Health Technology Assessment (HTA)

Stakeholder Feedback:

HTA Short Report

Folate tests for suspected folate deficiency

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Preface

This document details the authors' responses to stakeholder feedback on the HTA Short Report on the *effectiveness, safety, costs and cost-effectiveness of folate testing.*

The stakeholder feedback and corresponding author responses are detailed in tables. The tables are listed by stakeholder, in alphabetical order.

1. Curafutura

Domain	Comment	Author response
General comment on the HTA report	In general, the report is clearly structured and methodically structured. A substantive statement is difficult: No studies were identified that could make a statement about the impact of folic acid testing on the health of patients. There is also no meaningful data on changes in treatment decisions with and without folate test results. The diagnostic accuracy of the tests is also unclear; there is no study available on the current test procedure in Switzerland. It is not possible to derive consequences from this for the provision of services in practice.	Thank you for your feedback. No action required.
Efficacy, Effectiveness and Safety	No comment provided.	NA
Health economic evaluation and budget-impact analysis	No comment provided.	NA
Ethical, social, legal and organisational aspects	No comment provided.	NA
Discussion and conclusions	No comment provided.	NA

2. FAMH

Domain	Comment	Author response
General comment on the HTA report	The objective was to assess HTA of folate (serum and RBC) testing aiming at restricting the reimbursement to valid indications of prescription due the increasing number of prescriptions in CH. The initial design was an "outcome"-oriented study, challenging the diagnostic accuracy of folate testing for folate deficiency. Folate testing in a specific clinical context being the only current measurable mean to quantify folate, adressing such question in absence of a valid comparator constitutes a conundrum. We support the concepts of biomarkers (BM) reimbursement according to sound medical indications and the use of outcomes studies as the highest level of proof of a biomarker-related value. Grounding a HTA report on a conundrum contributes to the lack of quality data and evidences availability noted in the present conclusions. This report does not allow deciding in favor or against current folate testing. Yet, valorizing any BM according to prescription indications respect is key.	Thank you for your feedback. No action required.
Efficacy, Effectiveness and Safety	Initial litterature screening is adequate; the selection due to the conundrum ascribed to the reseach question raises adequation and exhaustivity concerns. EES commentaries are overall reserved with 1 exception: Efficacy: • Over more than 8k studies (including >150 RCT meta-analyses) only 10 case/control/observational studies were finally considered. Among these, 8 indicated that despite all the valid concerns around folates testing, low results triggered medical management change. The interpretation provided does not take these results into account being derived from non-RCT studies. Low/moderate grade of evidence still need to be adequately reflected/taken into account in the interpretation and conclusions, especially in presence of limited data availability. • Outcomes studies are theoretically the highest grade of proof of a biomarker-related medical value but are generally lacking for the vast majority of biomarkers. Alternatives should be defined beforehand.	The quality of the evidence and its limitations were discussed in the report and considered with respect to interpretation of the evidence. Different appraisal tools were used depening on the study design in question. For the umbrella review of meta-analyses a modified AMSTAR 2 checklist was used, for the diagnostic accuracy study the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool was used and for the single-arm trials the Institute of Health Economics (IHE) quality appraisal checklist for case series was used. No action required.
Health economic evaluation and	No comment provided.	NA

budget-impact analysis		
Ethical, social, legal and organisational aspects	ELSO: due to the possible hazards of undifferentiated folate supplementation among risk groups, the 2020 umbrella review intrinsically emphasizes the importance of a guided/informed supplementation instead of "blind" one, especially in the case of considering supplementation at the population level and asymptomatic indivuals.	Thank you for your feedback. The report does not recommend any change in clinical practice owing to the limited amount of evidence to inform decision making. No action required.
Discussion and conclusions	We concur with the conlcusions regarding the lack evidence. We note that the discussion merely reflects the 2015 WHO/2014 British Committee for Standards recommandations. The latter being among others: • "A blood film showing oval macrocytes and hypersegmented neutrophils in the presence of an elevated MCV may alert the clinician to the presence of underlying cobalamin or folate deficiency (Grade 2B)." • "Cobalamin and folate assays should be assessed concurrently due to the close relationship in metabolism (Grade 1A)."	Thank you for your feedback. No action required.

3. Pierre Fabre

Domain	Comment	Author response
General comment on the HTA report	See comments under 2. - 4.	NA
Efficacy, Effectiveness and Safety	The report makes only few reliable statements on the use of folic acid tests and their effects. On the one hand, due to a lack of evidence, the safety and effectiveness of folic acid tests are said to be uncertain. At the same time, it is noted that the occurrence of adverse events in patients who are not deficient but receive a supplement is low (rare cases of anaphylaxis and a possible increased risk of prostate cancer, colorectal adenomatous lesions and childhood asthma and wheezing). However, reviews of folic acid deficiency indicate an association between untreated folic acid deficiency and megaloblastic anemia, pancytopenia and elevated homocysteine levels (which is linked to cardiovascular disease and stroke). Conclusion: A weighing of interests is necessary here, which, however, cannot be taken from the report.	Due to the limited diagnostic data, we were unable to conduct a linked evidence analysis which is required to inform the risk vs. benefits of folic acid supplementation. Therefore, the report does not weigh the interests of treating with folic acid in false positive patients and not treating with folic acid in false negative patients. No action required.
Health economic evaluation and budget-impact analysis	Due to the comparatively deep evidence of the basics and the manageable costs, it must be ensured that the baby is not thrown out with the bathwater: Either the tests will be retained, but then they should continue to be reimbursed by the OKP, or the corresponding requirement is removed from the indication. In any case, it should be checked whether testing for folic acid deficiency is still justifiable for low-dose combination preparations - such as Gyno-Tardyferon. The protocol lists some SL folic acid supplements that are already indicated today without testing.	Thank you for your feedback. Checking whether it is justifiable to test for folic acid deficiency for low-dose combination preparations is outside the scope of this short report HTA. No action required.
Ethical, social, legal and organisational aspects	From an ethical, social and legal point of view, it must be ensured - as already justified - that the remuneration for folic acid diagnostics - if required by the label of the drug - continues to be paid by the OKP or - whether against the background of the comparatively low evidence-based statements of the report - the corresponding condition is to be removed.	Thank you for your feedback. The report does not recommend any change in clinical practice owing to the limited amount of evidence to inform decision making as you have noted. No action required.
Discussion and conclusions	No comment provided.	NA

4. Santésuisse

Domain	Comment	Author response
General comment on the HTA report	The HTA report is detailed and well structured. Methodology, results, discussion and conclusions are presented in a comprehensible way.	Thank you for your feedback. No action required.
Efficacy, Effectiveness and Safety	In the chapter Efficacy, Effectiveness and Safety it is well shown that the existing data are generally of poor evidence and due to the many limitations (old studies, single-arm studies etc.) no clear statements on the questions are possible. In addition, the test performance itself is subject to a high degree of variability and there are no precise threshold values for folate deficiency. We welcome the fact that existing guidelines have also been included in a separate chapter, which, however, are of little use for clinical practice due to the lack of evidence. Further studies would be necessary to provide clarity on the various points. According to the databases with ongoing studies that were also searched, none seems to have included the insufficiently investigated topic that exists here. In addition it remains open whether folate is currently being studied separately or increasingly together and in parallel with other parameters such as homocysteine.	Thank you for your feedback. No action required.
Health economic evaluation and budget-impact analysis	The results of the budget impact assessment can be reproduced. The remaining results are plausible. It was shown that the number of serum and blood cell folate tests increased by about 47% between 2016 and 2020. From santésuisse's point of view, it should be pointed out that reasons for this massive increase are open.	Thank you for your feedback. No action required.
Ethical, social, legal and organisational aspects	The results of the studies that investigated limitations in folate testing are specifically supported by santésuisse. These measures should be evaluated in more depth.	Thank you for your feedback. Conducting a primary research study to investigate the limitation of folate testing is outside the scope of this short report HTA. No action required.
Discussion and conclusions	As already pointed out in HTA reports from other countries, no clear statement on the efficacy and safety of folate tests (serum and RBC) and subsequent clinical measures is possible due to the generally inadequate evidence. We can therefore understand the conclusion that no clear interventions for the future use of these tests can be proposed on the basis of the analysed data found on folate	Thank you for your feedback. Analysing the increase in prescribing that has occurred in the last few years was outside the scope of this short report HTA. No action required.

	testing. Due to the increase in the number of diagnostic tests for folate (Serum ans RBC) without existing guidelines, the assumption could be made that these tests, together with other diagnostic tests, are sometimes prescribed routinely and without medical indication, but rather prophylactically. It is therefore all the more important to analyse this increase in prescribing in the last few years in greater depth (prescribers, patient population, etc.).	

5. SMVS

Domain	Comment	Author response
General comment on the HTA report	The current study raises the avowed question of the relevance of performing folic acid dosing in patients, but also of the economics of such tests in the management of patients with suspected folic acid deficiency. By accepting this type of study, we could see the risk of questioning multiple therapies. This kind of study is a real danger of seeing a system impose on doctors therapeutic choices on financial imperatives, and its conclusions will clash with clinical recommendations, to the detriment of clinical coherence and compliance with recommendations. We thus allow ourselves to conclude that this type of HTA "scoping report" concerning recognized examinations is not adapted nor adaptable to the clinic and should not be repeated for other examinations, because it is not adequate to use secondary data to define the economics of a treatment.	Thank you for your feedback. The report does not recommend any change in clinical practice owing to the limited amount of evidence to inform decision making. No action required.
Efficacy, Effectiveness and Safety	The HTA study concluded in the absence of safety and efficacy of folate testing, there is no direct evidence of the impact of folate testing. There are no studies examining changes in management based on folate test results compared to no folate test. These conclusions, based on guidelines focusing primarily on patients with bariatric surgery and neurological disorders, seem to us to be in opposition to the clinical recommendations issued by societies in the neurological, hematological and gastroenterological disciplines. Such conclusions, if they were to lead to limitations in the possibilities of folic acid dosage, would be in real contradiction with recognized clinical needs, to the detriment of patient safety.	Thank you for your feedback. The report does not recommend any change in clinical practice, including folic acid testing or prescribing, owing to the limited amount of evidence to inform decision making. No action required.
Health economic evaluation and budget-impact analysis	This type of study once again raises the relevance of transposing the conclusions of a formatted analysis, with initial questions directed at an economic and efficiency aspect. Its conclusions are based on guidelines also formatted on the same objective, and the main criticism that can be made of such HTA studies is that to a directed question, one can only obtain directed answers. A better understanding of the literature and the daily clinical necessities in which doctors must evolve is essential. The clinic cannot and must not be formatted by clinical studies or guidelines which can in no way embrace all the realities of the clinic in the field.	Thank you for your feedback. The report does not recommend any change in clinical practice owing to the limited amount of evidence to inform decision making. No action required.

Ethical, social, legal and organisational aspects	We do not doubt the seriousness of the methodology and the criteria used, but cannot reflect the heterogeneity of the patients that a doctor is called upon to see in his consultation. The questions that this study seeks to answer are not applicable, at least if the conclusions would go in the direction of restricting the doctor's therapeutic choices. Recommendations are desirable in order to guarantee the quality of any care for the sake of efficiency, but these recommendations must come from a real objective of quality and rationality, from the societies of disciplines on the basis of clinical criteria.	Thank you for your feedback. The results do not recommend any change in clinical practice as there is a limited amount of evidence to inform decision making. No action required.
Discussion and conclusions	How to justify that Swiss doctors, and especially patients, would be deprived of a freedom of diagnostic choice which is part of the recognized options? How to justify that a study raises the question of the "effectiveness" character of laboratory examinations that are a priori inexpensive, often essential, at the risk of missing diagnoses and having to call the patient back, with obviously higher costs. ? Accepting such a limitation raises the question, with seriousness, of the price that one is ready to accept for an effective and recognized treatment. A limitation would contradict clinical studies and international and national recommendations concerning the management of patients with potential folic acid deficiency, neurological disorders or deficiency pathology.	Thank you for feedback. The results do not recommend any change in clinical practice as there is a limited amount of evidence to inform decision making. No action required.

6. SSCC

Domain	Comment	Author response
General comment on the HTA report	This report calls on a relevant analysis of the available medical and scientific literature. Its objective was to be able to comment on the efficacy and safety as well as on the economic impact of requests for folate analyzes (serum or erythrocyte). However, the evidence is very limited, which is well highlighted by this report.The conclusions drawn by the report are therefore cautious, and rightly so.	Thank you for your feedback. No action required.
Efficacy, Effectiveness and Safety	The literature selected to analyze the efficiency of folate measurement is scarce. It consists mainly of retrospective studies. His analysis highlights the problem of measurement methods and cut-off values used for the interpretation of folate results. Clinical practice guidelines (moreover rare) specific to Switzerland on the subject have not been identified.	Thank you for your feedback. No action required.
Health economic evaluation and budget-impact analysis	Due to a lack of data, the analysis of this aspect is limited to an analysis of the growth in the number of applications in Switzerland.	Thank you for your feedback. No action required.
Ethical, social, legal and organisational aspects	Policies restricting the request for folate analysis, whether hospital or laboratory-based (Canada, Turkey, Saudi Arabia) are effective in reducing the number of requests.	Thank you for your feedback. This was addressed in the short HTA report. No action required.
Discussion and conclusions	They are not called into question by similar reports produced by other agencies (Canada; Australia).	Thank you for your feedback. No action required.

7. SVDI

Domain	Comment	Author response
General comment on the HTA report	First of all, it is to be welcomed that the report has dealt with the suggestions we made in some parts and, for example, takes into account a linked evidence approach. The methodological approach of the report appears to be appropriate and robust. The main conclusions are understandable. However, the question relevant to the policy measure regarding the background and causes of the increase in folic acid testing in recent years remains unanswered. To what extent has this increase been considered relative to population growth?	Thank you for your feedback. An investigation into the cause of the increase in folate testing in Switzerland was not within the scope of the report; however, we do agree this information would be useful for decision makers. No action required.
Efficacy, Effectiveness and Safety	The final comments are understandable. As correctly described, the cited paper from 1984 is outdated, only examined a limited population and has limited transferability to the Swiss setting. It is not clear from the report what exclusion criteria were used and why 559 of 569 studies were excluded in the PRISMA chart based on incorrect study outcome. An explanation is needed for this. (1) How are "underlying medical disorders or external factors" defined? (Research Question Diagnostic Accuracy (line 259, Table 3)) Does this include a specific risk group? (2) To what extent is the effectiveness and possible harm of folic acid. (3)	Responses are provided per issue (1), (2) and (3) raised by the Stakeholder as follows: (1) It is HTA practice to provide broad reasons for exclusion in the PRISMA diagram. In this report, studies excluded for the reason of 'incorrect study outcome' either did not provide diagnostic accuracy data or information on change in patient management. Given the number of excluded studies, it is not feasible to provide detailed reasons for every study. Instead, broad reasons and lists of excluded studies are provided for transparency. (2) In the PICO, "underlying medical disorders or external factors" do not refer to specific risk groups, rather we were trying to capture any patient who undergoes folate testing for any reason. (3) The effectiveness of folic acid supplementation was not investigated in the report as the limited diagnostic accuracy data available meant the linked evidence approach could not be carried out. No change is required for the above.
Health economic evaluation and budget-impact analysis	Due to the lack of evidence, no cost-benefit analysis could be drawn up, only a budget impact analysis based on modeling from recent years. The budget impact analysis was calculated using the analysis list tariffs before their comprehensive 10% reduction in August 2022. In any case, this would require an adjustment.	Thank you for your feedback. The budget impact analysis assumes the average historical growth between 2016 and 2020 occurs from 2021. The analysis can be updated if 2022 data can be provided, or different growth could be expected.

	The question arises as to whether the assumption of a continuous increase in folic acid testing over the next few years is justified.	The growth assumption is a scenario and is uncertain. As above, a different growth scenario could be included.
Ethical, social, legal and organisational aspects	The conclusions are understandable.	Thank you for your feedback. No action required.
Discussion and conclusions	From our perspective, the conclusion that no statement can be made about the safety and effectiveness of folate testing due to a lack of evidence is understandable. However, we would like to point out that this should not be misunderstood as "evidence of the lack of benefit".	Thank you for your feedback. We believe the report clearly states that there is a lack of evidence to inform decision making regarding folate testing and not that there is “evidence of the lack of benefit” of folate testing. No action required.