The accuracy of diagnostic tests for GH deficiency in adults: a systematic review and meta-analysis

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Abstract

Context: The diagnostic accuracy of tests used to diagnose GH deficiency (GHD) in adults is unclear.

Objective: We conducted a systematic review and meta-analysis of studies that provided data on the available diagnostic tests.

Data sources: We searched electronic databases (MEDLINE, EMBASE, Cochrane CENTRAL, Web of Sciences, and Scopus) through April 2011.

Study selection: Review of reference lists and contact with experts identified additional candidate studies. Reviewers, working independently and in duplicate, determined study eligibility.

Data extraction: Reviewers, working independently and in duplicate, determined the methodological quality of studies and collected descriptive, quality, and outcome data.

Data synthesis: Twenty-three studies provided diagnostic accuracy data; none provided patient outcome data. Studies had fair methodological quality, used several reference standards, and included over 1100 patients. Several tests based on direct or indirect stimulation of GH release were associated with good diagnostic accuracy, although most were assessed in one or two studies decreasing the strength of inference due to small sample size. Serum levels of GH or IGF1 had low diagnostic accuracy. Pooled sensitivity and specificity of the two most commonly used stimulation tests were found to be 95 and 89% for the insulin tolerance test and 73 and 81% for the GHRH arginine test respectively. Meta-analytic estimates for accuracy were associated with substantial heterogeneity.

Conclusion: Several tests with reasonable diagnostic accuracy are available for the diagnosis of GHD in adults. The supporting evidence, however, is at high risk of bias (due to heterogeneity, methodological limitations, and imprecision).

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Introduction

GH and the insulin-like growth factor 1 (IGF1) are involved in the regulation of somatic growth in children. In adults, this axis plays a role in maintaining normal body composition, skeletal mass, cardiovascular risk factors, and physical and physiological functioning (1). GH deficiency (GHD) has been related to insulin insensitivity, increased body fat, and decreased muscle mass; other studies have implicated that low levels of IGF1 are associated with increased risks of myocardial infarction, ischemic cardiac disease, and stroke (2). Thus, there has been interest in the clinical use of GH replacement in patients with GHD with the expectation that this agent could normalize body composition, enhance physical function, and prevent cardiovascular disease.

Among other indications, GH is approved for use in patients with hypothalamic–pituitary disease and GHD (3). GH is commonly used as an ‘anti-aging agent’ in patients without established deficit; in such instance, the evidence does not suggest substantial benefit (4). The therapeutic recommendation to use GH, therefore, rests in part on the ability to clinically diagnose patients who are truly deficient.

Expert reviews and consensus statements consider insulin-induced hypoglycemia (insulin tolerance test; ITT) as the reference standard for the diagnosis of this condition (3, 5). Alternative stimulation tests use GHRH+arginine, GHRH+GH-releasing peptide
(GHRP), glucagon stimulation, and GHRP. To date, a summary of the available literature assessing the accuracy of the available tests for GHD in adult patients suspected of having the condition has not been conducted.

The aim of this systematic review and meta-analysis is to appraise and summarize the available evidence of the diagnostic accuracy of tests for GHD in adults.

Materials and methods

The protocol for this review is consistent with the available methodological guidelines for conducting diagnostic accuracy systematic reviews (6).

Eligibility criteria

We included cross-sectional and longitudinal studies that enrolled adult patients suspected of having GHD, i.e. clinicians had true diagnostic uncertainty about the patients’ GH status. Studies that enrolled patients with pre-existing diagnosis of GHD, as well as those that enrolled patients who were clearly healthy, were excluded because they would likely overestimate the diagnostic accuracy of the tests (7). Eligible studies assessed the accuracy of diagnostic tests by evaluating the true disease status in all enrolled participants according to a reference standard. We accepted any reference standard chosen by the included studies’ authors. When a reference standard was either unclear or not specified, we chose one of the tests of interest reported in the same study as a reference standard, usually opting for the ITT when available.

The ideal study design for our purpose was a randomized trial of testing treatment strategies in adult patients with suspected GH that evaluate a test for GHD in one arm versus no test or an alternative test. This design does not only yield accuracy data but also evidence about the utility of a particular management option based on a diagnostic test. However, we did not find any studies with such design.

Study identification and selection

An expert reference librarian (P J E) designed and conducted an electronic search strategy with input from study investigators with expertise in conducting systematic reviews (M H M and V M M). In order to identify eligible studies, we searched electronic databases (MEDLINE, EMBASE, Web of Science, Scopus, and citation search for key articles) through April 2011. The detailed search strategy is available on request. Furthermore, we sought references from experts in the field.

Two reviewers, working independently, considered the potential eligibility of each of the abstracts and titles that resulted from executing the search strategy. Following the same procedures, reviewers evaluated the full-text reports (all available versions of each study) for eligibility. Subsequently, disagreements were harmonized by consensus; if not possible, by arbitration (i.e. a third reviewer adjudicated the disagreement).

Data extraction

Reviewers working independently and in duplicate used a standardized web-based form to extract the description of study participants, comorbidities, and chosen reference standard and cutoff value.

To assess diagnostic accuracy, we used the cutoff values chosen by the study authors. When multiple or no cutoff values were reported, we tended to borrow a cutoff value from another study that described the same test. In the instances that a study was assessing a test that had not been described in the previous literature, we chose the cutoff value that yielded the highest diagnostic accuracy of the test.

Author contact

Letters were sent to the corresponding authors (or if not reported the first and last authors) of each of the 28 studies that reached data extraction level by electronic mail (regular mail when an e-mail was not obtainable). We asked authors to verify the data we extracted and to complete missing data that we could not identify in the published record.

Statistical analysis

We used Meta-DiSc Software for Meta-analysis for Screening and Diagnostic tests version 1.4. We used random effect meta-analyses to pool the sensitivities, specificities, likelihood ratios, and diagnostic odds ratio (DOR) and estimate the 95% confidence intervals for the outcomes. The DOR of a test describes the ratio of the odds of a positive test result in patients with disease compared to patients without disease (8) and can be calculated as the ratio of the likelihood ratios for a positive and a negative test. Its main advantage lies in it being a single value that is indicative of a general test performance compared to the gold standard.

Summary receiver operating characteristic (ROC) curves facilitate visual assessment of the consistency of results across studies and the accuracy of the test, estimated by the area under the summary ROC curve, in differentiating between patients with GHD and patients without GHD. Unlike ROC curves in which individual data points represent different test cutoffs, each point in a summary ROC curve represents a study (9). In order to assess the inconsistency across studies, we have used the $I^2$ statistic, which represents the proportion of variability across studies that is not attributable to
chance. I^2 values of 25, 50, and 75% indicate low, moderate, and high heterogeneity respectively.

**Subgroup analyses**

A priori hypotheses to explain the potential heterogeneity across studies included choice of reference standard, history of childhood onset GHD, presence of other pituitary hormone deficiencies, presence of known pituitary disease (history of meningitis, brain trauma, subarachnoid hemorrhage, and head irradiation), and choice of threshold (data driven, assay driven, from previous study). We tested these hypotheses using a test for interaction (10) considering P<0.05 as significant. There were not enough studies to use meta-regression as a strategy to identify predictors of test accuracy and explain inconsistency in results across studies.

**Results**

**Study identification**

Initial search of the literature yielded 952 publications, of which 117 were potentially relevant to this review based on the titles and abstracts. After full-text review, we found 28 eligible studies. We excluded seven studies from analysis because they did not report sufficient data for meta-analysis or did not measure the outcomes of interest. Attempts had been made to contact the authors of these studies and were either unsuccessful or unfruitful (11–18).

We asked authors to verify the data we extracted and to complete missing data that we could not identify in the published record. We were able to establish contact with 17 (60%) of the authors of the 28 studies, of whom 14 (82%) responded either by providing missing data or by confirming the accurate representation of their studies.

**Study characteristics**

Table 1 summarizes the baseline characteristics of eligible studies. Fifteen studies assessed the diagnostic accuracy of the serum IGF1, six the GHRH+arginine stimulation test (AST), three the ITT, three the serum GH levels, two the GHRP6, two the GHRH+GHRP6, two the GHRH+pyridostigmine, two the GHRH stimulation test, one the acipimox+GHRH test, one the hexarelin stimulation test, one the GHRH+GHRP2 test, one the GHRH+clonidine test, one the AST, one the glucagon stimulation test, and one the GHRH+somatostatin (SMS) test.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Population characteristics</th>
<th>Population description (% from total)</th>
<th>Reference standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>36.4 ± 2.1</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(32)</td>
<td>R: 18–75</td>
<td>4.1</td>
<td>ITT</td>
</tr>
<tr>
<td>(33)</td>
<td>M: 39.7, F: 40.3</td>
<td>0</td>
<td>ITT</td>
</tr>
<tr>
<td>(34)</td>
<td>52 (23–77)</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(29)</td>
<td>R: 28–64</td>
<td>0</td>
<td>ITT</td>
</tr>
<tr>
<td>(35)</td>
<td>26 (20–33)</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(36)</td>
<td>65.8 (60–72)</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(37)</td>
<td>19.2 ± 0.2 (S.E.M.)</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(9)</td>
<td>23 (16–35.7)</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(38)</td>
<td>24.3</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(39)</td>
<td>4.6 ± 10</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(40)</td>
<td>43.1 (21–59)</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(41)</td>
<td>24.5</td>
<td>NR</td>
<td>Clonidine</td>
</tr>
<tr>
<td>(42)</td>
<td>25.7 ± 5.7</td>
<td>NR</td>
<td>Clonidine</td>
</tr>
<tr>
<td>(43)</td>
<td>R: 18–59</td>
<td>0</td>
<td>ITT</td>
</tr>
<tr>
<td>(44)</td>
<td>53.32 (31–76)</td>
<td>NR</td>
<td>AST</td>
</tr>
<tr>
<td>(45)</td>
<td>R: 19–66</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(46)</td>
<td>23.2 ± 1.4</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(47)</td>
<td>40.2 ± 12.1</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(48)</td>
<td>41 ± 13</td>
<td>NR</td>
<td>Concordance of ITT, AST, and GHRH+IGF1 in addition to a positive test if discordant</td>
</tr>
<tr>
<td>(49)</td>
<td>53.2 ± (S.E.M.)</td>
<td>NR</td>
<td>ITT</td>
</tr>
<tr>
<td>(50)</td>
<td>22.5</td>
<td>NR</td>
<td>GHRH+PD</td>
</tr>
<tr>
<td>(51)</td>
<td>35.76</td>
<td>NR</td>
<td>Glucagon stimulation test</td>
</tr>
</tbody>
</table>

GHD, GH deficiency; NR, not reported; ITT, insulin tolerance test; PD, pyridostigmine; AST, arginine stimulation test; IGF1, insulin-like growth factor 1, CGHD, childhood onset GHD; PD, pituitary disease; PHD, pituitary hormone deficiencies; COM, comorbidities. * presumed GHD, otherwise healthy.
analyses explored were not associated with significant
decrease to some extent the overestimation of test
dependence when applying these results at the point of care.
Inferences presented in this review are limited by the
heterogeneity of gold standard definition and cutoffs and in
the prevalence of GHD across studies. Imprecision was
present in several analyses and lowers the quality of the
evidence. This was evident for GHRP6, GHRH, acipimox+
GHRH, GHRH+GHRP6, GHRH+GHRP2, hexarelin stimulation,
GHRH+clonidine, arginine stimulation, GHRH+pyridostigmine,
GHRH+SMS, and glucagon stimulation test that were evaluated in
only one or two studies leading to estimates with very wide
certainty intervals. Clinicians need to interpret imprecise
results with caution and have lower confidence when applying
these results at the point of care. Imprecision has likely affected
subgroup analyses as well, and a true interaction might have existed but was
undetected by the underpowered analyses.
We were unable to evaluate the presence of
publication bias because the studies included in each
analysis of a diagnostic test were < 20 and hetero-
genre was significant. Under these conditions, all the
available methods (funnel plots symmetry, Egger's
regression, etc.) are unreliable and function under the
wrong assumptions (19).
This review successfully summarizes all available
evidence in a systematic (i.e.: protocol-driven) approach
leading to reproducible results (20). By restricting our
criteria to include studies that had exclusively enrolled
patients with a diagnostic uncertainty (21), we have
decreased to some extent the overestimation of test
accuracy that can otherwise result, namely, in studies
that enroll patients who have a pre-established
diagnosis of GHD and compare them to healthy adults.

Discussion

Summary of findings
We conducted a systematic review and meta-analysis to
evaluate the diagnostic accuracy of tests for GHD. Twenty-three studies provided diagnostic accuracy
data; none provided patient outcome data. Studies had
fair methodological quality (assessed using the QUADAS
checklist), used several reference standards, and included
over 1100 patients. Tests involving GH
stimulation had good diagnostic accuracy (DOR > 50).
Heterogeneity was significant in most analyses. The
only significant subgroup interaction was found with
relation to serum IGF1 level test and the presence or
lack, thereof, of known pituitary disease.

Limitations and strengths
Inferences presented in this review are limited by the
heterogeneity of gold standard definition and cutoffs and in
the prevalence of GHD across studies. Imprecision was
present in several analyses and lowers the quality of the
evidence. This was evident for GHRP6, GHRH, acipimox+
GHRH, GHRH+GHRP6, GHRH+GHRP2, hexarelin stimulation,
GHRH+clonidine, arginine stimulation, GHRH+pyridostigmine,
GHRH+SMS, and glucagon stimulation test that were evaluated in
only one or two studies leading to estimates with very wide
certainty intervals. Clinicians need to interpret imprecise
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these results at the point of care. Imprecision has likely affected
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criteria to include studies that had exclusively enrolled
patients with a diagnostic uncertainty (21), we have
decreased to some extent the overestimation of test
accuracy that can otherwise result, namely, in studies
that enroll patients who have a pre-established
diagnosis of GHD and compare them to healthy adults.

Figure 1: Reported QUADAS quality elements. AAA, was the
spectrum of pts representative of pts who will receive the test in
practice? AAB, did the whole sample or random selection of
pts receive same reference standard regardless of the index test
results? ABB, was the reference standard independent of the index
test? ABC, were the results of the index test interpreted without
knowledge of the results of the reference standard? ACA, were the
results of the reference standard interpreted without knowledge of
the results of the index test? ACB, were the same clinical data
available when study was done as would be when test is used in
practice? ACC, were drop-outs explained?

Study quality
Figure 1 provides a summary of the methodological
quality of the 23 included studies. The selection criteria
were clearly described in 18 (78%) studies. Participants
21 (91%) studies received a reference standard that
either diagnosed or excluded GHD.

Meta-analysis
Pooled likelihood ratios for test results as well as DORs
and $I^2$ statistic are reported in Table 2. Figure 2A–D
shows summary ROC curves for the tests of interest
(restricted to tests that were described in at least three
studies).

Pooled sensitivity, specificity, likelihood ratios, and
DORs of all studies of interest are presented in
Table 2. A test with a high likelihood ratio for a positive
result indicates that the test is helpful in ruling out
disease, while one with a high likelihood ratio for a
negative result indicates that the test is helpful in ruling
out a disease. A high DOR (above 50) indicates a test
that is significantly accurate while correcting for study
heterogeneity (8).

Subgroup analysis
The lack of known pituitary disease was associated with
a statistically significant increase in diagnostic accuracy
for the serum IGF1 test ($P < 0.05$). All other subgroup
analyses explored were not associated with significant

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Table 2: Meta-analyses results – summary of diagnostic accuracy measures.

<table>
<thead>
<tr>
<th>Test</th>
<th>No. of studies</th>
<th>Gold standard</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood ratio of a positive test</th>
<th>Likelihood ratio of a negative test</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pooled (95% CI)</td>
<td>I² (%)</td>
<td>Pooled (95% CI)</td>
<td>I² (%)</td>
<td>Pooled (95% CI)</td>
</tr>
<tr>
<td>GHRP6 Serum IGF1 levels</td>
<td>2</td>
<td>ITT</td>
<td>0.85 (0.70–0.94)</td>
<td>NA</td>
<td>0.97 (0.82–0.99)</td>
<td>NA</td>
<td>16.93 (3.54–80.94)</td>
</tr>
<tr>
<td>GHRH arginine + Acipimox + GHRH</td>
<td>6</td>
<td>ITT</td>
<td>0.70 (0.60–0.80)</td>
<td>82.5</td>
<td>0.82 (0.71–0.90)</td>
<td>77.9</td>
<td>2.41 (0.81–7.15)</td>
</tr>
<tr>
<td>GHRH + GHRP6 Hexarelin stimulation GHRH + GHRP2</td>
<td>2</td>
<td>ITT</td>
<td>0.90 (0.73–0.98)</td>
<td>NA</td>
<td>1.00 (0.54–1.00)</td>
<td>NA</td>
<td>12.37 (0.85–179.30)</td>
</tr>
<tr>
<td>GHRH + GHRP6 Acipimox + arginine + GHRH + GHRP6</td>
<td>2</td>
<td>AST, ITT</td>
<td>0.95 (0.62–0.97)</td>
<td>NA</td>
<td>0.95 (0.75–1.00)</td>
<td>NA</td>
<td>10.06 (2.12–47.76)</td>
</tr>
<tr>
<td>Hexarelin stimulation GHRH + GHRP2</td>
<td>2</td>
<td>ITT</td>
<td>0.85 (0.5–0.93)</td>
<td>NA</td>
<td>1.00 (0.84–1.00)</td>
<td>NA</td>
<td>16.96 (2.45–117.32)</td>
</tr>
<tr>
<td>GHRH + GHRP6 Acipimox + arginine + GHRH + GHRP6</td>
<td>2</td>
<td>ITT</td>
<td>0.80 (0.59–0.92)</td>
<td>NA</td>
<td>1.00 (0.63–1.00)</td>
<td>NA</td>
<td>13.97 (0.94–208.00)</td>
</tr>
<tr>
<td>Arginine stimulation GHRH + GHRP2</td>
<td>1</td>
<td>ITT</td>
<td>0.77 (0.5–0.93)</td>
<td>NA</td>
<td>1.00 (0.84–1.00)</td>
<td>NA</td>
<td>16.96 (2.45–117.32)</td>
</tr>
<tr>
<td>GHRH + GHRP6 Acipimox + arginine + GHRH + GHRP6</td>
<td>2</td>
<td>ITT</td>
<td>0.94 (0.59–1.00)</td>
<td>NA</td>
<td>0.17 (0.00–1.00)</td>
<td>NA</td>
<td>13.97 (0.94–208.00)</td>
</tr>
<tr>
<td>Arginine stimulation GHRH + GHRP2</td>
<td>1</td>
<td>ITT</td>
<td>0.94 (0.59–1.00)</td>
<td>NA</td>
<td>0.17 (0.00–1.00)</td>
<td>NA</td>
<td>13.97 (0.94–208.00)</td>
</tr>
</tbody>
</table>
| GHRP, GH-releasing peptide; ITT, insulin tolerance test; AST, arginine stimulation test; SMS, somatostatin; IGF1, insulin-like growth factor 1; PD, pyridostigmine.
By using the DOR, we hope to have sufficiently compensated of inconsistencies across included studies, in terms of choice of cutoffs.

Implications for practice and research

Several clinical practice guidelines on the diagnosis and management of adult GHD recommend the use of provocative tests of GH secretion within an appropriate clinical context and also refer to published diagnostic cutoff criteria (3, 5, 22). Most of the studies included in this review analyzed the two most commonly recommended tests in these consensus statements, namely the ITT and the GHRH-arginine test, but only the former was reported to have good diagnostic accuracy based on the DOR.

From the clinical practice point of view, it is important to recognize that the diagnostic accuracy of provocative tests of GH secretion is hampered by a lack of standardization of GH assays (23). Thus, the same patient blood sample sent to different laboratories can yield different GH concentrations. This discrepancy between GH assays can be attributed to a number of factors including variable antibody recognition of GH isoforms, the use of different GH preparations for calibration, lack of consensus regarding units of measurement for reporting GH, and variability of unit conversion factors (24). It is, therefore, important for clinicians to know which GH analytic method their laboratory uses and whether diagnostic cutoff values for GH provocative tests have been adjusted for that particular assay. Patient characteristics can also influence accuracy of interpretation of GH provocation tests. Obese normal subjects have been shown to exhibit a blunted GH response to provocative stimuli to a degree that sometimes overlaps with the results obtained from severe GH-deficient adults (25). It has, therefore, been suggested that diagnostic cutoff criteria should be adjusted for body mass index to avoid the potential of a false-positive result. Fortunately, IGF1 levels are not low in obese normal patients, and hence, a positive GH stimulation test coupled with a low IGF1 in an obese patient in the appropriate clinical setting is often reassuring to the clinician that the diagnosis of GHD is accurate.

This review’s finding of poor diagnostic accuracy of the IGF1 concentration in patients suspected of having GHD is in keeping with reports that IGF1 levels show considerable overlap between normal and GH-deficient adults. Hence, a normal IGF1 level does not rule out GHD. However, the presence of a low IGF1 level in patients with hypopituitarism associated with three or more pituitary hormone deficiencies is considered highly indicative of GHD (26, 27), and clinical guidelines suggest that provocative tests of GH stimulation are optional in such cases. Another confounder when using IGF1 assays is that some reference

![SROC curve](image)

**Figure 2** (A) ITT SROC curve. (B) Serum IGF1 SROC curve. (C) GHRH+arginine SROC curve. (D) Serum GH SROC curve.
laboratories do not have adequate age-adjusted 95% confidence intervals.

In this review, many of the analyzed studies used GHRH as part of the stimulus for GH secretion. In practice, clinicians have increasingly adopted the GHRH-arginine test as an alternative to the ITT, which has long been considered the reference standard against which other provocative tests are compared. In addition to its inclusion as a recommended test in clinical consensus guidelines on adult GHD (3, 5, 22), the increased popularity of the GHRH-arginine test can likely be attributed to a number of factors including favorable patient tolerability, ease of use, and wider patient applicability compared with the ITT, which is contraindicated in certain clinical situations such as seizure disorders or coronary artery disease. Interestingly, in 2008, the US manufacturer of the recombinant GHRH used in GHD studies made a business decision to indefinitely cease production of GHRH (other forms of GHRH are available outside of the US). The other GH secretagogues used in the studies analyzed by this review are also not available for clinical use in the US. This has now raised the question of which GH stimulation test should be used in clinical practice when the ITT is contraindicated or cannot be performed due to lack of required resources. Based on the review of available data, Yuen et al. (28) have advocated the glucagon stimulation test as an alternative to the ITT until another recombinant form of GHRH or alternative GH secretagogue becomes available (phase III studies of an oral ghrelin agonist are in process). The American Association of Clinical Endocrinologists has also recommended the glucagon stimulation test in place of the GHRH-AST (22). The advantages of the glucagon test are mainly its wide availability in the United States, the ease with which the 4 h test can be completed, and its high relative tolerability. We found one recently published study that assessed the diagnostic accuracy of glucagon stimulation test and reported a high sensitivity and specificity and we calculated a DOR of over 70 (29). Two other studies assessed the accuracy of the glucagon stimulation test but had to be excluded from our meta-analysis due to the fact that the studies enrolled patients who had a pre-established diagnosis of GHD (30, 31). The two studies reported sensitivity and specificity ranges of 97–100 and 88–100% respectively.

Conclusion

Several GH stimulation tests with fairly good diagnostic accuracy are available for the diagnosis of GHD in adults. The supporting evidence, however, is indirect (as is not directly informative of patient outcomes) and at high risk of bias.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-11-0476.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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