Review

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# Tackling access and payer barriers for growth hormone therapy in Saudi Arabia: a consensus statement for the Saudi Working Group for Pediatric Endocrinology

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**Abstract:** Prompt diagnosis and early treatment are key goals to optimize the outcomes of children with growth hormone deficiency (GHD) and attain the genetically expected adult height. Nonetheless, several barriers can hinder prompt diagnosis and treatment of GHD, including payer-related issues. In Saudi Arabia, moderate-to-severe short stature was reported in 13.1 and 11.7 % of healthy boys and girls, respectively. Several access and payer barriers can face pediatric endocrinologists during the diagnosis and treatment of GHD in Saudi Arabia. Insurance coverage policies can restrict access to diagnostic tests for GHD and recombinant human growth hormone (rhGH) due to their high costs and lack of gold-standard criteria. Some insurance policies may limit the duration of treatment with rhGH or the amount of medication covered per month. This consensus article gathered the insights of pediatric endocrinologists from Saudi Arabia to reflect the access and payer barriers to the diagnostic tests and treatment options of children with short stature. We also discussed the current payer-related challenges endocrinologists face during the investigations of children with short stature. The consensus identified potential strategies to overcome these challenges and optimize patient management.

**Keywords:** barriers; growth hormone; short stature; payer; access; Saudi Arabia

## Background

Growth hormone deficiency (GHD) is a rare yet treatable cause of short stature and growth failure in pediatrics [1]. It is a multifaceted condition with a myriad of etiologies that are typically classified into congenital (such as POU1F1 and PROP1 variants), acquired (such as traumatic brain injury or tumors), and idiopathic causes [2]. While growth failures and diminished height velocity are the most prominent consequences of GHD, children with persistent GHD are prone to impaired metabolism, leading to insulin resistance, altered lipid profile, and decreased lean body mass (LBM) in adulthood [3]. GHD can also impact the cognitive and psychosocial development of children, and it is associated with memory and attention deficits, poor self-esteem, anxiety, and depression [4, 5].

Thus, early diagnosis and prompt treatment are key goals to optimize the outcomes of the affected patients and attain the genetically expected adult height [6–8]. Nonetheless, the diagnosis of GHD remains challenging due to the lack of a universally accepted cut-off value for peak GH level, introducing variability in diagnostic criteria and risks of false positives and negatives [9, 10]. Additionally, insulin-like growth factor (IGF)-1 can be affected by patient-specific factors, poor diagnostic yield in some conditions, and high variability in the reported cut-off values [1]. The treatment with recombinant human growth hormone (rhGH) therapy can be changeling due to the lack of standard criteria for

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treatment discontinuation, high rate of treatment non-adherence, and high cost [11]. GH treatment is costly, and most families cannot cover the treatment as an out-of-pocket payment. Hence, insurance companies play a vital role in treatment access [12]. Reimbursement issues can significantly hinder the appropriate management of GHD in children due to restrictive measures [13].

In Saudi Arabia, moderate-to-severe short stature was reported in 13.1 and 11.7 % of healthy boys and girls, respectively [14]. Several challenges face pediatric endocrinologists during the diagnosis and treatment of GHD in Saudi Arabia, including the genetic and ethnic variations, lack of locally-adopted diagnostic criteria, low awareness of the differential diagnosis of short stature in primary and secondary care, and the lack of well-established recommendations for the initiation and discontinuation of rhGH [15]. In addition to these challenges, access and payer barriers can significantly burden the management of GHD in Saudi Arabia [16]. Insurance coverage policies can restrict access to diagnostic tests for GHD and rhGH due to their high costs and lack of gold-standard criteria. Some insurance policies may limit the duration of treatment with rhGH or the amount of medication covered per month [17].

This consensus article gathered the insights of pediatric endocrinologists from Saudi Arabia to reflect the access and payer barriers to the diagnostic tests and treatment options of children with short stature. We also discussed the current payer-related challenges endocrinologists face during the investigations of children with short stature. The consensus identified potential strategies to overcome these challenges and optimize patient management.

# Consensus development

This consensus gathered the opinions of Consultant Pediatric Endocrinologists and representatives from insurance companies during a meeting on the 9th of March, 2023. The Saudi Working Group for Pediatric Endocrinology organized the meeting to discuss the access and payer barriers to the diagnosis, management, and insurance coverage issues related to GHD in children in Saudi Arabia. In addition to the insights gathered from the meeting, a comprehensive literature search was conducted to supplement the discussion and ensure that the consensus was based on the most recent and robust evidence. The literature search was performed using multiple databases, including PubMed, Scopus, Cochrane Central, EMBASE, and Google Scholar. The search strategy included terms related to GHD, pediatric endocrinology, diagnosis, management, and health insurance. The search was limited to articles published in English. All relevant articles, including original research, reviews, and guidelines, were included.

# Understanding pediatric GHD

## Diagnostic recommendations for GHD

Familial and constitutional factors account for the majority of short stature causes in children. Hence, evaluating a child with short stature aims primarily to identify the presence of pathologic causes, such as GHD and Turner syndrome. The classical phenotype of GHD in children involves short stature (height ≤−2 standard deviation score [SDS]), mid-facial hypoplasia, and truncal adiposity. However, a considerable proportion of children with GHD do not exhibit this classical phenotype, contributing to delayed diagnosis [2]. GHD should be suspected in children with short stature and impaired height velocity or growth failure. According to the Growth Hormone Research Society (GRS), GHD should even be suspected in children without short stature if there is a deviation in the height target or height deflection of 0.3 SDS/year [6].

Thus, auxological criteria were proposed to inform primary healthcare providers about the need for referral of children with short stature to secondary care. Table 1 shows the recommended criteria for referral by the GRS [6] and a previous consensus from the Gulf Council Cooperation (GCC) countries [15]. Children with short stature may present with clinical symptoms and signs of the underlying causes of short stature, such as dysmorphisms in genetic disorders [18].

**Table 1:** Criteria for referral for assessment of short statue.

| GRS 2019 update [6] | GCC consensus [15] |
|---|---|
| Height≤−2 SDS | Infants (<3 years old)<br>– Height SDS≤3 or<br>– Height SDS≤2 on two or more occasions within one year |
| Height<−1.5 SD below the mid-parental height | Children (3–10)<br>– Height SDS>1.6 below TH SDS; AND<br>– Height SDS≤2.5; AND<br>– Height deflection of SDS>1 over an undetermined time interval (minimum four months) |
| A height deflection of at least 0.3 SDS/year unexplained by other causes | – |
| Signs of hypoglycaemia and/or midline defects/pathologies in neonates | – |
| Signs of multiple pituitary failure | – |

In the case of clinical findings suggestive of GHD, laboratory assessment should be initiated. GH provocation tests are essential in the diagnosis of GHD and help evaluate the capacity of the pituitary gland to release GH in response to stimuli [19]. The GH peak cut-off for diagnosis is debated, between 5 and 10 μg/L [18, 20–24]. Lab discrepancies can be reduced by using standard calibration. The 22 kDa isoform is recommended as the best measurement of pituitary GH secretion [20, 25, 26].

Puberty and the use of sex steroids both cause an increase in GH secretion [27]. Guidelines recommend sex steroid priming before GH testing in prepubertal males >11 years and females >10 years to enhance GH secretion and reduce false-positive results [20], but it remains controversial due to the risk of non-physiological GH secretion causing false-negative tests [28], limiting potentially beneficial replacement therapy [21, 23].

The interpretation of GH provocative test results should incorporate other biochemical parameters, such as IGF1 and IGF binding protein 3 (IGFBP3), due to their positive correlation with GH secretion [29]. Unlike the pulsatile secretion pattern of GH, IGF1 and IGFBP3 exhibit minimal circadian variation, thereby making a single measurement of these parameters potentially more reliable than that of GH. As a result, IGF1 and IGFBP3 have been explored as potential alternatives to GH stimulation testing [30–32] and suggested as indicators of GH treatment [33]. While IGF1 has shown good to moderate specificity but low sensitivity in diagnosing GHD [23, 34], IGF1 values ≤−2.0 SDS are highly predictive of GHD, and values >0.0 SDS adjusted for age, sex, and pubertal maturation render GHD unlikely [34, 35]. Notably, the diagnostic sensitivity of IGF1 is particularly low in children who underwent cranial irradiation [36]. Conversely, IGFBP3 may offer additional diagnostic information in young children due to its correlation with integrated GH secretion [25].

While IGF1 levels are often utilized as preliminary diagnostic metrics for GHD, reliance solely on this biomarker can pose significant challenges in clinical practice [37], especially since there are no internationally accepted guidelines that recommend GH stimulation testing based on normal IGF-1 levels alone. This issue is exacerbated by the broad range of what is considered a 'normal' IGF-1 level, often spanning a wide numerical range (e.g., 110–500) [37], leading to misleading interpretations. Moreover, most laboratory tests do not adjust IGF-1 levels based on the patient's stage of pubertal maturation – a significant oversight given that many physicians also do not specify this stage when requesting tests. As such, a 'normal' IGF-1 result may not be universally applicable or informative, raising concerns about the adequacy of using IGF-1 as the sole criterion for approving or denying further GH testing.

To ensure accurate diagnosis, excluding other medical conditions that may present with similar clinical features as GHD is essential. Thyroid function tests, for instance, are vital as hypothyroidism can mimic GHD due to its similar growth-retarding effects [38]. Additionally, a complete blood count and erythrocyte sedimentation rate may help identify chronic diseases or inflammatory conditions that can adversely affect growth [39]. Serum electrolytes, calcium, and phosphorus levels, alongside renal function tests, can aid in excluding renal disorders, which are often associated with poor growth [40]. Genetic testing may also be warranted in certain cases to rule out genetic syndromes associated with short stature, such as Turner syndrome or Prader–Willi syndrome [41, 42]. Bone age radiographs are further instrumental in differentiating between GHD and familial short stature, the latter being a common benign cause of short stature in children [43]. Moreover, a thorough endocrinological evaluation, including adrenal function tests, is crucial to exclude other endocrinopathies that could manifest as impaired growth [44]. By using a comprehensive battery of tests, clinicians can ensure accurate diagnosis and optimal management of growth disorders in children.

## Clinical indications for GH therapy

The United States Food and Drug Administration (FDA) has approved the use of GH therapy for a variety of pediatric conditions, with GHD being the most common indication [20]. Additionally, GH therapy is approved for treating genetic conditions like Turner syndrome and Prader–Willi syndrome, both of which result in short stature and delayed development [45–47]. It has also shown promise in promoting growth for children suffering from chronic renal insufficiency, a condition often associated with growth failure [48, 49]. Furthermore, children born small for gestational age (SGA) who do not achieve catch-up growth by the age range of 2–4 years can benefit from GH treatment [50, 51]. The therapy is also applicable for cases of idiopathic short stature, where the cause of growth failure is unknown [20, 52]. Another genetic condition that results in short stature, SHOX deficiency and, recently, Noonan syndrome, can also be effectively managed through GH therapy [53, 54]. This regulatory approval highlights the diverse applicability and therapeutic benefits of GH therapy across a spectrum of pediatric growth disorders.

In addition, there are relative clinical indications for GH therapy. These include conditions where GH therapy may be beneficial but is not approved by the US. FDA. These include Down syndrome, cystic fibrosis, neurofibromatosis type 1, and cerebral palsy [55–58].

In Saudi Arabia, insurance companies approve GH therapy treatment on an individualized basis, and there is a lack of clear guidelines for insurance companies in Saudi Arabia regarding the approval of GH therapy for patients with GHD. There is a considerable variation in the indications of GH therapy among insurance companies in Saudi Arabia.

## Breakthroughs in growth hormone deficiency (GHD) treatment

In recent years, a significant breakthrough in GHD treatment has been observed. Notably, the advent of longer-acting formulations, such as Jintrolong, Lonapegsomatropin, Somapacitan, and Somatrogon, has revolutionized the therapeutic landscape by providing patients with a more convenient and less frequent dosing regimen [59, 60]. Unlike traditional short-acting GH formulations requiring daily injections, these new formulations offer weekly or bi-weekly dosing schedules, improving patient compliance and quality of life [61]. Furthermore, non-invasive and patient-friendly options have been developed in non-injection delivery systems, such as the inhaled, transdermal, and oral routes [62, 63]. In Saudi Arabia, insurance companies offer long-acting GH. However, if the insurance agreement excludes endocrine disorders, the budget is generally restricted to GHD only.

The concept of combination therapies and genetic therapies has also enhanced the paradigm of GHD treatment. Combination therapies address the multiple hormonal deficiencies often associated with GHD by co-administering GH with other hormone replacement therapies, such as thyroid hormone, sex hormones, or corticosteroids, thus providing a more comprehensive treatment approach [64, 65]. Genetic therapies, on the other hand, hold promise for treating GHD at its root cause. Gene therapy, employing vectors to deliver functional genes, can correct the underlying genetic defects causing GHD [66]. As science and technology continue to evolve, the future of GHD treatment appears promising, characterized by more efficient, convenient, and comprehensive therapeutic strategies.

# Access barriers to diagnostic tests

## Insurance coverage

The experts highlighted that insurance companies often refuse to perform provocative GH testing, which represents the main diagnostic barrier in Saudi Arabia. The high rejection rate is attributed to several factors. One of these factors is the high cost of diagnostic tests for GHD, such as GH provocation tests or measuring IGF-1 levels (Table 2). The mainstay of GHD diagnosis – GH provocation tests and measurement of IGF-1 levels – are notably expensive. These high costs, compounded by the need for frequent IGF-1 testing to monitor the disease course and response to treatment, can place a considerable financial burden on individuals and families, especially when health insurance companies deny testing [67]. Moreover, the cost-sharing models prevalent in many health policies may still present a prohibitive expense for many families [68]. Efforts to mitigate these financial barriers could include health policy reforms to expand insurance coverage for GHD diagnostic tests and related procedures [69]. Additionally, implementing cost-effective strategies in healthcare delivery could reduce the overall cost burden [70].

**Table 2:** Experts' insights on the insurance-related access barriers to the diagnosis.

| Barriers to insurance coverage |
|---|
| 1. Insurance companies often refuse to perform provocative GH testing, which represents the main diagnostic barrier in Saudi Arabia. The high rejection rate is attributed to several factors. |
| 2. Diagnostic tests for GHD, such as GH provocation tests or measuring IGF-1 levels, can be expensive. The cost of these tests may pose a financial burden for individuals or families without adequate insurance coverage. |
| 3. Insurance companies frequently deny GH stimulation testing if IGF-1 levels are within the 'normal' range, even though normal IGF1 encompasses a wide range (e.g., 110–500). |
| 4. Lack of clear policy or guidelines for approving GH stimulation tests for short-stature pediatric patients |
| 5. Diagnosis of GHD relies on assessing multiple factors, including clinical evaluation, growth parameters, and other laboratory tests. This dependence on multiple factors can lead to further challenges in gaining approval from insurance companies. |
| 6. Clinicians often have to provide repeated justifications and rationale for requesting GH stimulation tests, even multiple times, without guaranteeing approval. |
| 7. Insurance companies often reject requests for laboratory tests to exclude other conditions that could cause short stature, further exacerbating the diagnostic dilemma for patients suspected of GHD. |
| 8. There is a lack of standardized, unified recommendations among insurance companies for diagnosis and treatment of short stature. |

Another factor contributing to the high rejection rate is the wide range of "normal" IGF-1 tests. Insurance companies in Saudi Arabia decide on GH provocation testing based on the results of IGF-1 in most cases; they frequently deny GH stimulation testing if IGF-1 levels are within the "normal" range, even though normal IGF1 encompasses a wide range (e.g., 110–500) [37]. This creates a substantial barrier to accurate diagnosis, particularly for children who may be notably shorter than their peers (Table 2). Moreover, IGF-I

and IGFBP-3 have demonstrated limited sensitivity despite their high specificity for GHD [71, 72]. The difficulty of interpreting IGF-1 levels in infants under three years of age is recognized, and IGFBP-3 may be of greater value for diagnosing GHD in these subjects [73]. Furthermore, their efficacy is compromised by factors such as food intake, chronic nutritional status, and issues related to assay precision [74].

In addition, the diagnosis of GHD deficiency can be challenging due to the shortcomings of the provocative GH testing [75]. The interpretation of GH provocation test results can be challenging due to a significant number of false-positive outcomes, indicating low specificity and poor reproducibility [22, 76]. These challenges stem from several factors, including the non-physiological nature of the stimuli, which fails to replicate the normal secretory dynamics. Additionally, the periodic secretion of somatostatin may influence the response of somatotrophs [77]. Moreover, various other factors such as obesity, undernutrition, sex, age, and puberty have an impact on GH secretion [78]. For instance, GH responses to stimulation tests tend to decrease with increasing body mass index (BMI) [79]. The reproducibility of these tests is also questionable, with various studies indicating inconsistencies in repeated test results on the same subject using diverse stimuli [80]. The GH assays exhibited variable reactivity to different GH isoforms, leading to significant discrepancies in results from different commercial assays [81, 82]. In return, several cut-off values have been reported for the GH provocative tests to define GH deficiency, and it was reported that the GH stimulation test poorly differentiates between GHD and other related conditions [83–85].

Owing to these limitations, the experts stated that the approval of payers and insurance companies for diagnostic tests for GHD in pediatric patients is inconsistent (Table 2). This inconsistency is observed among different insurance companies and within the same company. Consequently, healthcare providers are often left in a difficult position, navigating the complicated insurance landscape to secure approval for necessary tests. This lack of uniformity significantly hinders the timeliness and accessibility of GHD diagnosis. A contributing factor to this inconsistency is the absence of clear policies or guidelines regarding the approval of GH stimulation tests for pediatric patients. Without standardized guidelines, it becomes difficult for clinicians to understand the specific criteria needed to secure approval for diagnostic tests. As a result, pediatric patients may face delays or even denial of important diagnostic services. The inconsistency in the approval process and policies can lead to inequity in access to GHD diagnostic tests. Some insurance plans may not fully cover these diagnostic procedures, leading to significant out-of-pocket costs for families [86].

Another issue arises from the fact that the diagnosis of GHD relies on a thorough evaluation of multiple factors, including clinical presentation, growth parameters, and various laboratory tests. As such, insurance companies often require evidence from multiple sources in case of abnormal IGF-1, further complicating the approval process and delaying diagnosis [75, 85]. Compounding these challenges is the frequent requirement for clinicians to provide repeated justifications for requesting GH stimulation tests. This cycle can cause significant delays, affecting the timeliness of GHD diagnosis and potentially delaying the start of necessary treatments (Table 2).

Lastly, insurance companies often reject requests for laboratory tests to exclude other conditions that could cause short stature, further exacerbating the diagnostic dilemma for patients suspected of GHD. These tests are essential in differential diagnosis, helping to rule out other potential causes of growth issues and to affirm GHD [38–40]. Without approval for these tests, clinicians may face significant difficulties in establishing a firm GHD diagnosis (Table 2).

## Healthcare system-related barriers

The lack of awareness among healthcare providers and patients regarding the importance of early identification is one of the major issues in the diagnosis and management of GHD [87]. The clinical presentation of GHD can be subtle, often resulting in it being overlooked during routine pediatric evaluations. Additionally, the nonspecific nature of symptoms can lead to misdiagnosis or delay in seeking appropriate help [75]. The responsibility for evaluating GHD in children lies primarily on general pediatricians or family physicians, who are typically referred infants or children identified as short in primary care settings. Nevertheless,

**Table 3:** Experts' insights on the healthcare system-related access barriers to the diagnosis.

| Barriers related to the healthcare system |
|---|
| 1. There could be a lack of awareness among healthcare providers and patients about the importance of early diagnosis of GHD. This can result in delayed or missed opportunities for testing. |
| 2. Specialists who perform GHD diagnostic tests may not be readily available in all areas, especially in less populated regions. This can create access challenges for individuals who need these tests but cannot access specialized healthcare providers easily. |
| 3. Even when the tests are available, there may be long wait times for appointments or test scheduling, further delaying the diagnostic process. |

experts have noted an opportunity for enhancing the level of education and expertise among general pediatricians in the specialized area of childhood growth and growth disorders (Table 3). It is essential to prioritize medical education to equip pediatricians with the necessary skills in clinical assessment, including history taking, physical examination, height measurement techniques, and the use of growth charts [15]. Some studies suggest an urgent need for better education and training among healthcare providers to improve recognition and understanding of this condition and expedite referral to specialist services [88].

The availability of specialists trained to diagnose GHD in children is a major factor affecting the accessibility of diagnostic testing, particularly in rural or less populated areas, as stated by Saudi experts (Table 3). In several regions, there is a noticeable gap in the availability of specialized centers (such as King Abdulaziz Medical City in Jeddah) for conducting and interpreting advanced endocrine tests like the GH stimulation test [15]. This scarcity of specialists can create health disparities among pediatric populations, where children from urban areas, where the concentration of healthcare providers is relatively high, can readily access diagnostic tests, while those in rural locations cannot [89]. This regional imbalance contributes to an uneven distribution of healthcare resources, exacerbating existing inequities in healthcare access [90].

Attempts to bridge these gaps, including telemedicine and mobile diagnostic units, have demonstrated some success but are not without their own set of challenges [91]. Telemedicine, for instance, has shown potential in providing families in remote locations access to pediatric endocrinology consultations [92]. However, technical limitations, lack of familiarity with digital platforms among patients and physicians, and unresolved questions around reimbursement and legal issues present barriers to its widespread adoption [93]. Therefore, while innovative solutions show promise, more comprehensive efforts are needed to ensure equitable access to GHD diagnostic tests across various regions.

Long wait times for appointments and test scheduling pose another substantial barrier to promptly diagnosing GHD in children (Table 3). According to the literature, the prolonged wait times can be attributed to several factors, including a shortage of specialists, high demand for services, and inefficiencies in the healthcare system [94]. Therefore, children with suspected GHD often encounter significant delays before they can receive diagnostic testing, leading to the potential progression of their condition and delayed start of necessary treatment [75].

Efforts to shorten the waiting times include refining scheduling procedures, increasing workforce capacity, and adopting new technologies or strategies to enhance efficiency [95]. However, these initiatives require further validation and wider implementation. As in the case of the limited availability of specialists, innovative solutions such as telemedicine may also play a role in addressing this issue. It has been demonstrated to be particularly effective in reducing wait times in other areas of pediatric medicine, potentially providing a framework for its application in pediatric endocrinology [96].

## Access barriers to GH therapy

As previously mentioned, the indications of rhGH have substantially expanded over the past few decades from GHD to include idiopathic short stature and short stature with SGA, among others [97]. However, the prescription of rhGH is a shared decision-making between pediatric endocrinologists and healthcare payers. From a payer perspective, the rejection of GH therapy can be broadly attributed to the variations in insurance policies and cost-containment strategies [98].

### Barriers related to insurance policies

The current evidence suggests diverse criteria for the identification of potential candidates for GH therapy. While there is little disagreement regarding the use of rhGH in classical GHD, debate still exists regarding the use of GH therapy in children with non-GHD short stature [99]. Additionally, the response to GH therapy was found to vary between patients according to age, sex, and indications, among other factors [100]. A considerable proportion of children with GHD show a poor response (defined as an increase in height SDS<0.3 or <0.5; an increase in HV<3 cm/year; and/or an increase in HV SDS<+1 SD compared with healthy children the same age and sex [101]) to rhGH; however, there is a lack of validated criteria to predict response to GH therapy, adding another management dilemma [15, 102]. In a nationwide survey, nearly 90 % of pediatric endocrinologists stated that there is no universal consensus for factors predicting response to GH therapy [103].

With the lack of universal criteria and the views that rhGH is a life-enhancer medication that does not treat life-threatening conditions, payers may restrict GH therapy access and limit the approval rate [104–106]. Interestingly, a previous report investigated the discrepancy between physician recommendations and private insurance decisions regarding rhGH for children with short stature. The results showed that 28 % of the physician-recommended

rhGH was rejected by insurance companies. The discrepancy rate was even higher for nontraditional indications of rhGH, such as idiopathic short stature. This was attributed mainly to the substantial variations in the insurance policies for covering non-GHD conditions, leading to discrepancies in treatment access [17].

Insurance companies typically have internal review processes and policies to approve rhGH treatment, particularly for nontraditional indications where guidelines and consensus are lacking. A retrospective review of claim databases by Grimberg and Kanter found that insurance coverage of GH therapy for idiopathic short stature varies widely across the US. Some insurance plans cover the full cost of treatment, while others only cover a portion of the cost or do not cover the treatment at all [107]. This inconsistency in coverage can create disparities in access to GH therapy, with individuals in lower-income households being less likely to receive treatment. Even when insurance plans cover GH therapy, there can be significant barriers to access. These can include strict eligibility criteria, lengthy approval processes, and the requirement for frequent monitoring and re-approval of treatment. It was also previously reported that insurance coverage may disagree with physician recommendations regarding the dose and frequency of GH therapy [13]. These barriers can delay or prevent individuals from receiving the necessary treatment.

In Saudi Arabia, insurance companies approve GH therapy treatment on an individualized basis, considering the provided data and the proposed guidelines. However, consultant endocrinologists stated that there is a lack of clear guidelines for insurance companies in Saudi Arabia regarding the approval of GH therapy for patients with GHD (Table 4). This can create a significant barrier when prescribing rhGH. The varied policies can lead to confusion and uncertainty for patients and healthcare providers, as they may need to navigate different requirements and processes for each insurance company. The authorization process can be time-consuming, leading to delayed approval of GH therapy. Additional insurance-driven barrier to rhGH access is the need for documented evidence of GHD diagnosis. While this requirement is understandable from a medical and financial perspective, it can also create barriers, which were discussed in Access barriers to diagnostic tests. The requirement for multiple tests to confirm the diagnosis may delay the initiation of treatment.

**Table 4:** Experts' insights on the insurance-related access barriers to GH therapy.

| Barriers to treatment access |
|---|
| 1. Insurance companies often have their own coverage policies and criteria for approving GHD treatment. |
| 2. Many insurance companies require documented evidence of GHD diagnosis, often through GH stimulation tests, before approving treatment, even for conditions that do not need GH stimulation test, such as Turner syndrome, SGA, and kidney insufficient. |
| 3. Delays in approval can occur depending on the complexity of the case or insurance company procedures. |
| 4. Insurance companies may also take into account cost considerations when reviewing and approving GHD treatment. |

## Cost-related barriers

In terms of treatment cost, rhGH is a highly expensive medication, despite its cost-effectiveness compared to no treatment [108], due to its complex production process. The cost of GH therapy can range from USD 10,000 to 60,000 per year, depending on the dosage and the specific GH product used. Previous reports estimated that rhGH costs nearly USD 14,000 per child weighting <20 kg [17]. Recent reports from Saudi Arabia showed that rhGH costs nearly USD 1,717 and 2,820 per centimeter gained in children with GHD and SGA, respectively; these figures were based on the prices listed by the Saudi FDA, and it is expected to be 20 % higher in patients treated in private settings [109]. Meanwhile, the cost of a 10 mg pen of long-acting rhGH is USD 267 in Saudi Arabia. Hence, most families may find it difficult to cover the cost of treatment as an out-of-pocket payment. In agreement with the previous consensus from GCC countries [110], experts highlighted that the high cost of rhGH serves as a significant barrier to prescribing the therapy for children with growth disorders and to securing insurance approval, thereby leading to more restrictive approval procedures (Table 4).

## Barriers related to treatment duration

Several studies highlighted the importance of early initiation of GH therapy [111, 112]. However, the long-term effects of GH therapy remain a subject of debate. Some studies reported positive outcomes for short stature in children with SGA and that the growth effect increased following dose escalation, even in the low responders in the initial two-year treatment, indicating the effectiveness of dose escalation [113, 114]. On the contrary, a systematic review found that while treatment with rhGH improves short-term linear growth, its long-term effect is inconsistent, and the treatment duration should be individualized according to the patient's response [115]. With the lack of consistent long-term data, the Saudi expert stated that insurance companies may be reluctant to cover long-term GH therapy. Even when GH therapy is covered by

insurance, there may be limitations on the duration of treatment. Some insurance policies may only cover treatment until the child reaches a particular age (15 years for boys and 13 for girls) or height or until bone growth plates have closed. This can lead to premature discontinuation of treatment, potentially limiting the effectiveness of the therapy (Table 4).

## Call for action

Several strategies are needed to overcome the access barriers faced by children with GHD or non-GHD short stature indicated for rhGH therapy (Figure 1). Raising awareness about the importance of early diagnosis and treatment of GHD among healthcare providers, patients, and insurance companies is crucial to ensure optimal patient outcomes. An adequate awareness can improve treatment access and maintain uninterrupted GH therapy for patients with documented GHD. Likewise, educating insurance companies about the benefits and long-term cost-effectiveness of timely GHD diagnosis and treatment is another important strategy. RhGH has several metabolic benefits, including an increase in resting metabolic rate (RMR) and fat-free mass and a decrease in fat mass, as well as increased insulin sensitivity and dose-dependent increase in IGF-1 [116, 117]. Timely diagnosis and treatment of GHD can potentially lead to significant cost savings in the long run by reducing the need for additional healthcare services and improving patient outcomes. Interestingly, untreated GHD was found to be associated with higher non-GH healthcare costs than treated GHD [118].

Another crucial strategy is to work toward standardized guidance for insurance coverage policies. In response to the variations in insurance policies and procedures, the Saudi Council of Health Insurance (CHI) is working on streamlining the approval processes to increase their efficiency. This regulatory effort is expected to reduce the time taken for treatment authorization, thereby facilitating quicker access to necessary healthcare services. Furthermore, the CHI is encouraging scientific societies to submit their guidelines for endorsement. These guidelines, particularly those related to

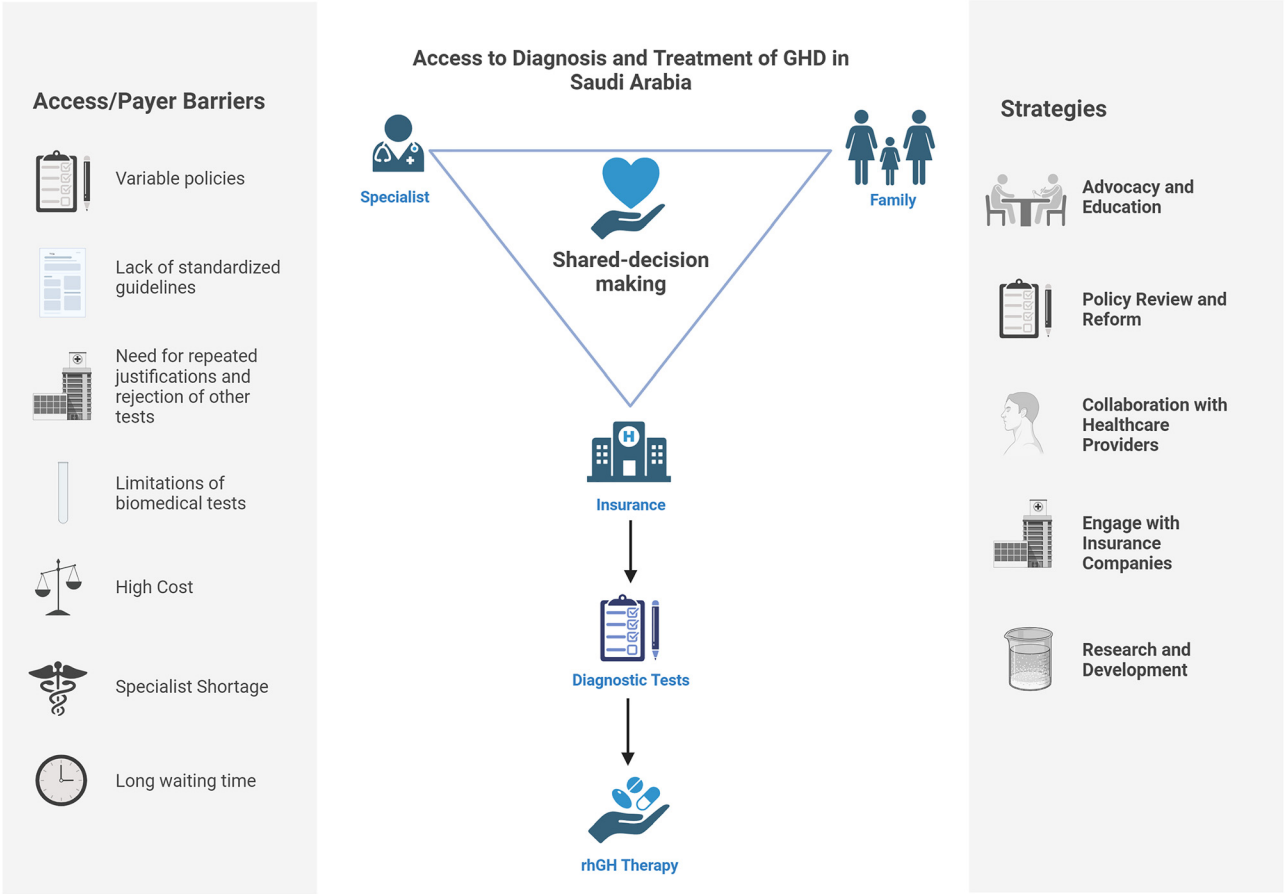


**Figure 1:** Barriers to access to diagnostic tests and GH therapy in Saudi Arabia and strategies to overcome them. Created with BioRender.com.

GHD diagnosis and treatment, are requested in an easy-to-follow algorithm format. This approach is intended to simplify the understanding and application of these guidelines, making it easier for insurance companies to review and approve treatments. Identifying gaps, inconsistencies, or restrictive criteria that hinder access to proper diagnosis and treatment is another key strategy. Developing recommendations for policy reforms to improve coverage for GHD diagnostic tests and treatment is also important.

However, engaging with insurance companies to implement these guidelines and policy reforms is a multifaceted approach that should involve several key steps. It is important to standardize and unify the diagnostic approach and provide recommendations to start and stop rhGH in children and adolescents with SS among all insurance companies in Saudi Arabia. Hence, the first step is establishing communication channels with insurance company representatives to discuss the importance of GHD diagnosis and treatment. Building a relationship with insurance companies can help to ensure that they understand the needs of patients with GHD and are willing to consider changes to their coverage policies. Once these communication channels have been established, supporting the argument for early diagnosis and treatment of GHD with evidence-based literature and data is crucial. This can be followed by advocacy efforts to simplify the insurance approval process and remove restrictive criteria.

It is worth noting that engaging with insurance companies should be coupled with fostering partnerships and collaborations with healthcare providers to ensure streamlined referral pathways and efficient coordination for GHD diagnosis and treatment. In addition, disseminating evidence-based guidelines and best practices should involve healthcare providers to promote standardized approaches for diagnosis and treatment.

Lastly, supporting and encouraging research efforts to further understand and improve diagnosis techniques and treatment efficacy for GHD is a crucial strategy. Research is pivotal in enhancing our understanding of GHD, refining diagnostic techniques, and improving treatment efficacy.

## Conclusions

In conclusion, children with GHD or other conditions resulting in short stature who are candidates for rhGH therapy may encounter several barriers to treatment access in Saudi Arabia. Insurance policies can significantly delay both diagnostic testing and the timely initiation of therapeutic interventions. Moreover, insurance companies often reject GH provocation test due to high cost or inaccurate IGF-1 results, which represent major access barriers for GHD diagnosis in Saudi Arabia. Several strategies are needed to overcome these barriers and ensure timely diagnosis and treatment, leading to optimal growth outcomes and long-term cost savings by reducing the need for additional healthcare services.

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