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Health Technology Assessment (HTA)

HTA Short Report Protocol

Title	Folate testing
Technology	Diagnostic folate testing (serum folate/red blood cell folate)
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Executive Summary

This protocol outlines the methodological approach for a health technology assessment (HTA) short report evaluating the effectiveness, safety, costs and cost-effectiveness of folic acid supplementation after folate testing compared to supplementation without folate testing. The populations of interest include the asymptomatic general population, and patients with suspected folate deficiency due to the presence of symptoms, underlying medical disorders, or other external factors.

For the evaluation of clinical outcomes, a systematic literature search of biomedical databases (PubMed, Embase, Cochrane Library) will be conducted. Direct from test to health outcomes evidence will be sought and included if it is applicable to the scope of the review. In the absence of direct from test to health outcomes evidence, a linked evidence approach (involving the evaluation of diagnostic accuracy, change in management and the impact of a change in management on patient outcomes) will be implemented. The highest-level evidence will be selected, analysed and critically appraised for risk of bias using design-appropriate tools, and meta-analysis will be performed to synthesise outcomes where appropriate.

For the evaluation of economic outcomes, a systematic literature search of biomedical and economic databases (PubMed, Embase, EconLit) will be conducted. Existing economic models will be included where available. If existing models do not exist, and if direct from test to health outcomes evidence is available, the HTA will construct a *de novo* cost-utility of supplementation after folate testing compared to supplementation without testing, combined with a budgetary impact analysis. If no direct evidence is identified, only a budgetary impact analysis will be conducted.

In addition, evidence relating to the ethical, legal, social and organisational issues associated with folate testing will be investigated and synthesised narratively.

Finally, Swiss and international clinical practice guidelines on folate testing will be identified and described narratively.

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Abbreviations and acronyms

AMSTAR	A Measurement Tool to Assess systematic Reviews
CADTH	Canadian Agency for Drugs and Technologies in Health
CHF	Swiss franc
CPG	clinical practice guideline
DNA	deoxyribonucleic acid
DRG	diagnosis-related group
EAE	effectiveness, appropriateness and economic efficiency
EQ-5D	EuroQol 5-dimension questionnaire
FOPH	Federal Office of Public Health
GRADE	Grading of Recommendation, Assessment, Development and Evaluations
HTA	Health Technology Assessment
NHMRC	National Health and Medical Research Council
p.a.	per annum
PICO	population, intervention, comparator, outcome
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomised controlled trial
SF-36	Short Form 36

Objective of the HTA Protocol

Based on a preliminary screening of the literature, the objective of the HTA Protocol is to formulate the research question(s); to define the population, intervention, comparator, outcomes (PICO); and describe the methodology to conduct a systematic literature search, extract, analyse and synthesise the data in the HTA report on the topic. Key questions are defined, addressing the main HTA domains; that is, efficacy/effectiveness/safety, costs/budget impact/cost-effectiveness, ethical/legal/social and organisational issues.

1 Policy question

Each HTA topic entails a policy and a research question. In healthcare, a ***policy question*** is a request to regulate a reimbursement policy and is aimed at securing financing of health technologies. Such a request, related to a particular health technology, typically addresses an existing controversy around a technology.

In Switzerland, there are currently no limitations on mandatory insurance coverage of folate tests.[1] A sharp increase in the number of folate tests has been observed (an approximate 55% increase in total costs for folate testing from 2015 to 2018), with no corresponding change in medical necessity.[2] Limitation of coverage (e.g. to specific indications) could be considered if the effectiveness, appropriateness and economic efficiency (EAE) criteria are not fulfilled or in light of the increasing utilisation patterns.[1] Therefore, this HTA Short Report has been proposed to evaluate the EAE criteria of carrying out folate tests.

2 Medical background

Folate is the natural form of vitamin B9, an essential water-soluble vitamin required for synthesis of nucleic acids. It is found in leafy green vegetables and animal products including eggs, seafood, and cheese. Folic acid is the synthetic form of folate that is used in supplements and the fortification of foods.[3] As folate is poorly stored by the body, deficiency can develop in weeks or months in individuals with inadequate diets (i.e. those with poor nutrient intake or highly processed diets).[4]

Folate deficiency has been linked to a range of different medical disorders and conditions. Severe folate deficiency can cause megaloblastic anaemia, leukopenia and thrombopenia.[5] Symptoms of anaemia include weakness, fatigue, difficulty concentrating, irritability, headache, palpitations and shortness of breath.[6] Folate deficiency in pregnancy can cause several complications including placental abruption, congenital malformations (especially neural tube defects) and severe language delay in the offspring.[7-9] Recent research has suggested folate may also play a role in autism spectrum disorder, cancer, dementia, cognitive function and Alzheimer's disease, and depression.[10] Emerging evidence suggest that periconceptional folic acid supplementation may reduce the risk of autism; although the mechanisms of this are unclear, it may be related to folic acid's role in deoxyribonucleic acid (DNA) methylation, which affects neurodevelopment.[10] It is thought folate may suppress some cancer types during their early stages of development or, when taken in high doses, promote cancer development and progression after preneoplastic lesions have been established.[10] Again, the mechanisms of this are

unclear, but are thought to be related to folic acid's role in one-carbon metabolism and subsequent effects on DNA replication and cell division.[10] As folate is required for the conversion of homocysteine to methionine, folate deficiency may also result in homocysteine accumulation, which has been associated with Alzheimer's disease and dementia[10] as well as cardiovascular disease.[11] Finally, low folate status has been linked with depression and poor response to antidepressants in some studies. The reason for this is unknown, but is thought to be related to folate's role in methylation reactions in the brain, neurotransmitter synthesis and homocysteine metabolism.[6,10] It should be noted that biochemical and clinical evidence of deficiency can be observed in the absence of clinical symptoms.[5]

Folate deficiency can arise directly, due to the presence of a congenital disorder, or indirectly, due to malabsorption or increased folate need. Several genetic variations have been identified in the genes that encode proteins involved in folate metabolism.[12] People with a mutation in the methylenetetrahydrofolate reductase gene have an impaired ability to convert folate to the active form required by the body.[13]

There are several medical conditions that increase the risk of folate deficiency because they affect nutrient absorption. These conditions include tropical sprue, coeliac disease, short bowel syndrome and inflammatory bowel disease.[4] External factors that can affect folate absorption include alcohol and medications. Alcohol interferes with folate absorption and uptake, accelerates folate breakdown and increases its excretion by the kidneys.[14] In addition, people who are heavily dependent on alcohol can develop folate deficiency owing to their poor diet resulting in inadequate nutrient intake. Some drugs, including methotrexate, phenytoin, sulfasalazine and trimethoprim, can lead to folate deficiency due to either inhibiting its absorption or conversion to its active form.[4] Pregnant women are at risk of folate deficiency due to the increased requirement for folate during pregnancy owing to its role in nucleic acid synthesis.[4,12,15]

Ferrari et al. (2016) showed that in Europe the folate status of the general population was variable across countries, with some populations characterised by a suboptimal folate intake.[16] A recent cohort study investigating folate levels specifically in Swiss women (171 of reproductive age and 177 who were pregnant) reported that 19.9% of women of reproductive age and 2.8% of pregnant women were folate deficient (red blood cell folate concentration <340 nmol/L). Of the women who were of pregnant, 83% were on supplements containing folate compared with 11% of women of reproductive age.[17]

Folate deficiency is treated with folic acid supplementation; the amount necessary is dependent on the reason for the deficiency. Guidelines by the British Committee for Standards in Haematology recommend those outlined by the British National Formulary (Grade 1A level of evidence). These are summarised in the guidelines as follows:

- Folate deficient megaloblastic anaemia (due to dietary insufficiency, pregnancy or antiepileptics) – 5 mg of folic acid daily for 4 months, except in pregnancy where it is continued until term, and up to 15 mg daily for 4 months in malabsorptive states
- Chronic haemolytic states and renal dialysis – the prophylactic dose suggested is 5 mg daily to weekly, depending on the diet and rate of haemolysis
- Pregnancy – the prophylactic dose suggested is 200 to 500 µg daily.[5]

Given the need for adequate folate levels prior to conception to prevent neural tube defects, many health organisations recommend women of reproductive age to take folic acid supplements. Some countries have mandatory folic acid fortification of staple foods. Across European countries, voluntary and mandatory fortification policies vary.[16] There is no nationwide folic acid supplementation of food in Switzerland. Efforts in fortifying foods are privately initiated.[1]

3 Technology description

Folate levels can be measured either in serum or red blood cells. Serum folate concentration reflects recent folate status. Red blood cell folate levels give an assessment of the tissue folate status over the lifetime of the red blood cells and are therefore regarded as an indicator of long-term folate levels in the body.[18]

There is debate as to which test is the best for assessing body folate status. Serum folate is not strictly a diagnostic test for body folate depletion as serum folate level depends on recent dietary intake, and folate concentration may become subnormal after only 3 weeks of negative balance. Also, recent alcohol abuse may result in a low serum folate concentration without body depletion.[18] In comparison, red blood cell folate can differentiate between negative folate balance and body folate depletion with red blood cell folate levels falling after around 4 months of negative folate balance.[18] However, subnormal red blood cell folate levels may occur in patients with severe vitamin B12 deficiency and return to normal following vitamin B12 supplementation alone.[18] Red blood cell folate is a more complex and expensive test to perform than the serum folate assay.[5]

Currently, both types of folate tests are reimbursed through mandatory health insurance in Switzerland. The ‘Analysenliste’ positions for these 2 tests are (per 1 April 2021)[1]:

- 1329.00, ‘Folat, Blut’ (at a cost of 13.1 taxpoints)
- 1330.00, ‘Folat, Erythrozyten’ (at a cost of 21.0 taxpoints)

A total of 725,000 folate tests (serum or red blood cell) were ordered in 2018. The total costs for both types of tests amounted to CHF10.2 million. There was an approximate 55% increase in folate testing in Switzerland between 2015 and 2018, which may indicate overuse.[1]

There are currently no limitations imposed on mandatory insurance coverage of folate tests in Switzerland.[1]

4 Research Questions

To answer a ***policy question***, research questions must be defined and answered. The ***research questions*** are an answerable inquiry into the HTA topic, which require data collection and analysis. Research questions are specific and narrow.

In this section, the research questions, associated PICO criteria, eligible study designs and relevant languages are defined. The proposed questions addressing each component of the EAE criteria are described separately.[1]

4.1 Effectiveness outcomes: direct from test to health outcomes evidence

For the evaluation of clinical outcomes, direct from test to health outcomes evidence (***Table 1***) will be sought preferentially. This evidence will be selected preferentially because it directly addresses the policy question. Direct from test to health outcomes evidence refers to evidence from studies that measure the impact of conducting a test on a health outcome.[19] This includes studies in which the treatment decisions are directly linked to a test result, and health outcomes are differentiated based on test results and subsequent treatment decisions.[19]

Table 1 Research question and study selection criteria for direct from test to health outcomes evidence

Research question	What are the benefits and harms of folate testing prior to folic acid supplementation in an asymptomatic general population, and in patients with suspected folate deficiency due to the presence of symptoms, underlying medical disorders, or external factors, compared to supplementation without prior folate testing?
Population*	1. Asymptomatic general population 2. Patients with suspected folate deficiency due to the presence of symptoms, underlying medical disorders, or external factors
Intervention†	1. Diagnostic folate testing (Serum folate test) 2. Diagnostic folate testing (Red blood cell folate test)
Comparator	No folate testing
Outcome(s)‡	1. Folic acid status 2. Symptoms associated with folate deficiency (e.g. symptoms of anaemia, megaloblastic anaemia, thrombocytopenia and hyperhomocysteinaemia) 3. Rates of congenital malformations (such as neural tube defects) 4. Adverse events from testing (blood draw) or treatment side effects
Study design(s)	1. Systematic reviews and/or meta-analyses of randomised controlled trials (RCTs) and/or observational studies. 2. In the absence of systematic reviews, RCTs will be considered. 3. In the absence of RCTs, prospective non-randomised controlled trials will be considered.
Language(s)§	English, French, German and Italian

Abbreviations
RCT = randomised controlled trial.
Notes
* Data from each population will be presented separately unless reported in combination or if the population is not well defined.
† Data from each test will be reported separately. The evaluation will also consider and report results where tests are conducted sequentially.
‡ Outcomes will be reported at longest follow-up. Additionally, the list of symptoms associated with folate deficiency reported here is not exhaustive. All outcomes reported in the included literature will be considered, with prioritisation by a clinical expert if needed.
§ French, German and Italian were selected as they are 3 of the 4 official languages of Switzerland.

4.2 Effectiveness outcomes: linked evidence approach

Where direct evidence is not available, a linked evidence approach will be undertaken to evaluate the impact of folate testing on patient outcomes. In a linked evidence approach, the evidence generated in direct from test to health outcomes evidence is broken down into stages, each representing a different component of the test to outcome pathway.

The first step in the linked evidence approach is to investigate the performance of the test (***Table 2***). Early phase studies establishing the analytical validity of the tests (e.g. test-retest reliability, etc.) will not be included. Subsequently, the impact of the test outcomes on patient management is evaluated (***Table 3***). The final step in the linked evidence approach is to investigate the impact of any potential changes in management on patient outcomes (***Table 4***).

Table 2 Research question and study selection criteria for linked evidence: diagnostic accuracy of folate testing

Research question	In the asymptomatic general population or in those with suspected folate deficiency due to the presence of symptoms, underlying medical disorders, or external factors, what is the diagnostic accuracy of folate testing?
Population*	1. Asymptomatic general population 2. Patients with suspected folate deficiency due to the presence of symptoms, underlying medical disorders, or external factors
Presentation	1. Symptoms of folate deficiency (see background section of protocol) 2. Increased requirement for folate (e.g. pregnancy) 3. Asymptomatic but with chronic disease linked to folate deficiency (see background section of protocol)
Prior tests	Not applicable
Index test(s)†	1. Diagnostic folate testing (Serum folate test) 2. Diagnostic folate testing (Red blood cell folate test)
Comparator test(s)	No test
Purpose	To quantify folic acid levels, in order to diagnose a symptomatic or asymptomatic folate deficiency (first-line diagnosis)
Outcome(s)	**Test accuracy**: sensitivity, specificity, false positives, false negatives, invalid/uninterpretable results, positive predictive value and negative predictive value (detection of subclinical deficiency). **Diagnostic yield**
Reference standard	There is no accepted reference test for folate deficiency. For the purposes of validating diagnostic accuracy results, any other test of folate (serum or red blood cell), or clinical monitoring of symptoms, may be used.
Study design(s)	1. Systematic reviews and/or meta-analyses of diagnostic accuracy studies. 2. In the absence of systematic reviews for any of the index tests, primary diagnostic accuracy studies will be considered. 3. In the absence of diagnostic accuracy studies, diagnostic yield studies‡ will be considered.
Language(s)	English, French, German and Italian

Notes

* Data from each population will be presented separately unless reported in combination or if the population is not well defined.

† Data from each test will be reported separately. The evaluation will also consider and report results where tests are conducted sequentially.

‡ Diagnostic yield studies evaluate the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard.[20]

Table 3 Research question and study selection criteria for linked evidence: impact of folate testing on clinical management

Research question	In the asymptomatic general population or in those with suspected folate deficiency due to the presence of symptoms, underlying medical disorders, or external factors, does folate testing prior to folate supplementation affect supplementation commencement, route and frequency compared to no testing?
Population*	1. Asymptomatic general population 2. Patients with suspected folate deficiency due to the presence of symptoms, underlying medical disorders, or external factors
Intervention†	1. Diagnostic folate testing (Serum folate test) 2. Diagnostic folate testing (Red blood cell folate test)
Comparator	No folate testing
Outcome(s)	% change in patients treated with supplementation % change in patients with a condition other than folate deficiency treated with unnecessary supplementation % change in the dosage, route or frequency of supplementation
Study design(s)	1. Systematic reviews and/or meta-analyses of RCTs or single arm trials 2. RCTs 3. Single arm trials (i.e. diagnostic before-and-after studies, historical control studies)
Language(s)	English, French, German and Italian

Abbreviations
RCT = randomised controlled trial.
Notes
* Data from each population will be presented separately unless reported in combination or if the population is not well defined.
† Data from each test will be reported separately. The evaluation will also consider and report results where tests are conducted sequentially.

Table 4 Research question and study selection criteria for linked evidence: impact of clinical management decisions on health outcomes

Research question(s)	1. Do changes in management have an impact on patients with folate deficiency (i.e. true positives)? 2. Do changes in management have an impact on patients suspected of folate deficiency who are incorrectly diagnosed (i.e. false positive and false negatives)?
Population*	1. Asymptomatic general population 2. Patients with suspected folate deficiency due to the presence of symptoms, underlying medical disorders, or external factors
Intervention	Folate supplementation
Comparators	No treatment
Outcomes†	1. Adverse events associated with folate supplementation in patients with folate deficiency (e.g. interactions with other medications, masking of vitamin B12 deficiency) 2. Adverse events associated with folate supplementation in patients with adequate folate levels (e.g. interactions with other medications, masking of vitamin B12 deficiency) 3. Resolution of symptoms associated with folate deficiency (anaemia, megaloblastic anaemia, leukopenia, thrombocytopenia and hyperhomocysteinemia) 4. Quality of life (improved or maintained) 5. Time to administration of appropriate method of supplementation 6. % change in patients taking prescribed supplements **Disease natural history** Natural progression of condition when untreated (morbidity)
Study design(s)	1. Systematic reviews and/or meta-analyses of RCTs or non-randomised studies. 2. In the absence of systematic reviews and/or meta-analyses, RCTs will be considered. 3. In the absence of RCTs, non-randomised studies will be considered.
Language(s)	English, French, German and Italian

Abbreviations
RCT = randomised controlled trial.
Notes
* Data from each population will be presented separately unless reported in combination or if the population is not well defined.
† Outcomes will be reported at longest follow-up. Additionally, the list of symptoms associated with folate deficiency reported here is not exhaustive. All outcomes reported in the included literature will be considered, with prioritisation by a clinical expert if needed.

4.3 Economic efficiency outcomes

Economic efficiency outcomes relate to the cost and cost-effectiveness or cost-utility of the medical service, ultimately reflecting the value for money offered by the service. These outcomes will be evaluated by considering existing published literature where available, and through a *de novo* economic evaluation when existing literature is not available. A *de novo* economic evaluation will only be conducted if direct test to health outcomes evidence exists. Budgetary impact analysis will be conducted regardless of whether or not a *de novo* economic evaluation is conducted.

Table 5 Research question and study selection criteria for economic outcomes

Research question(s)	1. What is the annual budgetary impact of folate testing and subsequent supplementation? 2. What is the cost-effectiveness or cost-utility of supplementation based on folate testing, compared to supplementation without testing?*
Population†	1. Asymptomatic general population 2. Patients with suspected folate deficiency due to the presence of symptoms, underlying medical disorders, or external factors
Intervention‡	1. Diagnostic folate testing (Serum folate test) 2. Diagnostic folate testing (Red blood cell folate test)
Comparator	No testing
Outcomes	Direct medical costs (CHF): pharmaceutical costs; laboratory costs; outpatient and inpatient medical care costs. Quality-adjusted life years (e.g. calculated using SF-36, EQ-5D, or equivalent metric) Incremental cost-effectiveness ratio or incremental cost utility ratio (i.e. cost per quality-adjusted life year)
Study design(s)	Cost-effectiveness/cost-utility analyses Budgetary impact analyses
Language(s)	English, French, German and Italian

Abbreviations
CHF = Swiss francs, **EQ-5D** = EuroQol five-dimensions questionnaire, **SF-36** = Short Form 36.
Notes
* Cost-utility analysis will only be conducted if direct from test to health outcomes evidence is identified during the clinical evaluation. In either case, budgetary impact analysis will be conducted.
† Data from each population will be presented separately unless reported in combination or if the population is not well defined.
‡ Data from each test will be reported separately. The evaluation will also consider and report results where tests are conducted sequentially.

4.4 Appropriateness outcomes

The final domain in the EAE criteria deals with the appropriateness of the intervention. Issues related to ethical, legal, social or organisational matters relating to the use of folate testing will be investigated in this domain, noting that issues will only be described if they are directly relevant to the policy question.

Table 6 Research question and study selection criteria for appropriateness outcomes

Research question	Are there ethical, legal, social or organisational issues associated with folate testing?
Population	Patients eligible for folate testing
Intervention	Supplementation following folate testing
Comparator	Supplementation with no testing
Outcomes*	**Ethical**: balance of benefits and harms (e.g. are there hidden or unintended consequences of conducting the test, etc.), autonomy (e.g. is the value of testing augmented by its impact on the autonomy of patients, etc.), equity (e.g. does the implementation of testing have impacts on equitable access to care across the population, etc.). **Legal**: can the limitation of this technology to certain populations pose ethical challenges which have not been considered in existing legislations and regulations. **Social**: patient preferences and expectations about folate testing, caregiver preferences and expectations about folate testing. **Organisational**: structure of the health system (e.g. are there standard cut-offs used to define folate deficiency, etc.), process-related costs (e.g. how would services be re-oriented in the absence of folate testing, and what costs would these incur, etc.), culture (e.g. how is folate testing accepted in practice, etc.).
Study design(s)	Systematic reviews, narrative reviews, randomised controlled trials, observational studies, cross-sectional studies (i.e. surveys), government reports.
Language(s)	English, French, German and Italian

Notes
* These outcomes have been defined in accordance with the EUnetHTA Core Model 3.0.[21]

5 Methodology: effectiveness outcomes

5.1 Literature searches strategy

5.1.1 Databases and other sources

A systematic search of the scientific peer-reviewed literature addressing the research questions will be performed in 4 databases (PubMed, Embase, Cochrane Library, EconLit). No date restrictions will be applied. An example of the search terms to be used for the PubMed database is presented in ***Table 11*** (***Appendix B***). Search terms will be adapted to other databases as appropriate.

Searches will be conducted in ClinicalTrals.gov and the EU Clinical Trials Registry to identify ongoing clinical trials related to the research questions. Grey literature searches will be conducted on HTA agency websites and the International HTA Database (***Appendix A***, ***Table 9***) using combinations of the keywords 'folate', 'folic acid', 'folacin', 'folate deficiency', 'folic acid deficiency', 'vitamin B9', 'vitamin B9 deficiency' and 'test*' to identify existing HTA reports on the same topic. References lists of included studies will be pearled to identify additional studies.

5.1.2 Inclusion and exclusion criteria

Studies will be selected for inclusion according to the research questions, PICO criteria, study designs and languages defined in ***Section 4***.

For the clinical questions, the literature search will initially focus on retrieving existing systematic reviews (of moderate to high quality, per the A Measurement Tool to Assess Systematic Reviews 2 [AMSTAR 2] checklist) of any study design addressing each research question.[22] Included systematic reviews will be updated by a search for primary research studies published after the review search date.

Where eligible systematic reviews are not available, primary studies that meet the inclusion criteria will be selected for inclusion, starting with the highest level of evidence relevant to each research question according to the National Health and Medical Research Council (NHMRC) hierarchy of evidence.[20]

Conference abstracts, letters to the editor and author responses, case reports and animal studies will be excluded from the review.

5.1.3 Study selection

Two reviewers will split the screening of the titles and abstracts retrieved using the search strategies reported in ***Appendix B***. Articles will be screened by titles and abstracts in batches of 300 studies by 2 independent reviewers until sufficient inter-rater reliability is established. A Cohen's Kappa score >0.8 will be considered acceptable to justify the split screening and assessment. Once inter-rater reliability has been established, the remaining studies will be split equally between the reviewers. The full text of articles deemed potentially relevant will then be reviewed independently by 2 reviewers. Any disagreement on article inclusions will be resolved by consensus; if consensus cannot be reached, a third independent reviewer will be consulted to determine inclusion.

5.2 Data extraction, appraisal and synthesis

5.2.1 Data extraction

One reviewer will independently extract data into a standardised template, which will be checked against the original study record by a second reviewer. Disagreements will be settled by discussion or by a third independent reviewer. Data of interest includes:

- study information: country, year, number of institutions, study design, inclusion/exclusion criteria, withdrawals, length of follow-up
- demographic information: number of participants, age, sex, comorbidities, indication for testing, prior testing
- intervention and comparator: type and method of intervention/comparator (including index test, reference test, dose and administration route), concomitant interventions

- outcomes of interest: diagnostic accuracy data, baseline, final or change from baseline scores in any of the predefined outcomes outlined in ***Section 4***.
- any noteworthy features, limitations or differences in the study.

5.2.2 Critical appraisal

Two independent researchers will conduct critical appraisal, with differences settled via consensus or by an independent reviewer where consensus cannot be reached. Critical appraisal will be conducted by different tools depending on the study design. For example, included systematic reviews will be appraised using the AMSTAR 2 checklist[22]; RCTs will be evaluated using the RoB 2 (Cochrane risk-of-bias tool, version 2) tool[23]; non-RCTs by the ROBINS-1 (Cochrane risk of bias in non-randomised studies) tool[24]; and single-arm trials by the Institute of Health Economics quality appraisal checklist for case series.[25] Systematic reviews of diagnostic accuracy studies will be appraised using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool[26] and risk of bias in comparative diagnostic accuracy studies appraised using the QUADAS-C tool.[27]

The quality of the evidence for each outcome will be evaluated using the GRADE (Grading of Recommendation, Assessment, Development and Evaluations) approach.[28,29] The five domains of the GRADE framework (imprecision, inconsistency, indirectness, risk of bias, and publication bias) will be assessed according to the decision algorithm developed by Pollock et al. (2016).[28,30] The overall strength of the evidence will be presented in 'Summary of Findings' tables generated in GRADEpro.[29,31]

5.2.3 Data synthesis

Data from each population will be presented separately. In addition, data for each type of folate test (i.e. serum folate test and red blood cell folate test) will also be presented separately. If data is available, results relating to the following subgroups will be discussed:

- Outcomes for subpopulations (e.g. patients planning to become pregnant, pregnant patients, elderly)
- Outcomes from studies conducted in settings with folate deficiency levels similar to those found in Switzerland
- Any other subgroup in the included studies, determined before the analysis of results, decided in conjunction with a clinical expert.

The approach to data synthesis for each research question will depend on the available evidence. Where appropriate, existing systematic reviews and/or meta-analyses will be summarised narratively for all research questions. Where existing systematic reviews are not available, primary studies will be included, and the type of analysis will depend on the research question being addressed, as follows:

5.2.3.1 Diagnostic accuracy

Where appropriate, meta-analysis will be conducted on diagnostic accuracy studies reporting sensitivity and specificity data. The full method of any meta-analyses will be detailed in the HTA. Where meta-analysis is not appropriate, primary studies will be summarised in a narrative fashion, and reported using descriptive statistics.

5.2.3.2 Change in management

The results of existing systematic reviews and/or meta-analyses, and any primary studies (in the absence of existing reviews) will be summarised narratively.

5.2.3.3 Impact of clinical management decisions on health outcomes

The results of existing systematic reviews and/or meta-analyses, and any primary studies (in the absence of existing reviews) will be summarised narratively.

6 Methodology: economic efficiency outcomes

The proposed methodology for the economic evaluation will be dependent on 1) the availability of existing, published economic models that are relevant to the Swiss context, and 2) in the absence of existing published models, the availability of direct from test to health outcomes evidence. Only Swiss-specific economic evaluations will be included to directly inform the results of the economic section due to limitations in translating results from other settings to the Swiss context. In the absence of directly applicable evidence, a *de novo* cost-effectiveness or cost-utility analysis may be conducted, guided by existing economic evaluations from other settings. However, a *de novo* evaluation will only be considered if direct test to health outcomes evidence exists. Where neither existing models, nor direct from test to health outcomes evidence exists, a *de novo* economic evaluation will not be conducted. Budgetary impact analysis will be conducted regardless of whether economic modelling is conducted.

6.1 Literature search strategy

6.1.1 Databases and other sources

The systematic literature searches outlined in ***Section 5.1.1*** and ***Appendix B*** will be used to identify economic studies related to the research question. No date restrictions will be applied.

6.1.2 Inclusion and exclusion criteria

Studies will be selected for inclusion according to the research questions, PICO criteria, study designs and languages defined in ***Section 4***.

6.2 Data extraction, appraisal and synthesis

6.2.1 Data extraction

One reviewer will independently extract data into a standardised template, which will be checked against the original study record by a second reviewer. Disagreements will be settled by discussion or by a third independent reviewer. Data of interest will include:

- study details: author, year, country, currency
- demographic information: age, sex, comorbidities, indication for testing, prior testing
- outcomes of interest: choice of health outcomes, measurement of effectiveness (single study or synthesis), incremental costs and outcomes
- methods: study perspective, structural assumptions, health states, discount rate, time horizon, evaluation type (e.g. model-based or single study-based), choice of model, assumptions, analytical methods
- results data (from directly applicable studies only).

6.2.2 Critical appraisal

Economic studies that are included in the HTA to inform the results of the economic section will undergo critical appraisal. Relevant economic studies will be appraised using an appropriate checklist (e.g. the Drummond criteria for determining the quality of economic evaluations).[32] If a *de novo* modelling approach is required, critical appraisal will not be conducted on existing economic studies, because these studies will not be used to inform the results of the HTA.

6.3 Proposed *de novo* modelling approach

If *de novo* modelling is required, the proposed methodology for the economic evaluation will be aligned with published models, and in accordance with the EUnetHTA Core Model 3.0[21] and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[33] An overview of the proposed modelling methodology is provided in ***Table 7***.

If a *de novo* model is needed, it will be developed using TreeAge Pro (TreeAge Software, Inc.)[34] and used for the base case and comparisons included for sensitivity analyses. The analysis will be conducted from a Swiss healthcare payer perspective. Direct medical costs for services covered by Swiss mandatory health insurance will be included, however non-medical and indirect costs will not be included. Cost inputs will be sourced from the Analysenliste, Swiss diagnosis-related group (DRG) costs (i.e. associated with adverse events related to untreated folate deficiency [i.e. due to false negative test results]), the Swiss Spezialitätenliste for medicines costs and TARMED positions.[35] Ideally, a cost utility analysis will be conducted, with effectiveness expressed using the quality adjusted-life year (QALY).

Relevant model inputs such as probabilities and utilities will be derived from evidence identified in the clinical evaluation or alternate literature sources. Costs and effects will be discounted at 3% per annum in the base case analysis.

Deterministic and probabilistic sensitivity analysis will be undertaken to account for uncertainty in the input parameters. Cost-effectiveness acceptability curves will be presented as part of sensitivity analyses, along with results based on differing time horizon, discount rates, medicine prices, unit costs, clinical input and quality of life (QoL) estimates.

6.3.1 Proposed evaluation methodology

Table 7 Summary of the proposed economic evaluation methodology

Perspective	Swiss healthcare payer*
Patient population	• Asymptomatic general population • Patients with suspected folate deficiency due to the presence of symptoms, underlying medical disorders, or external factors
Intervention	Supplementation following folate testing
Comparator	Supplementation with no testing
Type of economic evaluation	Cost-utility analysis
Time horizon	1, 5 and 10 years
Sources of inputs	Published systematic reviews, RCTs, observational studies, Spezialitätenliste, Analysenliste, TARMED, Swiss diagnosis-related group (DRG), expert opinion EQ-5D, SF-36 or equivalent weights will be sourced from clinical evidence or literature review
Costs	Direct medical costs (CHF): pharmaceutical costs; laboratory costs; outpatient and inpatient medical care costs.
Effect measure	QALYs
Discount rate	3% p.a. for both costs and QALYs; 0 and 6% as sensitivity analyses

Abbreviations
CHF = Swiss francs, **DRG** = diagnosis-related group, **EQ-5D** = EuroQol 5-dimension questionnaire, **p.a.** = per annum, **QALYs** = quality-adjusted life years, **RCT** = randomised control trial, **SF-36** = Short Form 36.
Notes
***** The analysis will be performed from a healthcare payer perspective. Costs of healthcare services covered by the Swiss mandatory health insurance will be analysed, irrespective of the actual payer (mandatory health insurance, other social insurance, government, out-of-pocket). The analysis will not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs.

6.3.2 Budgetary impact analysis

Projected costs (in CHF) to the payer from the use of folate testing and associated treatments (i.e. folic acid supplementation) over the next 5 years under current policy/practice conditions will be evaluated. Budgetary impact analysis will be conducted to examine the financial implications for different reimbursement scenarios. Usage data for Switzerland for the intervention will be sourced from © COGE GmbH Tarifpool © SASIS AG.[2] The utilisation of folate testing will be evaluated based on usage data from the Analysenliste (i.e. 1329.00, 1330.00), and may be complemented by an epidemiological approach. Folate supplementation will be considered in the analysis, noting that publicly reimbursed folate supplements are not limited to patients with a diagnosed deficiency (i.e. Andreafol, Acidum

Folicum, Dialvit, Fertifol, Metofol, etc.). The utilisation of publicly reimbursed folate supplements will be evaluated based on usage data from the Spezialitätenliste. Key assumptions will be summarised in an evidence table that precedes the base results. Sensitivity analyses will be included for major assumptions.

7 Methodology: appropriateness outcomes

In addition to the clinical evidence, the review will evaluate ethical, legal, social and organisational issues related to folate testing, and any potential changes to the reimbursement status of folate testing in Switzerland.

Restricting the provision of folate testing to a certain group of patients must be based on objective reasons. The EAE criteria are objective reasons.[36] Moreover, the restriction of provision or the complete cessation of this service by the social health insurance company may under no circumstances be unilaterally at the expense of vulnerable groups (e.g. the elderly, geriatric patients, dementia patients or patients unable to form a judgement, patients with a migration background, or patients with rare diseases, etc.). However, there is hardly any danger of discrimination if folate testing is only partially administered or removed from social health insurance for objective reasons (differentiated assessment of the EAE criteria on the basis of the HTA) and do not concern unilaterally vulnerable groups.

7.1 Literature search strategy

7.1.1 Databases and other sources

A literature search for studies reporting ethical, legal, social and organisational issues associated with folate testing will be conducted in PubMed and Embase (OVID). In addition, studies included in the clinical section of the report will be pearled for citations relating to these auxiliary domains. Grey literature searches will be conducted on specialty and HTA websites (***Appendix A***, ***Table 8*** and ***Table 9***) using combinations of the keywords ‘folate’, ‘folic acid’, ‘folacin’, ‘folate deficiency’, ‘folic acid deficiency’, ‘vitamin B9’, ‘vitamin B9 deficiency’ and ‘test*’.

7.1.2 Inclusion and exclusion criteria

Table 6 demonstrates the populations, interventions and comparators to be applied. Narrative reviews and surveys will be included for the ethical (e.g. impact on patient autonomy), social (e.g. patient preference), organisational issues (e.g. staff training, facility requirements) and legal issues where appropriate. Literature in English, German, French and Italian languages will be considered, and no date restrictions will be implemented.

7.2 Data extraction, analysis and synthesis

7.2.1 Study selection

The targeted search for studies reporting on ethical, legal, social and organisational issues associated with folate testing will be conducted by a single reviewer.

7.2.2 Data extraction

One reviewer will independently extract data into a standardised template, which will be checked against the original study record by a second reviewer. Disagreements will be settled by discussion or by a third independent reviewer. Data of interest will include:

- study information: country, year, study design, research question, inclusion/exclusion criteria
- demographic information: number of participants, age, sex, comorbidities, indication for testing
- outcomes of interest: results relating to ethical, legal, social or organisational issues
- any noteworthy features, limitations or differences in the study.

7.2.3 Data synthesis

The results of existing reviews and any primary studies included in the review will be described narratively.

Data from each population will be presented separately. In addition, data for each type of folate test (i.e. serum folate test and red blood cell folate test) will also be presented separately. If data is available, results relating to the following subgroups will be discussed:

- Outcomes for subpopulations (e.g. patients planning to become pregnant, pregnant patients, elderly)
- Outcomes from studies conducted in settings with folate deficiency levels similar to those found in Switzerland
- Any other subgroup in the included studies, determined before the analysis of results, decided in conjunction with a clinical expert.

8 Methodology: clinical practice guideline review

8.1 Literature search strategy

8.1.1 Databases and other sources

The systematic literature searches outlined in ***Section 5.1.1*** and ***Appendix B*** will be used to identify clinical practise guidelines (CPGs) related to the research question.

Grey literature searches will be conducted for CPGs on specialty websites (***Appendix A***, ***Table 8***) using combinations of the keywords relating to 'folate', 'folic acid', 'folacin', 'folate deficiency', 'folic acid deficiency', 'vitamin B9', 'vitamin B9 deficiency', and keywords relating to 'guideline, CPG*'. In addition, searches will be conducted on the CPG websites listed in ***Table 10*** (***Appendix A***) using the keywords 'folate', 'folic acid', 'folacin', 'folate deficiency', 'folic acid deficiency', 'vitamin B9' and 'vitamin B9 deficiency'.

8.1.2 Inclusion and exclusion criteria

Any Swiss or international guidelines providing recommendation(s) on the appropriateness of folate testing, or on how management should be guided by test results, will be assessed for inclusion. Only guidelines published in English, French, German or Italian languages will be eligible for inclusion.

A guideline will be included if it meets the following criteria, adapted from Graham et al. (2011):

1) It contains the word 'guideline' or 'recommendation' in its title or introduction, or contains recommendations on folate or folic acid testing, and;
2) It was developed by at least 2 authors, and;
3) It was developed based on a systematic search of the literature.

Guidelines that are not developed based on a systematic search of the literature will be excluded. For example, consensus statements that contain recommendations based only on expert opinion. Only guidelines published after 1 January 2017 will be included as guidelines are considered to be outdated 5 years after publication.[37,38]

8.1.3 Search terms

An example of the search terms to be used the PubMed database for guidelines is presented in **Table 11** (***Appendix B***). Search terms will be adapted to other databases as appropriate.

8.2 Data extraction, analysis and synthesis

8.2.1 Study Selection

The selection of CPGs will be conducted by a single reviewer.

8.2.2 Data extraction

Recommendations (and grade of recommendation) on folate testing and treatment strategies will be extracted and tabulated from identified guidelines by a single reviewer and checked by a second reviewer. Disagreements will be settled by discussion or by a third independent reviewer.

8.2.3 Data synthesis

Findings from the guideline review will be reported narratively.

Data from each population will be presented separately. In addition, data for each type of folate test (i.e. serum folate test and red blood cell folate test) will also be presented separately. If data is available, results relating to the following subgroups will be discussed:

- Outcomes for subpopulations (e.g. patients planning to become pregnant, pregnant patients, elderly)
- Outcomes from studies conducted in settings with folate deficiency levels similar to those found in Switzerland
- Any other subgroup in the included studies, determined before the analysis of results, decided in conjunction with a clinical expert.

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10 Appendices

10.1 Appendix A: Literature sources

Table 8 Specialty websites (clinical nutrition and metabolism, geriatric, haematology, neurology)

Society	Website
European Society for Clinical Nutrition and Metabolism (ESPEN) National Societies	
Australasian Society for Parenteral and Enteral Nutrition	www.auspen.org.au
Flemish Society for Clinical Nutrition and Metabolism Vlaamse Vereniging voor Klinische Voeding en Metabolisme	www.vvkvm.be
Société Belge de Nutrition Clinique Belgian Society of Clinical Nutrition	https://www.sbnc.site/
Canadian Nutrition Society Société Canadienne de Nutrition	www.cns-scn.ca
Hrvatsko društvo za klinicku prehranu, Hrvatskog liječničkog zbora	www.cspen.com.hr
Croatian Society of Clinical Nutrition Croatian Medical Association	https://www.hlz.hr/
Česká společnost klinické výživy a intenzivní metabolické péče České lékařské společnosti Jana Evangelisty Purkyně The Czech Society for Clinical Nutrition and Intensive Metabolic Care within the Czech Medical Association of J.E. Purkyně	www.skvimp.cz
Dansk Selskab for Klinisk Ernæring Danish Society for Clinical Nutrition	www.dske.dk
The Finnish Society for Clinical Nutrition and Metabolism	www.fispen.fi
Société Francophone Nutrition Clinique et Métabolisme French Speaking Society of Clinical Nutrition and Metabolism	www.sfncm.org
Deutsche Gesellschaft für Ernährungsmedizin German Society for Nutritional Medicine	www.dgem.de
Ελληνική Εταιρεία Ιατρικής/Κλινικής Διατροφής και Μεταβολισμού Hellenic Society for Clinical Nutrition and Metabolism	www.grespen.org
Irish Society for Clinical Nutrition and Metabolism	www.irspen.ie
Hachevra Letzona Clinit The Israeli Society for Clinical Nutrition	ISCN website
Società Italiana di Nutrizione Artificiale e Metabolismo Italian Society for Artificial Nutrition and Metabolism	www.sinpe.org
日本静脈経腸栄養学会 Japanese Society for Clinical Nutrition and Metabolism	https://www.jspen.or.jp/
Norsk Selskap for Klinisk Ernæring Norwegian Society for Clinical Nutrition and Metabolism	www.nske.no
Associação Portuguesa de Nutrição Entérica e Parentérica Portuguese Association of Enteral and Parenteral Nutrition	www.apnep.pt
Society for Parenteral and Enteral Nutrition (Singapore)	http://www.singspen.com
Slovensko Združenje za Klinično Prehrano Slovenian Society for Clinical Nutrition	http://klinicnaprehrana.si/

Society	Website
Sociedad Española de Nutrición Clinica y Metabolismo Spanish Society of Clinical Nutrition and Metabolism	www.senpe.com
The Swedish Society for Clinical Nutrition and Metabolism	www.swespen.se
Gesellschaft für Klinische Ernährung der Schweiz/Société Suisse de Nutrition Clinique Swiss Society for Clinical Nutrition	www.geskes.ch
Nederlandse Vereniging voor Gastro-Enterologie Netherlands Society for Parenteral and Enteral Nutrition	https://www.nvge.nl/
British Association of Parenteral and Enteral Nutrition	www.bapen.org.uk
American Society for Parenteral and Enteral Nutrition	www.nutritioncare.org
Geriatric	
European Geriatric Medicine Society	https://www.eugms.org/home.html
Australian and New Zealand Society for Geriatric Medicine	http://www.anzsgm.org/
Schweizerische Fachgesellschaft für Geriatrie Swiss Geriatric Society	https://www.sfgg.ch/
Haematology	
Belgian Hematology Society	http://www.bhs.be
Cyprus Society of Haematology	www.cyhaema.com
Česká Hematologická Společnost CLS JEP Czech Society of Hemtology	http://www.hematology.cz
Dansk Haematologisk Selskab Danish Society of Hematology	http://www.hematology.dk
Suomen hematologiyhdistys Finnish hematology Association	www.hematology.fi/en
Société Française d'Hématologie French Society of Hematology	http://sfh.hematologie.net
Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie German Society of Hematology	http://www.dgho.de
Eliniki Ematologhiki Eteria Hellenic Society of Hematology	http://www.eae.gr
Haematology Association of Ireland	http://www.haematologyireland.org
Israel Society of Hematology and Transfusion Medicine	http://www.hematology.org.il
Società Italiana di Ematologia Italian Society of Hematology	http://www.siematologia.it
Société Luxembourgoise d'Oncologie	https://www.slo.lu
Sociedade Portuguesa de Hematologia Portugese Society of Hematology	http://www.sph.org.pt
Zdruzenja Hematologov Slovenije Slovenian Society of Hematology	http://www.hematologija.org
Sociedad Española de Hematología y Hemoterapia	http://sehh.es/es/
Svensk Förening för Hematologi Swedish Society of Hematology	http://www.sfhem.se
Schweizerische Gesellschaft für Hämatologie Swiss Society for Hematology	http://www.sgh-ssh.ch
Nederlandse Vereniging voor Hematologie Dutch Society of Hematology	https://www.hematologienederland.nl

Society	Website
British Society for Haematology	http://www.b-s-h.org.uk
Neurology	
Brain Research Society of Finland	https://www.brsf.org/
British Neuroscience Association	https://www.bna.org.uk/
Hrvatski Institut za Istraživanje Mozga Croatian Society for Neuroscience	http://www.hiim.unizg.hr/
Czech Neuroscience Society	https://www.biomed.cas.cz/cns/index.php/en/
Dansk Selskab for Neurovidenskab Danish Society for Neuroscience	https://dsfn.dk/
Dutch Neurofederation	https://neurofederatie.nl/
German Neuroscience Society	https://nwg-info.de/
Hellenic Society for Neuroscience	https://www.hsfn.gr/
Israel Society for Neuroscience	https://www.isfn.org.il/
Società Italiana di Neuroscienze Italian Society for Neuroscience	http://www.sins.it/EN/index.xhtml
Malta Neuroscience Network	http://mnn.mt/
Neuroscience Ireland	https://neuroscienceireland.com/
Norwegian Neuroscience Society	https://www.ntnu.edu/nns
Slovenian Neuroscience Association	http://www.sinapsa.org/naslovnica/
Sociedad Española de Neurociencia Spanish Society of Neuroscience	https://www.senc.es/en/
Sociedade Portuguesa de Neurociências Portuguese Society for Neuroscience	http://www.spn.org.pt/
Societé des Neurosciences The French Neuroscience Society	https://www.neurosciences.asso.fr/
Swiss Society for Neuroscience	https://www.swissneuroscience.ch/

Table 9 HTA agency websites

HTA Websites	
Australia	
Adelaide Health Technology Assessment (AHTA)	https://www.adelaide.edu.au/ahta/pubs/
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S)	https://www.surgeons.org/research-audit/research-evaluation-inc-asernips
Austria	
Austrian Institute for Health Technology Assessment (AIHTA)	https://aihta.at/page/homepage/en
Gesundheit Österreich GmbH (GOG)	http://www.goeg.at
Argentina	
Institute for Clinical Effectiveness and Health Policy (IECS)	http://www.iecs.org.ar
Belgium	
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be
Brazil	
National Committee for Technology Incorporation (CONITEC)	http://conitec.gov.br/en/
Agência Nacional de Saúde Suplementar/ National Regulatory Agency for Private Health Insurance and Plans (ANS)	https://www.gov.br/ans/pt-br

Canada	
Institute of Health Economics (IHE)	http://www.ihe.ca
Institut National d'Excellence en Santé et en Services (INESSS)	https://www.inesss.qc.ca/en/home.html
The Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/
Ontario Health (OH)	https://www.ontariohealth.ca/
Colombia	
Instituto de Evaluación Tecnológica en Salud (IETS)	http://www.iets.org.co
Denmark	
Social & Health Services and Labour Market (DEFACTUM)	http://www.defactum.net
Finland	
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/HTA-julkaisuja.aspx
France	
French National Authority for Health (Haute Autorité de Santé; HAS)	http://www.has-sante.fr/
Assistance Publique – Hôpitaux de Paris	http://cedit.aphp.fr
Germany	
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	https://www.g-ba.de/english/
Ireland	
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie
Italy	
Agenzia Sanitaria e Sociale Regionale (ASSR)	http://www.inahta.org/members/assr/
HTA Unit in A. Gemelli Teaching Hospital (UVT)	https://www.policlinicogemelli.it/
National Agency for Regional Health services (Agenas)	http://www.agenas.it
Kazakhstan	
Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development (RCHD)	http://www.rcrz.kz
Korea	
National Evidence-based healthcare Collaborating Agency (NECA)	www.neca.re.kr/eng
Malaysia	
Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAS)	http://www.moh.gov.my
The Netherlands	
The Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl
Zorginstituut Nederland (ZIN)	https://www.zorginstituutnederland.nl/
Norway	
The Norwegian Institute of Public Health (NIPHNO)	http://www.fhi.no/
Peru	
Institute of Health Technology Assessment and Research (IETSI)	http://www.essalud.gob.pe/ietsi/
Poland	
Agency for Health Technology Assessment and Tariff System (AOTMiT)	http://www.aotm.gov.pl
Republic of China, Taiwan	
Center for Drug Evaluation (CDE)	http://www.cde.org.tw

Russian Federation	
Center for Healthcare Quality Assessment and Control (CHQAC)	www.rosmedex.ru
Singapore	
Agency for Care Effectiveness (ACE)	Agency for Care Effectiveness (ACE) (ace-hta.gov.sg)
Spain	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I / Health Technology Assessment Agency (AETS)	http://publicaciones.isciii.es/
Agency for Health Quality and Assessment of Catalonia (AQuAS)	http://aquas.gencat.cat
Andalusian HTA Agency	http://www.aetsa.org/
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.eus/web01-a2ikeost/en/
Galician Agency for Health Technology Assessment (AVALIA-T)	http://acis.sergas.es
Health Sciences Institute in Aragon (IACS)	http://www.iacs.es/
Sweden	
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Switzerland	
Swiss Federal Office of Public Health (SFOPH)	http://www.bag.admin.ch/hta
Tunisia	
INEAS – National Authority for Assessment and Accreditation in Healthcare, TUNISIA	http://www.ineas.tn/fr
United Kingdom	
Healthcare Improvement Scotland (HIS)	http://www.healthcareimprovementscotland.org
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
Health Technology Wales (HTW)	http://www.healthtechnology.wales
National Institute for Health Research (NIHR), including HTA programme	http://www.nets.nihr.ac.uk/programmes/hta
United States	
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/index.html
Uruguay	
Health Assessment Division, Ministry of Public Health (HAD)	http://www.msp.gub.uy

Source
Based on the INAHTA members list.[39]

Table 10 Clinical practice guideline websites

Database	Website
Guidelines International Network (GIN)	https://www.g-i-n.net/library/international-guidelines-library
Association of Scientific Medical Societies (AWMF)	https://www.awmf.org/awmf-online-das-portal-der-wissenschaftlichen-medizin/awmf-aktuell.html
National Guideline Clearinghouse	https://www.ahrq.gov/gam/index.html
Scottish Intercollegiate Guidelines Network	https://www.sign.ac.uk/
Swiss Medical Weekly	https://smw.ch/en/
TRIP Database	http://www.tripdatabase.com/
Emergency Care Research Institute (ECRI) Guidelines Trust	https://guidelines.ecri.org/

10.3 Appendix B: Search strings

Table 11 PubMed search strategy for investigating folate testing and supplementation

#	*
1	Folic Acid[majr] OR Folic Acid Deficiency[majr] OR Homocysteine[majr] OR (folate*[ti] OR folic acid*[ti] OR folacin[ti] OR homocysteine[ti] OR methylenetetrahydrofol*[ti] OR tetrahydrofolate*[ti] OR tetrahydrofolic*[ti] OR vitamin B9[ti] OR folate*[ot] OR folic acid*[ot] OR homocysteine[ot] OR methylenetetrahydrofol*[ot] OR tetrahydrofolate*[ot] OR tetrahydrofolic*[ot] OR vitamin B9[ot])
2	Blood Chemical Analysis[majr:noexp] OR Diagnosis[majr:noexp] OR (analys*[ti] OR analyz*[ti] OR assay*[ti] OR biomarker*[ti] OR bio-marker*[ti] OR blood[ti] OR determin*[ti] OR diagnos*[ti] OR level[ti] OR levels[ti] OR measur*[ti] OR red cell[ti] OR red cells[ti] OR serum*[ti] OR status*[ti] OR test*[ti] OR analys*[ot] OR analyz*[ot] OR assay*[ot] OR biomarker*[ot] OR bio-marker*[ot] OR blood[ot] OR determin*[ot] OR diagnos*[ot] OR level[ot] OR levels[ot] OR measur*[ot] OR red cell[ot] OR red cells[ot] OR serum*[ot] OR status*[ot] OR test*[ot])
3	Folic Acid/blood[majr] OR Folic Acid Deficiency/blood[majr] OR Folic Acid Deficiency/diagnosis[majr] OR Homocysteine/blood[majr]
4	Dietary Supplements[mh:noexp] OR Folic Acid Deficiency[mh] OR Vitamins[mh] OR (deficien*[all] OR fortifi*[all] OR fortify*[all] OR supplement*[all] OR multivitamin*[ti] OR multivitamin*[ot] OR multi-vitamin*[ti] OR multi-vitamin*[ot] OR vitamin*[ti] OR vitamin[ot])
5	Diagnostic[tiab] OR diagnosis[tiab] OR sensitivity[tiab] OR specificity[tiab] OR positive predictive value[tiab] OR negative predictive value[tiab] OR accuracy[tiab]
6*	"Economics"[Mesh:NoExp] OR "Costs and Cost Analysis"[mh] OR "Economics, Nursing"[mh] OR "Economics, Medical"[mh] OR "Economics, Pharmaceutical"[mh] OR "Economics, Hospital"[mh] OR "Economics, Dental"[mh] OR "Fees and Charges"[mh] OR "Budgets"[mh] OR budget*[tiab] OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR "pharmaco-economic*"[tiab] OR expenditure[tiab] OR expenditures[tiab] OR expense[tiab] OR expenses[tiab] OR financial[tiab] OR finance[tiab] OR finances[tiab] OR financed[tiab] OR "value for money"[tiab] OR "monetary value*"[tiab] OR "models, economic"[mh] OR "economic model*"[tiab] OR "markov chains"[mh] OR markov[tiab] OR "monte carlo method"[mh] OR "monte carlo"[tiab] OR "Decision Theory"[mh] OR "decision tree*"[tiab] OR "decision analy*"[tiab] OR "decision model*"[tiab]
7	"adverse effects"[subheading] OR complications[subheading] OR drug effects[subheading] OR safe[tw] OR safety[tw] OR side effect*[tw] OR undesirable effect*[tw] OR treatment emergent[tw] OR tolerability[tw] OR toxicity[tw] OR ADRs[tw] OR (adverse*[tw] AND (effect[tw] OR effects[tw] OR reaction[tw] OR reactions[tw] OR event[tw] OR events[tw] OR outcome[tw] OR outcomes[tw]))
8†	"Clinical protocols"[MESH] OR "Consensus"[MESH] OR "Consensus development conferences as topic"[MESH] OR "Critical pathways"[MESH] OR "Guidelines as topic" OR "Practice guidelines as topic"[MESH] OR "Health planning guidelines"[MESH] OR "Clinical Decision Rules"[MESH] OR "guideline"[pt] OR "practice guideline"[pt] OR "consensus development conference"[pt] OR "consensus development conference, NIH"[pt] OR position statement*[tiab] OR policy statement*[tiab] OR practice parameter*[tiab] OR best practice*[tiab] OR standards[TI] OR guideline[TI] OR guidelines[TI] OR standards[ot] OR guideline[ot] OR guidelines[ot] OR guideline*[cn] OR standards[cn] OR consensus*[cn] OR recommendat*[cn] OR practice guideline*[tiab] OR treatment guideline*[tiab] OR CPG[tiab] OR CPGs[tiab] OR clinical guideline*[tiab] OR guideline recommendation*[tiab] OR consensus*[tiab] OR ((critical[tiab] OR clinical[tiab] OR practice[tiab]) AND (path[tiab] OR paths[tiab] OR pathway[tiab] OR pathways[tiab] OR protocol*[tiab] OR bulletin[tiab] OR bulletins[tiab])) OR recommendat*[ti] OR recommendat*[ot] OR (care[tiab] AND (standard[tiab] OR path[tiab] OR paths[tiab] OR pathway[tiab] OR pathways[tiab] OR map[tiab] OR maps[tiab] OR plan[tiab] OR plans[tiab])) OR (algorithm*[tiab] AND (screening[tiab] OR examination[tiab] OR test[tiab] OR tested[tiab] OR testing[tiab] OR assessment*[tiab] OR diagnosis[tiab] OR diagnoses[tiab] OR diagnosed[tiab] OR diagnosing[tiab])) OR (algorithm*[tiab] AND (pharmacotherap*[tiab] OR chemotherap*[tiab] OR chemotreatment*[tiab] OR therap*[tiab] OR treatment*[tiab] OR intervention*[tiab]))
9	(#1 AND #2) OR #3
10	#4 AND #9
11	#5 AND #9
12	#6 AND #9

13	#7 AND #9
14	#8 AND #9
15	#10 OR #11 OR #12 OR #13 OR #14
16	Animals[MESH]
17	Humans[MESH]
18	#16 NOT (#16 AND #17)
19	Editorial[pt]
20	Letter[pt]
21	News[pt]
22	Congress[pt]
23	#19 OR #20 OR #21 OR #22
24	#15 NOT #18
25	#24 NOT #23

Notes

* Canadian Agency for Drugs and Technologies in Health (CADTH) search strings for economic evaluations & models.[42]

† CADTH search strings for guidelines.[43]

Table 12 Search strings for ethical, legal, social and organisational aspects of folate testing

Ethical aspects	("Folate deficiency" OR "folic acid deficiency" OR "folate" OR "folic acid" OR "folacin" OR "vitamin B9" OR "vitamin B9 deficiency") AND (ethic* OR bioethics OR moral* OR principlism OR patient rights OR patient autonomy OR autonomy OR social justice OR patient rights OR ethical issues OR normative)
Legal aspects	(("Folate deficiency" OR "folic acid deficiency" OR "folate" OR "folic acid" OR "folacin" OR "vitamin B9" OR "vitamin B9 deficiency") AND test)) AND (legal OR law OR case)
Social aspects	("Folate deficiency" OR "folic acid deficiency" OR "folate" OR "folic acid" OR "folacin" OR "vitamin B9" OR "vitamin B9 deficiency") AND (patient experience OR quality of life OR social aspects of OR medical decision-making process OR personal autonomy OR autonomy OR social justice OR patient rights OR patient expectations OR patient attitude)
Organisational issues	("Folate deficiency" OR "folic acid deficiency" OR "folate" OR "folic acid" OR "folacin" OR "vitamin B9" OR "vitamin B9 deficiency") AND process OR framework OR pathway OR guideline OR substitut* OR organisation OR organization OR staff OR resource