Diagnostic accuracy of premanipulative vertebrobasilar insufficiency tests: A systematic review

Nathan Hutting, Arianne P. Verhagen, Veerle Vijverman, Martin D.M. Keesenberg, Gillian Dixon, Gwendolijne G.M. Scholten-Peeters

Department of Manual Therapy, Faculty of Medicine and Pharmacology, Vrije Universiteit Brussel, Brussels, Belgium
HAN University of Applied Sciences, Nijmegen, The Netherlands
Het Centrum Physical therapy & Manual therapy, Rijen, The Netherlands
Department of General Practice, Erasmus University Medical Center, Rotterdam, The Netherlands
University of Applied Sciences, Research Group Diagnostics, Breda, The Netherlands
Corpus Mentis, Center for Physical Therapy & Science, Leiden, The Netherlands
Nursing Home Antonius Binnenweg, Rotterdam, The Netherlands

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Abstract

Study design: A systematic review of diagnostic accuracy studies.
Objective: To evaluate the diagnostic accuracy of the premanipulative vertebrobasilar insufficiency (VBI) tests.
Summary of background data: The aim of premanipulative vertebrobasilar testing is to evaluate the adequacy of blood supply to the brain, by compressing the vertebral artery and examining for the onset of signs and symptoms of cerebrovascular ischemia. Although clinicians consider pre-manipulative testing important before applying spinal manipulations, the diagnostic accuracy has not been systematically reviewed.
Methods: A search was made in PUBMED, CINAHL and EMBASE databases from their date of inception until 2nd May 2012. Studies were included if they compared a VBI test with a reference test, and sensitivity and specificity were reported or could be calculated. The methodological quality of the studies was evaluated using QUADAS. Agreement between reviewers was calculated and expressed as a percentage and quantified by kappa statistics.
Results: Of the 1677 potential citations only 4 studies were included, all of questionable quality. Sensitivity was low and ranged from 0 to 57%, specificity from 67 to 100%, positive predictive value from 0% to 100%, and negative predictive value from 26 to 96%. The positive likelihood ratio ranged from 0.22 to 83.25 and the negative likelihood ratio from 0.44 to 1.40.
Conclusion: Based on this systematic review of only 4 studies it was not possible to draw firm conclusions about the diagnostic accuracy of premanipulative tests. However, data on diagnostic accuracy indicate that the premanipulative tests do not seem valid in the premanipulative screening procedure. A surplus value for premanipulative tests seems unlikely.

1. Introduction

The vertebral arteries provide blood flow to the hindbrain (i.e. brain stem, medulla oblongata, pons, cerebellum, and vestibular apparatus) (Kerry and Taylor, 2006). Abnormal stress on the vertebral artery may cause a reduction of blood supply to specific parts of the hindbrain, which is referred to as vertebrobasilar insufficiency (VBI) (Kerry and Taylor, 2006). Symptoms of VBI include dizziness, drop attacks, diplopia, dysarthria, dysphagia, ataxia, nausea, numbness and nystagmus. VBI can develop into a cerebral or brain stem ischemia, leading to severe morbidity or even death (Asavasopon et al., 2005).

It is important to prevent the incidence of serious complications after spinal manipulation. The incidence of serious neurovascular complications (e.g. cerebrovascular accident or stroke) of the cervical spine is not known. Estimations vary between one dissection of the...
vertebral artery in 5,000,000 therapy sessions, to one cerebrovascular accident in 400,000 cervical manipulations, and one cerebrovascular accident in 100,000 patients aged <45 years (Rivett et al., 2005). Abnormal stress on the vertebral artery can change the blood supply in the artery and can be caused by rotation (Vidal, 2004) during physical therapy, manual therapy or chiropractic treatments.

The aim of premanipulative vertebrobasilar testing is to evaluate the adequacy of the blood supply to the brain, by compressing the vertebral artery (Kerry and Taylor, 2006) and examining for the onset of signs and symptoms of cerebrovascular ischemia (Rivett et al., 2005). These premanipulative tests are based on the premise that cervical spine positioning may reduce the lumen and blood flow in the vertebral arteries and allow the practitioner to identify those patients at risk of serious pathology following cervical spine manipulation (Gibbons and Tehan, 2001).

The maneuver is usually performed by a combined extension rotation of the cervical spine (Vidal, 2004), or rotation alone (Zaina et al., 2003). The test examines the ability of the vertebrobasilar system to maintain adequate hindbrain perfusion. When symptoms of hindbrain ischemia occur during the maneuver it is generally considered as a positive test result (Thiel and Rix, 2005). However, there are conflicting results with regard to the effects of sustained premanipulation positional maneuvers on vertebral blood flow. Studies inconsistently indicate either a decrease (or disappearance), or insignificant to no change of blood flow parameters (Thiel and Rix, 2005). According to the Australian Physiotherapy Association treatment guideline (Asavasopon et al., 2005) provoking these symptoms by premanipulative testing is generally considered a contraindication for manipulation of the cervical spine. A positive test can be regarded as an indicator of the patient’s risk of getting vertebrobasilar complications during a cervical manipulation (Mann and Refshauge, 2001) and spinal manipulation is therefore contraindicated. Although clinicians consider premanipulative testing to be important before applying spinal manipulations (Vidal, 2004), the diagnostic accuracy has not yet been systematically reviewed. Therefore, this systematic review evaluates the diagnostic accuracy of the VBI tests in terms of sensitivity, specificity, predictive values and likelihood ratios in adults.

2. Materials and methods
2.1. Study identification

A search was made in PUBMED, CINAHL and EMBASE databases from their date of inception until 2nd May 2012; for this MeSH Terms (PUBMED), Thesaurus (EMBASE, CINAHL) and free-text words were used. The search was performed independently by a librarian and one reviewer (NH). We used search terms related to VBI, vertebral artery, diagnostic parameters, spinal manipulation and movements of the cervical spine. The full search terms are presented in Appendix 1.

2.2. Study selection

Studies were included if they met both of the following criteria: studies comparing a premanipulative test with a reference test in which sensitivity and specificity were reported or could be calculated using a 2 × 2 table; and full paper reports. Excluded were abstracts, congress reports and animal or cadaver studies. Two reviewers (NH, DMK) independently screened the titles and abstracts, followed (as required) by a screening of full publications. A third reviewer solved possible discrepancies (GGMSP). The references of the included studies were also checked for relevant studies possibly missed in the electronic databases.

2.3. Assessment of methodological quality

The methodological quality of the included studies was evaluated by QUADAS (Whiting et al., 2003) (Appendix 2). This tool is used to assess the quality of diagnostic studies (Whiting et al., 2003, Whiting et al., 2006). QUADAS items cover the most significant forms of bias in diagnostic research such as spectrum bias (item 1), reference standard bias (item 3), disease progression bias (item 4), verification bias (items 5 and 6), incorporation bias (item 7), review bias (items 10–12), and the potential bias associated with subject withdrawal, as well as aspects of external validity (items 2, 8 and 9).

Two reviewers (NH, GLD) independently scored the items as “yes”, “no” or “unclear”. Items were equally weighted. Differences in assessment were discussed and where necessary solved by a third reviewer (GGMSP). Agreement between reviewers was calculated and expressed as a percentage agreement and also quantified by kappa (κ) statistics: <0.00 = poor agreement; 0.00–0.20 = slight agreement; 0.21–0.40 = fair agreement; 0.41–0.60 = moderate agreement; 0.61–0.80 = substantial agreement; and 0.81–1.00 = almost perfect agreement (Landis and Koch, 1977).

2.4. Data extraction

One reviewer (NH) performed data extraction using a standardized data extraction form, while another reviewer (GGMSP) randomly checked the data extraction. The following data were extracted: authors, year of publication, characteristics of the study population, and index and reference test. Data on sensitivity, specificity, predictive value and likelihood ratio were also extracted.

2.5. Data analysis

If possible, all diagnostic parameters were recalculated. In case no diagnostic accuracy data were reported, we used the extracted raw data to calculate them using a 2 × 2 table. Because of substantial clinical and methodological heterogeneity, no statistical pooling was performed. Instead, we chose to provide a qualitative descriptive analysis. We considered a sensitivity, specificity or predictive value of at least 80% as sufficient. Also, a positive likelihood ratio (LR+) of >10 and a negative likelihood ratio (LR−) of <0.1 was considered to be sufficient (Guyatt et al., 2008).

3. Results

3.1. Study selection

Fig. 1 presents a flowchart of the study selection. The search identified 1677 potential citations. After removal of double citations and excluding articles not fulfilling the inclusion criteria based on the abstract, 19 studies possibly met the inclusion criteria. After checking the full publications, 4 studies (Côté et al., 1996; Petersen et al., 1996; Li et al., 1999; Sakaguchi et al., 2003) finally met the inclusion/exclusion criteria. Screening of the references lists of the included studies provided no additional studies.

3.2. Study characteristics

The subjects of the included studies differed greatly. One study included a series of consecutive patients undergoing neurovascular examination (Sakaguchi et al., 2003), one study included 2 groups of non-selected asymptomatic persons (Li et al., 1999), one study included a selected group with a positive Wallenberg test and a healthy control group (Côté et al., 1996) and another study included a preliminarily selected group of patients with vertebrobasilar ischemia and a healthy control group (Petersen et al.,
1996). The average age of the population was 45.9 (±16.8) years. Other study characteristics are presented in Table 1.

3.3. Index and reference tests

As index test, three studies used a combined extension rotation maneuver (Côté et al., 1996; Li et al., 1999; Sakaguchi et al., 2003) and one study used a cervical rotation maneuver (Petersen et al., 1996). The end range was sustained for 10 s (Sakaguchi et al., 2003) to 30 s (Côté et al., 1996; Petersen et al., 1996). One study did not report how long the position was sustained (Li et al., 1999). One study used duplex as reference test, another study used color-coded duplex, and two studies used transcranial Doppler as reference test. Additional study characteristics are presented in Table 1.

3.4. Methodological quality

Overall, the studies suffered from various types of bias. The results of the methodological quality assessment using QUADAS and the different types of bias are presented in Table 2. In all studies, incorporation bias (item 7), spectrum bias (item 1), test review bias (item 10) and clinical review bias (items 11 and 12) were found.

Regarding methodological quality, there was 80% agreement between the two assessors. The kappa statistic was 0.65 (95% confidence interval 0.47–0.84) indicating substantial agreement between the assessors. Disagreements appeared in seven items (1, 2, 7, 8, 9, 12, 13) and were mainly due to reading errors, or differences in interpretation. All disagreements were solved during a consensus meeting.

3.5. Diagnostic accuracy

The diagnostic accuracy data of the included studies are presented in Table 3. Sensitivity is low (range 0–57%) and is considered

![Fig. 1. Flowchart of study selection.](image-url)
Each criterion was scored as: + (yes), − (no), ? (unclear).

not sufficient. Specificity (range 67–100%) is considered moderate to good. There is high variability in the data concerning positive and negative predictive values. Positive predictive values ranged from 0 to 100% and the negative predictive values from 26 to 96%. Positive likelihood ratios ranged from 0.22 to 83.25, with large confidence intervals; negative likelihood ratios ranged from 0.44 to 1.40.

4. Discussion

The aim of this systematic review was to evaluate the diagnostic accuracy of the premanipulative tests in adults. However, it is impossible to draw firm conclusions about the diagnostic accuracy of these tests because only 4 articles could be included, each of questionable quality. Due to the wide confidence intervals for diagnostic accuracy, the non-representativeness of patients treated in clinical practice, and the low prevalence of the condition, it was difficult to draw firm conclusions about the accuracy of premanipulative tests. A surplus value for premanipulative tests seems unlikely.

Sensitivity ranged from 0 to 57%, indicating low sensitivity resulting in too many being missed (false-negatives). In premanipulative screening procedures we aim to identify patients with a possible risk of complications. Because it is important to prevent false-negative results, the sensitivity of these tests should be high because these patients will receive cervical manipulation. Specificity ranged from 67 to 100%. High specificity indicates the ability of a test to prevent false-positive results. Although the specificity of the cervical premanipulative test is generally sufficient, specificity is less important than sensitivity because a false-positive result of the test is not potentially harmful for the patient.

Pre-manipulative tests are used as an add-on test in the diagnostic process. When there are no signs of VBI or other contra-indications for manipulation, these tests are performed to filter false-negative test results on history taking. Therefore, premanipulative tests should have a high sensitivity. Unfortunately, this systematic review showed low sensitivity values of the premanipulative tests. Therefore, because of the questionable quality of the studies and the inadequate patient selection, it seems reasonable to assume that the accuracy values found here are overestimated.

Positive predictive values were variable, with values ranging from 0 to 100%. The main reason for this variability is the absence of false-positive findings in two studies (mostly using healthy controls) (Petersen et al., 1996; Li et al., 1999); therefore, these data must be interpreted with caution. Negative predictive values of the studies ranged from 26 to 96%. Positive likelihood ratios ranged from 0.22 to 83.25, and negative likelihood ratios from 0.44 to 1.40.

Moreover, the prevalence of complications of manipulation (pre-test probability) is very low: this implies that, although accuracy is high, the usefulness of the test is almost zero (post-test probability). Even if the premanipulative test had sufficient sensitivity and/or specificity, the predictive value is questionable because of the low prevalence of the condition.

We found wide confident intervals for sensitivity, specificity, predictive values and likelihood ratios indicating a lack of precision (Richter and Reinking, 2005), mostly due to low sample sizes.

We calculated diagnostic accuracy values with the data provided by Li et al. (1999) and Sakaguchi et al. (2003). Also, we considered a decrease in blood flow velocity and VBI symptoms as positive findings. However, this premise is debatable because a small decrease in blood flow velocity might not produce symptoms. The cut-off point of a decrease in blood flow velocity of >20%, as used by Petersen et al. (1996), might yield more accurate results. Nevertheless, the remaining diagnostic accuracy parameters calculated from the data of Li et al. (1999) are consistent with the other values.

The study of Coté et al. (1996) included only 42 patients who were preselected with a positive premanipulative test; this population is probably not representative for the group of patients with headache or neck pain without clinical VBI symptoms usually treated in clinical practice (Coté et al., 1996). Moreover, not all of the subjects included in the other studies of this systematic review were representative for patients usually treated in clinical practice. For example, because healthy controls and students are not representative for patients indicated for manipulation, the representativeness of the study is limited. Moreover, due to the higher prevalence in studies using separate groups of volunteers with and without the condition, these studies overestimate significant diagnostic accuracy compared with patients included consecutively (Lijmer et al., 1999). Only Sakaguchi et al. (2003) included consecutive patients.

Whereas most studies used blood flow velocity to express the impact of the maneuver on blood flow, Coté et al. (1996) used blood flow velocity ratios. According to Johnson et al. (2000) conclusions based on velocity ratios are less reliable because they provide only a raw quantification of blood vessel narrowing and are possibly only useful in detecting severe stenosis.

Most of the included studies were older articles. The selection criteria and performance of both the index and reference tests were not always sufficiently reported, making it difficult to reproduce the studies. In most cases it was unclear what information about the subjects was available during the performance of the tests. Several studies compared continuous wave Doppler with the gold standard angiography (Thomas et al., 2008). These studies show high

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### Table 2
Methodological quality of the included studies evaluated by QUADAS.

<table>
<thead>
<tr>
<th>First author and year of publication</th>
<th>Criterion number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coté et al. (1996)</td>
<td>–</td>
<td>–</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Li et al. (1999)</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>?</td>
<td>–</td>
<td>–</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Petersen et al. (1996)</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>?</td>
</tr>
<tr>
<td>Sakaguchi et al. (2003)</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>?</td>
</tr>
</tbody>
</table>

Each criterion was scored as: + (yes), – (no), ? (unclear).

### Table 3
Diagnostic accuracy of the included studies.

<table>
<thead>
<tr>
<th>First author and year of publication</th>
<th>Test</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>+PV</th>
<th>–PV</th>
<th>+LR</th>
<th>–LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coté et al. (1996)</td>
<td>R</td>
<td>ER 0% (0%–23%)</td>
<td>86% (67%–96%)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>ER 0% (0%–46%)</td>
<td>67% (49%–81%)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Li et al. (1999)</td>
<td>ER</td>
<td>21% (10%–38%)</td>
<td>100% (75%–100%)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Petersen et al. (1996)</td>
<td>KO</td>
<td>57% (18%–90%)</td>
<td>100% (95%–100%)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Sakaguchi et al. (2003)</td>
<td>KR</td>
<td>9% (3%–20%)</td>
<td>98% (97%–99%)</td>
<td>19%</td>
<td>81%</td>
<td>4.24</td>
<td>0.44</td>
</tr>
</tbody>
</table>

+PV = positive predictive value, −PV = negative predictive value, +LR = positive likelihood ratio, −LR = negative likelihood ratio, ER = combined extension rotation, KO = rotation, KR = right vertebral artery, L = left vertebral artery.
sensitivity (85–91%) and specificity (94–100%) for detecting stenosis (>60%) in the vertebral artery. However, it is not obvious that these values are representative for the values of the group of patients in whom cervical manipulation is considered (Thomas et al., 2008).

Overall, the studies suffered from various types of bias. Calculating a cumulative methodological score using QUADAS is not advocated (Whiting et al., 2005). Because choices on how to weight and calculate quality scores are generally fairly arbitrary, it seems impossible to produce an objective quality score (Whiting et al., 2003). Moreover, because there are no quality scores and cut-off points for good quality (Whiting et al., 2005), we did not calculate cumulative methodological scores and did not set a cut-off for acceptable quality a priori.

This systematic review focuses on the vertebral artery, not on the carotid artery. However, internal carotid artery blood flow can also be influenced by cervical spine movements (Rivett et al., 1999; Kerry and Taylor, 2006) and, in general, carotid artery dissection is 3–5 times more common than vertebral artery dissection (Lleva et al., 2012). Therefore, this artery should not be overlooked.

We recommend that further research on premanipulative screening tests should test the whole cervical vascular system with a cluster of tests, and should include a large sample of consecutive patients with neck pain or headache who are indicated for spinal manipulation in primary care. However, the premanipulative test only tests the adequacy of maintaining hindbrain perfusion in case of injury of the vertebral artery. We cannot assume a pre-existing vertebral artery insufficiency as a risk factor for developing a vertebral artery dissection. The question remains whether the risk of developing complications after spinal manipulation can be predicted, or whether these complications are unpredictable.

Traumatic vertebral artery dissections can be caused by major trauma, cervical manipulation of trivial injury of the cervical injury (Haldeman et al., 1999; Ernst, 2002; Bowler et al., 2011; Lleva et al., 2012). In contrast, Cassidy et al. (2008) investigated the association between chiropractic visits and verteobasilar artery stroke; their main conclusion was that the increased risk of verteobasilar artery stroke is likely due to patients with headache and neck pain from pre-existing verteobasilar artery complaints seeking care. Neck pain and headache are the most common complaints in patients with extracranial vertebral arterial dissection and are common reasons for seeking care. This suggests that the association between manipulation and extracranial vertebral arterial dissection is confounded by indication (Cassidy et al., 2012).

However, many cases of extracranial vertebral arterial dissection are thought to occur spontaneously (Marshman et al., 2007; Cassidy et al., 2008; Lleva et al., 2012; Metso et al., 2012) and, in such cases, other factors such as connective tissue disorders, migraine, hypertension, infection, atherosclerosis and cigarette smoking are general risk factors of dissection (D’Anglejan-Chatillon et al., 1989; Inamasu and Guiot, 2005; Rubinstein et al., 2005; Schievink and Roiter, 2005; Pezzini et al., 2006; Marshman et al., 2007). Spontaneous dissections occur most commonly in an older population and in those with known cardiovascular comorbidities, while traumatic dissections are more prevalent in the younger age group (Lleva et al., 2012; Metso et al., 2012).

It is not yet established which risk factors predispose patients to arterial dissection after neck manipulation (Haneline and Rosner, 2007). We suggest that further research focus on the potential risks and benefits of the intervention.

Although the prevalence of cervical artery dysfunction is likely to be very low, and the chance that a patient’s head/neck pain is caused by arterial dysfunction is also very low (Kerry and Taylor, 2009), we suggest some items for patient history taking and risk-benefit analyses. For example, acute onset of symptoms, history of cervical trauma, and non-ischemic signs and symptoms of vertebral and carotid artery dissection. Also, potential risk factors for arterial dissection, such as atherosclerosis (Kerry and Taylor, 2009), could be evaluated.

Overall we recommend that future research focus on risk factors for vascular trauma and the risk-benefit ratio, rather than focusing on premanipulative tests alone. However, also in this context, due to the extremely low prevalence of serious adverse events, it is difficult to analyze meaningful regressions to decide which specific risk factors are directly related to spinal manipulation.

Appendix 1

Search terms.

**PUBMED**

Vertebral artery AND verteobasilar insufficiency AND manipulation.

Vertebral artery flow AND cervical spine rotation.


“Vertebral Artery”[Mesh] AND (premanipulative OR pre-manipulative).

“Vertebral Artery”[Mesh] AND “Sensitivity and Specificity”[Mesh].


“Vertebral Artery”[Mesh] and “Vertebrobasilar Insufficiency”[Mesh] AND manipulation.


“Vertebral Artery” AND “Vertebral Artery” AND “Vertebral Artery” AND “Sensitivity and Specificity”[Mesh].

**CINAHL**

“Vertebral-artery” and manipulation.

“Vertebral-artery” and (premanipulative OR pre-manipulative)


“Vertebral-Artery” and testing.

(“Vertebral-Artery” OR “Vertebral-Artery-Dissections”) and (extension or flexion or rotation).

(“Vertebral-Artery” OR “Vertebral-Artery-Dissections”) and “Sensitivity-and-Specificity”

Vertebrobasilar insufficiency and “Sensitivity-and-Specificity”.

**EMBASE**

“Vertebral-artery” and manipulation.

“Vertebral-artery” and (premanipulative OR pre-manipulative)

“Vertebral-artery” and “Sensitivity-and-Specificity” and manipulation.

“Vertebral-artery” and testing.

“Vertebral-artery” and “Sensitivity-and-specificity” and test.

“Vertebral-artery” and “Sensitivity-and-specificity”

“Vertebral-artery” and testing.

“Vertebrobasilar-insufficiency” and (extension or flexion or rotation).

“Vertebrobasilar-insufficiency” and “Sensitivity-and-specificity”
### Appendix 2. Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool (Whiting et al, 2003).

<table>
<thead>
<tr>
<th>Item</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Was the spectrum of patients representative of the patients who will receive the test in practice?</td>
</tr>
<tr>
<td>2.</td>
<td>Were selection criteria clearly described?</td>
</tr>
<tr>
<td>3.</td>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>4.</td>
<td>Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?</td>
</tr>
<tr>
<td>5.</td>
<td>Did the whole sample or a random selection of the sample, receive verification using the standard of diagnosis?</td>
</tr>
<tr>
<td>6.</td>
<td>Did patients receive the same references standard regardless of the index test result?</td>
</tr>
<tr>
<td>7.</td>
<td>Was the reference standard independent of the index test?</td>
</tr>
<tr>
<td>8.</td>
<td>Was the execution of the index test described in sufficient detail to permit replication of the test?</td>
</tr>
<tr>
<td>9.</td>
<td>Was the execution of the reference standard described in sufficient detail to permit its replication?</td>
</tr>
<tr>
<td>10.</td>
<td>Were the index test results interpreted without knowledge of the result of the reference standard?</td>
</tr>
<tr>
<td>11.</td>
<td>Were the reference standard results interpreted without knowledge of the results of the index test?</td>
</tr>
<tr>
<td>12.</td>
<td>Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice?</td>
</tr>
<tr>
<td>13.</td>
<td>Were uninterpretable/intermediate test results reported?</td>
</tr>
<tr>
<td>14.</td>
<td>Were withdrawals from the study explained?</td>
</tr>
</tbody>
</table>

### References