



# Need for improved monitoring in patients with acromegaly

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## Abstract

Acromegaly is a rare and insidious disease characterized by the overproduction of growth hormone (GH) and insulin-like growth factor 1 (IGF1) and is most commonly due to a pituitary adenoma. Patients with acromegaly who experience prolonged exposure to elevated levels of GH and IGF1 have an increased mortality risk and progressive worsening of disease-related comorbidities. Multimodal treatment with surgery, medical therapy, and radiotherapy provides biochemical control, defined by recent acromegaly clinical guidelines from the Endocrine Society as a reduction of GH levels to  $<1.0$  ng/ml and normalization of IGF1 levels, to a substantial proportion of patients and is associated with improved clinical outcomes. Patients with acromegaly, even those without clinical symptoms of disease, require long-term monitoring of GH and IGF1 levels if the benefits associated with biochemical control are to be maintained and the risk of developing recurrent disease is to be abated. However, suboptimal monitoring is common in patients with acromegaly, and this can have negative health effects due to delays in detection of recurrent disease and implementation of appropriate treatment. Because of the significant health consequences associated with prolonged exposure to elevated levels of GH and IGF1, optimal monitoring in patients with acromegaly is needed. This review article will discuss the biochemical assessments used for therapeutic monitoring in acromegaly, the importance of monitoring after surgery and medical therapy or radiotherapy, the consequences of suboptimal monitoring, and the need for improved monitoring algorithms for patients with acromegaly.

## Key Words

- ▶ rare disease/syndromes
- ▶ neuroendocrinology
- ▶ growth factors

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## Introduction

Acromegaly is a rare hormonal condition that develops most commonly from benign somatotroph pituitary adenomas and has a prevalence of 36–69 cases per million and an incidence of 3–4 cases per million per year (1, 2, 3, 4). However, prevalence estimates between 115 and 295 cases per million have been reported (5). Acromegaly remains an underdiagnosed and under-recognized disease, with mean times to diagnosis of ~7 to 10 years having been reported (6, 7). The clinical manifestations associated with acromegaly are a consequence of the chronic

overproduction of growth hormone (GH) and insulin-like growth factor 1 (IGF1) (1, 8). Systemic complications commonly associated with the chronic hypersecretion of GH and IGF1 include visceromegaly, arthralgia, and soft tissue changes, and comorbidities include hypertension, type 2 diabetes, sleep apnea, and carpal tunnel syndrome (2, 9, 10). If left untreated, long-term exposure to GH/IGF1 hypersecretion in patients with acromegaly can be associated with increased morbidity and mortality risk, worsening comorbidities, and poor health-related quality



of life (11, 12, 13). Additionally, studies have reported that persistent exposure to elevated hormone levels can be associated with a worsened psychosocial profile (14). This includes increased anxiety, body image distortion, depression, impaired short- and long-term memory, and social withdrawal.

Surgery, medical therapy, and radiotherapy are the current multimodal treatment options available for the management of acromegaly (1). The overall therapeutic goals include improving control of GH and IGF1 levels, decreasing tumor volume, improving signs and symptoms of the disease, lowering mortality risk, and managing comorbidities (1, 15). The aforementioned multimodal treatment approaches provide biochemical control to a large number of patients, and this biochemical control is associated with the normalization of mortality risk (1, 16). However, a substantial proportion of patients do not achieve biochemical remission despite surgery, medical therapy, and/or radiotherapy, or they experience recurrent disease following treatment (17). For these patients, monitoring is essential to detect active disease (15, 18, 19). Additionally, for patients who have achieved normal hormonal levels after multimodal treatment, active monitoring is essential to follow the effects of therapy and maintain their benefit. Furthermore, detection of persistent or recurrent disease is compromised when patients are not properly monitored. For example, higher rates of active disease have been reported in a small study in patients with suboptimal monitoring who were lost to follow-up (20). Similarly, in a large cohort study, a proportion of patients lost to follow-up had not received optimal monitoring and follow-up care (21). The lack of monitoring can have deleterious long-term consequences due to continued exposure to elevated levels of GH and IGF1. This review article will discuss current monitoring recommendations, highlight the significant levels of suboptimal monitoring in patients with acromegaly, and discuss the consequences of suboptimal monitoring and potential options for improving monitoring in these patients.

### Role of monitoring in acromegaly

In addition to tumor control, the goal of therapy for patients with acromegaly is to achieve biochemical control by reducing GH levels and normalizing IGF1 levels, which are associated with improved mortality (1, 22). Monitoring of hormone levels (GH and IGF1) serves a number of important roles, including the assessment of treatment effectiveness and detection of persistent or recurrent acromegaly.

The biochemical parameters that constitute controlled disease, which is defined as the control of GH levels and normalization of IGF1 levels, have been a topic of discussion for more than a decade, and the criteria for GH control and normalization of IGF1 levels have changed over time (23). As set forth by the Acromegaly Therapy Consensus Development Panel of 1993, the earliest definition considered controlled acromegaly to be GH levels <2.0 ng/ml after an oral glucose tolerance test (OGTT) and serum GH levels <2.5 ng/ml, as well as the normalization of circulating levels of free and total IGF1 (24). These consensus criteria proposed, for the first time, that serum GH levels should be less than 2.5 ng/ml, which is a level that has been associated with the normalization of the mortality risk to a risk level similarly observed in the control population, as was demonstrated by the results of a meta-analysis study in acromegaly (16). However, with the advent of more sensitive assays to detect GH and IGF1 levels, more stringent definitions of biochemical control in patients with acromegaly have been proposed by various groups (1, 23, 25). According to guidelines from the American Association of Clinical Endocrinologists (AACE), patients with acromegaly who demonstrate GH levels <1.0 ng/ml after OGTTs and/or have random fasting GH levels of <2.5 ng/ml, as well as age-adjusted normal levels of IGF1, are considered to have biochemically controlled disease (1). Because of the higher sensitivity of current GH assays, a reduced cutoff of 0.4 ng/ml for the serum GH nadir is recommended but has not been officially adopted (1, 22). However, recent clinical guidelines from the Endocrine Society (ENDO) indicate that a serum GH level of <1.0 ng/ml and an age-adjusted normal serum level of IGF1 signify controlled disease (26). The AACE guidelines and the consensus criteria also established, for the first time, that a composite endpoint should be used for the monitoring of active acromegaly (Fig. 1).

There are important benefits associated with the assessment of composite biochemical endpoints. Monitoring both GH and IGF1 levels provides complementary information regarding residual tumor activity (GH) and overall disease activity (IGF1) (27, 28, 29). Additionally, the evaluation of these biomarkers is the most direct method of detecting persistent or recurrent disease in patients with acromegaly following surgery, medical therapy, and/or radiotherapy. The current monitoring recommendations for patients with acromegaly who undergo multimodal treatment are discussed in the following sections.

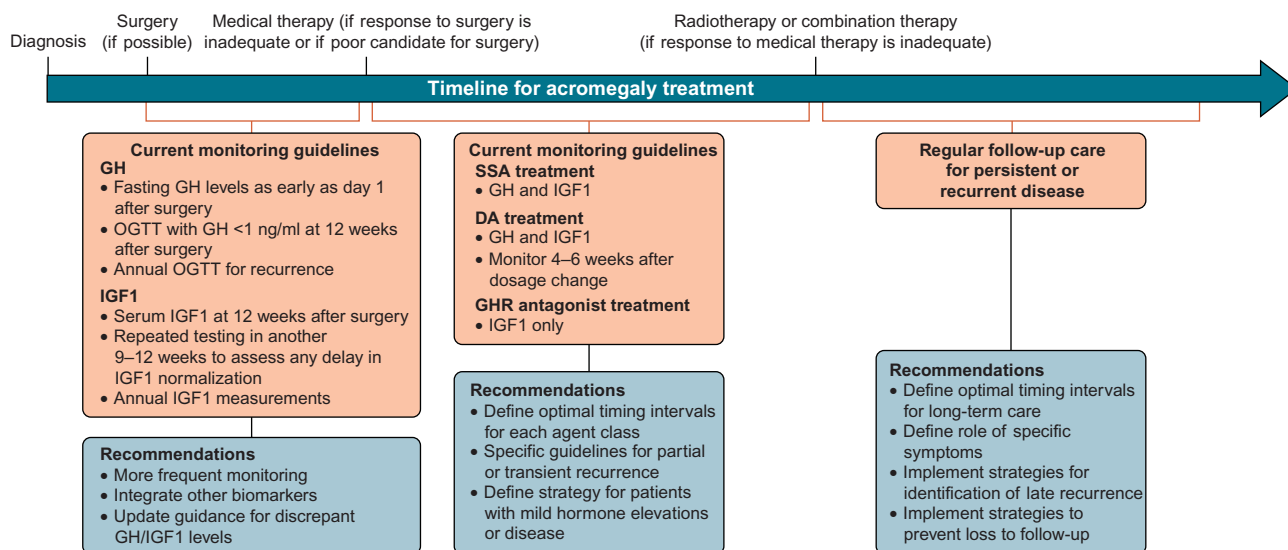


Figure 1

Guidelines and recommendations for improvement in monitoring (1, 15, 26). DA, dopamine agonist; GH, growth hormone; GHR, growth-hormone receptor; IGF1, insulin-like growth factor 1; OGTT, oral glucose tolerance test; SSA, somatostatin analog.

## Current recommendations for monitoring

Clinical guidelines from AACE (1) and ENDO (26) provide the most recent criteria for the management of patients with acromegaly.

### Postsurgery

Transsphenoidal surgery is the first-line treatment for patients with acromegaly and provides biochemical control in >80% of patients with microadenomas and in 40–50% of those with macroadenomas, with the control rates depending on the expertise of the neurosurgeon performing the procedure (1, 8, 9). Postsurgical biochemical monitoring of both GH and IGF1 levels in patients is critical for appropriate clinical management and, if necessary, for guiding additional treatment (1, 22). The AACE and ENDO clinical guidelines recommend that serum IGF1 levels should be measured postoperatively at 12 weeks, while repeat testing should be considered in another 9–12 weeks, because a delay in normalization of IGF1 levels may occur (1, 22, 26). Additionally, AACE guidelines recommend that fasting GH levels can be measured as early as the first day after surgery (1). An OGTT that indicates GH levels of <1.0 ng/ml at 12 weeks after surgery is indicative of surgical remission. By contrast, ENDO guidelines define

serum GH of <0.14 ng/ml as achieving surgical remission and serum GH <1.0 ng/ml as indicating surgical control and normalization of mortality risk. Furthermore, assessing a random GH at 12 weeks or later is recommended, because an immediate postoperative evaluation may have limited value due to increased GH levels reflective of surgical stress (26). However, if the patient's GH level is >0.4 ng/ml following surgery, a measurement of GH after a glucose load may be helpful to further guide treatment decision making.

Because up to 20% of patients who achieve post-surgical biochemical remission will have recurrent disease, careful monitoring is needed (30). According to AACE clinical guidelines, all patients should have IGF1 levels assessed annually, at a minimum, because recurrence has been reported 10–20 years after surgical cure (1). Additionally, annual OGTTs may also be performed in patients to assess for recurrence of acromegaly.

In most cases, both GH and IGF1 test results are in concordance. However, up to 35% of patients with active acromegaly have demonstrated discrepant GH and IGF1 test results after surgery (31). The most common discordant results involve elevated IGF1 levels despite GH suppression, while normal IGF1 levels with abnormal GH suppression are infrequently observed (1, 9, 27). The AACE and ENDO guidelines do not provide specific recommendations regarding the management of patients

with discordant GH and IGF1 levels following surgery (1, 26). However, recent consensus criteria suggest that, in the presence of elevated IGF1 levels at 3–6 months after surgery, repeated testing of GH with an OGTT and multiple GH sampling (3–5 times over 2 h) should be performed (22). It has also been suggested that repeated testing of GH and IGF1 levels should be implemented 3 or 4 months after a discrepant result for the determination of possible causes (27). In instances in which the cause of a discrepant result cannot be determined, it has been suggested that IGF1 levels should guide further monitoring and treatment decisions. The fact that there is no single consensus on the proper clinical course for patients with discrepant test results underscores the need for periodic monitoring of both GH and IGF1 levels and appropriate interpretation of discordant hormonal values, as these might signify mild disease activity and changes in disease status. Additionally, it highlights the need for the improvement of current monitoring algorithms for patients with acromegaly.

### Patients receiving medical therapy

Medical therapy is an option for patients who do not achieve biochemical control with surgery and for patients who are poor surgical candidates (1). There are currently three classes of medications available for the treatment of patients with acromegaly: somatostatin analogs (SSAs), dopamine agonists, and GH-receptor antagonists (15). Medical therapy, most commonly SSAs, is effective in achieving biochemical control in a substantial proportion of patients with persistent or recurrent disease following surgery and in those who do not undergo surgery (1). Depending on the class of medical therapy used, biochemical monitoring of GH and/or IGF1 levels is recommended for assessing treatment response and guiding therapeutic decisions.

For patients with acromegaly who are treated with SSAs, which target the pituitary tumor directly, AACE guidelines recommend that both GH and IGF1 levels should be monitored for assessing response to treatment (1). Octreotide short-acting injection, octreotide long-acting release (LAR), lanreotide Autogel (Ipsen Biopharmaceuticals Inc, Basking Ridge, NJ, USA), and pasireotide LAR are the currently available SSAs approved by the Food and Drug Administration for the treatment of patients with acromegaly (32, 33, 34, 35). Approximately 50% of patients with acromegaly achieve biochemical control with lanreotide as secondary therapy, and ~60–70% achieve biochemical control with octreotide administered

after surgery, radiotherapy, or treatment with other medical therapy; reductions in tumor volume have been reported in ~40–90% of patients (36). For patients who achieve long-term control with SSAs, continued and lifelong monitoring of GH and IGF1 levels is essential if the benefits associated with therapy are to be sustained (1, 22). Conversely, patients with inadequate response to SSA therapy will require additional treatment and further biochemical monitoring, particularly if dosage increase with current SSAs or combination treatment of SSAs with other medical therapy is considered (1). Monitoring of adverse events (AEs) is also recommended when using SSAs, particularly monitoring for gastrointestinal disorders, which are the most commonly reported adverse reactions (32, 33, 34, 35). Additionally, because treatment with pasireotide LAR can induce hyperglycemia, it is recommended that patients on pasireotide LAR be monitored periodically for changes in glucose levels during therapy, as well as following initiation and discontinuation of therapy (32). Patients who develop significant hyperglycemia while on pasireotide LAR should initiate or adjust the dose or type of antidiabetic therapy or adjust the dose of or discontinue treatment with pasireotide LAR. ENDO guidelines indicate that efficacy of SSAs should be based on the assessment of GH and IGF1 levels; however, no specific recommendations for the monitoring of patients on SSAs are provided (26).

As in patients treated with SSAs, AACE guidelines recommend that both GH and IGF1 levels should be monitored in patients who are being treated with pituitary-acting dopamine agonists such as cabergoline (1). Cabergoline is recommended in patients with mild disease, defined as IGF1 levels less than two times the upper limit of normal, and in cases of co-secretion with prolactin (1, 15). In clinical studies, ~30% of patients with acromegaly achieved biochemical control with cabergoline, particularly when used at high doses (15, 37). However, this initial response to cabergoline is lost over time (26). While AACE and ENDO guidelines do not specify the timing of monitoring for patients receiving cabergoline, AACE guidelines recommend that GH and IGF1 levels be monitored 4–6 weeks after each dose change (1). Cardiac valvular abnormalities have been linked to cabergoline in patients with Parkinson's disease; however, there is no evidence of this association in patients with acromegaly who are treated with lower doses (38, 39). As observed with SSAs, gastrointestinal discomfort is the AE most widely reported to be associated with cabergoline (40).

Pegvisomant is a GH-receptor antagonist approved for the treatment of patients with acromegaly (41). Because



pegvisomant does not target the tumor or inhibit GH production, and it cross-reacts with GH in many of the currently available assays, measuring GH levels is not recommended for the monitoring of treatment response to pegvisomant in patients with acromegaly (1). Rather, it is recommended that monitoring of only IGF1 levels be performed (1, 22). However, no specific recommendations are given in AACE and ENDO guidelines regarding the appropriate timing for the monitoring of IGF1 levels. There are concerns over potential tumor growth in patients treated with pegvisomant (42, 43). Increased tumor growth has been reported in some small studies, but these results are largely variable. Because of these concerns, AACE and ENDO guidelines recommend close monitoring for tumor enlargement by serial magnetic resonance imaging at 6-month intervals during the first year of treatment, followed by monitoring at annual intervals thereafter (1, 26). Abnormal results on liver function tests (LFTs) are the most frequently reported AEs associated with pegvisomant treatment. Thus, AACE guidelines recommend that the monitoring of LFT results in patients with acromegaly who are treated with pegvisomant occur for the first 6 months, quarterly for the following 6 months, and biannually thereafter (1). For patients with elevated baseline LFT results at the start of initial pegvisomant treatment, frequent monitoring on a regular basis is recommended. Similarly, ENDO guidelines suggest that patients receiving pegvisomant undergo monthly LFTs for the first 6 months and discontinue treatment if transaminase levels are elevated by more than threefold (26).

### Patients receiving radiotherapy

Radiotherapy is another treatment option for patients who have not been cured with surgery, have not responded adequately to medical therapy, or are considered not appropriate candidates for surgery or medical therapy (1, 44, 45). Generally, radiotherapy has variable effects on reducing GH and IGF1 levels, and response rates can be delayed for up to 10 years (46). For this reason, patients are usually placed on medical therapy as a bridge until radiation therapy has had its full effect. In general, stereotactic radiosurgery (SRS), which includes modalities such as gamma knife, CyberKnife (Accuray Inc, Sunnyvale, CA, USA), linear accelerator, and proton beam, when available, is preferred over conventional radiotherapy unless there is a large amount of residual tumor or the tumor is in close proximity to the optic chiasm (19, 26). In a series that included 884 patients

treated with conventional radiotherapy, IGF1 levels normalized in 63% of patients after 10 years (47). Remission rates for SRS have been reported to be 10–60% in patients followed up to 15 years (26).

Patients receiving radiotherapy are at risk of developing hypopituitarism, radiation-induced secondary tumors, and radionecrosis (48, 49). Although a wide range of incidence has been reported, the overall risk of hypopituitarism is similar with conventional radiotherapy and SRS and occurs in more than 50% of patients after 5–10 years (26). For recurrent disease, re-irradiation with fractionated conventional radiotherapy or SRS could be acceptable modes of treatment following a 3- to 4-year gap after receiving previous primary pituitary radiotherapy. However, there are considerably higher risks associated with the cumulative effects of radiation over time, such as damage to the optic apparatus, cranial nerves, and normal brain tissues. Thus, AACE guidelines recommend annual follow-up visits that assess serial pituitary function to evaluate for hypopituitarism and the monitoring of GH and IGF1 levels in patients receiving radiotherapy (1). ENDO guidelines recommend annual hormonal testing to monitor the efficacy of radiotherapy in patients following withdrawal from medical therapy, as well as monitoring for hypopituitarism and other delayed radiation effects (26).

### Patients with comorbidities

Cardiovascular disease, diabetes mellitus, hypertension, sleep apnea, and arthritis are common comorbidities associated with acromegaly (18). Improvements in several comorbidities have been reported in patients with acromegaly who achieved biochemical control. In a meta-analysis study, patients with acromegaly who achieved at least a 50% decrease in GH or IGF1 levels with octreotide or lanreotide showed significant improvements in interventricular septum thickness, left ventricular posterior wall thickness, and left ventricular mass (50). Additionally, normalization of shoulder thickening (61%) and knee thickening (89%) were observed in patients who achieved disease control after SSA treatment for 12 months, while 61% of patients also demonstrated improvements in sleep apnea (18). However, there remains a high prevalence of comorbidities in many patients who achieve control of GH and IGF1 levels. In a single-center study, it was reported that joint-related complications (77%), snoring (57%), paresthesias (40%), and hypertension (37%) continued to persist in patients with long-term control of acromegaly (51). In such cases,



additional supportive care may be needed for effective management of comorbidities that could enhance the quality of life in these patients (18). It is recommended by clinical guidelines that all comorbidities be actively treated and monitored regardless of whether hormone levels are controlled (Table 1) (1). For musculoskeletal complications, management options include physical therapy, anti-inflammatory and analgesic medications, or joint replacement surgery. A routine echocardiography is recommended in patients whose cardiac performance does not improve with biochemical remission. For patients in remission with impaired glucose tolerance and type 2 diabetes, management with antidiabetic medications may be necessary.

### Suboptimal monitoring in patients with acromegaly

A substantial number of patients (48.0–72.4%) will have persistent acromegaly despite treatment with surgery, medical therapy, and/or radiotherapy (52, 53), and ~2–8% of patients who achieve remission with surgery will experience disease recurrence within 5 years (26). While the clinical benefit of optimal monitoring of these patients is clear, suboptimal monitoring is nonetheless common.

There is a lack of large studies evaluating compliance with monitoring in patients with acromegaly and, thus, the exact proportion of patients who are adequately monitored, particularly over the long term, is unclear. However, in a recently published pilot study, Kasuki *et al.* (20) reported that nearly 17.6% of patients with acromegaly who were receiving medical therapy were lost to follow-up. Notably, 88% of the evaluable patients who were lost to follow-up had active disease. The most common reasons reported by patients for nonadherence to follow-up included the absence of symptoms or the presence of mild symptoms that did not improve with current therapy. A similar rate of loss to follow-up was observed in a large multicenter study conducted in France (ACROSPECT) (21). In this study, 20% of patients who were lost to follow-up had elevated IGF1 levels and 21% had uncontrolled disease. In this case, the primary reason for nonadherence to follow-up was that patients were not aware that follow-up care was necessary. A key finding of these studies was that the inability to closely monitor and treat patients was associated with a high rate of active disease. Thus, in addition to a need for improving the definition of parameters and timing for patient monitoring, there is also a need to improve adherence to monitoring in patients with acromegaly.

**Table 1** Monitoring and managing recommendations for comorbidities in patients with acromegaly (1, 14).

Comorbidities	Monitoring and managing recommendations
Skeletal and dental manifestations	Corrective surgical procedure, such as maxillofacial correction or dental malocclusion, should be postponed until GH and IGF1 levels have normalized for at least 6 months. Signs and symptoms of carpal tunnel syndrome should be monitored, and directed care should be considered for persistent or progressive symptoms. Arthropathy may persist despite long-term biochemical remission and should be managed by physical therapy, anti-inflammatory medications, or joint replacement, when appropriate. For osteoporosis, antiresorption therapy should be considered if improvements are not observed with the correction of GH and IGF1 excess, hypogonadism, and hypercalcemia.
Respiratory disorders	Screening tests for sleep apnea, such as formal overnight polysomnography or home overnight oximetry, should be performed if symptoms are suggestive in patients with acromegaly who have active or biochemically controlled disease.
Cardiovascular disease and cardiovascular risk factors	Despite biochemical control, hypertension may persist and blood pressure should be monitored. In patients with worsening glucose control while on SSA therapy, reduction of SSA dose, addition or substitution with GH-receptor antagonist, or management with antidiabetic medications should be considered.
Neoplasms	Colonoscopy should be performed in patients after diagnosis of acromegaly. Patients with polyps at screening or with persistently elevated IGF1 levels should have follow-up colonoscopies performed. Standard screening guidelines for other cancers should be followed.
Psychosocial complications	Psychological intervention and attention to quality-of-life issues should be implemented for all patients with active acromegaly.

GH, growth hormone; IGF1, insulin-like growth factor 1; SSA, somatostatin analog.



## Discussion

A wealth of studies demonstrate that, once a patient with acromegaly initiates treatment for his/her disease, monitoring of GH and IGF1 levels is an integral component for assessing treatment response, guiding therapeutic decisions, and detecting persistent or recurrent disease. With optimal monitoring, proper detection and appropriate treatment of patients who have persistent or recurrent disease and improvement in clinical outcomes can be achieved. However, a number of unresolved questions regarding proper monitoring of patients with acromegaly remain. One key question is whether current monitoring is optimal. For example, a recent study suggests that the use of the last available values for GH/IGF1 assessments, which have been invariably used in most clinical studies, may not accurately estimate mortality risk in patients with acromegaly (54). Additionally, given that there can be a delay in normalization of IGF1 levels (55), as well as a fairly high rate of discordance between GH and IGF1 values, it is important to consider whether monitoring should be performed more frequently and/or whether additional biomarkers might be useful in the monitoring of patients.

Recent studies have identified a new serum biomarker that could potentially be used to complement GH and IGF1 as indicators of active acromegaly. Excessive levels of soluble Klotho (sKlotho) have been observed in patients with acromegaly (56), and these appear to be comparable to IGF1 at reflecting disease activity (57, 58). While it is clear that additional research will be needed in this field, it is nonetheless of interest to speculate about whether sKlotho or similar types of biomarkers could potentially be useful to guide treatment decisions when discordant GH and IGF1 test results are obtained, which occurs in up to 35% of patients with active acromegaly (31, 59, 60). Furthermore, additional studies are needed to determine whether it would be appropriate to incorporate biomarkers such as sKlotho into the monitoring algorithm for patients with acromegaly.

Another important question relates to how we can improve adherence/compliance with monitoring. In the study by Kasuki *et al.* (20), up to 88% of evaluable patients with acromegaly, having failed to comply with follow-up visits, had active disease after self-reporting that they lacked symptoms following treatment or had mild symptoms that did not improve with their current treatment regimens. Moreover, another primary reason for nonadherence to follow-up visits by patients with acromegaly was being uninformed that follow-up care was necessary (21). While

this further highlights the need for increased compliance by patients with follow-up visits during the course of treatment, an additional element is the need for clear guidance on how the health care provider and patient can work together to achieve improved compliance.

With an improved array of therapeutic options available, it is possible to provide long-term disease control to a majority of patients with acromegaly. Monitoring is an integral component in the management of patients with acromegaly. However, while there is a good consensus regarding the treatment algorithm for patients with acromegaly, guidance regarding what constitutes optimal monitoring for these patients is not as clear. Given the critical role of monitoring in achieving improved outcomes, we think that a reexamination of current criteria is needed. We propose suggestions to the current recommendations regarding potential areas of improvement in the monitoring of patients with acromegaly. These include integrating other clinical and molecular biomarkers to complement GH/IGF1 in assessing treatment response, such as sKlotho (as previously described) (56, 57, 58), increased Ki-67 levels, positive *AIP* mutation, large tumor size, or sparse granular pattern (61). Updating guidance on discrepant GH/IGF1 levels could also improve clinical outcomes, because guidance is not provided in the AACE (1) or ENDO (26) clinical guidelines. Additionally, improved clinical outcomes could be achieved by defining optimal timing intervals for each class of medical therapy used and implementing strategies to identify recurrent disease and prevent loss of patients to follow-up.

### Declaration of interest

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