HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Genetic Testing in Austria

Part A:
Application Fields and Prioritisation Criteria

Final report

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List of abbreviations

AIHTA .....Austrian Institute for Health Technology Assessment
AT.....Austria
AWMF .....Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BGD .....Big Genomic Data
CADTH .....Canadian Agency for Drugs and Technologies in Health
CA .....Clinical Actionability
CPG.....Comprehensive Genomic Profiling
ctDNA.....Circulating Tumour DNA
DVSV .....Dachverband der Sozialversicherungsträger
DLBCL .....Diffuse Large B-Cell Lymphoma
DNA.....Deoxyribonucleic Acid
ENG .....England
EBM .....Einheitlicher Bewertungsmaßstab
FFPE.....Formalin-Fixed, Paraffin-Embedded
FISH.....Fluoreszenz in situ Hybridisierung
FH .....Familiäre Hypercholesterinämie
GER.....Germany
GLH .....Genomic Laboratory Hub
GMS .....Genomic Medicine Service
GÖG .....Gesundheit Österreich GmbH
HR.....Hormonrezeptor
HAS.....Haute Autorité de Santé
HIQA.....Health Information and Quality Authority
HTA .....Health Technology Assessment
HTW .....Health Technology Wales
IHC .....Immunhistochemie
HQO.....Health Quality Ontario
IQWiG.....Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IVDR.....In Vitro Diagnostic Regulation (EU 2017/746)
IVF .....In Vitro Fertilisation
KCE.....Belgian Health Care Knowledge Centre
LDT.....Laboratory Developed Test
LDLR.....Low Density Lipoprotein Receptor
LKF.....Leistungsorientierte Krankenanstaltenfinanzierung
LOH .....Loss of Heterozygosity
MPS.....Massively Parallel Sequencing
MSAC.....Medical Services Advisory Committee
MVZ .....Medizinisches Versorgungszentrum
NGS.....Next Generation Sequencing
NHS .....National Health Service
NICE.....National Institute for Health and Care Excellence
NIHR .....National Institute for Health Research
NIPH.....Norwegian Institute of Public Health
NL .....Netherlands
OGAC .....Ontario Genetics Advisory Committee
OHIP.....Ontario Health Insurance Plan
OHTAC .....Ontario Health Technology Advisory Committee
OSF .....Open Science Framework
PCR.....Polymerase Chain Reaction
PGx.....Pharmacogenomic testing
RT-PCR.....Reverse Transcription Polymerase Chain Reaction
RQ .....Research Question
SBU .....Swedish Agency for Health Technology Assessment
SCID .....Severe Combined Immunodeficiency
SI .....Social Insurance
SMA .....Spinale Muskelatrophie
SMN .....Survival Motor Neuron
TGS .....Third Generation Sequencing
TKI.....Tyrosine Kinase Inhibitor
TREC .....T-cell Receptor Excision Circles
V .....Indication Volume
VUS .....Variant of Uncertain Significance
WES .....Whole Exome Sequencing
WGS .....Whole Genome Sequencing
WIGEV .....Wiener Gesundheitsverbund
ZIN.....Zorginstituut Nederland

Glossary

General Terms

Term	Definition	Source
Application field	Refers to the context in which genetic testing is used. In this report, the 4 main application fields considered are: diagnostic, clinical predictive, pharmacogenomic, and tumour testing (as detailed in the Health Education England's Genomics Education Programme).	[1]
Genetic testing	Genetic testing, sometimes called genomic testing, finds changes in genes that can cause health problems. It's mainly used to diagnose rare/inherited conditions and some cancers. Technically, genetics studies individual genes and inheritance (often including gene panels, looking at multiple genes at once), while genomics studies the whole genome, including interactions and complex disease factors. In this report, terms are used interchangeably. The scope is indicated by specific tests (e.g., whole exome sequencing/ whole genome sequencing (WES/WGS).	[2, 3]
Genomic medicine	An emerging medical discipline focusing on the use of genomic information and technologies. A person's genome contains information that can influence disease development and treatment response. Genomic medicine, therefore, can determine disease risk, diagnosis and prognosis, and the selection of optimal therapeutic interventions for individual patients.	[4]
Big data in genomics	Vast and complex datasets, sometimes termed big genomic data (BGD), generated by genomic sequencing technologies and related methods that exceed conventional data processing capabilities in terms of volume, velocity, and variety.	[5]

Terms for Sequencing Technologies

Term	Definition	Source
Sanger sequencing	The (first generation) method of DNA sequencing, also known as chain-termination or dideoxy sequencing. It's a fast way to read the sequence of small, targeted regions of the genome and is widely used for testing known familial variants and validating results.	[6]
High throughput sequencing	High throughput sequencing is often defined as an umbrella term that encompasses a variety of modern sequencing technologies with the capability to generate DNA or RNA sequence data at a massive scale. The term is often used synonymously with massive parallel sequencing (MPS) and next-generation sequencing (NGS)	[7]
Massively parallel sequencing (MPS)	Modern high-throughput techniques that read thousands to billions of DNA/RNA fragments or strands simultaneously. MPS is often used synonymously with NGS.	[8]
Next-generation sequencing (NGS)	A collective term for a diverse group of post-Sanger sequencing technologies that have transformed the speed and cost of DNA sequencing, enabled by MPS technology. While "NGS" has been broadly adopted by the scientific community and literature, it is not a precisely defined technical term. The term is sometimes used to include third-generation sequencing technologies, such as long-read sequencing, though this broader usage is not strictly accurate, as third-generation sequencing represents a distinct technological advancement beyond the original scope of NGS. For technical accuracy and clarity, this report uses "NGS" specifically for second-generation and/or short-read sequencing technologies and refers to third-generation technologies separately.	[9], expert input
Second-generation sequencing	Refers to high-throughput DNA sequencing methods that emerged after Sanger sequencing, characterised by massively parallel analysis of millions of short DNA fragments. Unlike third-generation methods, second-generation sequencing typically requires DNA amplification before sequencing and typically produces shorter reads. In this report second generation sequencing includes MPS and NGS, both of which are associated with Short-Read Sequencing.	expert input
Third-generation sequencing (TGS)	Refers to high-throughput DNA sequencing methods that emerged after second generation sequencing, that work by sequencing single molecules of DNA in real time. Unlike previous generations, TGS does not require DNA amplification, allowing for much longer reads, useful for complex genomic regions. In this report third generation sequencing is associated with Long-Read Sequencing.	[10]

Terms for Types of Sequencing by Scope

Term	Definition	Source
Gene panel sequencing	Gene panel sequencing looks at a curated set of genes with variants known to be associated with the development of a condition or a collection of clinical symptoms under investigation.	[11]
Virtual gene panel sequencing	Virtual panels applied to data from whole exome sequencing (WES) or whole genome sequencing (WGS). In this case, although sequencing data are generated for all genes, only the genes in the virtual panel(s) relevant to the patient's condition are analysed.	[11]
RNA sequencing (RNA-seq)	A massively parallel sequencing approach used to detect the presence and quantity of RNA molecules in a sample (transcriptomics). It can be used to study differential gene expression, alternative splicing, and detect coding and non-coding RNAs, including fusion transcripts.	[12]
Whole exome sequencing (WES)	Whole exome sequencing (WES) is a next-generation sequencing (NGS)-based test in which the protein-coding regions of all of a patient's genes (known as the exome) are sequenced simultaneously.	[13]
Whole genome sequencing (WGS)	Whole genome sequencing (WGS) is a next-generation sequencing (NGS)- and third-generation-based test and refers to DNA sequencing of the entire genome, including both coding and non-coding regions.	[14]

Terms for Types of Sequencing by Read Length

Term	Definition	Source
Long-read sequencing	Long-read sequencing (often associated with Third-generation sequencing – TGS) has technical advantages for the detection of specific types of genetic variation. It can sequence long strands of DNA or RNA in one go.	[15]
Short-read sequencing	Within Massively Parallel Sequencing (MPS) approaches, short-read sequencing is currently the most commonly used type and has a wide range of diagnostic applications. The genome is broken into small fragments (usually 50 to 300 bases) before being sequenced.	[16]

Visual Abstract

Abkürzungen:
HTA: Health Technology Assessment
n: Anzahl (im Zusammenhang mit der Anzahl der identifizierten Berichte/Themen)
NHS: National Health Service (England)
NICE: National Institute for Health and Care Excellence (England)
MSAC: Medical Services Advisory Committee (Australien)

Executive Summary

Introduction

Technological advances in genetic testing have enabled simultaneous analysis of multiple genetic targets, creating new opportunities increasing the need for evidence-based decision-making regarding their integration into routine clinical care. This scoping review provides the methodological basis for topic prioritisation for assessments of genetic tests by Austrian decision-makers and informs two subsequent Health Technology Assessment (HTA) reports within this genetics project.

Methods

A systematic literature search in the INAHTA database and Cochrane Library (2020-2025) was supplemented by manual searches of 14 HTA institution websites. The country analysis was based on a review of official documents from countries with established reimbursement processes. A multidisciplinary workshop in July 2025 with representatives from various Austrian stakeholders (n=8) supported development of prioritisation criteria.

Results

A total of 49 reports from 15 organisations were identified, with highest number of HTA reports in Canada (n=14), the United Kingdom (n=11), and Australia (n=7). Reports cover four application fields: diagnostic testing (n=14, including familial hypercholesterolaemia, rare diseases, inherited cardiac conditions), clinical predictive testing (n=8, including carrier screening, newborn screening), pharmacogenomic testing (n=11, including psychiatry, stroke management), and tumour testing (n=16, including lung cancer, breast cancer, haematological malignancies). Most genetic tests (43/49) were positioned as add-on to existing approaches.

England, Australia, and Ontario pursue indication-specific approaches. England maintains a National Genomic Test Directory with over 280 indications and dual evaluation pathways (NHS England, NICE). Australia documents 123 submissions since 2002 using a Clinical Utility Card emphasising actionable results. Ontario operates a Genetic Test Directory with over 600 tests using genetics-specific prioritisation criteria.

The workshop with Austrian decision makers identified three core criteria for priority setting for HTA of genetic tests: (1) Clinical actionability (extent to which a test leads to changes in patient management), (2) Resource intensity (organisational and economic burden, particularly regarding data storage and genetic counselling), and (3) Indication volume (frequency of test requests). A preliminary scoring system with double weighting of clinical actionability yielded 16 (out of 49 HTA reports) highly prioritised topics across all application fields.

Discussion and conclusions

For Austria, formalising existing genetic testing practice through granular, indication-specific criteria is recommended. A pragmatic first step would be establishing steering committees (including experts in genetics, pathology, and laboratory medicine) to develop an indication-specific catalogue based on current standard of care, with annual updates and formal evidence reports for selected indications – an approach successfully implemented in England. Such a process requires transparent governance structures and regular review cycles aligned with evolving clinical evidence.

Once a formalised evidence-based reimbursement process is established, the developed prioritisation criteria – clinical actionability, resource intensity, and indication volume – can serve as initial reference. However, broader consultation and iterative refinement through systematic engagement with multidisciplinary stakeholder groups will be essential prior to formal adoption for topic prioritisation within such a process.

Zusammenfassung

Einleitung

Genetische Untersuchungen umfassen diverse Methoden zur Analyse des menschlichen Erbguts. Die Hochdurchsatz-Sequenzierung, darunter Next Generation Sequencing (NGS) – hat sich dabei als Schlüsseltechnologie etabliert. Diese Verfahren ermöglichen die gleichzeitige Analyse zahlreicher genetischer Zielstrukturen bzw. Nukleinsäuren (z. B. DNA und RNA), wodurch genetische Diagnostik schneller wurde und die Anwendungsmöglichkeiten in der medizinischen Versorgung erheblich erweitert wurden. Diese Entwicklung schafft neue Möglichkeiten in der Diagnostik und Therapieplanung, wirft jedoch zugleich komplexe Fragen zur Evidenzbewertung, Integration in die Regelversorgung und zu den ethischen Implikationen auf. Die zunehmende Verfügbarkeit dieser Technologien macht evidenzbasierte Entscheidungsprozesse in Gesundheitssystemen erforderlich.

Hochdurchsatz-Sequenzierung kommt bei einigen genetischen Tests zur Anwendung, wobei in dieser Arbeit grob zwischen folgenden Verfahren unterschieden wird:

- Targeted-gene panel Sequenzierung: Panels mit 20–500+ relevanten Genen,
- Whole Exome Sequencing (WES): Sequenzierung von ca. 20.000 protein-kodierenden Genen,
- Whole Genome Sequencing (WGS): Umfassende Sequenzierung des nahezu gesamten Genoms, und
- Virtuelle Genpanel-Sequenzierung: Gezielte Analyse vordefinierter Gene auf Basis von WES- oder WGS-Daten.

Der vorliegende Bericht zielt darauf ab, einen Überblick über Anwendungsgebiete von genetischen Tests basierend auf Hochdurchsatz-Sequenzierung zu liefern und auf Basis internationaler Erfahrung Zugänge für eine evidenzbasierte Erstattungsentscheidung ebendieser zu beschreiben. Zusätzlich soll der Bericht Überlegungen zu einem Ansatz zur Priorisierung dieser Tests für die Durchführung von Health Technology Assessments (HTA) für Österreich liefern.

Als erster Teil eines umfangreichen Genetik-Projekts liefert dieser Bericht ebenfalls die Grundlage für die Themenauswahl für zwei weitere HTAs, die im Zuge dieses Projekts erstellt wurden.

Methoden

Es wurde eine systematische Literatursuche in der INAHTA-Datenbank und Cochrane Library (2020-2025) durchgeführt, ergänzt durch eine manuelle Recherche auf den Websites von 14 HTA-Institutionen. Eingeschlossen wurden HTA-Berichte und Cochrane Reviews, die genetische Testung mittels Hochdurchsatz-Sequenziertechnologien bewerten. Die identifizierten Berichte wurden nach vier gängigen Anwendungsfeldern kategorisiert, die vom NHS definiert wurden: diagnostische Testung, klinisch prädiktive Testung, pharmakogenomische Testung und Tumortestung.

Für die Länderanalyse wurden offizielle Dokumente aus Ländern mit etablierten evidenzbasierten Erstattungsprozessen analysiert. Die Auswahl dieser Länder basierte auf der Anzahl der identifizierten HTA-Berichte, wobei ein höheres Volumen publizierter HTA-Berichte auf einen formalisierten und etablierten Prozess hindeutet. Die Untersuchung wurde entlang der vier idealen Schritte evidenzbasierter Erstattungsprozesse strukturiert: Priorisierung, Assessment, Appraisal und Entscheidung.

Ein multidisziplinärer Workshop im Juli 2025 mit österreichischen Entscheidungsträger:innen (n=7) diente der Entwicklung von Priorisierungskriterien für Durchführung von HTAs in einem zukünftigen Erstattungsprozess. Die Workshop-Teilnehmer:innen erhielten vorab eine „Long-List“ mit 49 HTA-Berichten zu genetischen Dienstleistungen und bereiteten jeweils einen relevanten Anwendungsfall vor. Die gesammelten Begründungen wurden gemeinsam in Hauptkategorien geclustert, die in klinische, ökonomische und organisatorische Aspekte strukturiert wurden.

Ergebnisse

Anwendungsgebiete nach HTA Berichten

Es wurden 49 Berichte von 15 Organisationen identifiziert, mit der höchsten Anzahl an Berichten aus Kanada (n=14), dem Vereinigten Königreich (n=11) und Australien (n=7). Die Berichte verteilen sich wie folgt auf vier Anwendungsfelder: diagnostische Testung (n=14), klinisch prädiktive Testung (n=8), pharmakogenomische Testung (n=11) und Tumortestung (n=16).

- Bei der **diagnostischen Testung** wurden folgende Hauptindikationen identifiziert: familiäre Hypercholesterinämie (4 Berichte), seltene Erkrankungen und Entwicklungsstörungen (4 Berichte), hereditäre Herzerkrankungen (3 Berichte), neonatale Diagnostik (1 Bericht) sowie Tuberkulose-Resistenztestung und Hörverlust bei Kindern (je 1 Bericht). Die Teststrategien umfassten Genpanel-Sequenzierung, WES und WGS, wobei häufig virtuelle Panels auf WES- oder WGS-Daten angewendet wurden.
- **Klinisch prädiktive Testung** wurde in sieben Berichten evaluiert: präkonzeptionelles oder pränatales Trägerscreening (4 Berichte), Neugeborenenscreening (2 Berichte), Reproduktionsmedizin (1 Bericht) und kardiovaskuläre Erkrankungen (1 Bericht). Diese Tests zielen darauf ab, das Risiko einer Erkrankung vor Symptombeginn zu bewerten.
- **Pharmakogenomische Testung** wurde in elf Berichten adressiert: Psychiatrie (4 Berichte), Clopidogrel-Eignung nach ischämischem Schlaganfall (3 Berichte), Fluoropyrimidin-Toxizität (2 Berichte) und präemptive Multi-Gen-Testung in der Primärversorgung (2 Berichte). Diese Tests informieren über genetische Variation, die die Arzneimittelreaktion beeinflusst.
- **Tumortestung** war mit 16 Berichten das am häufigsten evaluierte Anwendungsfeld: nicht-kleinzelliges Lungenkarzinom (4 Berichte), Brustkrebs (3 Berichte), hämatologische Malignome (3 Berichte), tumorübergreifende Testung (2 Berichte), Hirntumoren (2 Berichte) sowie Lynch-Syndrom bei Endometriumkarzinom und Prostatakarzinom (je 1 Bericht).

Über alle Anwendungsfelder hinweg wurden die meisten Tests (43/49) als Add-on-Strategien zu bestehenden Ansätzen positioniert. WES wurde explizit in sechs Berichten erwähnt, WGS in zehn Berichten.

Erstattungsprozesse

England, Australien und Ontario (Kanada) wurden als Länder mit der höchsten HTA-Aktivität identifiziert. Alle drei Länder verfolgen einen indikationsspezifischen Ansatz.

- England unterhält ein *National Genomic Test Directory* mit über 280 Indikationen (66 seltene/hereditäre Erkrankungen, 214 Krebsindikationen). Der Prozess ist durch zwei Evaluationspfade charakterisiert: NHS England evaluiert spezialisierte genomische Tests, während NICE Tests mit breiterem NHS-Impact bewertet. Das Directory wird jährlich aktualisiert.
- Australiens *Medical Services Advisory Committee (MSAC)* hat seit 2002 insgesamt 123 Einreichungen dokumentiert (99 für genetische Testanwendungen, 24 für genetik-bezogene Anwendungen). MSAC verwendet eine Clinical Utility Card, die besonderen Wert auf handlungsfähige Ergebnisse legt, einschließlich Kaskadenscreening. Akzeptierte Empfehlungen werden durch Änderungen des Medicare Benefits Schedule umgesetzt.
- Ontario führt ein *Genetic Test Directory* mit über 600 finanzierten Tests. Die Priorisierung erfolgt auf Basis speziell für genetische Tests entwickelter Kriterien: klinischer Nutzen, Schaden, Kosteneffektivität, Ressourcenauswirkung, Diffusionsdruck, Auswirkung und Gerechtigkeit sowie Rezeptoren im Gesundheitssystem. Alle Kriterien werden gleichwertig gewichtet.

Mögliche Priorisierungskriterien für HTA

Der Workshop mit österreichischen Entscheidungsträger:innen identifizierte drei mögliche Priorisierungskriterien:

- (1) Klinische Handlungsfähigkeit (Ausmaß, in dem Tests zu Änderungen im Patient:innenmanagement führen),

- (2) Ressourcenintensität (organisatorische und ökonomische Belastung, insbesondere in Hinblick auf Datenspeicherung und genetische Beratung) und
- (3) Indikationsvolumen (Häufigkeit der Testanforderungen).

Ein vorläufiges Scoring-System wurde entwickelt, das klinische Handlungsfähigkeit doppelt gewichtet. Die tatsächliche Entscheidung zur Themenauswahl sollte allerdings durch multidisziplinäre Expert:innendeliberation erfolgen. Die Anwendung dieser Kriterien ergab 16 (aus 49 HTA-Berichten) hochpriorisierte Themen über alle Anwendungsfelder hinweg.

Diskussion und Schlussfolgerungen

Die Ergebnisse zeigen, dass substanzielle HTA-Aktivitäten vor allem in Ländern mit formalisierten Bewertungs- und Erstattungsprozessen stattfinden, insbesondere in England, Australien und Kanada (Ontario). Alle drei Erstattungsprozesse wenden einen indikationsspezifischen Ansatz an, der Test-Evaluation mit definierten klinischen Kontexten und Patient:innenpopulationen verknüpft.

Für Österreich sollte die bestehende Praxis zur Einführung genetischer Testungen in die Versorgungspraxis durch granulare, indikationsspezifische Kriterien standardisiert werden, anstatt ein vollständig neues System aufzubauen. Ein pragmatischer erster Schritt wäre die Etablierung von Expert:innenkomitees (etwa aus den Bereichen Genetik, Pathologie und Labormedizin), die beauftragt werden, einen indikationsspezifischen Katalog basierend auf dem aktuellen Versorgungsstandard zu entwickeln. Die internationalen Testverzeichnisse können hierbei ebenfalls zur Identifikation von etablierten Tests/Indikationen herangezogen werden. Dieser Katalog könnte dann jährlich aktualisiert werden, wobei Steuerungskomitees ausgewählte Indikationen und Technologien identifizieren, die formale Evidenzberichte erfordern – ein Ansatz, der beispielsweise im Vereinigten Königreich erfolgreich implementiert wurde. Für einen solchen Prozess sind transparente Governance-Strukturen und regelmäßige Review-Zyklen notwendig, die sich an der jeweils aktuellen klinischen Evidenz orientieren.

Sobald ein formalisierter evidenzbasierter Erstattungsprozess etabliert ist, können die während des Stakeholder-Workshops entwickelten relevantesten Priorisierungskriterien – klinische Handlungsfähigkeit, Ressourcenintensität und Indikationsvolumen – als initiale Referenz dienen. Bevor diese Kriterien formell zur Themenpriorisierung verwendet werden, ist es entscheidend, sie durch umfassende Konsultationen und iterative Anpassungen mit multidisziplinären Stakeholder-Gruppen weiterzuentwickeln.

1 Introduction

Humangenetik-Projekt 2025: Teil A Überblick und Priorisierung

This scoping review is part of a comprehensive AIHTA project on genetic testing, with a focus on sequencing technologies. This first report forms the basis for topic prioritisation for assessments of genetic tests by Austrian decision makers [17]. Subsequent reports in this project [18, 19] address selected applications identified through the prioritisation process described in this report.

Herausforderungen und Risiken erfordern evidenzbasierte Entscheidungen

Genetic testing includes a range of methods for analysing genetic material. Technological advances have enabled the simultaneous analysis of multiple DNA fragments, increasing both the speed and scope of genetic testing and supporting new application fields in medical care. These developments present important opportunities for diagnosis and therapy, but also raise challenges for evidence assessment, integration into routine care, and ethical considerations. Robust, evidence-based decision-making is increasingly essential as the field continues to expand [20].

1.1 The development of sequencing technologies

Entwicklung der Sequenziertechnologien: Sanger-Sequenzierung als 1. Generation

Genetic testing capabilities have evolved through successive technological developments, beginning with **Sanger sequencing,** also referred to as **first-generation sequencing**, as the original DNA sequencing method. This chain-termination approach established the foundation for genetic analysis and continues to serve specific clinical functions in targeted analysis and validation of results from more advanced sequencing methods [6].

Second-Generation: Next-Generation Sequencing

Second-generation sequencing refers to high-throughput DNA sequencing methods that emerged after Sanger sequencing, enabling parallel analysis of millions of short DNA fragments (short-read sequencing). Second-generation sequencing is often used interchangeably with next-generation sequencing (NGS), and massively parallel sequencing (MPS), though NGS is sometimes applied more broadly across technological generations [8, 9]. These technologies have become established in clinical practice and form the basis for most current genetic testing applications. The terminology reflects some variability in literature usage, with NGS sometimes applied more broadly across different technological generations.

Third-Generation: Long-read für komplexe Genomregionen

Third-generation sequencing refers to high-throughput DNA sequencing methods that emerged after second-generation sequencing, enabling real-time analysis of single DNA molecules without amplification. This technology produces longer reads compared to previous generations, making it particularly valuable for analysing complex genomic regions and detecting specific variant types. Third-generation sequencing is therefore often associated with long-read sequencing, though these technologies remain primarily within research applications but are progressing toward providing evidence for clinical practice implementation [10].

Short-read vs. Long-read: unterschiedliche methodische Ansätze

According to input provided by experts, short-read sequencing and long-read sequencing represent distinct technical approaches that can both generate whole genome sequencing (WGS) results, though through different methodological pathways. The choice between approaches depends on analytical re-

quirements and technical considerations specific to the clinical question. Short-read sequencing additionally enables whole exome sequencing (WES) applications, focusing analysis on protein-coding genomic regions while utilising the established technical infrastructure of second-generation methods [16].

Genpanel-Testung: direkt oder als virtuelles Panel

Targeted gene panel testing can be implemented using NGS short-read approaches [16] for direct targeted analysis. Alternatively, virtual panels can be applied to WES or WGS data [13, 14], where broader sequencing data is generated but analysis is restricted to predefined gene sets relevant to specific clinical conditions.

1.2 Different approaches to gene sequencing

Fokus auf 4 Sequenzierungsansätze:

Given the complexity of different technologies and often unstandardised terminology, this report focuses on the following, using a nomenclature, incorporating technological and resource implications related to the scope of analysis:

- Targeted gene panel sequencing
- Whole exome sequencing (WES)
- Whole genome sequencing (WGS)
- Virtual gene panel sequencing using WES or WGS

Targeted Genpanels: kostengünstiger, begrenzte Reichweite

Targeted gene panels sequence 2-1000+ specific disease-related genes. The cost of targeted gene panel is comparatively lower with deep coverage for detecting mosaicism, but miss genes outside the panel and can't detect copy number variants (CNV) or structural changes [21].

Exom-Sequenzierung: 1-2% des Genoms

WES sequences all ~20,000 known coding regions of genes, representing approximately 1-2% of the genome. It can identify novel genetic causes of disease without requiring updates like targeted panels and produces fewer variants of uncertain significance compared to WGS. However, it has lower sequencing depth than targeted panels (reducing sensitivity for mosaicism detection), misses mutations in non-coding regions, and has limited ability to detect structural variants [13, 21].

Genom-Sequenzierung: umfassend, aber kostenintensiv

WGS sequences nearly the entire genome, including both coding and non-coding regions. It provides the best method for detecting copy number variants and structural rearrangements due to uniform coverage and may identify disease-causing variants in regulatory or intronic regions. However, it is the most expensive option, generates massive amounts of data requiring secure storage, produces the highest number of variants of uncertain significance, and carries the greatest risk of incidental findings [21].

virtuelle Genpanels: gezielte Analyse umfassender Daten

Virtual gene panels apply targeted analysis to comprehensive WES or WGS data, analysing only genes relevant to the patient's condition while retaining the full dataset for potential future reanalysis [22].

RNA-Sequenzierung als ergänzende Methode

RNA sequencing (RNA-Seq) is another high-throughput sequencing approach that quantifies RNA molecules to study gene expression, splicing, and fusion transcripts [12]. It is often used adjunctively alongside DNA-based sequencing methods and, as such, is not described separately in this report.

Table 1-1 provides an overview of differences between targeted gene panel, WES and WGS by scope.

Table 1-1: Overview of genetic testing approaches by scope

Feature	Targeted gene panel	Whole exome sequencing (WES)	Whole genome sequencing (WGS)
Number of genes	2-1000+ genes	Around 20,000 coding regions of genes (1%-2% of genome)	Almost the entire genome (all coding and non-coding regions, though some parts are difficult to sequence)
Cost per test (UK)[1]	€150-600	€600	€850 (and falling)
Advantages	Customisable. Lowest cost. Deep coverage (detects mosaicism). May identify novel genetic causes of disease.	No need to update as new genetic associations discovered. Fewer variants of uncertain significance (VUS) than WGS. May identify novel genetic causes of disease.	May identify disease-causing variants in regulatory intronic/ enhancer regions. Best for detecting copy number variants (CNVs) and structural rearrangements.
Disadvantages	Does not identify variants in genes not already known to cause a particular condition. Difficult to update. Usually less sensitive in detecting CNVs/structural rearrangements.	Poor sequencing depth (may not detect mosaicism). Misses intronic and regulatory/enhancer mutations. Increased risk of incidental findings. Limited ability to detect CNVs/structural rearrangements.	Highest cost. Huge data volume. Highest chance of identifying VUS. Significant burden of clinical interpretation. Increased risk of incidental findings. More VUS identified (compared with targeted gene panel).

Table retrieved and slightly adapted from [21]; further sources: [11, 13, 14]
Price ranges are based on published UK list prices and were converted to Euro using the OeNB reference exchange rate from October 24, 2025.
For improved clarity, values were rounded to the nearest €50 or €100 [23].

Abbreviations: CNV … copy number variant; NGS … next-generation sequencing; VUS … variant of uncertain significance; WES … whole exome sequencing; WGS … whole genome sequencing.

[1] According to expert information, the cost in Austria of WES and WGS is approximately 200-300€ higher. In the absence of cost data, no precise cost data can be inferred.

1.3 Diverse application fields of genetic testing in medicine

Hochdurchsatz-Sequenzierung:

In recent years, the scope and variety of genetic testing in medicine have expanded substantially, covering rare diseases, hereditary cancer predisposition, pharmacogenomics, non-invasive prenatal screening, and more.

neue klinische Anwendungen

Therefore, a recent AIHTA Rapid Review [24] summarised technological aspects and application fields of high-throughput sequencing technologies. The report hereby included any published studies with no restriction on study design to describe the application fields of MPS, noting that these technologies have fundamentally transformed DNA and RNA analysis in recent years. Increased throughput, shorter run times, and reduced costs relative to early implementations have made a wide range of new clinical uses possible. Continuous advancement of established technologies, alongside innovations in sequencing methods, is driving rapid development and competition across the market. It is stressed that while implementation of MPS presents technical and practical challenges, these technologies are poised to move beyond research into routine clinical care. Despite diverse opportunities, rigorous evaluation of real patient benefit remains essential for successful adoption in healthcare [24].

Mapping vorliegender HTA-Bewertungen erforderlich

Against this backdrop, it is essential to consider an evidence-based approach when assessing and implementing these new technologies. Hence, it appears important to map which indications have already been assessed.

1.4 Cross country analysis on genetic testing services

GÖG-Ländervergleich: Steuerung humangenetischer Leistungen

In 2024, the Austrian Public Health Institute (German: Gesundheit Österreich GmbH/GÖG) conducted a cross-country analysis on how genetic testing is implemented in different healthcare systems [25]. Germany, England, and the Netherlands were identified as key reference countries for Austria. The report highlights significant differences in the organisational, regulatory, and financial frameworks for these services. While all three countries have publicly funded genetic testing services, the way they are delivered and reimbursed varies considerably.

Deutschland: Bottom-up-Ansatz mit EBM-Vergütung

- **Germany:** This country is characterised by a "bottom-up" approach, where the healthcare landscape was shaped by initiatives from various research and medical practice groups. The provision of services is a mix of university hospitals, medical care centers (MVZ), and private practices. Reimbursement is guided by a federal-level uniform valuation standard (German: Einheitlicher Bewertungsmaßstab, EBM), which is regularly updated through negotiations between the associations of statutory health insurance funds and physicians.

England: Top-down-Ansatz mit zentralem Test Directory

- **England:** This system is a clear example of a "top-down" approach, driven by a national strategy. The NHS Genomic Medicine Service (GMS) centrally coordinates services, supported by a National Genomic Test Directory that details which tests are covered and the criteria for ordering them. This centralised model allows for a standardised approach to service delivery and facilitates the creation of a unified data infrastructure for research and a national genomic research library.

- **The Netherlands:** This country's approach is described as "rather bottom-up" and is based on a regulated market of private health insurers offering a mandatory basic package of services. Genetic care is provided by seven university-affiliated clinical genetics centers and the National Cancer Institute. There are national guidelines for core gene panels, and maximum tariffs for services are set by the Dutch Healthcare Authority.

Niederlande: Regulierter Markt mit Höchsttarifen

- **Austria:** Austria's healthcare system is based on mandatory public social insurance and is organised in a predominantly bottom-up manner. Genetic services are mainly delivered by four university clinics and six additional providers. Hospital-based diagnostic testing is documented within the LKF (German: Leistungsorientierte Krankenhausfinanzierung) system, which operates under a global budget principle for these services rather than explicit service-level regulation, while outpatient provision relies on individual service contracts. The defined scope is limited and outdated, with formal eligibility criteria restricted to hereditary breast and ovarian cancer syndrome; referral is common. Furthermore, molecular diagnostics like tumour profiling are in practice at several public and private institutes for pathology as well as laboratory medicine.

Österreich: Bottom-up-Organisation; LKF nur zur Dokumentation, Globalbudget statt Leistungssteuerung

Table 1-2 provides a brief overview on the cross-country analysis on genetic testing services.

Table 1-2: Comparison of governance of genetic health services across countries

	AT	GER	ENG	NL
Healthcare System	Public SI, mandatory	Public SI, mandatory	NHS	Public/private SI, mandatory
Organisation	Bottom-up	Bottom-up	Top-down	Rather bottom-up
Regulation*	■ Individual contracts ■ + hospital provision (within „Leistungsorientierte Krankenanstaltenfinanzierung“, LKF**)	■ Uniform value scale (“Einheitlicher Bewertungsmaßstab”, EBM) ■ + Selective contracts	■ NHS Genomic Medicine Service	■ Individual contracts (insurers/clinics) ■ + national guidelines
Service Provision	■ 4 university clinics ■ + 6 other providers	■ Office-based specialists (with laboratories) ■ Medical care centres (MVZ, often hospital-run) ■ University clinics (especially selective contracts)	■ 7 Genomic Lab Hubs ■ + affiliated labs	■ 7 university clinics ■ + 1 national cancer institute
Scope	■ Eligibility criteria only for hereditary breast and ovarian cancer syndrome (outdated)	■ Indication-specific tiered service catalogue	■ Test directory for hereditary and rare diseases, cancer, and future pharmacogenomics.	■ Minimum requirements for core gene panels and detailed requirements for tumor genetics.
Access Restrictions	■ Referral is common	■ Referral is necessary.	■ Referral by a hospital specialist to the Clinical Genomic Service.	■ None, as it is part of the basic package; a referral is necessary.
Financing Mechanisms	Inconsistent service contracts	Uniform service catalogue and selective contracts.	Funding through the NHS.	Nationally uniform maximum tariffs.
Whole Genome Sequencing (WGS)	WGSmed project and participation in the "Genome of Europe" project.	Pilot project under SGB V.	Genomics England develops data infrastructure and acts as an “enabler”. WGS is in the test directory and is used in certain circumstances.	WIDE feasibility study and routine use for certain metastatic cancers.

Table retrieved and slightly adapted from [25].
*Individual contracts refer to separately negotiated agreements between individual payers and providers.
Selective contracts refer to optional contracts for specific services or innovative technologies beyond the standard service catalogue.
(common term in German healthcare for innovation contracts).
**In Austria, hospital-based diagnostic testing services are funded through global budgets of the laboratories, with LKF serving primarily for documentation.

Abbreviations: AT … Austria; ENG … England; GER … Germany; NHS … National Health Service; NL … Netherlands; SGB … Sozialgesetzbuch; SI … Social Insurance; WGS … Whole Genome Sequencing.

Recommendations from GÖG report

Empfehlungen des GÖG-Berichts: Standardisierung der Tarife, Kriterienkatalog und Förderung der Beratungsangebote

Based on this international comparison and the analysis of the Austrian system, the report makes several key recommendations aiming at modernising and standardising genetic testing in Austria. These recommendations are not about a single approach but rather a menu of options to improve the Austrian health care system [25]:

- **Standardise Contracts and Tariffs**: The report recommends introducing a framework agreement for genetic testing with a uniform service catalogue and a system of base services with "add-ons" for complex cases. This would provide a more consistent and up-to-date remuneration structure that reflects the actual effort involved in analysis and counselling.
- **Establish Clear Criteria for Access:** It is suggested that a separate, regularly updated catalogue of eligibility criteria should be developed for when genetic testing should be covered. This would address the current lack of detailed guidelines, which can lead to legal uncertainty and inconsistent access to services. The report also recommends promoting a public debate about the role of genetic testing to increase public acceptance and prevent the private market from dominating the discussion.
- **Improve Genetic Counselling and Integrated Care:** The report highlights the need to finalise a quality standard for genetic counselling and to ease access to these services. This can be achieved by defining the roles of both physicians and non-physician genetic counsellors, promoting network structures for knowledge transfer, and clearly outlining the procedures for different types of consultations.

offene Umsetzung: Kartierung neuer Anwendungsfelder und Reflexion zu HTA-Prozess

While the GÖG report presents a menu of options for improving the Austrian health care system, decisions on the concrete adoption and implementation of these recommendations remain open. This project aims to inform subsequent steps by mapping the clinical applications of genetic testing and describing evidence-based reimbursement processes.

2 Objectives and scope

2.1 Research questions

Forschungsfragen zu neuen Indikationen, existierenden Erstattungsprozessen und Priorisierungskriterien für Österreich

This report has the following two objectives: gaining greater insights into clinical indications for genetic testing and developing prioritisation criteria for a potential evidence-based reimbursement process in Austria. Based on these two objectives, the following three research questions (RQ) are formulated:

- **RQ1:** What clinical indications for genetic testing, structured by application fields, were evaluated in health technology assessment (HTA) reports and Cochrane reviews?
- **RQ2:** How are the steps of prioritisation, assessment, appraisal, and decision organised in the evidence-based reimbursement process for genetic testing in selected countries?
- **RQ3:** Which criteria for prioritisation are regarded as relevant by Austrian stakeholders in the evaluation and selection of genetic testing for HTA?

2.2 Inclusion criteria

Einschlusskriterien für Literatursuche

Inclusion criteria for identifying relevant HTA reports and Cochrane reviews for RQ1 are summarised in Table 2-1.

Table 2-1: Inclusion and Exclusion criteria

	Inclusion Criteria	Exclusion Criteria
Population	Individuals with a clinical indication for genetic testing	Healthy subjects, animal models
Intervention	The application of high-throughput sequencing technologies, such as: ■ Targeted gene panel sequencing ■ Whole exome sequencing (WES) ■ Whole Genome Sequencing (WGS) ■ Virtual gene panel sequencing using WES or WGS	Sanger Sequencing
Context	The evaluation of these technologies as presented in the international evaluations, with a focus on application fields, clinical indications, position in care pathway, reference standards and comparators and technological aspects.	Exclusively technical parameters without clinical reference
Study design	HTA reports and Cochrane reviews	Narrative reviews, scoping reviews, primary studies, non-Cochrane systematic reviews, conference abstracts, editorials, commentaries
Language	English, German	All other languages
Publication Period	From 2020 and later	Before 2020

3 Methods

dreiphasiger Ansatz: Scoping, Ländervergleich und Workshop

A scoping review methodology with a multi-stage approach was used to prepare the report on genetic testing using high-throughput sequencing technologies. The approach consisted of three distinct phases: 1) scoping of indications structured by application fields according to international health technology assessment (HTA) reports and Cochrane reviews, 2) identifying and describing evidence-based reimbursement processes of selected countries and 3) reflection on potential prioritisation criteria to guide the selection of topics for HTA assessment in Austria.

Präregistrierung auf Open Science Framework

The review was pre-registered on the Open Science Framework (OSF) platform where the AIHTA protocol was published [17]. All protocol deviations are documented on the OSF platform and added in the discussion section.

Throughout this report, genetic and molecular biology terminology is consistently used in abbreviated form without spelling out the full terms (e.g., gene names, mutations, DNA, RNA).

3.1 RQ1: Scoping of clinical indications according to HTA reports and Cochrane Reviews

systematische Suche in 2 Datenbanken

We conducted a systematic search in the INAHTA database, and the Cochrane Library on the 21 May 2025. The systematic search was limited to the years 2020 to 05/2025 and to articles published in English or German. After deduplication, overall 353 citations were included. The specific search strategy employed can be found in the Appendix. Furthermore, a web-based manual search was conducted between 12th of May 2025 to 20th of May 2025. In addition to the systematic search within the INAHTA database, 14 HTA-institutes were selected for in-depth search on their respective websites. The selected HTA-institutes can be found in the Appendix (see Literature search strategies).

Einschluss: HTA-Berichte und Cochrane Berichte

We included any HTA report and Cochrane review dealing with genetic testing using high-throughput sequencing technologies. Articles dealing with non-genetic diagnostics or exclusively investigating genetic tests without high-throughput sequencing technology, like for example Polymerase Chain Reaction (PCR) tests, were excluded.

Kategorisierung nach NHS

We then categorised each article into four common application fields [1] defined by the National Health Service (NHS) (diagnostic, clinical predictive, pharmacogenomic and tumour testing). For each application field, an overview table was created highlighting how the technologies were evaluated in existing HTA/Cochrane reviews:

- Medical specialty
- Clinical indications
- Position in clinical pathway or test strategy with an emphasis on whether and how the high-throughput sequencing technology was used as add-on, replacement or triage
- Reference standard (if analytical or diagnostic accuracy was evaluated in HTA report) and comparator (if embedded test/treatment strategies were compared)

- Sequencing technology focusing scope (gene panel sequencing, RNA sequencing, Whole Exome Sequencing, Whole Genome Sequencing) read length (short read, long read)
- Target of analysis: e.g., how many biomarkers or genetic variants are examined

Vier-Augen-Prinzip bei allen Arbeitsschritten

Relevant information was influenced by technological considerations and established evaluation frameworks for diagnostic tests [26, 27]. All working steps were conducted by one person (GG or RJ) and cross checked by a second person (RJ or GG). Results are summarised in the Appendix (Table A-1 to Table A-4).

3.1.1 Flow chart of study selection

insgesamt 370 Publikationen identifiziert

Overall, 370 hits were identified. The references were screened by two independent researchers and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

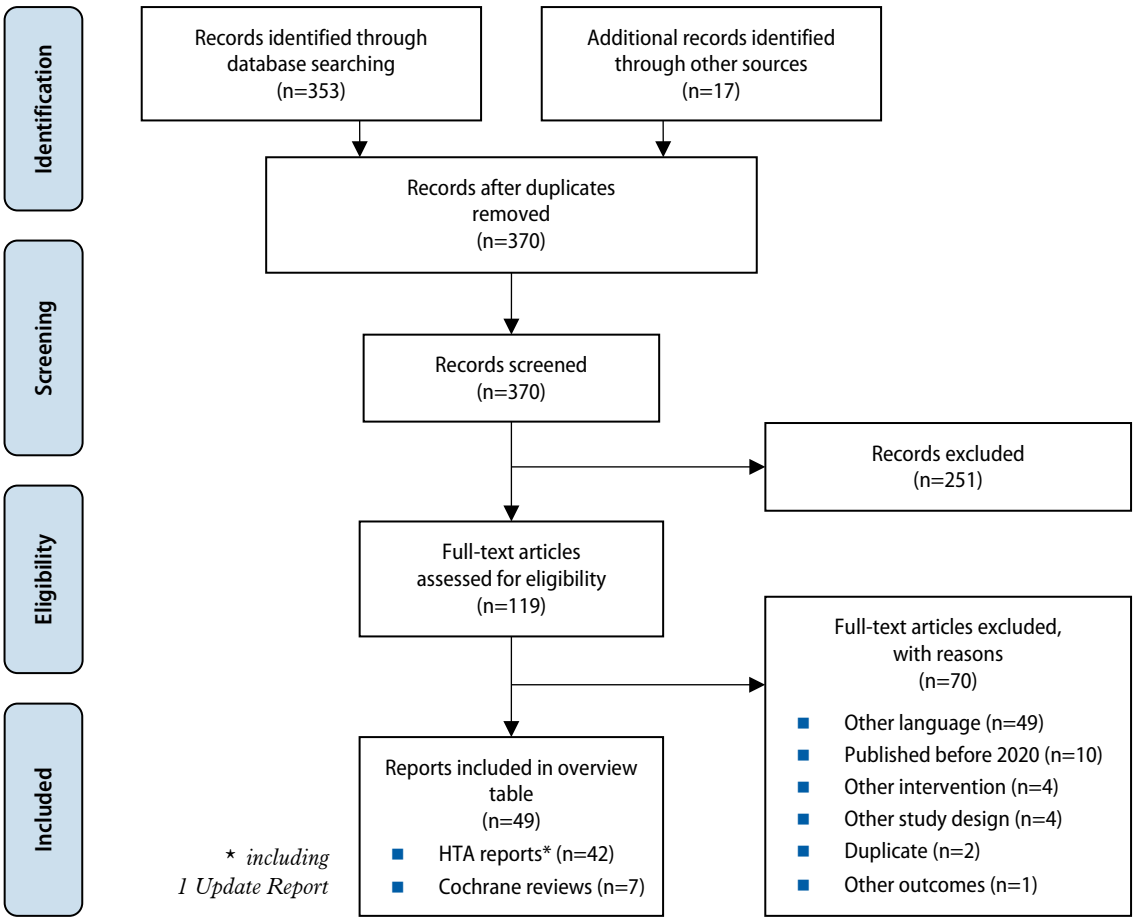

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2 RQ2: Evidence-based reimbursement process in selected countries

vergleichende Analyse etablierter HTA-Prozesse

Länderauswahl nach HTA Aktivität

A comparative analysis of publicly available official documents from countries with established evidence-based reimbursement processes for genetic testing was performed to answer Research Question (RQ) 2. The selection of these countries was based on the number of HTA reports identified for RQ1, with a higher volume of published HTA reports indicating a more formalised and established process. The examination of official documents (i.e., documents on governmental and HTA webpages) and expert input was structured around the four ideal steps of evidence-based reimbursement processes: prioritisation, assessment, appraisal, and decision.

- **Prioritisation:** How are genetic tests selected for formal HTA evaluation? It will detail the specific criteria and the entities responsible for this initial scoping and prioritisation phase.
- **Assessment:** Who conducts the assessment and what evidence is required?
- **Appraisal:** Which committees are involved and how they consider a broad range of aspects, including clinical, economic, social, legal and organisational (ESLO) issues?
- **Decision:** This final step will identify the specific entities or authorities that make the reimbursement or coverage decision. It will explain how the HTA recommendations are formally adopted into the country's healthcare policy.

Überblick über Test-Directories und Indikationen

If available, we provided a brief overview of the major disease groups and the quantity of specific indications as depicted in the official test directories and similar official documents from these countries. Where a public test directory was not available, we analysed key publications to provide a quantitative overview of the number of submissions on genetic testing to their HTA bodies.

Validierung durch Expert*innen

To ensure accuracy and content validity, the narrative analysis of the selected official documents was reviewed by a subject matter expert.

3.3 RQ3: Workshop with Austrian stakeholders

Workshop mit Vertreter:innen von Kostenträgern und Versorgungseinrichtungen

Prioritisation criteria were developed during a multidisciplinary in-person workshop held on July 3, 2025. The workshop participants (n=7) included representatives and clinical experts from relevant Austrian institutions, including AIHTA (Austrian Institute for HTA), DVSV (Umbrella Association of Social Insurance Institutions), WIGEV (Vienna Health Association), and GÖG (Gesundheit Österreich GmbH, GÖG). The composition of participants ensured a broad perspective, encompassing clinical, economic, organisational, as well as the viewpoints of service providers and payers.

Preparation Phase

Long-List mit 49 HTA-Berichten

In preparation for the workshop, participants were provided on June 20, 2025 with a "Long-List" including an overview table of 49 HTA reports on genetic services. DVSV and WIGEV were tasked with selecting one relevant use case for genetic testing in clinical practice from this list and preparing a brief (five-minute) oral justification for their choice. These case examples served as a concrete basis for discussion to identify crucial factors for selecting genetic test for an HTA evaluation.

Workshop Methodology for Criteria Development

Methodik: Impulsvorträge und moderierte Diskussion

The workshop followed a structured agenda. Two impulse presentations provided an introductory overview: the first presentation covered general principles of evidence-based reimbursement processes, while the second part offered insights into genetics in an international comparison (Germany, England, Netherlands). Subsequently, the prepared case examples (Carrier Screening from the social insurance perspective and Oncological Diagnostics from the hospital perspective) were discussed in moderated sessions. During these discussions, the justifications for the priority of the respective diagnostic application or tumor profiling were collected.

strukturierte Diskussion mit thematischer Analyse

In a subsequent phase, the collected justifications were jointly clustered into main categories, which were structured into clinical, economic and organisational aspects. It was discussed to what extent existing criteria (e.g., from established prioritisation from other HTA processes in Austria or internationally) could serve as a guide, or whether specific adaptations or new criteria were necessary. The collected themes were narratively described and overarching prioritisation criteria relevant for HTA in Austria were conceptualised.

Application of Prioritisation Criteria

Anwendung und Verfeinerung der Kriterien mit Experteninput

Following the workshop, a preliminary scoring approach was explored to support the systematic application of the selected criteria. One researcher (BY) applied the potential criteria to the topics identified in RQ1 and a clinical external expert (SP) provided feedback to refine the criteria.

Folgeberichte zu ausgewählten Themen

For two selected and prioritised topics, pilot assessments will be conducted in subsequent reports. These will be based on an overview of reviews and guideline synopses of specific technologies within defined indications.

4 Results for RQ1: Overview of indication evaluations

49 Berichte von 15 HTA-Organisationen identifiziert

This chapter presents clinical indications for genetic testing using high-throughput sequencing that were evaluated in Cochrane reviews and health technology assessment (HTA) reports. We organised the indications by four common application fields as defined by the National Health Service (NHS) (Diagnostic testing, clinical predictive testing, pharmacogenomic testing and tumour testing), which align with common use-cases of high-throughput sequencing described in the prior rapid review [1, 24].

Through combined systematic search and structured hand search, we identified a total of 49 reports (including 1 update report; see Table A-5 in Appendix and Figure 3-1). A total of 15 organisations are represented in our analysis, and the number of reports per institution were Cochrane (n=7), Health Quality Ontario – HQO (n=7), Medical Services Advisory Committee – MSAC (n=6), National Institute for Health and Care Excellence – NICE (n=5), Canada's Drug Agency – CADTH (n=5[2]), Health Technology Wales – HTW (n=4), Health Information and Quality Authority – HIQA (n=3), Technology Assessment at SickKids – TASK (n=2), Scottish Health Technologies Group – SHTG (n=2), Norwegian Institute of Public Health – NIPH (n=2), Austrian Institute for HTA – AIHTA (n=2), Institute for Quality and Efficiency in Health Care German: – IQWiG (n=1), Washington State HTA (n=1), National Institute for Health and Care Research – NIHR (n=1) and Belgian Health Care Knowledge Center – KCE (n=1).

4.1 Diagnostic testing

14 Berichte zu diagnostischer Testung

We classified a total of 14 reports to this category [28-42]. Diagnostic tests are most often requested when a clinician suspects, based on the patient's symptoms, that a particular genetic condition may be present. In such cases, the test can confirm the suspected diagnosis, exclude it as a cause of the symptoms, or help distinguish between conditions with overlapping clinical features. Diagnostic tests should usually give a yes or no result in regard to known pathogenic genetic alterations. The diagnostic testing may focus on a single gene variant or allele, or on a small panel of genes known to be associated with that disorder. In contrast, for many patients with an undiagnosed rare disease, a broader approach is required. Increasingly, this involves sequencing large parts of the genome, often using whole genome sequencing (WGS). The resulting data can then be compared against multiple gene panels linked to known conditions, thereby maximising the likelihood of reaching a diagnosis. This approach is exemplified by the 100,000 Genomes Project's rare disease programme. In case no relevant findings are identified, the sequence data can be stored and re-analysed as new evidence or gene-disease associations become available [1]. The following indications for diagnostic testing were identified in the included reports, which are described in greater detail below.

[2] Four reports and one update report.

Familial hypercholesterolemia (FH) was evaluated within four reports. The AIHTA (2020) report evaluated genetic testing as an add-on after a clinical FH diagnosis, with cascade screening of family members. The comparator was standard clinical diagnosis based on lipid profiles, history, and symptoms. Sequencing strategies included panel sequencing and whole-exome sequencing (WES), targeting germline mutations in relevant genes such as LDLR, ApoB, PCSK9, and LDLRAP1. The report further highlighted organisational considerations for cascade implementation. The Cochrane (2021) review compared different screening strategies for FH, with High throughput sequencing included as an add-on in some approaches. The comparators were various screening methods, and mode of diagnosis (genetic vs. clinical) was analysed in subgroups. The HQO (2022) assessment examined targeted gene panel sequencing for known FH genes in both confirmatory and cascade testing. Genetic testing was considered an add-on to clinical evaluation and compared with clinical diagnosis alone. Pathogenic variants were sought in genes such as ABCG5, ABCG8, AobB, APOE, LDLR, LDLRAP1, LIPA, and PCSK9. The IQWiG (2024) report addressed universal FH screening of asymptomatic children and adolescents (<18 years). A two-step approach was considered: lipid testing followed by confirmatory genetic analysis. Comparators were no universal screening and, as reference standard, molecular genetic testing. Both whole-genome sequencing (WGS) and targeted sequencing were applied to germline DNA, with a focus on LDLR, ApoB, and PCSK9 [28, 32, 33, 39] .

familiäre Hypercholesterinämie: 4 Berichte

Rare diseases and developmental disorders were assessed in four reports. The MSAC (2023) report addressed mitochondrial disease. Genetic testing was an add-on to current diagnostic pathways, which often included invasive muscle biopsy for suspected mitochondrial disease (rare genetic metabolic disorder affecting energy production of the body, which can affect multiple organs). Testing comprised virtual panel-based WGS/WES and mitochondrial DNA sequencing, targeting over 350 genes in nuclear and mitochondrial DNA. The TASK (2025) study reported on whole-genome sequencing in children with suspected rare genetic disorders after non-diagnostic prior testing. Using the NovaSeq 600 platform, WGS was compared to WES. The patient population included syndromic and non-syndromic intellectual and developmental disabilities, multiple congenital anomalies, and single- or multi-system disorders. The HQO (2020) assessment considered sequencing for unexplained developmental disabilities or multiple congenital anomalies. Sequencing could be applied as a first or second tier or following standard genetic testing (chromosomal microarray or targeted panels). Both WES and WGS were used to detect causal variants. The Washington State HTA (2024) report evaluated WGS for children and adults with suspected genetic disorders. WGS was considered either a replacement or add-on to standard diagnostic evaluation, including clinical, laboratory, imaging, and various genetic tests (e.g., single-gene, panels, WES, CMA, karyotype) [35, 36, 38, 42].

seltene Erkrankungen und Entwicklungsstörungen: 4 Berichte

Inherited cardiac conditions (arrhythmias and cardiomyopathies) were evaluated in three reports. The MSAC (2020) report covered inheritable arrhythmias such as long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. Genetic diagnosis was considered an add-on to standard care, with cascade testing of family members. Testing involved a 20-gene panel including *KCNQ1, KCNH2, SCN5A, RYR2*, and others, benchmarked against Sanger sequencing. The MSAC (2021) report investigated heritable cardiomyopathies (hypertrophic, dilated, arrhythmogenic). Genetic testing was used to confirm or exclude a cause in patients with suspected disease, followed by cascade testing for relatives and partners. A

hereditäre Herzerkrankungen: 3 Berichte

broad gene panel was applied, targeting at least 22 genes depending on phenotype (e.g., *MYBPC3, MYH7, LMNA, DSP, PKP2*). The comparator was clinical diagnosis without genetic testing. The TASK (2020) study reported on children with heterogeneous cardiac diseases (cardiomyopathies, congenital heart defects, arrhythmias). Whole-genome sequencing (*Illumina HiSeq X™*) was applied, with 1,500-2,000 genetic variants examined and 15-20 flagged for further pathogenicity analysis. Pharmacogenomic profiling was performed for probands [29, 30, 40].

neonatale Diagnostik: 1 Bericht

Neonatal diagnostics was assessed in one report. The Cochrane (2025) review [37] focused on diagnosis of neonatal bacterial and fungal sepsis. Sequencing approaches, including Polymerase Chain Reaction (PCR) and metagenomic high throughput sequencing, were positioned as potential replacements for blood cultures, aiming for faster and more sensitive detection of bacterial and fungal nucleic acids (DNA, 16S rRNA, ITS regions) in blood or cerebrospinal fluid. Technically, these sequencing approaches target pathogen genetic information (rather than human DNA).

Antibiotikaresistenz bei Tuberkulose: 1 Bericht

Tuberculosis (drug resistance profiling) was evaluated in one report, evaluating antimicrobial drug susceptibility testing in *Mycobacterium tuberculosis*. WGS was used as an add-on to phenotypic testing to detect resistance in the pathogen genome. The comparator was phenotypic drug susceptibility testing alone [31].

Hörverlust bei Kindern: 1 Bericht

Childhood hearing loss was addressed in one report. The MSAC (2022) report covered genetic testing for hearing impairment in children. The testing pathway started with *GJB2/GJB6*, followed by a virtual gene panel if no diagnosis was achieved. Virtual panel-based WES and copy number variant analysis restricted analysis to known hearing loss genes. The comparator was the absence of such virtual gene panel analysis [41].

4.2 Clinical predictive testing

8 Berichte zu prädiktiver Testung

We classified a total of eight reports to this category [34, 43-49]. Predictive tests assess an individual's risk of developing a condition before symptoms appear. In clinical settings, they are typically performed when a causative variant has already been identified in a family member, allowing targeted testing. They are most often used for actionable conditions, where interventions or surveillance can reduce risk, or for severe non-actionable conditions where results may guide life choices. Predictive value varies: fully penetrant variants (e.g., Huntington's disease) provide certainty, while most tests (e.g., BRCA1) indicate elevated but not absolute risk. Variable expressivity further complicates interpretation. Nonetheless, such testing can enable prevention and early management, as in hereditary haemochromatosis, where diagnosis helps avoid long-term complications [1]. The following indications for clinical predictive testing were identified in the included reports, which are described in greater detail below.

Trägerscreening: 4 Berichte

Preconception or prenatal carrier screening was evaluated in four reports. The AIHTA (2022) report reviewed non-invasive prenatal testing (NIPT) for trisomies 21, 18, and 13. NIPT was positioned as either first-line or second-line screening, with invasive tests used for confirmation and ultrasound for structural anomalies. High throughput sequencing of fetal cell-free DNA in

maternal plasma was used, with some studies extending to whole-genome sequencing [34]. The Cochrane (2021) review addressed genetic risk assessment in women and their partners identified as carriers of thalassaemia, sickle cell disease, cystic fibrosis, or Tay-Sachs disease. Systematic preconception carrier screening was positioned as an add-on compared to usual care. Sequencing was performed using high throughput sequencing, though details were not further specified. The CADTH (2021) assessment examined preconception or prenatal carrier screening more broadly. Carrier panels included conditions such as cystic fibrosis, fragile X syndrome, hemoglobinopathies, and spinal muscular atrophy, with expanded panels also considered. Testing was positioned as an add-on compared to no carrier screening. Sequencing technologies included high throughput sequencing or microarray approaches. The HQO (2023) report focused on preconception or prenatal carrier screening programs, specifically for cystic fibrosis, fragile X, hemoglobinopathies, and spinal muscular atrophy. The report compared universal to risk-based approaches, with sequencing considered as an add-on to no screening. High-throughput sequencing technologies could be applied to germline DNA to detect pathogenic carrier variants [44, 47, 48].

Neugeborenenscreening: 2 Berichte

Newborn screening was addressed in two reports from HIQA. The first (HIQAa, 2023) examined universal screening for severe combined immunodeficiency (SCID) and T-cell lymphopenias. Testing was considered as a first-tier add-on to enable early diagnosis and timely treatment (e.g., stem cell transplantation). The comparator was no universal screening. Approaches included high throughput sequencing using embedded gene panels or T-cell Receptor Excision Circles (TREC)-based screening via quantitative PCR, with TRECs serving as biomarkers of T-cell production. The second (HIQAb, 2023) focused on universal newborn screening for spinal muscular atrophy (SMA). Screening was positioned as a first-tier test, with positive results triggering confirmatory testing and early treatment. The comparator was no universal screening. Sequencing technologies included high throughput sequencing or PCR methods targeting SMN1 gene deletions and SMN2 copy number [45, 46].

Reproduktionsmedizin: 1 Bericht

Reproductive medicine was examined in one report. This report examined predictive testing in the context of assisted reproduction. The Cochrane (2020) review focused on preimplantation genetic testing for aneuploidy (PGT-A) in women undergoing in vitro fertilisation (IVF). PGT-A was positioned as an add-on to IVF, compared with IVF without PGT-A (morphological selection) or genetic analysis using Fluorescence In Situ Hybridisation (FISH). Whole-genome sequencing was used on DNA from oocytes (polar bodies) or embryos (blastomeres or trophectoderm cells) [49].

kardiovaskuläre Erkrankungen und FH: 1 Bericht

Cardiovascular disease and familial hypercholesterolemia were examined in one report. The report assessed predictive testing for cardiovascular disease (CVD) and familial hypercholesterolemia. The HTW (2020) assessment considered genetic risk prediction as an add-on to conventional screening, aiming to estimate risk of CVD onset or recurrence. The comparator was no genetic risk prediction. The GEN inCode tests were evaluated, including Cardio inCode for multiple CVD-associated variants and Lipid inCode for variants in seven FH-associated genes, using high throughput sequencing [43].

4.3 Pharmacogenomic testing

11 Berichte zu pharmakogenomischer Testung

We classified a total of eleven reports including one update [50-60] to this category. Pharmacogenomics examines how genetic variation influences drug response. Testing provides clinicians with information on whether a medication is likely to be effective, ineffective, or associated with an increased risk of side effects. These results are considered alongside other clinical factors, such as age, weight, and comorbidities, to guide treatment selection and dosing. By supporting more precise prescribing, pharmacogenomic testing has the potential to reduce side effects, avoid ineffective treatments, and lower healthcare costs. Currently, drug treatments are estimated to be effective in only 30-60% of patients, and around one in 15 hospital admissions in the UK is linked to adverse drug reactions. Although highlighted as a priority in the Generation Genome report by the Chief Medical Officer for England, pharmacogenomic testing is not yet routinely implemented within the NHS Genomic Medicine Service [1][3]. The following indications for pharmacogenomic testing were identified in the included reports, which are described in greater detail below.

Psychiatrie: 4 Berichte

Pharmacogenomic testing for **psychiatry (psychotropic/antidepressant therapy)** was evaluated in four reports[4]. The CADTH (2023) report covered pharmacogenomic testing in mental, behavioural, or neurodevelopmental psychiatric disorders as an add-on to optimise medication selection by analysing polymorphisms predictive of psychotropic response, compared with treatment as usual. Sample types included saliva, blood, or buccal swab for germline variant detection. The CADTH (2020) report (and its 2022 update) focused on adults (18-60 years) with diagnosed depression, positioning testing as an add-on to inform antidepressant/psychotropic selection or dosing versus treatment as usual without testing. Technologies were not specified. The target was germline variants in genes affecting drug response. The HQO (2021) report examined multi-gene (two or more) pharmacogenomic tests for adults with major depression requiring pharmacological treatment, as an add-on to guide selection compared with usual care without pharmacogenomic guidance. The target was germline variants in genes influencing drug response [57-60].

Clopidogrel-Eignung nach Schlaganfall: 3 Berichte

Pharmacogenomic testing for **Clopidogrel suitability after ischaemic stroke/ transient ischemic attack (Neurology)** was assessed in three reports. The SHTG (2024) report evaluated pre-treatment CYP2C19 genotyping in patients who had just experienced an ischaemic stroke or transient ischaemic attack, as an add-on to guide clopidogrel use; clopidogrel-resistant patients were to receive an alternative antiplatelet. The comparator was no testing. Testing involved laboratory-based CYP2C19 assays (gene sequencing or targeted genotyping) on blood to detect CYP2C19 changes. The NICE (2024) guidance

[3] Based on external reviewer input, there are currently three PGx tests in the NHS test directory:
DPYD: Testing is required before starting systemic fluoropyrimidine cancer chemotherapy (e.g., 5-fluorouracil), due to the risk of severe toxicity.
TPMT/NUDT15: Testing is commissioned for patients with Acute Lymphoblastic Leukaemia (ALL) who require treatment with 6-mercaptopurine.
MT-RNR1: Testing is commissioned to assess the risk of hearing loss due to aminoglycoside antibiotics.

[4] Including one update: the Canadian Agency for Drugs and Technologies in Health (CADTH) 2020 report was updated in 2022.

likewise assessed testing before starting clopidogrel in the same population, recommending not to delay antiplatelet treatment. The comparator was no genotype testing. CYP2C19 testing could be laboratory-based or point-of-care, targeting relevant CYP2C19 alleles. The NIHR (2024) assessment focused on identifying CYP2C19 loss-of-function alleles associated with clopidogrel resistance to guide antiplatelet selection, compared with no testing. Laboratory genotyping could include high throughput sequencing, using targeted short-read sequencing of germline DNA [50-52].

Fluoropyrimidin-Toxizität: 2 Berichte

Pharmacogenomic testing for **Fluoropyrimidines/Dihydropyrimidine dehydrogenase (DPYD)** was evaluated in two reports. The SHTG (2020) report addressed pre-treatment screening for patients prescribed fluoropyrimidine-based chemotherapy (across colorectal, oesophageal, gastric, breast, head and neck cancers). Positioned as a first-line add-on before therapy, it compared pre-treatment screening with no testing (reactive testing for adverse events). Methods included PCR followed by Sanger sequencing or the Elucigene DPYD multiplex assay; clinically significant DPYD variants listed were c.1905+1G >A, c.2846A>T, c.1679T>G, and c.1236G>A/HapB3 (with c.1601G>A noted as not significantly increasing risk). The HQO (2021) report considered pre-treatment DPYD genotyping for patients with planned cancer therapy, as an add-on to usual care (standard dosing without pre-treatment genotyping). Sequencing technology was not specified (but high throughput sequencing could be used). The target was germline DPYD variants causing DPD deficiency and heightened toxicity risk [53, 54].

präemptive Testung in Primärversorgung: 2 Berichte

Pharmacogenomic testing for **primary care (pre-emptive/multi-gene panels)** was addressed in two reports. The HTW (2023) report considered broad, pre-emptive multi-gene pharmacogenomic panels for any patient initiating new drug treatment where a gene–drug interaction is known, as an add-on compared with standard care. Various (unspecified) technologies were used for pharmacogenomic analysis to predict drug response and reduce adverse reactions. The KCE (2023) report also addressed broad implementation (pre-emptive or reactive testing) to guide treatment and reduce adverse drug reactions. Comparators spanned implementation scenarios (single-gene tests vs. complex tests vs. phenotyping). Technologies included gene panels, WES, and WGS on germline DNA to detect inherited variants (single nucleotide variations and copy number variations) in pharmacogenes [55, 56].

4.4 Tumour testing

16 Berichte zu Tumordiagnostik

We classified a total of 16 reports [61-76] to this category. Sequencing tumour DNA can reveal mutations that are actionable (where targeted therapies are available), as well as alterations that indicate likely resistance to certain treatments, or alterations that warrant further research. For example, therapies such as trastuzumab target specific genetic alterations; however, as only a minority of patients currently benefit from such treatments, additional targeted options are required to address the molecular diversity of cancer. Comparing tumour and normal genomes can also identify cancer-driving mutations, providing new research targets and informing trial design. High-throughput sequencing generates large volumes of data that can aid understanding of cancer progression and support patient stratification for clinical trials. Notably, about half of the findings from the 100,000 Genomes Project cancer

programme indicated potential for therapy or trial enrolment [1]. The following indications for tumour testing were identified in the included reports, which are described in greater detail below.

nicht-kleinzelliges Lungenkarzinom: 4 Berichte

Four reports focused on **non-small cell lung cancer (NSCLC)**. The HQO (2020) report examined liquid biopsy for detecting the EGFR T790M mutation in patients with disease-progression after first- or second-generation EGFR tyrosine kinase inhibitors. The CADTH (2022) report assessed liquid biopsy-based comprehensive genomic profiling as replacement or add-on to conventional molecular testing. The MSAC (2022) review evaluated small gene panels as replacements for sequential single-gene testing. The HQO (2024) assessment examined liquid biopsy panels as add-on to tissue-based testing [69-72].

Brustkrebs: 3 Berichte

Three reports addressed **breast cancer**. The NIPH (2022) review evaluated testing for PIK3CA mutations in advanced HR+/HER2– breast cancer, guiding treatment decisions for PI3K inhibitor therapy. The NICE (2024) and HIQA (2024) reports both focused on early HR+/HER2– breast cancer in the adjuvant setting, assessing multigene assays (e.g., Oncotype DX, Prosigna, EndoPredict, MammaPrint) to refine risk stratification and chemotherapy decisions [73-75].

hämatologische Malignome: 3 Berichte

Three reports covered **haematologic malignancies**. Two NICE (2021) evaluations addressed minimal residual disease testing (clonoSEQ in myeloma, acute lymphoblastic leukaemia and chronic lymphocytic leukaemia) and gene expression profiling (MMprofiler in multiple myeloma). The HTW (2021) report analysed diffuse large b-cell lymphoma molecular classification, comparing sequencing platforms with immunohistochemistry-based algorithms to subtype tumours for prognosis and treatment guidance [64-66].

tumorübergreifende Testung: 2 Berichte

Two reports assessed **broad tumour testing across multiple cancer types**. The NIPH (2022) review addressed identification of NTRK fusions for treatment selection using DNA and RNA based High-throughput sequencing and targeted panels in over 25 tumour types. The Cochrane (2025) review examined comprehensive genomic profiling in advanced or refractory solid and haematological cancers as add-on to guide matched therapy, compared with standard or non-matched treatments [61, 62].

Hirntumoren: 2 Berichte

Two Cochrane reviews assessed molecular markers in **brain tumours (neuro-oncology**). The Cochrane (2021) review evaluated MGMT promoter methylation testing in individuals with glioblastoma treated with temozolomide for prognosis and treatment guidance, compared to PCR and immunohistochemistry. The Cochrane (2022) review examined 1p/19q codeletion in gliomas, as add-on typically performed after initial histological assessment and other molecular tests, used for diagnosis, prognosis, and therapeutic planning [67, 68].

Lynch-Syndrom bei Endometriumkarzinom: 1 Bericht

One report evaluated tumour testing for **lynch syndrome in endometrial cancer**. The NICE (2020) report investigated testing strategies (combined MMR protein expression immunohistochemistry, MSI testing, MLH1 promoter methylation, and confirmatory germline sequencing) to identify patients requiring surveillance and cascade testing [63].

Prostatakarzinom: 1 Bericht

Prostate cancer was assessed in one report. The HTW (2022) report analysed genomic expression panels (e.g., Prolaris, Oncotype DX, Decipher) in prostate cancer to guide decisions between active surveillance and immediate treatment, based on genomic risk scores. The analysis generates a genomic score predictive of tumour aggressiveness, risk of adverse pathology, metastasis, or cancer-specific mortality [76].

4.5 Analysis across application fields

Tests häufig als Add-on zu bestehenden Ansätzen;

Genpanels am häufigsten

Across the four fields of applications for genetic testing (diagnostic, clinical predictive testing, pharmacogenomic and tumour testing), most tests (43/49 reports) were positioned as add-on strategies to existing approaches. In three assessments, the test strategy was classified as both add-on or replacement in the clinical pathway (3/49 reports). In two cases, the assessed test strategy was reported as replacement of existing testing approaches (2/49 reports), while one assessment did not report on whether the testing strategy was seen as add-on or replacement (1/49 reports). Sequencing technologies often referred to high-throughput sequencing, with technologies referring to this technology in the majority of reports. WES was explicitly mentioned in six reports, and WGS in ten reports. Overall, the analysis illustrates both the variety of clinical contexts where sequencing can be applied and a tendency to integrate sequencing as an add-on test to refine diagnosis, prognosis or treatment selection rather than as full replacements of existing approaches.

meiste HTA-Aktivität in Kanada, UK und Australien

We identified most HTA activities for genetic testing in Canada, the United Kingdom and Australia, with 14, eleven and seven identified published HTA reports, respectively. Table 4-1 provides an overview of the distribution of the 49 identified reports across the four application fields and by country of origin.

Table 4-1: Distribution of HTA reports and Cochrane reviews by application field and country/organisation (ranked by total reports)

Country	Organisation(s)	Diagnostic testing	Clinical Predictive testing	Pharmacogenomic testing	Tumour testing	Total
Canada	HQO, CADTH, TASK	4	2	5	3	**14**
United Kingdom	NICE, HTW, SHTG, NIHR	0	1	4	6	**11**
International	Cochrane	2	2	0	3	**7**
Australia	MSAC	4	0	0	2	**6**
Ireland	HIQA	0	2	0	1	**3**
Austria	AIHTA	1	1	0	0	**2**
Norway	NIPH	0	0	0	2	**2**
Germany	IQWiG	1	0	0	0	**1**
USA	Washington State HTA	1	0	0	0	**1**
Belgium	KCE	0	0	1	0	**1**
Total	-	14	8	11	16	**49**

Abbreviations: AIHTA … Austrian Institute for Health Technology Assessment; CADTH … Canada's Drug Agency; HIQA … Health Information and Quality Authority; HQO … Health Quality Ontario; HTW … Health Technology Wales; IQWiG … Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; KCE … Belgian Health Care Knowledge Centre; MSAC … Medical Services Advisory Committee; NICE … National Institute for Health and Care Excellence; NIHR … National Institute for Health and Care Research; NIPH … Norwegian Institute of Public Health; SHTG … Scottish Health Technologies Group; TASK … Technology Assessment at SickKids.

5 Results for RQ2: Overview of evidence-based reimbursement processes in selected countries and indications in routine clinical practice

evidenzbasierte Erstattungsprozesse in England, Australien und Ontario

The regulation and reimbursement of genetic services was already extensively analysed in selected countries within the GÖG (German: Gesundheit Österreich GmbH) report [25] as summarised in Section 2.4. While that analysis focused on organisational structures and governance models, this chapter examines the specific health technology assessment (HTA) processes employed in countries with formalised evidence-based reimbursement processes for genetic testing. Countries with the highest volume of published HTA reports on genetic testing identified in RQ1 were selected: England (United Kingdom), Australia, and Ontario (Canada).

Erstattungsprozess in 4 Phasen beschrieben

For each country, the reimbursement process is described according to four stages: prioritisation, assessment, appraisal, and decision-making. Where available, we mapped currently reimbursed tests quantitatively based on official test directories or submission databases.

In this chapter, "evidence-based reimbursement process" is used as an umbrella term. For the decision-making phase, this covers both classic reimbursement decisions (Australia, Ontario) and commissioning decisions (England). In the England section, we use the term "commissioning" to reflect that England operates a nationally integrated health service where National Health Service (NHS) England directly determines which tests are funded and provided, rather than reimbursing independent provider.

5.1 England (United Kingdom)

National Genomic Test Directory in England

In the United Kingdom, HTA reports on genetic testing were identified from the National Institute for Health and Care Excellence (NICE), Health Technology Wales (HTW), Scottish Health Technologies Group (SHTG), and the National Institute for Health Research (NIHR). While devolved nations (Wales, Scotland, Northern Ireland) maintain separate HTA processes, this section focuses on England, where NHS England operates the most comprehensive system with a dedicated National Genomic Test Directory.

koordinierte Prozesse zwischen NHS England und NICE

In England [77, 78], the HTA and reimbursement process for genomic testing is structured around coordinated, but independently-operated processes involving NHS England and the National Institute for Health and Care Excellence (NICE). These organisations collaborate to identify, prioritise, assess, and commission genomic tests for adoption within the NHS.

Test Directory umfasst seltene Erkrankungen und Krebsdiagnostik

The NHS Test Directory currently covers **rare/inherited disease testing** and **cancer genomic testing**. Tests included in the directory are those that have completed the NHS England/NICE testing pathway and are nationally commissioned for use in NHS England. Population screening programmes are overseen by the UK National Screening Committee with separate process including separate systematic evidence reviews and stakeholder consultations to advise the NHS and government on screening policy [79].

Prioritisation Process

Priorisierung: Anträge ganzjährig möglich

Applications to update the National Genomic Test Directory can be submitted by any stakeholder throughout the year. In addition, NHS England and NICE conduct **horizon scanning** and receive notifications about emerging genomic tests, including those linked to new medicines or policies. Both organisations (NICE and NHS England) work closely on identifying and triaging these applications.

Priorisierung durch Genomics Clinical Reference Group

The Genomics Clinical Reference Group (Genomics CRG), supported by the expert test evaluation working groups, reviews and prioritises applications based on **clinical need, strength of evidence**, **cost implications**, and **NHS operational factors**. The CRG meets multiple times annually to maintain oversight and recommend amendments for evaluation and funding [80].

Patient:innenbeteiligung und Fast-Track-Option

Public and patient representatives contribute to the prioritisation process, ensuring relevance and equity. Urgent amendments can be fast-tracked outside the usual update cycle when required by new policies or to address critical needs [77, 78].

Weiterleitung an NICE bei breitem NHS-Impact

Formal referral to NICE is possible for tests with **wider NHS impact**, and the process may include annual stakeholder workshops. Where appropriate, provisional commissioning can occur alongside real-world evidence collection [77, 78].

Assessment Phase

zwei Assessment-Pfade: NHS England oder NICE

Evaluations can be conducted by the Genomic Test Evaluation Working Group (NHS England) or NICE [78]:

- NHS England evaluates specialist genomic tests (e.g., diagnostic tests for rare diseases) through its Genomic Test Evaluation Working Group, focusing on clinical validity, utility, and integration into the NHS Genomic Medicine Service (GMS)
- NICE evaluates testing where relevant as part of reviews of genomically-enabled medicines and, when required, may also evaluate genomic testing interventions that address an NHS need and may have a significant impact on services, pathways or NHS resources, such as triage testing or pharmacogenomic profiling [78]

NICE-Prozess integriert Test-Evaluation-Impact-Assessment

NICE [78] integrates a Test Evaluation impact assessment in parallel from the scoping stage, with an opportunity to input NHS GMS testing delivery requirements and costs, alongside any further detail NICE receive from the company (where relevant). Both pathways assess clinical and scientific validity, clinical utility, and economic impact. There is a further impact assessment phase which involves collaboration with the Genomic Laboratory Hubs (GLHs) to evaluate operational feasibility, workforce capacity, and financial implications of implementing the change across NHS services [81].

Appraisal Phase

Appraisal-Phase: Empfehlung für nationale Erstattung

Following assessment, the appraisal phase determines whether a test should be recommended for national commissioning [80].

- If assessed by NHS England, the Genomics CRG reviews findings and makes commissioning recommendations
- If evaluated by NICE, the decision follows its standard technology appraisal or diagnostics guidance process, resulting in formal recommendations

In both cases, if the test is intended for delivery via the NHS GMS, a Test Directory impact assessment is considered in the appraisal phase. This final step ensures alignment with national genomic service specifications, including laboratory capacity, reporting standards, and eligibility criteria [80].

Wartungsprozess Test Directory

Decision phase

Recommended tests are implemented through an update to the National Genomic Test Directory, following the formal process outlined in NHS England's Updating the National Genomic Test Directory policy document [82]. The directory is the authoritative source for commissioned genomic testing in England and is developed by multidisciplinary experts to ensure equitable, evidence-based access to tests that are likely to change patient management [83].

bei positiver Entscheidung: Aufnahme in Test Directory

NHS Test Directory

The National Genomic Test Directory lists all genomic tests in England. Key entry terms within the directory include [83]:

Struktur des Test Directory: u. a., Indikationen, Methoden, Kriterien

- Clinical Indication: The specific condition or group of symptoms for which a test is relevant (e.g., cystic fibrosis)
- Target/Genes: The gene, gene panel, or genomic region to be tested.
- Test Method: The technology used, ranging from targeted testing and gene panels to whole genome sequencing (WGS)
- Commissioning Category: Classifies the test as a Core, Specialist, or Highly Specialist Test
- Specialist Test Group: The medical discipline to which the test belongs (e.g., Cardiology, Neurology)
- Eligibility Criteria: A supplementary document that guides which patients are eligible for testing and which specialties can request it

The Test Directory [83] is split into two unique documents: 1) rare and inheritable diseases and 2) cancer.

National Genomic **Test Directory for rare and inherited diseases** encompasses 66 distinct clinical indications. These are organised across several specialist areas, with the most common being

66 Indikationen für seltene Erkrankungen, meist Einzelgen- oder Panel-Tests

- **Endocrinology** (24 indications)
- **Neurology** (23 indications)
- **Cardiology** (13 indications)

The test methods listed are varied, but the most frequently cited are Single Gene Sequencing (45 entries) and Small Panels (41 entries). WES or WGS are also common, with a combined total of over 40 entries, and are typically used for complex, undiagnosed conditions.

The **National Genomic Test Directory for Cancer** is a list of clinical indications for genetic testing in cancer patients. It is designed to ensure tests are ordered only when they are likely to change a patient's clinical management, which includes guiding therapeutic decisions or enrolling patients in clinical trials. The Test Directory for Cancer is split into:

Krebs-Directory: 214 Indikationen in 5 Gruppen

- **Sarcoma**: 48 indications
- **Paediatric tumors**: 46 indications
- **Haematological:** 43 indications

- **Neurological Tumours**: 42 distinct indications
- **Solid Tumours:** 35 distinct indications

ressourcenintensive Technologien mit Restriktionen

Of note, highly resource-intensive technologies such as WES or WGS are listed under various indications but are subject to restrictive eligibility criteria that vary by indication. One such exception is that all malignant tumours diagnosed in paediatric patients are eligible for WGS, except for sarcomas. Appropriateness is overseen by the local Genomic Laboratory Hub (GLH). For a full list of test methods (incl. scope of indications) and specific eligibility criteria per indication, the reader is referred to the NHS Test Directories [83].

jährlicher Update-Zyklus

The directory is formally updated annually, with amendments published in December and fully implemented by April each year [82].

5.2 Australia

MSAC als zentrale HTA-Institution in Australien

Australian HTA reports on genetic testing were primarily identified from the Medical Services Advisory Committee (MSAC), an independent expert committee that advises the federal government on public funding for health services [84].

Prioritisation Process

Priorisierung: Anträge von Industrie und Leistungserbringern

MSAC receives submissions primarily from industry sponsors and service providers seeking public funding for genetic tests by listing on the Medicare Benefits Schedule (MBS). Before submission, applicants may participate in pre-submission meetings with the Department of Health to discuss application framing and appropriate assessment approaches. The prioritisation of applications is influenced by factors such as the **evidence**, **clinical need,** and **system capacity** [84].

Assessment Phase

unabhängiges Assessment mit Clinical Utility Card

Following the application submission, the assessment phase begins with the preparation of an independent assessment report. This report is prepared by contracted HTA groups or MSAC's internal experts based on the dossier from the applicant. The dossier contains clinical (effectiveness and safety) and economic evidence [85, 86]. MSAC uses technical guidelines specific to investigative services and codependent technologies [87], plus a Clinical Utility Card (CUC) Proforma [86, 88] tailored for genetic testing particularly for heritable conditions. The assessment particularly weighs clinical utility defined by actionable results leading to changes in health outcomes for patients and family members, including cascade testing (testing of biological relatives).

Appraisal Phase

Appraisal durch MSAC unter Einbindung von Stakeholdern

An Evaluation Sub-Committee (ESC), a sub-committee of MSAC, reviews the assessment report and provides advice. MSAC then considers consultation feedback and other stakeholder input during an appraisal meeting. MSAC, incorporating expert advice and evidence from the assessment, appraises comparative health gain, cost-effectiveness, and predicted use in practice, along-

side less quantifiable factors like ethical, psychological, and social considerations. Special attention is given to the complex nature of genetic tests, including family impact and technological innovation that rapidly evolves.

Decision Phase

MSAC-Empfehlung an Gesundheitsminister:in, Umsetzung via Medical Benefits Schedule (MBS)

MSAC is an independent expert committee appointed by the Minister for Health, which advises the Commonwealth Minister on whether the technology should be publicly funded and under what circumstances. MSAC's decisions include recommendations to fund, defer, reject, or recommend further research or review. Their advice is formally delivered to the Minister for Health and is published publicly. The role includes advising on MBS listing and other funding arrangements relevant to the Australian health system. MSAC may recommend review periods and conditions for ongoing data submission or reassessment [84, 89]. Accepted recommendations are subsequently implemented through amendments to the MBS.

Medicare Benefits Schedule (MBS)

kein separates Test Directory, Integration in MBS

In Australia all reimbursable tests are listed online [89] in the (standard) MBS, which lists all item numbers, service descriptions, fees, and eligibility criteria for every funded medical service, including genetic tests. To date, 123 MSAC submissions have been recorded between 2002 and 2025, comprising 99 for genetic testing applications and 24 for genetic-related applications [90].

Unterscheidung: genetische Tests versus genetik-bezogene Anwendungen

Genetic testing applications refer to cases where the test itself involves genetic analysis – sequencing or examining DNA or RNA to detect mutations, variants, or molecular profiles used for diagnosis, prognosis, or treatment decisions. Examples include BRCA gene sequencing, carrier screening, and pharmacogenomic testing [90]. Genetic-related applications encompass submissions where genetic testing is not the primary method. This includes gene therapies and screening programs where genetic testing is only used as a confirmatory step within a broader screening strategy. For example, familial hypercholesterolemia (FH) screening often starts with clinical assessment and cholesterol testing, with genetic testing reserved for confirmation [90].

unterschiedliche Antragsteller (z. B. Hersteller)

The majority of genetic testing MSAC submissions originate from pharmaceutical companies, while most genetic-related applications are submitted by professional bodies such as the Royal College of Pathologists of Australasia [90].

laufende MBS-Aktualisierung

MBS is updated on a rolling basis as MSAC recommendations are accepted by the Minister for Health. MSAC and its subcommittees typically meet three times per year to consider applications [91]

5.3 Ontario (Canada)

Provincial Genetic Test Directory in Ontario

In Canada, HTA reports on genetic testing were identified from Health Quality Ontario (HQO), Canada's Drug Agency (CADTH, now CDA-AMC), and Technology Assessment at SickKids (TASK), a hospital-based paediatric assessment unit [92]. While CADTH produces national-level evidence reviews [93], funding and implementation decisions are made provincially. Hence, this section focuses on Ontario, where HQO conducts evidence reviews to inform the provincial Genetic Test Directory [94].

Prioritisation Process

Priorisierung mit für genetische Tests entwickelten Kriterien

In Ontario, several committees coordinated by HQO are involved in the prioritisation process. The Ontario Health Technology Advisory Committee (OHTAC) prioritise topics for genetic topics on the basis of the following (expanded) prioritisation criteria [95]:

- Clinical benefit (e.g., potential to improve health outcomes or provide useful information to patients/families relative to the standard of care or alternatives)
- Harms (e.g., Potential to reduce harm to patients/families/caregivers relative to existing practice or alternatives)
- Cost effectiveness (e.g., Potential cost-effectiveness, Potential savings to the health care system or other sectors)
- Potential resource impact (e.g., Potential to induce major change(s) to the health care system, clinical pathways, or specific groups of providers)
- Diffusion pressure and stakeholder demands (e.g. potential unmet need, patients accessing health technology outside of publicly funded health system)
- Impact and equity (e.g., Ethical implications for patients, families, and others affected by the test, potential health equity impact, alignment with societal preferences and values)
- Potential receptors in the health care system (e.g., ability of current processes of care, institutions, and care providers to implement the test)

There is no ranking or weighting to specific criteria. All criteria are weighed equally.

Assessment Phase

Assessment durch HQO

Assessment is conducted by Health Quality Ontario (HQO), which produces rapid and full evidence reviews on genetic tests, including analytical validity, clinical utility, and cost-effectiveness [96].

Appraisal Phase

multidisziplinäres Appraisal mit Genetik-Subkomitee

Appraisal is performed by multidisciplinary committees weighing scientific evidence, clinical guidelines, health system readiness, and broader ethical and policy considerations. In Ontario, the Provincial Genetics Advisory Committee and disease/technology-specific working groups play key roles in issuing implementation recommendations and eligibility criteria aligned with Ontario's health system needs:

- **Ontario Health Technology Advisory Committee (OHTAC)** consisting of several volunteer members across the province, including health experts, patients and other relevant stakeholders [97].
- **Ontario Genetics Advisory Committee (OGAC):** a sub-committee of OHTAC with focused genetics expertise providing recommendations to HQO [98].

Decision Phase

Entscheidung auf Provinzebene

Final decisions on funding and implementation are made at the provincial level. In Ontario, this is operationalised via the Ontario Genetic Test Directory – a public, detailed registry managed by Ontario Health that lists over 600 funded genetic tests, with defined clinical indications, test types (e.g., single gene, gene panel, WES, WGS), responsible laboratory, and up-to-date eligibility criteria [94].

Ontario Genetic Test Directory

öffentlich zugängliches Directory mit über 600 Tests

The Ontario Genetic Test Directory is a publicly accessible, evidence-based registry that lists genetic tests available in Ontario for rare and inherited diseases. It includes molecular genetic, constitutional cytogenetic, and pharmacogenetic tests that are publicly funded under the Ontario Health Insurance Plan (OHIP). The directory is maintained by Ontario Health and supports equitable, standardised access to genetic testing across the province [94]. The directory includes over 600 tests, searchable by clinical indication, test type, or laboratory. Key fields include:

- **Clinical Indication** (e.g., 22q11.2 deletion syndrome)
- **Test Type** (e.g., single gene, gene panel, WES, WGS)
- **Responsible Laboratory** (e.g., The Hospital for Sick Children, London Health Sciences Centre)
- **Eligibility Criteria** (based on clinical guidelines)

Entscheidung auf Provinzebene, Umsetzung via Test Directory

Complementing this, Genome-wide sequencing Ontario (GSO) is a clinical collaboration between the specialised hospitals and genetics diagnostic laboratories providing publicly funded WES and WGS. GSO codevelops and manages granular patient eligibility criteria for these highly resource intensive sequencing technologies. Specific indications – such as unexplained neurodevelopmental disorders – are reimbursed under defined criteria managed by the Provincial Genetics Program [99].

kontinuierliche Aktualisierung

The Ontario Genetic Test Directory is updated regularly based on evidence reviews from Health Quality Ontario (HQO) and recommendations from expert committees, ensuring ongoing equitable and standardised access across the province [94, 100]. Yet, no information was found indicating that updates follow a fixed annual schedule.

Table 5-1 provides an overview of evidence-based reimbursement processes in England, Australia and Ontario.

Table 5-1: Overview of evidence-based reimbursement processes in England, Australia and Ontario

Feature	England (United Kingdom)	Australia	Ontario (Canada)
Pathway structure	◆ Dual pathway: NHS England (specialist genomic tests) or NICE (broader NHS impact tests)	○ Single pathway: All applications through MSAC	○ Single pathway: All applications through HQO/OHTAC
Genetics-specific adaptations in HTA process	■ Prioritisation: Genomics Clinical Reference Group (CRG), patient/public input ■ Assessment: Genomic Test Evaluation Working Group, GLH impact assessment ■ Appraisal: Genomics CRG or NICE committees	■ Assessment: Clinical Utility Card (CUC) Proforma, emphasis on cascade testing & family impact ■ Appraisal: Focus on family impact, technological innovation	■ Prioritisation: Genetics-specific additional criteria developed ■ Appraisal: OGAC (genetics sub-committee), GSO for WES/WGS
Decision authority	NHS England (national commissioning for England)	Federal Minister for Health (based on MSAC advice)	Provincial government (Ontario Health)
Test listing/registry	NEW National Genomic Test Directory ~280 indications (66 rare/inherited + 214 cancer) England-specific	Medicare Benefits Schedule (MBS) 123 genetic test submissions (2002-2025) National, integrated system	NEW Ontario Genetic Test Directory 600+ tests Province-specific
Maintenance	■ Annual updates (Dec publication, Apr implementation) ■ Year-round applications and fast-track options	■ Rolling updates (as applications approved, ~3 MSAC meetings/year)	■ Regular updates (based on HQO reviews, no fixed schedule)

◆ = *Dual/parallel pathway;* ○ = *Single pathway;* NEW = *Dedicated genetics directory;* = *Integrated in general system.*

Abbreviations: *CUC … Clinical Utility Card; GLH … Genomic Laboratory Hub; GSO … Genomics Service Ontario; HQO … Health Quality Ontario; HTA … Health Technology Assessment; MBS … Medicare Benefits Schedule; MSAC … Medical Services Advisory Committee; NHS … National Health Service; NICE … National Institute for Health and Care Excellence; OGAC … Ontario Genetics Advisory Committee; OHTAC … Ontario Health Technology Advisory Committee; WES … Whole Exome Sequencing; WGS … Whole Genome Sequencing.*

6 Results for RQ3: Criteria for Prioritising Genetic Tests for Health Technology Assessment

6.1 Development of Prioritisation Criteria: Workshop Findings

Workshop zu Priorisierungskriterien

During the workshop, a variety of criteria for prioritising genetic services in Health Technology Assessment were discussed in detail. These criteria are partially based on established evidence-based reimbursement processes and considered clinical, economic and organisational aspects. The discussions highlighted that the development of comprehensive prioritisation criteria requires a multidisciplinary approach to adequately address the specific demands of genetic services.

Clinical Aspects

klinische Aspekte: z. B. Behandelbarkeit und Prävalenz

Workshop participants discussed several clinical aspects and reflected on their potential for deriving prioritisation criteria for genetic testing services:

- *Prevalence of the Disease:* Prevalence was considered a familiar prioritisation criterion from other health technology assessment (HTA) processes. It allows for an estimation of how many people will actually require a genetic test, thus supporting targeted and efficient resource planning.
- *Disease Burden:* Evaluating the disease burden provides insight into the overall public health impact of the target condition. Parameters such as prevalence, incidence, severity, morbidity, mortality, and quality-of-life reduction are considered.
- *Treatability:* Following an intensive discussion, it became clear that "treatability" should be prioritised over "disease burden" as a criterion. Genetic tests that lead to improved patient care should be favoured over tests that "only" provide more information without therapeutic consequences.
- *Approval Date:* The approval date was discussed as a potential criterion but was deemed not to be a useful one. This is because genetic services can be regulated either as a medical device or an In-Vitro Diagnostic (IVD), but in many cases, tests are used under clinical validation without formal approval for specific indications.
- *Timing of the Test:* This aspect includes the question of at what point in the treatment pathway the test should be performed, as well as further information on the population to be screened (e.g., all individuals or only high-risk patients).
- *Alternatives (Comparator):* This aspect considers the availability of effective alternative diagnostic or treatment methods compared to the genetic service.
- *Clinical Impact/Evidence:* This includes the evaluation of the clinical benefit and the scientific evidence supporting the use of the genetic test.

Clinical Actionability als zentrales Konzept

During workshop discussions, participants emphasised that not all clinical aspects carry equal weight. Prevalence and treatability emerged as particularly important, with the rationale that tests enabling therapeutic or preventive interventions should be prioritised over purely informational tests. However, this was later refined to the broader concept of "clinical actionability" (see Section 7.2) to acknowledge that non-treatable conditions may still warrant testing when results inform prognosis, prevent unnecessary interventions, or enable family screening. In contrast, the approval date was considered of limited value given the heterogeneous regulatory pathways for genetic services.

Economic and organisational Aspects

ökonomische und organisatorische Aspekte

Economic aspects were mainly discussed in the context of *cost thresholds*: The question was raised whether thresholds should be defined per test, per month, or per year.

- *Replacement/Add-on:* This involves distinguishing whether the costs are additional or if the service replaces an existing one.
- *Comparability/Sensitivity Threshold*: This point relates to the comparability of costs and the setting of thresholds concerning the sensitivity of the test.

Ressourcenintensität als ökonomischer und organisatorischer Faktor

Resource Intensity was discussed as a further aspect potentially relevant for prioritisation. This point was considered particularly relevant for genetic services, as it affects both economic (higher costs) and organisational aspects. Specifically, the potential necessity to store data for 30 years in Austria[5] and the high data storage requirements of more complex tests like Whole Genome Sequencing (WGS) were highlighted. Next to higher costs and more resources needed, the following topics were further discussed in this context:

- *Data Volume Cut-Off:* This aspect addresses the maximum amount of data that can be processed and stored for genetic tests and how this affects feasibility.
- *Data Protection*: Considering data protection requirements and regulations is an essential organisational aspect.
- *Boundaries between routine pathology and specialised genetic counselling:* Discussants explored the competencies and boundaries between different medical specialties, such as pathology, laboratory medicine and genetics, in the context of genetic testing. This topic addresses legal fundamentals and the implication this has for genetic testing in general.

[5] Section 10 KAKuG stipulates that medical records must be retained for at least 30 years. Provincial legislation may establish shorter periods (minimum 10 years) for certain components (e.g., X-rays) or outpatient treatment. Since genetic data are not explicitly mentioned, the retention period remains legally unclear; however, they are likely subject to the 30-year requirement as part of medical records.

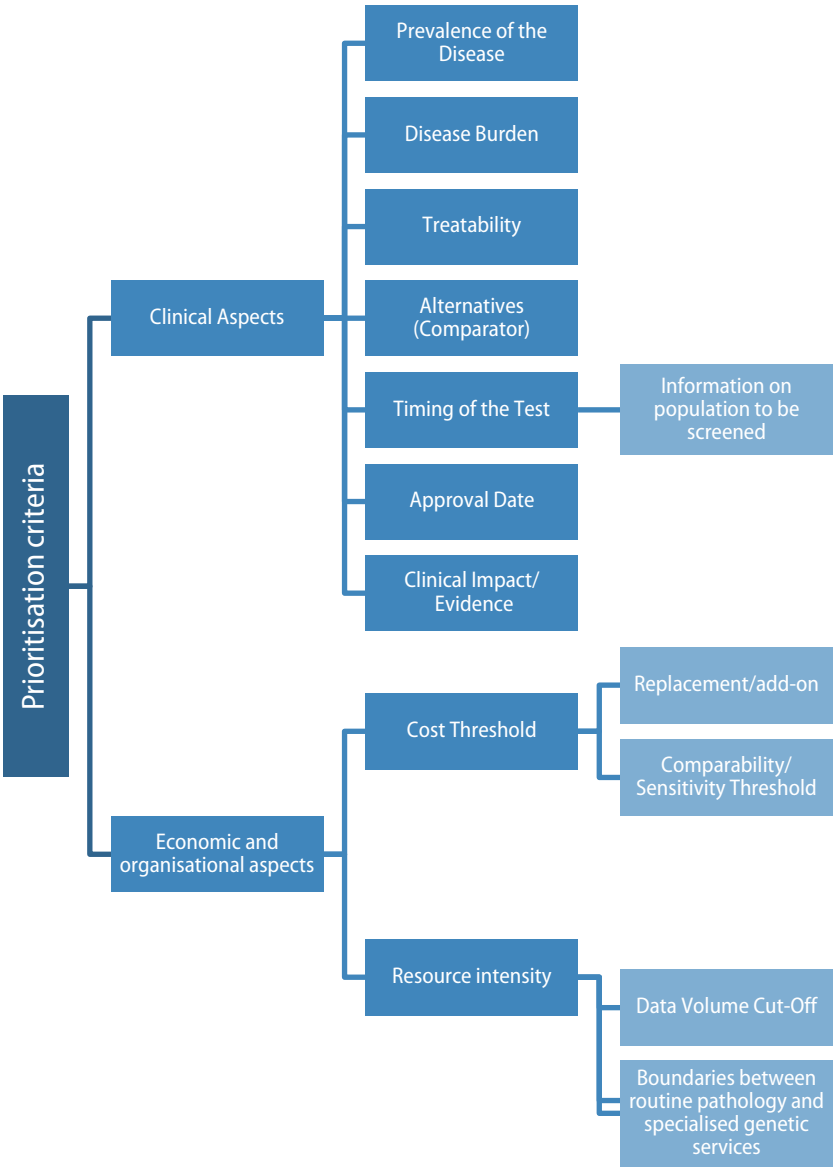

Figure 6-1: Overview of thematic analysis on potential prioritisation criteria for Austria

6.2 Proposed Application of Developed Criteria

Vorschlag für strukturierte, flexible Priorisierung

Based on the workshop findings and informed by established HTA principles, the following section outlines a proposed framework for the practical operationalisation of prioritisation processes for genetic testing topics within HTA. The considerations include clinical, economic, and organisational criteria, with a focus on clinical actionability and resource implications. These prioritisation criteria aim to provide a structured yet flexible approach that supports transparent, consistent, and context-sensitive prioritisation of topics for HTA[6].

Table 6-1: Proposed criteria, definitions and rationale for prioritising topics for an assessment

Criterion	Definition	Rationale
Clinical Actionability (CA)	The extent to which the test leads to a change in patient management: ■ High: Prerequisite for therapy or prevention of severe disease ■ Medium: Enables diagnosis, prognosis, or family screening ■ Low: Primarily informational, no clear action plan	Aligns with HTA principles that prioritise interventions with direct patient benefit.
Resource Intensity (R)	The organisational and economic burden of the test: ■ High: WGS or WES (data storage, interpretation, counselling) ■ Medium: Large multi-gene panel ■ Low: Single-gene or small panel test	Reflects system capacity constraints, especially in data management and genetic counselling.
Indication Volume (V)	The number of patients likely to be tested: ■ High: Common or broad indications ■ Medium: Less common diseases ■ Low: Rare or ultra-rare diseases	Informs scalability and budget impact.

Abbreviations: CA … Clinical Actionability; HTA … Health Technology Assessment; R … Resource Intensity; V … Indication Volume; WES … Whole Exome Sequencing;WGS … Whole Genome Sequencing.

zweistufiger Prozess: Scoring und Deliberation

To support prioritisation of topics for an assessment, a two-stage process could be considered:

1. **Preliminary Scoring (Optional)**

   To enable preliminary ranking, a simple scoring system is applied:

   - High is assigned 3 points,
   - Medium is assigned 2 points,
   - Low is assigned 1 point.

   These values are used in the preliminary scoring step to calculate a priority score using the formula:

   $$Score = R + (CA \times 2) + V$$

   This is not a decision rule, but a tool to highlight differences and guide discussion. The formula reflects that Clinical Actionability (CA) was regarded as the most important criterion during the prioritisation workshop and is therefore double-weighted in the scoring.

[6] Naturally, these prioritisation criteria are intended only to decide which topics should undergo a full HTA, given limited resources. They are not reimbursement criteria and do not determine whether a test may be used or financed; a low prioritisation score therefore does not mean that a test (including lower-threshold options such as RT-PCR) is clinically irrelevant.

2. **Expert Deliberation (Required)**

   A multidisciplinary group – including, e.g., clinicians, experts in the field of molecular testing , health economists, and patient representatives – reviews the scored list. The discussion focuses on general HTA prioritisation principles (e.g., clinical benefit, cost-effectiveness, equity) and genetic-specific considerations identified in the workshop (e.g., resource intensity, data storage, need for genetic counselling, boundaries of care). The actual decision on topic selection takes place in this step.

6.3 Application of the proposed set of Prioritisation Criteria

Anwendung ergibt 16 hoch-priorisierte Themen

When applying the prioritisation in the quantitative scoring to the long-list of 49 HTA reports, 16 topics emerged as highly ranked (score >11; maximum score is 12) across all four application fields. *Diagnostic testing* yielded five prioritised topics, including tuberculosis resistance testing, unexplained developmental disabilities, familial hypercholesterolaemia, and paediatric cardiac disease evaluation spanning clinical microbiology, paediatrics, and cardiology. *Clinical predictive testing* identified three priorities in neonatology, obstetrics, and reproductive medicine. *Pharmacogenomic testing* highlighted three topics in primary care and psychiatry (pre-emptive multi-gene testing, depression medication selection). *Tumour testing* contributed five topics encompassing comprehensive genomic profiling, NTRK fusion detection, Lynch syndrome, and PIK3CA mutation testing across general oncology, gynaecologic oncology, and senology.

Table 6-2: Overview of highly ranked topics by medical specialties and testing type

Testing Type	Examples of highly ranked topics	Medical specialties
Diagnostic Testing	■ Tuberculosis antimicrobial susceptibility [31] ■ Unexplained developmental disabilities [38]; familial hypercholesterolaemia screening and management [28, 39] ■ whole genome sequencing for paediatric cardiac disease [40]	Clinical microbiology, paediatrics, paediatric cardiology (2), cardiology
Clinical Predictive Testing	■ Universal newborn screening for SCID [45] ■ preconception/prenatal carrier screening [48] ■ aneuploidy screening in IVF [49]	Neonatology, obstetrics, reproductive medicine
Pharmacogenomic Testing	■ Pre-emptive multi-gene testing for drug-gene interactions [55] ■ medication selection for depression [60]	Primary care, psychiatry
Tumour Testing	■ Advanced/refractory cancers [62] ■ NTRK fusions in metastatic solid tumours [61] ■ Lynch syndrome in endometrial cancer [63] ■ comprehensive genomic profiling [70] ■ PIK3CA mutations in breast cancer [73]	General oncology (2), gynaecologic oncology, pulmonary oncology, senology

Highly ranked topics (>11); the full list of HTA reports with applied prioritisation criteria can be found in Table A-5 in the Appendix.

Abbreviations: IVF … In Vitro Fertilization; NTRK … Neurotrophic Tyrosine Receptor Kinase; PIK3CA … Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; SCID … Severe Combined Immunodeficiency.

7 Discussion

Summary of main results

49 Berichte zeigen breites Anwendungsspektrum

This report focuses on genetic testing in Austria, emphasising high-throughput sequencing technologies and the importance of evidence-based decision-making for the introduction and reimbursement of these tests. Drawing upon 49 health technology assessment (HTA) reports and Cochrane reviews, the analysis covers four main application fields: diagnostic testing (n=14), predictive testing (n=8), pharmacogenomic testing (n=11), and tumour testing (n=16). These reports encompass indications such as rare disease diagnosis, familial hypercholesterolaemia, inherited arrhythmias, tumour profiling, carrier screening, and pharmacogenomic assessment. Overall, the reports highlighted numerous clinical scenarios in which sequencing technologies can be applied in practice. In most instances, sequencing was implemented as an add-on test rather than fully replacing existing diagnostic approaches.

drei Länder mit formalisierten, indikationsspezifischen evidenzbasierten Prozessen identifiziert

Another finding is that robust HTA activity is concentrated in countries where formalised assessment and reimbursement processes are established, notably the United Kingdom (UK), Australia (Medical Services Advisory Committee, MSAC) and Canada (with most structured activity in Ontario). All three jurisdictions apply an indication-specific approach, linking test evaluation to defined clinical contexts and patient populations. The UK's National Genomic Test Directory defines over 200 indications and appropriate sequencing methods. In Australia, reimbursement of genetic tests is embedded within MSAC, evaluating each test individually based on context, disease severity, utility, and methodology. In Ontario, Health Quality Ontario conducts evidence reviews to inform the provincial Genetic Test Directory, which lists over 600 funded tests with defined indications and criteria.

Workshop identifiziert 3 potenzielle Priorisierungskriterien: klinische Handlungsfähigkeit, Ressourcenintensität und Indikationsvolumen

A dedicated stakeholder workshop – bringing together representatives from social insurance, hospitals, clinical pathology, and health policy – explored the clinical, economic, and organisational aspects of genetic testing. A key challenge highlighted was defining the circumstances under which high-resource sequencing methods, such as whole-genome sequencing, are warranted, versus scenarios where targeted sequencing approaches are sufficient. Based on these discussions, the following prioritisation criteria were identified as highly relevant:

- Clinical actionability (potential for therapeutic or preventive action),
- Resource intensity (cost and complexity of testing and data management), and
- Indication volume (frequency of test requests in clinical practice).

A provisional scoring system was developed to facilitate the prioritisation of genetic testing topics in future HTA reports, assigning double weight to clinical actionability to reflect its central role in decision-making. The system is intended as a practical tool to support the shortlisting of genetic tests for HTA reports, but further validation and structured stakeholder engagement are required prior to its formal adoption. The scoring system is considered optional, whilst expert deliberation in prioritising topics for an HTA is considered required

Contextualisation of results

identifizierte Länder mit höchster HTA-Aktivität übereinstimmend mit rezenter Analyse

A systematic review by Sciurti et al. [101] also mapped HTA activities for genetic and genomic testing, equally finding that most assessments were conducted in high-income countries – particularly the UK, Australia, and Canada. Our analysis independently identified the same three countries as having the highest volume of HTA reports on genetic testing. While Sciurti et al. focused on methodological aspects such as evaluation frameworks and evidence gaps, our analysis maps the application fields of genetic testing and providing a description of reimbursement processes in countries with high HTA activity.

erarbeitete Priorisierungskriterien zeigen Überschneidung mit internationalen Ansätzen

The results of the Austrian stakeholder workshop demonstrated similarities with international best practices: there is overlap of the prioritisation criteria established and those employed in the United Kingdom and Australia and Canada. In these countries, reimbursement decisions for genetic tests are fundamentally indication-specific, meaning that assessments are systematically linked to clearly defined clinical scenarios and disease contexts. However, the countries diverge in their structural approaches: England and Ontario established a dedicated genomic test directory. Yet, in England, the reimbursement process is characterised by two evaluation pathways – National Health Service(NHS) England and National Institute for Health and Care Excellence (NICE), both feeding into a single NHS England Commissioning framework. Australia, by contrast, embeds genetic test assessment within its broader HTA and reimbursement processes (MSAC), using targeted supplementary tools to address the unique aspects of genomics, and maintaining an "add-on" approach for nuanced evaluation.

fragmentierte Governance in Österreich, Umsetzung offen

As outlined in the GÖG (German: Gesundheits Österreich GmbH) report [25], governance of genetic testing in Austria currently relies on a fragmented, bottom-up structure: provision is largely limited to four university clinics and a handful of additional providers, underpinned by individual contracts and inconsistent service arrangements. Regulation and reimbursement are public and mandatory, but notable inconsistencies persist due to locally negotiated contracts and the narrow scope of services, such as the prescription of genetic testing primarily for hereditary breast and ovarian cancer syndrome. The GÖG report [25] recommended the establishment of clearer, more standardised governance mechanisms to enhance national coordination, access, and quality assurance in the delivery of genetic testing. While these structural recommendations set the stage, the specifics of how genomic medicine should be integrated into Austria's complex health financing and reimbursement systems is still unresolved. The key policy question ahead is whether Austria should introduce a stand-alone national test directory or instead develop indication-specific "add-on" guidance within the existing HTA framework. This decision will shape the transparency, coherence, and adaptability of genomics integration for years to come.

EU-IVDR mit Ausnahmen für In-house-Tests

The EU In Vitro Diagnostic Regulation (IVDR; EU 2017/746) does regulate many commercial genetic tests as in vitro diagnostics (IVDs), now typically under Class C rules for genetic tests, requiring CE marking and conformity assessment. However, hospitals and clinical laboratories are allowed to develop and operate their own in-house laboratory developed tests (LDTs) under certain exemptions in Article 5(5) of the IVDR. These in-house devices (e.g., NGS panels validated on-site using platforms like Thermo Fisher or Illumina) are exempt from the most stringent IVDR requirements, provided they are used within the same health institution, justified by unmet clinical needs, and meet established safety and quality standards [102].

Test Directory könnte Harmonisierung unterstützen

Laboratories must demonstrate clinical validation, performance, and maintain a quality management system, but do not have to undergo the full commercial CE-IVD process if they are not placing the test on the EU market (i.e., when used internally under clinical exemption). This regulatory split creates variability: some genetic tests are tightly regulated as commercial IVDs, while many "in-house" assays remain subject to local clinical validation and expert oversight – particularly where no equivalent CE-IVD is available or suitable [102]. On this backdrop, it appears essential to consider the establishment of an indication-specific test directory to better guide evidence-based integration and harmonise access to genetic services in Austria. Such an approach would offer clarity and consistency, supporting equitable decision-making across both commercial and clinical laboratory-developed genetic testing.

UK Generation Study: Genomsequenzierung bei 100.000 Neugeborenen, flächendeckende Integration geplant bis 2030

In parallel to evidence-based clinical integration, genetic testing is also the focus of ambitious research and policy initiatives [103, 104] and debate. In the UK, the Generation Study is evaluating whole genome sequencing for up to 100,000 newborns, and by 2030, the NHS aims to offer genome sequencing to all newborns as part of a major public health strategy [103, 104]. However, these plans highlight important challenges: genome sequencing in some areas such as predictive testing produces risk estimates rather than definitive diagnoses, and a genetic flag does not equate to certainty of disease. To avoid confusion, clear communication and education for clinicians and parents are critical, and the demand for specialist genetic counselling – already a known bottleneck – will inevitably increase, becoming a prerequisite for effective population-scale screening [105].

Risiken prädiktiver Tests: z. B. Fehlinterpretation, emotionale Belastung

Another area of debate is the increasing use of genetic "predictive" tests beyond the clinic [1, 106], often targeting less informed users through direct-to-consumer offerings (or as part of research projects). These tests claim to inform individuals of their lifetime risk of developing certain diseases, either by identifying single-gene variants linked to increased risk, or by calculating so-called polygenic risk scores [107] that estimate risk in comparison to the average population. These tests are often "information only" with limited clinical utility. Their results can be misleading and difficult to interpret, whilst risking unnecessary emotional distress for individuals and their families – particularly when findings are misunderstood or provoke unnecessary concern about health risks [106, 107]. A rise in direct-to-consumer genetic tests may also pose risks with regard to increased work-load and a need for subsequent preparedness and policy response from a health system perspective [108].

Limitations

Limitationen: Fokus auf Indikations-Mapping, vorläufige Kriterien, keine Implementierungsaspekte

The results of our report should be interpreted in view of its limitations. First, our overview of HTA reports and Cochrane reviews was restricted to mapping clinical indications, application fields, and technical characteristics, without formally analysing how these technologies were methodologically evaluated or assessed for effectiveness. Further, the mapping exercise excludes systematic reviews on the topic and sources not available in English or German were excluded. Second, the developed prioritisation criteria are intended as initial guidance from a decision-making perspective; formal HTA processes, especially in other countries, involve broader stakeholder input beyond what is reflected here. When setting up an HTA and reimbursement process for genetic testing in Austria, more stakeholders such as patient

representatives and geneticists should be involved to develop and refine the process (including prioritisation criteria). Third, implementation aspects – such as requirements for personnel, quality assurance, and governance – are outside the scope of this report.

Protokollabweichungen auf OSF dokumentiert

Furthermore, we pre-registered our work; due to its scope, the project was divided into three separate reports. All project deviations are transparently reported in the Open Science Framework (OSF) platform [17]. For this report, two research questions (research question 2 and 3) were added after first upload of the protocol in the OSF platform. These were added due to stakeholder needs.

Implementation and Quality Recommendations

AWMF-Leitlinie 2025 zu Qualität und Governance

Recent guidance – such as the 2025 AWMF (German: Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) S1 guideline for high-throughput sequencing – provides comprehensive recommendations on the use and governance of high-throughput sequencing in diagnostic settings. These include[109]:

- **Test Indications and Quality**: High-throughput sequencing must be justified by clinical context and carried out under accredited, quality-assured conditions. Orders should be reviewed for feasibility, with clarification sought before proceeding. Research findings should be clearly distinguished and confirmed by diagnostic tests.
- **Informed Consent:** Compliance with legal requirements is mandatory, including consent for sample use, data storage, and handling of incidental findings.
- **Targeted Analysis:** Only genes with established links to disease should be analysed, and interpretation must focus on the clinical question to minimise incidental findings.
- **Personnel and Training:** Staff involved in all process components – sample handling, wet lab, bioinformatics, and variant interpretation – must be suitably qualified and undergo continuous training.
- **Sample Management:** Traceability through unique identifiers and barcode systems is essential for all samples and derived materials. Validation is required for samples with known quality limitations.
- **Bioinformatics:** Pipelines must utilise the most current reference genomes (GRCh38 recommended), follow standardised data formats, and are subject to validation and ongoing updates. Continuous quality monitoring is expected.
- **Variant Interpretation:** Comprehensive clinical data should accompany interpretation using standardised classification systems (five-tier system as defined by American College of Medical Genetics and Genomics). Structural variants require specific nomenclature and use of cytogenetic databases.
- **Reporting:** Reports must transparently describe test methods, limitations, results, and interpretation criteria. Only clinically relevant variants, including certain variants of uncertain significance (VUS), are reported. Laboratories must have explicit policies for managing incidental and secondary findings.

- **Data Sharing and Archiving:** Variants and their interpretations should be submitted to public databases, and long-term archiving of raw and processed data is required for reproducibility and patient follow-up.
- **Reanalysis:** Routine systematic reanalysis is not expected; it should be done only on request or for internal quality assurance, particularly when new clinical information or improved methods emerge.

Interested readers and decision-makers are referred to the GÖG report [25] on human genetic healthcare and current AWMF S1 guidelines [109] for further operational and governance detail.

Outlook

Evidenz für patient:innenrelevante Endpunkte oft schwach, Potentiale für neue Studiendesigns

Evaluation of diagnostic and genetic tests typically relies on frameworks designed for different levels of evidence synthesis: For instance, the European Network for Health Technology Assessment Core Model [27] for HTA reports, and the Ferrante di Ruffano et al. framework for primary studies [26]. Both address clinical pathway impact and patient outcomes. While our overview captured some of these structural elements, the majority of genomic medicine evidence remains weak or inconclusive regarding patient-relevant endpoints [110, 111]. Advances in genomic medicine offer the potential for more informative study designs in genetic testing, by enabling targeted patient selection and the use of validated surrogate markers, thereby supporting more efficient and adaptive trials [112].

Fragmentierung in HTA-Methodik, Reflexion auch zu HTA-Methodik erforderlich

A recent systematic methodological review of HTA reports identified considerable heterogeneity in evaluation approaches for genetic and genomic applications. Key gaps included under-assessment of analytical and clinical accuracy, persistent evidence gaps, and limited generalisability of findings. The authors highlighted the need for both improved study designs specifically tailored to evaluate the utility of genetic tests, and for enhancements and standardisation of HTA assessment frameworks [101]. Future research could investigate more systematically whether standard frameworks sufficiently address the unique challenges posed by advanced genetic technologies – such as handling of large-scale data, variant interpretation, ethical/legal/social implications, and the evaluation of broader personal utility. As Austria further develops its reimbursement processes and test directories, systematic dialogue with multidisciplinary stakeholder groups and continuous methodological advancement will be crucial to ensuring effective, safe and high-quality genetic service delivery.

zukünftig auch genomische digitale Gesundheitstechnologien

Advanced sequencing technologies can be coupled with artificial intelligence or machine learning. One such genomic-enabled digital health technology (DHTs) was evaluated in one identified HTA report from Wales [43] in the context of cardiovascular diseases, assessing a person's risk based on their genes, using sequencing technologies and machine learning algorithms to analyse genetic and clinical data for advanced risk prediction. Such technologies are a signal that HTA methodologies need to evolve holistically, integrating standards for both genomic and digital evaluation domains to adequately assess the benefits of such technologies.

Implementierung evidenzbasierte Erstattungsprozesse in Österreich bedürfen breiter Stakeholder-Beteiligung

In parallel, as Austria seeks to establish or refine reimbursement processes, potential test directories, and clinical pathways for genetic testing, it will be crucial to ensure these are developed with broad stakeholder input. The prioritisation criteria presented in this report are intended to provide initial guidance from a decision-maker's perspective. Drawing on the experience of coun-

tries with formalised HTA processes [83, 89, 94], future implementation in Austria should systematically involve multidisciplinary steering groups – including clinicians, scientists, health economists, and patient/public representatives – to ensure that resulting HTA processes and test governance structures effectively address national needs and support transparent, evidence-based policy decisions.

8 Conclusion

Identifikation von breiten Anwendungsfeldern

This scoping review identified four key application fields for genetic testing relevant to Austria: diagnostic, clinical predictive, pharmacogenomic and tumour testing. International HTA experience indicates that effective reimbursement processes require an indication-based approach with explicit testing criteria – that is, clearly defined conditions specifying which patients should be tested, under what clinical circumstances, using which validated methods – rather than broad, technology-focused benefit catalogues, where reimbursement decisions are based primarily on the type of technology rather than the specific clinical context or patient need.

internationale Referenzmodelle für evidenzbasierte Erstattung

The NHS Test Directory (UK), MSAC process (Australia) and Ontario Test Directory (Canada) provide models for maintaining evidence-based catalogues with transparent inclusion criteria and regular updates. Austria can draw on these examples when developing its own indication-driven reimbursement process.

pragmatischer Ansatz: Testverzeichnis basierend auf aktuellem Versorgungsstandard

Austria should formalise existing genetic testing practice through granular, indication-specific criteria rather than building an entirely new system. A pragmatic first step would be to establish steering committees (involving experts in the field of genetics, pathology and laboratory medicine) tasked with developing an indication-specific catalogue based on the current standard of care and/or cross-referencing the detailed indications in other international directories to establish a "base catalogue" of high-consensus, established tests. This catalogue could then be updated annually, with steering committees identifying selected indications and technologies requiring formal evidence reports – an approach successfully implemented, for instance, in the UK. Such a process requires transparent governance structures and regular review cycles aligned with evolving clinical evidence.

Priorisierungskriterien als ein Teil eines evidenzbasierten Erstattungsprozess

Once a formalised evidence-based reimbursement process is established, the most relevant prioritisation criteria developed during the stakeholder workshop – clinical actionability, resource intensity, and indication volume – can serve as an initial reference. However, broader consultation and iterative refinement through systematic engagement with multidisciplinary stakeholder groups will be essential prior to their formal adoption for topic prioritisation within such a process.

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Appendix

Overview tables of HTA reports and Cochrane reviews on high-throughput sequencing technologies: clinical indications structured by application fields

Table A-1: Diagnostic Testing

HTA Report (Inst., Year [REF])	Medical specialty	Clinical Indications	Position in Clinical Pathway/ Test Strategy (Add-on or replacement)	Reference Standard/ Comparator	Sequencing Technology (Scope, Read Length)	Target of Analysis
AIHTA, 2020 [28]	Cardiology	Screening and management of heterosygous familial hypercholesterolemia (FH)	**Add-on:** Genetic testing after clinical FH diagnosis, cascade screening of family members	**Comparator:** Standard clinical diagnosis (lipid profile, personal/ family history, clinical symptoms)	Panel sequencing and WES (MPS of mutations in relevant genes)	Germline DNA – genetic sequencing of mutations in relevant genes (LDLR, ApoB, PCSK9, LDLRAP1)
MSAC, 2020 [29]	Cardiology	**Inheritable cardiac arrhythmias** (long QT syndrome, Brugada syndrome, Catecholaminergic polymorphic ventricular tachycardia)	**Add-on:** Genetic diagnosis for affected individuals and thus estimates their predisposition for future risk of further disease; Cascade testing for family members	**Comparator:** Standard care without genetic testing **Reference standard:** Sanger sequencing	Genetic testing for variants in gene panel	20-gene panel (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, RYR2, CASQ2, CAV3, SCN4B, AKAP9, SNTA1, KCNJ5, ALG10, CALM1, CALM2, ANK2, TECRL, and TRDN)
MSAC, 2021 [30]	Cardiology	**Heritable cardiomyopathies** (hypertrophic, dilated, arrhythmogenic)	**Add-on:** Genetic testing for individuals with suspected or confirmed heritable cardiomyopathies to determine genetic cause and specific type; Cascade testing of family members and reproductive partners, regardless of symptoms	**Comparator:** Clinical diagnosis without genetic testing	Broad gene panel testing and variant-specific detection	A minimum of 22 genes associated with inherited cardiomyopathies to confirm or exclude a genetic cause (HCM: MYBPC3, MYH7, TNNI3, TNNT2, TPM1, ACTC1, MYL2, MYL3 plus "mimic" genes PRKAG2, LAMP2, GLA. DCM: LMNA, SCN5A, TTN, RBM20, PLN, DSP, MYH7. ARVC: DSC2, DSG2, DSP, JUP, PKP2, and TMEM43)
MSAC, 2021 [31]	Clinical Microbiology	Antimicrobial drug susceptibility testing for **tuberculosis patients** with confirmed **Mycobacterium tuberculosis** (five indications)	**Add-on:** Additional test for mycobacterial infections to detect antimicrobial resistance in the pathogene genome	**Comparator:** Phenotypic drug susceptibility testing alone	WGS plus traditional phenotypic testing	Mycobacterium tuberculosis complex
Cochrane, 2021 [32]	Cardiology	**Familial hypercholesterolemia** (FH) screening strategies	**Add-on:** MPS as part of different screening strategies compared	**Comparator:** Various screening approaches	Mode of diagnosis for FH (genetic vs. clinical) considered in subgroup analysis	FH diagnosis approaches
HQO, 2022 [33]	Cardiology	Screening or confirmatory testing for **Familial hypercholesterolemia** (FH) and cascade screening of relatives	**Add-on:** Confirm FH diagnosis in index cases and identify new cases via cascade screening	**Comparator:** Clinical evaluation without genetic testing; no cascade screening	Targeted MPS panels for known FH genes	Germline DNA to detect pathogenic variants in FH-associated genes (ABCG5, ABCG8, APOB, APOE, LDLR, LDLRAP1, LIPA, PCSK9)
MSAC, 2023 [35]	Medical Genetics	**Mitochondrial disease** in patients with suspected acute or chronic disease	**Add-on:** Genetic diagnosis for affected individuals and cascade testing for relatives and reproductive partner testing	**Comparator:** Current diagnostic process including muscle biopsy (minor surgery to take a sample of muscle tissue)	Virtual panel-based WGS or WES and mitochondrial DNA sequencing	350+ genes cause mitochondrial disease. Most are in nuclear DNA, some in mitochondrial DNA

HTA Report (Inst., Year [REF])	Medical specialty	Clinical Indications	Position in Clinical Pathway/ Test Strategy (Add-on or replacement)	Reference Standard/ Comparator	Sequencing Technology (Scope, Read Length)	Target of Analysis
TASK, 2025 [36]	Medical Genetics	Various rare diseases, mostly targeted patient population consists of children with **suspected genetic conditions**	**Add-On:** After non-diagnostic testing (e.g., chromosomal microarray or targeted gene tests) with genetic causes strongly suspected	**Comparator:** WES using NovaSeq 6000 platform	WGS using NovaSeq 6000 platform	No individual genes or defined gene panel was targeted in this analysis. Identification of syndromic intellectual disabilities (ID)/developmental disabilities (DD), multiple congenital anomalies without ID/DD, multisystem disorder without ID/DD, single system disorder without ID/DD and isolated ID/DD
Cochrane, 2025 [37]	Neonatology	Diagnosis of **neonatal bacterial** and **fungal sepsis**	**Replacement:** May replace blood cultures with more sensitive/earlier results	**Comparator:** Blood culture	Various, incl. PCR and Metagenomic MPS	Bacterial or fungal nucleic acids (e.g., DNA, 16S ribosomal RNA gene, Internal Transcribed Spacer regions) in neonatal clinical samples (primarily blood, Cerebrospinal Fluid).
HQO, 2020 [38]	Paediatrics	Unexplained **developmental disabilities** or **multiple congenital anomalies**	**Replacement/Add-on:** First tier, second tier, or after standard testing	**Comparator:** Standard genetic testing (chromosomal microarray, targeted gene tests/panels)	WGS, WES	Causal variants in germline DNA via exome or genome analysis
IQWIG, 2024 [39]	Paediatric Cardiology	Universal screening of asymptomatic children/adolescents (<18 years) for **Familial Hypercholesterolemia** (FH)	**Add-on:** Universal screening with first-tier lipid test (e.g., LDL-cholesterol), followed by confirmatory genetic testing	**Comparator:** No universal screening **Reference Standard:** Molecular genetic testing to evaluate the accuracy of the lipid screening test	WGS and targeted sequencing of known FH genes on Illumina MiSeq platform Read Length: low-read and high-read depth.	Germline DNA targeting FH-associated genes (LDLR, APOB, PCSK9).
TASK, 2020 [40]	Pediatric Cardiology	Children with **heterogeneous cardiac diseases** (cardiomyopathies, congenital heart defects, arrhythmias)	NR	NR	WGS (Illumina HiSeq X™ platform)	From 1,500-2,000 genetic variants examined, 15-20 variants of interest were flagged and further analysed by genome analysts for pathogenicity, gene function effects, and disease association. Pharmacogenomic analysis was additionally performed for probands only.
MSAC, 2022 [41]	Pediatric Otolaryngology	**Hearing impairment** in children (<18 years) with moderate to severe hearing loss	**Add-on:** Testing GJB2/GJB6 first, then virtual gene panel if no diagnosis	**Comparator:** No virtual gene panel analysis	Virtual gene panel-based WES and copy number variant analysis	Virtual gene panel testing sequences all genes but restricts analysis to hearing loss-associated genes (e.g., GJB2, GJB6 in children).
Washington State HTA, 2024 [42]	Various	Children or adults with **suspected genetic disorder**	**Replacement/Add-on:** WGS alone or as part of testing pathway	**Comparator:** Standard of care diagnostic evaluation, including clinical, laboratory, or imaging; single gene tests, multigene panels; chromosomal microarray; karyotype; WES	Short-read WGS	Germline DNA to identify causal genetic variants across entire genome

Abbreviations: DD … developmental disabilities; DNA … Deoxyribonucleic Acid; FH … familial hypercholesterolemia; ID … intellectual disabilities; MPS … massively parallel sequencing; NGS … next generation sequencing; PCR … Polymerase Chain Reaction; RNA … Ribonucleic Acid; Seq … sequencing; WES … whole exome sequencing; WGS … whole genome sequencing.

Table A-2: Clinical Predictive Testing – Used to determine susceptibility to a condition or predict future health outcomes, often in asymptomatic individuals or for risk stratification

HTA Report (Inst., Year [REF])	Medical specialty	Clinical Indications	Position in Clinical Pathway/ Test Strategy (Add-on or replacement)	Reference Standard/ Comparator	Sequencing Technology (Scope, Read Length)	Target of Analysis
HTW, 2020 [43]	Cardiology	**Cardiovascular disease** risk assessment (Screening) and genetic testing for **familial hypercholesterolemia**	**Add-on:** Risk prediction to assess cardiovascular disease (CVD) onset/recurrence risk	**Comparator:** No genetic risk prediction	GEN inCode tests – sequencing via MPS	Cardio inCode: Multiple genetic variants associated with CVD risk. Lipid inCode: Variants in 7 genes associated with FH
AIHTA, 2022 [34]	Gynaecology	**Non-invasive prenatal screening for fetal anomalies (Trisomies 21, 18, 13) in pregnant women**	**Add-on: Varies by country for NIPT. First-line or second-line screening for aneuploidies, invasive tests for confirmation, second-trimester ultrasound for structural anomalies**	NR	NIPT uses MPS/NGS of fetal cell-free DNA	Fetal cell-free DNA in maternal plasma for aneuploidies (T21, T18, T13); some broader (e.g. WGS in Netherland's TRIDENT study)
Cochrane, 2021 [44]	Medical Genetics	Women and their partners who are identified as carriers of thalassaemia, sickle cell disease, cystic fibrosis or Tay-Sachs disease in healthcare settings	**Add-on:** Systematic preconception genetic risk assessment	**Comparator:** Usual Care (not further reported)	MPS utilised (not further reported)	Carrier screening focuses thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease
HIQA, 2023 [45]	Neonatology	Universal screening of asymptomatic newborns for **Severe Combined Immunodeficiency** (SCID) and **T-cell lymphopenias**	**Add-on:** First-tier population screening for early diagnosis and timely treatment (stem cell transplant)	**Comparator:** No universal screening	MPS (embedded gene panel) or TREC-based screening via quantitative PCR	TRECs as biomarker for T-cell production
HIQA, 2023 [46]	Neonatology	Universal screening of asymptomatic newborns for **Spinal Muscular Atrophy**	**Add-on:** First-tier population screening test. Positive screen triggers confirmatory testing and early therapy	**Comparator:** No universal screening	MPS or PCR methods for targeted SMN1/ SMN2 analysis (typically short-read)	Germline DNA from newborn bloodspot – SMN1 gene deletion and SMN2 gene copy number
CADTH, 2021 [47]	Obstetrics	Preconception or prenatal carrier screening for **inherited conditions**	**Add-on:** Carrier screening for individuals/couples	**Comparator:** No carrier screening	MPS or microarray technologies	Carrier screening focuses on Cystic Fibrosis, Fragile X, Hemoglobinopathies, Spinal Muscular Atrophy, and expanded panels
HQO, 2023 [48]	Obstetrics	Preconception or prenatal carrier screening for **specific inherited conditions** (Cystic Fibrosis, Fragile X, Hemoglobinopathies, Spinal Muscular Atrophy)	**Add-on:** Universal vs. risk-based screening using standard or expanded panels	**Comparator:** No carrier screening	MPS can be used (among other sequencing techniques)	Germline DNA to identify pathogenic carrier variants in genes associated with specific conditions
Cochrane, 2020 [49]	Reproductive Medicine	**Aneuploidy** screening in women undergoing In-Vitro-Fertilisation (IVF) treatment	**Add-on:** PGT-A to IVF	**Comparator:** IVF without PGT-A (morphological selection), genetic analysis with FISH	WGS, read-length: NR	DNA from oocytes (polar bodies) or embryos (blastomeres/trophectoderm cells) for aneuploidy screening

Abbreviations: CVD … cardiovascular disease; DNA … Deoxyribonucleic Acid; FH … familial hypercholesterolemia; FISH … Fluorescence In Situ Hybridisation; IVF … In Vitro Fertilisation; MPS … massively parallel sequencing; NIPT … Non-Invasive Prenatal Testing; PCR … Polymerase Chain Reaction; PGT-A … Preimplantation Genetic Testing for Aneuploidy; SCID … Severe Combined Immunodeficiency; SMN … Survival Motor Neuron; TREC … T-cell receptor excision circles; WES … whole exome sequencing; WGS … whole genome sequencing.

Table A-3: Pharmacogenomic Testing

HTA Report (Inst., Year [REF])	Medical specialty	Clinical Indications	Position in Clinical Pathway/ Test Strategy (Add-on or replacement)	Reference Standard/ Comparator	Sequencing Technology (Scope, Read Length)	Target of Analysis
SHTG, 2024 [50]	Neurology	Assessment of clopidogrel suitability in patients who have just had an **ischaemic stroke** or **transient ischaemic attack**	**Add-on:** Pre-treatment test to guide clopidogrel use. Clopidogrel resistant should receive alternative antiplatelet	**Comparator:** Compared with no testing	Laboratory-based CYP2C19 genotype testing (gene sequencing or targeted genotyping assays). Laboratory tests use blood sample	Changes in CYP2C19 gene
NICE, 2024 [51]	Neurology	Assessment of clopidogrel suitability in patients who have just had an **ischaemic stroke** or **transient ischaemic attack**	**Add-on:** Pre-treatment test to guide clopidogrel use (testing recommended before starting – don't delay antiplatelet treatment)	**Comparator:** No genotype testing before using clopidogrel	Genetic testing of CYP2C19 gene, either by laboratory-based or point-of-care testing	CYP2C19 gene alleles
NIHR, 2024 [52]	Neurology	Individuals who have experienced **ischaemic stroke** or **transient ischaemic attack**	**Add-on:** Identify individuals with CYP2C19 genetic variants leading to clopidogrel resistance, guide antiplatelet therapy selection	**Comparator:** No testing	Laboratory based CYP2C19 genotyping may include MPS. Targeted sequencing (typically short-read)	Germline DNA to detect inherited CYP2C19 loss-of-function alleles associated with reduced clopidogrel metabolism
SHTG, 2020 [53]	Oncology	Pre-treatment screening for patients prescribed fluoropyrimidine-based chemotherapy (colorectal, oesophageal, gastric, breast, head and neck cancers)	**Add-on:** First-line test (pre-treatment screening before initiating fluoropyrimidine chemotherapy)	**Comparator:** No-testing (reactive testing for adverse events)	PCR followed by Sanger single gene sequencing. Alternative: Elucigene DPYD multiplex assay; MPS not mentioned in assessment report, but MPS can be used for DPYD analysis	DPYD gene variants: c.1905+1G>A, c.2846A>T, c.1679T>G, c.1236G>A/ HapB3 (clinically significant toxicity risk), c.1601G>A (no significant increase)
HQO, 2021[54]	Oncology	Patients with **various cancers** for whom treatment is planned	**Add-on:** Pre-treatment DPYD genotyping to identify high-risk patients, guide dose modifications and improve safety	**Comparator:** Usual care (standard fluoropyrimidine dose without pre-treatment DPYD genotyping)	Not specified, MPS can be used	Germline DNA to detect inherited variants in DPYD gene causing DPD enzyme deficiency, leading to increased drug toxicity risk
HTW, 2023 [55]	Primary Care	Broad application for **any patient initiating new drug treatment** where **gene-drug interaction** is known	**Add-on:** Pre-emptive, multi-gene pharmacogenomic panel to guide drug prescribing, reduce adverse drug reactions	**Comparator:** Standard of care	Various (not specified)	Pharmacogenomic analysis for drug response prediction
KCE, 2023 [56]	Primary Care	Broad; **patients initiating drugs** with **known actionable gene-drug interactions**	**Add-on:** Pre-emptive or reactive pharmacogenomic testing to guide treatment and reduce adverse drug reactions	**Comparator:** Different implementation scenarios: single-gene tests vs. complex tests vs. phenotyping	Gene panel testing, WES, WGS	Germline DNA to identify inherited variants (single nucleotide variations and copy number variations) in pharmacogenes
CADTH, 2023 [57]	Psychiatry	Mental, behavioural or neurodevelopmental **psychiatric disorders**	**Add-on:** Optimize medication selection by analysing polymorphisms to predict psychotropic medication response	**Comparator:** Treatment as usual (without pharmacogenetic testing)	Various (not specified)	Germline DNA (saliva, blood, buccal swab) to identify inherited genetic variants (polymorphisms) relevant to drug response
CADTH, 2020 [58] and CADTH, 2022 (Update) [59]	Psychiatry	Adults (18-60 years) with diagnosed **depression** of various severities	**Add-on:** Inform and personalise antidepressant/psychotropic drug selection or dosage adjustments	**Comparator:** Treatment as usual (without pharmacogenetic testing)	Various (not specified)	Germline DNA to identify inherited variants in genes that affect drug response
HQO, 2021 [60]	Psychiatry	Adults (aged 18 years and over) with a primary diagnosis of major **depression** requiring pharmacological treatment	**Add-on:** Inform and personalise depression medication selection	**Comparator:** Treatment as usual (No pharmacogenomic testing to guide depression medication selection or dose adjustment)	Multi-gene (two or more genes) pharmacogenomic tests (not further specified)	Germline DNA to identify inherited variants in genes that affect drug response

Abbreviations: DNA … Deoxyribonucleic Acid; MPS … massively parallel sequencing; PCR … Polymerase Chain Reaction; WES … whole exome sequencing; WGS … whole genome sequencing.

Table A-4: Tumour Testing

HTA Report (Inst., Year [REF])	Medical specialty	Clinical Indications	Position in Clinical Pathway/ Test Strategy (Add-on or replacement)	Reference Standard/ Comparator	Sequencing Technology (Scope, Read Length)	Target of Analysis
NIPH, 2022 [61]	Oncology (general)	Adults and children with **locally advanced or metastatic solid tumours** (across >25 tumour types)	**Add-on:** Diagnostic test to identify actionable NTRK fusions for treatment selection. May use IHC for pre-screening, followed by MPS confirmation	**Comparator:** Head-to-head comparisons of different testing methods (IHC, FISH, RT-PCR, NGS). RNA-based NGS often serves as reference	DNA and RNA based MPS, targeted panels	Somatic NTRK1, NTRK2, or NTRK3 gene fusions (DNA rearrangements or RNA fusion transcripts) in tumour tissue
Cochrane, 2025 [62]	Oncology (general)	**Advanced/refractory solid or haematological cancers** progressed on ≥1 line of standard systemic therapy	**Add-on:** Treatment planning, genetic test guiding targeted therapies	**Comparator:** Standard-of-care treatment, non-matched targeted therapies or best supportive care	Various (gene panels, WES, or WGS, depending on trials). Predominantly short-read for clinical NGS	Somatic mutations in tumour DNA from tissue, blood, or bone marrow to identify targets for matched therapies
NICE, 2020 [63]	Oncology (gynecologic oncology)	Diagnose **Lynch syndrome** in **endometrial cancer** patients for future surveillance and cascade testing	**Add-on:** Post-endometrial cancer diagnosis: Tumour IHC for MMR proteins → MLH1 promoter methylation → confirmatory germline testing	**Comparator:** No testing	Strategy incorporates MPS: MSI testing (tumour) – MPS-based (targeted panels or broader short-read). MLH1 promoter methylation: pyrosequencing. Confirmatory germline testing: primarily MPS	Tumour: MMR protein expression (IHC), MSI status, MLH1 promoter methylation. Germline: Pathogenic variants in MMR genes (MLH1, MSH2, MSH6, PMS2, EPCAM)
NICE, 2021 [64]	Oncology (hematologic oncology)	Testing for **multiple myeloma, acute lymphoblastic leukaemia**, and **chronic lymphocytic leukaemia**	**Add-on:** During treatment or after remission	**Comparator:** Multiparametric flow cytometry and allele-specific oligonucleotide PCR	Product name: clonoSEQ (diagnostic medical device); uses PCR and MPS technology	Minimal residual disease assessment
NICE, 2021 [65]	Oncology (hematologic oncology)	Newly diagnosed, relapsed or refractory **multiple myeloma**	**Add-on:** To standard care marker tests aiming to improve personalized drug treatment regimens	**Comparator:** Standard care marker tests	Product name: Mismatch Repair profiler (MMprofiler)	Bone marrow sample for gene expression profiling of 92 genes
HTW, 2021 [66]	Oncology (hematologic oncology)	Classification of **Diffuse Large B-Cell Lymphoma** (DLBCL) into cell of origin subtypes for prognosis and treatment guidance	**Add-on:** Used on tumour biopsy sample after diagnosis of DLBCL to determine molecular subtype (cell of origin)	**Comparator:** Alternatives such as IHC panels (Hans algorithm) and conventional microarray-based gene expression profiling	HTG EdgeSeq platform, run on Illumina MiSeq sequencer. Gene expression profiling (specific gene set)	Gene expression levels (RNA transcripts) from Formalin-Fixed, Paraffin-Embedded (FFPE) tumour tissue to determine the cell of origin molecular subtype
Cochrane, 2021 [67]	Oncology (neuro-oncology)	Individuals with **glioblastoma** treated with temozolomide	**Add-on:** Test after glioblastoma diagnosis to inform prognosis and guide treatment decisions. Eight methods compared	**Comparator:** PCR and Immunohistochemistry	Pyrosequencing: sequencing-by-synthesis method, typically for shorter reads	MGMT gene promoter methylation status in glioblastoma tumour tissue/DNA; MGMT protein expression (for IHC methods)
Cochrane, 2022 [68]	Oncology (neuro-oncology)	Determining 1p/19q codeletion status in adults with **glioma** for diagnosis (oligodendroglioma), prognosis, and treatment decisions	**Add-on:** Typically performed after initial histological assessment and other molecular tests (IDH mutation, ATRX expression)	**Comparator:** FISH vs. PCR-based LOH	Various (Sequencing-by-synthesis, sequencing-by-ligation and ion semiconductor sequencing)	DNA from tumour tissue (FFPE or frozen) to detect complete (absolute) codeletion of chromosomal arms 1p and 19q
HQO, 2020 [69]	Oncology (pulmonary oncology)	Patients with **Non-Small Cell Lung Cancer** with known EGFR-sensitizing mutation, whose disease has progressed after treatment with first- or second-generation EGFR Tyrosine Kinase Inhibitor (TKI)	**Add-on:** At disease progression on first- or second-generation EGFR-TKI therapy. Liquid biopsy (cell-free circulating tumour DNA) evaluated as triage test (if negative, followed by tissue biopsy) or standalone test	**Comparator:** Tissue biopsy for detecting the EGFR T790M mutation	Liquid biopsy for EGFR T790M detection can use Next-Generation Sequencing (NGS/MPS). Targeted sequencing of EGFR gene (specifically for T790M and other relevant mutations). Typically short-read	Somatic EGFR T790M resistance mutation in cell-free circulating tumour DNA (ctDNA) from plasma (liquid biopsy)

HTA Report (Inst., Year [REF])	Medical specialty	Clinical Indications	Position in Clinical Pathway/ Test Strategy (Add-on or replacement)	Reference Standard/ Comparator	Sequencing Technology (Scope, Read Length)	Target of Analysis
CADTH, 2022 [70]	Oncology (pulmonary oncology)	Individualised treatment for various **cancers**, primary focus: **Non-Small Cell Lung Cancer**	**Replacement/Add-on:** Liquid biopsy based CPG as alternative or complement to conventional molecular testing	**Comparator:** Conventional molecular testing strategies (single-gene assays like PCR, smaller gene panels), tissue-based testing	MPS (FoundationOne Liquid CDx, Guardant360 CDx, Follow It). Large gene panels (38 to over 500 genes) and assessment of global genomic changes	Somatic genomic alterations in tumour DNA. DNA can be from tissue biopsy (solid tumour) or from circulating tumour DNA (ctDNA) in plasma sample (liquid biopsy)
MSAC, 2022 [71]	Oncology (pulmonary oncology)	**Non-squamous non-small cell lung cancer** for biomarker testing to determine suitability for targeted treatments	**Replacement:** Small gene panels positioned to replace sequential single-gene testing	**Comparator:** Sequential single-gene testing	Small MPS panels	Several biomarkers; most common include: EGFR, ALK, ROS1, and MET genes
HQO, 2024 [72]	Oncology (pulmonary oncology)	Identification of actionable genomic alterations to guide targeted therapy decisions for patients with **Non-Small Cell Lung Cancer**	**Add-on:** Liquid biopsy (plasma-based CGP) to standard pathway of tissue testing. Strategies: liquid biopsy when tissue insufficient, or tissue-first, liquid-first, or combined approaches	**Comparator:** Current standard of care in Ontario: tumour testing using DNA and RNA panels from tissue biopsy samples alone	MPS (not further specified). Large targeted DNA panels. Examples include FoundationOne (300+ genes), Guardant360 (74 genes), and Tempus xF (105 genes)	Somatic genomic alterations in cell-free tumour DNA from plasma (liquid biopsy). Assesses detection of variants in genes including BRAF, EGFR, ERBB2, KRAS, ALK, PIK3CA, MET, RET, and ROS1
NIPH, 2022 [73]	Oncology (senology)	PIK3CA mutations in HR+/HER2- advanced or **metastatic breast cancer** progressed during endocrine treatment	**Add-on:** Guide treatment decisions for PI3K inhibitor eligibility (e.g. Alpelisib)	**Comparator:** Different molecular tests for head-to-head comparisons (Sanger sequencing, PCR, NGS, Liquid Chip Technology)	Various molecular tests; NGS products: FoundationOne CDx, FoundationOne Liquid CDx, InVisionSeq, Oncomine, Access Array	Somatic PIK3CA mutations in tumour-derived DNA (from FFPE tissue or plasma ctDNA)
NICE, 2024 [74]	Oncology (senologic oncology)	ER-positive, HER2-negative, **early breast cancer** (stages 1 or 2) with 0 to 3 positive lymph nodes	**Add-on:** Post-surgery (adjuvant setting). Refine risk stratification and aid adjuvant chemotherapy decision-making	**Comparator:** Decision making for adjuvant chemotherapy without tumour profiling tests based on clinical and pathological features	Product names: Oncotype DX, Prosigna, EndoPredict, IHC4, Mammaprint. No further technology details reported	Various
HIQA, 2024 [75]	Oncology (senologic oncology)	Hormone receptor-positive (HR+), HER2-negative, early-stage (I-IIIa) **invasive breast cancer**	**Add-on:** Post-surgery (adjuvant setting). Refine risk stratification and aid adjuvant chemotherapy decision-making	**Comparator:** Decision making with genetic profiling using Oncotype DX	Various. Product names: EndoPredict, MammaPrint, and Prosigna.	Various
HTW, 2022 [76]	Oncology (urologic oncology)	To inform management decisions for men with **prostate cancer**, particularly newly diagnosed, low- or intermediate-risk localised disease	**Add-on:** Genomic tests are used to risk-stratify patients and guide decisions between active surveillance and immediate treatment. Analysis generates a genomic score predictive of tumour aggressiveness, risk of adverse pathology, metastasis, or cancer-specific mortality.	**Comparator:** Standard care without genomic testing	Gene expression panels (Prolaris, Oncotype DX, Decipher). These tests may use MPS or non-MPS (such as specific forms of PCR)	Gene expression levels (RNA) from prostate cancer tissue (biopsy).

Abbreviations: CPG … Comprehensive Genomic Profiling; ctDNA … Circulating Tumour DNA; DLBCL … Diffuse Large B-Cell Lymphoma; DNA … Deoxyribonucleic Acid; FFPE … Formalin-Fixed, Paraffin-Embedded; FISH … Fluorescence In Situ Hybridisation; IHC … Immunohistochemistry; LOH … Loss of Heterozygosity; MPS … massively parallel sequencing; MSI … Microsatellite Instability; NGS … next generation sequencing; RNA … Ribonucleic Acid; RT-PCR … Reverse Transcription Polymerase Chain Reaction; TKI … Tyrosine Kinase Inhibitor; WES … whole exome sequencing; WGS … whole genome sequencing

Table A-5: List of HTA reports with applied prioritisation criteria

HTA Report (Inst., Year [REF])	Medical Specialty	Clinical Indications	R Score	CA Score	V Score	Final Score
MSAC, 2021 [31]	Clinical Microbiology	Antimicrobial drug susceptibility testing for tuberculosis patients with confirmed *Mycobacterium tuberculosis*	3	3	2	11
Cochrane, 2020 [49]	Reproductive Medicine	Aneuploidy screening in women undergoing In-Vitro-Fertilisation (IVF) treatment	3	3	2	11
KCE, 2023 [56]	Primary Care	Broad; patients initiating drugs with known actionable gene-drug interactions	3	2	3	10
Cochrane, 2025 [62]	Oncology (general)	Advanced/refractory solid or haematological cancers progressed on ≥1 line of standard systemic therapy	2	3	3	11
HIQA, 2023 [45]	Neonatology	Universal screening of asymptomatic newborns for SCID and T-cell lymphopenias	2	3	3	11
CADTH, 2021 [47]	Obstetrics	Preconception or prenatal carrier screening for inherited conditions	1	3	3	10
HQO, 2023 [48]	Obstetrics	Preconception or prenatal carrier screening for specific inherited conditions	2	3	3	11
HTW, 2023 [55]	Primary Care	Pre-emptive pharmacogenetic (PGx) testing using a multiple gene panel	2	3	3	11
CADTH, 2023 [57]	Psychiatry	An Overview of Pharmacogenomic Testing for Psychiatric Disorders	2	2	3	9
CADTH, 2020 [58] and CADTH, 2022 (Update) [59]	Psychiatry	Pharmacogenomic Testing in Depression	2	2	3	9
HQO, 2021 [60]	Psychiatry	Multi-gene pharmacogenomic testing to guide medication selection for people with major depression	2	3	3	11
NIPH, 2022 [61]	Oncology (general)	NTRK gene fusions in locally advanced or metastatic solid tumours	2	3	3	11
CADTH, 2022 [70]	Oncology (pulmonary oncology)	Comprehensive Genomic Profiling Technologies to Inform Cancer Care	2	3	3	11
HQO, 2024 [72]	Oncology (pulmonary oncology)	Plasma-based Comprehensive Genomic Profiling (CGP) Assay for advanced NSCLC	2	2	3	9
NIPH, 2022 [73]	Oncology (senology)	PIK3CA mutations in HR+/HER2- advanced or metastatic breast cancer	2	3	3	11
Cochrane, 2025 [37]	Neonatology	Diagnosis of neonatal bacterial and fungal sepsis	2	3	2	10
HIQA, 2023 [46]	Neonatology	Universal screening of asymptomatic newborns for Spinal Muscular Atrophy (SMA)	1	3	3	10
SHTG, 2024 [50]	Neurology	Genotype testing to guide clopidogrel use after ischaemic stroke or TIA	1	3	3	10
NICE, 2024 [51]	Neurology	CYP2C19 genotype testing to guide clopidogrel use after ischaemic stroke or TIA	1	3	3	10
NIHR, 2024 [52]	Neurology	Clinical and cost-effectiveness of clopidogrel resistance genotype testing	1	2	3	8
SHTG, 2020 [53]	Oncology	Pre-treatment DPYD genetic testing for patients prescribed fluoropyrimidine-based chemotherapy	1	3	3	10
HQO, 2021[54]	Oncology	DPYD genotyping in patients with cancer treated with fluoropyrimidines	1	3	3	10
HQO, 2020 [69]	Oncology (pulmonary oncology)	Cell-Free Circulating Tumour DNA Blood Testing to Detect EGFR T790M Mutation in NSCLC	1	2	3	8
MSAC, 2022 [71]	Oncology (pulmonary oncology)	Non-squamous non-small cell lung cancer for biomarker testing	1	2	3	8
TASK, 2020 [40]	Pediatric Cardiology	Microcosting of whole genome sequencing (WGS) of trios in heterogeneous pediatric cardiac population	3	3	2	11
Washington State HTA, 2024 [42]	Various	Whole Genome Sequencing: Final Evidence Report (suspected genetic disorder)	3	2	2	9

HTA Report (Inst., Year [REF])	Medical Specialty	Clinical Indications	R Score	CA Score	V Score	Final Score
AIHTA, 2020 [28]	Cardiology	Genetic testing in the context of familial hypercholesterolaemia management	3	3	3	12
Cochrane, 2021 [32]	Cardiology	Strategies for screening for familial hypercholesterolaemia in primary care	2	2	3	9
HQO, 2022 [33]	Cardiology	Genetic testing for familial hypercholesterolemia	2	2	3	9
AIHTA, 2022 [34]	Gynaecology	Non-invasive prenatal screening for fetal anomalies (Trisomies 21, 18, 13)	2	2	3	9
TASK, 2025 [36]	Medical Genetics	A Micro-costing and Cost Consequence Analysis (WGS vs. WES for genetic diagnosis)	3	2	1	8
HQO, 2020 [38]	Paediatrics	Genome-Wide Sequencing for Unexplained Developmental Disabilities or Multiple Congenital Anomalies	3	3	3	12
IQWIG, 2024 [39]	Paediatric Cardiology	Screening zur Früherkennung einer familiären Hypercholesterinämie bei Kindern und Jugendlichen	2	3	3	11
MSAC, 2022 [41]	Pediatric Otolaryngology	Hearing impairment in children (<18 years) with moderate to severe hearing loss	3	2	3	10
HTW, 2020 [43]	Cardiology	Genetic risk prediction for onset of cardiovascular disease and recurrence of cardiovascular events	2	2	3	9
MSAC, 2020 [29]	Cardiology	Inheritable cardiac arrhythmias	2	2	2	8
MSAC, 2021 [30]	Cardiology	Heritable cardiomyopathies	2	2	2	8
MSAC, 2023 [35]	Medical Genetics	Mitochondrial disease in patients with suspected acute or chronic disease	3	2	1	9
NICE, 2020 [63]	Oncology (gynecologic oncology)	Testing strategies for Lynch syndrome in people with endometrial cancer	2	3	3	11
NICE, 2021 [64]	Oncology (hematologic oncology)	clonoSEQ for minimal residual disease assessment in multiple myeloma, ALL, CLL	1	2	2	7
NICE, 2021 [65]	Oncology (hematologic oncology)	MMprofiler for prognostic risk classification in multiple myeloma	2	2	2	8
HTW, 2021 [66]	Oncology (hematologic oncology)	Next generation sequencing for DLBCL classification	2	2	2	8
NICE, 2024 [74]	Oncology (senologic oncology)	Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer	2	2	3	9
HIQA, 2024 [75]	Oncology (senologic oncology)	Gene expression profiling tests for guiding the use of adjuvant chemotherapy in early stage invasive breast cancer	2	2	3	9
HTW, 2022 [76]	Oncology (urologic oncology)	Genetic testing for prostate cancer care	2	2	3	9
Cochrane, 2021 [67]	Oncology (neuro-oncology)	Prognostic value of test(s) for O6-methylguanine–DNA methyltransferase (MGMT) promoter methylation	2	2	2	8
Cochrane, 2022 [68]	Oncology (neuro-oncology)	Diagnostic test accuracy and cost-effectiveness of tests for codeletion of chromosomal arms 1p and 19q in people with glioma	1	2	1	6

Abbreviations: C … Clinical Actionability; R … Resource Intensity; V … Indication Volume·Final Score: A higher score indicates a higher priority for in-depth HTA evaluation.

Literature search strategies

Search strategy for Cochrane

Search date: 21.05.2025	
ID	Search
1	MeSH descriptor: [Sequence Analysis] explode all trees
2	(sequence* NEXT anal*):ti,ab,kw
3	MeSH descriptor: [Genetic Testing] explode all trees
4	(gen* NEXT (test* OR carrier*)):ti,ab,kw
5	("Massive parallel sequencing") (Word variations have been searched)
6	("Next generation sequencing") (Word variations have been searched)
7	(NGS):ti,ab,kw
8	("Third generation sequencing") (Word variations have been searched)
9	("Whole genome sequencing") (Word variations have been searched)
10	("Exome sequencing") (Word variations have been searched)
11	(RNA-Seq*):ti,ab,kw
12	(Pharmacogenetic*) (Word variations have been searched)
13	(Pharmacogenomic*) (Word variations have been searched)
14	("Gene panel") (Word variations have been searched)
15	("High-throughput sequencing") (Word variations have been searched)
16	("Noninvasive prenatal testing") (Word variations have been searched)
17	("Non-invasive prenatal testing") (Word variations have been searched)
18	#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
19	#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 in Cochrane Reviews, Cochrane Protocols
Total hits: 77	

Search strategy for HTA-INAHTA

Search date: 21.05.2025		
No.	Search query	Results
#15	(NGS) OR ("Non-invasive prenatal testing") OR ("Noninvasive prenatal testing") OR (High-throughput sequencing) OR (Pharmacogenomics) OR (Pharmacogenetics) OR ("Whole exome sequencing") OR ("Whole genome sequencing") OR ("Third generation sequencing") OR ("Next generation sequencing") OR ("Massively parallel sequencing") OR ("Massive parallel sequencing") OR ("Genetic Testing"[mhe]) OR ("Sequence Analysis"[mhe])	276
#14	NGS	44
#13	"Non-invasive prenatal testing"	5
#12	"Noninvasive prenatal testing"	6
#11	High-throughput sequencing	10
#10	Pharmacogenomics	15
#9	Pharmacogenetics	6
#8	"Whole exome sequencing"	12
#7	"Whole genome sequencing"	10
#6	"Third generation sequencing"	0
#5	"Next generation sequencing"	41
#4	"Massively parallel sequencing"	3
#3	"Massive parallel sequencing"	2
#2	"Genetic Testing"[mhe]	169
#1	"Sequence Analysis"[mhe]	105
Total hits: 276		

List of Agencies consulted for manual search

Name of Agency	Country
Agenas– The Agency for Regional Healthcare	Italy
AIHTA– Austrian Institute for Health Technology Assessment	Austria
AOTMiT – Agency for Health Technology Assessment and Tariff System	Poland
AVALIA-T – Galician Agency for Health Technology Assessment	Spain
CDA-AMC – Canada's Drug Agency (L'Agence des médicaments du Canada)	Canada
HAS – Haute Autorité de santé	France
HIQA – Health Information and Quality Authority	Ireland
HTW – Health Technology Wales	United Kingdom
IQWiG – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE – Belgian Health Care Knowledge Centre	Belgium
NICE – National Institute for Health and Care Excellence	United Kingdom
NIPH – Norwegian Institute of Public Health	Norway
SBU – Swedish Agency for Health Technology Assessment and Assessment of Social Services	Sweden
ZIN – Zorginstituut Nederland (National Health Care Institute)	Netherlands

The search terms used were:

- Massive parallel sequencing; Massively parallel sequencing; Next generation sequencing; Third generation sequencing; Pharmacogenetic; Pharmacogenomic; Whole exome sequencing; Whole genome sequencing; Noninvasive prenatal testing; High-throughput sequencing.
- Additional German search terms were Gentest; Massiv parallele Sequenzierung; Hochdurchsatz-Sequenzierung; Pharmakogenetik; Pharmakogenomik; Exomsequenzierung; Genomsequenzierung; Genpaneldiagnostik; Nichtinvasive Pränataldiagnostik.
- Optional search terms were Gene panel; Genetic testing; Genetic; Genomic; Sequencing. Excluded search terms were MPS; Genome; WES; WGS; NIPT; DNA.

In total, 402 potentially relevant references were identified through the structured hand search on HTA website, with 8 additional relevant references identified through additional hand search on Google and reference list searches. From these 410 references, 17 were selected and included for the analysis of the first research question.

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