Received: 9 September 2023 | Revised: 20 November 2023 | Accepted: 23 November 2023

DOI: 10.1111/cen.15000

ORIGINAL ARTICLE

WILEY

IGF-1 as screening tool for acromegaly and adult-onset growth hormone deficiency in the Netherlands

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Abstract

Objective: Insulin-like growth factor 1 (IGF-1) measurements play a central role in the diagnosis and follow-up of acromegaly and growth hormone deficiency. However, improving health care outcomes for these patients involves an intricate process of laboratory diagnostics and skilled health care professionals. The integrated effects of IGF-1 reports on diagnosis and treatment decisions are yet unknown.

Design, Patients and Measurements: Extended quality assessment, distributing the description of five (real) patient cases with accompanying blood samples. Patients suspected or during follow up for acromegaly or adult onset of growth hormone deficiency were included. Laboratory specialists and endocrinologists in the same centre were asked to interpret their centre-specific IGF-1 results by using a laboratory and medical questionnaire. This way, insight could be obtained into the combined effects of different assays, assay harmonisation, reference value sets, and individual physician interpretation in relation to guidelines, thus reviewing the entire diagnostic and management process.

Results: Limited variation (CV 13.8 ± 2.8) was found in IGF-1 concentrations despite different use of the harmonization sample and factor among laboratories. This interlaboratory variation increased upon conversion to SD scores (CV 15.7 ± 40.7) as a consequence of the use of different reference value sets. Furthermore, there was a lack of adherence to international guidelines among endocrinologists.

Conclusions: Highly variable diagnostic and treatment outcomes in acromegaly and AGHD in the Netherlands can be attributed to increased variability of IGF-1 upon conversion to SD scores and low adherence to clinical guidelines.

KEYWORDS

acromegaly, adult-onset growth hormone deficiency, IGF-1

1 | INTRODUCTION

Insulin-like growth factor 1 (IGF-1) measurements play a central role in the diagnosis and follow-up of acromegaly and growth hormone deficiency, conditions that are biochemically characterized by an excess or deficiency of IGF-1.

IGF-1 measurements of the same sample may vary considerably when different assay methods are used,[1,2] despite the use of the International Reference Preparation coded 02/254 for IGF-1.[3] Therefore, harmonization and acceptable comparability of IGF-1 assays are required to provide useful guidelines for the management of disorders of the GH-IGF-1 axis.[4]

To be able to interpret a patient's IGF-1 value, age, and sex dependent reference values are needed. Between 2003 and the publication of the IGF-1 reference value set for the IDS iSYS assay by Bidlingmaier and colleagues in 2014,[5] at least 22 studies reporting normative data for different IGF-1 assay platforms have been published. Although most reference values are established by using IS 02/245 standardized assays, the published reference values may differ significantly.[6] It is often believed that harmonizing these different IGF-1 assays may result in better interlaboratory comparison. For this purpose, a harmonization sample for IGF-1 was introduced in the Netherlands in April 2013, intending to decrease variation in IGF-1 results between laboratories despite the use of different assays, assay platforms and reference value sets.

IGF-1 results are reported as a concentration (in nmol/L or ng/mL) in combination with an age- and sex-adjusted standard deviation (SD score or *Z* score) calculated using a specific reference value set. Ideally, laboratories that measure IGF-1 should obtain a similar result when asked to measure the same blood sample. However, it is even more important that endocrinologists in these hospitals come to correct conclusions by interpreting these values, resulting in comparable diagnostic outcomes and treatment decisions for individual patients. Misinterpreted laboratory results can lead to under- and overtreatment of patients and unequal health care outcomes.

A physician's interpretation of results is not only dependent on the absolute IGF-1 value or its SD score but also on endocrine knowledge of laboratory variation, the disease itself and adherence to guidelines. This part has not been studied extensively, but is important for health outcomes.

Therefore, we performed an extended quality assessment by distributing the description of five (real) patient cases with accompanying blood samples. Laboratory specialists and endocrinologists in the same centre were asked to interpret their centre-specific IGF-1 results by using a laboratory and medical questionnaire. This way, insight could be obtained into the combined effects of different assays, assay harmonisation, reference value sets and individual physician interpretation, thus reviewing the entire diagnostic and management process.

2 | METHODS

2.1 | Aim and research questions

The aim of this study was to review the diagnostic and management process of acromegaly and growth hormone deficiency by comparing IGF-1 results in different laboratories, and comparing the subsequent clinical decisions made by endocrinologists based on these results.

Our main research questions were:

1. What is the value and quality of the current harmonization of absolute IGF-1 concentrations?
2. What is the quality of the conversion of absolute IGF-1 concentrations to SD scores based on reference value sets used in the different centres?
3. What is the influence of (differences in) assays and reference value sets on clinical decision-making in the diagnosis and treatment of acromegaly and growth hormone deficiency?

2.2 | Sample collection and questionnaires

Five patient cases were selected based on medical history and local IGF-1 values from Groningen, especially those that raised an interesting internal discussion. Patients were asked for approval and after informed consent was obtained, blood was drawn. Samples were left to coagulate for 30 min at room temperature, centrifuged and aliquoted into 26 coded Screw Cap Tubes (Sarstedt) and stored at −80°C. These coded serum samples were sent to all laboratories that participated in the SKML EQAS. Two questionnaires were sent; one to the clinical chemist, containing questions regarding the used IGF-1 assay and reference value set, correction and/or harmonisation factors and a sample result form (Table 1). The five different serum

TABLE 1 Laboratory specialist questionnaire.

Laboratory specialist questionaire	
1	Which assay is used by your laboratory
2	Is this assay standardized against a reference preparation? If yes, which one?
3	In which units is the result reported?
4	Which reference values are used. What is the source?
5	Are SD or *Z* scores calculated?
6	The national harmonisation sample, is it frequently measured? When and how often?
7	Are all patient results corrected using the harmonisationfactor?
8	Are all patient results corrected using the another correctionfactor?
9	Do you report concentrations, SD scores/*Z* scores or upper limit of normal values (ULN), or a combination?

samples were analysed according to the local protocol and reported to the investigators as if it was a regular patient.

A second questionnaire was sent to the endocrinologist containing the locally measured IGF-1 results, five corresponding patient descriptions, and questions concerning interpretation and subsequent diagnostic decisions based on these data. It is important to note that questions were asked conditionally, meaning that if an endocrinologist answered 'no' for any question they were not asked the next question for that patient case, but were directed to the next case. In addition, they were offered the opportunity to explain every answer in a comments box.

2.3 | Participating centres (laboratory and endocrinologist)

In the Netherlands, 24 laboratories in 24 medical centres routinely analyse IGF-1. All these laboratories participated in this EQAS. Additionally, one or two endocrinologists from each of these centres was asked to participate. These 28 endocrinologists were all familiar with the locally used IGF-1 method and its reported results (concentrations and/or SD values). Of these 28 endocrinologists, 7 work at 6 academic centres that perform pituitary surgery.

2.4 | Selected patients

Patient cases are described in more detail in Table 2.

We obtained nearly 2 years of follow-up for all patients to assess the effect of actual diagnostic and treatment decisions on their disease course.

The study was approved by the Medical Ethics Review Board of the UMCG (Research Registry 201800219). The study fulfilled all requirements for patient anonymity and was in agreement with regulations of our University Hospital for publication of patient data as well as with the Dutch Civil Code (Article 458 on use of data for scientific research).

3 | RESULTS

3.1 | Assays

IGF-1 is analysed in the Netherlands mainly on Immulite (Siemens, 5 laboratories), iSYS (Immunodiagnostic Systems [IDS], 5 laboratories) and Liaison (Diasorin, 13 laboratories) platforms. Only one laboratory performed IGF-1 analysis on the Elecsys module of Roche Cobas Pro. All but two laboratories reported that their assay is standardized against the WHO IS 02/254 standard. Of these two, one mentioned WHO NIBSC 1st IRR 87/518 standardization (Immulite 2000), whereas the other stated the use of a manufacturer supplied standard, indirectly standardized against a non-stated WHO standard (Immulite XPi). Six laboratories reported IGF-1 results in ng/mL, or µg/L, whereas the other laboratories reported results in nmol/L. For this study all units were converted to nmol/L (1 ng/mL = 0.131 nmol/L).

Results are presented for each study question:

3.1.1 | Study question 1. What is the value and quality of the current harmonization of absolute IGF-1 concentrations?

Most laboratories harmonized against a national harmonization sample, which is a commutable human serum sample with a target concentration of 23 nmol/L. However, the frequency and reason to do so differed significantly between laboratories. The frequency ranged from 'only when needed' to 'at each new lot number of reagents', 'monthly', 'every 3-4 months' or 'once a year'. Only five laboratories did not harmonize their results. IGF-1 concentrations of the five cases are depicted in Figure 1A as IGF-1 concentrations per assay (Siemens, iSYS, Liaison). Although these results were obtained using different IGF-1 assays with or without correction for a harmonization factor, IGF-1 concentrations per case were quite similar. Interlaboratory CV over all was 13.8 ± 2.8%, but differed between the assays used (Table 2). iSYS users had the lowest interlaboratory CV, both on individual cases (4.4%–8.4%) and as a mean over all cases (6.5%), Liaison users showed an interlaboratory CV of 9.9%–12.0% on individual cases and 10.7% as a mean over all cases. For Immulite users the interlaboratory CV ranged from 17.4% to 29.2% with a mean of 17.6%.

In conclusion, there is only limited variability in absolute IGF-1 concentrations, despite the use of different assays and a lack of uniformity in use of a national harmonization sample.

3.1.2 | Study question 2. What is the quality of the conversion of absolute IGF-1 concentrations to SD scores based on reference values used in the different centres?

Figure 2 gives an overview of the different reference value sets used in the Netherlands. Table 3 depicts the effect of conversion to SD scores using the locally used reference values on interlaboratory CV's per case and per assay platform, clustered by assay, by reference value set and by combination of assay and designated reference value set.

Interlaboratory CV increased upon conversion from concentration to SD scores (from 13.8 ± 2.8 to 15.7 ± 40.7%). iSYS users had the lowest interlaboratory CV, both on individual cases (14.5%–27.5%) and as a mean over all cases (25.3%), Liaison users showed an interlaboratory CV of 20.0%–95.1% on individual cases and 45.9% as a mean over all cases. For Immulite users the interlaboratory CV ranged from 18.9% to 30.2% with a mean of 30.3%.

When sorted by reference value set and by combination, it became clear that the combination of the IDS iSYS assay with the

TABLE 2 Description of patient cases, questions asked and follow-up results.

Case	Case description	Questions	Follow-up
1	A 63-year-old man with a history of acromegaly diagnosed in 2007 and treated with transsphenoidal surgery visits the outpatient clinic at yearly intervals. In 2008, 6 months after surgical treatment, he is deemed to be in complete remission based on IGF-1 and growth hormone nadir after oGTT. Equally good results are established during follow-up visits. However, during the last visit, he complains of tiredness and excessive sleepiness. On physical examination large wide hands, coarse facial features and diastemata are noted.	1. Is this IGF-1 elevated? (yes/no) 2. Would you perform an oral glucose tolerance test (OGTT)? (yes/no) 3. GH nadir during OGTT is 1.32 mU/L (0.44 μg/L). Does this patient have a recurrence of acromegaly? (yes/no) 4. Would you request an MRI of the sellar region? (yes/no) 5. The MRI shows an unchanged residual adenoma. What would you decide? a. No therapeutic intervention at this time b. Refer for transsphenoidal re-exploration c. Refer for radiotherapy d. Start a somatostatin analogue (octreotide or lanreotide) e. Start a growth hormone receptor antagonist (pegvisomant)	This patient was diagnosed with a recurrence of acromegaly, upon which octreotide LAR was prescribed in August 2019. The somatostatin analogue resulted in IGF-1 normalization, but was unfortunately accompanied with abdominal complaints as a side effect, which clearly improved upon cessation of the drug in December 2020. Currently, the IGF-1 SD score is slightly increased (2.44) but the absolute value of 28.7 nmol/L was considered acceptable.
2	A 60-year-old woman undergoes a CT scan after an ischemic stroke. A pituitary macroadenoma is incidentally found. Retrospectively, she realizes her ring and shoe size have increased over the past years and she complains of headache, excessive sweating and snoring. There are no visual field defects.	1. Is this IGF-1 elevated? (yes/no) 2. Would you perform an OGTT? (yes/no) 3. GH nadir during OGTT is 2.7mU/L (0.9 μg/L). Does this patient have acromegaly? (yes/no) 4. Would you request an MRI of the sellar region? (yes/no) 5. The MRI shows a macroadenoma without cavernous sinus invasion or compression of the optic chiasm. Would you proceed to treatment? (yes/no)	In this patient, a densely granulated somatotroph adenoma was excised with transsphenoidal surgery in January 2020, upon which her acromegaly was considered to be in remission based on IGF-1 and OGTT results from 3 months postoperatively. She was discharged to a peripheral hospital in June 2021, where she was reported to be in persistent remission in June 2022.
3	A 75-year-old man with a history of a nonfunctioning pituitary macroadenoma diagnosed in 1978 visits the outpatient clinic. He was treated with surgery in 1978 and 2001 and with radiotherapy in 1978 and 2003. Since then, he suffers from hypopituitarism and receives hormone suppletion with levothyroxine, hydrocortisone and testosterone. He complains of headache when bending down or lifting groceries and is tired when getting up in the morning. He has a very limited exercise tolerance. His wife does not notice any snoring or apnea at night. His BMI is 44.51 kg/m^2.	1. Does this patient have growth hormone deficiency? (yes/no/stimulation test needed) 2. The stimulation test confirms the diagnosis of growth hormone deficiency (sentence shown only when 'stimulation test needed' was selected as answer to question 1). 3. Would you treat this patient with recombinant GH? (yes/no)	This patient was diagnosed with AGHD based on having documented panhypopituitarism and an IGF-1 SD score of −1.92. He received growth hormone replacement therapy from October 2019 until March 2020, when it was discontinued due to a lack of effect on his symptoms. His tiredness was deemed to be caused by previously undiagnosed obstructive sleep apnea, for which treatment was initiated.

(Continues)

TABLE 2 (Continued)

Case	Case description	Questions	Follow-up
4	A 73-year-old woman has been in endocrine follow-up since an intrasellar pituitary macroadenoma was incidentally found on cerebral MRI in 2010. She has no signs or symptoms of acromegaly and on subsequent MRI's, the lesion has not grown in size. There is no supra- or parasellar extension and no compression of the optic chiasm.	1. Is this IGF-1 elevated? (yes/no) 2. What would be your course of action? a. Repeat IGF-1 measurement b. Perform an oGTT. c. No further diagnostics	This patient was deemed not to have acromegaly and the IGF-1 SD decreased from 2.25 to 1.76 without treatment. Her clinical situation has been unchanged since inclusion into the study.
5	A 72-year-old woman suffers from panhypopituitarism due to chronic recurring lymphocytic hypophysitis treated with (methyl)prednisolone, azathioprine, mycophenolate mofetil and radiotherapy. She uses levothyroxine, prednisone and desmopressin. She has been extremely tired for years and reports a low quality of life.	1. Does this patient have growth hormone deficiency? (yes/no/stimulation test needed) 2. The stimulation test confirms the diagnosis of growth hormone deficiency (sentence shown only when 'stimulation test needed' was selected as answer to question 1). Would you treat this patient with recombinant GH? (yes/no)	This patient was known to have AGHD and received growth hormone replacement therapy before inclusion into the study, which was stopped due to side effects.

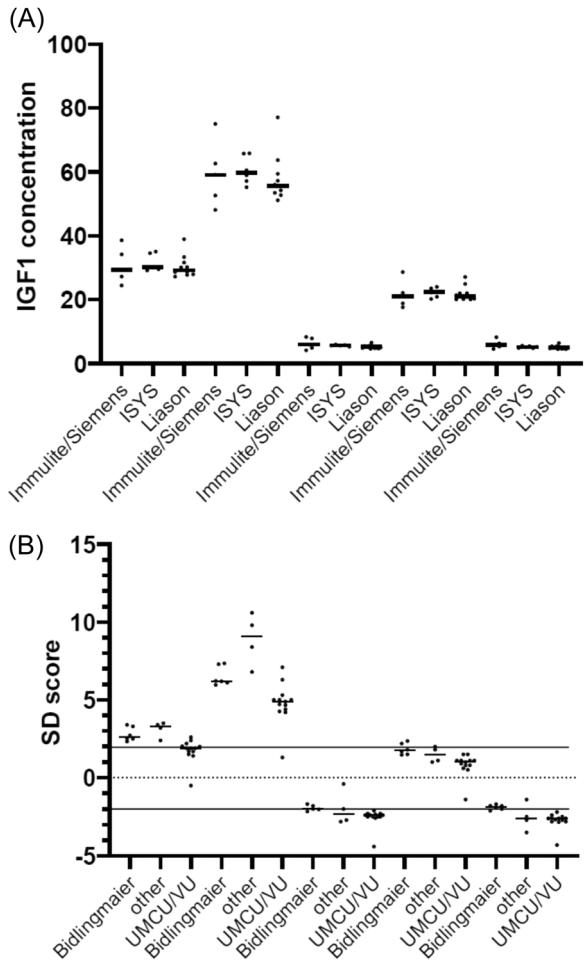

FIGURE 1 Absolute IGF1 concentrations (nmol/L) per patient case for each assay (A). IGF1 SD scores per patient case for each reference value set (B).

Bidlingmaier reference value set results in the lowest interlaboratory CV.

As can be seen in Figure 1B, the choice of reference value set leads to differences in reported SD scores (use of UMCU/VU set results in lower SD scores than the Bidlingmaier set).

In conclusion, the interlaboratory CV's increased upon conversion to SD scores caused by use of different reference value sets. The UMCU reference value set results in lower SD scores compared to the Bidlingmaier reference value set.

3.1.3 | Study question 3. Influence of assays and/or reference value differences on clinical decision-making

Several observations can be made on the influence of differences in absolute IGF1 concentrations and SD scores on clinical decision-making, of which Figure 3 is a schematic representation.

3.1.4 | Case 1

Sixteen out of 28 endocrinologists considered the IGF-1 to be increased, all of them after receiving a SD-score of ≥2 from their laboratory. Three endocrinologists from two centres considered the IGF-1 not to be increased despite a SD-score of ≥2. All endocrinologists whose laboratories used the Bidlingmaier reference value set considered the IGF-1 to be increased. Out of 15 endocrinologists who wanted to perform an OGTT, 7 incorrectly concluded that the result was normal despite a nadir GH ≥ 1.2 mU/L (0.4 μg/L). Thus, only 8 out of 28 (29%) endocrinologists correctly interpreted both the IGF-1 and OGTT-results according to Giustina et al.[7] four of them

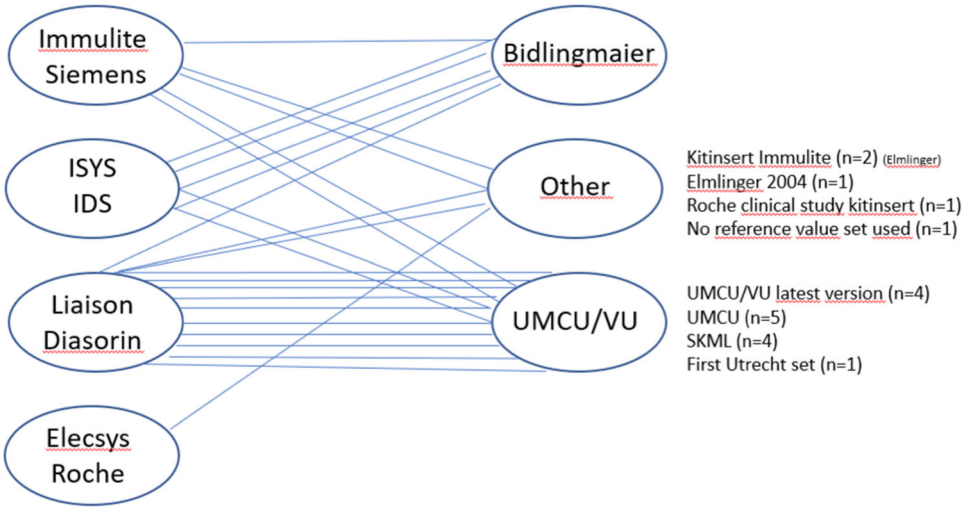

FIGURE 2 IGF-1 assay platforms and reference value sets used in the Netherlands.

being academic endocrinologists. Out of those eight, one performed no therapeutic intervention at this time, one chose to refer for transsphenoidal re-exploration and six opted to start a first-generation somatostatin analogue (octreotide or lanreotide) in this case of acromegaly recurrence, three of them being academic endocrinologists.

3.1.5 | Case 2

The results in this case of active acromegaly were less varied. A total of 25 out of 27 endocrinologists considered the IGF-1 to be increased. Interestingly, two endocrinologists from the same centre whose laboratory used the UMCU/VU reference value set considered an IGF-1 of 51.10 nmol/L not to be increased despite a SD-score of 4.26, while an endocrinologist from another centre deemed an IGF-1 of 55.62 nmol/L to be increased despite an SD-score of 1.30. Subsequently, seven endocrinologists (two of whom work academically) did not perform an OGTT to confirm the diagnosis of acromegaly because they found this unnecessary and 2 out of 18 endocrinologists who did perform an OGTT incorrectly concluded that the result was normal despite a nadir GH ≥ 1.2 mU/L (0.4 µg/L). All endocrinologists who considered the patient to have acromegaly requested a MRI, upon which only one out of 16 did not proceed to treatment.

3.1.6 | Case 3

Only one endocrinologist dismissed the diagnosis of AGHD without performing a stimulation test despite an IGF-1 SD-score of −2. Out of 26 endocrinologists who diagnosed AGHD, 17 (six of whom work academically) did so after performing a stimulation test despite the patient having documented anterior pituitary insufficiency, that is, documented deficiencies of thyroid-stimulating hormone (TSH), corticotropin (ACTH) and gonadotropins (LH/FSH). Interestingly, only seven of those who performed a stimulation test decided to start growth hormone replacement therapy (GHRT). All three endocrinologists whose laboratories measured an IGF-1 SD-score > −2 (two of whom work academically and use the Bidlingmaier reference set) opted to perform a stimulation test, but decided not to start treatment for various reasons.

3.1.7 | Case 4

Only one endocrinologist considered the IGF-1 to be increased, but chose not to perform any further diagnostics because there was only a limited increase in IGF-1, and the patient had no symptoms of acromegaly. Interestingly, in three cases the endocrinologist considered the IGF-1 not to be increased despite an SD-score >2 (two of whom work academically and use the Bidlingmaier reference set).

3.1.8 | Case 5

In this second case of AGHD, out of 25 endocrinologists who correctly diagnosed the condition, 22 (five of whom work academically) did so after performing a stimulation test despite the patient having documented panhypopituitarism and in 16 cases also an IGF-1 SD-score < −2. Interestingly, five of those who performed a stimulation test decided not to start GHRT.

3.1.9 | Follow-up

Of these five cases 2 year follow-up is available and described in detail in Table 2.

TABLE 3 The effect of conversion of IGF-1 results to SD scores on interlaboratory CV's, sorted by assay, by reference value set and by combination.

	Inter-lab CV (conc)		Inter-lab CV (SD score)	
*Sorted by assay**				
Immulite 1	18.4%	17.60%	25.3%	30.30%
Immulite 2	17.4%		30.2%	
Immulite 3	29.2%		51.4%	
Immulite 4	19.8%		18.9%	
Immulite 5	23.0%		25.7%	
ISYS 1	8.4%	6.50%	20.10%	25.30%
ISYS 2	7.3%		14.50%	
ISYS 3	4.4%		16.6%	
ISYS 4	6.6%		27.50%	
ISYS 5	6.0%		26.30%	
Liason 1	10.7%	10.70%	50.1%	45.90%
Liason 2	12.0%		41.2%	
Liason 3	10.2%		23.1%	
Liason 4	9.9%		95.1%	
Liason 5	10.8%		20.0%	
Sorted by reference value set				
Bidlingmaier 1	11.67	10.60	17.69	13.08
Bidlingmaier 2	10.68		10.36	
Bidlingmaier 3	9.95		9.86	
Bidlingmaier 4	10.35		18.89	
Bidlingmaier 5	8.25		8.57	
Elmlinger 1	13.96	17.51	15.97	31.8
Elmlinger 2	12.83		18.76	
Elmlinger 3	32.47		56.14	
Elmlinger 4	8.80		33.84	
Elmlinger 5	19.50		34.28	
UMCU/VU 1	10.30	13.11	43.13	40.14
UMCU/VU 2	10.85		27.68	
UMCU/VU 3	16.37		22.23	
UMCU/VU 4	10.62		89.39	
UMCU/VU 5	17.43		18.27	
Sorted by combination				
Liason/UMCU/VU 1	7.497%	6.46%	49.65%	47.41%
Liason/UMCU/VU 2	7.325%		28.46%	
Liason/UMCU/VU 3	9.842%		24.58%	
Liason/UMCU/VU 4	7.287%		114.2%	
Liason/UMCU/VU 5	10.21%		20.14%	
ISYS/Bidlingmaier 1	9.388%	6.34%	14.62%	12.14%
ISYS/Bidlingmaier 2	9.183%		9.518%	
ISYS/Bidlingmaier 3	6.018%		8.850%	
ISYS/Bidlingmaier 4	8.479%		20.50%	
ISYS/Bidlingmaier 5	7.134%		7.199%	

*Numbers refer to patient case.

4 | DISCUSSION

In this extended quality assessment scheme we found limited inter-laboratory variation in IGF-1 concentrations within and between assays, despite a lack of uniformity in use of a national harmonization sample. However, this interlaboratory variation increased considerably upon conversion to SD scores as a consequence of the use of different reference value sets. These reference value sets were not always specific for the assay used. The differences in reported SD scores within the cases strongly affected clinical-decision making. Furthermore, there was a lack of adherence to international guidelines among endocrinologists. To optimize outcomes in the care for patients with acromegaly and GHD both laboratory and clinical aspects need to be addressed.

The group of Chanson and colleagues[8,9] has produced reference intervals for eight commercially available IGF-1 assay kits in one and the same cohort of healthy control samples. They demonstrated a large variability in the reference ranges of the eight studied IGF-1 assays, despite the fact that all IGF-1 assays were obtained in the same large healthy population and were calibrated against the same recommended standard. This highlights the importance of using the reference value set best suited for the assay used.

The aim of using a nationwide harmonisation sample was to limit assay differences and support the use of a certain reference value set. The use, however, of a single harmonisation value to correct patient results may correct results in the harmonisation sample concentration range, but not in the lower or higher ranges. Therefore, the use of a harmonisation sample may be of limited value and may even introduce a standard error when it concerns assay specific differences. One could argue that the use of assay specific reference values established on one single cohort of healthy controls that represents the intended population may be a better solution for the observed assay differences than the use of a single harmonisation sample.

Pokrajac and colleagues performed a study similar to ours, in which they sent a serum sample of a patient with potential acromegaly to 23 centres participating in the UK National External Quality Assessment Service (NEQAS) using six different IGF-1 assays.[8] These centres were asked to measure IGF-1, interpret the result and provide the source of their reference ranges (RRs). Thirty percent of results were found to be in the normal range, 70% were consistent with acromegaly. Little agreement was found in the RR's quoted by centres using the same assay method and it was concluded that variability in assay performance, coupled with

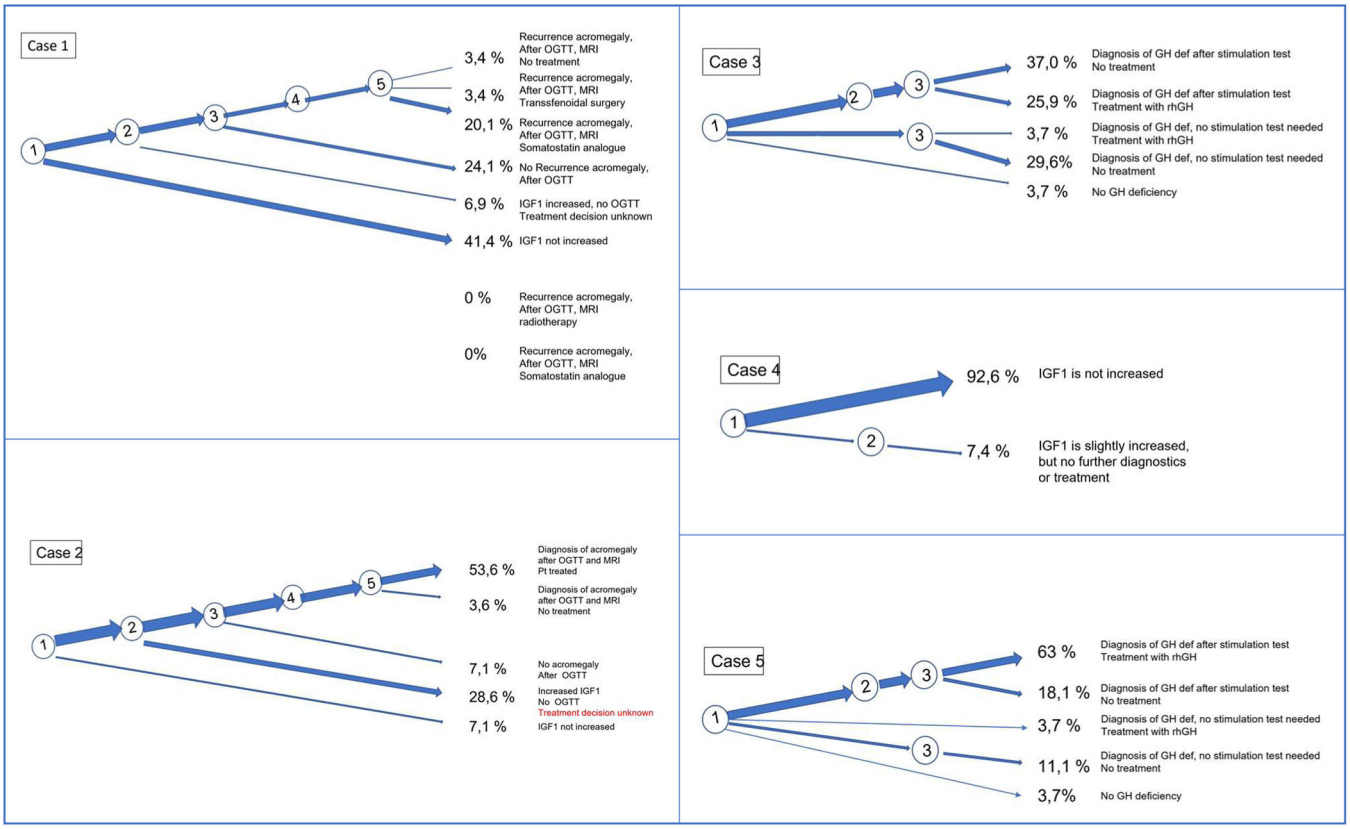

FIGURE 3 Schematic presentation of decisions made by endocrinologists of five different cases. Numbers represent different questions in the case specific questionares. For the different questions, see Table 2.

use of inappropriate conversion factors and RRs, undermines the applicability of international consensus criteria to local practice.

Our study demonstrates that in accordance with the publications of Chanson, Pokrajac,[10] Ankaert[1] and Varewijck,[11,12] differences in used assays and reference ranges result in significant differences in reported IGF-1 concentrations and SD-scores, but we have extended these findings by illustrating that current practice indeed leads to different clinical interpretations in both acromegaly and GHD.

Furthermore, our study shows that there was a lack of adherence to international guidelines among clinicians. Many Dutch endocrinologists did not apply the official OGTT cut-off for the diagnosis of acromegaly or the determination of a persistent postoperative growth hormone excess, which is a nadir GH of ≥1.2 mU/L (0.4 μg) if modern and ultrasensitive GH assays are used, as was the case in all assays.[7] In addition, biological and pharmacological factors have an influence on the GH concentration and should be considered when evaluating GH nadir, including BMI (GH nadir is lower in overweight/obese patients), sex (GH nadir is higher in women compared to men) and oral E2 (GH nadir increases and therefore OGTT should not be performed under oral E2 intake). Additionally, in our questionnaire the decision whether or not to perform a GH stimulation test seemed rather independent of whether or not the endocrinologist intended to start GHRT, which can be considered remarkable given the unpleasant nature of the hypoglycaemia induced by an insulin tolerance test for individual patients, and the fact that patients with ≥3 pituitary hormone deficiencies, low serum IGF-I levels (SD-score < −2) and a history of sellar mass lesions, pituitary surgery or radiation therapy are very likely (>95%) to have GH deficiency, and therefore can forego GH stimulation testing.[13] Finally, it is remarkable that only 8 out of 26 (31%) endocrinologists who diagnose AGHD in case 3 and 17 out of 25 (68%) who do so in case 5 decide to start GHRT. Current guidelines recommend offering GHRT to all patients with proven AGHD without contra-indication in the form of active malignancy.[14–16] Available evidence shows clear benefit of GHRT on body composition, exercise capacity, bone health, several cardiovascular risk factors, and QoL.[17,18] In addition, GHRT has proven to be safe in terms of de novo cancer risk and pituitary tumour recurrence.[19]

Differences in reported IGF-1 results have a profound influence on clinical decision-making in the management of acromegaly and AGHD among Dutch endocrinologists.

Our results show that in all five cases endocrinologists consider the SD cut-offs of −2 and +2 SD of paramount importance in deciding whether or not a patient has acromegaly or AGHD (with or without performing a stimulation test). In our view, it is important to nuance the relevance of these cut-offs and remind our readers that IGF-1 results represent a biochemical snapshot in time of one patient with his/her own biological variation, which is 9.4% for IGF-1[20] and with an intra-assay variation for the measurement, which for example is 3.8% for the IDS iSYS assay. These are factors not applicable to a reference value cohort, which in addition to an interindividual variation of 27% for IGF-1,[20] can result in a large variation in IGF-1

results without an actual biological abnormality being present. There may even be seasonal differences in IGF-1 due to the influence of vitamin D levels.[21] For these reasons, the instrument of time is crucial in the clinical interpretation of IGF-1 results and we would like to argue for repeating IGF-1 measurements in case of equivocal results when the condition of the patient allows to do so.

The strength of our study is that it is performed as a nationwide quality assessment, with an integrated overview of lab quality and subsequent decision-making. On the other hand, our findings have a descriptive nature, physicians were confronted with 'paper' patients and our questionnaires were not validated.

In conclusion, highly variable diagnostic and treatment outcomes in acromegaly and AGHD in the Netherlands can be attributed to increased variability of IGF-1 upon conversion to SD scores and low adherence to clinical guidelines. Both will need to be addressed to improve care for these patients.

ACKNOWLEDGEMENTS

We express our thanks to all participating centres, especially all participating clinical chemists and endocrinologists for their analyses, and sharing their time and information in answering the questionnaires.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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How to cite this article: Postma MR, van Beek AP, van der Klauw MM, Lentjes EGWM, Muller Kobold AC. IGF-1 as screening tool for acromegaly and adult-onset growth hormone deficiency in the Netherlands. *Clin Endocrinol (Oxf)*. 2024;100:260-268. doi:10.1111/cen.15000