Stakeholderrückmeldungen zum HTA Short Report-Protokoll: "Folate Testing"

Folgende Stakeholderverbände wurden zur Stellungnahme zum Protokoll angeschrieben:

ACSI - Associazione dei consumatrici e consumatori della Svizzera Italiana

BLV/ EEK eidg. Ernährungskommission

BSV - Bundesamt für Sozialversicherung, Invalidenversicherung

curafutura - Die innovativen Krankenversicherer

DVSP - Dachverband Schweizerischer Patientenstellen

FAMH - Die medizinischen Laboratorien der Schweiz

FMH - Verbindung der Schweizer Ärztinnen und Ärzte

FRC - Fédération romande des consommateurs

GDK - Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und -direktoren

GSASA - Schweizerischer Verein der Amts- und Spitalapotheker

H+ - Die Spitäler der Schweiz

Interpharma - Verband der forschenden pharmazeutischen Firmen der Schweiz

KMH - Kollegium für Hausarztmedizin

Konsumentenforum

labmed - Schweizerischer Berufsverband der biomedizinischen Analytikerinnen und Analytiker

Magendarmliga Schweiz

mfe - Haus und Kinderärzte Schweiz

MTK - Medizinaltarif-Kommission

pharmaSuisse - Schweizerischer Apothekerverband

PUE - Preisüberwachung

SAMW - Schweizerische Akademie der Medizinischen Wissenschaften

santésuisse - Die Schweizer Krankenversicherer

SAPhW - Schweizerische Akademie der Pharmazeutischen Wissenschaften

Schweizerische Gesellschaft für Gastroenterologie

SDGV-SSDV - Schweizerische Gesellschaft für Dermatologie und Venerologie

SGAIM - Schweiz. Gesellschaft allgemeine Innere Medizin

SGE - SSN Schweiz. Gesellschaft für Ernährung

SGED-SSED - Schweiz. Gesellschaft für Endokrinologie und Diabetologie

SGGG - Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe

SGH/SSH - Schweizerische Gesellschaft für Haematologie

SGV - Schweizerische Gesellschaft der Vertrauens- und Versicherungsärzte

SKS - Stiftung für Konsumentenschutz

SPO - Patientenschutz

SSCC - Schweizerische Gesellschaft für Klinische Chemie

SULM - Schweiz. Union für Labormedizin

SVBG/FSAS - Schweizerischer Verband der Berufsorganisationen im Gesundheitswesen

SVDI - Schweizerischer Verband der Diagnostikindustrie

Swiss Medtech

Swiss Vitamin Institute

VIPS - Vereinigung Pharmafirmen in der Schweiz

Folgende Stakeholder haben eine Stellungnahme zum Protokoll eingereicht: curafutura, FAMH, Santésuisse, SGH-SSH, SVDI

Die individuellen Kommentare der Stakeholder zum vorliegenden Protokoll sowie die Würdigung der Kommentare durch die Sektion HTA des BAG und durch die Auftragnehmer sind nachfolgend aufgeführt.

Preface:

This document details the authors' responses to stakeholder feedback on the protocol for an HTA short report on *folate testing.*

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

Where multiple stakeholders provided similar feedback, the authors have only provided a response to the first comment; subsequent comments instruct the reader to cite the original response.

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1. curafutura

Domain	Comment	Author Response
1. Comments on research question	1. Für die Diagnose von Folatmangel empfehlen die Leitlinien 2 Verfahren: Die Messung des Folatgehalts in Erythrocyten oder im Serum. Die Testung in den Erythrocyten ist aussagekräftiger, aber auch aufwendiger. Im HTA wird dabei das Serum ODER die Erythrocyten-Variante angeschaut. Es geht aus dem Protokoll nicht klar hervor, ob auch die Testung von Serum UND Erythrocyten angeschaut wird, d.h. dass im Nachgang zum Serumtest ein Erythrozyten-Test gemacht wird, was medizinisch und ökonomisch in Frage gestellt werden kann. 2. Weiter sollte die Frage aufgrund der bekannten Daten schon früher ansetzen: Wann macht eine Laborabklärung auf die Parameter überhaupt Sinn (z.b. macht es bei Männern einen Sinn)? Liegen richtungsweisende Symptome/Befunde vor, welche abgeklärt werden müssen? Liegt eine akzeptable Wahrscheinlichkeit für eine therapeutische (oder präventive) Konsequenz vor (z.b. Kinderwunsch/kein Kinderwunsch)?	1. Thank you for bringing this issue to our attention. Where evidence is identified that reports on both diagnostic tests (i.e. serum folate test and the red blood cell folate test), this will be reported. The results will be investigated depending on the type or combination of tests conducted. A note has been added to each of the 'research questions and study selection criteria' tables (Table 1, 2, 3, 4, 5) to make this point clear. 2. Thank you for your feedback. If these elements are identified in the literature, they will be summarised under 'study characteristics' during the HTA phase. However, no changes have been made to the HTA protocol to incorporate these questions.
3. Comments on PICO	1. P: Generelle asymptomatische Population: Diese Population ist zu breit gewählt. Der Fokus sollte auf gebärfähige Frauen und Schwangere gerichtet werden, wie es bereits in der Einleitung gemacht wird. Bei Männern wird wissenschaftlich gar keine Folattestung empfohlen, weshalb die von der Population ausgenommen werden sollten. Andernfalls müsste man die Resultate nach Subpopulationen stratifizieren. Da Männer sich generell weniger auf Folat testen lassen und wenn sie sich testen lassen, dann wahrscheinlich eher einen Mangel haben, besteht hier die Gefahr eines Bias, der das Resultat verfälschen könnte.	1. Noted. However, this HTA will seek to identify all patients eligible for folate testing through the inclusion of a broad population. Under current reimbursement, men are eligible for folate testing, therefore, no limits will be placed on the population to exclude men. However, if information is found to support that is it 'not scientifically recommended' to conduct testing in men, this will be addressed in the HTA report. Where evidence is identified addressing certain subgroups of the two specified populations this will also be reported. 2. Thank you for the feedback. Where evidence is identified, both patients who plan to become pregnant and pregnant

	2. Auch die Stratifizierung nach präventivem Testing (Frau mit Kinderwunsch) und therapeutischem Testing (Frau während Schwangerschaft) wäre überprüfenswert. 3. I: Serum oder/UND Erythrozyten Testing. 4. C: i.o. 5. O: i.o.	patients will be investigated. This has been clarified in Section 5.2.3. 3. Thank you for the feedback. Please see author response to **comment 1.1.1.** 4. Thank you for the feedback. 5. Thank you for the feedback
4. Comments on database and search strategy	Nil	Not applicable
5. Comments on data extraction, analysis and synthesis	Nil	Not applicable

2. FAMH

Domain	Comment	Author Response
1. Comments on research question	Les 6 questions de recherche des 4 domaines analysés (4.1 à 4.4) sont adéquates et complètes pour permettre de répondre aux objectifs du protocole. Il est notamment pris en considération l'aspect de ne pas utiliser une valeur seuil unique du fait de l'absence de standardisation des méthodes de dosage. La prise en compte d'un contexte social suisse spécifique est judicieuse, notamment du point de vue du suivi des grossesses.	Thank you for the feedback.
2. Comments on PICO	Les populations sont bien définies et les interventions étudiées, comparaisons attendues et résultats cliniques évoqués sont complets pour argumenter quant à l'efficience et la pertinence de l'analyse du folate plasmatique ou érythrocytaire.	Thank you for the feedback.
3. Comments on database and search strategy	La stratégie de recherche et les sources de données sont établies selon l'état de l'art du point de vue des aspects de résultats cliniques et de revue de recommandations. Les critères d'inclusion sont bien définis et semblent complets.	Thank you for the feedback.
4. Comments on data extraction, analysis and synthesis	L'exrtraction des données, leur analyse et leur synthèses sont adaptées aux objectifs du protocole. Les résultats de l'analyse des recommandations, de l'efficience et de la pertinence du dosage seront synthétisés de façon narrative.	Thank you for the feedback.

3. Santésuisse

Domain	Comment	Author Response
1. Comments on research question	The question focuses solely on folic acid tests in plasma or in erythrocytes (remuneration according to the list of analyses). It can be assumed that other parameters (e.g. homocysteine) are often determined at the same time in order to narrow down possible causes. Therefore, at least to some extent, the combination with other tests should be included in the question and literature search. The combination with other tests has a clear influence on the outcome.	Thank you for your feedback. However, only diagnostic studies using either the serum folate test or the red blood cell folate test will be included as we are not looking at the whole testing cascade at this stage, only folate testing. Therefore, secondary assessment of folate status via other markers such as total plasma homocysteine is outside the scope of this review. A broad discussion of how the tests fit together will be incorporated into the discussion section/interpretation of the results during the HTA phase.
2. Comments on PICO	1. The research question as well as the study criteria are defined for two different search strategies: "direct evidence" or "linked evidence approach". We consider these two different approaches to be very useful. However, both approaches should be included in any case. This is because more detailed statements can be expected from the "linked approach" (clearly evident in the PICO tables under the item Outcomes). The outcomes listed under the "linked approach" should be at least partially mentioned in the outcomes of "direct evidence". 2. Folate testing is defined as the intervention with both test forms used and reimbursed today summarized. In a later paragraph, reference is made to a possible subgroup analysis according to the test form. From our point of view, this differentiation is an important aspect in this HTA an should already be specified more precisely in all PICO tables (evidence and economic intervention) and considered from the beginning.	1. Thank you for the feedback. From a methodological perspective, if direct evidence sufficiently answers the research question, it should negate the need for a linked evidence approach. In practice, direct evidence is seldom available, or limited in its utility (e.g. due to small sample sizes, methodological concerns, etc.). As such, we plan to only include linked evidence if there is no, or insufficient direct evidence. “Insufficient” in this case would relate to how certain the evidence is, as scored by the GRADE approach. However, based on scoping searches, it is highly likely that a linked evidence approach will be necessary for this project due to the absence of direct evidence addressing the research questions. 2. Thank you for the feedback. The intervention in each of the ‘research questions and study selection criteria’ tables (Table 1, 2, 3, 5) will be amended to confirm that, where possible, results will be reported separately. Where the evidence does not report the test forms separately, data will be reported in combination.

3. Comments on database and search strategy	1. It is planned to search for literature in a selection of four databases. However, the search on platforms of ongoing studies is missing and should be included. 2. The explicit consideration of guidelines, which must fulfil clear criteria according to the description, can be very much supported. However, we do not agree with the exclusion of the legal aspect in the literature search as mentioned in the PICO table to appropriateness. The justification for this is not comprehensible, as there are also other legal aspects to be addressed (e.g. (no) testing in the context of different diseases). In this context, we consider it important to look beyond the national border for possible (reimbursement) restrictions of folate tests and the corresponding implications.	1. Thank you for your feedback. We will be conducting a search of ongoing clinical trials and have modified our protocol to include this. 2. Thank you for your feedback regarding our approach to searching for clinical practice guidelines. With regards to the appropriateness outcomes, we intend on searching for all four domains including legal issues. We understand this may not have been clear in the protocol, particularly the ELSO PICO where we state legal issue outcomes were not applicable. What was meant here was that information on legal issues as outlined in the EUnetHTA core model (i.e. for the introduction of the new service) are not anticipated because folate testing is already reimbursed through mandatory health insurance. We do however intend on including any information on legal issues pertaining to folate testing. To make this clearer the PICO has been amended as follows: “can the limitation of this technology to certain populations pose ethical challenges which have not been considered in existing legislations and regulations.” And the following sentence has been removed from Section 7.1.2: “Legal issues are not anticipated as the service is currently publicly reimbursed.” Finally, we agree data for the appropriateness outcomes should not limited by country (which is represented in the protocol); however, we will discuss the applicability of the included evidence to Swiss context where necessary.
4. Comments on data extraction, analysis and synthesis	1. In our view, the most important and relevant points are listed under data analysis and synthesis. As listed above, there are certain subgroup analyses that should already be addressed in depth and specifically during the data search. 2. We can very much support the approach of a "de novo modelling" with a cost utility analysis based on quality adjusted life year (QALY), if there is not enough evidence from economic studies. However, we consider it important	1. Thank you for the feedback. Please see author response to **comment 3.2.2.** 2. Thank you for the feedback. We are only conducting ‘de novo’ modelling if there are no economic models relevant to the Swiss context and direct from test to health outcomes evidence is available. This model would be guided by existing economic evaluations from other settings.

	that individual studies that are found are still assessed in depth as a supplement to a possible model calculation.	

4. SGH-SSH

Domain	Comment	Author Response
1. Comments on research question	Die Forschungsfrage basiert auf eine festgestellte Zunahme der Kosten für Folsäurebestimmungen um 55% in den Jahren 2015-2018 zudem wird behauptet, dass dafür keine veränderte medizinische Notwendigkeit bestehen würde. Als Quelle für diese grundlegende Feststellung wird "Tarifpool: SASIS AG. Data procured by the Federal Office of Public Health (FOPH) [" genannt. Dies ohne dass weiter auf diese Daten eingegangen wird. Man hätte sich erwartet, dass die Daten auf welche diese zentrale Fragestellung beruht genauer dargelegt und auch bewertet werden. Davon abgesehen ist die generelle Fragestellung zu "Sinn und Unsinn" der Folsäurebestimmung sicherlich interssant und wichtig.	Thank you for the feedback. The aim of conducting this HTA is not to investigate the possible causes which have led to this increase in Switzerland. No changes will be made to the HTA protocol. More detail and up-to-date data to support the claim regarding an increase in the cost and number of folic acid tests will be provided in the full HTA.
2. Comments on PICO	PICO ist eine weit akzeptierte und häufig verwendete Art zur Festlegung der Parameter welche eine Fragestellung beantworten können. Dies ist in der vorliegenden Arbeit akkurat erfolgt	Thank you for the feedback.
3. Comments on database and search strategy	Die Suchstrategie und auch die erwähnten Datenbanken erscheinen adäquat und vollständig.	Thank you for the feedback.
4. Comments on data extraction, analysis and synthesis	Dieser Abschnitt ist sehr kurz gehalten, erscheint aber adäquat: "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	Thank you for the feedback. No changes have been made to the HTA protocol.

	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"	

5. SVDI

Domain	Comment	Author Response
1. Comments on research question	1. (65) Policy Question: Was sind die Hintergründe und Ursachen für den Anstieg der Folsäure-Testung in den vergangenen Jahren? 2. Wird die Wirksamkeit und der mögliche Schaden der Folsäure Supplementierung vergleichend untersucht vor allem vor dem Hintergrund einer unselektiven Therapie (Übertherapie)? Welche unterschiedlichen Therapieformen sind verfügbar? 3. (236) Inwieweit wird untersucht, welche ethischen, legalen und regulatorische Aspekte beim Zugang zur Folat Supplementierung vorhanden sind? Werden Hindernisse im Zugang zur Therapie beachtet («Healthcare equity»)? Wird untersucht, ob durch eine eingeschränkte Testung neue Hürden generiert warden können, die die breite Zugänglichkeit weiter beeinträchtigen (z.B. durch Out of Pocket Bezahlung)?	1. The policy question for this HTA has been supplied by the FOPH, no reasoning has been provided for the increase in folic acid testing across Switzerland in recent years. No change has been made to the HTA protocol policy question. 2. Where evidence is identified, the safety profile of folic acid supplementation will be examined, including the potential treatment side effects of over-supplementation (see Table 1, Outcome 4). However, alternative therapies, other than folic acid supplementation, will not be considered as this is outside the scope of the review. 3. As per Table 6, the ethical, legal, social and organisational issues associated with folate testing will be addressed in accordance with the EUnetHTA Core Model 3.0. Where evidence is identified, issues relating to access and restrictions on testing will be examined and discussed. Also, slight changes have been made to amend the legal section of Table 6 and in the text.
2. Comments on PICO	1. Indikation und Setting brauchen eine klare Definition. Wofür wird die Testunggebraucht und wer sind die «eligible Patients». Braucht es bei gewissen Personen einen Nachweis, wie hoch ihr Folsäure-Level effektiv ist (Monitoring)? 2. Die Anwendung des Tests in unterschiedlichen Indikationen kann in verschiedenen Settings erfolgen (z.B. Spital-Setting oder Hausarzt-Setting). Werden in den Untersuchungen indikationsspezifische Aspekte berücksichtigt und getrennt verfolgt? 3. (205) Bei den Outcomes wird nicht mehr nach asymptomatischer und symptomatischer Population unterschieden, sondern nur noch nach solchen, die mit Folat	1. As mentioned in Section 5.2.3, outcomes from studies conducted in settings with folate deficiency levels similar to those found in Switzerland will be considered. This would likely include hospitals and general practice settings. Additionally, as mentioned in the 'research question and study selection criteria' tables (Table 1, 2, 3, 4, 5) eligible patients will include a broad population of those eligible for folate testing, including asymptomatic general population and patients with suspected folate deficiency due to the presence of symptoms, underlying medical disorders, or external factors. Further details of these settings and populations will be provided during the HTA phase under 'study characteristics' where evidence is identified.

	supplementiert wurden oder solche die aufgrund einer maskierten anderen Erkrankung falsch supplementiert wurden. Das verzerrt die Aussage der ursprünglichen Fragestellung.	2. Noted. Where evidence is identified that addresses different indications in different settings, this data will be synthesised/analysed separately as noted in Section 5.2.3. Further changes have also been made across the HTA protocol to ensure that it is clear that each population/folate test type will be reported separately where evidence is identified (see 'notes' that have been added to each of the 'research questions and study selection criteria' tables [Table 1, 2, 3, 5]). 3. Thank you for the feedback. The outcomes listed in Table 3 will be differentiated based on the two populations of interest. The HTA protocol has been amended to make this clearer.
3. Comments on database and search strategy	Keine Kommentare No comments	Not applicable
4. Comments on data extraction, analysis and synthesis	Economic efficiency outcomes (326): Es wird vorgeschlagen, zur vergleichenden Untersuchung der «effectiveness» unter anderem einen «linked evidence» Ansatz zu verfolgen. Warum soll keine Kosteneffektivitätsanalyse auf Basis der Ergebnisse einer «linked evidence» Analyse durchgeführt werden?	Conducting a cost-utility model in the absence of direct evidence from test to outcomes is outside the scope of this short HTA report. This is a specific policy-based decision that has been decided for this project.