Canada's Drug and Health Technology Agency

Choosing Wisely Canada™

CADTH Health Technology Review

# Minimum Retesting Intervals for Lab Tests

Technology Review

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## Context

Laboratory testing is a critical component of effective patient care and a high-volume medical activity in Canada.[1] However, lab test overuse can occur in several situations, including when the test results are unlikely to inform the course of treatment or management of the condition.[2]

Choosing Wisely Canada (CWC) is addressing reducing inappropriate lab testing through Using Labs Wisely. CWC is a national campaign to help reduce unnecessary testing and treatments in Canadian health care systems.[3] Using Labs Wisely is a consortium of more than 150 hospitals committed to making a measurable impact on reducing low-value lab tests in Canada so that lab resources can be used more appropriately.[4]

Hospitals participating in Using Labs Wisely identified a need for guidance on the minimum retesting intervals for 7 commonly repeated lab tests. CWC surveyed a small sample of hospitals participating in Using Labs Wisely and identified heterogeneity in the retesting intervals for these lab tests.

In partnership with CWC, we convened a time-limited advisory panel to support hospitals by developing guidance on minimum retesting intervals for 7 lab tests used in prespecified patient populations or clinical scenarios. The advisory panel considered focused literature reviews, patient group input, and clinical expertise to inform their development of consensus recommendations for each of the 7 selected lab tests.

This Technology Review includes the 7 literature reviews that were provided to the advisory panel on the following lab tests:

- antinuclear antibody (ANA)
- B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP)
- hemoglobin A1C
- lipase
- lipid panel
- serum protein electrophoresis (SPEP)
- thyroid-stimulating hormone (TSH).

Each literature review includes:

- an overview of the test and what it is used for
- published recommendations on minimum retesting intervals and testing frequency in the prespecified populations and/or clinical scenarios
- biological and physiological factors that impact the results of tests and could influence the retesting interval.

# Methods

## Literature Search Methods

For each test, an information specialist conducted a literature search on key resources, including MEDLINE, the International HTA Database, guidelines websites, and the sites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria.

The main search concepts for each of the lab tests were as follows:

- **ANA:** antinuclear antibody and testing
- **BNP and NT-proBNP:** BNP, NT-proBNP, and testing
- **Hemoglobin A1C:** hemoglobin A1C and testing
- **Lipid panel:** lipid panel and testing
- **SPEP:** serum protein electrophoresis and plasma cell dyscrasias
- **TSH:** thyroid-stimulating hormone, hypothyroidism or hyperthyroidism, and testing
- **Lipase:** lipase, pancreatitis, and testing.

CADTH-developed search filters were applied to limit retrieval to health technology assessments and guidelines.

Searches for each of the lab tests were completed on the following dates:

- **ANA:** November 14, 2023
- **BNP and NT-proBNP:** November 21, 2023
- **Hemoglobin A1C:** November 3, 2023
- **Lipid panel:** November 8, 2023
- **SPEP:** November 22, 2023
- **TSH:** November 7, 2023
- **Lipase:** December 4, 2023

The searches were limited to English-language documents.

### Lipase

For lipase, an additional literature search was conducted on the same resources used for the other tests, as well as on the Cochrane Database of Systematic Reviews. The main search concepts of this search were lipase and repeat or serial testing. For this search, no search filters were applied. Retrieval was limited to the human population. The search was completed on December 4, 2023, and limited to English-language documents.

For all tests except lipase, after the initial searches, the information specialist screened the results to limit to guidelines from countries with similar health systems to Canada (e.g., the US, the UK, Western Europe).

### Selection Methods

For each lab test, 1 author screened the literature search results and reviewed the full text of all potentially relevant publications. Publications were considered for inclusion if they met the selection criteria specific to that lab test. The inclusion criteria for each lab test are described in the relevant literature review section for that test.

For each lab test, we sought published recommendations about the minimum retesting interval in prespecified populations as well as information about biological or physiological factors that might impact the minimum retesting interval.

Recommendations for repeat or serial testing were included if they reported a minimum retesting interval or a testing frequency. Minimum retesting intervals specify the minimum time before a test should be repeated based on the properties of the test and the clinical situation in which it is used.[5] Testing frequency is the recommended time frame for patient monitoring to support overall health (e.g., to assess therapeutic response, safety, and adherence).

Recommendations were considered minimum retesting intervals if they did 1 or more of the following:

- specified the minimum time before a test should be repeated
- specified that a test would not be performed by a laboratory or should not be ordered within a set number of days of a previous result (i.e., restrictions on repeat testing)
- specifically called the recommendation a "minimum retesting interval."

Recommendations were considered to be on testing frequency if they did both of the following:

- suggested a time frame for patient monitoring (including at discharge)
- did not specify the minimum time before a test should be repeated.

### Synthesis

One author extracted relevant information from the included publication and summarized relevant information addressing the research questions. Equity considerations were not targeted in the literature search but were summarized as identified within relevant clinical guidelines and other literature. This report is not a systematic review and does not involve critical appraisal of the included publications.

## Literature Review: Minimum Retesting Intervals for ANA

### What Is ANA Testing and What Is it Used For?

ANAs are autoantibodies that bind to cellular components in the nucleus, cytoplasm, or mitotic apparatus, and are useful biomarkers for autoimmune diseases. An ANA (also known as antinuclear factor or ANF) test measures the amount and pattern of antibodies in the blood during an autoimmune reaction. In autoimmune

diseases, antibodies attach to protein cells (autoantigens) instead of foreign proteins (antigens), attacking the body's cells, joints, skin, and muscles.[6] People with autoimmune diseases have increased ANA levels. ANA testing is commonly used in the diagnosis of systemic autoimmune diseases, such as systemic lupus erythematosus, systemic sclerosis, Sjögren disease, and other rheumatic diseases.[7]

The most common test to detect ANA is indirect immunofluorescence.[7] This method of testing involves incubating a serum sample on a slide covered in a monolayer of human epidermoid carcinoma cells (used because of the high number of autoantigens in this cell line), washing the slides, and then applying a detection antibody binding human immunoglobulin with a fluorescent tag to identify any remaining antibodies bound to the cellular components.[8]

Enzyme-linked immunosorbent assay (ELISA) is an alternate test that is used. The ELISA method is fast and sensitive and can detect specific autoantibodies to different antigens.[9] The ELISA method is used as a screening test for ANA to offer quick results on whether a sample is positive or negative; however, indirect immunofluorescence is still often required for further analysis when ANA results are positive.[9]

ANA test positivity is determined through staining patterns and titre (or quantitation of ANA). Staining patterns are loosely associated with underlying autoimmune diseases; however, additional testing is often required to identify specific disease-associated autoantibodies.[7] Titre results reflect the quantification of ANA and are reported as ratios referring to the highest dilution of serum that produces visible fluorescence (e.g., 1:1,280 is a strong positive ANA test result and 1:160 is a weak borderline positive ANA test result).[8] If the ANA test result is positive (by staining and/or titre), secondary tests, including extractable nuclear antigen and anti–double-stranded DNA tests, are used to identify antibodies against specific nuclear components.[10]

Because of the nonspecific association of the presence of ANAs with autoimmune diseases in general, ANA testing is most effective in determining if a patient has a systemic autoimmune disease if there is already clinical evidence of a specific disease. However, using an ANA test indiscriminately (i.e., for screening purposes) can lead to an increase in false-positive results and may cause increased unnecessary testing.[7]

## Research Questions

1. What are the recommendations regarding the minimum retesting interval for antinuclear antibody testing in patients being monitored for autoimmune disease?
2. What are the biological or physiological factors that may impact whether antinuclear antibody testing should be repeated in patients with confirmed or suspected autoimmune disease?

### Inclusion Criteria

The selection of included literature was based on the inclusion criteria presented in Table 1.

## Table 1: Inclusion Criteria for ANA Testing

| Criteria | Description |
|---|---|
| **Population** | People being monitored for suspected or confirmed systemic autoimmune disease<br>Primary conditions of interest include patients with:<br>• systemic lupus erythematosus<br>• scleroderma or systemic sclerosis<br>• rheumatoid arthritis<br>• Raynaud phenomenon<br>Subgroups of interest include patients with:<br>• a pre-existing positive ANA test result<br>• a pre-existing negative ANA test result |
| **Test** | Serum ANA testing |
| **Types of information** | Q1: Recommendations regarding whether testing should be repeated; recommendations regarding the minimum time before a test should be repeated<br>Q2: Biological or physiological factors that impact whether and how often ANA testing should be repeated (e.g., the persistence of ANAs; whether test results change over time) |
| **Study designs** | No restriction on type of publication |

ANA = antinuclear antibody.

## Findings

### Clinical Guidelines

We identified 11 documents with recommendations regarding retesting ANA in patients being monitored for autoimmune disease (refer to Appendix 1). These include 2 guidelines with recommendations based on expert consensus,[11,12] 2 guidelines with unclear methodology,[13,14] and 7 recommendations based on laboratory guidance.[15-21] One consensus-based guideline reported the strength of recommendation to be weak based on evidence from expert opinion.[11]

We identified 2 types of recommendations for the patient populations of interest: those that recommended against initial or repeat ANA testing and those that specified a minimum retesting interval.

#### *Recommendations That Do Not Support Repeat ANA Testing*

Seven of 11 identified publications made general recommendations against repeating ANA tests. These documents recommend the following:

- Do not repeat ANA testing once a diagnosis is made (5 publications).[13,15,18-20]
- Do not use ANA testing for serial monitoring (6 publications).[13,15,17-20]
- Do not repeat ANA testing after a positive test result (3 publications).[14,17,20]

Two publications also provided exceptions in their recommendations for situations in which ANA retesting may be considered:

- Repeat ANA testing is not indicated unless a patient's clinical status has significantly changed (1 publication).[13]

- Do not repeat ANA testing following a negative test result unless there is a strong suspicion of evolving autoimmune disease or a change in the patient's illness suggesting revision of diagnosis (1 publication).[20]

Three publications specified indications for which ANA testing should not be used for diagnosis. These documents recommend the following:

- Do not use ANA testing to confirm a diagnosis of rheumatoid arthritis or osteoarthritis (2 publications).[19,20]
- Do not use ANA testing to evaluate fatigue, back pain, or other musculoskeletal pain unless accompanied with a strong suspicion of an autoimmune disease (2 publications).[19,20]
- Do not use ANA testing for the diagnosis or evaluation of juvenile dermatomyositis (1 publication).[11]

### *Minimum Retesting Interval for ANA Testing*

Three publications made recommendations regarding the minimum time between ANA tests for patients being monitored for suspected autoimmune disease. These documents recommend the following:

- Repeat ANA testing after a negative or borderline positive ANA test result is should only be used in patients with newly developed symptoms of systemic autoimmune rheumatic disease, and with a minimum retesting interval of 6 months.[17]
- Do not repeat ANA testing within 3 months (1 consensus-based guideline).[12]
- Do not repeat ANA testing more than once a year unless the patient's clinical picture has changed (1 laboratory guidance).[16]

The rationale for specifying a 3-month minimum retesting interval was not provided, and the guideline authors noted a high degree of variability in medical laboratory survey responses regarding whether and when ANA testing should be repeated.[12] The authors of the guideline further stated that ANA retesting timing intervals and the need for related antigen-specific testing should be based on the pathogenicity of the antibodies being tested and its importance for the diagnosis and follow-up of the specific disease, which should be determined between the requesting physician and testing laboratory.[12]

## Factors That Impact the Need for ANA Retesting

ANA testing generally has high sensitivity but low specificity for the diagnosis of systemic autoimmune diseases.[9,10] The relatively high prevalence of ANAs in individuals with other inflammatory conditions and in individuals without autoimmune diseases or inflammatory conditions can make a positive ANA result difficult to interpret.[8] This means that ANA testing can be useful for determining the presence of potential autoimmune diseases, but is not informative for confirming the diagnosis of a specific autoimmune disease so repeat ANA testing is generally not useful.[8] Because of this ambiguity in positive test results, evidence from the literature suggests that ANA testing not be considered in patients without symptoms or signs suggesting a systemic autoimmune disease.[9,13,18-20,22,23] Changes in ANA levels are not associated with autoimmune disease activity; therefore, repeat testing alone is not useful for determining disease progression and should not be performed unless there is a significant change in signs or symptoms of autoimmune disease.[8,20]

Negative ANA findings are common for certain autoimmune diseases, such as rheumatoid arthritis. As a result, screening and/or continued monitoring using ANA testing is not useful for negative ANA findings unless there is a strong suspicion of evolving autoimmune disease or if a change in the patient's illness suggests a revision of diagnosis.[8,20,22] The results of ANA testing can vary depending on multiple factors, including type of substrate and method used for detection, laboratory automation, experience of the observer, and characteristics of the microscopes.[9,24] These factors may affect the accuracy of test interpretation and can lead to false-positive results, prompting unnecessary secondary testing.[24]

We identified 1 retrospective cohort study[25] that aimed to evaluate the utility of repeat ANA testing for the diagnosis of rheumatological conditions. Of 7,875 repeat tests from 4,877 patients over a 7-year period in Australia, the results for 3,832 patients (78.4%) did not change. Of the 4,877 patients with repeat tests, 44.4% (n = 2,172) of tests remained persistently negative and 34% (n = 1,660) of tests remained persistently positive.

Of the patients with repeat tests (N = 4,877), 21.6% (n = 1,055) had an ANA test result that changed. For the patients who had an ANA test result that changed:[25]

- 452 (9.2%) changed from positive to negative
- 511 (10.5%) changed from negative to positive (representing 19.0% of the 2,683 patients with an initial negative result).

For a subset of 451 patients (88.2%) who had a change in their ANA test result from negative to positive and for whom clinical information was available, the authors found the following:[25]

- The median time to a first positive ANA test result was 1.74 years (interquartile range, 0.54 to 3.60 years).
- Five patients (1.1%) received a new ANA-associated rheumatological diagnosis after the repeat testing.
  - All 5 patients had clinical symptoms that persisted or developed after the initial negative ANA test result.
- The predictive positive value of a newly positive repeat ANA test after an initially negative test result was 1.1% (95% confidence interval, 0.4% to 2.7%).
  - This suggests that repeat ANA testing after a negative test result has low utility.

### Equity Considerations

When considering the retesting guidance for ANA in patients being monitored for autoimmune disease, decision-makers may want to consider the following information.

Studies suggest that the incidence and prevalence of autoimmune diseases can vary based on factors such as age, sex, socioeconomic status, and environmental factors.[26,27] The incidence rate of autoimmune disease is higher in females and people living in low socioeconomic areas.[27] Additional factors such as diet, smoking status, air pollution, and other unrecognized environmental exposures are also likely to contribute to an individual's risk for developing an autoimmune disease.[27] It is unclear if higher incidence and prevalence of

autoimmune disease in these populations have any implications on the use or retesting intervals for ANA testing; however, given the current guidance on ANA testing, patient signs and symptoms of autoimmune disease should be considered in any decision to use or repeat an ANA test.

# Literature Review: Minimum Retesting Intervals for BNP and NT-proBNP

## What Are Natriuretic Peptides and What Are They Used For?

Natriuretic peptides are quantitative biomarkers for cardiac stress and heart failure.[28-30] BNP (also known as brain natriuretic peptide) is a natriuretic hormone. Cleavage of the prohormone proBNP produces BNP and the biologically inactive protein NT-proBNP.[30] BNP and NT-proBNP are exclusively produced by cardiac tissue and are primarily released from the heart ventricles in response to wall stress caused by increased ventricular blood volumes and pressure.[29,30]

Plasma concentrations of BNP and NT-proBNP are increased in patients with cardiac abnormalities (e.g., left ventricular dysfunction, right ventricular dysfunction, valvular dysfunction, increased pulmonary pressures, and atrial arrhythmias) and play important roles in diagnosis and prognostication.[28-31]

### Heart Failure

BNP and NT-proBNP levels can be used in conjunction with other clinical information to diagnose the presence and severity of heart failure.[32] Higher levels of BNP or NT-proBNP are strong predictors of the risk of adverse outcomes, including hospital readmission and the risk of death.[32] Measuring BNP and NT-proBNP levels (e.g., at discharge) can be useful for prognosticating risk and may aid in decision-making (e.g., intensity of therapy, type of follow-up tests).[28,32]

In people with heart failure, these biomarkers have been studied as potential markers of clinical response to medical therapy (i.e., has the patient received adequate decongestive therapy) and as a potential method for titrating therapy.[30,32] However, the effectiveness of using serial BNP and NT-proBNP measurements to guide medical treatment and to monitor the response to heart failure therapy is not well established.[28,30,32]

### Pulmonary Hypertension

Plasma levels of BNP and NT-proBNP can also be used in patients with pulmonary arterial hypertension to aid in diagnosis, to evaluate disease severity, for risk stratification, and for monitoring disease progression and response to treatment.[33,34]

## Research Questions

1. What are the recommendations regarding the minimum retesting interval for B-type natriuretic peptide testing in patients being monitored for treatment of heart failure or pulmonary arterial hypertension?

2. What are the recommendations regarding the minimum retesting interval for N-terminal pro B-type natriuretic peptide testing in patients being monitored for treatment of heart failure or pulmonary arterial hypertension?
3. What are the biological or physiological factors that may impact how often B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide tests should be repeated for patients being monitored for treatment of heart failure or pulmonary arterial hypertension?

### Inclusion Criteria

The selection of included literature was based on the inclusion criteria presented in Table 2.

## Table 2: Inclusion Criteria for BNP and NT-proBNP

| Criteria | Description |
|---|---|
| **Population** | Patients being monitored for treatment of heart failure<br>Patients being monitored for treatment of pulmonary arterial hypertension |
| **Test** | Plasma BNP test (also known as brain natriuretic peptide)<br>NT-proBNP test |
| **Types of information** | Q1 and Q2: Recommendations regarding whether testing should be repeated; recommendations regarding the minimum time before a test should be repeated<br>Q3: Biological or physiological factors that impact minimum retesting interval (e.g., half-life, production of BNP) |
| **Study designs** | No restriction on type of publication |

BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro B-type natriuretic peptide.

### Exclusion Criteria

Literature was excluded if it did not meet the criteria outlined in Table 2.

We excluded recommendations about BNP or NT-proBNP testing if they were:

- recommendations for diagnosing heart failure or pulmonary arterial hypertension
- recommendations that did not specify a time frame or testing frequency.

We excluded guidance documents published before 2013.

## Findings

### Clinical Guidelines

#### *Heart Failure: Adults*

We identified 13 documents that provided guidance regarding BNP or NT-proBNP testing for monitoring adults being treated for heart failure (refer to Appendix 2). These include 5 evidence-based guidelines,[35-39] 3 consensus-based guidelines,[28,40,41] 1 guideline with unclear methodology,[42] 3 documents with recommendations from clinical societies or associations with unclear methodology,[43-45] and 1 laboratory guidance document.[46]

As not all documents provided formal recommendations about BNP or NT-proBNP retesting, if applicable, we also included suggestions for clinical practice, testing algorithms, and discussions regarding repeat BNP or NT-proBNP testing for monitoring purposes.

We identified 4 types of guidance documents:

- those that specify a minimum retesting interval
- those that specify a testing frequency
- those that do not support repeat or serial BNP or NT-proBNP testing
- those that suggest that the evidence for repeat testing is conflicting or unclear.

### Minimum Retesting Interval

We identified recommendations from 1 clinical society[44] regarding the minimum time between BNP tests for adults with heart failure. This document[44] recommended the following:

- If serial BNP testing is conducted for any reason, do not repeat testing within 2 weeks.
- Ideally, no more than 4 BNP tests should be performed per year.

The authors of the clinical society recommendation also reported that BNP levels will often initially rise during the first few weeks of beta-blocker treatment (number of weeks not specified) and then decrease with sustained therapy.[44]

A minimum retesting interval of 2 weeks is supported by findings from 1 study of serial NT-proBNP monitoring (N = 71) that found that the relative change in NT-proBNP levels 2 to 4 weeks after starting therapy for heart failure were the most predictive of future adverse events, suggesting that retesting before 2 weeks may be less informative.[47]

However, the recommendation[44] that suggested the minimum retesting interval of 2 weeks also noted the following:

- Decreases in BNP may not occur in all patients after initiating therapy.
- Serial BNP measurements are not routinely recommended in all patients.
- Serial BNP measurements are likely only suitable if they will influence management decisions.
- If BNP levels are substantially elevated (not further defined) at diagnosis, then monitoring BNP may be considered as an additional marker of treatment efficacy.

We identified 1 guidance document from a medical laboratory with a minimum retesting interval for NT-proBNP.[46] This laboratory guidance document indicated that NT-proBNP can be used for risk stratification in patients with congestive heart failure and that the minimum repeat interval is 6 months.[46]

### Testing Frequency for BNP and NT-proBNP

**Treatment monitoring:** We identified 5 documents with guidance regarding the testing frequency for BNP and NT-proBNP for adults receiving treatment for heart failure that may provide further insight on minimum retesting intervals.

For patients with reduced ejection fraction heart failure who have been stabilized, it is suggested that BNP and NT-proBNP be measured every 3 to 6 months to assess response to therapy (as part of a testing algorithm from 1 consensus-based guideline).[28]

For patients hospitalized for heart failure, 5 documents recommended measuring BNP and NT-proBNP before discharge; however, they did not specify the timing of the test relative to the initial test used for diagnosing heart failure (includes 4 recommendations and 1 suggestion for clinical practice).[35,39,40,42,45] Predischarge levels of these biomarkers can provide information regarding the patient's risk of death or hospital readmission.[35,39,40]

One guideline also suggested that, for patients with persistently high levels of BNP or NT-proBNP, clinicians should consider delaying discharge to optimize therapy and further reduce the level of these biomarkers.[39]

**Treatment optimization:** We also identified 2 documents with recommendations for the use of serial measurements of BNP or NT-proBNP to guide therapy for heart failure; however, the timing of these repeat measurements was not specified.[38,39] The documents recommended the following:

- Clinicians should consider measuring BNP or NT-proBNP as part of a treatment optimization protocol (only within a specialist care setting) for patients younger than 75 years (2 evidence-based guidelines[38,39]).
  - The timing of the BNP or NT-proBNP tests should be determined by the patient's clinical status;[39] however, the timing of the tests was not further specified.
  - The benefit is uncertain in individuals older than 75 years.[39]

### Recommendations That Do Not Support Repeat BNP or NT-proBNP Testing

**Treatment monitoring:** We identified 3 documents that included recommendations against repeat or serial BNP and NT-proBNP testing for monitoring treatment in the majority of patients with heart failure.[42-44]

However, repeat tests may be considered in patients with heart failure showing clinical deterioration or who do not respond to therapy.[42,44]

In addition, we identified 2 documents that made recommendations for monitoring treatment response in patients with heart failure that did not include BNP nor NT-proBNP testing as part of the suggested assessments;[38,41] however, they also did not explicitly recommend against using these biomarkers for monitoring treatment response.

**Treatment optimization:** We identified 2 documents that did not support repeat or serial BNP and NT-proBNP testing for treatment optimization purposes in patients with heart failure.[36,37] These documents reported that the evidence does not support serial measurements of BNP or NT-proBNP to guide therapy for heart failure (included as part of the discussion or as a suggestion for clinical practice from 2 evidence-based guidelines[36,37]).

### Uncertain Evidence for Repeat BNP or NT-proBNP Testing

We identified 2 documents that reported that the usefulness of monitoring patients on treatment for heart failure using serial measurements of BNP or NT-proBNP is not well established (1 recommendation from a clinical society)[45] or the benefit is unclear (suggestion for clinical practice [due to limited or uncertain evidence] from 1 evidence-based guideline).[37]

We also identified 2 documents that reported that the evidence for BNP- or NT-proBNP–guided therapy is not well established (recommendations from 1 clinical society and 1 consensus-based guideline).[40,45]

#### *Heart Failure: Pediatrics*

We identified 1 evidence-based guideline that suggested that use of serial BNP or NT-proBNP measurements could potentially be used in children to guide treatment or to monitor heart failure status, but that the evidence for or against using these biomarkers to guide treatment is insufficient to allow for a formal recommendation.[48]

We did not identify any recommendations about the minimum retesting interval or the testing frequency for BNP or NT-proBNP in pediatric patients being monitored for treatment of heart failure.

#### *Pulmonary Arterial Hypertension*

We identified 1 evidence-based guideline[49] that provided guidance around the testing frequency for BNP or NT-proBNP to monitor adults being treated for pulmonary arterial hypertension (refer to Appendix 2).

We did not identify any recommendations about the minimum retesting interval or the testing frequency for BNP or NT-proBNP in pediatric patients being monitored for treatment of pulmonary arterial hypertension.

Regarding monitoring adults with pulmonary arterial hypertension, this guideline[49] recommended measuring BNP and NT-proBNP during follow-up as part of a multiparameter risk stratification tool.

Testing frequency for BNP and NT-proBNP were not specified in the formal recommendation, but the guideline[49] suggested the following timing for follow-up BNP or NT-proBNP tests:

- 3 to 6 months after changes in therapy
- every 3 to 6 months in stable patients
- if there is clinical worsening.

It was also suggested that clinicians adjust the interval between BNP or NT-proBNP tests according to the patient's needs, risk category, demographics, and comorbidities as well as the etiology of pulmonary arterial hypertension.

### Factors That Impact BNP and NT-proBNP Levels

There are multiple factors that impact BNP and NT-proBNP levels. Decision-makers may want to consider whether these factors may impact the minimum retesting interval.

### *Half-Life*

The plasma half-life of BNP is approximately 20 minutes, and the plasma half-life of NT-proBNP is approximately 25 to 70 minutes.[30] The plasma concentrations decrease following effective treatment for heart failure.[30]

### *Biological Variability*

Even in a stable physiological state, plasma levels of BNP and NT-proBNP change due to their large biological variability,[37,42] with approximately 40% of variation in these biomarkers attributed to genetic factors.[30] Biological variation is the variability of a biomarker in a stable physiological state; a change in a biomarker outside the accepted range in biological variation indicates a clinically significant worsening or improvement of a disease. In patients with heart failure, changes of 30% to 40% (or greater) for BNP and 25% to 30% (or greater) for NT-proBNP are reported as outside the accepted range for daily variation due to biological variability (2 guidelines).[32,37] Changes in these biomarkers of this magnitude (relative to the previous value) can be interpreted as clinically significant.[32,37]

To account for biological variability when BNP and NT-proBNP are measured serially for monitoring patients with stable heart failure, 1 guideline reported that changes of approximately 66% for BNP and 50% for NT-proBNP from the previous measurement are needed to indicate altered clinical status.[42]

### *Pharmacological Therapy*

Drug therapies for heart failure can have complex effects on BNP and NT-proBNP levels, and the mechanisms of action for these are not always well understood.

- Angiotensin receptor–neprilysin inhibitors (ARNIs):[30,37,50]
  - BNP is a neprilysin substrate, thus BNP levels are increased with ARNI use; however, the beneficial effect of ARNIs on heart failure reduce BNP production. The result of these opposite effects is a small increase in overall BNP levels.
  - NT-proBNP is not a neprilysin substrate and its levels are reduced with ARNI use.
- Beta-blockers:
  - There is an initial increase in BNP and NT-proBNP levels followed by a later reduction.[37,44]
  - One study (N = 16) reported that plasma BNP and NT-proBNP levels were significantly increased after 6 weeks in patients with stable heart failure after the introduction of the beta-blocker metoprolol (but this did not imply a worsening of the management of heart failure).[51]
  - In another study, the beta-blocker carvedilol was associated with a sustained decline in BNP levels at 6 and 12 months, and a decline in NT-proBNP at 12 months, in patients with heart failure.[52]
- Diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists reduce BNP and NT-proBNP levels (due to their effect on intracardiac filling pressure).[37,53]

In addition, decision-makers may also want to consider the time to onset of the beneficial effects of the therapies for heart failure as well as the dose titration interval. The beneficial effects of the primary therapies for heart failure with reduced ejection fraction (e.g., ARNIs, beta-blockers, mineralocorticoid receptor antagonists, sodium glucose cotransporter 2 [SGLT2] inhibitors) are evident within weeks to months of starting therapy.[54]

Regarding primary pharmacological therapies for heart failure with reduced ejection fraction in adults, the minimum dose titration interval varies based on the drug; it can range from 1 to 4 weeks or may not be applicable (for fixed dose therapies).[55] For secondary pharmacological therapies for heart failure with reduced ejection fraction in adults, the minimum dose titration interval is 2 to 4 weeks or as tolerated.[55] Dose increases might also be performed more rapidly depending on the clinical situation and management program.[55]

When deciding when or whether to retest BNP and NT-proBNP levels, decision-makers should consider the other therapies their patient is taking, the dose of the drug, when the patient started the drug treatment, and the potential impact of the drug on clinical symptoms and natriuretic peptide levels.

### *Biological Factors*

There are numerous biological factors and conditions that impact BNP and NT-proBNP levels (refer to Table 3). Testing natriuretic peptides may not be suitable in all patient groups, especially those who may have reduced natriuretic peptide levels (e.g., people living with obesity).[53] Decision-makers should consider the clinical situation and the individual needs of their patients when interpreting the results of these tests and when determining the testing frequency for BNP and NT-proBNP for their patients.

## Table 3: Biological Factors That Impact BNP and NT-proBNP Levels

| Condition or factors | Effect on BNP and NT-proBNP levels |
|---|---|
| Body mass index[30,31,40,50] | Lower in those with a higher body mass index |
| Age[30,31,40,50] | Increases with age |
| Biological sex[30,31,40] | Higher in females |
| Renal failure or chronic kidney[30,40,50] | Elevates |
| Chronic obstructive disease[40] | Elevates |
| Atrial fibrillation[50] | Elevates |
| Anemia[50] | Elevates |
| Obstructive sleep apnea[50] | Elevates |
| Severe pneumonia[50] | Elevates |
| Critical illness[50] | Elevates |
| Bacterial sepsis[50] | Elevates |
| Severe burns[50] | Elevates |
| Liver cirrhosis[50] | Elevates |

BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro B-type natriuretic peptide.

### Equity Considerations

From the included documents, 1 guideline included 2 recommendations regarding health equity and social determinants of health given their link to the risk of cardiovascular disease and heart failure outcomes (refer to Appendix 2, Table 14).[35] These recommendations are not specific to BNP or NT-proBNP retesting, but are intended to be more broadly applied when treating people with heart failure.

This guideline[35] recommends the following:

- Clinicians should monitor and address patients' health disparities.
- For patients who are members of equity-deserving groups who have a higher risk of heart failure, heart failure risk assessments and multidisciplinary management strategies should target both social determinants of health and the risks of cardiovascular disease.

When considering the minimum retesting interval for BNP and NT-proBNP for monitoring patients with heart failure, decision-makers may also want to consider the following:

- Sex and gender
  - Heart failure is more common in men than women.[53]
  - In women, heart failure generally presents later in life with more comorbidities.[35]
  - Women may have lower access to specialty heart failure care than men because women are less likely to be referred to specialty care.[35]
- Age
  - Heart failure is more common in people older than 65 years.[53]
  - Older patients with heart failure have a higher risk of adverse outcomes (e.g., cognitive decline, frailty) and polypharmacy.[35]
  - For older adults, low income, social isolation, and lack of caregiver support increases the risk of heart failure mortality and lower quality of life.[35]
  - Older in-patients may be at risk of inadequate guideline-directed medical therapy; however, interventions implemented in care facilities can improve delivery of care for heart failure.[35]
- Race and ethnicity
  - The incidence of heart failure is highest in people who self-identify as Black.[35]
  - The mortality and hospitalization rates for patients who are Black are higher than for patients who are white; these differences are mostly driven by social determinants of health (e.g., income, employment, education).[35]
  - One guideline reported that there is little evidence that the criteria to diagnose heart failure differs among racial populations and that the diagnostic performance of the biomarker NT-proBNP is similar in individuals who are Black and who are not Black.[39]
  - The incidence of heart failure is higher in patients who are Hispanic compared with patients who are non-Hispanic white (but not as high as the incidence in patients who are Black).[35]

- Patients who are Black and Hispanic may have less access to specialized inpatient heart failure care.[35]
- Language barriers may present potential barriers to optimal disease management.[35]
- One guideline reported that there have been very few published population-based epidemiological studies or large-scale randomized controlled studies of heart failure in countries outside of North America, Europe, and Australia. Thus, there is limited evidence from the regions where most of the racialized populations who reside in North America, Europe, and Australia emigrated.[39]

- Socioeconomic status
  - Patients with lower socioeconomic status may have a greater risk of heart failure and may have an increased risk of heart failure mortality.[35]

# Literature Review: Minimum Retesting Intervals for Hemoglobin A1C

## What Is the Hemoglobin A1C Test and What Is It Used For?

The hemoglobin A1C test is used to assess chronic glycemia and to evaluate a person's overall level of glucose management.[56,57] Hemoglobin A1C is relatively unaffected by acute changes in blood glucose levels, making it useful for diagnosing diabetes and monitoring the overall effectiveness of treatment for diabetes.[56]

Hemoglobin is a protein found exclusively in red blood cells. Red blood cells are permeable to glucose, and as red blood cells circulate through the blood stream, glucose enters the blood cells and the hemoglobin becomes glycated (or coated) with glucose (i.e., glycated hemoglobin or hemoglobin A1C).[56,57] This bond is irreversible; glucose remains attached to the hemoglobin over the lifespan of the red blood cell.[56] The degree of glycation reflects the average glucose exposure over the half-life of the hemoglobin in the red blood cell, which is approximately 60 days.[56] Hemoglobin A1C test results correlate best with the average blood glucose level over the past 60 to 90 days (i.e., 2 to 3 months).[56,58]

The degree of glycation is dependent on the interaction between blood glucose concentration and the lifespan of the red blood cells, which is a maximum of 100 to 120 days.[59] However, hemoglobin A1C test results reflect the weighted mean blood glucose levels (not the simple mean) over the preceding 120 days, with more recent blood glucose levels contributing larger proportions of the hemoglobin A1C level.[56,58,60] It is estimated that 50% of the hemoglobin A1C test result is determined by the blood glucose level in the 30 days immediately preceding the blood test. Blood glucose levels from days 31 to 90 before the test contribute 40% of the hemoglobin A1C test result and blood glucose levels from days 91 to 120 before the test contribute the remaining 10% of the test result (as summarized in Table 4).[59-62]

## Table 4: Estimated Blood Glucose Level Contribution to Hemoglobin A1C Test Result[59-62]

| Days preceding the blood sample | Percentage blood glucose level contribution to hemoglobin A1C test result |
|---|---|
| 30 days | 50% |
| 31 to 90 days | 40% |
| 91 to 120 days | 10% |

## Research Questions

1. What are the recommendations regarding the minimum retesting interval for hemoglobin A1C in people who are being monitored for diabetes treatment?
2. What is the biological half-life of hemoglobin A1C and how does this affect the minimum retesting interval for people who are being monitored for diabetes treatment?

### Inclusion Criteria

The selection of included literature was based on the inclusion criteria presented in Table 5.

## Table 5: Inclusion Criteria for Hemoglobin A1C

| Criteria | Description |
|---|---|
| **Population** | People living with diabetes who are being monitored for diabetes treatment (i.e., oral medicine, insulin, or lifestyle treatment) |
| **Test** | Hemoglobin A1C |
| **Types of information** | Q1: Recommendations regarding whether testing should be repeated; recommendations regarding the minimum time before a test should be repeated<br>Q2: Biological half-life |
| **Study designs** | No restriction on type of publication |

## Findings

### Clinical Guidelines

#### *Adults*

We identified 20 documents with recommendations regarding retesting hemoglobin A1C in adults with type 1 or type 2 diabetes (refer to Appendix 3). These include 2 health technology assessments,[63,64] 10 evidence-based guidelines,[5,58,62,65-71] 1 guideline with unclear methodology,[72] 3 documents with recommendations from clinical societies or associations developed with unclear methodology,[73-75] and 4 guidance documents from medical laboratories.[76-79]

Nine of the 10 evidence-based guidelines reported the strength of the recommendation and/or the quality of the evidence that informed the recommendation.[5,58,62,65-69,71] There was a mix of strong recommendations (i.e., an intervention that should be offered), moderate strength recommendations (i.e., actions that should be

considered), and weak recommendations. The recommendations were largely based on expert consensus or clinical experience, or low- to moderate-quality evidence.

We identified 2 types of recommendations: those that specified a minimum retesting interval and those that specified a testing frequency.

### Minimum Retesting Interval for Hemoglobin A1C

Five publications made recommendations regarding the minimum time between tests for hemoglobin A1C for adults with diabetes. These documents recommend:

- Do not test hemoglobin A1C within 60 days of a previous result unless there is a valid reason (guidance from 1 medical laboratory[79]).
- The minimum retesting interval for hemoglobin A1C in people living with type 2 diabetes is 2 to 6 months if glycemic targets are not being met; it is 6 months once glucose levels are stable (1 evidence-based guideline[5]).
- Do not test hemoglobin A1C within 80 days of a previous result (guidance from 1 medical laboratory[78]).
- Do not order hemoglobin A1C testing more frequently than every 3 months once glucose levels are stable (guidance from 1 clinical society[73] and 1 medical laboratory[77]).

### Testing Frequency for Hemoglobin A1C

The other documents provided recommendations regarding the testing frequency for hemoglobin A1C for monitoring adults with diabetes but did not specify the minimum time before a test should be repeated. However, the testing frequency guidance for hemoglobin A1C may provide further insight for the minimum retesting interval. The guidance differs based on whether glucose levels are stable.

**If glycemic targets are not being met or if therapy has recently changed:** The included publications recommended the following regarding testing frequencies for hemoglobin A1C if glycemic targets are not being met or if therapy has recently changed:

- every 2 to 6 months[70]
- at least every 3 months[67,69,71]
- every 3 months[58,62,63,72,75-77]
- every 3 to 6 months.[65,66,68,74]

It was also recommended that the frequency of testing should depend on the clinical situation, and that clinicians should consider more frequent testing based on the clinical circumstances (e.g., pregnancy, significant changes to therapy, frequent or severe hypoglycemia, changing health status, suspicion of rapidly changing blood glucose).[62,66,68,71]

**If glycemic targets are being met:** The included publications recommended the following testing frequencies for hemoglobin A1C in individuals whose glycemic targets are being met:

- at least 2 times per year[58,62,67,69,71,77]

- every 6 months.[63,65,72,75,76]

In addition, 2 health technology assessments recommended that hemoglobin A1C be measured a maximum of 4 times per year.[63,64] Although this may be interpreted to imply a frequency of once every 3 months, the documents did not specify the amount of time between tests.

### *Pediatrics*

We identified 6 evidence-based guidelines with recommendations regarding retesting hemoglobin A1C specific to children and adolescents with diabetes (refer to Appendix 3). These recommendations were based on limited low-quality evidence or on expert opinion.

With respect to hemoglobin A1C retesting for monitoring children and adolescents with diabetes, these guidelines recommend:

- The minimum retesting interval for hemoglobin A1C is 2 months in children and adolescents with type 1 diabetes.[5]
- Measure hemoglobin A1C every 3 months (3 guidelines[61,80]).
- Measure hemoglobin A1C at least twice a year, with more frequent monitoring (e.g., every 3 months) in youth who are growing and developing.[71]
- Measure hemoglobin A1C 4 times a year (1 guideline[81]) but consider more frequent hemoglobin A1C testing in patients with type 1 diabetes if they are having difficulty with blood glucose management.[81]
- Consider testing hemoglobin A1C every 6 months in those with type 2 diabetes if hemoglobin A1C concentrations remain relatively stable.[82]

### *Pregnancy*

We identified 2 evidence-based guidelines that make recommendations regarding retesting hemoglobin A1C levels specific to pregnancy in people living with diabetes (refer to Appendix 3).

With respect to hemoglobin A1C testing and pregnancy in people with pre-existing diabetes, these guidelines recommend:

- Do not use hemoglobin A1C levels for monitoring management of glucose levels in the second and third trimesters of pregnancy (may also apply to individuals with gestational diabetes).[5,83]
- Consider measuring hemoglobin A1C at the booking appointment and in the second and third trimesters in pregnant people with pre-existing diabetes to determine the level of risk to the pregnancy.[5,83]
- In people planning to become pregnant, offer monthly measurement of hemoglobin A1C.[5,83]

None of the included publications included guidance about using hemoglobin A1C to monitor glucose levels in the first trimester.

## Factors That Impact Hemoglobin A1C Testing

There are several conditions that can result in invalid hemoglobin A1C test results (i.e., the hemoglobin A1C test results do not accurately reflect the person's overall level of glucose management; refer to

Appendix 3). These conditions affect the rate of red blood cell turnover or alter the structure of hemoglobin, which can affect the exposure time of the hemoglobin to blood glucose. Conditions that increase the rate of red blood cell turnover result in a greater proportion of younger red blood cells, which can result in falsely low hemoglobin A1C test results. Conversely, conditions that reduce red blood cell turnover result in a disproportionate number of older red blood cells, which can result in falsely high hemoglobin A1C test results. Hemoglobin A1C test results in individuals with these conditions should be interpreted with caution, and blood glucose testing may be required instead of hemoglobin A1C for monitoring treatment of diabetes in these populations.[58]

Recommendations from 2 guidelines suggest that clinicians and laboratories should consider that hemoglobin A1C test results in individuals with these conditions may not be accurate reflections of a person's level of glucose management.[58,69] A third guidance document recommends that the hemoglobin A1C test should not be ordered for individuals with altered red blood cell turnover (refer to Appendix 3).[77]

### Equity Considerations

When considering the minimum retesting interval for hemoglobin A1C for monitoring individuals living with diabetes, decision-makers may also want to consider the following:

- The documents included in this report that provide minimum retesting intervals and testing frequency recommendations were primarily developed in high-income countries situated in the global north; therefore, the recommendations for hemoglobin A1C retesting may not be generalizable to everyone.
- Patients do not need to have fasted for an hemoglobin A1C test.[76] This is useful for people who may have increased risks associated with fasting (e.g., hypoglycemia in people with diabetes)[84] or people who may have difficulty with attending a health care facility while fasted (e.g., people without access to reliable transportation, people living in rural or remote areas).
- Hemoglobin A1C tests can be performed using a lab-based test or a point-of-care test.[56] Point-of-care tests increase convenience, particularly for people who may experience barriers to accessing health care (e.g., people without access to reliable transportation, people living in rural or remote areas) or in facilities with limited resources for laboratory testing.
- Some studies suggest that hemoglobin A1C concentrations are higher in individuals who are Black, Asian, and Hispanic than in individuals who are white with similar plasma glucose concentrations.[58,62,67,85] However, concerns about the small sample sizes and the comprehensiveness of the blood glucose levels limit the interpretation of these findings.[58] In addition, the 2024 American Diabetes Association's *Standards of Care in Diabetes*[71] reports that there is "controversy regarding the clinical significance of racial differences in A1C" (p. s112). They report there is emerging understanding of genetic determinants that modify the relationship of hemoglobin A1C and glucose levels; therefore, race is not a good proxy of these genetic differences and should not be a consideration for how hemoglobin A1C is used clinically for monitoring glycemia.[71]
- It is unclear whether racial differences in hemoglobin A1C concentrations have any implications on the retesting intervals for people of different races given that current recommendations for retesting

intervals for hemoglobin A1C are not determined by the absolute values of the test results (they are largely based on red blood cell turnover and the half-life of hemoglobin in the red blood cell).

# Literature Review: Minimum Retesting Intervals for Lipase

## What Is Serum Lipase Testing and What Is It Used For?

Lipase is a type of digestive enzyme primarily produced in the pancreas to break down fats.[86] Lipase is typically measured through routine blood tests to assess for pancreatitis.[86,87] Although small amounts of lipase are often found in plasma, elevated lipase levels can indicate pancreatitis because the pancreas releases lipase when damaged or inflammed.[86] Initial high levels of serum lipase can be an indicator of acute pancreatitis; however, higher than normal levels of serum lipase may also be associated with other pancreatic diseases, chronic kidney disease, peptic ulcer, gallbladder disease, intestinal issues, diabetes, salivary gland disorders, or alcohol use disorder.[86,87] Acute pancreatitis is characterized by the presence of at least 2 signs or symptoms, including typical abdominal pain, serum lipase levels at least 3 times greater than the upper limit of normal (ULN) range (i.e., 0 to 160 ULN), and positive morphology findings in imaging.[87] Chronic pancreatitis is characterized by recurrent inflammatory episodes (or persistent acute pancreatitis episodes) resulting in potentially permanent damage to pancreatic tissue and endocrine or exocrine functions.[87,88] Permanent or chronic damage to the pancreas may result in low or normal levels of serum lipase, thus serum lipase testing for patients with chronic pancreatitis may not be informative.[86]

## Research Questions

1. What are the recommendations regarding the minimum retesting interval for lipase in patients being monitored for pancreatitis?
2. What are the biological or physiological factors that may impact how often serum lipase testing should be repeated for patients being monitored for pancreatitis?

### Inclusion Criteria

The selection of included literature was based on the inclusion criteria presented in Table 6.

## Table 6: Inclusion Criteria for Lipase

| Criteria | Description |
|---|---|
| **Population** | Patients being monitored for acute or chronic pancreatitis |
| **Test** | Serum lipase testing |
| **Types of information** | Q1: Recommendations regarding whether testing should be repeated; recommendations regarding the minimum time before a test should be repeated<br>Q2: Biological or physiological factors that impact minimum retesting interval (e.g., half-life, production of lipase) |
| **Study designs** | No restriction on type of publication |

## Findings

### Clinical Evidence

We identified 6 documents that provided evidence statements regarding the use of repeat serum lipase testing for patients being monitored for acute pancreatitis (refer to Appendix 4). We did not identify any recommendations or evidence statements regarding the use of repeat serum lipase testing for patients being monitored for chronic pancreatitis. None of the identified documents provided formal recommendations about repeat serum lipase testing; therefore, evidence from discussion sections of guidance documents or review articles regarding serum lipase testing was used to inform these findings. The identified documents included 1 publication with recommendations developed using unclear methodology[89] and 5 narrative reviews.[90-94]

We identified 2 types of evidence statements:

- those that do not support repeat serum lipase testing for monitoring purposes
- those that considered repeat serum lipase testing under certain clinical conditions.

No timing intervals regarding the frequency of repeat testing were provided in the identified evidence.

#### *Evidence That Does Not Support Repeat Serum Lipase Testing*

Six publications made general evidence statements against repeating serum lipase testing for monitoring patients with acute pancreatitis. The identified evidence generally did not support repeat lipase testing because there is little value in using lipase to measure acute pancreatitis prognosis or management.[89-92,94] These documents reported the following:

- Do not repeat serum lipase testing after a diagnosis of acute pancreatitis has been established (3 publications).[91,93,94]
- Do not use repeat serum lipase testing to monitor acute pancreatitis disease prognosis (4 publications).[89-92]

#### *Evidence for Repeat Serum Lipase Testing Under Certain Conditions*

Four publications made general evidence statements for the use of repeat serum lipase testing under certain clinical conditions.

Repeat serum lipase testing may be considered when patients have signs and symptoms of:

- acute pancreatitis and if the initial presentation is within 4 to 5 hours of the onset of abdominal pain with normal levels of lipase or amylase (1 publication)[91]
  - when clinical suspicion of acute pancreatitis is high and these conditions are met at presentation, repeat lipase testing “in the next couple of hours”[91]
- persisting pancreatic or peripancreatic inflammation (2 publications)[89,91]
- blockage of the pancreatic duct (3 publications)[89,91,93]
- development of a pseudocyst (4 publications)[89-91,93]
- lack of clinical improvement after 1 or more weeks (2 publications)[91,93]

- pain fails to resolve or worsen during a prolonged hospitalization (1 publication).[90]

### Factors Impacting Serum Lipase Retesting

It is recommended to use lipase versus amylase as the primary serum test to determine the presence of pancreatitis because lipase has a prolonged elevation in plasma with a half-life of 6.7 to 13.7 hours.[89,93] Lipase levels do not provide value in determining the severity or prognosis specifically for acute pancreatitis because they follow a generally consistent pattern over time from onset of acute pancreatitis regardless of clinical status.[91] In patients with acute pancreatitis, lipase levels increase within 4 to 8 hours of acute pancreatitis onset and peak at approximately 24 hours.[91,93] Lipase starts to decrease within 8 to 14 days.[91,93] Because of these fluctuations in lipase levels over time, repeat measuring of serum lipase may be misleading without additional measures of clinical status such as imaging and risk stratification scores to measure severity.[93]

Risk stratification scores use laboratory and clinical data to determine clinical severity of pancreatitis status; however, lipase is not measured or used to inform the score outcome.[93] Improper interpretations of high lipase levels may cause unnecessary additional testing for patients who may be clinically improving. Conversely, patients who have normal or lower lipase levels at admission or follow-up but who are not showing signs of clinically improving could have early-stage chronic pancreatitis and may be at risk of misdiagnosis due to improper interpretation of lipase levels.[88,93] Serum lipase measurements alone may be challenging to interpret accurately and could delay proper additional workup necessary for pancreatitis management.[93]

### Equity Considerations

When considering the need or conditions for repeat serum lipase testing in patients being monitored for acute or chronic pancreatitis, decision-makers should acknowledge the impact that personal health factors may have when determining the presence of pancreatitis. The clinical presentation of chronic pancreatitis can vary and have overlapping features with acute pancreatitis.[95] The etiology of both acute and chronic pancreatitis is commonly associated with addiction and substance use issues related to alcohol consumption and smoking which cause prolonged pancreatic damage.[87,95] It is important to incorporate a comprehensive assessment of a patient's medical history when determining potential pancreatitis. Serum lipase levels may fluctuate depending on the test timing and may be challenging to interpret in isolation for determining pancreatitis status.[93] Repeat lipase testing does not provide prognostic value and can impact decision-making around proper pancreatitis management or treatment if pancreatitis status is misdiagnosed; therefore, repeat lipase testing is not recommended to guide patient treatment.[91,93,95]

## Literature Review: Minimum Retesting Intervals for Lipid Panel

### What Is Lipid Panel Testing and What Is It Used For?

Lipid panel (or lipid profile) testing typically includes assessment of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, and sometimes apolipoprotein B.[96] A standard serum lipid panel test measures the concentration of total cholesterol, HDL cholesterol, and

triglycerides in the blood sample, from which the LDL cholesterol concentration can be estimated.[96] Lipid panel testing can be measured in the fasting or nonfasting state.[96] There are small, clinically insignificant differences in total and HDL cholesterol levels between fasting and nonfasting samples; however, triglyceride levels can be impacted by recent food intake (e.g., high fat meals).[96] In general, nonfasting lipid panels are recommended unless there is a history of elevated triglyceride levels or if an initial fasting lipid test reveals high triglyceride levels.[97]

Common indications for ordering a complete lipid panel include:[96,98]

- screening for familial lipid disorder
- establishing the risk of cardiovascular disease (CVD) in an individual without prior disease
- screening patients for a suspected lipid disorder (e.g., dyslipidemia, hypertriglyceridemia, hypercholesterolemia)
- monitoring response to treatment (e.g., lipid-lowering therapy, lifestyle modifications).

Lipid-lowering therapy can reduce a person's relative risk of CVD.[99] Screening for and treating lipid disorders is important to reduce the risk of CVD.[99] There are several different drug classes of lipid-lowering therapies, including statins (i.e., hydroxymethylglutaryl-CoA reductase inhibitors), fibric acid derivatives, bile acid sequestrants, cholesterol absorption inhibitors, and nicotinic acid.[100] These treatments vary by mechanism of action, which lipids are affected, and the percent change in lipid levels (i.e., the range of expected change in the lipid profile).[100] When making decisions about treatment, clinicians and patients should consider the potential risks and benefits of treatment and the patient's baseline CVD risk.[99]

After a patient starts lipid-lowering therapy, lipid levels are retested to evaluate whether treatment targets have been met, the potential need for treatment modifications, and to monitor adherence to the medication.[99] Although target levels of LDL cholesterol are often used to monitor and assess treatment efficacy,[99] target levels of HDL cholesterol and apolipoprotein B can also be used to determine whether treatment intensification is needed.[101]

## Research Questions

1. What are the recommendations regarding the minimum retesting interval for lipid panel in patients being monitored for treatment with oral lipid-lowering therapy?
2. What are the biological or physiological factors that may impact how often a lipid panel should be repeated in patients being monitored for treatment with lipid-lowering therapy?

### Inclusion Criteria

The selection of included literature was based on the inclusion criteria presented in Table 7.

## Table 7: Inclusion Criteria for Lipid Panel

| Criteria | Description |
|---|---|
| **Population** | Patients being monitored for treatment with oral lipid-lowering therapy<br>Primary conditions of interest include patients with:<br>• dyslipidemia<br>• hypertriglyceridemia<br>• hypercholesterolemia<br>• familial lipid disorders |
| **Test** | Lipid panel<br>• includes total cholesterol, LDL and HDL cholesterol, and TG<br>• fasting or nonfasting sample |
| **Types of information** | Q1: Recommendations regarding whether testing should be repeated; recommendations regarding the minimum time before a test should be repeated<br>Q2: Biological or physiological factors that impact minimum retesting interval (e.g., half-life of cholesterol, LDL and HDL cholesterol, and triglycerides) |
| **Study designs** | No restriction on type of publication |

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Note: Additional population subgroups of interest included patients with atherosclerotic cardiovascular disease, diabetes mellitus, and chronic kidney disease.

## Findings

### Clinical Guidelines

We identified 26 documents with recommendations regarding lipid panel retesting in patients being monitored for treatment with oral lipid-lowering therapy (refer to Appendix 5). These include 1 health technology assessment,[102] 14 evidence-based guidelines,[5,103-115] 4 consensus-based guidelines,[116-119] 4 guidelines with unclear methodology,[120-123] and 3 documents with recommendations from clinical societies or associations with unclear methodology.[124-126]

All 14 evidence-based guidelines reported the strength of the recommendation and/or the quality of the evidence that informed the recommendation.[5,103-115] There was a mix of strong recommendations (i.e., an intervention that should be offered) supported by high-quality evidence, moderate strength recommendations (i.e., actions that should be considered), and weak recommendations that were largely consensus-based (i.e., expert opinion) or very low–quality evidence.

All the included recommendations were specific to people being treated with lipid-lowering therapy. Fourteen of the documents specified a particular condition (e.g., diabetes, dyslipidemia);[102-104,107-114,118,120,123] in the other 12 documents, the population was more general (i.e., people treated with statins[105,106,117,119,121,122,124,126] or people treated with lipid-lowering therapy[5,115,116,125]).

The following populations were included in the summarized recommendations:

- Pediatric patients with dyslipidemia (1 document)[120]
- Adults

- treated with statins (9 documents)[105,106,117,119,121,122,124,126]
- treated with lipid-lowering therapy (therapy not further specified) (4 documents)[5,115,116,125]
- with any of the following
  - dyslipidemia (3 documents)[102,108,110]
  - hypercholesterolemia (1 document)[123]
  - familial hypercholesterolemia (1 document)[111]
  - CVD (1 document)[103]
  - chronic coronary disease (1 document)[104]
  - acute coronary syndrome (1 document)[109]
  - stroke or transient ischemic attack (1 document)[114]
  - diabetes (4 documents)[107,112,113,118]

We identified 3 types of recommendations: those that specified a minimum retesting interval, those that specified a testing frequency, and those that did not support repeat lipid panel testing.

### *Adults: Minimum Retesting Intervals*

Two publications made recommendations regarding the minimum time between lipid panel tests for adults being monitored for treatment with lipid-lowering therapy. One document was broadly applicable to people treated with lipid-lowering therapy,[5] and the other further specified people with hypercholesterolemia.[123]

These documents recommended the following minimum retesting intervals for the lipid panel:

- After initiating or changing lipid-lowering therapies
  - 4 weeks or more (1 guideline with unclear methodology)[123]
  - 3 months (1 evidence-based guideline)[5]
- On stable lipid-lowering therapy
  - 1 year (1 evidence-based guideline)[5]

The rationale given by the guideline that suggested a minimum retesting interval of 4 weeks or more was that the maximum therapeutic effect of statins is usually achieved within 4 weeks and that there is "little benefit in rechecking within 4 weeks" (p. 5).[123] The guideline that made the recommendation for a 3-month minimum retesting interval based their recommendation on a 2019 Clinical Knowledge Summary by the National Institute for Health and Care Excellence (NICE), but did not provide a further rationale.

We also identified 1 guideline with unclear methodology[122] specific to retesting lipid levels in patients treated with statins in the context of an acute shortage of blood collection tubes, which may provide insight for the minimum retesting interval. In the context of an acute blood collection tube shortage, this guideline[122] recommends the following:

- For patients treated with statins for primary prevention of CVD, routine monitoring of lipid levels is not required, with the exception of 3 months after initiating statins.

- For patients who are high risk for CVD or treated with statins for secondary prevention of additional CVD events, annual lipid testing is recommended.

### *Adults: Testing Frequency for Lipid Panels*

The other documents provided recommendations regarding the testing frequency for lipid panels for monitoring adults being treated with lipid-lowering therapy but did not specify the minimum time before a test should be repeated.[102-121,124-126] However, the testing frequency guidance for lipid panels may provide further insight for the minimum retesting interval.

The guidance differs based on whether patients have recently initiated or modified their lipid-lowering therapy (i.e., to ensure treatment targets are being met) or they are on stable therapy (i.e., to monitor treatment response and assess adherence to therapy). In addition, some documents recommend against retesting lipid panels.

We summarized the testing frequency recommendations based on whether the guidance was broadly applicable to patients being monitored for treatment with lipid-lowering therapy (without further specifying a condition) or if it was specific to certain populations or conditions of interest (i.e., dyslipidemia, hypertriglyceridemia, hypercholesterolemia, and familial lipid disorders). Additional subgroups of interest — atherosclerotic cardiovascular disease, diabetes mellitus, and chronic kidney disease — were included if identified.

#### Patients Being Monitored for Treatment With Statins or Lipid-Lowering Therapies (Therapy Not Specified)

We identified 10 documents[105,106,115-117,119,121,124-126] with recommendations regarding testing frequency for lipid panels in people being monitored for treatment with lipid-lowering therapy, of which 7 documents were specific to patients treated with statins;[105,106,117,119,121,124,126] the other 3 documents[115,116,125] did not specify the type of lipid-lowering therapy.

**After starting lipid-lowering therapy or following a dose adjustment:** The included publications recommended the following testing frequencies for lipid panels in patients being monitored for lipid-lowering therapy who have just initiated the therapy or who have had a dose adjustment to assess response to the therapy:

- 4 to 6 weeks[116,125]
- 4 to 12 weeks[105,106,116,117]
- 2 to 3 months[115]
- 3 months (specifically in patients treated with statins)[119]
- 6 to 12 months (specifically in patients treated with statins).[126]

**Once patients are on stable lipid-lowering therapy:** The included publications recommended the following lipid panel testing frequencies for patients who are on stable lipid therapy:

- every 3 to 12 months (specifically in patients treated with statins)[105,106,117]
- annually.[116,126]

**Recommendations against lipid panel retesting:** We also identified 2 documents that recommended against repeat lipid panel testing in patients treated with statins:

- Do not monitor or repeat lipid levels after a patient beings statin therapy (1 guideline with unclear methodology).[121]
  - The authors of this 2015 recommendation reported that. at the time of developing the guideline, there was no evidence to support repeat lipid panel testing after starting statin therapy nor was there evidence that repeating lipid levels would improve treatment adherence.[121]
- To assess response to statin therapy and adherence to therapy, a full lipid panel is not required. Instead, measure non-HDL cholesterol or apolipoprotein B within 3 to 6 months of starting statin therapy (recommendation from 1 clinical society with unclear methodology).[124]

### Familial Hypercholesterolemia

Annual lipid panel testing is recommended in all patients with familial hypercholesterolemia (1 evidence-based guideline).[111]

### Dyslipidemia

We identified 3 documents[102,108,110] with recommendations regarding testing frequency for lipid panels in people with dyslipidemia who are being treated with lipid-lowering therapy. A 2014 health technology assessment from Health Quality Ontario[102] reported that there was insufficient evidence at the time to make a recommendation on the frequency of lipid panel testing for patients with dyslipidemia, and it recommended that clinicians consider the 2012 Canadian Cardiovascular Society Guidelines for dyslipidemia.[127]

With respect to lipid panel testing frequency for patients with dyslipidemia, 1 guideline recommends retesting:

- 6 weeks after therapy initiation[110]
- at 6-week intervals until the treatment goals are achieved[110]
- every 6 to 12 months once on stable lipid therapy.[110]

The other guideline recommends against routine monitoring of lipid levels for patients who are being treated with statins, and suggests instead that monitoring lipid levels should be based on individual need rather than a routinely scheduled test.[108] The rationale provided by the authors of this guideline was that the comparative effectiveness of treating patients to achieve specific lipid levels and using a fixed dose of statins based on the initial risk assessment can only be determined indirectly. They only identified studies that evaluated the benefits and harms of different treatment intensities of statin therapy; they did not identify any direct evidence evaluating the effectiveness titrating medications to achieve target LDL or non-HDL cholesterol levels.[108]

### Hypercholesterolemia

With respect to testing frequency for lipid panels for people with hypercholesterolemia, 1 guideline with unclear methodology[123] recommends:

- retesting 2 months after therapy changes

- retesting annually if patients are within target values
- considering a patient's clinical condition to determine whether to test more or less frequently.

### Atherosclerotic Cardiovascular Disease

We identified 5 documents that included recommendations regarding testing frequency for lipid panels specific to different types of atherosclerotic cardiovascular disease, including CVD (not further specified),[103] chronic coronary disease,[104] acute coronary syndrome,[109] acute atherosclerotic event,[116] and stroke or transient ischemic attack.[114]

With respect to testing frequency for lipid panels in patients with atherosclerotic cardiovascular disease, 4 guidelines recommend the following:

- After starting lipid-lowering therapy or following a dose adjustment, measure lipid levels at:
  - 4 to 6 weeks[109,116]
  - 4 to 12 weeks.[104,114]
- Once patients are on stable lipid-lowering therapy, measure lipid levels:
  - every 3 to 12 months based on need to assess response or adherence to therapy.[104,114]

The other guideline recommends against repeat lipid panel testing after a patient begins lipid-lowering therapy.[103] The authors of this 2023 guideline reported that, at the time of writing the recommendation, the best available evidence did not support repeat lipid testing and they found the treat-to-target approach was not desirable. The authors considered the challenge of achieving lipid targets, biological variation in lipid testing, as well as the costs and inconvenience of repeat testing.[103]

### Diabetes

We identified 4 documents with recommendations regarding testing frequency for lipid panels in people with diabetes.[107,112,113,118] These guidelines recommend the following testing frequencies for lipid panels based on whether patients have recently initiated or modified their lipid-lowering therapy or they are on stable therapy:

Regarding testing frequency for lipid panels in people with diabetes, 3 guidelines recommend the following after starting lipid-lowering therapy or following a dose adjustment:

- 4 to 12 weeks[112]
- 6- to-12-week intervals (until goal achieved)[118]
- 3 to 6 months.[107]

Regarding testing frequency for lipid panels in people with diabetes, 3 guidelines recommend the following once patients are on stable lipid-lowering therapy:

- every 6 months[118]
- annually.[112,113]

### *Pediatrics*

In pediatric patients with dyslipidemia, 1 guideline with unclear methodology[120] recommends the following testing frequencies for lipid panels:

- Measure lipid levels at 4 to 8 weeks after starting statin therapy or a dose adjustment
  - if LDL targets are not achieved, adjust dose and retest at 4 weeks
  - if LDL targets are achieved, repeat every 3 to 6 months.

### Factors That Impact the Frequency of Lipid Panel Retesting

A key factor that impacts the minimum retesting interval for lipid panels for patients being monitored for treatment with lipid-lowering therapy is the time it takes for a therapeutic response to be observed following initiation of lipid-lowering therapy or a dosage change. One guideline suggested that the maximum therapeutic response in blood lipid levels is usually achieved within 4 to 12 weeks after initiation of or a change in lipid-lowering therapy.[104] Another guideline reported that the maximum therapeutic response to statins is usually achieved within 4 weeks, thus there is little value in retesting lipid levels within 4 weeks of initiating or changing therapy.[123]

Decision-makers should consider that treatment response may vary by lipid-lowering therapy (refer to Table 8), and this may impact the minimum time before a test should be repeated, especially for patients initiating or changing a lipid-lowering therapy.

## Table 8: Approximate Time to Therapeutic Response of Different Lipid-Lowering Therapies

| Lipid-lowering therapy | Usual time of initial response | Usual time of maximum response |
|---|---|---|
| Statins (e.g., atorvastatin, fluvastatin)[123,128-130] | 2 weeks | 4 weeks |
| Cholesterol absorption inhibitors (e.g., ezetimibe)[131] | — | 2 weeks |
| Fibrates (e.g., fenofibrate, gemfibrozil)[128,132] | — | 4 to 12 weeks |
| Bile acid sequestrates (e.g., colestipol)[133] | 24 to 48 hours | 4 weeks |

Note: This table provides examples of time to therapeutic response, but it is not intended to be a comprehensive summary of all lipid-lowering therapies. Response times may vary between and within classes of lipid-lowering therapies.

If patients maintain their lipid-lowering therapy, the therapeutic response of the medication is usually maintained.[112,129,130,132,133] This means that once treatment targets are obtained, decision-makers may choose to reduce the frequency of lipid panel screening for these patients based on individual patient needs.

There are many factors that may affect blood lipid levels which may require increased testing frequency. These factors include:

- deterioration of glucose management[110]
- initiation of a drug known to affect lipid levels[110]
- progression of atherothrombotic disease[110]
- substantial weight gain[110]

- unexpected adverse change in any lipid parameter[110]
- development of a new atherosclerotic cardiovascular disease risk factor (e.g., high blood pressure, chronic kidney disease, diabetes)[110]
- menopause[99]
- change in health status[99]
- severe illness.[99]

Decision-makers should consider the clinical situation and the individual needs of their patients when determining the testing frequency for lipid panels for their patients.

### Equity Considerations

From the included documents, 3 guidelines included recommendations regarding health equity and social determinants of health given their links to CVD risk and outcomes.[104,105,114] These recommendations are not specific to lipid panel retesting but are intended to be more broadly applied when treating people with or at risk of atherosclerotic cardiovascular disease (refer to Appendix 5). These guidelines recommended the following:

- To reduce health care disparities and to inform patient-centred health care decisions, clinicians should routinely evaluate and address social determinants of health (e.g., mental health, literacy level, psychosocial stressors, sociocultural influences [language, religious affiliation, body image], financial strain, barriers to adherence to a heart healthy diet [food security], housing, and transportation barriers) (2 guidelines).[104,114]
- To allow for health inequities to be identified and addressed, clinicians should monitor whether patients are achieving the nationally accepted performance measures (1 guideline).[114]
- Clinicians should review how a patient's race and ethnicity could affect atherosclerotic cardiovascular disease risk and adjust the treatment accordingly (1 guideline).[105]

When considering the minimum retesting interval for lipid panels for monitoring patients treated with lipid-lowering therapies, decision-makers may also want to consider the following:

- The documents included in this report that provided minimum retesting interval and testing frequency recommendations were primarily developed in high-income countries situated in the global north; therefore, the recommendations for lipid panel retesting may not be generalizable to all patients.
- People from racialized populations, including people who are Black, Hispanic, Latino, Filipino, Japanese, or Vietnamese, have higher risk of dyslipidemia than people who are white.[105]
- People from racialized populations may respond differently to lipid-lowering therapy:
  - People who are Japanese may be more sensitive to statins and may benefit from lower doses.[105]
- Certain populations have increased atherosclerotic cardiovascular disease risk, including:
  - racialized populations (e.g., people who are Black, Asian, Hispanic, or Latino)[104,105,114]
  - women[104,114]
  - people living in rural and remote areas[104,114]

- people living in dense urban areas[104]
- older adults[114]
- individuals with low socioeconomic status[104,105,114]
- people who are gay, lesbian, or bisexual[114]
- people who are transgender.[114]

- Social determinants of health can affect treatment adherence and atherosclerotic cardiovascular disease outcomes, including:
  - health care access[104]
  - mental illness[114]
  - lack of health literacy[114]
  - exposure to adversity (e.g., home or community violence, trauma exposures, safety concerns)[114]
  - economic stability[104,114]
  - inadequate housing conditions[114]
  - lack of food security (i.e., access to affordable and nutritious food)[114]
  - structural and individual discrimination[114]
  - inadequate social support.[114]

# Literature Review: Minimum Retesting Intervals for SPEP

## What Is SPEP and What Is It Used For?

SPEP is primarily used as a screening procedure to detect the presence and concentration of monoclonal immunoglobulin (M protein). M protein identification is used to support the diagnosis and subsequent monitoring of patients with suspected or confirmed plasma cell dyscrasias, which are a heterogenous group of diseases characterized by the number of monoclonal bone marrow cells that produce monoclonal immunoglobulins.[134] Multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), smouldering (asymptomatic) myeloma, Waldenström macroglobulinemia, and amyloidosis are common groups of plasma cell dyscrasias.[135]

Electrophoresis is a method of separating proteins based on their physical properties.[136] In SPEP, an electrical charge is applied to a small amount of blood serum on a specific medium which causes the proteins in the serum to migrate across the medium at different rates based on the net charge and type of protein.[137] In routine SPEP, the proteins will separate into albumin and globulins (alpha$_1$, alpha$_2$, beta, and gamma).[137] If an M protein is identified, it can be quantitated using agarose gel tracing.[138] SPEP can detect the presence or absence of an M protein in the serum and provide a measurement of M protein concentration (or size).[138] M protein typically presents as a single narrow spike in the gamma, beta, or alpha$_2$ regions of the serum sample or as a dense discrete band on the agarose gel.[138] The M protein presentation, concentration, and region from the SPEP sample can indicate the type of plasma cell dyscrasia; however,

further testing using more sensitive methods are required for accurate diagnosis and patient management strategies.[138,139] Initial SPEP testing should be performed in combination with serum immunofixation to determine and confirm monoclonality and immunoglobulin class if an M protein is identified.[138] Additional SPEP testing if often required for monitoring in patients with a diagnosed plasma cell dyscrasia disease either as watchful waiting or for monitoring treatment response.[140]

## Research Questions

1. What are the recommendations regarding the minimum retesting interval for the SPEP test in patients being monitored for plasma cell dyscrasias?
2. What are the biological or physiological factors that may impact how often SPEP should be repeated?

### Inclusion Criteria

The selection of included literature was based on the inclusion criteria presented in Table 9.

## Table 9: Inclusion Criteria for SPEP

| Criteria | Description |
|---|---|
| Population | Patients being monitored for plasma cell dyscrasias |
| Test | Serum protein electrophoresis testing |
| Types of information | Q1: Recommendations regarding whether testing should be repeated; recommendations regarding the minimum time before a test should be repeated<br>Q2: Biological or physiological factors that impact minimum retesting interval (e.g., half-life, production of albumin, alpha$_1$ globulin, alpha$_2$ globulin, beta globulin, gamma globulin [i.e., the different fractions of SPEP]) |
| Study designs | No restriction on type of publication |

SPEP = serum protein electrophoresis.

## Findings

### Clinical Guidelines

We identified 16 documents with recommendations regarding retesting SPEP in patients being monitored for various plasma cell dyscrasia–related diseases (refer to Appendix 6). These include 6 evidence-based guidelines,[5,141-145] 3 consensus-based guidelines,[139,146,147] 2 guidelines with unclear methodology,[148,149] 3 publications that provided recommendations from clinical societies or associations,[150-152] and 2 laboratory guidance documents.[153] Two publications reported the grade or strength of recommendations,[147,151] and 2 publications reported the quality of evidence that informed the recommendations.[5,147] When reported, the recommendations were weak recommendations (i.e., a suggested intervention) and based on low- to moderate-quality evidence and expert opinion. The 2 laboratory guidance documents did not specify a patient population in their recommendation; however, it is reasonable to assume that the recommendation regarding SPEP testing is associated with patients being monitored for plasma cell dyscrasia–related diseases.[153,154]

We identified 3 types of recommendations relevant to the patient populations of interest: those against ordering an initial or repeat SPEP test, those that specified a minimum retesting interval, and those that specified a testing frequency.

### *Recommendations Against Ordering SPEP Testing*

We identified 1 publication that recommended against ordering SPEP testing in asymptomatic patients with an absence of hypercalcemia, renal insufficiency, anemia, or lytic bone lesions.[152]

### *Minimum Retesting Interval for SPEP Testing*

Four publications made recommendations regarding the minimum time between tests for SPEP in nonspecified patient populations, patients suspected of having plasma cell dyscrasia, and in patients with MGUS. These documents recommend the following:

- For general SPEP minimum retesting intervals for nonspecified patient populations
  - minimum retesting interval of 4 or more weeks and any test ordered before 28 days will be cancelled (2 publications)[153,154]
- For patients suspected of plasma cell dyscrasia
  - 3-month minimum retesting interval (1 guideline)[5]
- For monitoring patients with MGUS
  - 6-month minimum retesting interval for monitoring progression for smouldering (asymptomatic) MGUS (1 publication)[139]
  - 1-year minimum retesting interval for monitoring progression of MGUS (2 publications)[5,139]
  - 5-year minimum retesting interval for monitoring progression of sub-MGUS (1 publication)[139]
- For monitoring patients receiving treatment for MGUS
  - 1-month retesting interval for monitoring patient response to bone marrow transplant treatment (1 publication)[139]
  - 3-month retesting interval for monitoring patient response to chemotherapy treatment (1 publication)[139]
- For monitoring patients with MGUS in remission
  - 6-month retesting interval unless significant clinical change for monitoring for relapse (1 publication)[139]

### *Testing Frequency for SPEP Testing in Various Patient Populations*

Ten publications made recommendations regarding the frequency of SPEP testing for patients being monitored for various conditions, including MGUS, multiple myeloma, smouldering multiple myeloma (SMM), Waldenström macroglobulinemia, and relapsed or refractory B-cell malignancies.

Regarding repeat SPEP testing for patients with MGUS, 3 documents recommend the following:

- At 3 to 6 months after initial diagnosis of MGUS to exclude multiple myeloma or Waldenström macroglobulinemia (2 publications).[149,151]

- For monitoring patients with low-risk MGUS:
  - every 6 months (2 publications)[141,149]
  - annually (1 publication)[141] or every 2 to 3 years (2 publications)[149,151] once low-risk MGUS becomes stable.
- For monitoring patients with intermediate- and high-risk MGUS
  - every 6 months (2 publications)[141,149]
  - annually once intermediate and high-risk MGUS becomes stable (3 publications).[141,149,151]

Regarding repeat SPEP testing for patients with multiple myeloma, 4 documents recommend the following:

- In 1-month intervals (1 publication).[150]
- For patients with extramedullary disease
  - every month (1 guideline)[142]
  - every 3 months once condition is stable (1 guideline).[142]
- For patients who have completed myeloma treatment and have recovered
  - every 3 months (1 guideline).[143]
- For monitoring patients after autologous stem cell transplant treatment
  - every month (1 publication)[147]
  - every 3 months once condition is stable (1 publication).[147]

Regarding repeat SPEP testing for patients with SMM, 4 documents recommend the following:

- In general, repeat SPEP testing either
  - every 3 to 6 months for 1 year (2 publication)[144,149] then every 6 to 12 months once SMM becomes stable (1 publication)[149]
  - every 3 months for 5 years then decide frequency for further monitoring based on long-term stability of disease (1 guideline).[143]
- For monitoring patients with low and intermediate-risk SMM, repeat SPEP testing
  - every 3 to 4 months for 1 year (1 guideline)[141]
  - every 6 months once SMM becomes stable (1 guideline).[141]
- For monitoring patients with high-risk SMM, repeat SPEP testing
  - every 2 to 3 months within the first year of initial diagnosis of SMM (2 publications)[141,149] and then, if stable, every 4 to 6 months for 5 years or until SMM progression (1 publication)[141]
  - if stable, repeat evaluation every 6 months for life or until SMM progression.[141]

Regarding repeat SPEP testing for patients with Waldenström macroglobulinemia: 2 documents recommend the following:

- One guideline recommends:
  - every 3 months for 2 years (1 publication)[148]

    - every 4 to 6 months for the next 3 years (1 publication)[148]
    - every 6 to 12 months after year 5 (1 publication).[148]
- One guideline recommends for patients with asymptomatic or minimally symptomatic Waldenström macroglobulinemia:
    - every 12 months in patients who are at low risk (1 guideline)[40]
    - every 6 months in patients who are at intermediate risk (1 guideline)[40]
    - every 3 months in patients who are at high risk (1 guideline).[40]

Regarding repeat SPEP testing for patients with relapsed or refractory B-cell malignancies, 1 document recommends the following:

- Every 1 to 3 months during medium-term (day 28 to 100) follow-up (1 publication).[146]
- At every subsequent visit for long-term follow-up (1 publication)[146] at recommended visit frequencies
    - monthly from day 100 to 1 year[146]
    - every 6 months for the next 1 to 2 years[146]
    - annually from year 2 to year 15.[146]

### Factors That Impact SPEP Retesting

SPEP testing can be impacted by the patient condition and the method of SPEP testing. Patients experiencing acute inflammatory processes, including bacterial and viral infections, can have reactive changes in immunoglobulin levels.[155] These changes in immunoglobulins can be mistaken for changes in M proteins, and can affect the sensitivity and specificity of the SPEP test to determine the presence or absence of plasma cell dyscrasias.[155] In addition, certain electrophoresis methods are subject to increased interference from imaging contrast dyes, the use of antibiotics, and certain types of monoclonal therapies.[139,155,156] Electrophoresis interference can cause misinterpretation about the absence or presence of M protein in the serum sample and may lead to improper patient management or unnecessary additional testing.[155,156] The changes in immunoglobulins from acute inflammation or test interference may present SPEP results similar to that of plasma cell dyscrasias. This can often lead to additional follow-up SPEP testing and increased use of additional testing such as immunofixation, which is a highly sensitive test for determining M protein concentration.[155] Clinicians should be aware of potential sources of test interference when interpreting results and making decisions for additional testing.

Acute reactions due to patient conditions, including inflammation, trauma, necrosis, infarction, burns, and chemical injuries, often produce reasonably predictable changes in plasma protein levels.[136] These changes in plasma protein levels involve increases in fibrinogen, alpha$_1$-antitrypsin, haptoglobin, ceruloplasmin, C-reactive protein, and alpha$_1$-acid glycoprotein.[136] These conditions produce decreased albumin levels[136] and may impact the ability to properly interpret SPEP findings, requiring increased monitoring or further testing. Determining the need for additional testing should also be informed by the suspected or diagnosed patient condition and whether treatment may impact SPEP testing results. For example, evidence from 1 guideline suggested that patients with very low concentrations of M proteins are unlikely to progress to multiple myeloma and therefore would require less frequent follow-up testing.[139]

### Equity Considerations

When considering the minimum retesting interval for SPEP testing in patients being monitored for various plasma cell dyscrasia–related diseases, decision-makers may also want to consider the following:

- The documents included in this report that provided minimum retesting interval and testing frequency recommendations were primarily developed in high-income countries situated in the global north; therefore, the recommendations for SPEP retesting may not be generalizable to all patients.
- Limited evidence suggests that various plasma cell dyscrasia–related diseases, such as multiple myeloma and MGUS, may disproportionately impact different patient populations. One guideline found that, in Canada, men have a higher annual incidence of multiple myeloma compared to women.[141] The prevalence of MGUS has been reported to be higher among individuals who are Black than individuals who are white. MGUS affects approximately 3% of people older than 50 years and increases with age.[149,157] It is unclear if higher incidence and prevalence of various plasma cell dyscrasia diseases in these populations have any implications on the use of or retesting intervals for SPEP; however, given the current guidance, patients with suggested or confirmed plasma cell dyscrasia–related diseases are likely to have consistent SPEP monitoring.
- The interpretation of SPEP results can often be limited by few agreed-upon criteria for reporting results and a lack of universally agreed-upon standards for quality control or technology for test use.[139] Because of this lack of consistency, interpretation of results may vary depending on setting or region, thus impacting retesting frequencies and patient experience.[139]

## Literature Review: Minimum Retesting Intervals for TSH

### What Is TSH Testing and What Is It Used For?

Thyroid hormones T4 (thyroxine) and T3 (triiodothyronine) are regulated by pituitary TSH.[158] Small changes in T4 concentration may be difficult to measure, although these small changes typically cause large changes in TSH concentrations.[158] As a result, thyroid function is typically assessed by serum TSH testing.[158] Serum TSH is usually determined using an automated immunometric chemiluminescent third-generation TSH level test.[158] Serum TSH testing is used to evaluate thyroid dysfunction, primarily for the detection and treatment monitoring of hyperthyroidism and hypothyroidism.

Hypothyroidism is characterized by an underactive thyroid gland and is often treated with levothyroxine replacement therapy and monitored by assessing serum TSH. Hyperthyroidism is characterized by an overly active thyroid gland and is often treated with antithyroid drugs, radioiodine, or surgery, which can initially cause low TSH concentrations.[158] Once thyroidal function steady-state conditions are assured for hyperthyroidism, serum TSH measurements can be used to assess the efficacy of treatment.[158] Table 10 presents the serum TSH levels that correspond to the various types of thyroid dysfunction.

## Table 10: Classification of Thyroid Dysfunction Based on TSH Level[159]

| Condition | TSH concentration |
|---|---|
| Overt hypothyroidism | > 4.5 mIU/L |
| Overt hyperthyroidism | < 0.1 mIU/L or undetectable |
| Subclinical hypothyroidism | TSH level > 4.5 mIU/L but ≤ 10 mIU/L |
| Subclinical hyperthyroidism | TSH level ≥ 0.1 mIU/L but < 0.4 mIU/L |

TSH = thyroid-stimulating hormone.

## Research Questions

1. What are the recommendations regarding the minimum retesting interval for serum TSH concentration in people being monitored for treatment of hypothyroidism?
2. What are the recommendations regarding the minimum retesting interval for serum TSH concentration in people being monitored for treatment of hyperthyroidism?
3. How long does it take TSH to reach a new steady state in the blood stream after a dose adjustment of thyroid replacement therapy or treatment for hyperthyroidism, and how does this affect the minimum retesting interval for people being treated for hypothyroidism or hyperthyroidism?

### Inclusion Criteria

The selection of included literature was based on the inclusion criteria presented in Table 11.

## Table 11: Inclusion Criteria for TSH

| Criteria | Description |
|---|---|
| Population | Q1 and Q3: People being monitored for treatment with thyroid replacement therapy for hypothyroidism<br>Q2 and Q3: People being monitored for treatment of hyperthyroidism |
| Test | Serum TSH concentration |
| Types of information | Q1 and Q2: Recommendations regarding whether testing should be repeated; recommendations regarding the minimum time before a test should be repeated<br>Q3: Time to reach steady-state TSH level after dose adjustment and biological or physiological factors (e.g., half-life) that affect time to steady state |
| Study designs | No restriction on type of publication |

TSH = thyroid-stimulating hormone.

### Exclusion Criteria

Literature was excluded if it did not meet the criteria outlined in Table 11.

We excluded recommendations about TSH if:

- TSH was used to monitor people who were not being treated with thyroid replacement therapy
- TSH was used to monitor people who had stopped taking thyroid replacement therapy or antithyroid drugs
- TSH was used to diagnose hypothyroidism or hyperthyroidism

- a time frame or testing frequency was not included.

If a recommendation for TSH testing also included guidance around T3 or T4 testing, this information was reported. However, we excluded recommendations that were specific to measuring T3 or T4 if they did not mention measuring TSH level or did not provide context for the TSH test recommendation.

## Findings

### Clinical Guidelines

One evidence-based guideline was identified that provides recommendations that are specified as minimum retesting intervals for TSH testing in people being monitored for treatment of hypothyroidism and hyperthyroidism.[5] One document from a medical laboratory association provided minimum TSH retesting intervals for people being monitored for hypothyroidism treatment.[160] In addition, 1 low-quality guideline with unclear methodology was identified that specifies a minimum TSH retesting interval for people being monitored for treatment of Grave disease or other causes of hyperthyroidism.[161] The majority of identified documents provide recommendations related to measuring TSH and retesting frequency in people being monitored for treatment of hypothyroidism and hyperthyroidism, which may provide insight for minimum retesting intervals.

Considerations for T3 or T4 testing that were included in the identified recommendations for TSH retesting intervals were captured and reported in the summary of recommendations tables presented in Appendices 2, 3, and 4. A summary of the number of recommendations that provided considerations for T3 or T4 testing are presented subsequently.

The focus of this literature review is on people receiving treatment for hypothyroidism or hyperthyroidism; however, additional recommendations of potential interest related to TSH retesting frequencies and monitoring for untreated people with hypothyroidism or hyperthyroidism are presented in Appendix 7.

#### *Hypothyroidism*

We identified 9 documents with recommendations regarding TSH minimum retesting intervals or testing frequencies for people living with hypothyroidism (refer to Appendix 7).[5,160-167] These included 6 evidence-based guidelines,[5,162,163,165-167] and 4 documents with recommendations from clinical societies or associations with unclear methodology.[160,161,164,168] Four evidence-based guidelines and 1 document with unclear methodology reported the strength of recommendations and/or the quality of evidence that informed the recommendation.[5,163,164,166,167] There was a mix of both strong recommendations (i.e., an intervention that should be followed) and weak recommendations (i.e., a suggested intervention). The recommendations were largely based on low to moderate quality of evidence and expert opinion. One evidence-based guideline provided recommendations specifically for monitoring subclinical hypothyroidism.[166]

#### Minimum TSH Retesting Interval for Hypothyroidism: Adults

One evidence-based guideline made recommendations that are specified as minimum retesting intervals for TSH testing in people living with hypothyroidism.[5] In addition, 2 guidance documents with unclear

methodology provided recommendations for a minimum retesting interval for TSH testing following treatment.[160,161]

For monitoring of hypothyroidism treatment with thyroid replacement therapy, the guidelines recommend the following:

- Do not retest thyroid function before a minimum of 2 months after a change of dose (1 guideline).[5]
- Do not retest TSH before a minimum of 4 to 6 weeks after initiating or changing a thyroid replacement therapy dose or a change in the person's clinical status (2 publications).[160,161]
- Retest TSH annually for people stabilized on long-term thyroxine treatment (1 guideline).[5]

The guidance document with unclear methodology that recommended a 6-week minimum retesting interval noted that TSH values change slowly, thus frequent repeat testing is not indicated.[161]

One guidance document with unclear methodology also mentions including free T3 (FT3) and free T4 (FT4) tests with TSH measurements.[160]

### TSH Retesting Frequency for Hypothyroidism: Adults

For monitoring of hypothyroidism treatment with thyroid replacement therapy, measure TSH:

- at 1- to 2-month intervals when initiating treatment and establishing dose (3 publications)[163,164,167]
- every 3 to 6 months until TSH levels become stable (3 publications)[162,163,165]
- annually after TSH levels become stable (5 publications).[161-163,165,168]

Two evidence-based guidelines also mention measuring FT4 at the same time as TSH.[162,167]

For monitoring downtitration of thyroid replacement therapy in adults with hypothyroidism, measure TSH:

- 4 to 6 weeks after downtitration to check the adequacy of the replacement therapy (1 guideline).[167]

This evidence-based guideline also mentions measuring FT4 with TSH.[167]

For the monitoring treatment of subclinical hypothyroidism, measure TSH:

- 1 to 2 months after treatment initiation (1 publication)[166]
- annually once treatment dosage has been established (1 publication).[166]

### TSH Retesting Frequency for Hypothyroidism During Pregnancy and Postpartum

We identified 6 documents with recommendations regarding TSH retesting frequencies for people who are pregnant or postpartum and living with hypothyroidism (refer to Appendix 7).[161,163,169-172] These include 4 evidence-based guidelines,[163,169,171,172] 1 guideline with consensus-based recommendations,[170] and 2 guidelines with unclear methodology.[161,168] All 4 evidence-based guidelines and 1 consensus-based guideline reported the strength or grade of recommendation and/or the quality of evidence that informed the recommendation.[163,169-172] There was a mix of strong recommendations (i.e., an intervention that should be followed), moderate strength recommendations (i.e., actions that should be considered), and weak recommendations (i.e., a suggested intervention). The recommendations were largely based on limited high-quality evidence but were primarily low to moderate quality of evidence and expert opinion. One evidence-

based guideline provided recommendations for congenital hypothyroidism,[172] while 1 consensus-based guideline provided recommendations for consideration of monitoring postpartum hypothyroidism.[170]

For monitoring treatment of hypothyroidism during pregnancy, measure TSH:

- every 4 to 6 weeks when initiating treatment and establishing dose (6 publications)[161,163,168-171]
- once during the second and third trimester when treatment dose has been established (3 guidelines)[163,169,171]
- every 4 to 6 weeks during the first trimester and at least once during the second and third trimester (3 guidelines)[163,169,171]
- do not retest TSH if measurements are within the target range at 30 weeks' gestation (1 guideline).[170]

Two of these publications also mention measuring FT4 with TSH.[163,170]

For the monitoring and treatment of pregnancy with congenital hypothyroidism, measure TSH:

- every 4 to 6 weeks to monitor for acceptable treatment range (i.e., < 2.5 mU/L) (1 guideline).[172]

This evidence-based guideline also mentions measuring FT4 with TSH.[172]

For monitoring of postpartum hypothyroidism in all people who had hypothyroidism during pregnancy, measure TSH:

- 6 weeks postpartum (1 publication).[170]

This publication also mentions measuring FT4 with TSH.[170]

### TSH Retesting Frequency for Hypothyroidism in Pediatrics

We identified 4 documents with recommendations regarding TSH retesting frequencies for infants and pediatric patients with hypothyroidism (refer to Appendix 7).[165,172-174] These included 2 evidence-based guidelines[165,172] and 2 guidelines with unclear methodology.[173,174] One evidence-based guideline reported the strength of recommendation and/or quality of evidence that informed the recommendation.[172] There was a mix of both strong recommendations (i.e., an intervention that should be followed) and weak recommendations (i.e., a suggested intervention). The recommendations were largely based on low to moderate quality of evidence and expert opinion. Four publications provided recommendations for newborns and infants.[165,172-174]

For monitoring of primary hypothyroidism in children aged 2 years and older who are taking levothyroxine, measure TSH:

- every 6 to 12 weeks until TSH levels have stabilized (3 publications)[165,173,174]
- every 4 to 6 months after stabilization until puberty (3 publications)[165,173,174]
- annually after puberty (3 publications).[165,173,174]

All included publications also mention measuring FT4 with TSH.[165,172-174]

For monitoring of primary hypothyroidism in newborns and infants who are taking levothyroxine, measure TSH:

- 1 to 2 weeks after treatment initiation (3 publications)[172-174]
- every 4 to 8 weeks after this until the TSH level is stabilized (3 publications)[165,172,173]
- every 2 to 3 months after stabilization during the first year of life (4 publications)[165,172-174]
- every 3 to 4 months during the second year of life (4 publications).[165,172-174]

All included publications also mention measuring FT4 with TSH.[165,172,173]

### *Hyperthyroidism*

We identified 5 documents with recommendations regarding TSH retesting intervals for people living with hyperthyroidism (refer to Appendix 7).[5,160,161,165,175] These included 3 evidence-based guidelines[5,165,175] and 2 guidelines with unclear methodology.[160,161] Two evidence-based guidelines reported the strength of recommendation and/or quality of evidence that informed the recommendation.[5,175] When reported, each evidence-based guideline provided strong recommendations (i.e., an intervention that should be followed) and recommendations that were largely based on low-quality evidence or expert opinion.

#### Minimum TSH Retesting Interval for Hyperthyroidism: Adults

One evidence-based guideline made recommendations that are specified as minimum retesting intervals for TSH testing in people living with hyperthyroidism.[5] In addition, 1 low-quality guideline with unclear methodology was identified that specifies a minimum TSH retesting interval for adults receiving treatment for Grave disease or other causes of hyperthyroidism.[161]

For monitoring adults receiving treatment for Grave disease or other causes of hyperthyroidism, including excessive thyroid hormone replacement treatment, subacute thyroiditis, toxic multinodular goitre, and toxic adenoma, the following intervals are suggested:

- do not retest TSH for at least 1 month (1 publication)[161]
- retest TSH at 1- to-2-month intervals until results are stable (1 guideline)[5]
- after results are stable, retest TSH annually.[5]

One document provided a rationale for its recommended 1-month minimum retesting interval related to the prolonged suppression of TSH secretion observed with hyperthyroidism.[161]

One guideline mentions measuring FT4 and total T3 with TSH following radioactive iodine treatment for toxic multinodular goitre or toxic adenoma.[5] The other document mentions measuring FT4 with TSH for the treatment of Grave's disease or other causes of hyperthyroidism.[161]

#### TSH Retesting Frequency for Hyperthyroidism: Adults

For monitoring of adults receiving radioactive iodine treatment for hyperthyroidism, measure TSH:

- every 4 to 6 weeks for the first 6 months until TSH level is within reference range (2 guidelines)[165,175]
- every 9 to 12 months after treatment (2 guidelines)[165,175]

- if TSH level is within reference range 12 months after treatment, measure every 6 months (2 publications).[165,175]

Both evidence-based guidelines also mention measuring FT4 and FT3 or total T3 with TSH, including considerations for cascading.[165,175]

For monitoring of adults who received surgery for hyperthyroidism, measure TSH:

- at 2 and 6 months after surgery (2 guidelines);[165,175]
- every 1 to 2 months until TSH levels stabilize for adults receiving thyroid hormone replacement treatment (2 guidelines)[165,175]
- after results are stable, annually for TSH level monitoring (2 guidelines).[165,175]

One evidence-based guideline also mentions measuring FT4 with TSH, including considerations for cascading.[165]

For monitoring of adults receiving antithyroid drugs for hyperthyroidism, measure TSH:

- every 6 weeks until the TSH level is within reference range (1 guideline)[165]
- every 3 months until treatment is stopped (1 guideline)[165]
- at 4 to 8 weeks after treatment is stopped (1 guideline)[165]
- every 3 months during first year of no treatment (1 guideline)[165]
- every 6 months during the second year of no treatment (1 guideline)[165]
- annually after the second year of no treatment (1 guideline).[165]

The evidence-based guideline also mentions measuring FT4 and FT3 with TSH, including considerations for cascading.[165]

In addition, we identified 1 guideline with unclear methodology[160] that suggested that the efficacy of antithyroid treatment is monitored by measuring FT4 and FT3 (rather than TSH) because suppressed levels of TSH are slow to respond to antithyroid medications and can take 3 to 4 months to fully adjust.

### TSH Retesting Frequency for Hyperthyroidism During Pregnancy and Postpartum

We identified 3 evidence-based guidelines with recommendations regarding TSH retesting intervals for people who are pregnant or postpartum living with hyperthyroidism (refer to Appendix 7).[169,176,177] Each included evidence-based guideline reported strength of recommendation and/or quality of evidence that informed the recommendation. There was a mix of both strong recommendations (i.e., an intervention that should be followed) and weak recommendations (i.e., a suggested intervention). The recommendations were largely based on low to moderate quality of evidence and expert opinion. One evidence-based guideline provided recommendations for consideration of monitoring postpartum hyperthyroidism.

For monitoring of treatment with antithyroid drugs for hyperthyroidism during pregnancy, measure TSH:

- every 2 weeks following treatment initiation (3 guidelines)[169,176,177]
- every 2 to 6 weeks after achieving target TSH levels (3 guidelines).[169,176,177]

All 3 evidence-based guidelines also mention measuring FT4 or total T4 with TSH.[169,176,177]

For monitoring of pregnant people with hyperthyroidism following antithyroid drug treatment cessation, measure TSH:

- every 1 to 2 weeks to assess maternal and fetal thyroid function (1 guideline)[169]
- every 2 to 4 weeks during the second and third trimester if TSH levels remain stable (1 guideline).[169]

This evidence-based guideline also mentions measuring FT4 or total T4 with TSH.[169]

For monitoring of hyperthyroidism postpartum in people who received antithyroid drug treatment, measure TSH:

- at 6 weeks after childbirth with regular follow-up testing (no indication of timing for follow-up testing was provided) (1 guideline).[177]

The evidence-based guideline also mentions measuring FT4 with TSH.[177]

### Factors Affecting TSH Retesting Intervals Following Treatment

#### *Hypothyroidism*

Hypothyroidism is typically managed with thyroid hormone replacement therapy, usually levothyroxine, which is as an oral form of the T4 hormone. In most cases, symptoms of hypothyroidism begin to improve within 2 weeks of levothyroxine initiation.[158] In more severe cases, treatment may be required for several months before symptoms are fully recovered.[158] The serum half-life of levothyroxine is 5 to 7 days.[178] After initiation of levothyroxine treatment or a change in dose, a new steady state for TSH level is reached in as few as 5 weeks to 2 months; therefore, it is not recommended to assess thyroid function before this period.[5,25] Once optimal doses have been identified, annual TSH monitoring is recommended or more often as needed.[5,165,179] The majority of people with hypothyroidism require lifelong treatment, and monitoring and dosing of levothyroxine may need to be adjusted over time.[158]

Bexarotene, octreotide, mitotane, metformin, dopamine, and glucocorticoids are drugs that suppress TSH secretion.[25] People taking these drugs may need to have thyroid hormone replacement therapy, which may require routine TSH measurements to establish appropriate treatment dosage.[25]

#### *Hyperthyroidism*

Limited information was identified from the focused literature search related to the time needed for TSH to reach steady state after treatment for hyperthyroidism and the factors affecting minimum TSH retesting intervals.

Hyperthyroidism may be treated using antithyroid drugs, radioiodine therapy, or surgery. Blood thyroid hormone levels are typically reduced during antithyroid drug therapy.[179] Methimazole is the preferred antithyroid drug; the typical prescription is 5 mg to 20 mg orally 2 or 3 times a day.[180] For people being treated with methimazole, steady-state TSH levels lag behind the normalization of T4 and T3 hormone levels by at least 1 week.[180] Therefore, when T4 and T3 levels normalize, treatment dosage is decreased to the lowest effective amount to avoid inducing hypothyroidism.[180] Pituitary secretion of TSH may be

reduced for longer than expected following treatment for hyperthyroidism,[161] with 1 publication suggesting that efficacy of antithyroid treatment is best monitored by measuring FT4 and FT3 levels due to the slow and unpredictable response of TSH levels to antithyroid medications, which often take 3 to 4 months to fully respond.[160] If antithyroid drugs are stopped, TSH retesting is usually performed 4 to 8 weeks later, and continued measurements are repeated over 12 months to determine if blood thyroid hormone levels remain within target range over time.[181]

Radioiodine therapy is a permanent way to treat hyperthyroidism; however, regular TSH measurements are needed after treatment to monitor for hypothyroidism or recurrent hyperthyroidism.[181]

Surgical removal of the thyroid is a permanent cure for hyperthyroidism but requires regular TSH measurements to monitor for signs of hypothyroidism and recurrent hyperthyroidism.[181] Many people develop hypothyroidism after surgery and require treatment with thyroid replacement therapy.[181]

### Equity Considerations

The identified documents that provided recommendations were primarily developed in high-income countries situated in the global north; therefore, the recommendations for TSH level retesting may not be generalizable to all people being treated for hypothyroidism or hyperthyroidism.

When considering the retesting interval for TSH for monitoring people with hypothyroidism or hyperthyroidism, decision-makers may want to consider the following:

- Factors such as age, sex, race, and geographic location and the presence of thyroid autoantibodies are strong predictors of the rate of progression from subclinical hypothyroidism to overt hypothyroidism.[159] People that progress to overt hypothyroidism are likely to undergo regular monitoring of TSH levels, which can be at least annually once they are stabilized on long-term thyroid replacement therapy.[5]
- In general, the prevalence of thyroid dysfunction increases with age, and it has been shown to be higher among females who are white.[159] Populations with a higher prevalence of thyroid dysfunction may be more likely to undergo more frequent TSH retesting to determine diagnosis and establish adequate treatment.
- For treatment considerations, the required dosage of thyroid replacement therapy varies depending on weight, sex, age, or whether the individual is at risk of cardiovascular disease.[164,175]

## How This Information Was Used

This Technology Review is a supporting document for the Advisory Panel Guidance on Minimum Retesting Intervals for Lab Tests. The 7 literature reviews in this report were provided to the advisory panel, along with input from patient groups and a discussion guide. This background material and the clinical expertise of the panel helped to inform the discussions. Through facilitated discussion, the advisory panel developed recommendations for the minimum retesting interval(s) for 5 of the 7 lab tests in the prespecified population(s), which are available on our website.

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# Appendix 1: Supplementary Tables for ANA Testing

Note that this appendix has not been copy-edited.

## Table 12: Published Recommendations for ANA Retesting

| Guideline, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Consensus-based guidelines** | | | |
| **Spanish Society of Immunology**<br>Laboratory and Clinical Practices in Antinuclear Antibody Detection and Related Antigens: Recommendations from a Spanish Multicentre Survey, 2023[12] | "ANA determination and testing for antigenic specificities (with the exception of dsDNA) should not be repeated until at least 3 months have passed." (p. 757) | NR | Based on the consensus of a targeted survey. |
| **Single Hub and Access point for pediatric Rheumatology in Europe**<br>Consensus-based recommendations for the management of juvenile dermatomyositis, 2017[11] | "There is no significant diagnostic benefit gained from measurement of antinuclear antibody in juvenile dermatomyositis." | Level of evidence: 4 (expert opinion)<br>Strength of recommendation: D (based on expert opinion)<br>Agreement: 100% | The authors reported that although ANA are frequently positive in patients with juvenile dermatomyositis, that the diagnostic value has not been established. They also noted that at the time publication, there was insufficient evidence to recommend measuring ANA for risk stratification due to a lack of validation and data from patients with different ethnicities. |
| **Guidelines with unclear methodology** | | | |
| **British Society for Rheumatology**<br>Choosing Wisely UK Rheumatology Recommendations, 2018[13] | "Testing ANA and ENAs should be reserved for patients suspected to have a diagnosis of connective tissue disease, e.g., lupus. Testing ANA and ENAs should be avoided in the investigation of widespread pain or fatigue alone. Repeat testing is not normally indicated unless the clinical picture changes significantly." (p. 2) | NR | Expert consensus |
| **American Academy of Family Physicians**<br>A Primer for Family Physicians, 2018[14] | Included as part of the discussion:<br>"Once a patient has a positive ANA titer, it is rarely helpful to repeat the test; ANA levels fluctuate and do not reflect disease activity" (p. 165) | NR | NR |

| Guideline, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Laboratory guidance** | | | |
| **London Health Sciences Centre**<br>Anti Nuclear Antibody, 2023[17] | For repeat ANA testing:<br>"ANA should not be used to monitor disease activity. Positive ANA other than anti-dsDNA should not be repeated. If ANA was tested positive previously, repeat testing will not be processed." (p. 3) | NR | NR |
| | For negative ANA results:<br>"If ANA is negative or borderline positive (1:80), repeat testing is allowed only if the patient has developed new symptoms of SARD and the minimum retesting interval is limited to 6 months. If ANA was negative of borderline positive, repeat testing within 6 months will not be processed." (p. 3) | | |
| **National Health Service**<br>Division of Laboratory Medicine, 2023[16] | For ANA testing<br>"Repeat frequency: Not more than once a year, unless clinical picture has changed" (p. 1) | NR | NR |
| **Auckland City Hospital**<br>Medical Diagnostic Laboratory Guidance, 2019[21] | ANA should not be ordered for monitoring a connective tissue disease | NR | "ANA are not useful for monitoring the activity of systemic lupus erythematosus and should only be ordered for diagnostic purposes." |
| **Alberta Public Laboratories**<br>ANA Testing Recommendations, 2019[15] | "ANA cannot be used to monitor disease progression and should not be repeated once a diagnosis is made." (p. 1) | NR | NR |
| **Royal College of Physicians of Ireland**<br>Laboratory Testing for Antinuclear Antibodies, 2018[18] | "ANA testing is indicated when there are features suggestive of connective tissue disease such as SLE, Sjogren's syndrome, scleroderma, polymyositis/ dermatomyositis or autoimmune liver disease. If features of these conditions are not present an ANA test should not be ordered." (p. 2) | NR | NR |
| | Repeat ANA testing:<br>• "Repeat ANA testing is rarely required.<br>• Serial monitoring of ANA is not indicated even in the setting of connective tissue disease as titres | | |

| Guideline, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| | do not correlate with disease activity." (p.4) | | |
| **British Columbia Ministry of Health**<br>Antinuclear Antibody (ANA) Testing Protocol, 2013[20] | For the diagnosis of CTD:<br>"ANA testing is not indicated:<br>• unless a CTD is a significant clinical possibility<br>• to confirm a diagnosis of rheumatoid arthritis or osteoarthritis<br>• to evaluate fatigue, backpain, or other musculoskeletal pain unless accompanied by one or more of the clinical findings listed above<br>Repeat ANA testing is rarely indicated:<br>• in general, ANA testing need only be ordered once<br>• positive tests need not be repeated and there is no role for serial monitoring of ANAs since changes in ANA titres do not correlate with disease activity<br>• Negative tests rarely need to be repeated except when there is a strong suspicion of an evolving CTD or a change in the patient's illness suggesting revision of diagnosis." (p. 2) | NR | NR |
| **British Columbia Ministry of Health**<br>Rheumatoid Arthritis: Diagnosis, Management and Monitoring, 2012[19] | ANA testing for rheumatoid arthritis:<br>"Diagnostic value:<br>• ANA is rarely positive in RA. Unless there are other clinical features indicating SLE or other connective tissue disease, ordering ANA is not indicated<br>Disease Activity Monitoring:<br>• No value – do not repeat." (p. 3) | NR | NR |

ANA = antinuclear antibody; CTD = connective tissue disease; ENA = extractable nuclear antigen; NR = not reported; RA = rheumatoid arthritis; SARD = systemic autoimmune rheumatic disease; SLE = systemic lupus erythematosus

Note: Guidance documents were classified as consensus-based guidelines (i.e., recommendations were informed by expert opinion, with or without consideration for evidence collected using nonsystematic methods); guidelines with unclear (i.e., not reported in detail) methodology; or laboratory guidance (i.e., testing rules implemented in medical labs).

# Appendix 2: Supplementary Tables for BNP and NT-proBNP

## Table 13: Published Recommendations for BNP and NT-proBNP Testing for Patients

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| **Evidence-based guidelines** | | | | |
| **AHA-ACC-HFSA**<br>Guideline for Management of Heart Failure, 2022[35] | Heart failure | "In patients hospitalized for heart failure, a predischarge BNP or NT-proBNP level can be useful to inform the trajectory of the patient and establish a postdischarge prognosis" (p. e282) | Class of recommendation: 2a (moderate strength)<br>Level of evidence: B-NR (Moderate quality evidence from 1 or more well-designed, well-executed nonrandomized studies) | The authors reported that predischarge BNP and NT-proBNP levels are strong predictors of the risk of death or hospital readmission for heart failure.<br>They also reported that although patients with decreased levels of BNP or NT-proBNP following guideline-directed medical therapy had better outcomes than those with an increase or no change in these biomarkers despite appropriate treatment, targeting certain levels in these natriuretic peptides has not consistently been shown to be effective at improving outcomes. |
| **ERC/ERS**<br>2022 Guidelines for Pulmonary Arterial Hypertension[49] | Pulmonary arterial hypertension | "For risk stratification during follow-up, the use of a four-strata model (low, intermediate-low, intermediate-high, and high risk) based on WHO-FC, 6MWD, and BNP/NT-proBNP is recommended, with additional variables taken into account as necessary" (p. 49)<br>Suggested timing for follow-up of patients with pulmonary arterial hypertension was provided (but was not included as part of a formal recommendation). | Class of recommendation: I (i.e., evidence or general agreement that this is beneficial, useful, effective)<br>Level of evidence: B (i.e., data derived from a single randomized clinical trial or large nonrandomized studies) | Risk assessment for pulmonary arterial hypertension is based on a multiparameter approach. In various validation studies, WHO-FC, 6MWD and BNP or NT-proBNP emerged as the variables with the highest predictive value. |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | BNP or NT-proBNP:<br>• Baseline<br>• 3 to 6 months after changes in therapy<br>• Every 3 to 6 months in stable patients<br>• In case of clinical worsening<br>Intervals to be adjusted according to patient needs, disease etiology, risk category, demographics, and comorbidities. | | |
| **European Society of Cardiology**<br>Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure, 2021[36] | Heart failure | Included as part of the discussion about monitoring with biomarkers – not a formal recommendation.<br>"Current evidence, therefore, does not support the routine measurement of BNP or NT-proBNP to guide titration of therapy." | Not applicable | The authors report that conflicting results have been observed in studies investigating the use of BNP and NT-proBNP to guide pharmacotherapy for heart failure.<br>While natriuretic peptides are useful for prognosticating risk, the evidence is not clear regarding the benefit of a treatment strategy informed by monitoring these biomarkers. |
| **NICE**<br>Chronic Heart Failure in Adults, 2018[38] | Heart failure | "Consider measuring NT-proBNP (N-terminal pro-B-type natriuretic peptide) as part of a treatment optimization protocol only in a specialist care setting for people aged under 75 who have heart failure with reduced ejection fraction and an eGFR above 60 mL/min/1.73 $m^2$." (p. 22)<br>Note: no testing frequency provided. | The strength of the recommendation is reflected in the wording. The use of the word 'consider' reflects an action that could be offered due to less certainty. | Guideline developed based on a systematic review. Evidence summary not available. |
| | | NICE also makes recommendations for monitoring treatment for heart failure. BNP and NT-proBNP are not listed as part of the suggested assessments. It is recommended that the frequency of monitoring heart failure | – | – |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | patients should depend on the clinical situation and stability of the patient. The monitoring interval should be at least every 6 months for stable people, but could be days to weeks if the condition has changed. | | |
| **NHFA and CSANZ**<br>Australian Guidelines for Heart Failure, 2018[37] | Heart failure | "The clinical impact and change in management resulting from the prognostic information gained from BNP and NT proBNP levels is less clear. There are also many other prognostic markers in heart failure. It is unclear whether and how changes in BNP and NT proBNP levels should alter management to improve patient care." (p. 1147) | Practice advice<br>(i.e., provided in situations with a limited evidence base or where the impact on clinical outcomes was considered modest, rather than a recommendation) | – |
| | | "Current evidence does not support routine measurement of plasma BNP and NT proBNP levels to guide titration of pharmacological therapy in ambulatory heart failure, in view of conflicting evidence that this will decrease mortality or hospitalization" (p. 1148) | | The authors report that the evidence from small to medium-sized randomized controlled trials has been mixed with regard to effectiveness of using BNP or NT proBNP guided therapy (compared to usual care). And while a meta-analysis suggests a benefit, a larger study from 2017 failed to show a benefit of a natriuretic guided management strategy. |
| **Canadian Cardiovascular Society**<br>Heart Failure Management Guidelines Update, 2017[39] | Heart failure | "We suggest, in ambulatory patients with heart failure with reduced ejection fraction, measurement of BNP or NT-proBNP to guide management should be considered to decrease heart failure related hospitalizations and potentially reduce mortality. The benefit is uncertain in individuals older than 75 years of age." (p. 1354)<br>"Practical tip. The timing of NP measurements | Weak recommendation<br>Moderate quality evidence | The authors report that this recommendation is based on multiple small RCTs, most of which showed benefit, and 3 meta-analyses, which showed benefit. And that an ongoing RCT is likely to affect this recommendation. |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | in outpatient settings should be dictated according to clinical status; NP measurements should be used when they might aid in clinical decision-making." (p. 1354)<br>Note: a 2007 version of this guideline[182] recommended that "Sequential measurements of BNP/NT-proBNP levels may be considered to guide the therapy of patients with heart failure" (p. 35), but this recommendation was not included in the 2014 update. | | |
| | | "We suggest that measurement of BNP or NT proBNP in patients hospitalized for heart failure should be considered before discharge, because of the prognostic value of these biomarkers in predicting rehospitalization and mortality." (p. 1354)<br>"Practical tip: A patient with persistently elevated NP levels might need closer follow-up to reduce the risk of rehospitalization.<br>Practical tip: For patients who are about to be discharged from the hospital after a heart failure hospitalization, the NP level should be lower than that on admission. If NP levels remain elevated, clinicians should re-evaluate the patient's condition and consider the possibility of delaying discharge from the hospital to optimize therapy and further reduce the NP level." (p. 1354) | Strong recommendation<br>Moderate quality evidence | The authors report that this recommendation is based on multiple small RCTs, all of which showed an association with clinical outcomes. |
| **Canadian Cardiovascular Society**<br>Management of Heart Failure in Pediatrics, 2013[48] | Heart failure | Included as part of the discussion about biomarkers – not a formal recommendation.<br>"The use of serial BNP or NT-proBNP measurements in children to guide therapeutic intervention or to monitor heart failure status | Not applicable | – |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | shows some promise. The evidence for or against a benefit from this "BNP-guided therapy" strategy in pediatric heart failure is still insufficient to allow a formal Recommendation." (p. 1541) | | |
| **Consensus-based guidelines** | | | | |
| **Turkish Society of Cardiology**<br>How to Use Natriuretic Peptides in Heart Failure, 2023[40] | Heart failure | "In patients hospitalized for heart failure non-reduced ejection fraction, a predischarge BNP or NT-proBNP level can be useful to establish post-discharge prognosis" (p. 314) | — | The authors report that the prognostic capabilities of natriuretic peptides are well established, and that systematic reviews and meta-analyses show that different levels of these biomarkers can be used for predicting all-cause mortality, rehospitalization, and death due to heart failure. |
| | | "The benefit of NT-proBNP guided therapy in patients with chronic heart failure with non-reduced ejection fraction is not shown yet, nevertheless it might be beneficial in patients with heart failure with non-reduced ejection fraction after an acute heart failure episode." (p. 315) | — | The authors reported the findings from 1 study that showed that NT-proBNP–guided therapy had opposite outcomes in patients with reduced ejection fraction heart failure and preserved ejection fraction heart failure. |
| **American College of Cardiology**<br>Expert Consensus Decision Pathway, 2021[28] | Heart failure | Included as part of a testing algorithm:<br>In patients with heart failure with reduced ejection fraction who have been stabilized, assess response to therapy and cardiac monitoring every 3 to 6 months, including repeating laboratory tests such as BNP and NT-proBNP and basic metabolic panel. | — | — |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| **American College of Cardiology**<br>Expert Consensus Decision Pathway for Patients Hospitalized with Heart Failure, 2019[41] | Heart failure | Monitoring BNP and NT-proBNP levels are not included as part of the guidance for the daily trajectory check, rather the document focuses on targets for decongestion. | — | "Substantial reduction in B-type natriuretic peptide levels is anticipated during effective diuresis, frequently decreasing by 50% or more from admission, and a decrease in natriuretic peptide concentrations of at least 30% before discharge is strongly associated with better outcomes. **Targeting reduction in natriuretic peptide concentrations, however, did not result in better outcomes than treating congestion and optimizing other guideline-directed medical therapy empirically.**" (p. 1981) |
| **Guidelines with unclear methodology** | | | | |
| **Royal College of Physicians of Ireland**<br>National Laboratory Handbook, 2021[42] | Heart failure | "Repeat natriuretic peptide testing is not indicated in the vast majority of in-patients with heart failure and should be measured once, except for specific indications including clinical deterioration." (p. 4)<br>Who to retest?<br>Retesting may be appropriate in:<br>• Primary care: patients with chronic heart failure showing clinical deterioration<br>• Secondary care: if there is clinical deterioration or failure to respond to therapy<br>**Pre-discharge**: if prognosis is of clinical importance or may impact follow-up arrangements | — | "Pre-discharge repeat measurement has prognostic significance but has not been shown to alter outcome" (p. 8) |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | Who not to test?<br>"BNP or NT-proBNP testing is not recommended in the following patient cohorts: Monitoring treatment for heart failure. In general, natriuretic peptides should not be used to monitor or guide treatment.<br>However for specific patients where monitoring, natriuretic peptides may have value (e.g., < 75 years), clinicians should consider the large biological variability when interpreting result changes."(p. 7) | — | For adults less than 75 years of age, the authors reported 1 study where NT-proBNP–guided therapy was associated with a lower mortality rate (and hospitalization rate) at 3 years compared with either intensive clinical management or usual care.<br>For biologic variability where natriuretic peptides are measured serially for monitoring, the authors reported 1 study that concluded that changes or approximately 50% and 66% for NT-proBNP and BNP, respectively, are needed to indicate an altered clinical status in stable heart failure patients. |
| **Recommendations from clinical societies or association (unclear methodology)** | | | | |
| **BC Guidelines**<br>Heart Failure – Diagnosis and Management, 2023[43] | Heart failure | "BNP is not recommended for internal monitoring of disease severity or therapeutic response" (p. 3) | — | — |
| **Best Practice Advocacy Centre New Zealand**<br>Initiating and Escalating Treatment for Heart Failure, 2022[44] | Heart failure | "If BNP levels were found to be substantially elevated at diagnosis, monitoring for a decrease in these levels may be considered as a further marker of treatment efficacy.<br>However, serial measurements are not routinely recommended and decreases may not occur in all patients. This approach is likely only suitable if it will influence management decisions, particularly if there is uncertainty about the cause of a change in symptoms, e.g., whether | — | — |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | improvement in shortness of breath is due to the changing status of COPD or heart failure." | | |
| | | "If serial BNP testing is done for any reason, do not repeat tests within two weeks and ideally request no more than four tests per year." | — | "BNP levels often rise during the first few weeks of beta-blocker treatment, before dropping with sustained use." |
| **American Heart Association**<br>Scientific Statement – Role of Biomarkers in Heart Failure, 2017[45] | Heart failure | "Measurement of predischarge BNP or NT-proBNP during an heart failure hospitalization can be useful for establishing postdischarge prognosis." (p. e1066) | Suggestion or consideration for clinical practice (the evidence does not warrant a recommendation but there is a desire to provide some guidance to the community) | — |
| | | For the outpatient management of heart failure:<br>"BNP- or NT-proBNP–guided heart failure therapy is of uncertain benefit in clinical practice and cannot be universally advised. There are some data to support the use of serial measurement of biomarkers as a means to achieve ideal doses of guideline determined medical therapy, but the influence of this approach outside specialized heart failure centers with highly structured heart failure disease management programs is unknown." (p. e1071) | Contemporary clinical practice recommendation | Cites the 2013 American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines for Heart Failure[183]as the source of the recommendations. |
| | | For the outpatient management of heart failure:<br>"The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with heart failure is not well established." (p. e1071) | Contemporary clinical practice recommendation | |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | For the management of patients hospitalized with heart failure:<br>"The usefulness of BNP- or NT-proBNP–guided therapy for acutely decompensated heart failure is not well established" (p. e1072) | Contemporary clinical practice recommendation | |
| **Laboratory guidance** | | | | |
| **Exeter Clinical Laboratory**<br>NT-proBNP Blood Sciences Test, 2019[46] | Congestive heart failure | NT-proBNP is used to aid in the diagnosis of congestive heart failure and is further indicated for risk stratification in patients with congestive heart failure.<br>Minimum repeat interval = 6 months | — | — |

6MWD = 6-minute walking distance; ACC = American College of Cardiology; AHA = American Heart Association; BNP = b-type natriuretic peptide; CSANZ = Cardiac Society of Australia and New Zealand; HFSA = The Heart Failure Society of America; NHFA = National Heart Foundation of Australia; NICE = National Institute for Health and Care Excellence; NR = not reported; NT-proBNP = N-terminal proBNP; WHO-FC = WHO functional class.

Notes: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature), consensus-based (i.e., recommendations were informed by expert opinion, with or without consideration for evidence collected using non-systematic methods), guidelines or recommendations from clinical societies or associations with unclear (i.e., not reported in detail) methodology, or as laboratory guidance (i.e., testing rules implemented in medical labs).

This table has not been copy-edited.

## Table 14: Published Recommendations Regarding Equity Considerations in Heart Failure

| Guideline, year | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **AHA-ACC-HFSA** Guideline for Management of Heart Failure, 2022[35] | "In vulnerable patient populations at risk for health disparities, heart failure risk assessments and multidisciplinary management strategies should target both known risks for cardiovascular disease and social determinants of health, as a means toward elimination of disparate heart failure outcomes" (p. e356) | Strength of recommendation: 1 (strong)<br>Level of evidence: C-LD (limited data were used to inform the recommendation) | "Among patients with established heart failure, social and medical vulnerabilities can impede successful delivery of guideline-directed medical therapy and are associated with poorer outcomes" (p. e356) |
| | "Evidence of health disparities should be monitored and addressed at the clinical practice and the health care system levels" | Strength of recommendation: 1 (strong)<br>Level of evidence: C-LD (limited data were used to inform the recommendation) | Health care system factors, such as sex, race, socioeconomic status, are potential sources of disparate care for patients with heart failure and outcomes. |

ACC = American College of Cardiology; AHA = American Heart Association; HFSA = The Heart Failure Society of America.
Note: This table has not been copy-edited.

# Appendix 3: Supplementary Tables for Hemoglobin A1C

Note that this appendix has not been copy-edited.

## Table 15: Published Recommendations Regarding Retesting for Hemoglobin A1C

| Guideline, year | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Health technology assessments** | | | |
| **Australian Medical Services Advisory Committee**<br>HbA1c point of care tests for diabetes, 2020[64] | For the monitoring of established diabetes:<br>"a maximum of 3 Point of Care [HbA1c] tests in a 12 month period and a maximum of 4 HbA1c tests in total (Point of Care and laboratory) in a 12 month period." (p. 8) | NR | Decisions to list point-of-care hemoglobin A1C tests was based on evidence regarding comparative safety, clinical effectiveness, and cost-effectiveness. |
| **Ontario Health Technology Advisory Committee**<br>Hemoglobin A1c Testing in Diabetes, 2014[63] | "Adult patients with diabetes (without hematologic contraindication) have hemoglobin A1c tested every three months if glycemic targets (generally hemoglobin A1c < 7%) are not met, or every six months if glycemic targets are being met." | NR | Recommendation was based on an evidence analysis, a budget impact analysis, and a rapid review.<br>The 2014 rapid review[184] examined how often hemoglobin A1C should be tested to assess glycemic control in people with type 2 diabetes. No systematic reviews were identified. Conclusions were based on 1 rapid review (with 3 included guidelines) and 6 clinical practice guidelines. |
| | "Hemoglobin A1c should not be tested more than four times per year in adult patients with diabetes." | NR | |
| **Evidence-based guidelines** | | | |
| **American Diabetes Association**<br>Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes, 2024[71] | "Assess glycemic status by A1C and/or appropriate continuous glucose monitoring (CGM) metrics at least two times a year. Assess more frequently (e.g., every 3 months) for individuals not meeting treatment goals, with frequent or severe hypoglycemia or hyperglycemia, changing health status, or growth and development in youth." (p. S111) | Recommendation based on expert consensus or clinical experience | HbAc1c reflects average glycemia from the previous 2 to 3 months.<br>Adults with stable glycemia may do well with hemoglobin A1C testing only twice per year.<br>Individuals with unstable glycemia or who are not achieving treatment goals may require more frequent testing (e.g., every 3 months, with interim assessments as needed) |

| Guideline, year | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| | "Assess glycemic status at least quarterly and as needed in individuals whose therapy has recently changed and/or who are not meeting glycemic goals." (p. S111) | Recommendation based on expert consensus or clinical experience | |
| **American Diabetes Association**<br>Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus, 2023[58] | In non-pregnant individuals living with type 1 or type 2 diabetes:<br>"HbA1c should be measured routinely (usually every 3 months until acceptable, individualized targets are achieved and then no less than every 6 months) in most individuals with diabetes mellitus to document their degree of glycemic control." (p. e171) | Strong recommendation<br>Moderate quality evidence (i.e., future research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate and the recommendation) | Due to the absence of well-controlled studies that suggest a definite testing protocol, expert opinion suggests that testing frequency should depend on the clinical situation, the treatment regimen, and the clinician's judgment. |
| **NICE**<br>Type 2 diabetes in adults: management, 2022[65] | "Measure HbA1c levels in adults with type 2 diabetes every:<br>• 3 to 6 months (tailored to individual needs) until HbA1c is stable on unchanging therapy<br>• 6 months once the HbA1c level and blood glucose lowering therapy are stable." (p. 9) | The strength of the recommendation is reflected in the wording. The use of direct language (i.e., "measure") reflects an action that should be offered. | Recommendation was initially established in the 2015 version of this guideline. Evidence summary not available. |
| **NICE**<br>Type 1 diabetes in adults: diagnosis and management, 2022[66] | "Measure HbA1c levels every 3 to 6 months in adults with type 1 diabetes" (p. 17) | The strength of the recommendation is reflected in the wording. The use of direct language (i.e., "measure") reflects an action that should be offered. | Recommendations were initially established in the 2015 version of this guideline.<br>Based on evidence from 43 studies, most of which were observational studies that the authors graded as low quality (due to study design). |
| | "Consider measuring HbA1c levels more often in adults with type 1 diabetes if their blood glucose control is suspected to be changing rapidly; for example, if their HbA1c level has risen unexpectedly above a previously sustained target." (p. 17) | The strength of the recommendation is reflected in the wording. The use of the word 'consider' reflects an action that could be offered due to less certainty. | |
| **AACE**<br>Clinical Practice Guideline, 2022[67] | "A1C should be measured at least semiannually in all persons with diabetes mellitus and at least quarterly in persons not at their glycemic target." (p. 927) | Grade of recommendation: B (strong)<br>Best evidence level: 2 (intermediate evidence) | "A1C is considered the current gold standard for monitoring chronic hyperglycemia and provides an indication of the average of BG levels over the previous 3 months." (p. 942) |

| Guideline, year | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| | | | "A1C reflects average glycemia over the lifespan of the red blood cell (100 to 120 days), but 50% of A1C is determined by glycemia during the month preceding measurement." (p. 942)<br>Frequency of hemoglobin A1C testing should depend on clinical situation and treatment regimen. |
| **Royal College of Pathologists**<br>National minimum retesting intervals in pathology, 2021[5] | In patients with type 2 diabetes where glycemic targets are not being met, the minimum retesting interval for hemoglobin A1C is:<br>Two to 6 months (tailored to individual needs) until the blood glucose concentration is stable on unchanging therapy; use a measurement made at an interval of less than 3 months as an indicator of direction of change, rather than as a new steady state | Level of evidence: B (evidence levels not further described) | Recommendation based on the 2015 NICE guideline for type 2 diabetes. |
| | In patients with type 2 diabetes with stable concentration and blood glucose lowering therapy, the minimum retesting interval for hemoglobin A1C is: 6 months | | |
| **Diabetes Canada**<br>Monitoring Glycemic Control, 2018[62] | "For most individuals with diabetes, A1C should be measured approximately every 3 months to ensure that glycemic goals are being met or maintained. In some circumstances, such as when significant changes are made to therapy, or during pregnancy, it is appropriate to check A1C more frequently." (p. S50) | Recommendation grade: D (lowest grade)<br>Recommendation based on the consensus of the Steering and Executive Committees | "HbA1c is a reliable estimate of mean plasma glucose levels over the previous 8 to 12 weeks." (p. S47) |
| | Testing at least every 6 months should be performed in adults during periods of treatment and healthy behaviour stability when glycemic targets have been consistently achieved" (p. S50) | Recommendation grade: D (lowest grade)<br>Recommendation based on the consensus of the Steering and Executive Committees | NR |
| **International Diabetes Federation**<br>Global Guideline for Type 2 Diabetes, 2012[70] | "Measure HbA1c every 2 to 6 months depending on level, stability of blood glucose control and changes in therapy." (p. 43) | NR | NR |

| Guideline, year | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Ireland Department of Health**<br>Adult Type 1 Diabetes Mellitus, 2018[68] | "Measure HbA1c levels every 3 to 6 months in adults with type 1 diabetes." (p. 25) | The wording used in the recommendation denotes the strength of the recommendation. The use of the word 'measure' indicates an intervention that should be used (i.e., a "strong" recommendation) | NR |
| | "Consider measuring HbA1c levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA1c level has risen unexpectedly above a previously sustained target." (p. 25) | The wording used in the recommendation denotes the strength of the recommendation. The use of the word 'consider' suggests an intervention that could be used. | NR |
| **National Academy of Clinical Biochemistry Laboratory Medicine**<br>Practice Guidelines for Diabetes, 2011[69] | "Hb A1c testing should be performed at least biannually in all patients and quarterly for patients whose therapy has changed or who are not meeting treatment goals." (p. 29) | Strength of recommendation: B (i.e., a recommendation for adoption)<br>Overall quality of the evidence: low (i.e., further research is very likely to have an important impact on the confidence in the estimate and is likely to change the recommendation) | The authors report that there is no consensus on the frequency of hemoglobin A1C testing, and that the American Diabetes Association recommends that the frequency should depend on the clinical situation, the treatment regimen, and the judgment of the clinician (as per the).<br>The authors report that in the absence of well-controlled studies that suggest a testing protocol, the recommendations (by the American Diabetes Association) are based on expert opinion. |
| **Guidelines with unclear methodology** | | | |
| **New Zealand Society for the Study of Diabetes**<br>**Type 2 diabetes**<br>management guidance, 2023[72] | "HbA1c testing is preferred for assessing glycaemic control and should be performed every three months until the patient is to target, then every six months once at target." (p. 2) | – | – |
| **Recommendations from clinical societies or association (unclear methodology)** | | | |
| **Choosing Wisely Recommendation**<br>With the American Society of Clinical Laboratory Science and the American | "Don't repeat A1C testing in stable patients within three months of a previous result." | – | Given the average lifespan of a hemoglobin A1C is = 90 to 120 days, treatment effects (e.g., medication, lifestyle) will not be fully reflected in test results until all previous hemoglobin |

| Guideline, year | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| Society for Clinical Pathology, presumed 2023 (date unclear)[73] | | | A1C in circulation are replaced (~90 days). Retesting earlier than 3 months may not allow enough time to pass to reach the expected target.<br>Once glycemic targets are consistently achieved, consider testing at 6-month intervals. |
| **American Medical Group Association**<br>Together 2 Goal Toolkit, presumed 2023 (date unclear)[74] | For patients with type 2 diabetes:<br>"Measure HbA1c every 3 to 6 months" | — | Recommendation based on guidance from the American Diabetes Association |
| **BC Guidelines**<br>Diabetes Care, 2021[75] | "Measure A1C every 3 months to ensure that glycemic goals are being met and maintained." (p. 7) | — | — |
| | "Consider testing A1C every 6 months if treatment and lifestyle remain stable and if targets have been consistently met." (p. 7) | — | — |
| **Laboratory guidance** | | | |
| **Association for Diagnostics & Laboratory Medicine**<br>Hemoglobin A1c Optimal Testing Recommendations, 2022[77] | "To monitor diabetic patients, A1c should be ordered at least twice yearly in patients who have achieved stable glycemic control and quarterly in patients whose treatment has recently changed or who are not meeting their goals." | — | — |
| | "A1c should not be ordered more frequently than every 3 months" | — | — |
| **Nova Scotia Health**<br>Laboratory Utilization Guidelines – Specimen Cancellation rules, 2022[78] | Hemoglobin A1c will automatically be cancelled if ordered within 80 days (i.e., the utilization time frame). Cancellation occurs before collection. | — | Developed "in accordance with following the Choosing Wisely Canada recommendations" (no further information provided) |
| **Sunnybrook Health Sciences Centre**<br>Laboratory Medicine Bulletin, 2020[79] | Restriction on repeat hemoglobin A1C testing:<br>"Any bloodwork for HbA1c that is collected within 60 days of a previous result will not be performed by the laboratory without a valid reason" (p. 1) | — | Decision based on the 2018 Diabetes Canada guideline, with consideration of the Choosing Wisely Priority Areas for 2019 to 2020 for chronic disease laboratory testing. |

| Guideline, year | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Ontario Association of Medical Laboratories**<br>Communiqué, 2015[76] | "Quantitative analysis of HbA1c as follows:<br>• Every 6 months for adult patients who have demonstrated good long-term glycemic stability.<br>• Every 3 months when goals for glycemic control are not being met, or when modifying a patient's therapy for glucose control." (p. 2) | — | Recommendations based on 2013 from Diabetes Canada (formerly Canadian Diabetes Association) |

AACE = American Society of Clinical Endocrinology; HbA1c = hemoglobin A1c; NICE = National Institute for Health and Care Excellence; NR = not reported.

Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature); guidelines with unclear (i.e., not reported in detail) methodology; recommendations from clinical societies or associations with unclear methodology; or laboratory guidance (i.e., testing rules implemented in medical labs).

## Table 16: Published Recommendations Regarding Retesting for Hemoglobin A1C in Pediatric Patients

| Guideline, year | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Evidence-based guidelines** | | | |
| **NICE**<br>Diabetes (type 1 and type 2) in children and young people: diagnosis and management, 2023[81] | "Measure HbA1c level 4 times a year in children and young people with type 1 diabetes. Think about more frequent testing if they are having difficulty with blood glucose management." (p. 21) | The strength of the recommendation is reflected in the wording. The use of direct language (i.e., "measure") reflects an action that should be offered. | Recommendation was initially established in a 2004 version of this guideline and amended in 2015.<br>Limited evidence was identified regarding the frequency of monitoring hemoglobin A1C. |
| **ISPAD**<br>Glycemic targets and glucose monitoring for children, adolescents, and young people with diabetes, 2022[61] | For young people with diabetes:<br>"HbA1c assessments are recommended every 3 months" (p. 1271) | Expert consensus or clinical experience | Supporting evidence included:<br>• hemoglobin A1C reflects average blood glucose concentration in the preceding 8 to 12 weeks<br>• the maximum lifespan of erythrocytes (approximately 100 to 120 days) with an averaged age ranging from 40 to 60 days. |
| **Royal College of Pathologists**<br>National minimum retesting intervals in pathology, 2021[5] | For monitoring children and young people with type 1 diabetes, the recommended minimum retesting interval is 2 months | Level of evidence: A (evidence levels not further described) | Recommendation based on the 2004 NICE guideline for type 1 diabetes in children and young people. |

| Guideline, year | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Australasian Paediatric Endocrine Group**<br>Type 2 diabetes mellitus in children and adolescents, 2020[80] | In children and adolescents living with type 2 diabetes:<br>"HbA1c should be assessed every 3 months" (p. 32) | Grade: D (poor)<br>Body of evidence is weak, and recommendation should be applied with caution. | NR |
| **American Academy of Pediatrics**<br>Guideline for Type 2 Diabetes in Children and Adolescents, 2013[82] | In children and adolescents with type 2 diabetes:<br>"The committee suggests that clinicians monitor HbA1c concentrations every 3 months and intensify treatment if treatment goals for blood glucose and HbA1c concentrations are not being met." (p. 373)<br>Document also notes, that if hemoglobin A1C concentrations remain relatively stable, testing every 6 months could be considered. | Strength of the recommendation: Option (i.e., a course of action that may be taken)<br>Evidence quality: D (expert opinion or low-quality evidence) | Recommendation based on expert opinion (i.e., it is generally recommended that hemoglobin A1C be measured every 3 months) and studies conducted in other populations (i.e., studies in children with type 1 diabetes and adults with type 2 diabetes) |

HbA1c = hemoglobin A1c; ISPAD = International Society for Pediatric and Adolescent Diabetes; NICE = National Institute for Health and Care Excellence; NR = not reported.
Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature).

## Table 17: Published Recommendations Regarding Retesting for Hemoglobin A1C in Pregnancy

| Guideline, year | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Evidence-based guidelines** | | | |
| **Royal College of Pathologists**<br>National minimum retesting intervals in pathology, 2021[5] | For people with diabetes who are planning to become pregnant:<br>"monthly measurement of hemoglobin A1C" | Level of evidence: A (evidence levels not further described) | Recommendations based on the 2015 NICE guideline for diabetes in pregnancy. |
| | "hemoglobin A1C should not be used routinely for assessing glycaemic control in the second and third trimesters of pregnancy however consider measuring hemoglobin A1C for women with pre-existing diabetes to assess risk to pregnancy" | | |
| **NICE**<br>Diabetes in pregnancy, 2020[83] | "Do not routinely use HbA1c levels to assess a woman's blood glucose control in the second and third trimesters of pregnancy." (p. 16) | The wording used in the recommendation denotes the strength of the recommendation. The use of the words 'do not | The guideline development group reported that there is no evidence to recommend the routine use of hemoglobin A1C |

| Guideline, year | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| | | routinely use' indicates an intervention that should not be used. | in pregnancy as a measure of glucose control. |
| | "Offer up to monthly measurement of HbA1c levels for women with diabetes who are planning a pregnancy." (p. 8) | The strength of the recommendation is reflected in the wording. The use of direct language (i.e., "offer") reflects an action that should be offered. | Monthly measurement of hemoglobin A1C in the preconception period may improve blood glucose control in people with type 1 diabetes and reduced the progression of complications of diabetes. Good glucose control pre-pregnancy reduces the risk of adverse pregnancy outcomes. |
| | "Measure HbA1c levels at the booking appointment for all pregnant women with pre-existing diabetes, to determine the level of risk for the pregnancy." (p. 16) | The wording used in the recommendation denotes the strength of the recommendation. The use of the word 'measure' indicates an intervention that should be used. | The guideline development group reported that hemoglobin A1C is an indicator of risk of adverse outcome in diabetic pregnancies. |
| | "Consider measuring HbA1c levels in the second and third trimesters of pregnancy for women with pre-existing diabetes, to assess the level of risk for the pregnancy." (p. 16) | The wording used in the recommendation denotes the strength of the recommendation. The use of the word 'consider' suggests an intervention that could be used. | |

HbA1c = hemoglobin A1c; NICE = National Institute for Health and Care Excellence; NR = not reported.

Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature).

## Table 18: Factors and Conditions That Can Affect Hemoglobin A1C Test Accuracy

| Conditions or factors | Effect | Effect on hemoglobin A1C |
|---|---|---|
| **Hemolytic anemia**[57,85] | Increased red blood cell turnover (i.e., red blood cells are destroyed faster than they can be made) | Falsely low |
| **Iron deficiency anemia**[57,61,62] | Reduced red blood cell turnover | Falsely high |
| **Glucose-6-phosphate dehydrogenase deficiency**[61,85] | Increased red blood cell turnover (red blood cells are destroyed faster than they can be made) | Falsely low |
| **Sickle cell anemia**[57,61] | Increased red blood cell turnover (i.e., reduced lifespan red blood cells) | Falsely low |
| **Spherocytosis**[57] | Increased red blood cell turnover (i.e., red blood cells are destroyed faster than they can be made) | Falsely low |
| **Hemoglobin variant**[56,69] | Interferes with hemoglobin A1C assay methods | Falsely high or falsely low depending on the variant and assay |

| Conditions or factors | Effect | Effect on hemoglobin A1C |
|---|---|---|
| **Thalassemia**[56,61] | Increased red blood cell turnover (due to insufficient hemoglobin production which decreases red blood cell lifespan) | Falsely low |
| **B12 deficiency anemia**[56,57,61,62] | Reduced red blood cell turnover | Falsely high |
| **Cystic fibrosis**[61] | Increased red blood cell turnover | Falsely low |
| **Chronic kidney failure**[56,57,61,62,85] | Increased red blood cell turnover and altered glycation | Falsely low |
| **Liver cirrhosis**[57,185] | Likely due to altered lifespan of red blood cells (e.g., anemia) and altered protein metabolism | Falsely low |
| **Hemorrhage**[57,61] | Increased red blood cell turnover | Falsely low |
| **Pregnancy**[57,61,85] | Increased red blood cell turnover (second trimester) or reduced red blood cell turnover (third trimester) | Falsely low (second trimester) or falsely high (third trimester) |
| **Splenectomy**[62] | Increased red blood cell lifespan | Falsely high |
| **Splenomegaly**[62] | Decreased red blood cell lifespan | Falsely low |
| **Blood transfusion**[57,85] | Introduction of hemoglobin molecules exposed to donor glucose concentrations | Falsely low |
| **Erythropoietin administration**[56,57,62] | Increased red blood cell production | Falsely low |
| **Use of drugs that stimulate erythropoiesis**[85] | Increased red blood cell production | Falsely low |
| **Iron supplementation**[56,57,61,62] | Increased red blood cell turnover | Falsely low |
| **B12 supplementation**[56,61,62] | Increased red blood cell turnover | Falsely low |
| **Chemotherapy**[61] | Increased red blood cell turnover | Falsely low |
| **Vitamin C supplementation**[57,62] | Altered glycation | Falsely high or falsely low (depending on the assay method) |
| **Vitamin E supplementation**[62] | Altered glycation | Falsely low |

## Table 19: Published Recommendations Regarding Hemoglobin A1C Testing in People With Conditions That May Interfere With Test Results

| Publication, year | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Evidence-based guidelines** | | | |
| **American Diabetes Association**<br>Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus, 2023[58] | "HbA1c measurements in individuals with disorders that affect red blood cell turnover may provide spurious (generally falsely low) results regardless of the method used and glucose testing will be necessary for screening, diagnosis, and management." (p. e173) | Good practice point (i.e., recommendation derived from expert consensus and professional agreement) | Some conditions shorten RBC survival or decreases mean RBC age (e.g., recovery from acute blood loss, hemolytic anemia) and may falsely lower hemoglobin A1C test results.<br>Differences in mean red cell half-life may range from approximately 48 to 68 days (mean 58 days and 1 SD of 4.5 to 6.5 days). |
| **National Academy of Clinical Biochemistry Laboratory Medicine**<br>Practice Guidelines for Diabetes, 2011[69] | "Laboratories should be aware of potential interferences, including hemoglobinopathies, that may affect Hb A1c test results, depending on the method used. In selecting assay methods, laboratories should consider the potential for interferences in their particular patient population. In addition, disorders that affect erythrocyte turnover may cause spurious results, regardless of the method used." | Good practice point (i.e., a recommendation driven mostly by expert consensus and professional agreement) | Condition that shortens erythrocyte survival or decreases mean erythrocyte age (e.g., recovery from acute blood loss, hemolytic anemia) falsely lowers Hb A1c test results.<br>Iron deficiency anemia increases test results.<br>Hypertriglyceridemia, hyperbilirubinemia, uremia, chronic alcoholism, chronic ingestion of salicylates, and opiate addiction may falsely increase test results. |
| **Laboratory guidance** | | | |
| **Association for Diagnostics & Laboratory Medicine**<br>HbA1c Optimal Testing Recommendations, 2022[77] | "Do not order this test in patients with altered red cell turnover. Examples of such conditions include anemia, hemoglobinopathies, recent blood loss or transfusion, pregnancy, erythropoietin therapy and hemolysis." | — | — |

HbA1c = hemoglobin A1c; RBC = red blood cell.

Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature), or as laboratory guidance (i.e., testing rules implemented in medical labs).

# Appendix 4: Supplementary Tables for Lipase

Note that this appendix has not been copy-edited.

## Table 20: Evidence Regarding Considerations for Serum Lipase Testing

| Publication, year | Evidence statement or recommendation | Supporting evidence and/or rationale |
|---|---|---|
| **Recommendation from clinical societies or associations (unclear methodology)** | | |
| **American Society for Clinical Pathology; Choosing Wisely** Thirty-Five Things Physicians and Patients Should Question, 2020[89] | Included as supporting evidence for recommendation against serum amylase testing – not a formal recommendation<br>"Current guidelines and recommendations indicate that lipase should be preferred over total and pancreatic amylase for the initial diagnosis of acute pancreatitis and that the assessment should not be repeated over time to monitor disease prognosis. Repeat testing should be considered only when the patient has signs and symptoms of persisting pancreatic or peripancreatic inflammation, blockage of the pancreatic duct or development of a pseudocyst." (p. 3) | NR |
| **Narrative review** | | |
| Magier et al., 2023[93] | Included as supporting evidence for serum lipase measurement – not a formal recommendation<br>"Once a diagnosis of acute pancreatitis is established, routine serial lipase testing is recommended against. Subsequent serum lipase testing should be research only for rare instances where there is concern for pancreatic duct blockage, pseudocyst formation, or lack of clinical improvement after 1 week, and should be performed in conjunction with repeat cross-sectional imaging." (p. 341) | NA |
| Nichols, 2022[92] | Included as supporting evidence for serum lipase measurement – not a formal recommendation<br>"Key Insight:<br>• Repeat or serial monitoring of lipase is unnecessary." (p. 2) | The author reports that there is no role in trending lipase levels on a daily basis once the diagnosis is made because it is not useful for monitoring clinical improvement or guiding treatment. Monitoring levels serially during hospitalization does not reflect disease prognosis and repeat or serial measurement of lipase should not be used to guide disease progression or resolution. (p. 2) |
| Jasdanwala et al., 2015[91] | Included as supporting evidence for serum lipase measurement – not a formal recommendation<br>"There is no role of following the serial trend of lipase or amylase on the daily basis in patients with acute pancreatitis once the diagnosis has been established. It is not useful for monitoring clinical improvement in the short term." (p. 189 to 195)<br>"If the initial presentation is within 4 to 5 hours of the onset of abdominal pain and if the levels of either lipase or amylase are normal, it may be | NA |

| Publication, year | Evidence statement or recommendation | Supporting evidence and/or rationale |
|---|---|---|
| | worthwhile to repeat levels in the next couple of hours if the clinical suspicion of acute pancreatitis is high." (p. 189 to 195)<br>"If the patient continues to have pain or symptoms weeks after the presentation, checking a repeat lipase level may be useful as an elevated lipase can signify persistent pancreatic inflammation, pancreatic ductal obstruction or pseudocyst." (p. 189 to 195) | |
| Yegneswaran and Pitchumoni, 2010[94] | Included as supporting evidence for serum lipase measurement – not a formal recommendation<br>"In general, repeating serum amylase and lipase levels has no value once the diagnosis of acute pancreatitis has been made." (p. 230) | NA |
| Stevens et al., 2009[90] | Included as supporting evidence for serum lipase measurement – not a formal recommendation<br>"Daily monitoring of amylase and lipase has limited value in managing acute pancreatitis. Rechecking these concentrations may be reasonable if pain fails to resolve or worsen during a prolonged hospitalization, as this may suggest a recurrent attack of acute pancreatitis or a developing pseudocyst." (p. 698) | NA |

NA = not applicable; NR = not reported.

Note: Guidance documents were classified as recommendations from clinical societies or associations with unclear (i.e., not reported in detail) methodology or narrative reviews (reviews with non-systematic approach to collecting and synthesizing evidence). None of the included documents reported the strength of the recommendations or the quality of the evidence.

# Appendix 5: Supplementary Tables for Lipid Panel

## Table 21: Published Recommendations Regarding Lipid Panel Retesting

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| **Health technology assessments** | | | | |
| **Health Quality Ontario**<br>Frequency of Testing for Dyslipidemia, 2014[102] | Dyslipidemia | "For individuals currently being treated for dyslipidemia, there is insufficient evidence upon which the Ontario Health Technology Advisory Committee can make a recommendation on the frequency of lipid testing."<br><br>"Until higher quality evidence becomes available, the Ontario Health Technology Advisory Committee recommends that consideration be given to using the current Canadian Cardiovascular Society Guidelines." | — | Recommendation was based on a systematic review[186] in which no evidence for the frequency of lipid testing was identified. The review included guidelines in which the recommendations on testing frequency were based on expert consensus. |
| **Evidence-based guidelines** | | | | |
| **College of Family Physicians of Canada**<br>Clinical Practice Guideline, 2023[103] | Patients with or at risk of CVD who are treated with lipid-lowering therapy | "We recommend against the use of repeat lipid testing and cholesterol targets after a patient begins lipid-lowering therapy" (p. 678) | Strong recommendation against.<br>Certainty of the evidence = not applicable | The authors report that at the time of the evidence review, the best available evidence did not support repeat lipid testing. After the evidence review was completed, 3 more studies were published that support the recommendation.<br>"Given the large degree of analytic and biological variation in lipid testing, the associated costs and inconvenience of repeat testing (including visits to discuss repeat test results), and the challenge in achieving targets, the treat |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | | | to-target approach is less desirable" (p. 683) |
| **NICE**<br>CVD: risk assessment and reduction, including lipid modification, 2023[115] | People on lipid-lowering therapy | "Measure liver transaminase and full lipid profile at 2 to 3 months after starting or changing lipid-lowering treatment" (p. 25)<br>A full lipid profile includes measuring total cholesterol, HDL cholesterol, and triglyceride levels, then calculating non-HDL cholesterol and LDL cholesterol. | The strength of the recommendation is reflected in the wording. The use of direct language (i.e., "measure") reflects an action that should be offered. | The guideline development committee amended a previous recommendation. This amendment provides more flexibility in the timing of blood tests, which they reported was more reflective of actual clinical practice. They also added the recommendation to measure lipid profiles after changing lipid-lowering therapy.<br>(The previous iteration of the recommendation from May 2023[187] was only specific to people who had started high-intensity statin therapy, and recommended assessing lipids levels at 3 months. This was supported by a systematic review on the efficacy and safety of statins.) |
| **AHA/ACC/Multi-Society**<br>Guideline for Management of Patients with Chronic Coronary Disease, 2023[104] | Patients with chronic coronary disease treated with lipid-lowering therapy | "In patients with chronic coronary disease, adherence to changes in lifestyle and effects of lipid-lowering medication should be assessed by measurement of fasting lipids in 4 to 12 weeks after statin initiation or dose adjustment and then every 3 to 12 months thereafter based on need to assess response or adherence to therapy" (p. 865) | Class of recommendation = 1 (strong)<br>Level of evidence = A (high-quality evidence) | Although reductions in LDL cholesterol are expected with moderate- to high-intensity statin therapy, individual response can vary.<br>Obtaining a lipid profile every 3 to 12 months is associated with increased adherence to therapy, and the identification of patients requiring more intense therapy. |
| **American Diabetes Association**<br>Standards of Medical | Patients with diabetes at risk of CVD treated with lipid-lowering therapy | "Obtain a lipid profile at initiation of statins or other lipid lowering therapy, 4 to 12 weeks after initiation or a change in dose, and annually thereafter as | Level of evidence: E (i.e., expert consensus or clinical experience) | NR |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| Care CVD and Risk Management, 2022[112] | | it may help to monitor the response to therapy and inform medication adherence." (p. S151) | | |
| **AHA/ASA** Guideline for the Prevention of Stroke, 2021[114] | Patients with stroke or transient ischemic attack and dyslipidemia | "In patients with stroke or TIA and hyperlipidemia, patients' adherence to changes in lifestyle and the effects of LDL cholesterol lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter, based on need to assess adherence or safety." (p. e384) | Strength of recommendation: 1 (strong)<br>Level of evidence: A (high quality) | "Lifestyle changes and statin therapy are commonly introduced together. The maximum percentage change occurs 4 to 12 weeks after therapy is started, at which time drug efficacy or initial adherence to therapy can be evaluated." (p. e386) |
| **Royal College of Pathologists** National minimum retesting intervals in pathology, 2021[5] | Patients treated with lipid-lowering therapy | In patients on stable treatment, the minimum retesting interval for the non-fasting lipid profile is 1 year. | Level of evidence: GPP (good practice point) (evidence levels not further described) | Consensus opinion of the relevant expert working group |
| | | In patients who are initiating or changing therapies for primary or secondary prevention (including non-HDL cholesterol), the minimum retesting interval for the non-fasting lipid profile is 3 months. | Level of evidence: B (evidence levels not further described) | Recommendation based on the 2019 NICE Clinical Knowledge Summary. Evidence summary was not provided. |
| **US Department of Veterans Affairs** Clinical Practice Guideline for the Management of Dyslipidemia, 2020[108] | Patients with dyslipidemia at risk of CVD | "We suggest against the routine monitoring of lipid levels in patients taking statins." (p. 47) | Strength of recommendation: weak against<br>Quality of evidence: very low | The Work Group reviewed evidence identified via a systematic review which evaluated the effectiveness of statin treatment intensity. No studies were identified that targeted specific levels of LDL cholesterol. Therefore, the effectiveness of treating to specific LDL cholesterol targets can only be |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | | | determined indirectly.<br>Given that lipid levels are a simple and inexpensive way to measure adherence and treatment efficacy, the Work Group suggests that monitoring lipid levels should be based on individual need (decision between clinician and patient) rather than routine. |
| **ESC/EAS**<br>Guideline for Management of Dyslipidemias, 2019[109] | Patients with acute coronary syndrome treated with lipid-lowering therapy | "Lipid levels should be re-evaluated 4 to 6 weeks after acute coronary syndrome to determine whether a reduction of ≥50% from baseline and goal levels of LDL cholesterol <1.4 mmol/L (<55 mg/dL) have been achieved. Safety issues need to be assessed at this time and statin treatment doses adapted accordingly." (p. 157) | Class of recommendation: IIa (the action should be considered)<br>Level of evidence: C (i.e., consensus of opinion of the experts and/or small studies, retrospective studies) | NR |
| **Endocrine Society**<br>Clinical Practice Guideline for Treatment of Diabetes in Older Adults, 2019[113] | Older adults with diabetes treated with statin therapy | "In patients aged 65 years and older with diabetes, we recommend statin therapy and the use of an annual lipid profile to achieve the recommended levels for reducing absolute cardiovascular disease events and all-cause mortality." (p. 1540) | Strength of recommendation: 1 (i.e., strong)<br>Quality of evidence: high quality | Evidence to support an annual lipid panel was not reported. |
| **NICE**<br>Familial Hypercholesterolemia, 2019[111] | Familial hypercholesterolemia (presumed to be treated with lifelong lipid-lowering therapy) | "All people with familial hypercholesterolemia should be offered a regular structured review that is carried out at least annually." (p. 19)<br>Note: a structured review includes a fasting lipid profile. | The strength of the recommendation is reflected in the wording. The use of direct language (i.e., "offer") reflects an action that should be offered. | Recommendations were initially established in the 2008 version of this guideline. |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| **AHA/ACC/Multi-Society** Guideline on the Management of Blood Cholesterol, 2018[105] | Patients treated with statins to reduce the risk of atherosclerotic cardiovascular disease | "Adherence to changes in lifestyle and effects of LDL cholesterol lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter based on need to assess adherence or safety" (p. e311) | Class of recommendation = 1 (strong)<br>Level of evidence = A (high-quality evidence) | Informed by evidence review of randomized and nonrandomized studies.<br>The maximum percentage change in LDL cholesterol will occur within 4 to 12 weeks of starting statin therapy.<br>Periodic lipid monitoring can be used to assess adherence. |
| **Diabetes Canada** Clinical Practice Guidelines Dyslipidemia, 2018[107] | Patients with diabetes | "A lipid profile (i.e., total cholesterol, HDL cholesterol, triglycerides, calculated LDL cholesterol, and/or apolipoprotein B, or non-HDL cholesterol), fasting or nonfasting, should be measured routinely. (…) Repeat testing should be performed 3 to 6 months after treatment for dyslipidemia is initiated to verify lipid targets are being met." (p. s182) | Recommendation: Grade D<br>Level of evidence: Consensus based | NR |
| **AACE** Guidelines for Management of Dyslipidemia, 2017[110] | Patients with dyslipidemia | "Re-assess individuals' lipid status 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved. "(p. 18) | Recommendation Grade: D (i.e., expert opinion or lack of evidence)<br>Best evidence level: 4 (i.e., no evidence; opinion or consensus based) | NR |
| | | "While on stable lipid therapy, individuals should be tested at 6 to 12 month intervals." (p. 18) | Recommendation Grade: D (i.e., expert opinion or lack of evidence)<br>Best evidence level: 4 (i.e., no evidence; opinion or consensus based) | NR |
| | | "While on stable lipid therapy, the specific interval of testing should depend on individual adherence to therapy and lipid profile consistency; | Recommendation Grade: C (i.e., weak) (upgraded due to potential benefit)<br>Best evidence level: 4 (i.e., no | NR |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | if adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment." (p. 18) | evidence; opinion or consensus based) | |
| **Institute for Clinical Systems Improvement**<br>Lipid Management in Adults, 2017[106] | Patients treated with statins | "Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within 4 to 12 weeks after initiation or dose adjustment and every 3 to 12 months thereafter." (p. 11) | Class I (benefit is greater than the risk; procedure should be performed)<br>Level of evidence: A (high-quality evidence) | Recommendation originally from ACC/AHA.<br>"The work group agrees that a fasting lipid panel should be performed within 4 to 12 weeks after initiation or dose adjustment. However, because evidence is lacking regarding a specific testing interval, the timing of follow-up lipid testing should be done at the discretion of the clinician." (p. 11) |
| **Consensus-based guidelines** | | | | |
| **Spanish Societies for Vascular Risk (multiple societies)**<br>Consensus document for lipid profile testing, 2023[116] | Patients treated with lipid-lowering therapy | Once lipid-lowering treatment has been initiated, repeat laboratory analysis:<br>• 4 to 6 weeks after an acute atherosclerotic vascular event<br>• 4 to 12 weeks for patients who are stable in cardiovascular terms | — | Based on recommendations from the Spanish Society of Cardiology, which are supported by the Spanish Committee of Vascular Prevention. |
| | | Once a patient has reached the optimal lipid target, repeat lipid panel testing on a yearly basis. | — | |
| **NICE**<br>Quality Standard Cardiovascular risk assessment and lipid modification, 2023[119] | Patients treated with statin therapy | "Adults on a high-intensity statin have a repeat measurement of lipids and liver transaminases after 3 months of treatment" (p. 37) | — | Repeating lipid profiles is important to ensure effectiveness of statin therapy.<br>"A repeat lipid profile can be used to determine whether the expected 40% reduction in non-high-density lipoprotein (non-HDL) cholesterol has been achieved." (p. 37) |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| **AACE**<br>Consensus Statement Type 2 Diabetes Management, 2023 update[118] | Type 2 diabetes (treated with statins) | "Lipids should initially be monitored at 6 to 12 week intervals to determine if intensification of therapy is needed and then at less frequent intervals (e.g., 6 months) once goals are attained." (p. 313) | — | NR |
| **ACC**<br>Expert Consensus Decision Pathway, 2022[117] | Patients treated with statins | To determine a patient's adherence and response to therapy, repeat a fasting lipid panel 4 to 12 weeks following initiation of statin therapy. Followed by repeat lipid panels every 3 to 12 months as clinically indicated. | — | Recommendation based on the 2013 ACC/AHA and the 2018 AHA/ACC/ multi-society guidelines. |
| **Guidelines with unclear methodology** | | | | |
| **Canadian Cardiovascular Society/Canadian Pediatric Cardiology Association**<br>Clinical Practice Update, 2022[120] | Pediatric patients with dyslipidemia | Once statin therapy is initiated:<br>"Routine safety monitoring and LDL cholesterol treatment targets should be incorporated" (p. 1175)<br>As per the treatment algorithm:<br>After initiating statin therapy, repeat fasting lipid profile after 4 to 8 weeks.<br>If LDL target achieved, recheck fasting lipid profile every 3 to 6 months.<br>If LDL target not achieved, adjust dose, and recheck fasting lipid panel at 4 weeks. | — | The authors reported that the data that informed the treatment algorithm was from the 2011 National Heart, Lung, and Blood Institute Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. The recommendations in this guideline are aligned with those in the 2011 guideline. |
| **NHS**<br>Optimizing blood testing in primary care, 2021[122] | Patients treated with statin therapy | In the context of an acute shortage of blood tubes:<br>"Lipid levels for patients on statins for primary prevention do not require monitoring (except to confirm initial compliance/effect, e.g., after 3 months)." | — | — |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | In the context of an acute shortage of blood tubes:<br>"In high-risk patients/those on a statin for secondary prevention, annual testing is advised." | — | — |
| **Royal College of Physicians of Ireland**<br>National Laboratory Handbook, 2018[123] | Patients with hypercholesterolemia | "Patients on LDL cholesterol lowering medications will require lipid testing based on their individual clinical condition." (p. 4) | — | Clinicians should determine whether it is clinically appropriate to request a test more or less frequently based on the patient's clinical condition (e.g., CVD prevention). To assist with this decision, ideally clinicians will have access to all previously reported laboratory results at or before the time of requesting a new test. |
| | | "Retest annually in patients within target values is sufficient. The efficacy of therapy changes should be checked in 2 months." (p. 4) | — | |
| | | "The maximum therapeutic response for HMG-CoA reductase inhibitors (statins) is usually achieved within 4 weeks. Similarly, the adjustment of statin dose should be made at intervals of 4 weeks or more. Accordingly, there is little benefit in rechecking within 4 weeks." (p. 5) | — | — |
| **PEER simplified guideline**<br>Toward Optimized Practice Guideline, 2015[121] | Patients treated with statin therapy (for the prevention of CVD).<br>Excludes familial hypercholesterolemia | "DO NOT monitor/repeat lipid levels after a patient begins statin therapy" (p. 3) | — | The authors report that there is no evidence to support repeat lipid panel testing after initiation of statin therapy, including no evidence that suggests repeating lipid levels will increase adherence to therapy. |

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| **Recommendations from clinical societies or association (unclear methodology)** | | | | |
| **BC Guidelines**<br>Cardiovascular Disease – Primary Prevention, 2021[124] | Patients treated with statin therapy (population not further specified) | Within 3 to 6 months of initiation of statin therapy, measure non-HDL cholesterol or apolipoprotein B to assess response to therapy and adherence. A full lipid panel is not indicated. | — | — |
| **INESSS**<br>Quebec's National Medical Protocol, 2019[125] | Adults on lipid-lowering therapy as part of cardiovascular risk management | Measure the lipid profile (fasting or non-fasting) "once every 4 to 6 weeks until LDL is reduced as expected (target) based on intensity of prescribed treatment" (p. 2) | — | — |
| **Best Practice Advocacy Centre New Zealand**<br>Prescribing statins for cardiovascular risk, 2021[126] | Patients treated with statin therapy | "It is recommended to monitor non-fasting lipids every 6 to 12 months until the desired target is reached. Once achieved, annual monitoring is appropriate." (p. 3) | — | — |

ACC = American College of Cardiology; ACCE = American Association of Clinical Endocrinologists; AHA = American Heart Association; ASA = American Stroke Association; CVD = cardiovascular disease; EAC = European Atherosclerosis Society; ESC = European Society of Cardiology; HDL = high-density lipoprotein; HMG-CoA = 3-hydroxy-3-methyl glutaryl-CoA; INESSS = Institut national d'excellence en santé et an services sociaux; NICE = National Institute for Health and Care Excellence; NR = not reported; PEER = Patient, experience, evidence, research).

Notes: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature), consensus-based (i.e., recommendations were informed by expert opinion, with or without consideration for evidence collected using non-systematic methods), or as guidelines or recommendations from clinical societies or associations with unclear (i.e., not reported in detail) methodology.

This table has not been copy-edited.

## Table 22: Published Recommendations for Equity Considerations for People With Atherosclerotic Cardiovascular Disease

| Guideline, year | Population | Recommendation | Strength of the recommendation and quality of the evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| **AHA/ACC/ Multi-Society** Guideline for Management of Patients with Chronic Coronary Disease, 2023[104] | Patients with chronic coronary disease treated with lipid-lowering therapy | "In patients with chronic coronary disease, routine assessment by clinicians and the care team for social determinants of health is recommended to inform patient-centered treatment decisions and lifestyle change recommendations" (p. 854) | Class of recommendation = 1 (strong)<br>Level of evidence: B-R (i.e., moderate-quality evidence from 1 or more randomized study) | Integration of social determinants of health is based on evidence showing the effect of social determinants of health on long-term cardiovascular outcomes. |
| **AHA/ASA** Guideline for the Prevention of Stroke, 2021[114] | Patients with stroke or transient ischemic attack and dyslipidemia | "In patients with stroke or transient ischemic attack, evaluating and addressing social determinants of health (e.g., literacy level, language proficiency, medication affordability, food insecurity, housing, and transportation barriers) when managing stroke risk factors is recommended to reduce healthcare disparities" (p. e434) | Strength of recommendation: 1 (strong)<br>Level of evidence: consensus of expert opinion based on clinical experience | Socioeconomic inequalities are strong predictors of cardiovascular risk, and interventions should be tailored to patients' socioeconomic and educational status, as well as cultural, work, and home environments. |
| | | "In patients with stroke or transient ischemic attack, monitoring the achievement of nationally accepted, evidence based performance measures is recommended to allow inequities to be identified and addressed." (p. e434) | Strength of recommendation: 1 (strong)<br>Level of evidence: consensus of expert opinion based on clinical experience | — |
| **AHA/ACC/ Multi-Society** Guideline on the Management of Blood Cholesterol, 2018[105] | Patients treated with statins to reduce the risk of atherosclerotic cardiovascular disease | "For clinical decision-making in adults of different race/ethnicities, it is reasonable for clinicians to review race/ethnic features that can influence atherosclerotic cardiovascular disease risk so as to adjust choice of statin or intensity of treatment" (p. e316) | Strength of recommendation IIa (moderate)<br>Level of evidence: B-NR (moderate quality evidence from 1 or more well-designed nonrandomized study). | — |

ACC = American College of Cardiology; AHA = American Heart Association; ASA = American Stroke Association.

Note: This table has not been copy-edited.

# Appendix 6: Supplementary Tables for SPEP

Note that this appendix has not been copy-edited.

## Table 23: Published Recommendations Regarding Considerations for Serum Protein Electrophoresis

| Guideline, year | Patient condition | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| **Evidence-based guideline** | | | | |
| **National Comprehensive Cancer Network** Multiple Myeloma, 2023[144] | SMM | Follow-up and monitoring with SPEP:<br>• Every 3 to 6 months (p. MYEL-2) | NR | Recommendations are based on a literature search of high-quality evidence |
| **National Comprehensive Cancer Network** Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma, 2023[40] | Asymptomatic or minimally symptomatic Waldenström Macroglobulinemia | Follow-up for low-risk patients:<br>• Monitor every 12 months with SPEP (p. WM/LPL-2)<br>Follow-up for intermediate-risk patients:<br>• Monitor every 6 months with SPEP (p. WM/LPL-2)<br>Follow-up for high-risk patients:<br>• Monitor every 3 months with SPEP (p. WM/LPL-2) | NR | Recommendations are based on a literature search of high-quality evidence |
| **Royal College of Pathologists** National Minimum Retesting Intervals in Pathology, 2021[5] | Not specified | Retesting interval:<br>• 3 months (p. 55) | Level of evidence: D | Recommendation based on a limited evidence review |
| | MGUS | Retesting interval:<br>• Annually (p. 56) | Level of evidence: D | Recommendation based on a limited evidence review |
| **Myeloma Canada Research Network Consensus Guideline Consortium** Diagnosis of Multiple Myeloma and Related Disorders, 2020[141] | MGUS | Monitoring low intermediate, high intermediate, and high-risk MGUS:<br>• "Repeat CBC, calcium with albumin, SPEP, sFLC, and creatinine in 6 months<br>• If stable, repeat annually." (p. e357)<br>Monitoring low-risk MGUS:<br>• Repeat CBC, calcium with albumin, SPEP, sFLC, and creatinine in 6 months<br>• If stable, repeat annually." (p. e357) | NR | Recommendation based on a limited evidence review and consensus |

| Guideline, year | Patient condition | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | SMM | Monitoring high-risk SMM:<br>• "Repeat baseline investigation[a] in 2 to 3 months first year and, if stable, repeat every 4 to 6 months for 5 years or until progression<br>• If stable, evaluation can be lengthened to every 6 months, for life or until progression." (p. e359)<br>Monitoring low and intermediate-risk SMM:<br>• "Repeat baseline investigation in 3 to 4 months for 1 year<br>• If stable, repeat testing every 6 months, for life until progression." (p. e359) | NR | |
| **European Myeloma Network** Recommendations on Tools for the Diagnosis and Monitoring of Multiple Myeloma, 2018[142] | Multiple Myeloma | Monitoring of patients with extramedullary disease:<br>• "Follow-up with SPEP, UPEP and SFLC every month; if stable, increase intervals to 3 months." (p. 1777) | NR | Recommendations based on a review of clinical evidence and expert consensus was used to suggest recommendations where evidence was not available.<br>The authors note that the intervals between follow-up studies depend on the response obtained and the patients characteristics. (p. 1777) |
| **NICE** Myeloma: diagnosis and management, 2018[143] | Multiple myeloma and SMM | "Monitor people with smouldering myeloma every 3 months for the first 5 years, and then decide frequency for further monitoring based on long-term stability of disease." (p. 17)<br>"Monitor people who have completed myeloma treatment and recovered every 3 months." (p. 17)<br>"Monitoring for myeloma and smouldering myeloma should | NR | Recommendation is based on a review of evidence that included 1 observational study and 10 studies related to individual follow-up tests. |

| Guideline, year | Patient condition | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | include:<br>• Assessment of symptoms related to myeloma and myeloma treatment<br>• The following laboratory tests:<br>◦ Full blood count<br>◦ Renal function<br>◦ Bone profile<br>◦ Serum immunoglobulins and serum protein electrophoresis<br>◦ Serum-free light-chain assay." (p. 18) | | |
| **Consensus-based guidelines** | | | | |
| **European Society for Blood and Marrow Transplantation (EBMT), Joint Accreditation Committee of ISCT and EBMT, and European Haematology Association** Management of Adults and Children Receiving CAR T-cell Therapy, 2022[146] | Relapsed/refractory B-cell malignancies | Patient monitoring during medium-term follow-up:<br>• Test SPEP every 1 to 3 months (p. 269)<br>Patient monitoring during long-term follow-up:<br>• Test SPEP at every visit (p. 272)<br>• Visit frequencies:<br>◦ Monthly from day 100 to 1 year<br>◦ Every 6 months for 1 to 2 years<br>◦ Annually from 2 to 15 years | NR | Recommendations are based on the consensus view of the authors. |
| **Myeloma Australia** Clinical Practice Guideline: Multiple Myeloma, 2022[147] | Multiple myeloma | Monitoring of patients after ASCT treatment:<br>• "Patients should be followed up monthly until stable, then 3 monthly or less frequently if there appears to be disease stability<br>• Follow up assessment should include serum protein electrophoresis (immunofixation not required)." (p. 18) | Grade of recommendation: C<br>Level of evidence: 4 | Recommendation is based on expert consensus.<br>The authors report that patients should be followed up after ASCT treatment with clinical and laboratory assessments looking for evidence of relapse or progression. (p. 17) |

| Guideline, year | Patient condition | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| **Canadian Society of Clinical Chemists** Monoclonal Gammopathy Working Group, 2018[139] | MGUS | Minimum retesting frequency monitoring after initial diagnosis:<br>"Monitoring progression from sub-MGUS<br>• 5 years<br>Monitoring progression from MGUS<br>• Annual<br>Monitoring progression from Smouldering<br>• 6 months<br>Monitoring response to chemo treatment<br>• 3 months<br>Monitoring response to bone marrow transplant treatment<br>• 1 month<br>Monitoring for relapse<br>• 6 months unless significant change." (p.18) | NR | Review of previous recommendation, biological half-life of immunoglobulins, probability of disease progression and treatment cycles, and expert opinion. (p. 19) |
| **Guidelines with unclear methodology** | | | | |
| **European Society for Medical Oncology** Waldenström's Macroglobulinaemia, 2018[148] | Waldenström macroglobulinaemia | "Follow-up should include history, physical examination, blood count, routine chemistry and serum electrophoresis/ quantification of IgM every 3 months for 2 years, every 4 to 6 months for an additional 3 years, and every 6 to 12 months thereafter." (p. iv49) | NR | NR |
| **International Myeloma Working Group** Monoclonal Gammopathy of undetermined significance and Smoldering (Asymptomatic) Multiple Myeloma, 2010[149] | MGUS | After diagnosis:<br>• "Serum protein electrophoresis should be repeated 3 to 6 months after recognition of MGUS to exclude multiple myeloma or Waldenstrom's macroglobulinemia." (p. 1123)<br>Monitoring low-risk MGUS:<br>• "Patients should be followed with serum protein electrophoresis in 6 months, and if stable can be followed every 2 to 3 years or when symptoms suggestive of a | NR | NR |

| Guideline, year | Patient condition | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| | | malignancy arise." (p. 1123)<br>Monitoring intermediate and high-risk MGUS:<br>• "Patients should be followed with serum protein electrophoresis and complete blood count in 6 months and then annually for life." (p. 1123) | | |
| | SMM | "Serum protein electrophoresis, complete blood count, measurement of calcium and creatinine values and 24-h urine collection for electrophoresis and immunofixation should be performed at diagnosis and in 2 to 3 months after the initial recognition of SMM."<br>"If results are stable, the studies should be repeated ever 4 to 6 months for 1 year and if stable, evaluation can be lengthened to every 6 to 12 months." (p. 1124) | NR | NR |
| **Recommendations from clinical societies or associations (unclear methodology)** | | | | |
| **Choosing Wisely Canada** Medical Biochemistry, 2023[152] | Not specified | "Do not request a serum protein electrophoresis in asymptomatic patients in the absence of otherwise explained hypercalcemia, renal insufficiency, anemia or lytic bone lesions." | NR | The authors report that SPEP is mainly indicated to detect monoclonal gammopathy in patients who have clinical symptoms and signs related to multiple myeloma, amyloidosis, or Waldenström macroglobulinemia and SPEP is not a sensitive test to detect inflammation. |
| **Provincial Health Services Authority** British Columbia Cancer – Multiple Myeloma, 2023[150] | Multiple Myeloma | Serum protein electrophoresis test interval: 1 month | NR | NR |

| Guideline, year | Patient condition | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|---|
| **St. Louis University** 2013[151] | MGUS | "Patient with an initial diagnosis of MGUS should have an SPEP rechecked in 6 months."<br>"Low-risk patients should have SPEP every 2 to 3 years, while patients with higher-risk MGUS should have SPEP every year." (p. 13) | Strength of recommendation: C | Based on expert opinion. |
| **Laboratory guidance** | | | | |
| **Quality of Care Newfoundland and Labrador** Guidelines for Medical Laboratory Testing, 2018[153] | Not specified | Test reorder interval: 28 days | NR | Based on Choosing Wisely Canada recommendation[152] |
| **London Health Sciences Centre** Serum Protein Electrophoresis[154] | Not specified | SPEP collection frequency for repeat testing is limited to > 4 weeks. If an SPEP test is ordered in < 28 days since the collection date of the last run sample, the test will be cancelled | NR | NR |

ASCT = autologous stem cell transplant; IgM = immunoglobulin M; MGUS = monoclonal gammopathy of undetermined significance; NICE = National Institute for Health and Care Excellence; NR = not reported; SMM = smouldering multiple myeloma; SFLC = serum-free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature), consensus-based (i.e., recommendations were informed by expert opinion, with or without consideration for evidence collected using non-systematic methods), guidelines or recommendations from clinical societies or associations with unclear (i.e., not reported in detail) methodology, or as laboratory guidance (i.e., testing rules implemented in medical labs).

[a]Baseline investigation includes SPEP testing with immunofixation electrophoresis.

# Appendix 7: Supplementary Tables for TSH

Note that this appendix has not been copy-edited.

## Table 24: Published Recommendations Regarding TSH Test Frequency and Minimum Retesting Intervals for Hypothyroidism

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Evidence-based guidelines** | | | |
| **British Thyroid Association and Society for Endocrinology** Use of Liothyronine (T3) in Hypothyroidism, 2023[162] | "We recommend monitoring of levothyroxine replacement therapy in individuals with primary hypothyroidism with serum TSH measurements, with additional free T4 measurements if TSH is outside the reference range." (p. 211) | NR | The authors report that TSH levels should be checked roughly every 3 months until stable (defined as 2 similar measurements within the reference range 3 months apart) and then once a year thereafter. (p. 208) |
| | "We recommend repeat TSH blood testing 6 to 8 weeks following any change in prescription" (p. 212) | NR | — |
| **NICE** Thyroid Disease: Assessment and Management, 2023[165] | Follow-up and monitoring of primary hypothyroidism:<br>"For adults who are taking levothyroxine for primary hypothyroidism, consider measuring TSH every 3 months until the level has stabilized (2 similar measurements within the reference range 3 month apart), and then once a year." (p. 12 and 13) | NR | Evidence showed no clinically important benefit of maintaining TSH level in the lower rather than higher end of the TSH reference range.<br>The guideline committee agreed that TSH levels can take up to 6 months to return to the reference range if they have previously been very high or have been high for a long time.<br>The committee based recommendations about the timing of testing on their experience. The committee used their experience to agree which thyroid function tests are needed for monitoring. (p. 39) |
| **The Royal College of Pathologists** National Minimum Retesting Intervals in Pathology, 2021[5] | "The minimum period to achieve stable concentration after a change of dose of thyroxine is two months and TFTs should not normally be assessed before the period has elapsed.<br>Patients stabilized on long-term thyroxine therapy should have serum TSH checked annually." (p. 18) | Level of evidence: B | Recommendations based on previous evidence-based guideline from the British Thyroid Association |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **European Thyroid Association** Diagnosis and Management of Central Hypothyroidism, 2018[167] | For adults and pediatrics:<br>"In patients with CeH, we recommend to check adequacy of replacement therapy 6 to 8 weeks after the start of L-T4 replacement with concomitant FT4 and TSH measurements, provided that blood is withdrawn before the morning replacement dose or at least 4 hour after the L-T4 administration." (p. 234) | Strong recommendation<br>Moderate-quality evidence (intervention short of RCT or large observational studies) | — |
| | For adults:<br>Down-titration of the L-T4 dose is recommended patients with CeH who are older adults (especially those with cardiovascular comorbidities), or after parturition, menopause, or weight loss.<br>"In these cases, TSH and FT4 should be measured 4–6 weeks after the down-titration to check the adequacy of replacement." (p. 235) | Strong recommendation<br>Low-quality evidence (case series, case reports, expert opinion) | — |
| **European Thyroid Association** Management of Subclinical Hypothyroidism, 2013[166] | Treatment for subclinical hypothyroidism:<br>"The serum TSH should be re-checked 2 months after starting L-thyroxine therapy, and dosage adjustments made accordingly. The aim for most adults should be to reach a stable serum TSH in the lower half of the reference range (0.4 to 2.5 mU/l)." (p. 224) | Weak recommendation<br>Moderate quality of evidence (level 2) | Once started on L-thyroxine treatment, patients should have repeat serum TSH measurements after 8 to 12 weeks, and L-thyroxine dose adjusted, if necessary, to ensure that TSH has fallen into the reference range. (p. 224) |
| | Follow-up of treated patient with subclinical hypothyroidism:<br>"Once patients with SCH are commended on L-thyroxine treatment, then serum TSH should be monitored at least annually thereafter." (p. 225) | Strong recommendation<br>Moderate quality of evidence (level 2) | Several population-based studies of L-thyroxine treated hypothyroid patients have shown that 40% to 60% of individuals have biochemical evidence of under of over-replacement, indicating poor biochemical control. Therefore, once treatment has commenced, thyroid function should be monitored 2 to 3 months later to ensure serum TSH is controlled and then annually thereafter. (p. 225) |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **American Thyroid Association and American Association of Clinical Endocrinologists** Clinical Practice Guidelines for Hypothyroidism in Adults, 2012[163] | "Patients being treated for established hypothyroidism should have serum TSH measurements done at 4 to 8 weeks after initiating treatment or after a change in dose. Once an adequate replacement dose has been determined, periodic TSH measurements should be done after 6 months and then at 12 month intervals, or more frequently if clinical situation dictates otherwise." (p.1012) | Grade of recommendation: B<br>Best evidence level: 2 | Periodic follow-up evaluations with repeat TSH testing at 6-month and then 12-month intervals are appropriate, although some authors think that more frequent testing is advisable to ensure and monitor compliance with therapy (p. 1003) |
| | "In patients receiving L-thyroxine treatment for hypothyroidism, serum TSH should be remeasured within 4 to 8 weeks of initiation of treatment with drugs that decrease the bioavailability of alter the metabolic disposition of L-thyroxine dose." (p. 1016) | Grade of recommendation: A<br>Best evidence level: 1 | When medications are introduced or discontinued thyroid hormone levels should initially be checked within 4 to 8 weeks of doing so, and tests performed at least every 4 to 8 weeks until stable euthyroid indices have been documented while on the same dose of L-thyroxine. (p. 1006) |
| **Guidelines with unclear methodology** | | | |
| **Korean Thyroid Association** Management of Subclinical Hypothyroidism, 2023[164] | "The required dosage of LT4 varies depending on weight and sex, and for elderly patients or those at risk of cardiovascular disease, treatment should begin with a dose of 12.5 to 25 µg/day. Thyroid function tests should be monitored at intervals of 1 to 2 months, and the dosage adjusted with the aim of normalizing serum TSH levels." (p. 383) | Strong recommendation<br>Moderate-quality evidence | NR |
| **British Columbia Guidelines and Protocol Advisory Committee** Thyroid Function Testing and the Diagnosis and Monitoring of Thyroid Function Disorder, 2018[161] | Monitoring of hypothyroidism:<br>"Since TSH values change slowly, frequent repeat testing is not indicated. TSH may be repeated after at least 6 weeks following a change in thyroid hormone replacement dose or in a patient's clinical status." (p. 6)<br>"Once TSH has normalized with treatment, it should be checked annually unless a new indication arises." (p. 6) | – | – |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Toward Optimized Practice Endocrine Working Group** Investigation and Management of Primary Thyroid Dysfunction Clinical Practice Guideline, 2014[168] | "Wait for TSH equilibration – TSH equilibration required 8 to 12 weeks after any thyroxine dosage change." (p. 3)<br>"Order a yearly TSH once a stable dose is achieved – yearly TSH is sufficient." (p. 3) | – | – |
| **Ontario Association of Medical Laboratories** Guideline for the Use of Laboratory Tests to Detect Thyroid Dysfunction, 2007[160] | "Elevated serum levels of TSH, as seen in hypothyroidism, are slow to respond to thyroid hormone supplementation. For this reason, after initiating of adjusting thyroid hormone therapy, clinicians are advised to wait a minimum of 4 to 6 weeks and then test for TSH, FT3 and FT4. Results of these tests will detect alteration to hormone dosage." (p. 1) | – | – |

ATPOab = anti-thyroid peroxidase antibodies; CeH = central hypothyroidism; FT3 = free triiodothyronine; FT4 = free thyroxine; NICE = National Institute for Health and Care Excellence; SCH = subclinical hypothyroidism; TSH = thyroid-stimulating hormone.

Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature) or guidelines with unclear (i.e., not reported in detail) methodology.

## Table 25: Published Recommendations Regarding TSH Test Frequency for Hypothyroidism in Pregnancy

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Evidence-based guidelines** | | | |
| **European Reference Network** Congenital Hypothyroidism: A 2020 to 2021 Consensus Guidelines Update, 2021[172] | Treatment and monitoring of pregnant women with congenital hypothyroidism:<br>"FT4 (or total T4) and TSH levels should be monitored every 4 to 6 weeks during pregnancy, aiming at TSH concentrations in accordance with current guideline on treatment of hypothyroidism during pregnancy, this is, < 2.5 mU/l throughout gestation in patients treated with LT4." (p. 400) | Strong recommendation<br>Low-quality evidence | The authors report that careful monitoring of LT4 treatment of pregnant women with hypothyroidism is extremely important. (p. 401). |
| **American Thyroid Association** Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum, 2017[169] | "Women with overt and subclinical hypothyroidism (treated or untreated) or those at risk of hypothyroidism (e.g., patients who are euthyroid by TPOAb or TgAb positive, post-hemithyroidectomy, | Strong recommendation<br>High-quality evidence | Based on findings extrapolated from investigations of treated hypothyroid women from early pregnancy onwards, it is reasonable to evaluate these women for TSH elevation |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| | or treated with radioactive iodine) should be monitored with serum TSH measurement approximately every 4 weeks until midgestation and at least once near 30 weeks gestation." (p. 341) | | approximately every 4 weeks during pregnancy. (p. 341) |
| **European Thyroid Association** Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy and in Children, 2014[171] | "TSH values should be checked every 4 to 6 weeks during the first trimester and once during the second and third trimester, and the levothyroxine dose should be adjusted as necessary to reduce TSH to <2.5 mU/l or within the trimester-specific reference range." (p. 83) | Strong recommendation<br>Moderate quality of evidence (level 2) | The authors report that following the commencement of treatment with levothyroxine for subclinical hypothyroidism, TSH values should be checked every 4 to 6 weeks during the first trimester and once during the second and third trimesters. (p. 83) |
| **American Thyroid Association and American Association of Clinical Endocrinologists** Clinical Practice Guidelines for Hypothyroidism in Adults, 2012[163] | "Maternal serum TSH (and total T4) should be monitored every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation and L-thyroxine dosages adjusted as indicated" (p. 1015) | Grade of recommendation: B<br>Best evidence level: 2 | Serum TSH and total T4 measurements should be monitored every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation to ensure that the requirement for L-thyroxine treatment has not changed. Some experts suggest continued monitoring of thyroid indices after 32 weeks to confirm that thyroid indices are in the normal range. (p. 1008) |
| **Consensus-based guidelines** | | | |
| **Royal Australasian College of Physicians** Subclinical Hypothyroidism During Pregnancy: The Melbourne Public Hospitals Consensus, 2019[170] | "Free T4 and TSH should be re-checked 6 weeks after initiation of levothyroxine, and 6 weekly thereafter throughout the pregnancy to guide levothyroxine dose adjustment. If TSH is in the target range at 30 weeks' gestation, further thyroid function tests are not required for the rest of the pregnancy." (p. 998) | Level of evidence: III-3 (a comparative study without concurrent controls)<br>Grade of recommendation: C (body of evidence provides some support for recommendation but care should be taken in its application) | NR |
| | "All women should be advised to have a re-check of free T4 and TSH 6 weeks postpartum. Women will generally be asked to see their local doctor to discuss the results." (p. 998) | Level of evidence: III-3 (a comparative study without concurrent controls)<br>Grade of recommendation: C (body of evidence provides some support for recommendation but care should be taken in its application) | NR |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Guideline with unclear methodology** | | | |
| **British Columbia Guidelines and Protocol Advisory Committee** Thyroid Function Testing and the Diagnosis and Monitoring of Thyroid Function Disorder, 2018[161] | "In women with overt and subclinical hypothyroidism (treated or untreated) and women at risk for hypothyroidism (euthyroid patients who are TPO antibody positive, post-hemithyroidectomy or treated with radioactive iodine), TSH should be measured every 4 to 6 weeks until midgestation and at least once near 30 weeks gestation" (p. 8) | — | Cites the 2017 American Thyroid Association guideline[169] |
| | "After starting thyroid hormone replacement or a dose change during pregnancy, TSH should be remeasured every 4 to 6 weeks" (p. 8) | — | Cites guidance from the American College of Obstetricians and Gynecologists (2015)[188] and the Endocrine Society (2012)[189] |
| **Toward Optimized Practice Endocrine Working Group** Investigation and Management of Primary Thyroid Dysfunction Clinical Practice Guideline, 2014[168] | "Order TSH when pregnancy is confirmed and repeat every 4 to 6 weeks (due to increased demand for thyroxine during pregnancy)." (p. 3) | — | — |

LT4 = levothyroxine; PPT = postpartum thyroiditis; TgAb = thyroglobulin antibody; TPOAb = thyroid peroxidase antibody; TSH = thyroid-stimulating hormone.

Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature), consensus-based (i.e., recommendations were informed by expert opinion, with or without consideration for evidence collected using non-systematic methods), or guidelines with unclear (i.e., not reported in detail) methodology.

## Table 26: Published Recommendations Regarding TSH Test Frequency for Hypothyroidism in Pediatrics

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Evidence-based guideline** | | | |
| **NICE** Thyroid Disease: Assessment and Management, 2023[165] | Follow-up and monitoring of primary hypothyroidism for children aged 2 years and older:<br>"For children aged 2 years and over and young people taking levothyroxine for primary hypothyroidism, consider measuring FT4 and TSH:<br>• Every 6 to 12 weeks until the TSH level has stabilized (2 similar measurements within the reference range 3 months apart), then | NR | Evidence showed no clinically important benefits of maintaining TSH levels in the lower rather than higher end of the TSH refence range.<br>The guideline committee based recommendation about the timing of testing on their experience. They made separate recommendations for children under 2 years because in this age group the impact of poorly treated |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| | • Every 4 to 6 months until after puberty, then<br>• Once a year." (p. 13) | | hypothyroidism can be most severe, and the child is developing at such a rate that frequent dose changes may be needed. The committee agreed that children should have more frequent monitoring to ensure that dose adjustments are made promptly and because in the very young, under-treatment can lead to serious neurodevelopmental consequences. (p. 39) |
| | Follow-up and monitoring of primary hypothyroidism for children under 2 years:<br>"For children aged between 28 days and 2 years who are taking levothyroxine for primary hypothyroidism, consider measuring FT4 and TSH:<br>• Every 4 to 8 weeks until the TSH level has stabilized (2 similar measurements within the reference range 2 month apart), then<br>• Every 2 to 3 months during the first year of life, and<br>• Every 3 to 4 months during the second year of life." (p. 13) | NR | |
| **European Reference Network** Congenital Hypothyroidism: A 2020 to 2021 Consensus Guidelines Update, 2021[172] | Monitoring treatment for primary CH using TSH and FT4:<br>1. "The first clinical and biochemical follow-up evaluation should take place 1 to 2 weeks after the start of LT4 treatment"<br>2. "Subsequent (clinical and biochemical) evaluation should take place every 2 weeks until complete normalization of serum TSH is achieved; thereafter, the evaluation frequency can be lowered to once every 1 to 3 months until the age of 12 months"<br>3. "Between the ages of 12 months and 3 years, the evaluation frequency can be lowered to | 1. Strong recommendation; low-quality evidence<br>2. Strong recommendation; low-quality evidence<br>3. Strong recommendation; low-quality evidence<br>4. Weak recommendation; low-quality evidence<br>5. Weak recommendation; low-quality evidence | The authors report that there is no evidence for one optimal follow-up scheme. Recent studies focusing on optimization of biochemical thyroid function testing suggest the important of frequent laboratory monitoring and dose adjustment during the first year of life. Follow-up schemes in studies that reported normal IQ outcomes can be used as recommendation. The authors note that follow-up schemed have to be personalized according to parent's capabilities and compliance. (p. 398) |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| | every 2 to 4 months; thereafter, evaluations should be carried out every 3 to 6 months until growth is completed"<br>4. "If abnormal FT4 or TSH values are fond, or if compliance is questioned, the evaluation frequency should be increased"<br>5. "After a change of LT4 dose or formulation, an extra evaluation should be carried out after 4 to 6 weeks" (p. 398) | | |
| | Treatment and monitoring of central CH:<br>"In newborns with central CH, we recommend monitoring treatment by measuring FT4 and TSH according to the same schedule as for primary CH; serum FT4 should be kept above the mean/ median value of the age-specific reference interval; if TSH is low before treatment, subsequent TSH determinations can be omitted." (p. 399) | Strong recommendation<br>Low-quality evidence | The schedule for primary CH should be followed for treatment monitoring frequency. (p. 399) |
| **Guidelines with unclear methodology** | | | |
| **American Thyroid Association** Congenital Hypothyroidism: Screening and Management, 2023[174] | Monitoring during the first 3 years of life:<br>"Serum TSH and FT4 should be measured:<br>1. One to 2 weeks after the initiation of L-T4 treatment and every 2 weeks until serum TSH level is normal;<br>2. Every 1 to 2 months during the first 6 months of life (monthly in infants with sever CH [initial serum TSH > 100 mIU/L or FT4 < 0.4 ng/dL]);<br>3. Every 2 to 3 months during the second 6 months of life; and<br>4. Every 3 to 4 months between 1 and 3 years of age." (p. 6) | NR | NR |
| | Long-Term Follow-Up:<br>"After 3 years of age, measurements of TSH is recommended: | NR | NR |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| | 1. Every 6 to 12 months until growth is complete;<br>2. Four to 6 weeks after any change in L-T4 dose or formulation; and<br>3. At more frequent intervals in children with severe CH, problems with adherence to the L-T4 treatment plan, or TSH levels outside the age specific reference range." (p. 6) | | |
| **Polish Society of Paediatric Endocrinology and Diabetology** Congenital Hypothyroidism, 2016[173] | "Control laboratory tests: TSH and FT4:<br>• The first laboratory test recommended 7 to 14 days after treatment;<br>• Subsequent check-ups every 14 days until full TSH normalization;<br>• In the first year, every 1 to 3 months;<br>• In the second and third year of age, clinical and laboratory check-ups every 2 to 4 months;<br>• After the third year of age until complete growth, a check-up, according to needs every 3 to 12 months;<br>• More frequent check-ups recommended in the case of unsatisfactory cooperation between the patient/parents and abnormal laboratory test results;<br>• After change in the dose or change of thyroxine preparation, laboratory control should be performed 4 to 6 weeks after the change." (p. 539) | NR | The authors report that compliance with appropriate spacing between consecutive check-ups is very important for proper treatment monitoring. The dynamic physical development in the child's first year justified frequent laboratory testing, which, depending on the rate of body weight changes, should be carried out at 1- to 3-month intervals. In the second and third year, the check-ups may be less frequent, but not more rarely then once every 4 months. (p. 539) |

CH = congenital hypothyroidism; FT4 = free thyroxine; LT4 = levothyroxine; NICE = National Institute for Health and Care Excellence; NR = not reported; SCH = subclinical hypothyroidism; TgAb = thyroglobulin antibody; TPOAb = thyroid peroxidase antibody; TSH = thyroid-stimulating hormone.

Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature), or guidelines with unclear (i.e., not reported in detail) methodology.

## Table 27: Published Recommendations Regarding TSH Test Frequency and Minimum Retesting Intervals for Hyperthyroidism

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Evidence-based guidelines** | | | |
| **NICE** Thyroid Disease: Assessment and Management, 2023[165] | Monitoring after radioactive iodine treatment for hyperthyroidism:<br>"Consider measuring TSH, FT4 and FT3 levels in adults, children and young people every 6 weeks for the first 6 months after radioactive iodine treatment until TSH is within the reference range.<br>For adults, children and young people with TSH in the reference range 6 months after radioactive iodine treatment, consider measuring TSH (with cascading[a]) at 9 months and 12 months after treatment.<br>For adults, children and young people with TSH in the reference range 12 months after radioactive iodine treatment, consider measuring TSH (with cascading[a]) every 6 months unless they develop hypothyroidism." (p. 23) | NR | No evidence was identified on the most appropriate ways to monitor hyperthyroidism, so the committee made recommendation based on their experience. (p. 49) |
| | Monitoring hyperthyroidism after surgery:<br>"Consider measuring TSH and FT4 at 2 and 6 months after surgery, and then TSH (with cascading[a]) once a year for adults, children and young people who have had a hemithyroidectomy." (p. 24) | NR | |
| | Monitoring of antithyroid drugs for hyperthyroidism:<br>"For adults, children and young people who are taking antithyroid drugs for hyperthyroidism, | NR | |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| | consider measuring:<br>• TSH, FT4 and FT3 every 6 weeks until their TSH is within the reference range, then<br>• TSH (with cascading[a]) every 3 months until antithyroid drugs are stopped.<br>For adults, who have stopped antithyroid drugs, consider measuring:<br>• TSH (with cascading[a]) within 8 weeks of stopping the drug, then<br>• TSH (with cascading[a]) every 3 months for the first year, then<br>• TSH (with cascading[a]) once a year." (p. 24 to 25)<br>For children and young people who have stopped antithyroid drugs, consider measuring:<br>• TSH, FT4 and FT3 within 8 weeks of stopping the drug, then<br>• TSH, FT4 and FT3 every 3 months for the first year, then<br>• TSH (with cascading[a]) every 6 months for the second year, then<br>• TSH (with cascading[a]) once a year. | | |
| **The Royal College of Pathologists** National Minimum Retesting Intervals in Pathology, 2021[5] | Monitoring treatment in toxic multinodular goitre and toxic adenoma:<br>Following radioactive iodine treatment for toxic multinodular goitre or toxic adenoma:<br>"Measurement of FT4, total T3 and TSH should be repeated at 1 to 2 month intervals until stable results, and then annually thereafter." (p. 17)<br>Following surgery for toxic multinodular goitre: | Strong recommendation<br>Level of evidence: D (Weak evidence) | Recommendation based on evidence-based guidelines from the American Thyroid Association and American Association of Clinical Endocrinologists |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| | "TSH should be measured 1 to 2 monthly until stable and annually thereafter" (p. 17)<br>Following surgery for toxic adenoma:<br>"TSH and FT4 concentrations should be measured 4 to 6 weeks post-op" (p. 17) | | |
| **American Thyroid Association** Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis, 2016[175] | Patient follow-up after radioactive iodine for Graves disease:<br>"Follow-up within the first 1 to 2 months after RAI therapy for GD should include an assessment of free T4, total T3, and TSH. Biochemical monitoring should be continued at 4 to 6 week intervals for 6 months, or until the patient becomes hypothyroid and is stable on thyroid hormone replacement." (p. 1354) | Strong recommendation<br>Low-quality evidence | Recommendations are based on a systematic review of literature and expert opinion where appropriate. |
| | Patient follow-up after radioactive iodine therapy for toxic multinodular goitre or toxic adenoma:<br>"Follow-up within the first 1 to 2 months after RAI therapy for TMNG or TA should include an assessment of free T4, total T3, and TSH. Biochemical monitoring should be continued at 4- to 6-week intervals for 6 months, or until the patient becomes hypothyroid and is stable on thyroid hormone replacement." (p. 1366) | Strong recommendation<br>Low-quality evidence | |
| | Postoperative care:<br>"Following thyroidectomy for TMNG, thyroid hormone replacement should be started at a dose appropriate for the patient's weight (0.8 µg/lb or 1.6 µg/kg) and age, with elderly patients needing somewhat less. TSH should be measured every 1 to 2 months until stable, and then annually." (p. 1368) | Strong recommendation<br>Low-quality evidence | |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Guidelines with unclear methodology** | | | |
| **British Columbia Guidelines and Protocol Advisory Committee** Thyroid Function Testing and the Diagnosis and Monitoring of Thyroid Function Disorder, 2018[161] | "To monitor patient on treatment for Grave's disease or other causes of hyperthyroidism, allow at least one month or longer before repeating FT4 or TSH levels since pituitary secretion of TSH may be suppressed for protracted periods following hyperthyroidism." (p. 6) | — | — |
| **Ontario Association of Medical Laboratories** Guideline for the Use of Laboratory Tests to Detect Thyroid Dysfunction, 2007[160] | "Suppressed levels of TSH, as seen in hyperthyroidism, respond to anti-thyroid medications even more slowly. Furthermore, the TSH response to such treatment can be unpredictable and usually takes 3 to 4 months to fully adjust. Therefore, efficacy of treatment is best monitored by testing FT3 and FT4 every 4 to 6 weeks." | — | — |

ATD = antithyroid drugs; FT3 = free triiodothyronine; FT4 = free thyroxine; GD = Grave's disease; LT4 = levothyroxine; RAI = radioactive iodine; NICE = National Institute for Health and Care Excellence; TA = toxic adenoma; Tg = thyroglobulin; TMNG = toxic multinodular goitre; TSH = thyroid-stimulating hormone; TT4 = total thyroxine hormone.

Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature), or guidelines with unclear (i.e., not reported in detail) methodology.

[a]Cascading refers to measuring FT4 in the same sample if TSH is above the reference range and measuring FT4 and FT3 in the same sample if TSH is below the reference range.

## Table 28: Published Recommendations Regarding TSH Test Frequency and Minimum Retesting Intervals for Hyperthyroidism in Pregnancy

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Evidence-based guidelines** | | | |
| **European Thyroid Association** Guideline for the Management of Graves' Hyperthyroidism, 2018[176] | "Maternal FT4 (TT4) and TSH should be measured every 2 weeks after the initiation of therapy, and every 4 weeks after achieving the target value." (p. 178) | Strong recommendation<br>Low-quality evidence | Recommendation is based on a systematic review of literature and knowledge and experience of the panel. |
| **American Thyroid Association** Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum, 2017[169] | "Following cessation of antithyroid medication, maternal thyroid function testing (TSH, and FT4 or TT4) and clinical examination should be performed every 1 to 2 weeks to assess maternal and fetal thyroid status. If the pregnant women remains clinically and biochemically euthyroid, test intervals may be extended to 2 to 4 weeks during the second and third trimester." (p. 347) | Weak recommendation<br>Low-quality evidence | The authors report that for women who are pregnant and receiving ATD therapy but appear to be in remission would withdraw ATD therapy and perform repeated thyroid function testing during the first trimester of pregnancy. (p. 346) |
| | "In women being treated with ATD in pregnancy, FT4/TT4 and TSH should be monitored approximately every 4 weeks." (p. 347) | Strong recommendation<br>Moderate-quality evidence | The authors report that in settings of hyperthyroidism during pregnancy, maternal TT4/FT4 and TSH should be measured every 2 to 4 weeks following initiation of therapy, and every 4 to 6 weeks after achieving target values. (p. 347) |
| | "Pregnant women with thyroid cancer should be managed at the same TSH goal as determined preconception. TSH should be monitored approximately every 4 weeks until 16 to 20 weeks of gestation, and at least once between 26 and 32 weeks of gestations." (p. 355) | Strong recommendation<br>Moderate-quality evidence | The authors report that thyroid function should be evaluated as soon as pregnancy is confirmed. The adequacy of LT4 treatment should be checked 4 weeks after any dose change. The same laboratory should be used to monitor TSH and Tg levels before during and after pregnancy. (p. 355) |
| **Thyroid Department of the Brazilian Society of Endocrinology and Metabolism** Hyperthyroidism: Diagnosis and Treatment, 2013[177] | "Pregnant women using ATD should be monitored by measurement of FT4 and TSH every 2 to 6 weeks." (p. 220) | Level of evidence: D (troubling inconsistent or inconclusive studies of any level) | Recommendations are based on a systematic review of literature |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| | "Routine measurements of TSH and FT4 should be performed 6 weeks after delivery in patients who remain asymptomatic, and should be follow-up at regular intervals since relapse is common." (p. 220 and 221) | Level of evidence: B (consistent moderate-quality studies) | |

ATD = antithyroid drugs; FT4 = free thyroxine; LT4 = levothyroxine; Tg = thyroglobulin; TSH = thyroid-stimulating hormone; TT4 = total thyroxine hormone.
Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature).

## Table 29: Additional Recommendations of Interest — Monitoring Untreated Hypothyroidism

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Health technology assessment** | | | |
| **Agency for Healthcare Research and Quality** Screening and Treatment for Subclinical Hypothyroidism or Hyperthyroidism, 2011[159] | If antibody levels are high, repeat measurement of TSH annually. If they are low, repeat measurement of TSH every 3 years. Initiate treatment if the TSH level is greater than 10 mIU/L or the patient develops clinical findings of hypothyroidism." (p. 5) | — | Recommendations based on a 2006 evidence-based guideline from the British Thyroid Association[190] |
| **Evidence-based guideline** | | | |
| **NICE** Thyroid Disease: Assessment and Management, 2023[165] | Monitoring untreated subclinical hypothyroidism and monitoring after stopping treatment:<br>"For adults with untreated subclinical hypothyroidism or adults who have stopped levothyroxine treatment for subclinical hypothyroidism, consider measuring TSH and FT4:<br>• Once a year if they have features suggesting underlying thyroid disease, such as previous thyroid surgery or raised levels of thyroid autoantibodies, or<br>• Once every 2 to 3 years if they have no featured suggesting underlying thyroid disease." (p. 15 and 16) | NR | The committee reported that there was little evidence on treatment of people with subclinical hypothyroidism, with most of the evidence relating to older adults.<br>The committee discussed the tendency to over-rely on TSH levels when making decisions about treatment. They agreed that factors suggesting underlying thyroid disease should also be taken into account when deciding whether or not to treat subclinical hypothyroidism. (p. 40) |
| **The Royal College of Pathologists** National Minimum Retesting | Monitoring subclinical hypothyroidism:<br>"Subjects with subclinical hypothyroidism who are ATPOab | Level of evidence: B | Recommendations based on previous evidence-based guideline from the British Thyroid Association |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| Intervals in Pathology, 2021[5] | positive should have TSH and FT4 checked annually.<br>Subjects with subclinical hypothyroidism who are ATPOab negative should have TSH and FT4 checked every three years." (p. 19) | | |
| **European Thyroid Association** Diagnosis and Management of Central Hypothyroidism, 2018[167] | For adults and pediatrics:<br>"In patients under follow-up for hypothalamic-pituitary disorder, FT4 and TSH should be monitored during childhood at least biannually and later on a yearly basis, and we suggest that CeH diagnosis should be considered when serum FT4 falls in the lower quartile of the normal range, in particular when FT4 decrease > 20% of previous values is seen despite a low or normal TSH." (p. 233) | Weak recommendation<br>Very low-quality evidence (case reports, expert opinion) | The authors stated that the relative application of the tests and findings depend upon the different settings and local regulation. (p. 231) |
| **Department of the Brazilian Society of Endocrinology and Metabolism** Brazilian consensus for the clinical approach and treatment of subclinical hypothyroidism in adults, 2013[191] | "Persistent of progressive SCH must be differentiated from temporary causes of high TSH, which may regress during follow-up, especially in patients with serum TSH ≤ 10 mU/l. TSH should be repeated initially within 3 month to confirm persistent SCH." (p. 170) | Strength of recommendation: D (opinion without critical evaluation, based on consensus, physiological studies, or animal models) | Guideline was developed based on a systematic review of literature.<br>The authors report that a significant proportion of patients with SCH show normal TSH levels during the first 2 to 5 years of follow-up. Because of this, when there is suspicion of SCH, the determination of TSH should be repeated after 3 to 6 months to exclude laboratory error or temporary causes of TSH elevation. (p. 170) |
| **European Thyroid Association** Management of Subclinical Hypothyroidism, 2013[166] | Follow-up of untreated patients with subclinical hypothyroidism:<br>"If thyroid function has normalized following an initial abnormal serum TSH result, then no further testing is required in those who are asymptomatic, have negative thyroid autoantibodies or do not have giotre." (p. 224) | Strong recommendation<br>Moderate quality of evidence (level 2) | Thyroid function may normalize in 6% to 35% of subclinical hypothyroid patients depending on initial TSH levels, thyroid autoantibody status and length and frequency of follow-up; therefore, subclinical hypothyroidism may remain stable. (p. 224) |
| **Guidelines with unclear methodology** | | | |
| **British Columbia Guidelines and Protocol Advisory Committee** Thyroid Function Testing and the Diagnosis and | Monitoring of subclinical hypothyroidism:<br>"Monitoring of TSH in untreated patients with subclinical hypothyroidism is indicated at 6- to | – | – |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| Monitoring of Thyroid Function Disorder, 2018[161] | 12-month intervals, or sooner if the clinical situation changes." (p. 7) | | |

ATPOab = anti-thyroid peroxidase antibodies; CeH = central hypothyroidism; FT4 = free thyroxine; NICE = National Institute for Health and Care Excellence; SCH = subclinical hypothyroidism; NR = not reported; TSH = thyroid-stimulating hormone.

Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature), or guidelines with unclear (i.e., not reported in detail) methodology.

## Table 30: Additional Recommendations of Interest — Monitoring Untreated Hypothyroidism in Pregnancy

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Evidence-based guideline** | | | |
| **American Thyroid Association** Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum, 2017[169] | "Following the resolution of the thyrotoxic phase of PPT, serum TSH should be measured in approximately 4 to 8 weeks (or if new symptoms develop) to screen for the hypothyroid phase." (p. 362) | Strong recommendation<br>High-quality evidence | NR |
| | "Women with a prior history of PPT should have TSH testing annually to evaluate for the development of permanent hypothyroidism." (p. 363) | Strong recommendation<br>High-quality evidence | The authors report that approximately 10% to 50% of women in whom the hypothyroid phase of PPT initially resolves will ultimately go on to develop permanent hypothyroidism. (p. 363) |
| **Guideline with unclear methodology** | | | |
| **British Columbia Guidelines and Protocol Advisory Committee** Thyroid Function Testing and the Diagnosis and Monitoring of Thyroid Function Disorder, 2018[161] | "An annual TSH is recommended in patient with a history of postpartum thyroiditis." (p. 9) | — | — |

NR = not reported; PPT = postpartum thyroiditis; TSH = thyroid-stimulating hormone.

Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature), or guidelines with unclear (i.e., not reported in detail) methodology.

## Table 31: Additional Recommendations of Interest — Monitoring Untreated Hypothyroidism in Pediatrics

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Evidence-based guideline** | | | |
| **NICE** Thyroid Disease: Assessment and Management, 2023[165] | Monitoring untreated subclinical hypothyroidism and monitoring after stopped treatment:<br>"Consider measuring TSH and FT4 for children aged 2 years and over and young people with untreated subclinical hypothyroidism and TSH lower than 10 mIU/litre:<br>• Every 3 to 6 months if they have features suggesting underlying thyroid disease, such as thyroid dysgenesis or raised levels of thyroid autoantibodies, or<br>• Every 6 to 12 months if they have no features suggesting underlying thyroid disease.<br>Consider measuring TSH and FT4 every 1 to 3 months for children ages between 28 days and 2 years with untreated subclinical hypothyroidism.<br>Consider stopping TSH and FT4 measurement in children and young people if the TSH level has stabilized (2 similar measurements within the reference range 3 to 6 months apart) and there are no features suggesting underlying thyroid disease." (p. 16) | NR | The committee reported that there was little evidence on treatment of people with subclinical hypothyroidism, with most of the evidence relating to older adults. The committee noted that in very young patients it would not be appropriate to wait as long as for adults (3 months) to confirm a raised TSH with a second test. (p. 41) |
| **European Thyroid Association** Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy and in Children, 2014[171] | "In children with SCH > 3 years of age in whom thyroid auto-antibodies are negative initially, regular monitoring of serum TSH and TPOAb concentration is indicated. Because of the low risk of progression, monitoring can be performed in 1 years' time, and less frequently thereafter if no worsening is observed." (p. 89) | Strong recommendation<br>Moderate quality of evidence (level 2) | NR |
| | "The risk of progression to overt hypothyroidism appears to be increased in children with SCH due to CAT. Therefore it is suggested that in patients with an elevated TPOAb and/or TgAb concentration at presentation, TSH (+TPOAb) be monitored every 6 to | Weak recommendation<br>Moderate quality of evidence (level 2) | NR |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| 12 months. More frequent monitoring should be considered in patients whose initial TSH concentration is > 10 mU/l in whom a decision has been made not to treat." (p. 89) | | | |

CAT = chronic autoimmune thyroiditis; FT4 = free thyroxine; NICE = National Institute for Health and Care Excellence; NR = not reported; SCH = subclinical hypothyroidism; TgAb = thyroglobulin antibody; TPOAb = thyroid peroxidase antibody; TSH = thyroid-stimulating hormone.

Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature).

## Table 32: Additional Recommendations of Interest — Monitoring Untreated Hyperthyroidism

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Evidence-based guideline** | | | |
| **NICE** Thyroid Disease: Assessment and Management, 2023[165] | Managing and monitoring untreated subclinical hyperthyroidism:<br>"Consider measuring TSH every 6 months for adults, and every 3 months for children and young people with untreated subclinical hypothyroidism.<br>Consider stopping TSH measurements for adults, children and young people with untreated subclinical hyperthyroidism if the TSH level stabilizes (2 similar measurements within the reference range 3 to 6 months apart)." (p. 25) | NR | No evidence was identified on the most appropriate ways to monitor hyperthyroidism, so the committee made recommendation based on their experience. (p. 50) |
| **The Royal College of Pathologists** National Minimum Retesting Intervals in Pathology, 2021[5] | Monitoring adult subclinical hyperthyroidism:<br>"If serum TSH below reference range but > 0.1 mU/L is found, then the measurement should be repeated 1 to 2 months later along with T4 and T3 after excluding non-thyroidal illness and drug interferences.<br>If treatment is not undertaken, then serum TSH should be measured in the long term every 6 to 12 months, with follow-up with FT4 and FT3 if serum TSH is low." (p. 19) | Level of evidence: B | Recommendation based on evidence-based guidelines from the British Thyroid Association and British Thyroid Foundation |

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **European Thyroid Association** Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism, 2015[192] | Patients with endogenous subclinical hyperthyroidism and low or undetectable serum TSH:<br>"Serum TSH, free T4, and TT3 or free T3 should be evaluated every 6 to 12 months in untreated subclinical hyperthyroidism patients with persistently subnormal TSH, or as soon as the clinical picture changes." (p. 157) | Strong recommendation<br>Low-quality evidence | Recommendation was based on a systematic review of literature. |
| **Guideline with unclear methodology** | | | |
| **Cancer Care Alberta** Follow-up and Management of Checkpoint Inhibitor Related Toxicities in Cancer Patients, 2020[193] | "In patients with hyperthyroidism, monitor TSH and FT4 every 2 to 3 weeks after diagnosis as patients can develop transient thyroiditis which is then followed by hypothyroidism." (p. 17) | — | — |

FT3 = free triiodothyronine; FT4 = free thyroxine; NICE = National Institute for Health and Care Excellence; NR = not reported; TSH = thyroid-stimulating hormone; TT3 = total triiodothyronine hormone.

Note: Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature), or guidelines with unclear (i.e., not reported in detail) methodology.

## Table 33: Additional Recommendations of Interest — Monitoring Untreated Hyperthyroidism in Pregnancy

| Publication, year | Recommendation | Strength of recommendation and quality of evidence | Supporting evidence and/or rationale |
|---|---|---|---|
| **Guideline with unclear methodology** | | | |
| **British Columbia Guidelines and Protocol Advisory Committee** Thyroid Function Testing and the Diagnosis and Monitoring of Thyroid Function Disorder, 2018[161] | "During pregnancy, if TSH is low, repeat the TSH along with FT4 (using laboratory reported pregnancy specific reference intervals). If TSH is still low and FT4 is high, refer to a specialist in endocrinology or maternal-fetal medicine (e.g., obstetric internal medicine). If TSH is still low but FT4 is normal, **repeat testing in 4 weeks** is suggested. If TSH is still low referral to a specialist is recommended" (p. 8) | — | Cites the 2017 American Thyroid Association guideline[169] |

FT4 = free thyroxine; TSH = thyroid-stimulating hormone.

Note: Guidance documents were classified guidelines with unclear (i.e., not reported in detail) methodology.

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