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Federal Department of Home Affairs
Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
Section Health Technology Assessment

Supplemental Document

Short Report

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Technology	Thyroid dysfunction testing
Type of Technology	Laboratory analyses
Date	31 August 2022

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Executive Summary

Thyroid function tests are used for diagnosis and to monitor treatment of thyroid disorders. Since thyroid dysfunction affects many body systems, there is a wide range of possible indications for testing. This short report presents the methodology and results of a grey literature search to answer the question which populations should be targeted for thyroid dysfunction testing according to professional societies and guidelines.

A predefined list of 15 websites was searched with English and/or German search terms for grey literature documents (i.e. clinical guidelines, guidances, HTA reports, and white papers) on thyroid dysfunction published from 2000 onwards in Western countries. In total, 25 documents were selected to be screened in full-text and after applying the inclusion and exclusion criteria, three documents were included.

The American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) published an evidence-based guideline in 2012 and an evidence-based white paper in 2016 including a detailed list with diseases (e.g. diabetes mellitus type 1), symptoms (e.g. malaise and fatigue), medical history (e.g. history of thyroid dysfunction), and specific medication (e.g. lithium) as indications for thyroid dysfunction aggressive case finding. In 2019, the National Institute for Health and Care Excellence (NICE) published an evidence-based guideline with a short list of recommendations on who should be tested for thyroid disease: persons with diabetes mellitus type 1, depression or unexplained anxiety, and new onset atrial fibrillation. Furthermore, NICE reported two specific contraindications for thyroid dysfunction testing: do not test for thyroid dysfunction during an acute illness unless it is suspected that the acute illness is due to thyroid dysfunction, because the acute illness may affect the test results, and do not offer testing for thyroid dysfunction solely, because a person has diabetes mellitus type 2.

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Abbreviations and acronyms

AACE	American Association of Clinical Endocrinologists
AGREE	Appraisal of Guidelines for Research & Evaluation instrument
AHRQ	Agency for Healthcare Research and Quality
ATA	American Thyroid Association
ATF	Australian Thyroid Foundation
ESA	Endocrine Society of Australia
ESE	European Society of Endocrinology
ETA	European Thyroid Association
EUnetHTA	European Network for Health Technology Assessment
FOPH	Federal Office of Public health
fT3	Free triiodothyronine
fT4	Free thyroxine
GIN	Guidelines International Network
HTA	Health Technology Assessment
ICD	International Classification of Diseases and Related Health Problems
INAHTA	International Network of Agencies for Health Technology Assessment
NGC	National Guideline Centre
NICE	National Institute for Health and Care Excellence
PICO	Population, Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-analyses
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid stimulating hormone
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation
WHO - EU	World Health Organisation - Regional Office for Europe

1 Medical background and context

Thyroid function tests are used for diagnosis and to monitor treatment of thyroid disorders. A thyroid function test quantifies thyroid stimulating hormone (TSH) and the circulating thyroid hormones in serum, to assess the ability of the thyroid gland to produce and regulate thyroid hormone production.[1 2] Thyroid dysfunction can be classified as hypothyroidism or hyperthyroidism. Hypothyroidism develops from impaired thyroid hormone production (i.e. thyroxine (T4) or triiodothyronine (T3)) resulting in elevated levels of TSH; hyperthyroidism results from an overproduction of thyroid hormone, leading to decreased TSH levels.[3] Hypothyroidism is caused by autoimmune disorders, such as Hashimoto thyroiditis, or occurs as a sequela of hyperthyroidism treatment or after thyreoidectomy.[3] Causes of hyperthyroidism include Graves' disease, toxic multinodular goitre, and toxic adenoma.[3] Rarely, TSH levels do not correlate inversely with the (f)T3 and (f)T4 levels, for example in central hypothyroidism or syndromes of resistance to thyroid hormone. This short report does explicitly not apply to patients with a suspicion of certain rare disorders, such as pituitary disease or genetic syndromes of hormone resistance. When TSH levels are not within the reference range, but concentrations of free thyroxine (fT4) and free triiodothyronine (fT3) are within the reference range, this is referred to as subclinical thyroid dysfunction.[4]

Thyroid dysfunction affects many body systems, the symptoms are often non-specific, and most single symptoms alone are not predictive of thyroid dysfunction.[1 2] Therefore, there is a wide range of possible indications for testing.[2] Thyroid function tests have a high sensitivity and specificity therefore these tests are amongst the most widely requested blood tests and are the firstline investigation when a thyroid disorder is suspected.[1] Although symptoms and indications may vary widely between subjects with suspected thyroid disorders, professional societies have tried to define the indications for suspected thyroid disorder.

A health technology assessment (HTA) has been started to evaluate the available clinical and economic evidence associated with the one-step and the two-step test approaches in adults with suspected primary or secondary thyroid dysfunction. During the preparation of this HTA another research question came forward regarding which populations should be tested for thyroid dysfunction according to professional societies and guidelines. This type of information is rather found in the grey literature than in the peer-reviewed databases. In this short report, the methodology and results of a grey literature search are outlined on this additional question which populations should be tested for thyroid dysfunction according to professional societies and guidelines. Screening (i.e. presumptive identification of unrecognised disease with tests in people who do not have the symptoms of the disease and can identify a predisease abnormality or early disease[8]) is out of scope.

2 Research question

Which populations should be targeted for thyroid dysfunction testing according to professional societies and guidelines?

3 Population, Intervention, Comparator, Outcome (PICO)

The PICO framework was used to further specify the research question and facilitate the grey literature search; PICO is an acronym for Population, Intervention, Comparator, and Outcome.

Table 1. PICO

P:	Adults with a clinical suspicion of thyroid dysfunction
I:	Test for thyroid dysfunction
C:	Not applicable
O:	Clear description with sufficient detail which populations should be tested for thyroid dysfunction according to professional societies and guidelines

4 Methodology grey literature search

Peer-reviewed literature reports on primary research and is systematically indexed by major databases. Reports that are not considered primary research are typically documented in grey literature, such as guidelines, guidances, or policy reports. Compared to peer-reviewed literature, grey literature is less systematically included in databases.[5]

To answer the research question which populations should be tested for thyroid dysfunction according to professional societies and guidelines, we searched for clinical guidelines/guidances/HTA reports/white papers on thyroid dysfunction from Western countries in multiple data sources with a structured approach. This approach included the following steps:

- Search strategy for a pre-defined list of websites
- Selection process
- Critical appraisal
- Data extraction
- Data synthesis
- Quality control

4.1 Search strategy

Standard international sources for guidelines, HTAs, and grey literature databases formed the basis for the grey literature search. Guidelines published in the peer-reviewed literature were searched in the database PubMed (MEDLINE). In addition, topic-specific websites of thyroid or endocrinology associations/societies were found with a preliminary Google search. These websites were screened if they contained clinical guidelines/guidances/HTA reports/white papers on thyroid dysfunction, were discussed with the FOPH, and when relevant were added to a predefined list of websites to be searched in further detail. To avoid overlap between the PubMed (MEDLINE) search for guidelines and the Google Scholar search, we only searched on Google Scholar with English search terms for white papers and conducted a more extensive search with German search terms.

The predefined list contained the following sources and was searched for grey literature documents published from 2000 onwards in Western countries, with English search terms (thyroid/hypothyroidism/hyperthyroidism) and/or German search terms (Schilddrüse/Hypothyreose/Hyperthyreose):

- Agency for Healthcare Research and Quality (AHRQ)
- Guidelines International Network (GIN)
- National Institute for Health and Care Excellence (NICE)
- World Health Organisation (WHO) / WHO – EU
- Open grey
- International Network of Agencies for Health Technology Assessment (INAHTA)
- European Network for Health Technology Assessment (EUnetHTA)
- American Thyroid Association (ATA)
- American Association of Clinical Endocrinologists (AACE)
- Australian Thyroid Foundation (ATF)
- Endocrine Society of Australia (ESA)
- European Thyroid Association (ETA)
- European Society of Endocrinology (ESE)
- Google Scholar
- Guideline search on PubMed (MEDLINE), including a reference check of the selected articles

The weblinks and search term details used on each website are enclosed in Table I (Appendix). Since no guidelines were found with the search on Swiss websites of thyroid or endocrinology associations/societies, these were not added to the predefined list of websites.

4.2 Selection process

On the predefined list of websites mentioned above we searched for documents that could potentially answer the research question. Documents were included if the reported information was relevant and of sufficient quality. The process of selection and inclusion and exclusion of the documents was registered in Excel and documented in a PRISMA flow diagram and a table with the reasons for exclusion for the excluded documents.

4.2.1 Inclusion and exclusion criteria

Table 2. Inclusion and exclusion criteria for the grey literature search

	Inclusion	**Exclusion**
Period publication	2000-2021	<2000
Language of publication	English, German	All other languages
Geographical area	Western countries*	All other countries
Type of document	• Clinical guideline/guidance • HTA report • White paper	• Peer reviewed literature (i.e. reviews or original studies) • Non-pertinent publication types (e.g. letter to editor, editorial, comment, erratum) • Study protocol • Congress abstract
Document quality	Grey literature documents with a methods section and/or overview of the sources/references	Documents without a clear source/reference for the relevant information
Population	• Non-specific adult population with a clinical suspicion of thyroid dysfunction (i.e. a broad general population)	• Children • Adults with a diagnosis of thyroid dysfunction • Specific populations, e.g. pregnant women only
Intervention	• Test for thyroid dysfunction	• All other interventions • Screening (i.e. presumptive identification of unrecognised disease with tests in people who do not have the symptoms of the disease and can identify a pre-disease abnormality or early disease[8]) • Monitoring of thyroid dysfunction or treatment
Comparison	Not applicable	Not applicable
Outcomes	Clear description with sufficient detail which populations should be tested for thyroid dysfunction	All other outcomes

* Austria, Australia, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom, United States of America (reference: https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/WESP2019_BOOK-web.pdf)

4.3 Assessment of quality of evidence

Only grey literature documents with clearly-stated methods for compiling data and/or with clear data sources/references were included. The included documents were critically appraised with a selection of criteria derived from the AGREE (Appraisal of Guidelines for Research & Evaluation) instrument[6]:

- The overall objective(s) of the guideline is (are) specifically described;
- Systematic methods were used to search for evidence, and/or data sources/references were given;
- The recommendations are specific and unambiguous.

We applied a 5-point rating scale to score each of these three criteria: - - (very low quality), - (low quality), +- (acceptable quality), + (good quality), ++ (high quality).

The documents were classified as:

- Evidence-based: largely based on the scientific literature. Good clinical practices or expert opinions could be used to supplement the scientific literature; or
- Practice-based: reflecting expert opinion or information derived from good clinical practices; some literature references (not systematic) possibly included.

4.4 Data extraction and synthesis

Relevant data from the included documents found in the grey literature was extracted in an Excel file and further summarised in a summary table in Word. The indications for thyroid dysfunction testing were mainly categorised based on the main disease classifications of the International Classification of Diseases and Related Health Problems (ICD-10).

4.5 Quality control

The following quality control measures were applied:

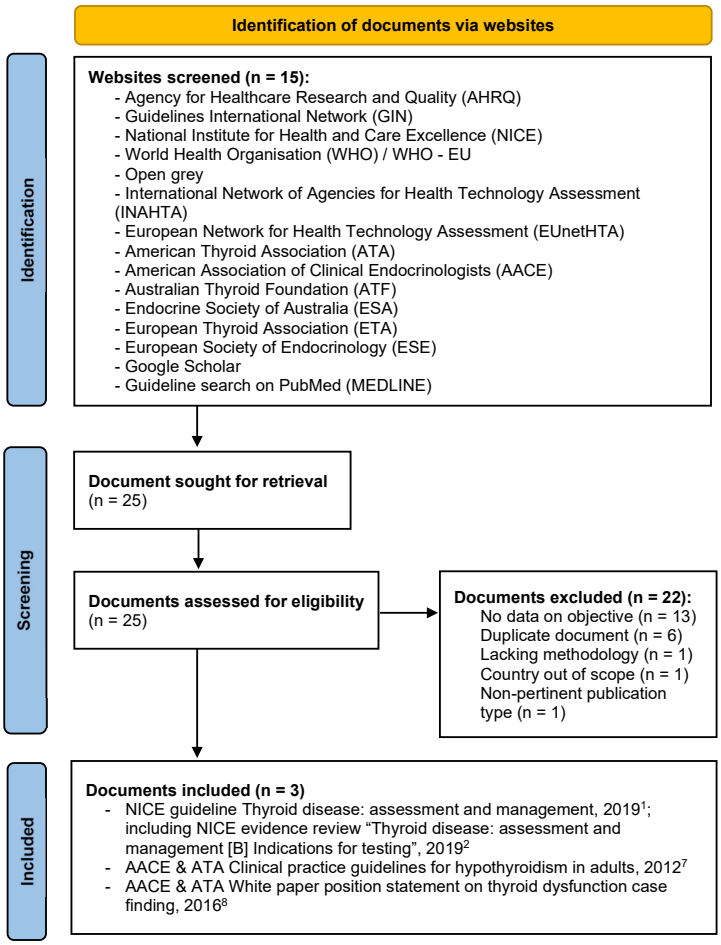
- The search strategies were checked by a second researcher.
- The selection was conducted by one researcher in close consultation with a second researcher. Any doubt documents were assessed in full-text. A random sample of the excluded documents was checked by a second researcher.
- Critical appraisal of the documents was performed by one researcher and reviewed by a second researcher.
- The data extraction tables and summary tables were fully reviewed by a second researcher.

5 Results grey literature search

5.1 PRISMA flow diagram

In total, 15 websites were screened to search for guidelines/guidances/HTA reports/white papers on thyroid dysfunction and 25 documents were selected to be screened in full-text. After applying the inclusion and exclusion criteria, three documents were included. The reasons for exclusion were: no data on objective (n = 13), duplicate document (n = 6), lacking methodology (i.e. no methodology nor references provided; n = 1), country out of scope (i.e. Latin America; n = 1), and non-pertinent publication type (i.e. erratum; n = 1). A complete overview of the selection process is given in the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) flow diagram (***Figure 1***); details of the number of selected and included documents per website is shown in Table I (Appendix). An overview of the reasons for exclusion per excluded document is enclosed in Table II (Appendix).

Figure 1. PRISMA flow chart grey literature search



5.2 Study characteristics and quality assessment

Three documents were included with our grey literature search (Table 3). The oldest document included is a paper published in 2012 with evidence-based guidelines of the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) for the clinical management of primary hypothyroidism.[7] In this guideline recommendations were formulated on whom to target with aggressive case finding for hypothyroidism. The evidence base of this guideline was a systematic review, however no details of the methodology and results were reported. The references for the recommendations were provided. In 2016, the AACE and ATA published an evidence-based white paper further elaborating on thyroid dysfunction aggressive case finding.[8] The methodology of the data source was not reported, but references for the indications for thyroid dysfunction testing were provided. The most recent evidence-based guideline covering the assessment of suspected thyroid disease was published in 2019.[1] Based on a systematic review including eight cross-sectional studies[2], the National Institute for Health and Care Excellence (NICE) formulated recommendations on who should be tested for thyroid disease.

Table 3. Study characteristics and quality assessment of included documents

Reference	Year	Organisation, country	Type of document	General scope	Data source for objective of interest	Quality assessment (based on 3 AGREE questions)		
				Objective of interest		Overall objective of the guideline is specifically described	Systematic methods were used to search for evidence and/or references were given	Recommendations are specific and unambiguous
Garber[7]	2012	AACE & ATA, USA	Evidence-based guideline	Clinical management of primary hypothyroidism in ambulatory patients	Systematic review (details of the methodology & results not reported; references provided for the recommendations)	++	+-	++
				Aggressive case finding for hypothyroidism: whom to target?				
Hennessey[8]	2016	AACE & ATA, USA	Evidence-based white paper with position statement	Difference between screening and aggressive case finding of thyroid dysfunction	Not reported (details of the methodology & results not reported; references provided for the indications)	++	-	++
				Thyroid dysfunction aggressive case finding				
UK NGC[1]	2019	NICE, UK	Evidence-based guideline	Assessment of suspected thyroid disease and managing primary thyroid disease	Systematic review[2] (including 8 cross-sectional studies)	++	++	++
				Indications for testing: who should be tested for thyroid disease?				

Keys: AACE = American Association of Clinical Endocrinologists, AGREE = Appraisal of Guidelines for Research & Evaluation instrument, ATA = American Thyroid Association, NGC = National Guideline Centre, NICE = National Institute for Health and Care Excellence, UK = United Kingdom, USA = United States of America

5.3 Findings grey literature search

5.3.1 Indications for thyroid dysfunction testing

Indications for thyroid dysfunction testing as reported in the three included documents are outlined in ***Table 4***. The indications are categorised based on the ICD-10 classification, as applied in the AACE and ATA documents, and two additional categories for medication and 'other categories'.

Table 4. Indications for thyroid dysfunction testing reported in the three included documents

	AACE & ATA guideline, 2012[7]	**AACE & ATA position paper, 2016**[8]	**NICE guideline, 2019**[1]
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism*			
Anaemia	- Anaemia, unspecified deficiency - Pernicious anaemia	- Common forms of anaemia - Anaemia, unspecified deficiency - Pernicious anaemia - Beta-thalassemia major - Fanconi anaemia - Anaemia in elderly patients - Anaemia following allogenic hematopoietic stem cell transplantation	*NR*
Endocrine, nutritional, and metabolic diseases*			
Diabetes mellitus	- Diabetes mellitus type 1	- Diabetes mellitus type 1	- Diabetes mellitus type 1
Disorders of other endocrine glands	- Adrenal insufficiency	- Adrenal insufficiency - Hyperprolactinemia - Polyglandular autoimmune syndrome	*NR*
Metabolic disorders	- Hypercholesterolemia - Mixed hyperlipidaemia	- Hypercholesterolemia - Mixed hyperlipidaemia	*NR*
Medical history of:	- Neck irradiation - ^{131}I treatment - Thyroid surgery - External beam radiotherapy for head and neck malignancies	- Neck irradiation - ^{131}I treatment - Thyroid surgery	*NR*
Mental and behavioural disorders*			
Psychiatric disorder	- Psychiatric disorder	- Psychiatric disorder	*NR*
Dementia	- Dementia	- Dementia	*NR*
Mental & behavioural disorders	*NR*	- Anxiety state	- Depression - Unexplained anxiety
Diseases of the nervous system*			
Myopathy	- Myopathy, unspecified	- Myopathy, unspecified	*NR*
Diseases of the eye and adnexa*			
Exophthalmos	*NR*	- Exophthalmos	*NR*
Diseases of the circulatory system*			
Rheumatic fever	*NR*	- Rheumatic fever	*NR*
Hypertension	- Hypertension	- Hypertension	*NR*
Pulmonary hypertension	*NR*	- Pulmonary hypertension	*NR*
Other forms of heart disease	- Cardiac dysrhythmia, unspecified - Congestive heart failure	- Cardiovascular health - Atrial fibrillation - Cardiac dysrhythmia, unspecified	- New onset atrial fibrillation

	- Prolonged QT interval	- Congestive heart failure - Heart failure - Prolonged QT interval	
Diseases of the digestive system*			
Diseases of intestines or digestive system	- Constipation	- Constipation - Celiac	*NR*
Diseases of the skin and subcutaneous tissue*			
Disorders of skin appendages of disorder of the skin and subcutaneous tissue	- Alopecia - Vitiligo	- Alopecia - Vitiligo	*NR*
Diseases of the musculoskeletal system and connective tissue*			
Arthropathies	*NR*	- Paediatric arthritis - Rheumatoid arthritis	*NR*
Systemic connective tissue disorders	*NR*	- Sicca syndrome [Sjögren] - Systemic lupus erythematosus	*NR*
Osteoporosis	*NR*	- Osteoporosis	*NR*
Diseases of the genitourinary system*			
Noninflammatory disorders of female genital tract	- Dysmenorrhea	- Dysmenorrhea	*NR*
Congenital malformations, deformations, and chromosomal abnormalities*			
Chromosomal abnormalities	*NR*	- Down syndrome - Turner syndrome	*NR*
Symptoms, signs, and abnormal clinical and laboratory findings*			
Abnormalities of heartbeat	*NR*	- Tachycardia	*NR*
Symptoms & signs involving the skin and subcutaneous tissue	- Change in skin texture	- Change in skin texture	*NR*
Symptoms & signs involving the digestive system and abdomen	*NR*	- Hyperdefecation	*NR*
Symptoms and signs involving cognition, perception, emotional state and behaviour	*NR*	- Nervousness	*NR*
General symptoms & signs	- Malaise and fatigue - Weight gain	- Hyperhydrosis - Sweating (excessive) - Malaise and fatigue - Weight gain - Weight loss	*NR*
Abnormal results of thyroid function studies	- Abnormal thyroid examination	- Abnormal thyroid examination	*NR*
Medication†			
Use of the following medication:	- Amiodarone - Lithium	- Amiodarone - Ketoconazole‡ - Lithium - Interferon-alpha - Interleukin-2 - Tyrosine kinase inhibitors	*NR*
Other categories†			
Autoimmune disease	- Those with autoimmune disease	- Those with autoimmune diseases (examples as provided in the paper are included in this table)	- Those with autoimmune diseases
History of thyroid dysfunction	- History of thyroid dysfunction	- History of thyroid dysfunction	*NR*
Non-autoimmune hypothyroidism	- Non-autoimmune primary and central hypothyroidism	- Non-autoimmune primary and central hypothyroidism	*NR*
Relatives with autoimmune thyroid disease	- First-degree relatives with autoimmune thyroid disease	- First-degree relatives with autoimmune thyroid disease	*NR*

Planning pregnancy	- Women who are planning pregnancy	*NR*	*NR*

Keys: AACE = American Association of Clinical Endocrinologists, ATA = American Thyroid Association, NICE = National Institute for Health and Care Excellence, NR = not reported. * Headings based on the ICD-10; † Other headings, based on the input; ‡ Controversial association.

5.3.2 Contraindications for thyroid dysfunction testing

Besides the indications outlined in the prior section, also two specific contraindications for thyroid dysfunction testing were reported:

- Do not test for thyroid dysfunction during an acute illness unless it is suspected that the acute illness is due to thyroid dysfunction, because the acute illness may affect the test results.[1]
- Do not offer testing for thyroid dysfunction solely, because a person has diabetes mellitus type 2.[1]

5.3.3 Other considerations

In the included documents the following general considerations were highlighted with respect to thyroid function testing:

- Thyroid dysfunction affects many systems in the body and the symptoms are often non-specific. Most single common symptoms alone are not predictive of thyroid dysfunction. The decision to test should be based on an overall clinical suspicion, taking into account the nature and severity of symptoms, clinical signs, and coexisting conditions.[1]
- Thyroid dysfunction should be frequently considered as a potential aetiology for many of the non-specific complaints that physicians face daily. The application and success of safe and effective interventions are dependent on an accurate diagnosis.[8]
- Consider tests for thyroid dysfunction if there is a clinical suspicion of thyroid disease, but bear in mind that one symptom alone may not be indicative of thyroid disease.[1]
- Be aware that in menopausal women (i.e. this includes women in perimenopause and post menopause), symptoms of thyroid dysfunction may be mistaken for menopause (e.g. weight gain). [1]
- It is important to be aware that medical conditions (e.g. thyroiditis), drugs (e.g. proton pump inhibitors), and other substances (e.g. multivitamins) might have direct and indirect effects on the thyroid status.[7] In the Appendix of this report an overview table (Table III) is enclosed with agents and conditions having an impact on L-thyroxine therapy and on the interpretation of thyroid tests.

6 Discussion

As the research question of this short report is not an HTA question, the HTA-inherent systematic data search and analysis methodology did not apply for this report. Instead, a grey literature search was conducted. The main data source used to answer the research question were clinical guidelines/guidances/white papers on thyroid dysfunction from Western countries and in addition we searched for HTAs. A limitation of grey literature is that documents are less systematically included in databases, which makes it more difficult to retrieve all relevant documents on a topic. To address this limitation we applied a structured approach as described in ***Chapter 4***.

Two American documents and one UK document were included. We did not find Swiss or European-level guidelines with data on which populations should be targeted for thyroid dysfunction testing. The indications listed in the American documents are more detailed in comparison with the NICE guideline, though all indications reported by NICE are covered by the AACE & ATA. Differences between the recommendations in medical guidelines are very common. These differences may reflect for example differences in the composition of the guideline panels that developed the guidelines, between the national financial structures covering healthcare costs, in methodologies applied to collect, analyse, and appraise evidence for the guideline, differences in consensus statements of experts, and cultural differences.

7 Conclusion

With a grey literature search on websites from 2000 onwards in Western countries, three documents were found on which populations should be targeted for thyroid dysfunction testing according to professional societies and guidelines. The American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) published an evidence-based guideline in 2012 and an evidence-based white paper in 2016 including a detailed list with diseases (e.g. diabetes mellitus type 1), symptoms (e.g. malaise and fatigue), medical history (e.g. history of thyroid dysfunction), and specific medication (e.g. lithium) as indications for thyroid dysfunction aggressive case finding. In 2019, the National Institute for Health and Care Excellence (NICE) published an evidence-based guideline with a short list of recommendations on who should be tested for thyroid disease: persons with diabetes mellitus type 1, depression or unexplained anxiety, and new onset atrial fibrillation. Furthermore, NICE reported two specific contraindications for thyroid dysfunction testing: do not test for thyroid dysfunction during an acute illness unless it is suspected that the acute illness is due to thyroid dysfunction, because the acute illness may affect the test results; and do not offer testing for thyroid dysfunction solely, because a person has diabetes mellitus type 2.

8 References

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9 Appendices

Table I. Grey literature search process

Data source	Website	Search date	Search terms	Number of hits	Number of selected documents	Number of included documents
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov	4 March 2021	Thyroid	775	2	0
			Hypothyroidism	416		
			Hyperthyroidism	133		
			Schilddrüse/Hypothyreose/Hyperthyreose	0		
Guidelines International Network (GIN)	https://www.g-i-n.net	4 March 2021	Thyroid	3	0	0
			Hypothyroidism	0		
			Hyperthyroidism	0		
			Schilddrüse/Hypothyreose/Hyperthyreose	0		
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk	4 March 2021	Thyroid	103	1	1
			Hypothyroidism	25		
			Hyperthyroidism	17		
			Schilddrüse/Hypothyreose/Hyperthyreose	0		
World Health Organisation (WHO) / WHO - EU	https://apps.who.int/iris	4 March 2021	(thyroid OR hypothyroidism OR hyperthyroidism); Date issued: [2000 TO 2021]; Language: English	1177 (first 500 hits screened)	1	0
			Schilddrüse OR Hypothyreose OR Hyperthyreose	12		
Open grey	http://www.opengrey.eu	4 March 2021	Thyroid	485	0	0
			Hypothyroidism	69		
			Hyperthyroidism	25		
			Schilddrüse/Hypothyreose/Hyperthyreose	4		

Data source	Website	Search date	Search terms	Number of hits	Number of selected documents	Number of included documents
International Network of Agencies for Health Technology Assessment (INAHTA)	https://database.inahta.org	5 March 2021	Thyroid	57	3	0
			Hypothyroidism	13		
			Hyperthyroidism	7		
			Schilddrüse/Hypothyreose/Hyperthyreose	0		
European Network for Health Technology Assessment (EUnetHTA)	https://www.eunethta.eu	5 March 2021	Thyroid	7	0	0
			Hypothyroidism	0		
			Hyperthyroidism	0		
			Schilddrüse/Hypothyreose/Hyperthyreose	0		
American Thyroid Association (ATA)	https://www.thyroid.org/professionals/ata-professional-guidelines	5 March 2021	Not applicable (i.e. all guidelines on the website were screened)	10	1	0
American Association of Clinical Endocrinologists (AACE)	https://pro.aace.com	9 March 2021	Thyroid	3	1	1
			Hypothyroidism	1		
			Hyperthyroidism	1		
Australian Thyroid Foundation (ATF)	https://thyroidfoundation.org.au	5 March 2021	Diagnos	27	0	0
			Test	26		
			Manage	12		
Endocrine Society of Australia (ESA)	https://www.endocrinesociety.org.au/position-statements.asp	5 March 2021	Not applicable (i.e. all position statements on the website were screened)	10	0	0
European Thyroid Association (ETA)	https://www.eurothyroid.com/guidelines/eta_guidelines.html	5 March 2021	Not applicable (i.e. all guidelines on the website were screened)	19	2	0

Data source	Website	Search date	Search terms	Number of hits	Number of selected documents	Number of included documents
European Society of Endocrinology (ESE)	https://www.ese-hormones.org/publications/guidelines	5 March 2021	Not applicable (i.e. all guidelines on the website were screened)	68	1	0
Google Scholar	https://scholar.google.com	8 March 2021	"white paper" AND (thyroid OR hypothyroidism OR hyperthyroidism); 2000-2021	7'510 (first 200 hits screened)	0	0
			Schilddrüse AND (Richtlinie OR Leitlinie OR "Health technology assessment" OR HTA OR "Gesundheitstechnologie-Bewertung" OR Diagnose OR Diagnostik OR Management); 2000-2021	16'300 (first 200 hits screened)		
			Hypothyreose AND (Richtlinie OR Leitlinie OR "Health technology assessment" OR HTA OR "Gesundheitstechnologie-Bewertung" OR Diagnose OR Diagnostik OR Management); 2000-2021	11'800 (first 200 hits screened)		
			Hyperthyreose AND (Richtlinie OR Leitlinie OR "Health technology assessment" OR HTA OR "Gesundheitstechnologie-Bewertung" OR Diagnose OR Diagnostik OR Management)	11'500 (first 200 hits screened)		
Guideline search on PubMed (MEDLINE)	https://pubmed.ncbi.nlm.nih.gov	9 March 2021	(("hypothyroidism"[mesh] OR "hyperthyroidism"[mesh] OR hypothyroid*[tiab] OR hyperthyroid*[tiab] OR thyroid*[tiab]) AND ("diagnosis"[mesh] OR diagnos*[tiab] OR "thyroid function tests"[mesh] OR test*[tiab] OR assay*[tiab] OR "disease management"[mesh] OR management[tiab])) AND guideline[pt] Filters: English, German, from 2000 – 2021	217	12	1
Reference check PubMed (MEDLINE) articles	Not applicable	9 March 2021	Not applicable	1	1	0

Table II. Excluded documents

Data source: reference	Reason for exclusion
AHRQ: Helfand M. Screening for thyroid disease. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]: Centre for Reviews and Dissemination (UK) 2004	No data on objective
AHRQ: Rugge B, Balshem H, Sehgal R, et al. Screening and treatment of subclinical hypothyroidism or hyperthyroidism. 2012	No data on objective
WHO: Heuck CC, Kallner A, Kanagasabapathy A, et al. Diagnosis and monitoring of diseases of the thyroid: World Health Organization, 2000	No data on objective
INAHTA: Scotland Healthcare Improvement. In the context of hypothyroidism, what is the evidence for the effectiveness of diagnostic tests and thyroid hormone replacement therapies?, 2014.	No data on objective
INAHTA: Rugge B, Balshem H, Sehgal R, et al. Screening and treatment of subclinical hypothyroidism or hyperthyroidism. 2012	Duplicate document
INAHTA: Helfand M. Screening for thyroid disease. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]: Centre for Reviews and Dissemination (UK) 2004	Duplicate document
ATA: Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid 2016;26(10):1343-421. doi: 10.1089/thy.2016.0229 [published Online First: 2016/08/16]	No data on objective
ETA: Pearce SH, Brabant G, Duntas LH, et al. 2013 ETA guideline: management of subclinical hypothyroidism. European thyroid journal 2013;2(4):215-28.	No data on objective
ETA: Biondi B, Bartalena L, Cooper DS, et al. The 2015 European Thyroid Association guidelines on diagnosis and treatment of endogenous subclinical hyperthyroidism. European thyroid journal 2015;4(3):149-63	No data on objective
ESE: Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid 2016;26(10):1343-421. doi: 10.1089/thy.2016.0229 [published Online First: 2016/08/16]	Duplicate document
PubMed (MEDLINE): No author. Screening for thyroid disease: recommendation statement. Ann Intern Med 2004;140(2):125-7. doi: 10.7326/0003-	Duplicate document

4819-140-2-200401200-00014 [published Online First: 2004/01/22]	
PubMed (MEDLINE): Baskin HJ, Cobin RH, Duick DS, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract 2002;8(6):457-69. [published Online First: 2004/07/21]	No data on objective
PubMed (MEDLINE): Brenta G, Vaisman M, Sgarbi JA, et al. Clinical practice guidelines for the management of hypothyroidism. Arq Bras Endocrinol Metabol 2013;57(4):265-91. doi: 10.1590/s0004-27302013000400003 [published Online First: 2013/07/06]	Country out of scope (Latin America)
PubMed (MEDLINE): Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract 2012;18(6):988-1028. doi: 10.4158/ep12280.Gl [published Online First: 2012/12/19]	Duplicate document
PubMed (MEDLINE): Gharib H, Tuttle RM, Baskin HJ, et al. Consensus Statement #1: Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. Thyroid 2005;15(1):24-8; response 32-3. doi: 10.1089/thy.2005.15.24 [published Online First: 2005/02/03]	No data on objective
PubMed (MEDLINE): Goichot B, Raverot V, Klein M, et al. Management of thyroid dysfunctions in the elderly. French Endocrine Society consensus statement 2019. Long version. Ann Endocrinol (Paris) 2020;81(2-3):89-100. doi: 10.1016/j.ando.2020.04.010 [published Online First: 2020/05/18]	Lacking methodology (i.e. no methodology nor references provided for whom to test for thyroid dysfunction)
PubMed (MEDLINE): Ladenson PW, Singer PA, Ain KB, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. Arch Intern Med 2000;160(11):1573-5. doi: 10.1001/archinte.160.11.1573 [published Online First: 2000/06/10]	No data on objective
PubMed (MEDLINE): LeFevre ML. Screening for thyroid dysfunction: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2015;162(9):641-50. doi: 10.7326/m15-0483 [published Online First: 2015/03/24]	No data on objective
PubMed (MEDLINE): Parretti H, Okosieme O, Vanderpump M. Current recommendations in the management of hypothyroidism: developed from a statement by the British Thyroid Association Executive. Br J Gen Pract	No data on objective

2016;66(651):538-40. doi: 10.3399/bjgp16X687493 [published Online First: 2016/10/01]	
PubMed (MEDLINE): Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid 2016;26(10):1343-421. doi: 10.1089/thy.2016.0229 [published Online First: 2016/08/16]	Duplicate document
PubMed (MEDLINE): Vasileiou M, Gilbert J, Fishburn S, et al. Thyroid disease assessment and management: summary of NICE guidance. Bmj 2020;368:m41. doi: 10.1136/bmj.m41 [published Online First: 2020/01/31]	Non-pertinent publication type (erratum)
Reference check PubMed (MEDLINE) articles: Helfand M. Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2004;140(2):128-41. doi: 10.7326/0003-4819-140-2-200401200-00015 [published Online First: 2004/01/22]	No data on objective

Table III. Agents and conditions having an impact on L-thyroxine therapy and on the interpretation of thyroid tests (data extracted from Garber et al., 2012*)

Interference with absorption	Thyroid gland hormone production & secretion	Direct & indirect effects on hypothalamic-pituitary-thyroid axis	Increased clearance	Peripheral metabolism
- Bile acid sequestrants (cholestyramine, colestipol, colesevelam) - Sucralfate - Cation exchange resins (Kayexelate) - Oral bisphosphonates - Proton pump inhibitors - Raloxifene[a] - Multivitamins (containing ferrous sulfate or calcium carbonate) - Ferrous sulfate - Phosphate binders (sevelamer, aluminum hydroxide) - Calcium salts (carbonate, citrate, acetate) - Chromium picolinate - Charcoal - Orlistat[b] - Ciprofloxacin - H2 receptor antagonists[a] - Malabsorption syndromes: • Celiac disease • Jejunoileal bypass surgery • Cirrhosis (biliary) • Achlorhydria - Diet: • Ingestion with a meal • Grapefruit juice[a] • Espresso coffee • High fiber diet • Soybean formula (infants) • Soy	Direct and indirect effects on the thyroid gland: - Iodine uptake • Iodine (including kelp • supplements) • Amiodarone • Ethionamide • Iodinated contrast (ipodate[c], iopanoic acid[c]) • Perchloratec - Hormone production • Iodine (including kelp supplements) • Amiodarone • Thionamides (carbimazole, methimazole, propylthiouracil) • Iodinated contrast (ipodate[c], iopanoic acid[c]) • Sulfonylureas • Sulfonamides • Ethionamide - Secretion • Lithium • Iodine (including kelp supplements) • Amiodarone • Iodinated contrast (ipodate[c], iopanoic acid[c]) - Thyroiditis • Induces ○ Amiodarone ○ Tyrosine kinase inhibitors (sunitinib, sorafenib) ○ Interferon alpha ○ Interleukins ○ Antiangiogenic (lenalidomide, thalidomide) ○ Lithium ○ Alemtuzumab ○ Denileukin diftitoxin • Ameliorates (if autoimmune) ○ Glucocorticoids - Development of Graves': • Interferon alpha • HAART (highly activeantiretroviral therapy) • Alemtuzumab - Amelioration of Graves': • Glucocorticoids	- TSH secretion, decrease: • Bexarotene • Dopamine • Dopaminergic agonists (bromocriptine, cabergoline) • Glucorticoids • Thyroid hormone analogues • Somatostatin analogues (octreotide, lanreotide) • Metformin • Opiates (e.g. heroin) • Interleukin-6 - TSH secretion, increase: • Dopamine receptor blockers (metoclopramide) • Hypoadrenalism • Interleukin 2 • Amphetamine • Ritonavir[b] • St. John's Wort[a] - TSH secretion, Hypophysitis: • Ipilimumab	- Phenobarbital - Primidone - Phenytoin - Carbamazepine - Oxacarbazepine[b] - Rifampin - Growth hormone - Sertraline[b] - Tyrosine kinase inhibitors (imatinib[b], sunitinib) - Quetiapine[b] - Stavudine[b] - Nevirapine[a,b]	- Glucocorticoids - Amiodarone - Propylthiouracil - Beta blockers (e.g. propranolol, nadolol) - Iodinated contrast (ipodate[c], iopanoic acid[c]) - Interleukin-6 - Clomipramine

* Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. En-docr Pract 2012;18(6):988-1028. [a] Impact uncertain; [b] Mechanism uncertain; [c] Not presently available in the United States.