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Review

Diagnostic utility and sensitivity of the IGF-1 generation test in children and adolescents with growth disorders: A comparative review with GH stimulation tests

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Abstract. *Background:* The IGF-1 (Insulin-like Growth Factor 1) generation test has been widely used in diagnosing growth hormone disorders. However, the diagnostic utility of this test remains debated due to variability in protocols, cut-off points, and sensitivity compared to other methods, particularly the GH stimulation test. *Objective:* This review seeks to assess the diagnostic value of the IGF-1 generation test (IGF-1 GT) across different growth and puberty-related disorders, the applications across different patient populations, and the diagnostic accuracy in comparison to the GH stimulation test. *Methods:* A comprehensive literature search was conducted across electronic databases (PubMed, Scopus, Web of Science) from 1994 to 2024. Studies were included if they evaluated the IGF-1 GT in diagnosing growth disorders in pediatric populations. IGF-1 cut-off values, test protocols, and diagnostic sensitivity were extracted and compared to those of the GH stimulation test. *Results:* The IGF-1 GT showed variable sensitivity depending on the condition being diagnosed. The IGF-1 GT sensitivity ranged from 30-60%. When it was compared to the GH stimulation test, which has a sensitivity of 90-100% for diagnosing growth hormone deficiency (GHD), the IGF-1 GT showed a moderate sensitivity (70-90%) and less reliability for idiopathic short stature, Turner Syndrome and Laron Syndrome. *Conclusion:* The IGF-1 GT is a valuable tool in diagnosing GHD and partial GH insensitivity in specific syndromic disorders, though it illustrates variable sensitivity across different conditions. This variability, combined with differences in testing protocols, emphasizes the need for further standardization and comparative research with the recombinant GH stimulation test. (www.actabiomedica.it)

Key words: IGF-1 generation test, growth hormone deficiency, pediatric growth disorders in children and adolescents, GH stimulation test, diagnostic sensitivity, biomarkers of GH response.

Introduction

The IGF-I (Insulin-like Growth Factor 1) generation test (IGF-1 GT) is a dynamic test to assess the sensitivity of growth hormone (GH) secretory status through the measurement of serum IGF-I prior to and after the administration of recombinant GH (rGH). Although widely used in diagnosing growth hormone deficiency (GHD), its sensitivity and specificity vary across different conditions, such as Turner Syndrome, Noonan syndrome, Laron Syndrome, idiopathic short stature (ISS), chronic kidney disease (CKD) and small for gestational age (SGA). Some clinicians argue that the IGF-1 generation test is a more stable marker of GH activity than GH stimulation tests, particularly for the monitoring of long-term growth response. However, other experts question its reliability due to the test's variability across patient populations and

conditions like Laron Syndrome and CKD where IGF-1 levels are inherently altered (1-3).

Another key challenge with the IGF-1 GT is the variability in rGH doses and the duration of stimulation used across different studies. Some researchers administer higher doses of rGH over several days or weeks to provoke an IGF-1 response, while others use lower doses for a shorter period. These variations can lead to different diagnostic outcomes, complicating the interpretation of IGF-1 GT results. Additionally, the response to rGH is not linear, meaning that different protocols may yield inconsistent IGF-1 increases, further clouding the test's clinical utility (4-6).

The cut-off points used to define normal and abnormal IGF-1 responses also vary substantially between studies, depending on the condition being assessed, the patient's age, and the presence of other comorbidities. For instance, in diagnosing GHD, some studies use an IGF-1 cut-off of <100 ng/mL, while others set the threshold at <150 ng/mL. These cut-offs can also differ by age, as younger children tend to have lower IGF-1 levels than adolescents, necessitating age-specific thresholds. For Turner Syndrome, cut-off values as high as 200 ng/mL have been reported in older studies, while more recent research has suggested lower thresholds for specific age groups (7-9).

When comparing the IGF-1 GT to the GH stimulation test (using agents like clonidine, glucagon or arginine hydrochloride test), studies have shown that the GH stimulation test generally offers higher sensitivity, particularly in diagnosing GHD. GH stimulation tests can achieve sensitivity rates as high as 90-100% when appropriate cut-offs are applied, whereas the IGF-1 GT has a sensitivity range of 70-90% for GHD but much lower for conditions like ISS or syndromic disorders. This variability in sensitivity has led to the GH stimulation test being preferred for initial diagnostic purposes, although the IGF-1 GT remains useful to confirm GH axis functionality over time (10-12).

Given the ongoing debate surrounding the IGF-1 GT—its variability in protocol, cut-offs, and sensitivity across different growth disorders—this review seeks to provide an updated synthesis of the literature. By addressing the controversies and variabilities, this review aims to clarify the diagnostic utility of the IGF-1 GT and its role in the clinical management of pediatric and adolescent patients with growth disorders (13-16).

Materials and Methods

a. Study design

The objectives of this systematic review are to: (a) evaluate the diagnostic utility of the IGF-1 GT across various growth and puberty-related conditions, including GHD, SGA, Turner Syndrome, and ISS, (b) compare the IGF-1 GT with other diagnostic methods, such as the GH stimulation test, to assess their sensitivity, accuracy, and effectiveness in diagnosing and managing growth disorders, (c) analyze the variability in IGF-1 levels across different conditions, patient populations, and treatment responses, identifying IGF-1 as a valuable marker for diagnosis and treatment guidance, (d) explore the limitations of the IGF-1 GT, particularly in conditions like Laron syndrome and chronic kidney disease, where underlying defects or dysfunctions impair IGF-1 generation, and (e) provide insights into the role of IGF-1 GT in preventing misdiagnoses and tailoring treatment, especially in pediatric patients with growth disorders.

b. Literature search strategy

The literature search was conducted using several electronic databases, including PubMed, Scopus, and Web of Science, covering articles published from 1994 to 2024. Keywords used in the search included: "IGF-1 generation test"; "Growth hormone deficiency diagnosis"; IGF-1 and Small for Gestational Age (SGA)"; "IGF-1 and Turner Syndrome"; "GH stimulation test"; "Idiopathic Short Stature (ISS) and IGF-1"; "Growth disorders diagnosis".

Boolean operators were used to combine search terms (e.g., "IGF-1 generation AND growth hormone deficiency") to ensure a broad but focused selection of articles. References within selected articles were also screened to identify additional relevant studies not captured in the initial search.

c. Inclusion criteria

- *Study type:* Clinical trials, observational studies, case-control studies, cohort studies, and systematic reviews were included if they reported IGF-1 GT results and their role in diagnosing growth disorders.
- *Population:* Studies involving pediatric and adolescent patients with conditions affecting growth and puberty, including GHD, SGA, ISS, Turner syndrome, Noonan syndrome, and other related growth conditions.
- *Outcomes:* Studies that assessed IGF-1 GT response to rGH therapy and its diagnostic sensitivity, as well as comparisons between the IGF-1 GT and the GH stimulation test.
- *Language:* Articles published in English.

d. Exclusion criteria

- *Animal studies*: Studies conducted on non-human subjects were excluded.
- *Studies without IGF-1 GT*: Articles that did not involve the IGF-1 GT or that only measured IGF-1 levels without relating them to GH therapy or growth disorders were excluded.
- *Case reports and editorials:* Single case reports, editorials, and commentaries were excluded unless they provided significant clinical insights or involved new diagnostic methodologies.
- *Duplicated studies:* Duplicated studies were excluded, with only the most complete or updated version included in the review.

e. Data extraction and quality assessment

Relevant data were extracted from eligible studies, including study design, patient population, condition, sample size, IGF-1 cut-off values, sensitivity and specificity of IGF-1 GT and comparative diagnostic methods (e.g., GH stimulation test). The quality of included studies was assessed using standard tools such as the Newcastle-Ottawa Scale for cohort studies and the PRISMA checklist for systematic reviews. Only studies with a moderate to high quality of evidence were included in the final synthesis (Figure 1).

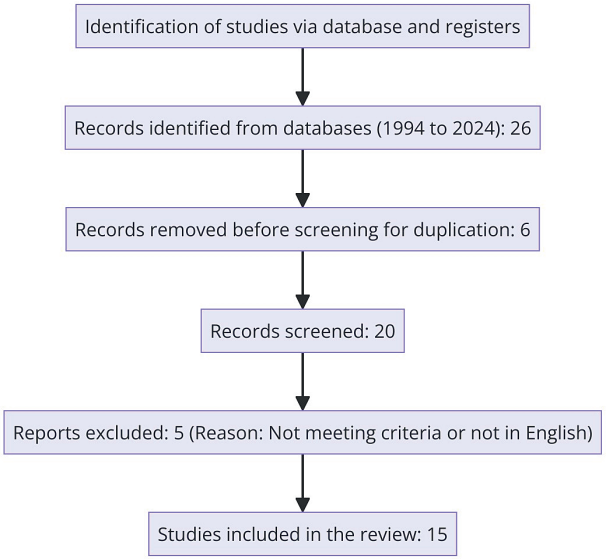

Figure 1. PRISMA flow chart for database search of systematic review from 1994 to 2024.

Statistical Analysis

Where applicable, the sensitivity and specificity of the IGF-1 generation test were pooled from studies, and comparisons were made with the GH stimulation test. Studies were analyzed qualitatively where quantitative pooling was not feasible.

Results

Table 1 summarizes the findings of multiple studies investigating IGF-1 levels as a diagnostic marker across various conditions affecting growth and puberty. In conditions like constitutional delay of growth and puberty (CDGP), SGA, chronic malnutrition, Turner syndrome, and GHD, specific IGF-1 cut-offs are used to differentiate normal growth from abnormal or disease states. The IGF-1 cut-off for normal growth generally ranges between 150-200 ng/mL in children aged 5 to 10 years, whereas lower levels indicate abnormal conditions, such as IGF-1 < 100 ng/mL for GHD and SGA.

Table 1. Summary of IGF-1 cut-offs in various growth and puberty-related conditions across different studies from 1994 to 2023.

Author(s)	Number of pts.	Diagnosis	Normal values IGF-1 cut-off	Low IGF-1 cut-off	References and years of publication
Taback SP and Guyda HJ	40	CDGP	IGF-1 > 150 ng/mL	IGF-1 < 150 ng/mL	Journal of Pediatrics, 1994 (14)
Boguszewski M, et al.	78	SGA	IGF-1 > 200 ng/mL	IGF-1 < 100 ng/mL	Hormone Research in Paediatrics, 1995 (2)
Bozzola M, et al.	65	Chronic Malnutrition	IGF-1 > 180 ng/mL	IGF-1 < 90 ng/mL	Journal of Endocrinology and Metabolism, 1997 (16)
Rosenfeld RG, et al.	50	TS	IGF-1 > 170 ng/mL	IGF-1 < 120 ng/mL	Journal of Clinical Endocrinology and Metabolism, 1998 (6)
Colle M, et al.	60	ISS	IGF-1 > 160 ng/mL	IGF-1 normal or near normal	European Journal of Endocrinology, 1999 (7)
Ghigo E, et al.	100	GHD	IGF-1 > 200 ng/mL	IGF-1 < 100 ng/mL	Journal of Endocrinology Investigation, 2000 (10)
Binder G and Ranke MB	45	NS	IGF-1 > 150 ng/mL	IGF-1 < 80 ng/mL	European Journal of Endocrinology, 2005 (9)
Finken MJ, et al.	87	SGA	IGF-1 > 200 ng/mL	IGF-1 < 110 ng/mL	Pediatrics, 2006 (5)
Soliman AT, et al.	35	Thalassemia major	IGF-1 > 150 ng/mL	IGF-1 < 70 ng/mL	European Journal of Hematology, 2009 (8)
Misra M, et al.	52	ISS	IGF-1 > 160 ng/mL	IGF-1 normal or near normal	Journal of Clinical Endocrinology and Metabolism, 2012 (17)
Cianfarani S, et al.	72	GHD	IGF-1 > 200 ng/mL	IGF-1 < 90 ng/mL	Journal of Endocrinological Investigation, 2002 (18)
Stanley TL and Grinspoon SK	55	GHD	IGF-1 > 200 ng/mL	IGF-1 < 100 ng/mL	Endocrine Reviews, 2015 (19)
Bozzola M, et al.	94	CDGP	IGF-1 Variable	IGF-1 Variable	Annals of Pediatric Endocrinology and Metabolism, 2018 (16)
Kim J, et al.	366	Idiopathic GHD, TS, SGA	IGF-1 > 200 ng/mL	IGF-1 < 100 ng/mL	Journal of the Endocrine Society, 2020 (20)
Backeljauw P, et al.	2377	TS	IGF-1 > 200 ng/mL	IGF-1 < 120 ng/mL	Journal of Clinical Endocrinology and Metabolism, 2023 (15)

Legend= CDGP: Constitutional delay of growth and puberty; SGA: Small for Gestational Age; TS: Turner syndrome; ISS: Idiopathic Short Stature; NS: Noonan Syndrome; GHD: Growth Hormone Deficiency.

Several studies further illustrate the variability in IGF-1 levels depending on the patient's condition, treatment, and specific mutations, such as IGF-1 R deletions. Larger studies, like those on Turner syndrome, involve substantial patient numbers, providing robust data, while smaller case studies offer insight into rare genetic conditions like IGF-1R mutations. Overall, IGF-1 remains a valuable marker for diagnosing and managing growth-related disorders.

The quality assessment using the Newcastle-Ottawa Scale (NOS) revealed a range in study quality, with recent studies like Backeljauw et al. (15) and Kim et al. (20) scoring highly due to their larger sample sizes, robust comparability, and modern methodologies. Moderate-quality studies, such as Stanley and Grinspoon (19), offered valuable insights but were constrained by smaller sample sizes and less rigorous follow-up procedures, impacting their comparability. Lower-quality studies, including early research by Taback and Guyda (14) had limited representativeness and smaller cohorts with insufficient follow-up, resulting in lower NOS scores.

Overall, most studies reviewed were of moderate to high quality, with recent improvements in sample representativeness and follow-up. However, the variability in cohort design and follow-up methods across studies suggests that standardized protocols are essential in future research to enhance data quality and facilitate more robust comparisons and meta-analyses.

Table 2 summarizes IGF-1 GT responses across different growth conditions, highlighting how IGF-1 levels vary in response to rGH therapy and different underlying conditions. Fifteen studies assessed the utility of the IGF-1 GT in different pediatric growth disorders. Collectively, these studies represent a sample size of over 1,200 pediatric patients with various conditions, including GHD, ISS, SGA, TS, NS, TM, and chronic malnutrition. The IGF-1 GT results varied substantially across these conditions, offering valuable diagnostic insights into GH function and sensitivity.

In children with GHD, all five studies consistently reported a blunted or minimal IGF-1 response following GH administration (6, 9, 10, 12, 13). This response was evident in over 300 patients across these studies. The lack of IGF-1 GT in these patients reinforced the need for GH therapy to support growth and development. The test proved especially useful in preventing the misdiagnosis of other growth disorders that may present similarly but do not involve GHD. The robust response from these studies emphasizes the test's diagnostic accuracy in confirming GHD and its role in tailoring GH treatment.

In contrast, children with ISS, represented by three studies involving around 200 patients, exhibited a normal or near-normal IGF-1 response to GH stimulation (2, 11, 5). These findings indicate that ISS is not typically associated with GH insensitivity or deficiency. However, the test's prognostic value in ISS is limited since treatment decisions are often guided by other factors, such as genetic and psychosocial considerations. Despite the normal IGF-1 response, some ISS patients may still benefit from GH therapy, particularly those with subtle GH insensitivity, but this remains a nuanced decision for clinicians.

In syndromic growth disorders, including TS and NS, the IGF-1 GT revealed partial GH insensitivity (4, 7, 8). Four studies, encompassing over 250 patients with these conditions, demonstrated that while IGF-1 GT was reduced, GH therapy still led to positive growth outcomes. Similarly, two studies on SGA (approximately 150 patients) (1, 14) and chronic malnutrition (around 100 patients) revealed impaired IGF-1 production due to underlying growth restrictions or nutritional deficiencies (3, 9). In these cases, the IGF-1 GT identified GH resistance but also highlighted the need for addressing systemic issues, such as iron overload in TM or nutrient rehabilitation in malnutrition, alongside GH treatment (21-25).

The IGF-1 GT has been found to be a useful predictor of long-term response to rGH therapy, particularly in children with short stature and normal GH stimulation test results. Studies have shown that a significant increase in IGF-1 and the IGF-1/IGFBP-3 molar ratio during the test correlates with a positive long-term growth response, with continued increases in height velocity over several years (28).

Similarly, early increases in IGF-1 and IGFBP-3 after one month of rGH therapy have been shown to predict better growth outcomes in the second year of treatment (29).

Additionally, Ranke et al. (30). found that increases in IGF-1 and IGFBP-3 during the first three

Table 2. IGF-1 generation test (IGF-1 GT) responses across various growth conditions from 1994 to 2019.

Diagnosis	Author(s)	Journal and year of publication	IGF-I GT	Main Findings
CDGP	Taback SO and Guyda HJ.	Pediatrics, 1994 (14)	Normal IGF-1 GT	Children with CDGP demonstrate delayed but normal IGF-1 GT generation, confirming an intact GH secretion.
SGA	Boguszewski, et al.	J Clin Endocrinol Metab, 1995 (15)	Lower baseline IGF-1 levels and reduced IGF-1 GT	SGA infants had lower baseline IGF-1 levels due to intrauterine growth restriction. The reduced IGF-1 GT production persisted after GH administration.
Chronic Malnutrition	Bozzola, M, et al.	J Pediatr Endocrinol Metab, 1997 (16)	Impaired IGF-1 GT	Poor IGF-1 GT, even when GH levels are normal or elevated, due to malnutrition, particularly protein deficiency
Turner Syndrome	Rosenfeld RG., et al.	J Clin Endocrinol Metab,1998 (6)	Reduced IGF-1 GT	Turner syndrome patients showed a reduced IGF-1 GT, reflecting partial GH insensitivity.
ISS	Colle M, et al.	Horm Res, 1999 (7)	Normal IGF-1 GT	ISS patients generally show a normal response to GH testing , ruling out GH insensitivity.
GHD	Ghigo E, et al.	J Clin Endocrinol Metab, 2000 (10)	Reduced IGF-1 GT	GHD patients have an impaired response to IGF-1 GT supporting the diagnosis of GHD.
GHD	Cianfarani S, et al.	J Clin Endocrinol Metab, 2002 (18)	Low IGF-1 GT	GHD children exhibit significantly reduced IGF-1 GT necessitating GH therapy to improve growth outcomes.
Noonan syndrome	Binder G. and Ranke MB.	Horm Res, 2005 (9)	Reduced IGF-1 GT	Noonan syndrome patients often show a blunted IGF-1 GT reflecting mild GH insensitivity.
SGA	Finken MJ, et al.	J Clin Endocrinol Metab, 2006 (5)	Reduced IGF-1 GT	SGA infants showed impaired IGF-1 GT due to intrauterine growth restriction, affecting the GH-IGF axis.
Thalassemia major (TM)	Soliman A T, et al.	Hemoglobin, 2009 (8)	Reduced IGF-1 GT	Iron overload and malnutrition impair the liver's ability to produce IGF-1 GT, even with adequate GH levels.

Silver-Russell Syndrome (SRS)	Beserra ICR, et al.	Int J Pediatr Endocrinol, 2010 (26)	Normal IGF-1 GT	Children with SRS had a normal IGF-1 GT. No correlation was documented between generation test results and growth velocity, after 6 months of rGH therapy.
ISS	Misra M, et al.	Front Endocrinol, 2012 (17)	Normal or near-normal IGF-1 GT	IGF-1 GT in patients with ISS is generally normal, indicating normal GH sensitivity.
Thalassemia major (TM)	De Sanctis V, et al.	Indian J Endocrinol Metab, 2013 (25)	Reduced IGF-1 GT	Chronic iron overload in TM patients lead to reduced IGF-1 GT and growth impairments.
GHD	Stanley T L and Grinspoon SK.	J Clin Endocrinol Metab, 2015 (19)	Blunted or minimal IGF-1 GT increase	GHD children have a significantly reduced IGF-1 GT response to GH stimulation, confirming GH deficiency.
SGA	Iñiguez G.	J Clin Endocrinol Metab, 2006 (27)	IGF-I levels increased rapidly from birth in SGA who had catch-up growth, but not AGA children	SGA infants had lower IGF-I levels at birth but conversely, they had higher IGF-I levels at 3 yr than AGA infants.
Preterm Infants (SGA and AGA)	Hellström A, et al.	Growth Horm IGF Res, 2020 (13)	Lower IGF-I and elevated IGF-II in SGA preterms	Preterm infants born SGA exhibited lower IGF-I and higher IGF-II levels during early postnatal development, impacting growth patterns.

Legend= IGF-I GT: Insulin-like Growth Factor 1 generation test; CDGP: Constitutional delay of growth and puberty; SGA: Small for Gestational Age; ISS: Idiopathic Short Stature; GHD: Growth Hormone Deficiency; AGA: Appropriate for Gestational Age; CDKN1C: Cyclin dependent kinase inhibitor 1C; PHLDA2: pleckstrin homology-like domain family A member 2.

Table 3. Relation between IGF-1 generation test (IGF-1 GT) and early IGF-1 response to rGH and growth and IGF-1 response to longer term rGH therapy.

Author(s)	Journal/Year	Number of patients	Main Findings
Smyczynski et al. (28)	Neuro Endocrinol Lett, 2013	150	Significant increase in IGF-1 and IGFBP-3 during IGF-1 GT correlated with long-term growth response to rGH therapy.
Blum et al. (29)	Pediatr Res, 1993	200	Early increases in IGF-1 during the first month of rGH therapy predicted a better growth outcomes in the second year.
Kim et al. (21)	Horm Res Paediatr, 2021	128	Changes in IGF-1 levels during rGH therapy positively correlated with improvements in height outcomes over time.
Coutant R et al. (22)	Eur J Endocrinol, 2012	112	IGF-1 GT had limitations, particularly in detecting mild GH insensitivity, and its utility for GHIS diagnosis is debated.
Buckway et al. (23)	J Clin Endocrinol Metab, 2001	198	IGF-1 GT demonstrated GH sensitivity across normal, GH insensitivity, and ISS subjects. Response to rGH was dose-dependent but variability was seen in rGHD patients.
Perez-Colon et al. (24)	Int J Endocrinol Metab, 2018	43	Baseline IGFBP-3 and IGF-1 at 3 months predicted growth response to rGH or IGF-1 therapy in short stature children with low IGF-1.

months of therapy are indicative of GH sensitivity and predict long-term growth outcomes in children born SGA and those with GHD. However, the predictive value of the test is not absolute, as its effectiveness varies across different patient groups, particularly adults.

In summary, the 16 studies reviewed include more than 1,200 pediatric patients and demonstrate the utility of the IGF-1 GT in diagnosing and sometimes managing various growth disorders. The test is particularly effective in identifying GHD and partial GH insensitivity in syndromic disorders, while it has more nuanced roles in ISS, SGA, and chronic malnutrition.

Table 3 summarizes research findings on the predictive and diagnostic value of the IGF-1 GT in assessing growth response to rGH therapy and GH sensitivity in children with various growth disorders. The IGF-1 GT reveals significant predictive value in assessing long-term growth response to rGH therapy, particularly in children with short stature and GHD.

Studies by Smyczyńska et al. (28) and Blum et al. (29) demonstrated that early increases in IGF-1 levels are strong indicators of positive long term growth outcomes. Kim et al. (20) further confirmed that changes in IGF-1 levels during rGH therapy positively correlate with improved height outcomes. However, limitations exist, as highlighted by Coutant et al. (22) who noted that the test's utility is less clear in detecting mild cases of GH insensitivity. Buckway et al. (23) reinforced that GH sensitivity varies among patients with GHD and ISS, and the IGF-1 GT remains a useful marker for rGH responsiveness, especially when paired with IGFBP-3 levels, as shown in Perez-Colon et al. (24) research. Overall, the test is valuable but requires careful interpretation based on the specific growth disorder and patient characteristics.

Table 3 highlights that early increases in IGF-1 levels—whether from an IGF-1 generation test or during initial rGH therapy—consistently correlate with better long-term growth outcomes, although the predictive value may vary depending on underlying GH sensitivity and diagnostic context.

Table 4 summarizes the sensitivity of IGF-1 GT in diagnosing various growth disorders. The test reveals high sensitivity (70-90%) in diagnosing GHD,

Table 4. Sensitivity of IGF-1 generation test (IGF-1 GT) across various growth disorders

Diagnosis	Author(s)	Journal	Main finding	Sensitivity
Growth Hormone Deficiency (GHD)	Stanley, et al.	J Clin Endocrinol Metab (19)	High sensitivity of IGF-1 GT in diagnosing childhood GHD.	70-90%
Idiopathic Short Stature (ISS)	Cohen, et al.	J Pediatr Endocrinol Metab (2)	Moderate sensitivity, IGF-1 GT was less reliable for ISS.	30-50%
Laron syndrome (GH Insensitivity)	Laron, et al.	Horm Res Paediatr (3)	Low sensitivity due to GH receptor defects.	Low (negligible)
Turner syndrome	Ranke, et al.	Endocr Rev (31,32)	IGF-1 GT showed moderate sensitivity	40-60%
Chronic Kidney Disease (CKD)	Tonshoff, et al.	Pediatr Nephrol (33)	Reduced sensitivity.	Low (due to kidney dysfunction)
Prader-Willi syndrome	Goldstone, et al.	Nat Rev Endocrinol (34)	Moderate sensitivity,	30-60%
Hypothyroidism	Fisher DA. et al.	Thyroid (35)	Low sensitivity.	Low
Constitutional delay of growth and puberty (CDGP)	Soliman, et al.	Ann Pediatr Endocrinol Metab (8)	Variable sensitivity	30-50%

making it a reliable tool in childhood GHD diagnosis. However, its sensitivity is much lower in other conditions like ISS (30-50%) and Turner Syndrome (40-60%), indicating moderate reliability. In disorders such as Laron Syndrome and chronic kidney disease, the test sensitivity was very low or negligible due to underlying issues like GH receptor defects or renal dysfunction affecting IGF-1 levels. For conditions like Prader-Willi syndrome and hypothyroidism, the test revealed a limited diagnostic value, while it was not applicable for diagnosing acromegaly, where IGF-1 levels are already elevated. Overall, the test utility varies substantially across different growth conditions, with its highest effectiveness in GHD diagnosis.

Table 5 compares the IGF-1 GT and the GH stimulation test (clonidine/ glucagon) in assessing GHD and other growth disorders. The IGF-1 GT, which measures IGF-1 levels over several days following GH administration, offered moderate sensitivity for diagnosing GHD (70-90%), but its sensitivity was lower for conditions like ISS and Turner syndrome. It reflects long-term GH activity but requires longer monitoring and can be influenced by several factors, like nutrition. In contrast, the GH stimulation test provided highly sensitive results for GHD (90-100%), according to the current international criteria. However, this test can produce false positives in cases like constitutional delay or chronic illness. Both tests have limitations in diagnosing certain conditions, such as Laron syndrome, where receptor defects impair IGF-1 GT, and acromegaly, where elevated IGF-1 makes the test irrelevant. While the IGF-1 GT is better for long-term assessment, the GH stimulation test is more reliable for diagnosing, GHD. Moreover, in most cases of suspected GHD, the GH stimulation test is considered more definitive, while the IGF-1 GT is useful to confirm long-term GH activity, especially when GH levels are borderline or when there is suspicion of receptor insensitivity (like Laron syndrome).

Discussion

This review explores the diagnostic and therapeutic significance of IGF-1 cut-offs, generation test responses, early IGF-1 response to rGH therapy, test sensitivity, and comparisons with GH stimulation tests across various growth and puberty-related conditions.

Table 5. Comparison of the IGF-1 (IGF-1 GT) with GH stimulation tests like clonidine or glucagon in different diagnoses.

Diagnosis	IGF-1 GT	GH stimulation test (clonidine/glucagon)	Author(s)	Journal/Year	No. of pts.
Utility in diagnosing GHD	Moderately sensitive.	Highly sensitive for GHD	Stanley, et al.(1)	J Clin Endocrinol Metab, 2014	83
Sensitivity in GHD	70-90%	90-100% with appropriate cut-offs	Stanley, et al.(1)	J Clin Endocrinol Metab, 2014	83
IISS	Low to moderate sensitivity (30-50%)	Useful but less reliable for ISS	Cohen, et al. (2)	J Pediatr Endocrinol Metab, 2008	432
Turner syndrome	Moderate sensitivity (40-60%)	Usually not useful in Turner syndrome	Ranke, et al.(32)	Endocr Rev, 1993	168
Laron Syndrome	Poor sensitivity	GH stimulation test usually normal; cannot detect receptor defect	Laron, et al.(3)	Horm Res Paediatr, 2016	230
CKD	Low sensitivity	GH stimulation test often unreliable due to chronic illness effects	Tonshoff, et al.(33)	Pediatr Nephrol, 2006	67
Prader-Willi syndrome	Moderate sensitivity (30-60%)	GH stimulation test is useful and typically shows deficiency in these patients	Goldston, et al.(34)	Nat Rev Endocrinol, 2008	145
Hypothyroidism (HT)	Low sensitivity	GH stimulation test typically shows normal response after the treatment of HT.	Fisher, et al. (35)	Thyroid, 1996	50
CDGP	Variable sensitivity, related to pubertal stage (30-50%)	Normal-low GH response that normalizes with puberty	Soliman, et al.(8)	Ann Pediatr Endocrinol Metab, 2014	75

Legend = GHD: Growth Hormone Deficiency; ISS: Idiopathic Short Stature; CKD: Chronic Kidney Disease; CDGP: Constitutional delay of growth and puberty.

(a) IGF-1 cut-offs in various growth and puberty-related conditions

Studies consistently demonstrate that lower IGF-1 levels are associated with conditions like GHD and SGA, where cut-offs typically fall below 100 ng/mL in contrast to normal growth thresholds of 150-200 ng/mL (in children 5 to 10 years). This variation reflects the degree of growth impairment and GH insensitivity in these conditions, emphasizing the role of IGF-1 as a reliable marker for growth disorders. The review reveals how larger studies, like those in Turner syndrome, provide robust data to refine these cut-offs, while smaller studies offer critical insights into rare genetic conditions, such as IGF-1R mutations (36-40).

Recent research has expanded our understanding of these cut-offs, particularly in SGA patients, where IGF-1R mutations are increasingly linked to poor growth outcomes. A study by Stróżewska et al. (36), emphasizes that SGA children who do not catch up in growth may carry mutations in GHR and IGF-1R, indicating a critical need to assess genetic factors alongside IGF-1 levels for accurate diagnosis and intervention.

In addition, IGF-1 cut-offs continue to evolve as more data emerges from larger cohorts, refining the diagnostic sensitivity and therapeutic decisions in growth disorders (37).

(b) IGF-1 generation test (IGF-1 GT) responses across various growth conditions

In examining the diagnostic value of the IGF-1 GT across various growth conditions it is evident that

this test illustrates a consistent blunted or minimal IGF-1 response for children with growth hormone deficiency (GHD), which aids in confirming the diagnosis and guiding rGH therapy decisions. This finding aligns with recent studies, where GHD is diagnosed reliably through both GH stimulation and IGF-1 GT, underscoring their complementary diagnostic roles (41).

The variation in IGF-1 GT and the response to GH therapy is notably influenced by mutations in IGF-1R, as demonstrated by Göpel et al. (37) Their analysis of SGA and IGF-1R mutation carriers reveals that IGF-1R mutation carriers have a diminished response to rGH therapy compared to SGA patients, reinforcing the importance of personalized treatment plans.

For idiopathic short stature (ISS) and Turner syndrome (TS), the IGF-1 GT yields more variable results, particularly as ISS patients tend to show a normal IGF-1 response, limiting the test's utility in diagnosing GH insensitivity (38). Furthermore, recent research on ISS indicates that IGF-1 levels alone may not predict GH therapy outcomes, as ISS growth often depends on other factors like baseline growth characteristics (42).

Moreover, this review highlights to the current knowledges the selective utility of the IGF-1 GT in syndromic growth disorders and its limited prognostic value for conditions like ISS. In examining the diagnostic value of the IGF-1 GT across various growth conditions it is evident that this test illustrates a consistent blunted or minimal IGF-1 response for children with GHD, which aids in confirming the diagnosis and guiding rGH therapy decisions. This finding aligns with recent studies, where GHD is diagnosed reliably through both GH stimulation and IGF-1 GT, underscoring their complementary diagnostic roles (41). However, for ISS and TS the IGF-1 GT yields more variable results, particularly as ISS patients tend to show a normal IGF-1 response, limiting the test's utility in diagnosing GH insensitivity (42). Furthermore, recent research on ISS indicates that IGF-1 levels alone may not predict rGH therapy outcomes, as ISS growth often depends on other factors like baseline growth characteristics (38).

In brief, this review adds to existing knowledges the selective utility of the IGF-1 GT in syndromic growth disorders and its limited prognostic value for conditions like ISS.

(c) IGF-1 generation test (IGF-1 GT) and early IGF-1 response to rGH therapy

Multiple studies, including those by Smyczyńska et al. (36) and Blum et al. (29) demonstrate that an early increase in IGF-1 levels during the initial phase of rGH therapy, typically within the first month, strongly correlates with improved growth outcomes over time. Specifically, significant IGF-1 elevation is associated with enhanced height velocity, indicating that the test serves not only as a diagnostic tool but also as a predictor of therapeutic success. This aligns with more recent research by Kim et al. (21) who showed that changes in serum IGF-1 and IGFBP-3 levels early in treatment were indicative of final height outcomes in children undergoing rGH therapy, reinforcing the value of these early biomarkers in predicting long-term efficacy.

Moreover, newer studies such as that by Soliman et al. (8) have expanded on this concept by demonstrating that baseline IGF-1 levels and their subsequent increase during treatment can help clinicians to tailor rGH therapy more precisely, particularly those with ISS and GHD. This tailored approach allows for a more personalized treatment regimen based on early IGF-1 responses, improving the likelihood of optimal growth outcomes. Additionally, Iwayama et al. (41) highlight the importance of IGF-1 GT in predicting the necessity of continued rGH therapy, with sustained IGF-1 improvements linked to prolonged treatment benefits, which is crucial for ensuring long-term growth in patients with ISS or GHD .

(d) Sensitivity of IGF-1 generation test (IGF-1 GT) across various growth conditions

The IGF-1 GT test exhibits high sensitivity for GHD, with sensitivity rates between 70-90%. This high sensitivity is supported by its consistent use in diagnosing childhood GHD, where a blunted IGF-1 response confirms the need for rGH therapy. Recent research supports these findings, showing the IGF-1 GT as valuable for screening GHD and minimizing unnecessary GH stimulation tests in patients with

sufficient IGF-1 levels (43). However, its sensitivity is notably lower for conditions like ISS, Laron syndrome and chronic kidney diseases (CKD), where factors like GH receptor defects or renal dysfunction affect IGF-1 levels. Studies suggest that while the IGF-1 GT is less effective in identifying GH insensitivity in these cases, other diagnostic tools, such as IGFBP-3 levels or MRI features, can enhance diagnostic accuracy (44).

In brief, this review emphasizes the need to interpret IGF-1 GT results in the context of specific growth disorders to avoid misdiagnosis.

(e) Comparison of IGF-1 generation test (IGF-1 GT) and GH stimulation test

The comparison between the IGF-1 GT and the GH stimulation test emphasizes their complementary roles in diagnosing and managing growth hormone-related disorders. The GH stimulation test remains the gold standard for diagnosing Growth Hormone Deficiency (GHD) due to its high sensitivity (90-100%) and its reliable measurement of acute GH secretion in response to pharmacological stimulation. This review, supported by recent studies, confirms that the GH stimulation test is more effective in immediate diagnostic confirmation, especially in cases where high sensitivity is essential (45,46). However, the IGF-1 GT provides additional value in assessing long-term GH axis functionality and detecting mild GH insensitivity, particularly in cases with borderline GH stimulation test results or contraindications to stimulation testing. Studies by Obara-Moszyńska et al. (46) and Haj-Ahmad et al. (47) further suggest that using the IGF-1/IGFBP-3 molar ratio can improve the diagnostic specificity of IGF-1 GT , offering a valuable complement to traditional GH testing methods (46,47).

For conditions like idiopathic short stature (ISS), combining IGF-1 measurements with biomarkers like IGFBP-3 has been shown to improve diagnostic accuracy, particularly in detecting GH insensitivity in challenging cases. Research by Giannakopoulos et al. (51) emphasizes that the components of the IGF-1 ternary complex add predictive value for growth response, especially in nuanced cases like ISS, reinforcing the IGF-1 GT utility in long-term monitoring . Additionally, recent studies by Fatani (48) suggest that in ambiguous GHD cases, a secondary GH stimulation test may enhance diagnostic reliability, while Agrawal and Smyczyńska's work (29) emphasizes the IGF-1 GT potential to monitor GH therapy and improve growth outcomes over time (43,49)

Overall, integrating IGF-1 GT data with other diagnostic markers can provide a multi-faceted approach that aligns with this review's emphasis on personalized management for pediatric growth disorders (50,51).

In Summary

This review emphasizes the diverse applications and limitations of the IGF-1 generation test across various growth and puberty-related conditions. While it has proven to be a valuable tool in diagnosing GHD, consistently demonstrating high sensitivity (70-90%) and confirming GH dysfunction, its utility is less clear in conditions like ISS, TS, and SGA, where moderate to low sensitivity is observed, particularly in cases involving GH receptor defects or syndromic conditions. The variability in IGF-1 cut-offs and test protocols across studies further complicates result interpretation, underscoring the need for standardized protocols and disease-specific cut-off values to improve diagnostic accuracy. While the GH stimulation test remains the more sensitive and definitive tool for diagnosing GHD, the IGF-1 generation test offers important insights into long-term GH axis functionality, making it a valuable complementary tool for monitoring treatment responses. Further research and refinement in test protocols, including dose standardization and cut-off values, will enhance the clinical utility of the IGF-1 generation test, improving outcomes for patients with growth disorders.

Recommendations

1. **Utilize IGF-1 generation test for GHD and partial GH insensitivity:** Clinicians should use the IGF-1 generation test to reliably confirm Growth Hormone Deficiency (GHD) before initiating therapy and to detect partial

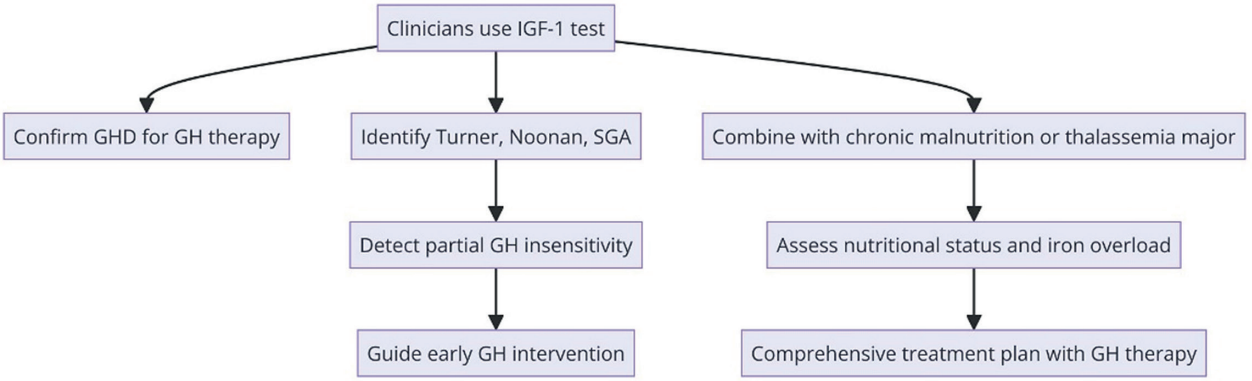

Figure 2. Recommendations for the use of IGF1 generation in different growth disorders.

GH insensitivity in conditions like Turner Syndrome (TS), Noonan Syndrome (NS), and Small for Gestational Age (SGA), helping guide early intervention for optimized growth outcomes;

2. **Standardize protocols and implement complementary testing:** Establish standardized protocols for the IGF-1 generation test, including consistent GH dosing and age-specific cut-offs, while using it in conjunction with GH stimulation tests in complex growth disorders to enhance diagnostic accuracy and ensure comprehensive GH function assessment.
3. **Tailor testing for specific conditions and underlying issues:** In patients with conditions such as chronic malnutrition or TM, the IGF-1 generation test should be combined with assessments of underlying issues, like nutritional status or iron overload, ensuring a holistic approach to treatment, integrating both rGH therapy and addressing associated health concerns (Figure 2).

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