for Cystic Fibrosis and Spinal Muscular Atrophy. Additionally, a complete blood count and screening for Thalassemias and Hemoglobinopathies should be included.	Type: Consensus-Based Recommendations Evidence certainty/Grade of recommendation: Not formally assessed
			Risk-Based Screening Recommendations Fragile X premutation carrier screening is recommended for women with a family history of Fragile X-related disorders or intellectual disability suggestive of Fragile X syndrome, or women with a personal history of ovarian insufficiency. Additional screening also may be indicated based on family history or specific ethnicity. Individuals with a family history of a genetic disorder may benefit from the identification of the specific familial mutation or mutations rather than carrier screening.	Fragile X premutation carrier screening is recommended for women with a family history of Fragile X-related disorders, intellectual disability, or a personal history of ovarian insufficiency. Additional screening may be necessary based on a patient's specific family history or ethnic background. For individuals with a known familial mutation, targeted testing may be more appropriate than a general screening panel.	Type: Consensus-Based Recommendations Evidence certainty/Grade of recommendation: Not formally assessed
			Criteria for Expanded Carrier Panels Given the multitude of conditions that can be included in expanded carrier screening panels, the disorders selected for inclusion should meet several of the following consensus-determined criteria: ■ have a carrier frequency of 1 in 100 or greater ■ have a well-defined phenotype ■ have a detrimental effect on quality of life ■ cause cognitive or physical impairment ■ require surgical or medical intervention or ■ have an onset early in life Carrier screening panels should not include conditions primarily associated with a disease of adult onset.	Disorders included in expanded carrier screening panels should meet criteria such as a carrier frequency of 1 in 100 or higher, a well-defined phenotype, significant impact on quality of life, and an early onset of symptoms. Panels should avoid conditions primarily associated with adult onset.	Type: Consensus-Based Recommendations Evidence certainty/Grade of recommendation: Not formally assessed
ACMG [23]	Accepted: April 27, 2021 Published: July 20, 2021 Updated	USA	Tiered Screening System: The ACMG proposes a tiered system for carrier screening to improve precision and equity. Tier 1: Screening for Cystic Fibrosis and Spinal Muscular Atrophy, which is an ethnic and population-neutral approach.	Tier 3 carrier screening (per genes listed in Tables 1-6) should be offered to all pregnant patients and individuals planning pregnancy. Tier 3 carrier screening for autosomal recessive conditions may be offered to the reproductive partners of pregnant patients or those planning pregnancy,	Type: Consensus-Based Recommendations Evidence certainty/Grade of recommendation: Not formally assessed.

Guideline	Date of issue	Country/ies to which applicable	Recommendation (verbatim)	Specific testing recommendation	Type, evidence quality, strength of recommendation
	October 2021			ideally via simultaneous screening.	
ACMG [23] *(contin.)*			Tier 2: Screening for conditions with a carrier frequency of at least 1/100 and at least moderate severity. The ACMG does not recommend this tier, as it may not be equitable across diverse populations. Tier 3: Screening for conditions with a carrier frequency of at least 1/200. The ACMG recommends offering this level of screening to all pregnant patients and those planning a pregnancy. Tier 4: Screening for conditions with a carrier frequency less than 1/200. Routine offering of this tier is not recommended, but it should be considered for pregnancies from consanguineous relationships or when family/personal medical history warrants it.	Screening for the specified X-linked genes as part of the Tier 3 panel should be offered to all XX patients. Tier 4 screening is not recommended routinely and should be considered for patients with specific clinical indications, such as known or possible consanguinity (second cousins or closer) or a relevant family/personal medical history. Tier 1 and/or Tier 2 carrier screening panels are not recommended, as they do not facilitate equitable evaluation across all racial/ethnic groups.	
			Carrier screening paradigms should be ethnic and population neutral and more inclusive of diverse populations to promote equity and inclusion.		Type: Consensus-Based Recommendations Evidence certainty/Grade of recommendation: Not formally assessed
			A diagnostic procedure should be offered when: ■ The partner is unavailable for testing ■ The partner declines testing ■ Testing is cost prohibitive ■ A partner's results would not be available in time for reproductive decision making ■ A diagnostic procedure is already planned for another indication.	A prenatal diagnostic procedure (e.g., CVS or amniocentesis) should be offered to a pregnant carrier when the partner's status cannot be determined for specified reasons (e.g., unavailability, cost, or time constraints for decision making).	Type: Consensus-Based Recommendations Evidence certainty/Grade of recommendation: Not formally assessed

Abbreviations: ACMG … American College of Medical Genetics and Genomics; ACOG … American College of Obstetricians and Gynecologists; AR … Autosomal Recessive; CF … Cystic Fibrosis; CLIA … Clinical Laboratory Improvement Amendments; CoE … Confidence of Evidence; CVS…Chorionic Villus Sampling; ECS … Expanded Carrier Screening; FSH … Follicle-Stimulating Hormone; IVF … In Vitro Fertilization; NSGC … National Society of Genetic Counselors; PGT … Preimplantation Genetic Testing; SMA … Spinal Muscular Atrophy; US/USA … United States/United States of America; VUS … Variants of Uncertain Significance; XL … X-linked.

Table A-3: AGREE II quality appraisal of the guidelines for carrier screening for Cystic Fibrosis, Fragile X Syndrome, Hemoglobinopathies and Thalassemia, and Spinal Muscular Atrophy

Domain	Item	Carelon [50]	NSGC [49]	ACOG [24]	ACMG [23]
Scope and Purpose	1. The overall objective(s) of the guideline is (are) specifically described.	7	7	7	7
	2. The health question(s) covered by the guideline is (are) specifically described.	7	7	7	7
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7	7	7	7
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	5,5	7	7	7
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	3,5	6	7	5,5
	6. The target users of the guideline are clearly defined.	7	7	7	7
Rigor of development	7. Systematic methods were used to search for evidence.	4,5	5	3	2,5
	8. The criteria for selecting the evidence are clearly described.	2,5	4	3,5	2
	9. The strengths and limitations of the body of evidence are clearly described.	2,5	5,5	3	4
	10. The methods for formulating the recommendations are clearly described.	3	6,5	3	5
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.	4,5	7	3	3
	12. There is an explicit link between the recommendations and the supporting evidence.	4,5	5,5	3	3,5
	13. The guideline has been externally reviewed by experts prior to its publication.	3,5	7	6,5	3
	14. A procedure for updating the guideline is provided.	6,5	7	7	3,5
Clarity of presentation	15. The recommendations are specific and unambiguous.	6,5	6,5	7	6
	16. The different options for management of the condition or health issue are clearly presented.	6,5	6	7	7
	17. Key recommendations are easily identifiable.	6,5	6	7	7
Applicability	18. The guideline describes facilitators and barriers to its application.	3	6	7	7
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	4,5	5,5	4,5	6
	20. The potential resource implications of applying the recommendations have been considered.	4,5	6	6,5	7
	21. The guideline presents monitoring and/or auditing criteria.	3,5	6,5	3	3
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.	3	6,5	7	6,5
	23. Competing interests of guideline development group members have been recorded and addressed.	2	6,5	7	6,5
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	5	6,5	5,5	4,5
Overall Guideline Assessment	2. I would recommend this guideline for use.	Yes	Yes	Yes, with modification (ACOG reaffirmed the 2017 guideline without further systematic search)	Yes, with modification (lack of systematic search)

Risk of bias tables

Table A-4: Risk of bias – study level (systematic reviews)

Name, year	D1: Study Eligibility	D2: Identification/ Selection of studies	D3: Data collection and study appraisal	D4: Synthesis and Findings	RoB in the Review	Rationale
HQO HTA, 2023 [3]	LOW	LOW	LOW	LOW	LOW	No major concerns. Some minor weaknesses (e.g., no independent screening process) identified.
Ramdaney, 2022 [30]	UNCLEAR[5]	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Given the multitude of unclear methodological descriptions, the reviews RoB was to be judged as unclear
Banzi, 2023 [10]	UNCLEAR	LOW	LOW	LOW	LOW	The SR lacked preregistration. Some minor concerns identified, e.g., some RoB tools were not ideal for the respective study designs, no sensitivity analysis conducted.
Wang 2023 [17]	LOW	LOW	LOW	LOW	LOW	Some smaller weaknesses identified (e.g., lack of clear description of whether some working steps were conducted independently).

Abbreviations: HQO HTA … Health Quality Ontario Health Technology Assessment; RoB … Risk of Bias; SR … Systematic Review

[5] Eligibility criteria not clearly defined, vague in- and exclusion criteria.

Applicability table

Table A-5: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	With respect to the population, no applicability concern was identified.
Intervention	No applicability concerns were identified with respect to the selected interventions. Yet, for expanded carrier screening, numerous different sequencing technologies may be used. The reviews and guidelines did not specifically report different sequencing technologies within the expanded carrier screening approach.
Comparators	Although not influencing applicability directly, the standard of care in multiple countries (such as the US) is increasingly universal, panethnic expanded carrier screening (ECS) for all reproductive-age couples, whereas in Austria there is no routine population-wide strategy. In Austria, there is currently no established standard governing carrier screening (no guideline recommendations applicable to Austria were identified).
Outcomes	Selected outcomes found in included reports and guidelines match the pre-defined outcomes, except safety.
Setting	Both systematic reviews/HTAs and guidelines are predominantly applicable to the US and or Canadian health care system, where genetic testing infrastructure and organisational pathways may differ from those in Austria. Carrier prevalence may also differ between countries.

The guidelines are predominantly applicable to the US health care system. There may be differences in the genetic testing infrastructure and the standard of care; for example, the US increasingly pursues universal, panethnic expanded carrier screening (ECS) for all reproductive-age couples, whereas Austria has no routine population-wide strategy and instead employs single-disease carrier screening based on family history or ancestry.

Research questions

Table A-6: Health problem and Current Use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Table A-7: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Table A-8: Clinical Effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0003	What is the effect of the technology on the mortality due to causes other than the target disease?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?
D0017	Was the use of the technology worthwhile?

Table A-9: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying the technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are the technology and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

Literature search strategies

The Medline search strategy is provided as an example in the Appendix.
The other searches are published on Open Science Framework (OSF) [57].

Search strategy for Medline via Ovid

Search Name: Database: Ovid MEDLINE(R) ALL <1946 to July 21, 2025>	
Search date: 21.7.2025	
ID	Search
1	Cystic Fibrosis/ (42049)
2	Cystic Fibrosis Transmembrane Conductance Regulator/ (11652)
3	((cystic adj2 fibrosis) or fibrocystic disease* or mucoviscidosis or CFTR).ti,ab,kf. (58842)
4	CF.ti. (3106)
5	Muscular Atrophy, Spinal/ (5495)
6	"Spinal Muscular Atrophies of Childhood"/ (1930)
7	((atroph* adj2 (spinal muscular or progressive muscular or myelopathic muscular)) or spinal amyotroph* or (neuropath* adj2 hereditary motor)).ti,ab,kf. (8922)
8	((survival adj2 (motor neuron* 1 or motor neuron* 2)) or SMN1 or SMN2).ti,ab,kf. (2084)
9	((werdnig hoffmann or dubowitz or kugelberg welander) adj2 disease*).ti,ab,kf. (341)
10	SMA.ti. (1584)
11	exp Hemoglobinopathies/ (53159)
12	(sickle adj3 (disease* or an?emia* or disorder* or trait* or h?emoglobin*)).ti,ab,kf. (30968)
13	(h?emoglobinopath* or h?emoglobulinopath* or hbp or hbps).ti,ab,kf. (11350)
14	(thalass?emia* or alphathalass?emia* or betathalass?emia* or deltathalass?emia* or (beta adj3 microcyt?emia*) or (an?emia* adj3 (cooley* or erythroblast* or mediterranean)) or target cell an?emia* or alpha thal or beta thal or delta thal).ti,ab,kf. (26828)
15	exp Hemoglobins, Abnormal/ (12147)
16	(h?emoglobin s or h?emoglobin c or h?emoglobin d or h?emoglobin e or h?emoglobin o or h?emoglobin h or h?emoglobin bart*).ti,ab,kf. (4756)
17	((hbs or hb s or hgbs or hgb s or hbc or hb c or hgbc or hgb c or hbd or hb d or hgbd or hgb d or hbe or hb e or hgbe or hgb e or hbo or hb o or hgbo or hgb o or hbh or hb h or hgbh or hgb h or hb Bart* or hgb Bart*) adj5 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait*)).ti,ab,kf. (3596)
18	(hbas or hbac or hb ac or hbad or hb ad or hbae or hb ae or hbao or hb ao).ti,ab,kf. (645)
19	(((h?emoglobin* or hb or hgb) adj3 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait* or subunit* or alpha* or beta*)) or hbb or hba1 or hba2 or alpha globin* or beta globin* or delta globin*).ti,ab,kf. (31914)
20	Fragile X Syndrome/ (5960)
21	Fragile X Mental Retardation Protein/ (3743)
22	(fragile x* or fraxa or frax a or fra x or mar x or marker x or martin bell or martinbell or FXS or FXTAS or FXPOI or FXAND or FXAD or FX associat*).ti,ab,kf. (9221)
23	(FMRP* or FMR1* or ((x linked or xlinked) adj3 (fragile or mental retard*))).ti,ab,kf. (6224)
24	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (179830)
25	Genetic Carrier Screening/ (8953)
26	(carrier* adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analys* or inform* or status or rate* or risk* or mother* or father* or parent or parents or couple* or marriage* or married or program*)).ti,ab,kf. (26711)
27	(massive* parallel sequenc* or ((sequential or parallel or panethnic or pan ethnic or multigene* or multi gene*) adj2 (screen* or panel*))).ti,ab,kf. (6334)
28	((Preconception* or Pre-conception* or Prepregnan* or Pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))) adj4 (screen* or test* or panel* or diagnos* or assess*)).ti,ab,kf. (3726)
29	25 or 26 or 27 or 28 (42598)
30	24 and 29 (3896)
31	carrier*.ti,ab,kf. (289304)

32	Preconception Care/ (2920)
33	(preconception* or pre-conception* or prepregnan* or pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))).ti,ab,kf. (57233)
34	Prenatal Care/ (34840)
35	(prenatal* or pre-natal* or antenatal* or ante-natal*).ti,ab,kf. (181775)
36	Family Planning Services/ (27208)
37	((pregnan* or conception* or family) adj3 plan*).ti,ab,kf. (58651)
38	Genetic Counseling/ (16423)
39	(counsel* adj4 genetic*).ti,ab,kf. (28122)
40	(couple* adj3 risk*).ti,ab,kf. (1986)
41	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 (607764)
42	exp Genetic Testing/ (58224)
43	((genetic* or genomic* or gene or genes) adj3 (screen* or test* or panel* or diagnos* or assess*)).ti,ab,kf. (188881)
44	High-Throughput Nucleotide Sequencing/ (52751)
45	(((high throughput or high through put) adj2 (sequenc* or analys*)) or deep sequenc*).ti,ab,kf. (53287)
46	(((next gen or nextgen or next generation) adj2 sequenc*) or NGS).ti,ab,kf. (79850)
47	Sequence Analysis, DNA/ (175419)
48	((DNA or parallel or target*) adj1 sequenc*).ti,ab,kf. (131885)
49	Heterozygote/ (51000)
50	Heterozygote Detection/ (8953)
51	((heterozygot* or heterozygous*) adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analy*)).ti,ab,kf. (5665)
52	((target* or universal or population or variant* or mutation* or recessive) adj2 (screen* or test* or panel* or assay* or analysis)).ti,ab,kf. (152212)
53	Chromatography, High Pressure Liquid/ (205193)
54	(high performance liquid chromatograph* or high pressure liquid chromatograph* or high speed liquid chromatograph* or HPLC).ti,ab,kf. (237930)
55	Blood protein electrophoresis/ (12465)
56	(((h?emoglobin or capillar*) adj2 electrophores#s) or southern blot*).ti,ab,kf. (49977)
57	exp Polymerase Chain Reaction/ (472220)
58	((multiplex ligation* adj2 probe amplification*) or polymerase chain reaction* or PCR or MLPA).ti,ab,kf. (842442)
59	42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 (2025103)
60	41 and 59 (85470)
61	24 and 60 (7047)
62	((expanded adj3 carrier* adj3 (screen* or test* or panel*)) or (carrier screen* adj3 (program* or service*))).ti,ab,kf. (474)
63	30 or 61 or 62 (8547)
64	exp Animals/ not Humans/ (5359134)
65	63 not 64 (8498)
66	Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (4660102)
67	65 not 66 (7196)
68	limit 67 to (english or german) (6547)
69	limit 68 to yr="2020 - 2025" (1308)
70	cystic fibrosis/ (42049)
71	cystic fibrosis transmembrane conductance regulator/ (11652)
72	((cystic adj2 fibrosis) or fibrocystic disease* or mucoviscidosis or CFTR).tw,kw. (57900)
73	CF.ti. (3106)
74	spinal muscular atrophy/ (5495)
75	exp Muscular Atrophy, Spinal/ (7162)

76	((atroph* adj2 (spinal muscular or progressive muscular or myelopathic muscular)) or spinal amyotroph* or (neuropath* adj2 hereditary motor)).tw,kw. (8624)
77	((survival adj2 (motor neuron* 1 or motor neuron* 2)) or SMN1 or SMN2).tw,kw. (2077)
78	((werdnig hoffmann or dubowitz or kugelberg welander) adj2 disease*).tw,kw. (318)
79	SMA.ti. (1584)
80	exp hemoglobinopathy/ (53159)
81	(sickle adj3 (disease* or an?emia* or disorder* or trait* or h?emoglobin*)).tw,kw. (30077)
82	(h?emoglobinopath* or h?emoglobulinopath* or hbp or hbps).tw,kw. (11276)
83	(thalass?emia* or alphathalass?emia* or betathalass?emia* or deltathalass?emia* or (beta adj3 microcyt?emia*) or (an?emia* adj3 (cooley* or erythroblast* or mediterranean)) or target cell an?emia* or alpha thal or beta thal or delta thal).tw,kw. (26488)
84	h?emoglobin* variant*.mp. (1827)
85	(h?emoglobin s or h?emoglobin c or h?emoglobin d or h?emoglobin e or h?emoglobin o or h?emoglobin h or h?emoglobin bart*).tw,kw. (4733)
86	((hbs or hb s or hgbs or hgb s or hbc or hb c or hgbc or hgb c or hbd or hb d or hgbd or hgb d or hbe or hb e or hgbe or hgb e or hbo or hb o or hgbo or hgb o or hbh or hb h or hgbh or hgb h or hb Bart* or hgb Bart*) adj5 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait*)).tw,kw. (3576)
87	(hbas or hbac or hb ac or hbad or hb ad or hbae or hb ae or hbao or hb ao).tw,kw. (644)
88	(((h?emoglobin* or hb or hgb) adj3 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait* or subunit* or alpha* or beta*)) or hbb or hba1 or hba2 or alpha globin* or beta globin* or delta globin*).tw,kw. (31752)
89	fragile X syndrome/ (5960)
90	fragile X mental retardation protein/ (3743)
91	(fragile x* or fraxa or frax a or fra x or mar x or marker x or martin bell or martinbell or FXS or FXTAS or FXPOI or FXAND or FXAD or FX associat*).tw,kw. (9214)
92	(FMRP* or FMR1* or ((x linked or xlinked) adj3 (fragile or mental retard*))).tw,kw. (6197)
93	70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 (177721)
94	heterozygote detection/ (8953)
95	(carrier* adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analys* or inform* or status or rate* or risk* or mother* or father* or parent or parents or couple* or marriage* or married or program*)).tw,kw. (26674)
96	(massive* parallel sequenc* or ((sequential or parallel or panethnic or pan ethnic or multigene* or multi gene*) adj2 (screen* or panel*))).tw,kw. (6262)
97	((Preconception* or Pre-conception* or Prepregnan* or Pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))) adj4 (screen* or test* or panel* or diagnos* or assess*)).tw,kw. (3743)
98	94 or 95 or 96 or 97 (42526)
99	93 and 98 (3871)
100	carrier*.tw,kw. (287347)
101	pre?pregnancy care.mp. (57)
102	exp Preconception Care/ (2920)
103	(preconception* or pre-conception* or prepregnan* or pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))).tw,kw. (57769)
104	prenatal care/ (34840)
105	(prenatal* or pre-natal* or antenatal* or ante-natal*).tw,kw. (181564)
106	family planning/ (27208)
107	((pregnan* or conception* or family) adj3 plan*).tw,kw. (38448)
108	genetic counseling/ (16423)
109	(counsel* adj4 genetic*).tw,kw. (26928)
110	(couple* adj3 risk*).tw,kw. (2021)
111	100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 (591914)
112	genetic screening/ (48699)
113	((genetic* or genomic* or gene or genes) adj3 (screen* or test* or panel* or diagnos* or assess*)).tw,kw. (187666)
114	high throughput sequencing/ (52751)
115	massively parallel signature sequencing/ (0)

116	massive* parallel signature sequencing.mp. (155)
117	(((high throughput or high through put) adj2 (sequenc* or analys*)) or deep sequenc*).tw,kw. (50530)
118	(((next gen or nextgen or next generation) adj2 sequenc*) or NGS).tw,kw. (72337)
119	sequence analysis/ (9792)
120	((DNA or parallel or target*) adj1 sequenc*).tw,kw. (130247)
121	heterozygote/ (51000)
122	((heterozygot* or heterozygous*) adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analy*)).tw,kw. (5678)
123	((target* or universal or population or variant* or mutation* or recessive) adj2 (screen* or test* or panel* or assay* or analysis)).tw,kw. (150802)
124	high performance liquid chromatography/ (205193)
125	(high performance liquid chromatograph* or high pressure liquid chromatograph* or high speed liquid chromatograph* or HPLC).tw,kw. (236277)
126	protein electrophoresis/ (12465)
127	capillary electrophoresis/ (19574)
128	(((h?emoglobin or capillar*) adj2 electrophores#s) or southern blot*).tw,kw. (49518)
129	exp polymerase chain reaction/ (472220)
130	multiplex ligation dependent probe amplification/ (7043)
131	((multiplex ligation* adj2 probe amplification*) or polymerase chain reaction* or PCR or MLPA).tw,kw. (836533)
132	112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 (1917369)
133	111 and 132 (80385)
134	93 and 133 (6536)
135	((expanded adj3 carrier* adj3 (screen* or test* or panel*)) or (carrier screen* adj3 (program* or service*))).tw,kw. (460)
136	99 or 134 or 135 (8433)
137	(exp animal/ or nonhuman/) not exp human/ (5359134)
138	136 not 137 (8384)
139	Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (2336108)
140	138 not 139 (8025)
141	limit 140 to (english or german) (7288)
142	limit 141 to yr="2020 - 2025" (1444)
143	69 or 142 (1483)
144	limit 143 to (meta analysis or "systematic review") (24)
145	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. (892487)
146	143 and 145 (56)
147	144 or 146 (59)
148	143 (1483)
149	limit 148 to (guideline or practice guideline) (3)
150	guideline*.mp. (703168)
151	143 and 150 (111)
152	147 or 151 (153)
153	remove duplicates from 152 (149)
Total hits: 2	

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