

Consensus on criteria for acromegaly diagnosis and remission

Giustina, Andrea; Biermasz, Nienke; Casanueva, Felipe f.; Fleseriu, Maria; Mortini, Pietro; Strasburger, Christian; Van der lely, A. j.; Wass, John; Melmed, Shlomo; Acromegaly Consensus Group; Karavitaki, Niki

DOI:

[10.1007/s11102-023-01360-1](https://doi.org/10.1007/s11102-023-01360-1)

License:

Creative Commons: Attribution (CC BY)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Giustina, A, Biermasz, N, Casanueva, FF, Fleseriu, M, Mortini, P, Strasburger, C, Van der lely, AJ, Wass, J, Melmed, S, Acromegaly Consensus Group & Karavitaki, N 2023, 'Consensus on criteria for acromegaly diagnosis and remission', *Pituitary*. <https://doi.org/10.1007/s11102-023-01360-1>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.



Consensus on criteria for acromegaly diagnosis and remission

Andrea Giustina¹ · Nienke Biermasz² · Felipe F. Casanueva³ · Maria Fleseriu⁴ · Pietro Mortini¹ · Christian Strasburger⁵ · A. J. van der Lely⁶ · John Wass⁷ · Shlomo Melmed⁸ · Acromegaly Consensus Group

Accepted: 17 October 2023
© The Author(s) 2023

Abstract

Purpose The 14th Acromegaly Consensus Conference was convened to consider biochemical criteria for acromegaly diagnosis and evaluation of therapeutic efficacy.

Methods Fifty-six acromegaly experts from 16 countries reviewed and discussed current evidence focused on biochemical assays; criteria for diagnosis and the role of imaging, pathology, and clinical assessments; consequences of diagnostic delay; criteria for remission and recommendations for follow up; and the value of assessment and monitoring in defining disease progression, selecting appropriate treatments, and maximizing patient outcomes.

Results In a patient with typical acromegaly features, insulin-like growth factor (IGF)-I > 1.3 times the upper limit of normal for age confirms the diagnosis. Random growth hormone (GH) measured after overnight fasting may be useful for informing prognosis, but is not required for diagnosis. For patients with equivocal results, IGF-I measurements using the same validated assay can be repeated, and oral glucose tolerance testing might also be useful. Although biochemical remission is the primary assessment of treatment outcome, biochemical findings should be interpreted within the clinical context of acromegaly. Follow up assessments should consider biochemical evaluation of treatment effectiveness, imaging studies evaluating residual/recurrent adenoma mass, and clinical signs and symptoms of acromegaly, its complications, and comorbidities. Referral to a multidisciplinary pituitary center should be considered for patients with equivocal biochemical, pathology, or imaging findings at diagnosis, and for patients insufficiently responsive to standard treatment approaches.

Conclusion Consensus recommendations highlight new understandings of disordered GH and IGF-I in patients with acromegaly and the importance of expert management for this rare disease.

Keywords Acromegaly · Growth hormone · Insulin-like growth factor I · Assays · Diagnosis · Remission criteria

Introduction

Acromegaly caused by a growth hormone (GH)-secreting pituitary adenoma can deleteriously affect patient quality of life (QOL) and mortality if not diagnosed early and properly treated [1]. Insulin-like growth factor (IGF)-I and GH measurements are commonly used as biochemical markers of disease activity for diagnosis and follow-up of acromegaly [2]: IGF-I levels are reflective of GH action on peripheral tissue, primarily in the liver, while GH levels reflect somatotroph adenoma secretory activity.

The first Acromegaly Consensus Conference held in 1999 in Cortina, Italy, concluded that a diagnosis of acromegaly is excluded if random GH is < 0.4 µg/L and age- and sex-matched IGF-I is normal, or if GH nadir is < 1 µg/L during 75-g oral glucose tolerance test (OGTT) and IGF-I is normal [3]. Biochemical control after treatment of acromegaly was

✉ Shlomo Melmed
melmed@csmc.edu

¹ San Raffaele Vita-Salute University and IRCCS Hospital, Milan, Italy
² Leiden University Medical Center, Leiden, The Netherlands
³ Santiago de Compostela University, Santiago de Compostela, Spain
⁴ Oregon Health and Science University, Portland, OR, USA
⁵ Charité Universitätsmedizin, Berlin, Germany
⁶ Erasmus University Medical Center, Rotterdam, The Netherlands
⁷ Churchill Hospital, Oxford, UK
⁸ Cedars-Sinai Medical Center, 8700 Beverly Blvd, NT 2015, Los Angeles, CA 90048, USA

defined as achieving normal IGF-I and, after surgery, nadir GH < 1 µg/L during OGTT (Table 1).

Revisiting this issue in 2010, the 7th Acromegaly Consensus Conference recommendations included two changes [4]: (1) OGTT is not required for diagnosis if IGF-I and GH levels are clearly elevated; and (2) definition of biochemical control could be adjusted to nadir GH < 0.4 µg/L during OGTT if using newer, ultrasensitive assays. In 2014, guidelines from the Endocrine Society further adjusted these criteria [5]. They recommended using IGF-I normalized to age but not sex for the diagnosis of acromegaly, confirmed by lack of suppression of GH < 1 µg/L during OGTT if necessary, and to use age-normalized IGF-I and random GH < 1.0 µg/L as a therapeutic goal.

Following on studies underscoring the challenges of uniformly applying results of GH and IGF-I assays in the clinic [6, 7], the 14th Acromegaly Consensus Conference held in 2022 in Stresa, Italy, once again revisited the question of how to define biochemical criteria for acromegaly diagnosis and evaluation of therapeutic efficacy. Key points from the discussions are presented here and are summarized in Table 2.

Materials and methods

The process for development of consensus recommendations by Acromegaly Consensus Group participants before and during the meeting has been described [8]. Briefly, participants (Table 3) were assigned specific topics related to acromegaly diagnosis and follow-up and conducted comprehensive literature searches for English-language papers published between January 2015 and September 2022. Search terms included “acromegaly” as well as terms associated

with each respective topic covered. After brief presentations to the entire group on each topic, breakout groups discussed current practice and recommendations, and a summary of the findings was reported back to the entire group. Consensus recommendations were developed based on all presentations and discussions and all participants voted on each recommendation. After the meeting, members of the Scientific Committee graded both the quality of the supporting evidence and the consensus recommendations based on principles for grading of evidence for guidelines and prior Acromegaly Consensus publications [9–11]. Evidence was graded by strength as very low quality (VLQ), low quality (LQ), moderate quality (MQ), or high quality (HQ), and recommendations were classified as discretionary (DR) or strong (SR) as indicated in Table 4.

Diagnostic assessment

Accurate measures of IGF-I and GH are critical to the diagnosis of acromegaly. Therefore, clinicians should know which assay is being used, which factors influence its performance, how normal ranges are obtained (SR), and how it has been calibrated and validated.

IGF-I and GH assays

In a patient with typical clinical signs and symptoms of acromegaly, IGF-I > 1.3 times the upper limit of normal (ULN) for age confirms the diagnosis (MQ). GH measured after overnight fasting may be useful for informing prognosis or complications, but is not required for diagnosis (SR). However, as it is still often used as first line biochemical assessment [12], a need for the use of validated GH assays

Table 1 Evolution of criteria for acromegaly diagnosis and evaluation of therapeutic efficacy

	Diagnosis	Therapeutic efficacy target
1st Acromegaly consensus [3]	IGF-I elevated for age and sex Confirm with random GH ≥ 0.4 µg/L <i>or</i> IGF-I elevated for age and sex Confirm with GH > 1 µg/L during OGTT	IGF-I normalized for age and sex GH < 1 µg/L during OGTT
7th Acromegaly consensus [4]	IGF-I elevated for age and sex <i>and</i> Random GH elevated	Random GH < 1 µg/L GH < 0.4 µg/L during OGTT
Endocrine society guidelines [5]	IGF-I elevated for age Confirm with GH > 1 µg/L during OGTT	IGF-I normalized for age Random GH < 1 µg/L
14th Acromegaly consensus (this publication)	IGF-I > 1.3 × ULN for age <i>and</i> Characteristic clinical signs of disease For equivocal results, IGF-I measurements can be repeated, and OGTT might additionally be useful	IGF-I normalized for age

GH growth hormone; IGF-I insulin-like growth factor I; OGTT oral glucose tolerance test; ULN upper limit of normal

Table 2 Key recommendations**Overall**

Referral to a multidisciplinary pituitary center should be considered for patients with equivocal biochemical, pathology, or imaging findings at diagnosis, and for patients insufficiently responsive to standard treatment approaches.

Diagnostic assessment

For all biochemical assessments, clinicians should know which assay is being used, which factors influence its performance, how normal ranges are obtained, and how it has been calibrated and validated.

In a patient with typical clinical signs and symptoms of acromegaly, IGF-I > 1.3×ULN for age confirms the diagnosis. Random GH measured after overnight fasting may be useful for informing prognosis, but is not required for diagnosis. For patients with equivocal results, IGF-I measurements can be repeated using the same validated assay, and OGTT might additionally be useful.

IGF-I and GH Assays

Well-validated IGF-I assays should be calibrated to the current international standard (02/254). Age-stratified reference ranges should be based on adequate numbers of subjects; sex-stratified reference ranges are likely not required beyond puberty if the normative population is sufficiently large.

BMI might influence normal IGF-I ranges, such that patients with high BMI have lower IGF-I levels for their age group. Nutritional, genetic, metabolic, and hepatic factors can also impact IGF-I concentrations, often inducing states of GH resistance.

There is currently no evidence that IGF-I measurement by mass spectrometry is superior to measurement by immunoassay.

Calibration to the current international standard for GH (98/574) should be standard with immunoassays but has not been validated for mass spectrometry.

OGTT

If OGTT is performed, 75 g glucose should be administered after fasting, and GH nadir assessed after 30, 60, 90, and 120 min.

BMI-based GH nadir cutoffs of < 0.4 µg/L for BMI < 25 kg/m² and < 0.2 µg/L for BMI ≥ 25 kg/m² can be considered.

Cessation of oral estrogen therapy 4 weeks prior to OGTT may avoid its effects on the GH axis.

OGTT can be safely performed among patients with impaired glucose tolerance or type 2 diabetes mellitus. However, in patients with uncontrolled diabetes, both random and post-OGTT GH levels should be interpreted with caution.

Measurement of basal and 120-minute glucose levels during OGTT is useful for detecting disturbances in glucose homeostasis.

Clinical, Imaging, and Pathology Assessments

A careful history and physical exam is required as it will often reveal unequivocal signs and symptoms related to local mass effect or secondary features of GH and IGF-I hypersecretion.

Gadolinium-enhanced pituitary MRI should be performed in patients at diagnosis using high-quality, high-resolution equipment.

Reporting should include information on invasion into surrounding structures based on modified Knosp grade.

Equivocal diagnosis of acromegaly associated with pituitary microadenomas should be referred for review by an experienced neuroradiologist before considering further imaging studies.

Standard pathology reporting should include immunohistochemistry assessment for pituitary hormones. Transcription factors can be used to define adenoma lineage and further characterize adenoma cell type when not classifiable on hormone expression alone.

Clinical implications of the 2022 WHO classification suggesting that pituitary adenomas could also be called pituitary neuroendocrine tumors remain unclear and the ongoing ramifications for acromegaly patients are not apparent.

Diagnostic delay

Prolonged exposure to excess GH with diagnostic delay leads to increased comorbidity and mortality risks with decreased QOL, and could lead to reduced treatment success and increased need for additional therapy.

Strategies aimed at reducing diagnostic delay should be implemented worldwide as they may reduce short-term and long-term morbidity and positively impact QOL.

All patients with a newly diagnosed pituitary mass should undergo IGF-I measurement.

Although widespread screening in the general population is not warranted, IGF-I screening could be considered in individuals with classical signs, symptoms, and comorbidities of acromegaly including acral enlargement and orofacial changes, particularly if these occur in conjunction with unexplained systemic manifestations such as sleep apnea or ventricular hypertrophy.

A systematic approach should be implemented among healthcare practitioners to increase awareness about acromegaly. Outreach strategies in collaboration with patient advocacy groups such as for other rare diseases could also help promote earlier referral for diagnostic testing.

Criteria for remission

The term “remission” indicating that active disease cannot be detected even if it might still be present is the most accurate descriptor for biochemical treatment outcome goals in acromegaly.

Although biochemical remission is the primary assessment of treatment outcome, it is not the only goal of treatment in acromegaly. In all cases, biochemical findings should be interpreted within the clinical context of acromegaly signs and symptoms.

Maintaining serum IGF-I level in the mid to upper half of the age-related reference range could be considered in clinically controlled patients to avoid induction of GH deficiency.

Postoperative remission

There are no definitive studies on the optimal assessment for postoperative remission, nor of the timing of its evaluation.

IGF-I should be measured at 12 weeks after surgery to determine postoperative biochemical remission. Early random GH assessment on day 1–14 and comparison with preoperative GH can inform the degree of adenoma removal and subsequent longer-term remission.

OGTT assessment may provide further predictive value.

Table 2 (continued)

In patients treated with preoperative SRL, assessment should be repeated at 3–6 months to confirm remission.

Remission With Adenoma-Directed Medical Therapy

For patients treated with injectable SRL, IGF-I level measurement in the last week before the next injection should be used to determine a need for dose titration or consideration of alternative treatment options if normalization is not achieved.

For patients treated with oral SRL administered daily, assessment of IGF-I for the purposes of dose titration should be done after at least 2 weeks of treatment.

Timing of IGF-I assessment is not critical for patients treated with cabergoline administered in more than once-weekly intervals.

With all of these agents, random GH assessment is not likely to provide additional information in all patients but could be considered for symptomatic patients with IGF-I levels at the higher end of the ULN.

Remission With Peripherally Directed Medical Therapy

For patients treated with medical therapy that targets the GH receptor or the estrogen receptor, efficacy assessment is limited to IGF-I normalization.

With these agents, GH assessment is not informative and should not be performed.

Follow up

Follow up assessments should consider biochemical evaluation of treatment effectiveness, imaging studies evaluating residual/recurrent adenoma mass, and clinical signs and symptoms of acromegaly and its complications and comorbidities.

Biochemical

Within the first postoperative year, IGF-I measurements every 3–6 months may be appropriate to confirm remission, and then every 6–12 months to monitor for potential recurrence. OGTT might be helpful in evaluating patients with borderline IGF-I levels and clinical signs of disease activity.

For patients who did not achieve postoperative remission and who are treated with adjuvant SRL, IGF-I should be assessed 3 months after initiation/dose adjustment of injectable SRL and 2–4 weeks after initiation/dose adjustment of oral SRL to establish an optimal dosing regimen, and then every 6–12 months thereafter once biochemical control is achieved. Random GH might be helpful in select cases where evaluation of adenoma behavior is a concern.

As pegvisomant and cabergoline have a shorter half-life than injectable SRL, IGF-I should be assessed every 1–3 months after initiation/dose adjustment to establish the dosing regimen, and then every 6–12 months thereafter.

In patients receiving medical therapy as a bridge until radiotherapy effect is seen, IGF-I should be assessed at the intervals appropriate for the medical therapy used. With sustained decline of IGF-I within the target range, treatment can be paused at least once each year depending on rapidity of the IGF-I decline to test for the onset of radiation-induced remission.

For all patients, ideally, the same well-validated IGF-I assay should be used for all assessments. New or persistent elevations in IGF-I levels should be interpreted within the context of the individual clinical scenario and account for factors that could affect results such as pregnancy, estrogen use, starvation, and metabolic changes.

Imaging

The same standards for imaging and results reporting should be used in follow up as in diagnosis.

MRI should be performed at 3–6 months postoperatively and used as baseline for further assessments.

MRI should be performed upon signs of biochemical or clinical disease progression, and when a change in therapeutic modality is considered, such as prior to a second surgery or radiotherapy.

An individualized approach to MRI is appropriate for patients treated with pegvisomant based on country-specific labeling requirements, as well as for those with genetic markers or prior imaging suggestive of highly aggressive disease.

Clinical assessment

This Workshop endorsed evaluation and treatment of disease comorbidities according to prior consensus recommendations. The need for assessment of common comorbidities, such as hypopituitarism, obstructive sleep apnea, and vertebral fractures depends on clinical symptoms and adenoma behavior, and follow up according to accepted guidelines was recommended.

There was no consensus at this Workshop on whether colonoscopy should be performed in all acromegaly patients at diagnosis regardless of age. For all other cancers with reported increased frequency in acromegaly, including thyroid cancer, there was consensus that screening be performed according to national/regional guidelines for the general population.

SAGIT and ACRODAT may be useful in current clinical practice for assessing changes in acromegaly disease severity and progression over time. A prospective study measuring a clinically beneficial effect of ACRODAT as a monitoring tool is underway.

Considerations for second- and third-line treatment selection

Follow up assessments identify patients more likely to show a favorable response to second- and third-line medical therapy options if needed.

Results of follow up assessments can also be used to identify patients who might benefit from treatment options that have an improved safety profile or more convenient dosing regimen.

BMI body mass index; *GH* growth hormone; *IGF-I* insulin-like growth factor I; *MRI* magnetic resonance imaging; *OGTT* oral glucose tolerance test; *QOL* quality of life; *SRL* somatostatin receptor ligand; *WHO* World Health Organization; *ULN* upper level of normal

Table 3 Acromegaly consensus group participants

Giuseppe Banfi (IT), Ariel Barkan (US), Albert Beckers (BE), Martin Bidlingmaier (DE), Nienke Biermasz (NL), Cesar Boguszewski (BR), Marcello Bronstein (BR), Thierry Brue (FR), Michael Buchfelder (DE), Felipe F. Casanueva (ES), Philippe Chanson (FR), Sabrina Chiloiro (IT), Annamaria Colao (IT), Eva Coopmans (NL), Daniela Esposito (SE), Diego Ferone (IT), Maria Fleseriu (US), Stefano Frara (IT), Mônica Gadelha (BR), Eliza B. Geer (US), Ezio Ghigo (IT), Andrea Giustina (IT), Yona Greenman (IS), Mark Gurnell (UK), Ken Ho (AU), Adriana Ioachimescu (US), Gudmundur Johannsson (SE), Jens Otto Jørgensen (DK), Ursula B. Kaiser (US), Niki Karavitaki (UK), Laurence Katznelson (US), Stephen Lamberts (NL), Marco Losa (IT), Anton Luger (AT), Raúl Luque (ES), Pietro Maffei (IT), Mónica Marazuela (ES), Shlomo Melmed (US), Pietro Mortini (IT), Sebastian Neggers (NL), Alberto Pereira (NL), Luca Persani (IT), Stephan Petersenn (DE), Martin Reincke (DE), Roberto Salvatori (US), Susan L. Samson (US), Katharina Schilbach (DE), Ilan Shimon (IS), Christian Strasburger (DE), Stylianos Tsagarakis (GR), A.J. van der Lely (NL), John Wass (UK), Maria Chiara Zatelli (IT)

Table 4 Grading of evidence and recommendations

Evidence	Very low quality (VLQ): expert opinion supported by one or few small uncontrolled studies Low quality (LQ): supported by large series of small uncontrolled studies Moderate quality (MQ): supported by one or few large uncontrolled studies or meta-analyses High quality (HQ): supported by controlled studies or large series of large uncontrolled studies with sufficiently long follow-up
Recommendations	Discretionary: based on VLQ or LQ evidence Strong: based on MQ or HQ evidence

Based on principles for grading of evidence for guidelines and prior Acromegaly Consensus publications [9–11]

worldwide is reinforced (SR). For patients with equivocal results, IGF-I measurements can be repeated using the same validated assay, and OGTT might additionally be useful (DR).

Inter-laboratory and inter-assay discrepancies with IGF-I assays are well known [6, 13, 14]; normal reference ranges are specific to each immunoassay, with the greatest differences seen at the highest values [6] (MQ). Well-validated IGF-I should be calibrated to the current international standard (02/254) [15]. Age-stratified reference ranges should be based on adequate numbers of subjects (SR), but sex-stratified reference ranges are likely not required beyond puberty if the normative population is sufficiently large [16] (DR). However, body mass index (BMI) might influence normal IGF-I ranges, such that patients with high BMI have lower IGF-I levels for their age group [16] (MQ). Nutritional, genetic, metabolic, and hepatic factors can also impact IGF-I concentrations, often inducing states of GH resistance [17–20].

Although mass spectrometry largely eliminates interference from IGF binding proteins that might affect immunoassay results, errors can be introduced during protein concentration and sample preparation, and variability is similar to that seen with immunoassay [21] (LQ). There is currently no evidence that IGF-I measurement by mass spectrometry is superior to measurement by immunoassay (LQ).

Variability in GH immunoassay assessments is commonly encountered because of differences in antibody and epitope binding of GH isoforms, and variability may be greatest with higher values [15] (MQ). Calibration to the current international standard for GH (98/574) should be standard

with immunoassays [15], but has not been validated for mass spectrometry methodologies and its use in this setting remains somewhat undefined (DR).

OGTT

GH nadir during OGTT correlates with spontaneous trough inter-pulse GH concentrations [22], which determine the magnitude of IGF-I production [23] (MQ). Thus, glucose-suppressed GH nadir is effectively an indirect assessment of IGF-I and a reflection of preserved GH neuroregulation [24]. However, there is no cutoff for glucose-suppressed GH that definitively excludes a diagnosis of acromegaly (MQ). GH nadirs in healthy adults vary depending on sex, BMI, and estrogen-containing oral contraceptive (OC) use [7], and the range of both spontaneous trough and glucose-suppressed levels in healthy adults can overlap those of acromegaly patients. Thus, glucose-suppressed GH nadirs in acromegaly patients with lower mean 24-hr GH levels can fall into the range of normal adults [25] (VLQ). Furthermore, up to one-third of patients with acromegaly may show a paradoxical increase in GH following OGTT and may demonstrate up to 50% increase or more in GH levels within 120 min after glucose ingestion [26].

In weighing the available evidence, consensus discussions considered that, in most cases, diagnosis is clear without a need for OGTT, and the interpretative difficulties of OGTT therefore outweigh the potential advantages. Thus, the consensus recommended that this test be reserved for patients in whom baseline hormone levels do not clarify the diagnosis (SR).

If OGTT is performed, 75 g glucose should be administered after fasting [27], and GH nadir assessed after 30, 60, 90, and 120 min [7] (SR). BMI-based GH nadir cutoffs can be considered for diagnosis, with $<0.4 \mu\text{g/L}$ for $\text{BMI} < 25 \text{ kg/m}^2$ and $<0.2 \mu\text{g/L}$ for $\text{BMI} \geq 25 \text{ kg/m}^2$ [7], although this may be assay dependent (DR). As healthy premenopausal females on estrogen-containing OC have higher GH nadirs [7], cessation of oral estrogen therapy 4 weeks prior to OGTT may avoid its effects on the GH axis.

OGTT can be safely performed in patients with impaired glucose tolerance or type 2 diabetes mellitus, with some applying BMI-based cutoffs [28, 29] (DR). However, due to the suppressive effect of hyperglycemia on GH levels [30], particularly in patients with uncontrolled diabetes [31], both random and post-OGTT GH levels should be interpreted with caution. Measurement of basal and 120-minute glucose levels during OGTT is useful for detecting disturbances in glucose homeostasis (MQ).

Other assays

A rapid decrease in soluble α -Klotho occurs after adenoma surgical resection, correlating with decreases in IGF-I, and associated with normal IGF-I levels in patients with discordantly elevated random GH levels [32] (LQ). Soluble α -Klotho, but not IGF-I, correlated with GH-dependent symptom scores and disease-specific QOL in patients receiving medical therapy [33] (VLQ). However, mechanisms driving soluble α -Klotho secretion in acromegaly as well as assay validation and confirmatory studies are required before it can be considered for use as a biochemical marker in clinical practice (SR).

Clinical examination

A careful history and physical exam in the initial assessment of patients with suspected acromegaly is required as it will often reveal unequivocal signs and symptoms related to local mass effect or secondary features of GH and IGF-I hypersecretion (SR).

Characteristic changes in the face and head, including widening and malocclusion of the jaw and macroglossia, as well as enlarged hands, occur insidiously but are often apparent at initial assessment [2, 17] (HQ). Moreover, due to diagnostic delay, disease comorbidities and complications including hypertension, diabetes mellitus, and kyphosis [34, 35] should not be overlooked (SR). In fact, they are signs of active disease and may be apparent at initial presentation [36] (LQ). (Diagnosis and management of acromegaly comorbidities are extensively discussed in a separate Consensus Statement [8].) Impaired QOL resulting from the clinical and psychological burden of disease may be present at all stages of disease [37] (VLQ).

Imaging

Gadolinium-enhanced pituitary MRI should be performed in all patients at diagnosis using high-quality, high-resolution equipment, such as 1.5T or 3T scanners, where available, including T1- and T2-weighted fast spin echo sequences, with coronal and sagittal planes in 2–3 mm slice thickness with no or minimal spacing (SR). Reporting should be standardized, and include information on invasion into surrounding structures based on modified Knosp grade [38] (SR). Adenoma dimensions; suprasellar and infrasellar extension; presence of cystic components; and T2 hypo-, iso-, or hyperintensity of the adenoma compared with adjacent temporal lobe can all be used to inform likelihood of treatment response [39–41] (MQ). Given the proven benefits of expert MRI review in patients with Cushing's disease microadenomas [42], equivocal diagnosis of acromegaly associated with pituitary microadenomas should be referred for review by an experienced neuroradiologist [43] before considering further imaging studies (SR). Very rarely, cross-sectional imaging and measurement of GH releasing hormone (GHRH) may be needed to identify an ectopic GHRH-secreting neuroendocrine tumor [44] (DR).

PET imaging using ^{11}C -methionine as a molecular tracer may be useful when MRI cannot identify an adenoma at initial diagnosis or, more commonly, a residual adenoma in patients with persistent GH hypersecretion following primary therapy [45, 46] (DR). However, limited availability of both the imaging technology and the tracer constrain their use.

Pathology

Differentiation of somatotroph, lactotroph, and thyrotroph cells in the pituitary is driven by the PIT1 transcription factor. Somatotroph adenomas are defined on pathology based on immunohistochemistry (IHC) GH expression, and adenomas that secrete/express GH and prolactin may also be seen [47] (HQ). Standard reporting should include IHC assessment for pituitary hormones. Transcription factors can be used to define adenoma lineage and further characterize adenoma cell type when not classifiable on hormone expression alone (SR).

Clinicopathologic classification of pituitary adenomas that considers adenoma invasiveness using Knosp grade and sphenoid sinus invasion as well as proliferation by Ki-67 and mitoses can distinguish adenomas with potentially more aggressive behavior [48], and thus identify patients at increased risk for progression [49, 50] (MQ). Somatostatin receptor immunopositivity, granulation pattern, and *AIP* mutation status have been reported to identify patients less likely to respond to somatostatin receptor ligand (SRL) therapy (DR) [51, 52]. Clinical implications of the 2022 WHO

classification suggesting that pituitary adenomas could also be called pituitary neuroendocrine tumors remain unclear [53] and the clinical ramifications for acromegaly patients are not apparent [54].

Effect of diagnostic delay

Signs and symptoms of acromegaly are nonspecific, and there may be a delay of 5–10 years or more between first symptom onset and diagnosis [55, 56] (HQ). The effect is more pronounced in older patients and in women [57, 58] (MQ) likely due to inappropriate attribution of acromegaly symptoms to normal aging and menopause. Prolonged exposure to excess GH with diagnostic delay leads to increased comorbidity and mortality risks with decreased QOL [55, 59, 60] (HQ).

Importantly, delayed diagnosis also allows for continued adenoma growth as well as invasion into the cavernous sinus, both of which limit successful surgical resection, regardless of surgical expertise [61] (HQ). In these patients, adjuvant medical therapy and/or radiotherapy targeted to the residual mass after debulking surgery might be needed [62] (MQ).

Strategies aimed at reducing diagnostic delay should be implemented worldwide as they may reduce short-term and long-term morbidity and positively impact QOL (SR). All patients with a newly diagnosed pituitary mass should undergo IGF-I measurement (SR). Although widespread screening in the general population is not warranted, IGF-I screening could be considered in individuals with classical signs, symptoms, and comorbidities of acromegaly (DR), including acral enlargement and orofacial changes, particularly if these occur in conjunction with unexplained systemic manifestations such as sleep apnea or ventricular hypertrophy [63]. A systematic approach should be implemented among healthcare practitioners to increase awareness about acromegaly. Outreach strategies in collaboration with patient advocacy groups such as for other rare diseases could also help promote earlier referral for diagnostic testing (SR).

Criteria for remission

Consensus recommendations previously adjusted criteria for therapeutic goals because of improvements in assay sensitivity and our evolving understanding of GH dynamics after glucose suppression [3–5] (LQ). Additionally, by definition, postoperative IGF-I normalization is a function of the reference values used for each respective assay [15] (HQ). Therefore, an absolute biochemical threshold to define postoperative “cure” does not seem feasible (DR). “Biochemical control,” indicating no biochemical evidence of adenoma GH hypersecretion, is similarly imprecise as measures of GH and/or IGF-I attenuation might be delayed despite

complete adenoma resection (DR). By contrast, the term “remission” indicates that active disease cannot be detected even if it might still be present. This was deemed the most accurate descriptor for biochemical assessment of treatment outcome in acromegaly and was adopted at this 14th Acromegaly Consensus Conference (SR).

Importantly, although biochemical remission is the primary assessment of treatment outcome, it is not the only goal of treatment in acromegaly. In all cases, biochemical findings should be interpreted within the clinical context of acromegaly signs and symptoms (SR). Maintaining serum IGF-I level in the mid to upper half of the age-related reference range could be considered in clinically controlled patients to avoid induction of GH deficiency [64] (HQ).

Postoperative remission

There are no definitive studies on the optimal assessment for postoperative remission, nor of the timing of its evaluation. Remission rates after surgery using OGTT results are influenced by the defined cutoff for GH normalization, timing of measurement, and adenoma characteristics. For example, some studies reported approximately 60% of patients achieve biochemical remission in the immediate postoperative period when defined as nadir GH < 1 µg/L during OGTT, with lower rates in patients with macroadenomas and in those treated with a microscopic approach [65, 66] (MQ). However, remission rates fell to approximately 40% when using stricter criteria of < 0.4 µg/L on postoperative day 2, and 20% of patients achieved GH below threshold after a delayed period of a median of 24 months of observation [67] (LQ). Of note, very early (and tighter) GH control might be predictive of later GH outcome, as nadir GH > 0.4 µg/L on postoperative day 2–5 predicted lack of remission after a mean follow-up of 44 months [68], and nadir < 0.4 µg/L at 2–5 days and at 3–6 months correlated better with remission than did < 1 µg/L [68, 69] (LQ).

Generally, IGF-I normalization measured 12 weeks after surgery defines surgical success [5, 70] (SR). Some studies defined early remission as normalization at 6 weeks [71], while others included patients who achieved remission after 12 weeks [72], or up to 12 months after surgery [73]. However, delayed IGF-I normalization has been seen as late as 24–57 months after surgery [74, 75]. When measuring random GH, studies have used gradually decreasing normal cutoffs, moving from < 3 to < 2 µg/L and ultimately to < 1 µg/L, with reported remission decreasing accordingly from 89–99% to 61–79% [76–79] (LQ). These studies showed that early postoperative assessment at 1 day after surgery predicted long-term remission, and others have confirmed that elevated random GH on postoperative day 1 or 2 strongly predicts persistent disease [80] (LQ).

Although significant age and sex differences in postoperative GH levels have been noted [81] (VLQ), population-specific thresholds for remission have not been established.

Discordant GH/IGF-I results may be an indicator of mild ongoing disease activity, reflecting dysregulated but persistent somatotroph GH secretion and tissue responsiveness [82, 83]. Discordant GH/IGF-I results may also reflect a delay in IGF-I return to normalization after surgery [70, 74], potentially determined by GH receptor polymorphism [84]. However, it may also be a function of assay variability and changed cutoffs of normal results (VLQ). In a meta-analysis of > 7000 patients evaluated over a 25-year period, 26% showed discordant GH/IGF-I when using a GH nadir cutoff of < 1 µg/L, while 31% showed discordance when using a cutoff of < 0.4 µg/L [85] (MQ). Evaluating GH levels from the mean of 3 consecutive assessments using the same validated assay rather than a single assessment can lessen the impact of GH cutoff on discordance [86] (VLQ).

IGF-I levels should be measured 12 weeks after surgery to determine postoperative biochemical remission (SR). As the magnitude of GH decrease in the immediate postoperative period likely reflects the degree of success in adenoma removal, early random GH assessment on day 1–14 and comparison with preoperative GH levels can inform the degree of adenoma removal and subsequent longer-term remission (DR). OGTT assessment may provide further predictive value (DR). As preoperative SRL, used in patients with risk factors for more adverse surgical outcomes [87], may have carryover effects that continue to influence postoperative IGF-I values [88] (MQ), assessment should be repeated at 3–6 months to confirm remission (DR).

Remission with adenoma-directed medical therapy

Long-term follow-up of patients with acromegaly shows no increase in mortality risk in patients who maintain normalized IGF-I [89] (MQ), and improved rates of biochemical control in more recent years has been attributed, at least in part, to effective GH suppression with use of SRL therapy [90, 91] (LQ). However, as injectable SRL is administered monthly, timing of assessment for IGF-I could influence determination of biochemical control. In one study [92], wide variability in IGF-I levels was seen upon weekly assessments in patients treated with long-acting octreotide or lanreotide, but not in acromegaly patients in continued postoperative remission not treated with SRL or in healthy controls (LQ). At least one IGF-I level ≥ 2 standard deviations above normal was seen in 10–20% of patients during the treatment cycle. As the last sampling just before the next injection was the best predictor of variability [92], consistent with the waning of QOL seen at the end of the treatment cycle [93] (LQ), this is the recommended timing for IGF-I assessment during injectable SRL therapy (DR). IGF-I level

measured in the last week before the next injection should therefore be used to determine a need for dose titration or consideration of alternative treatment options if normalization is not achieved (SR).

For patients treated with oral SRL administered daily, assessment of IGF-I for the purposes of dose titration should be done after at least 2 weeks of treatment (SR) [94]. Timing of IGF-I assessment is not critical for patients treated with cabergoline administered in more than once-weekly intervals; the timing of assessment for patients treated once weekly has not been systematically investigated (VLQ).

With all of these agents, random GH assessment is not likely to provide additional information in all patients, but could be considered for symptomatic patients with IGF-I levels at the higher end of the ULN (DR).

Remission with peripherally directed medical therapy

In clinical trials of the GH receptor antagonist pegvisomant as first-line medical therapy, 82–92% of patients achieved normalized IGF-I [95] (HQ). Real-world studies of pegvisomant used mostly as second- or third-line medical therapy show approximately 54–64% of patients maintain biochemical control over the long term [96, 97] (MQ). Lower rates are likely due, at least in part, to inadequate dose titration [98]. Nevertheless, regardless of IGF-I control, patients showed consistent improvements in QOL [99] (LQ) as well as decreased blood glucose in those with and without diabetes [100] (LQ), suggesting that suppression of peripheral GH action has a broader effect on disease activity beyond IGF-I control.

Estrogens and selective estrogen receptor modulators (SERMs) inhibit hepatic IGF-I production but currently have a limited role in acromegaly management [101, 102] (VLQ).

For patients treated with medical therapy that targets the GH receptor or the estrogen receptor, efficacy assessment is limited to IGF-I normalization (SR). With these agents, GH assessment is not informative and should not be performed.

Follow up

Acromegaly is a chronic disease, requiring lifelong monitoring to prevent or minimize deleterious effects of GH hypersecretion. Yet, acromegaly is also a heterogeneous disease, and complex treatment algorithms describe multiple potential monotherapy and combination therapy approaches depending on individual patient and adenoma characteristics [17]. Follow up assessments should therefore consider biochemical evaluation of treatment effectiveness, imaging studies evaluating residual or recurrent mass, and

clinical signs and symptoms of acromegaly complications and comorbidities (SR).

Biochemical assessments

Multiple groups have considered optimal timing for GH/IGF-I assessment in determining postoperative remission. However, there is currently no known optimal timing for continued biochemical assessment (VLQ). Given the high rates of biochemical remission after microadenoma resection [103] (HQ), and the very low rates of recurrence among those who achieve postoperative remission even after 10 years of follow up [104, 105] (MQ), rigorous studies to define optimal assessment timing are likely not feasible.

Within the first postoperative year, IGF-I measurements every 3–6 months may be appropriate to confirm remission and then every 6–12 months to monitor for potential recurrence (SR). OGTT might be helpful in evaluating patients with borderline IGF-I levels and clinical signs of disease activity (DR).

For patients who did not achieve postoperative remission and who are treated with adjuvant SRL, IGF-I should be assessed 3 months after initiation/dose adjustment of injectable SRL and 2–4 weeks after initiation/dose adjustment of oral SRL to establish an optimal dosing regimen [94], and then every 6–12 months thereafter once biochemical control is achieved (SR). Random GH might be helpful in select cases where evaluation of adenoma behavior is a concern (DR). As pegvisomant and cabergoline have a shorter half-life than injectable SRL, IGF-I should be assessed every 1–3 months after treatment initiation/dose adjustment to establish the dosing regimen, and then every 6–12 months thereafter. GH assessment is not informative in follow-up of pegvisomant and cabergoline and should not be performed (SR).

In patients receiving radiotherapy to the residual/recurrent mass, medical therapy is used as a bridge until radiation effect is seen [106]. In these patients, IGF-I should be assessed at the intervals appropriate for the medical therapy used (SR). With sustained decline of IGF-I within the target range, treatment can be paused at least once each year depending on rapidity of the IGF-I decline to test for the onset of radiation-induced remission (DR).

For all patients, ideally, the same well-validated IGF-I assay should be used for all assessments (SR). New or persistent elevations in IGF-I levels should be interpreted within the context of the individual clinical scenario and account for factors that could affect results such as pregnancy, estrogen use, starvation, and metabolic changes (SR).

Imaging studies

Long-term follow up of patients who achieve postoperative biochemical remission show that a vanishingly small percentage of those with recurrence show evidence of new tissue mass on MRI, and fewer still require a second surgery [104] (LQ). Similarly, while SRL use can result in adenoma shrinkage in approximately one-third of patients, particularly when used as primary medical therapy [107–109] (HQ) adenoma *growth* during SRL therapy is rare [110–112] (VLQ), and it is likely that such patients would first demonstrate biochemical changes if they recur. Even in patients treated with pegvisomant, after 14 years of follow up, central reassessment of equivocal MRIs led to only 1.4% of patients discontinuing treatment due to adenoma growth [96] (MQ).

Therefore, regular MRI follow-up is not indicated for all patients with acromegaly (SR). Patient-specific factors informing the need for follow up MRI (DR) include those older at presentation who are more likely to have smaller adenomas and less aggressive disease [113] (VLQ), and those with T2-weighted hypointensity who are more likely to demonstrate more favorable SRL responsiveness [41] (LQ), suggesting that these cohorts are less likely to exhibit clinically relevant adenoma re-growth on MRI.

The same standards for imaging and results reporting should be used in follow up as in diagnosis (SR). MRI should be performed at 3–6 months postoperatively and used as baseline for further assessments (SR). Thereafter, MRI should be performed upon signs of biochemical or clinical disease progression, and when a change in therapeutic modality is considered, such as prior to a second surgery or radiotherapy (SR). ¹¹C-methionine PET imaging may aid localization of residual adenoma in patients with persistent GH hypersecretion following primary (and subsequent) therapy when MRI findings are equivocal [45, 46] (DR). An individualized approach to MRI is appropriate for patients treated with pegvisomant based on country-specific labeling requirements, as well as for those with genetic syndromes or prior imaging suggestive of highly aggressive disease (DR).

Clinical assessments

Effective management of acromegaly disease comorbidities and complications over the long term is critical to maximizing patient outcomes. Although cardiovascular disease is no longer the leading cause of mortality in patients with acromegaly [114, 115] (MQ), hypertension and diabetes are associated with increased cardiovascular morbidity and mortality [116, 117] (MQ). This Workshop endorsed evaluation and treatment of disease comorbidities according to prior consensus recommendations [8] (SR). The need for assessment of common comorbidities, such as hypopituitarism, obstructive sleep apnea, and vertebral fractures

depends on clinical symptoms and adenoma behavior, and follow up according to accepted guidelines [8, 118] was recommended (SR).

Although acromegaly patients are at increased risk for colon cancer, increased rates of cancer-specific mortality have not been shown [119] (MQ). Guidelines for screening high-risk patients from the British Society of Gastroenterology and Association of Coloproctology for Great Britain and Ireland suggest regular screening beginning at age 40, and individualized considerations for repeat colonoscopy according to evidence of acromegaly disease activity and prior colonoscopy findings [120]. Nevertheless, there was no consensus at this Workshop on whether colonoscopy should be performed in all patients at diagnosis of acromegaly regardless of age, despite the discretionary recommendation in previous consensus publications [8]. For all other cancers with reported increased frequency in acromegaly, including thyroid cancer, there was consensus that screening be performed according to national/regional guidelines for the general population [8].

Tools for assessment

SAGIT and ACRODAT are scoring tools that use multiple disease-specific parameters to define severity of acromegaly [121, 122]. With SAGIT, clinicians have the opportunity to standardize scoring to evaluate signs and symptoms, associated comorbidities, GH levels, IGF-I levels, and adenoma characteristics. Although results from the validation study showed that IGF-I and GH levels drove disease activity scoring, non-biochemical indicators of disease activity influenced treatment decisions [121 (MQ)]. With ACRODAT, clinicians rate disease activity as stable, mild, or severe based on IGF-I level, adenoma status, comorbidities, symptoms, and QOL, and the validation study showed that elevated IGF-I and evidence of adenoma growth drove definition of disease severity [122] (MQ).

Both instruments may be useful in clinical practice for assessing changes in acromegaly disease severity and progression over time (DR). A prospective study measuring a clinically beneficial effect of ACRODAT as a monitoring tool is underway.

Considerations for selecting second and third-line medical therapy

Follow up assessments identify patients more likely to show a good response to second- and third-line medical therapy options if needed. For example, among patients unresponsive to octreotide/lanreotide, those with T2 MRI hyperintensity are more likely to show improved IGF-I levels while receiving pasireotide (VLQ), and those with lower SST2 and higher SST5 receptor expression are more likely to achieve

adenoma shrinkage with pasireotide [123] (LQ). By contrast, those with lower SST5 receptor expression are less likely to respond to pasireotide, and those with adenoma extension to the third ventricle are less likely to respond to both pasireotide and pegvisomant [124] (LQ). For patients demonstrating insufficient control on single-agent adenoma-targeting SRL, the addition of a peripherally targeting GH receptor antagonist could be beneficial; in such cases, the combination of low-dose SRL plus weekly pegvisomant is both highly effective and more cost-effective than higher doses or more frequent dosing of these agents [125] (MQ).

Results of follow up assessments can also be used to identify patients who might benefit from treatment options that have an improved safety profile or more convenient dosing regimen (SR). For example, pegvisomant can improve metabolic outcomes [126] (MQ), which may be indicated for patients demonstrating glycemic changes with SRL monotherapy (DR). Pasireotide might have a more effective shrinkage effect than octreotide and lanreotide [109] and may be indicated in patients with clinically relevant residual adenoma mass (DR). Oral octreotide has proven effective in maintaining biochemical control in patients previously controlled on octreotide LAR or lanreotide depot injection therapy [127] (HQ). The side effect profile is similar to that of octreotide LAR even when used at the highest doses, yet data from extension trials show that more patients prefer oral over injectable administration [128], and such an option could be considered to address QOL concerns (DR).

Conclusions

Acromegaly is an insidious disease with potential lethal consequences if not diagnosed and treated in a timely manner, as is unfortunately commonly reported. In this context, therapeutic inertia, as for other chronic diseases, is also frequently manifest. Therefore, the outcomes of the 14th Acromegaly Consensus Conference are particularly clinically relevant. The current statement updates and refines previous statements from our Group concerning the proper approach to diagnose acromegaly using biochemical, clinical, and imaging criteria. Moreover, the current statement also includes new recommendations on assessment of “remission” after each specific treatment tool. Recommendations on the optimal follow-up of acromegaly both in terms of timing and methodologies are presented. Worldwide application of the current recommendations should improve management of acromegaly, helping, at least in part, to mitigate the adverse impact of commonly observed diagnostic delay and therapeutic inertia.

Acknowledgements The authors dedicate the manuscript to our colleague and friend, the late Marcello Bronstein, in honor of his major contributions to the field.

Author contributions Steering Committee Members (AG, NM, FFC, MF, PM, CS, AJvdL, JW, and SM) conceptualized the consensus meeting and publication of its conclusions. AG and SM prepared the initial draft manuscript. Steering Committee Members critically revised the initial draft. All authors reviewed, edited, and approved the final manuscript.

Funding Open access funding provided by SCEL, Statewide California Electronic Library Consortium. The 14th Acromegaly Consensus Conference was supported by unrestricted educational grants from Amolyt Pharma, Amryt Pharma, Basecamp Bio, Crinetics Pharmaceuticals, Ionis Pharmaceuticals, and Recordati Rare Diseases. Supporters were invited to observe the highlight summaries, but did not observe the small group discussions, had no role in the development of consensus recommendations or topics for future research, and did not review the manuscript prior to publication.

Data Availability Not applicable.

Declarations

Competing interests AB, MB, AG, and RS are Editors of *Pituitary*. NB, CB, TB, FC, PC, MF, SF, MG, YG, KH, AI, GJ, JOJ, LK, NK, RL, PM, SN, SP, CS, IS, SLS, and AJvdL are Editorial Board Members of *Pituitary*. SM is Editor-in-Chief of *Pituitary*. MB has received research support, consultancy, and/or lecture fees from Camurus, Chiasma, Crinetics Pharmaceuticals, Diasorin, IDS, Ionis, IPSEN, Midatech, Novartis, Ono, OPKO, Pfizer, Recordati, Roche, and Strongbridge. CB has received support for investigator-initiated clinical trials from Crinetics and served as speaker or consultant for Ipsen, Recordati, and NovoNordisk. TB has received support for research grants from Pfizer, consultant/speaker agreements with Ipsen and Pfizer, and clinical trials for Crinetics and Debiopharm. PC has received unrestricted research and educational grants from Ipsen, Novartis, and Pfizer, Recordati, and Advanz; has served as an investigator for clinical trials funded by Crinetics, Chiasma, and Debiopharm; is a member of Advisory Boards for Ipsen, Pfizer, Crinetics, Recordati, and Amolyt; and is a speaker for Ipsen, Recordati, and Pfizer. SC has served as an investigator for clinical trials funded by Novartis, Pfizer, Ipsen, and Crinetics; received grants to the institution from Pfizer, Ipsen, and Recordati; and served as an Advisory Board member for Recordati. DE has received lecture fees from Ipsen and Pfizer. AB, MF has received grants to the institution from Amryt, Crinetics, Ionis, and Recordati, and occasional consulting fees from Amryt, Camurus, Crinetics, Ipsen, and Recordati. MF has served as an Advisory Board member for Recordati, Crinetics and Ipsen, received speaker fees from Recordati and Ipsen, and served as principal investigator for studies funded by Recordati and Crinetics. SF has received consultancy and speaker fees from Ipsen, Pfizer, Novartis, and Recordati. BG has received research grants to the institution from Amryt/Chiesi and Ionis, and served as an occasional consultant to Amryt/Chiesi and Crinetics. AG has served as a consultant for Ipsen, Pfizer and Recordati and received research grants to the institution from Pfizer and Recordati. MG has served as a member of a speakers bureau for Ipsen Ltd UK and Pfizer. AI has served as principal investigator for institution-directed research grants from Recordati, Xeris and Amryt/Chiesi, and as an occasional consultant for Recordati, Xeris, Amryt/Chiesi, Camurus, and Crinetics. GJ has served as consultant for NovoNordisk and AstraZeneca and received lecture fees from NovoNordisk and Pfizer. JOJ has received lecture fees and unrestricted research grants from Pfizer and Novo Nordisk. PM has received speaker and/or consultancy fees from Pfizer. UBK has served as consultant for

ModeX Therapeutics. LK has served as advisor for Camarus, Novo Nordisk, and Strongbridge, and received research funding from Camurus. NK has served as speaker for Pfizer, Ipsen, and Recordati Rare Diseases; as an investigator for Pfizer and Ipsen; and as a Scientific Advisory Board member for Pfizer, Ipsen, and Recordati Rare Diseases. AL has received honoraria for presentations from Pfizer and Ipsen. MM has served on advisory boards and as a speaker for Ipsen, Recordati, and Pfizer. PM has served as principal investigator, and has received consultation fees and research grants from Pfizer, Recordati, and Camurus. SM has received grants to the institution from Recordati and served as an adviser to Recordati, Crinetics, and Ionis. SN has received research grants Pfizer and consultancy grants from Recordati, NovoNordisk, and Crinetics. LP has received congress fees from Merck and Sandoz. SP has served as a speaker at workshops and Advisory Boards for Ipsen, Pfizer, and Recordati. MR has received consulting fees from Crinetics and Ipsen. CS has received speaker fees from Pfizer, and served as an advisor to Debiopharm, NovoNordisk, Chiasma, and Crinetics. IS has served as an investigator for Crinetics, Chiasma, and Debiopharm, and as speaker and consultant for Pfizer, Medison, and NovoNordisk. RS has served as a consultant for NovoNordisk, Amryt, and Camurus. SLS has served as principal investigator and conducted research studies supported by Novartis and Chiasma. ST has received grants to the institution from Crinetics, honoraria for lectures/presentations from Recordati, and support for attending meetings and/or travel from Pfizer, Ipsen, and Recordati, and has served as an Advisory Board member for Pfizer and Recordati. AJvdL has received speaker and/or consultancy fees from Pfizer, Ipsen, Crinetics, Tiburio, and Amolyt Pharma SA. All other authors declare no competing interests.

Ethical approval Not applicable.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Colao A, Grasso LFS, Giustina A, Melmed S, Chanson P, Pereira AM, Pivonello R (2019) Acromegaly. *Nat Rev Dis Primers* 5:20. <https://doi.org/10.1038/s41572-019-0071-6>
- Melmed S (2020) Pituitary-tumor endocrinopathies. *N Engl J Med* 382:937–950. <https://doi.org/10.1056/NEJMra1810772>
- Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K, Melmed S (2000) Criteria for cure of acromegaly: a consensus statement. *J Clin Endocrinol Metab* 85:526–529. <https://doi.org/10.1210/jcem.85.2.6363>
- Giustina A, Chanson P, Bronstein MD, Klubanski A, Lamberts S, Casanueva FF, Trainer P, Ghigo E, Ho K, Melmed S, Consensus A (2010) A consensus on criteria for cure of acromegaly. *J Clin Endocrinol Metab* 95:3141–3148. <https://doi.org/10.1210/jc.2009-2670>

5. Katznelson L, Laws ER Jr., Melmed S, Molitch ME, Murad MH, Utz A, Wass JA, Endocrine S (2014) Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 99:3933–3951. <https://doi.org/10.1210/jc.2014-2700>
6. Chanson P, Arnoux A, Mavromati M, Brailly-Tabard S, Massart C, Young J, Pickett ML, Souberbielle JC, Investigators V (2016) Reference values for IGF-I serum concentrations: comparison of six immunoassays. *J Clin Endocrinol Metab* 101:3450–3458. <https://doi.org/10.1210/jc.2016-1257>
7. Schilbach K, Gar C, Lechner A, Nicolay SS, Schwerdt L, Haenelt M, Dal J, Jorgensen JL, Stormann S, Schopohl J, Bidlingmaier M (2019) Determinants of the growth hormone nadir during oral glucose tolerance test in adults. *Eur J Endocrinol* 181:55–67. <https://doi.org/10.1530/EJE-19-0139>
8. Giustina A, Barkan A, Beckers A, Biermasz N, Biller BMK, Boguszewski C, Bolanowski M, Bonert V, Bronstein MD, Casanueva FF, Clemmons D, Colao A, Ferone D, Fleseriu M, Frara S, Gadelha MR, Ghigo E, Gurnell M, Heaney AP, Ho K, Ioachimescu A, Katznelson L, Kelestimur F, Kopchick J, Krsek M, Lamberts S, Losa M, Luger A, Maffei P, Marazuela M, Mazziotti G, Mercado M, Mortini P, Neggers S, Pereira AM, Petersenn S, Puig-Domingo M, Salvatori R, Shimon I, Strasburger C, Tsagarakis S, van der Lely AJ, Wass J, Zatelli MC, Melmed S (2020) A consensus on the diagnosis and treatment of acromegaly comorbidities: an update. *J Clin Endocrinol Metab*. <https://doi.org/10.1210/clinem/dgz096>
9. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ, Group GW (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 336:924–926. <https://doi.org/10.1136/bmj.39489.470347.AD>
10. Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JAH, Strasburger CJ, Luger A, Clemmons DR, Giustina A (2018) A Consensus Statement on acromegaly therapeutic outcomes. *Nat Rev Endocrinol* 14:552–561. <https://doi.org/10.1038/s41574-018-0058-5>
11. Swiglo BA, Murad MH, Schunemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM (2008) A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab* 93:666–673. <https://doi.org/10.1210/jc.2007-1907>
12. Giustina A, Bronstein MD, Casanueva FF, Chanson P, Ghigo E, Ho KK, Klibanski A, Lamberts S, Trainer P, Melmed S (2011) Current management practices for acromegaly: an international survey. *Pituitary* 14:125–133. <https://doi.org/10.1007/s11102-010-0269-9>
13. Sabbah N, Wolf P, Piedvache C, Trabado S, Verdelet T, Cornu C, Souberbielle JC, Chanson P (2021) Reference values for IGF-I serum concentration in an adult population: use of the VARIETE cohort for two new immunoassays. *Endocr Connect* 10:1027–1034. <https://doi.org/10.1530/EC-21-0175>
14. Bonert V, Carmichael J, Wu Z, Mirocha J, Perez DA, Clarke NJ, Reitz RE, McPhaul MJ, Mamelak A (2018) Discordance between mass spectrometry and immunometric IGF-1 assay in pituitary Disease: a prospective study. *Pituitary* 21:65–75. <https://doi.org/10.1007/s11102-017-0849-z>
15. Clemmons DR (2011) Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. *Clin Chem* 57:555–559. <https://doi.org/10.1373/clinchem.2010.150631>
16. Bidlingmaier M, Friedrich N, Emeny RT, Spranger J, Wolthers OD, Roswall J, Korner A, Obermayer-Pietsch B, Hubener C, Dahlgren J, Frystyk J, Pfeiffer AF, Doering A, Bielowhuby M, Wallaschofski H, Arafat AM (2014) Reference intervals for insulin-like growth factor-1 (igf-i) from birth to senescence: results from a multicenter study using a new automated chemiluminescence IGF-I immunoassay conforming to recent international recommendations. *J Clin Endocrinol Metab* 99:1712–1721. <https://doi.org/10.1210/jc.2013-3059>
17. Fleseriu M, Langlois F, Lim DST, Varlamov EV, Melmed S (2022) Acromegaly: pathogenesis, diagnosis, and management. *Lancet Diabetes Endocrinol* 10:804–826. [https://doi.org/10.1016/S2213-8587\(22\)00244-3](https://doi.org/10.1016/S2213-8587(22)00244-3)
18. Bianchi A, Mazziotti G, Tilaro L, Cimino V, Veltri F, Gaetani E, Pecorini G, Pontecorvi A, Giustina A, De Marinis L (2009) Growth hormone receptor polymorphism and the effects of pegvisomant in acromegaly. *Pituitary* 12:196–199. <https://doi.org/10.1007/s11102-008-0157-8>
19. de Menis E, Gola M, Giustina A (2006) Development of acromegaly in a patient with Anorexia Nervosa: pathogenetic and diagnostic implications. *J Endocrinol Invest* 29:821–825. <https://doi.org/10.1007/BF03347377>
20. Giustina A, Berardelli R, Gazzaruso C, Mazziotti G (2015) Insulin and GH-IGF-I axis: endocrine pacer or endocrine disruptor? *Acta Diabetol* 52:433–443. <https://doi.org/10.1007/s00592-014-0635-6>
21. Moncrieffe D, Cox HD, Carletta S, Becker JO, Thomas A, Eichner D, Ahrens B, Thevis M, Bowers LD, Cowan DA, Hoofnagle AN (2020) Inter-laboratory agreement of insulin-like growth factor 1 concentrations measured intact by Mass Spectrometry. *Clin Chem* 66:579–586. <https://doi.org/10.1093/clinchem/hvaa043>
22. Dimaraki EV, Jaffe CA, DeMott-Friberg R, Chandler WF, Barkan AL (2002) Acromegaly with apparently normal GH secretion: implications for diagnosis and follow-up. *J Clin Endocrinol Metab* 87:3537–3542. <https://doi.org/10.1210/jcem.87.8.8658>
23. Faje AT, Barkan AL (2010) Basal, but not pulsatile, growth hormone secretion determines the ambient circulating levels of insulin-like growth factor-I. *J Clin Endocrinol Metab* 95:2486–2491. <https://doi.org/10.1210/jc.2009-2634>
24. Giustina A, Veldhuis JD (1998) Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. *Endocr Rev* 19:717–797. <https://doi.org/10.1210/edrv.19.6.0353>
25. Ribeiro-Oliveira A Jr., Faje AT, Barkan AL (2011) Limited utility of oral glucose tolerance test in biochemically active acromegaly. *Eur J Endocrinol* 164:17–22. <https://doi.org/10.1530/EJE-10-0744>
26. Hage M, Janot C, Salenave S, Chanson P, Kamenicky P (2021) MANAGEMENT OF ENDOCRINE DISEASE: etiology and outcome of acromegaly in patients with a paradoxical GH response to glucose. *Eur J Endocrinol* 184:R261–R268. <https://doi.org/10.1530/EJE-20-1448>
27. Arafat AM, Muller L, Mohlig M, Mayr B, Kremenevskaya N, Pfeiffer AF, Buchfelder M, Schofl C (2011) Comparison of oral glucose tolerance test (OGTT) 100 g with OGTT 75 g for evaluation of acromegalic patients and the impact of gender on test reproducibility. *Clin Endocrinol (Oxf)* 75:685–691. <https://doi.org/10.1111/j.1365-2265.2011.04108.x>
28. Alexopoulou O, Bex M, Kamenicky P, Mvoola AB, Chanson P, Maiter D (2014) Prevalence and risk factors of impaired glucose tolerance and Diabetes Mellitus at diagnosis of acromegaly: a study in 148 patients. *Pituitary* 17:81–89. <https://doi.org/10.1007/s11102-013-0471-7>
29. Dobri G, Niwattisaiwong S, Bena JF, Gupta M, Kirwan J, Kennedy L, Hamrahian AH (2019) Is GH nadir during OGTT a reliable test for diagnosis of acromegaly in patients with abnormal glucose metabolism? *Endocrine* 64:139–146. <https://doi.org/10.1007/s12020-018-1805-z>

30. Giustina A, Wehrenberg WB (1994) Growth hormone neuroregulation in Diabetes Mellitus. *Trends Endocrinol Metab* 5:73–78. [https://doi.org/10.1016/1043-2760\(94\)90005-1](https://doi.org/10.1016/1043-2760(94)90005-1)
31. Giustina A, Bossoni S, Cimino A, Pizzocolo G, Romanelli G, Wehrenberg WB (1990) Impaired growth hormone (GH) response to pyridostigmine in type I diabetic patients with exaggerated GH-releasing hormone-stimulated GH secretion. *J Clin Endocrinol Metab* 71:1486–1490. <https://doi.org/10.1210/jcem-71-6-1486>
32. Schweizer J, Schilbach K, Haenelt M, Giannetti AV, Bizzi MF, Soares BS, Paulino E, Schopohl J, Stormann S, Ribeiro-Oliveira A, Bidlingmaier M (2021) Soluble Alpha Klotho in Acromegaly: comparison with traditional markers of Disease Activity. *J Clin Endocrinol Metab* 106:e2887–e2899. <https://doi.org/10.1210/clinem/dgab257>
33. Coopmans EC, El-Sayed N, Frystyk J, Magnusson NE, Jorgensen JOL, van der Lely AJ, Janssen J, Muhammad A, Neggens S (2020) Soluble Klotho: a possible predictor of quality of life in acromegaly patients. *Endocrine* 69:165–174. <https://doi.org/10.1007/s12020-020-02306-4>
34. Giustina A (2020) Acromegaly and vertebral fractures: facts and questions. *Trends Endocrinol Metab* 31:274–275. <https://doi.org/10.1016/j.tem.2020.01.011>
35. Frara S, Maffezzoni F, Mazziotti G, Giustina A (2016) Current and emerging aspects of Diabetes Mellitus in Acromegaly. *Trends Endocrinol Metab* 27:470–483. <https://doi.org/10.1016/j.tem.2016.04.014>
36. Frara S, Melin Uygur M, di Filippo L, Doga M, Losa M, Santoro S, Mortini P, Giustina A (2022) High prevalence of vertebral fractures Associated with preoperative GH levels in patients with recent diagnosis of Acromegaly. *J Clin Endocrinol Metab* 107:e2843–e2850. <https://doi.org/10.1210/clinem/dgac183>
37. Coopmans EC, Andela CD, Claessen K, Biermasz NR (2022) Evaluating the impact of Acromegaly on Quality of Life. *Endocrinol Metab Clin North Am* 51:709–725. <https://doi.org/10.1016/j.ecl.2022.04.004>
38. Micko AS, Wohrer A, Wolfsberger S, Knosp E (2015) Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. *J Neurosurg* 122:803–811. <https://doi.org/10.3171/2014.12.JNS141083>
39. Varlamov EV, Wood MD, Netto JP, Thiessen J, Kim J, Lim DST, Yedinak CG, Banskota S, Cetas JS, Fleseriu M (2020) Cystic appearance on magnetic resonance imaging in bihormonal growth hormone and prolactin tumors in acromegaly. *Pituitary* 23:672–680. <https://doi.org/10.1007/s11102-020-01075-7>
40. Heck A, Emblem KE, Casar-Borota O, Bollerslev J, Ringstad G (2016) Quantitative analyses of T2-weighted MRI as a potential marker for response to somatostatin analogs in newly diagnosed acromegaly. *Endocrine* 52:333–343. <https://doi.org/10.1007/s12020-015-0766-8>
41. Potora I, Beckers A, Bonneville JF (2017) T2-weighted MRI signal intensity as a predictor of hormonal and tumoral responses to somatostatin receptor ligands in acromegaly: a perspective. *Pituitary* 20:116–120. <https://doi.org/10.1007/s11102-017-0788-8>
42. Nasi-Kordhishti I, Grimm F, Giese S, Lorincz KN, Bender B, Honegger J (2022) The importance of MRI quality and reader's experience for detecting an adenoma in Cushing's Disease. *Eur J Endocrinol* 187:349–359. <https://doi.org/10.1530/EJE-22-0180>
43. Giustina A, Uygur MM, Frara S, Barkan A, Biermasz NR, Chanson P, Freda P, Gadelha M, Kaiser UB, Lamberts S, Laws E, Nachtigall LB, Popovic V, Reincke M, Strasburger C, van der Lely AJ, Wass JAH, Melmed S, Casanueva FF (2023) Pilot study to define criteria for pituitary tumors centers of excellence (PTCOE): results of an audit of leading international centers. *Pituitary* 26:583–596
44. Zendran I, Gut G, Kaluzny M, Zawadzka K, Bolanowski M (2022) Acromegaly caused by ectopic growth hormone releasing hormone secretion: a review. *Front Endocrinol (Lausanne)* 13:867965. <https://doi.org/10.3389/fendo.2022.867965>
45. Koulouri O, Kandasamy N, Hoole AC, Gillett D, Heard S, Powlson AS, O'Donovan DG, Annamalai AK, Simpson HL, Akker SA, Aylwin SJ, Brooke A, Buch H, Levy MJ, Martin N, Morris D, Parkinson C, Tysome JR, Santarius T, Donnelly N, Buscombe J, Boros I, Smith R, Aigbirhio F, Antoun NM, Burnett NG, Cheow H, Mannion RJ, Pickard JD, Gurnell M (2016) Successful treatment of residual pituitary adenoma in persistent acromegaly following localisation by 11 C-methionine PET co-registered with MRI. *Eur J Endocrinol* 175:485–498. <https://doi.org/10.1530/EJE-16-0639>
46. Bashari WA, Senanayake R, Koulouri O, Gillett D, MacFarlane J, Powlson AS, Fernandez-Pombo A, Bano G, Martin AJ, Scoffings D, Cheow H, Mendichovszky I, Tysome J, Donnelly N, Santarius T, Koliass A, Mannion R, Gurnell M (2020) PET-guided repeat transphenoidal Surgery for previously deemed unresectable lateral Disease in acromegaly. *Neurosurg Focus* 48:E8. <https://doi.org/10.3171/2020.3.FOCUS2052>
47. Melmed S, Kaiser UB, Lopes MB, Bertherat J, Syro LV, Raverot G, Reincke M, Johannsson G, Beckers A, Fleseriu M, Giustina A, Wass JAH, Ho KKY (2022) Clinical Biology of the Pituitary Adenoma. *Endocr Rev* 43:1003–1037. <https://doi.org/10.1210/endrev/bnac010>
48. Trouillas J, Roy P, Sturm N, Dantony E, Cortet-Rudelli C, Viennet G, Bonneville JF, Assaker R, Auger C, Brue T, Corneliuss A, Dufour H, Jouanneau E, Francois P, Galland F, Mougel F, Chapuis F, Villeneuve L, Maurice CA, Figarella-Branger D, Raverot G, Barlier H, Bernier A, Bonnet M, Borson-Chazot F, Brassier F, Caulet-Maugendre G, Chabre S, Chanson O, Cottier P, Delemer JF, Delgrange B, Di Tommaso E, Eimer L, Gaillard S, Jan S, Girard M, Lapras JJ, Loiseau V, Passagia H, Patey JG, Penfornis M, Poirier A, Perrin JY, Tabarin G (2013) A.: A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years post-operative follow-up. *Acta Neuropathol* 126:123–135. <https://doi.org/10.1007/s00401-013-1084-y>
49. Sahakian N, Appay R, Resseguier N, Graillon T, Piazzola C, Laure C, Figarella-Branger D, Regis J, Castinetti F, Brue T, Dufour H, Cuny T (2022) Real-life clinical impact of a five-tiered classification of pituitary tumors. *Eur J Endocrinol* 187:893–904. <https://doi.org/10.1530/EJE-22-0812>
50. Raverot G, Dantony E, Beauvy J, Vasiljevic A, Mikolasek S, Borson-Chazot F, Jouanneau E, Roy P, Trouillas J (2017) Risk of recurrence in Pituitary neuroendocrine tumors: a prospective study using a five-tiered classification. *J Clin Endocrinol Metab* 102:3368–3374. <https://doi.org/10.1210/jc.2017-00773>
51. Brzana J, Yedinak CG, Gultekin SH, Delashaw JB, Fleseriu M (2013) Growth hormone granulation pattern and somatostatin receptor subtype 2A correlate with postoperative somatostatin receptor ligand response in acromegaly: a large single center experience. *Pituitary* 16:490–498. <https://doi.org/10.1007/s11102-012-0445-1>
52. Kasuki L, Vieira Neto L, Wildemberg LE, Colli LM, de Castro M, Takiya CM, Gadelha MR (2012) AIP expression in sporadic somatotropinomas is a predictor of the response to octreotide LAR therapy Independent of SSTR2 expression. *Endocr Relat Cancer* 19:L25–L29. <https://doi.org/10.1530/ERC-12-0020>
53. Wan XY, Chen J, Wang JW, Liu YC, Shu K, Lei T (2022) Overview of the 2022 WHO classification of Pituitary Adenomas/Pituitary neuroendocrine tumors: clinical practices,

- controversies, and perspectives. *Curr Med Sci* 42:1111–1118. <https://doi.org/10.1007/s11596-022-2673-6>
54. Ho KKY, Gadelma M, Kaiser UB, Reincke M, Melmed S (2022) The NETting of pituitary adenoma: a gland illusion. *Pituitary* 25:349–351. <https://doi.org/10.1007/s11102-022-01235-x>
 55. Esposito D, Ragnarsson O, Johannsson G, Olsson DS (2020) Prolonged diagnostic delay in acromegaly is associated with increased morbidity and mortality. *Eur J Endocrinol* 182:523–531. <https://doi.org/10.1530/EJE-20-0019>
 56. Kreitschmann-Andermahr I, Siegel S, Kleist B, Kohlmann J, Starz D, Buslei R, Koltowska-Haggstrom M, Strasburger CJ, Buchfelder M (2016) Diagnosis and management of acromegaly: the patient's perspective. *Pituitary* 19:268–276. <https://doi.org/10.1007/s11102-015-0702-1>
 57. Nabarro JD (1987) Acromegaly. *Clin Endocrinol (Oxf)* 26:481–512. <https://doi.org/10.1111/j.1365-2265.1987.tb00805.x>
 58. Dal J, Skov BG, Andersen M, Feldt-Rasmussen U, Feltoft CL, Karmisholt J, Nielsen EH, Dekkers OM, Jorgensen JOL (2021) Sex differences in acromegaly at diagnosis: a nationwide cohort study and meta-analysis of the literature. *Clin Endocrinol (Oxf)* 94:625–635. <https://doi.org/10.1111/cen.14392>
 59. Siegel S, Streetz-van der Werf C, Schott JS, Nolte K, Karges W, Kreitschmann-Andermahr I (2013) Diagnostic delay is associated with psychosocial impairment in acromegaly. *Pituitary* 16:507–514. <https://doi.org/10.1007/s11102-012-0447-z>
 60. Sibeoni J, Manolios E, Verneuil L, Chanson P, Revah-Levy A (2019) Patients' perspectives on acromegaly diagnostic delay: a qualitative study. *Eur J Endocrinol* 180:339–352. <https://doi.org/10.1530/EJE-18-0925>
 61. Mortini P, Barzagli LR, Albano L, Panni P, Losa M (2018) Microsurgical therapy of pituitary adenomas. *Endocrine* 59:72–81. <https://doi.org/10.1007/s12020-017-1458-3>
 62. Giustina A, Chanson P, Kleinberg D, Bronstein MD, Clemmons DR, Klibanski A, van der Lely AJ, Strasburger CJ, Lamberts SW, Ho KK, Casanueva FF, Melmed S, Consensus A (2014) Expert consensus document: a consensus on the medical treatment of acromegaly. *Nat Rev Endocrinol* 10:243–248. <https://doi.org/10.1038/nrendo.2014.21>
 63. Giustina A, Bronstein MD, Chanson P, Petersenn S, Casanueva FF, Sert C, Houchard A, Melmed S (2019) Staging and managing patients with acromegaly in clinical practice: baseline data from the SAGIT(R) validation study. *Pituitary* 22:476–487. <https://doi.org/10.1007/s11102-019-00977-5>
 64. Melmed S (2019) Pathogenesis and diagnosis of growth hormone deficiency in adults. *N Engl J Med* 380:2551–2562. <https://doi.org/10.1056/NEJMra1817346>
 65. Chen CJ, Ironside N, Pomeranic IJ, Chivukula S, Buell TJ, Ding D, Taylor DG, Dallapiazza RF, Lee CC, Bergsneider M (2017) Microsurgical versus endoscopic transsphenoidal resection for acromegaly: a systematic review of outcomes and Complications. *Acta Neurochir (Wien)* 159:2193–2207. <https://doi.org/10.1007/s00701-017-3318-6>
 66. Phan K, Xu J, Reddy R, Kalakoti P, Nanda A, Fairhall J (2017) Endoscopic endonasal versus microsurgical Transsphenoidal Approach for Growth hormone-secreting pituitary adenomas-systematic review and Meta-analysis. *World Neurosurg* 97:398–406. <https://doi.org/10.1016/j.wneu.2016.10.029>
 67. Guo X, Zhang R, Zhang D, Wang Z, Gao L, Yao Y, Deng K, Bao X, Feng M, Xu Z, Yang Y, Lian W, Wang R, Ma W, Xing B (2022) Determinants of immediate and long-term remission after initial transsphenoidal surgery for acromegaly and outcome patterns during follow-up: a longitudinal study on 659 patients. *J Neurosurg*. <https://doi.org/10.3171/2021.11.JNS212137>
 68. Wang YY, Waqar M, Abou-Zeid A, Kearney T, Caputo C, Davis J, Trainer P, Higham C, Roncaroli F, Gnanalingham KK (2022) Value of early post-operative growth hormone testing in Predicting Long-Term Remission and residual Disease after transsphenoidal Surgery for Acromegaly. *Neuroendocrinology* 112:345–357. <https://doi.org/10.1159/000517476>
 69. Kim J, Hwang YA, Park YW, Moon JH, Kim EH, Hong JW, Lee EJ, Ku CR (2022) Revisiting growth hormone nadir cut-offs for remission in patients with acromegaly. *Eur J Endocrinol* 186:657–665. <https://doi.org/10.1530/EJE-21-1094>
 70. Feelders RA, Bidlingmaier M, Strasburger CJ, Janssen JA, Uitterlinden P, Hofland LJ, Lamberts SW, van der Lely AJ, de Herder WW (2005) Postoperative evaluation of patients with acromegaly: clinical significance and timing of oral glucose tolerance testing and measurement of (free) insulin-like growth factor I, acid-labile subunit, and growth hormone-binding protein levels. *J Clin Endocrinol Metab* 90:6480–6489. <https://doi.org/10.1210/jc.2005-0901>
 71. Kreutzer J, Vance ML, Lopes MB, Laws ER Jr. (2001) Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. *J Clin Endocrinol Metab* 86:4072–4077. <https://doi.org/10.1210/jcem.86.9.7819>
 72. Takahashi JA, Shimatsu A, Nakao K, Hashimoto N (2004) Early postoperative indicators of late outcome in acromegalic patients. *Clin Endocrinol (Oxf)* 60:366–374. <https://doi.org/10.1046/j.1365-2265.2003.01900.x>
 73. Coopmans EC, Postma MR, Wolters TLC, van Meyel SWF, Netea-Maier R, van Beek AP, Neggers S (2021) Predictors for remission after transsphenoidal Surgery in Acromegaly: a Dutch Multicenter Study. *J Clin Endocrinol Metab* 106:1783–1792. <https://doi.org/10.1210/clinem/dgab069>
 74. Espinosa-de-los-Monteros AL, Mercado M, Sosa E, Lizama O, Guinto G, Lopez-Felix B, Garcia O, Hernandez I, Ovalle A, Mendoza V (2002) Changing patterns of insulin-like growth factor-I and glucose-suppressed growth hormone levels after pituitary Surgery in patients with acromegaly. *J Neurosurg* 97:287–292. <https://doi.org/10.3171/jns.2002.97.2.0287>
 75. Shin MS, Yu JH, Choi JH, Jung CH, Hwang JY, Cho YH, Kim CJ, Kim MS (2013) Long-term changes in serum IGF-1 levels after successful surgical treatment of growth hormone-secreting pituitary adenoma. *Neurosurgery* 73:473–479. <https://doi.org/10.1227/01.neu.0000431480.87160.84>
 76. Kim EH, Oh MC, Lee EJ, Kim SH (2012) Predicting long-term remission by measuring immediate postoperative growth hormone levels and oral glucose tolerance test in acromegaly. *Neurosurgery* 70:1106–1113. <https://doi.org/10.1227/NEU.0b013e31823f5c16>
 77. Krieger MD, Couldwell WT, Weiss MH (2003) Assessment of long-term remission of acromegaly following Surgery. *J Neurosurg* 98:719–724. <https://doi.org/10.3171/jns.2003.98.4.0719>
 78. Jane JA Jr., Starke RM, Elzoghby MA, Reames DL, Payne SC, Thorner MO, Marshall JC, Laws ER Jr., Vance ML (2011) Endoscopic transsphenoidal Surgery for acromegaly: remission using modern criteria, Complications, and predictors of outcome. *J Clin Endocrinol Metab* 96:2732–2740. <https://doi.org/10.1210/jc.2011-0554>
 79. Freda PU, Wardlaw SL, Post KD (1998) Long-term endocrinological follow-up evaluation in 115 patients who underwent transsphenoidal Surgery for acromegaly. *J Neurosurg* 89:353–358. <https://doi.org/10.3171/jns.1998.89.3.0353>
 80. Cardinal T, Collet C, Wedemeyer M, Singer PA, Weiss M, Zada G, Carmichael JD (2021) Postoperative GH and Degree of reduction in IGF-1 predicts postoperative Hormonal Remission in Acromegaly. *Front Endocrinol (Lausanne)* 12:743052. <https://doi.org/10.3389/fendo.2021.743052>
 81. Park SH, Ku CR, Moon JH, Kim EH, Kim SH, Lee EJ (2018) Age- and sex-specific differences as predictors of Surgical

- Remission among patients with acromegaly. *J Clin Endocrinol Metab* 103:909–916. <https://doi.org/10.1210/jc.2017-01844>
82. Ho KY, Weissberger AJ (1994) Characterization of 24-hour growth hormone secretion in acromegaly: implications for diagnosis and therapy. *Clin Endocrinol (Oxf)* 41:75–83. <https://doi.org/10.1111/j.1365-2265.1994.tb03787.x>
 83. Freda PU (2009) Monitoring of acromegaly: what should be performed when GH and IGF-1 levels are discrepant? *Clin Endocrinol (Oxf)* 71:166–170. <https://doi.org/10.1111/j.1365-2265.2009.03556.x>
 84. Bianchi A, Giustina A, Cimino V, Pola R, Angelini F, Pontecorvi A, De Marinis L (2009) Influence of growth hormone receptor d3 and full-length isoforms on biochemical treatment outcomes in acromegaly. *J Clin Endocrinol Metab* 94:2015–2022. <https://doi.org/10.1210/jc.2008-1337>
 85. Kanakis GA, Chrisoulidou A, Bargiota A, Efstathiadou ZA, Papanastasiou L, Theodoropoulou A, Tigas SK, Vassiliadi DA, Tsagarakis S, Alevizaki M (2016) The ongoing challenge of discrepant growth hormone and insulin-like growth factor I results in the evaluation of treated acromegalic patients: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 85:681–688. <https://doi.org/10.1111/cen.13129>
 86. Campana C, Cocchiara F, Corica G, Nista F, Arvigo M, Amaru J, Rossi DC, Zona G, Ferone D, Gatto F (2021) Discordant GH and IGF-1 results in treated acromegaly: impact of GH Cutoffs and Mean values Assessment. *J Clin Endocrinol Metab* 106:789–801. <https://doi.org/10.1210/clinem/dgaa859>
 87. Apaydin T, Ozkaya HM, Keskin FE, Haliloglu OA, Karababa K, Erdem S, Kadioglu P (2017) Daily life reflections of acromegaly guidelines. *J Endocrinol Invest* 40:323–330. <https://doi.org/10.1007/s40618-016-0567-9>
 88. Yang C, Li G, Jiang S, Bao X, Wang R (2019) Preoperative somatostatin analogues in patients with newly-diagnosed acromegaly: a systematic review and Meta-analysis of comparative studies. *Sci Rep* 9:14070. <https://doi.org/10.1038/s41598-019-50639-6>
 89. Arnardottir S, Jaras J, Burman P, Berinder K, Dahlqvist P, Erfurth EM, Hoybye C, Larsson K, Ragnarsson O, Ekman B, Engstrom E (2022) Long-term outcomes of patients with acromegaly: a report from the Swedish Pituitary Register. *Eur J Endocrinol* 186:329–339. <https://doi.org/10.1530/EJE-21-0729>
 90. Bolfi F, Neves AF, Boguszewski CL, Nunes-Nogueira VS (2018) Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis. *Eur J Endocrinol* 179:59–71. <https://doi.org/10.1530/EJE-18-0255>
 91. Bolfi F, Neves AF, Boguszewski CL, Nunes-Nogueira VS (2019) Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis. *Eur J Endocrinol* 181:L5–L6. <https://doi.org/10.1530/EJE-19-0509>
 92. Maione L, Albrici C, Grunenwald S, Mouly C, Cimino V, Lecoq AL, Souberbielle JC, Caron P, Chanson P (2022) IGF-I variability over repeated measures in patients with acromegaly under long-acting somatostatin receptor ligands. *J Clin Endocrinol Metab* 107:e3644–e3653. <https://doi.org/10.1210/clinem/dgac385>
 93. Strasburger CJ, Karavitaki N, Stormann S, Trainer PJ, Kreitschmann-Andermahr I, Droste M, Korbonits M, Feldmann B, Zopf K, Sanderson VF, Schwicker D, Gelbaum D, Haviv A, Bidlingmaier M, Biermasz NR (2016) Patient-reported outcomes of parenteral somatostatin analogue injections in 195 patients with acromegaly. *Eur J Endocrinol* 174:355–362. <https://doi.org/10.1530/EJE-15-1042>
 94. Fleseriu M, Biller BMK, Freda PU, Gadelha MR, Giustina A, Katznelson L, Molitch ME, Samson SL, Strasburger CJ, van der Lely AJ, Melmed S (2021) A Pituitary Society update to acromegaly management guidelines. *Pituitary* 24:1–13. <https://doi.org/10.1007/s11102-020-01091-7>
 95. van der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, Klubanski A, Herman-Bonert V, Melmed S, Vance ML, Freda PU, Stewart PM, Friend KE, Clemmons DR, Johannsson G, Stavrou S, Cook DM, Phillips LS, Strasburger CJ, Hackett S, Zib KA, Davis RJ, Scarlett JA, Thorner MO (2001) Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 358:1754–1759. [https://doi.org/10.1016/s0140-6736\(01\)06844-1](https://doi.org/10.1016/s0140-6736(01)06844-1)
 96. Fleseriu M, Fuhrer-Sakel D, van der Lely AJ, De Marinis L, Brue T, van der Lans-Bussemaker J, Hey-Hadavi J, Camacho-Hubner C, Wajnrajch MP, Valluri SR, Palladino AA, Gomez R, Salvatori R (2021) More than a decade of real-world experience of pegvisomant for acromegaly: ACROSTUDY. *Eur J Endocrinol* 185:525–538. <https://doi.org/10.1530/EJE-21-0239>
 97. Buchfelder M, van der Lely AJ, Biller BMK, Webb SM, Brue T, Strasburger CJ, Ghigo E, Camacho-Hubner C, Pan K, Lavenberg J, Jönsson P, Hey-Hadavi JH (2018) Long-term treatment with pegvisomant: observations from 2090 acromegaly patients in ACROSTUDY. *Eur J Endocrinol* 179:419–427. <https://doi.org/10.1530/eje-18-0616>
 98. Giustina A, di Filippo L, Uygur MM, Frara S (2023) Modern approach to resistant acromegaly. *Endocrine* 80:303–307. <https://doi.org/10.1007/s12020-023-03317-7>
 99. Salvatori R, Maffei P, Webb SM, Brue T, Loftus J, Valluri SR, Gomez R, Wajnrajch MP, Fleseriu M (2022) Patient-reported outcomes in patients with acromegaly treated with pegvisomant in the ACROSTUDY extension: a real-world experience. *Pituitary* 25:420–432. <https://doi.org/10.1007/s11102-022-01206-2>
 100. Brue T, Lindberg A, van der Jan A, Akerblad AC, Koltowska-Haggstrom M, Gomez R, Droste M, Hey-Hadavi J, Strasburger CJ, Camacho-Hubner C (2019) Diabetes in patients with acromegaly treated with pegvisomant: observations from acrostudy. *Endocrine* 63:563–572. <https://doi.org/10.1007/s12020-018-1792-0>
 101. Duarte FH, Jallad RS, Bronstein MD (2015) Clomiphene citrate for treatment of acromegaly not controlled by conventional therapies. *J Clin Endocrinol Metab* 100:1863–1869. <https://doi.org/10.1210/jc.2014-3913>
 102. Magalhaes J, Ventura N, Lamback EB, Da Silva D, Camacho AH, Chimelli L, Gadelha MR, Kasuki L (2022) A prospective study on the efficacy of oral estrogen in female patients with acromegaly. *Pituitary* 25:433–443. <https://doi.org/10.1007/s11102-021-01204-w>
 103. Starnoni D, Daniel RT, Marino L, Pitteloud N, Levivier M, Messerer M (2016) Surgical treatment of acromegaly according to the 2010 remission criteria: systematic review and meta-analysis. *Acta Neurochir (Wien)* 158:2109–2121. <https://doi.org/10.1007/s00701-016-2903-4>
 104. Freda PU, Bruce JN, Reyes-Vidal C, Singh S, DeLeon Y, Jin Z, Khandji AG, Cremers S, Post KD (2021) Prognostic value of nadir GH levels for long-term biochemical remission or recurrence in surgically treated acromegaly. *Pituitary* 24:170–183. <https://doi.org/10.1007/s11102-020-01094-4>
 105. Nomikos P, Buchfelder M, Fahlbusch R (2005) The outcome of Surgery in 668 patients with acromegaly using current criteria of biochemical ‘cure’. *Eur J Endocrinol* 152:379–387. <https://doi.org/10.1530/eje.1.01863>
 106. Giustina A, Barkhoudarian G, Beckers A, Ben-Shlomo A, Biermasz N, Biller B, Boguszewski C, Bolanowski M, Bollerslev J, Bonert V, Bronstein MD, Buchfelder M, Casanueva F, Chanson P, Clemmons D, Fleseriu M, Formenti AM, Freda P, Gadelha M, Geer E, Gurnell M, Heaney AP, Ho KKY, Ioachimescu AG, Lamberts S, Laws E, Losa M, Maffei P, Mamelak A, Mercado M, Molitch M, Mortini P, Pereira AM, Petersenn S, Post K, Puig-Domingo M, Salvatori R, Samson SL, Shimon I, Strasburger C, Swearingen B, Trainer P, Vance ML, Wass J, Wierman ME, Yuen

- KCJ, Zatelli MC, Melmed S (2020) Multidisciplinary management of acromegaly: a consensus. *Rev Endocr Metab Disord* 21:667–678. <https://doi.org/10.1007/s11154-020-09588-z>
107. Melmed S, Sternberg R, Cook D, Klibanski A, Chanson P, Bonert V, Vance ML, Rhew D, Kleinberg D, Barkan A (2005) A critical analysis of pituitary Tumor shrinkage during primary medical therapy in acromegaly. *J Clin Endocrinol Metab* 90:4405–4410. <https://doi.org/10.1210/jc.2004-2466>
 108. Mazziotti G, Giustina A (2010) Effects of lanreotide SR and autogel on Tumor mass in patients with acromegaly: a systematic review. *Pituitary* 13:60–67. <https://doi.org/10.1007/s11102-009-0169-z>
 109. Mondin A, Manara R, Voltan G, Tizianel I, Denaro L, Ferrari M, Barbot M, Scaroni C, Ceccato F (2022) Pasireotide-Induced shrinkage in GH and ACTH secreting pituitary adenoma: a systematic review and Meta-analysis. *Front Endocrinol (Lausanne)* 13:935759. <https://doi.org/10.3389/fendo.2022.935759>
 110. Bevan JS (2005) Clinical review: the antitumoral effects of somatostatin analog therapy in acromegaly. *J Clin Endocrinol Metab* 90:1856–1863. <https://doi.org/10.1210/jc.2004-1093>
 111. Grandgeorge N, Barchetti G, Grunenwald S, Bonneville F, Caron P (2022) MRI follow-up of patients with acromegaly being treated with first-generation somatostatin receptor ligands after Surgery. *Clin Endocrinol (Oxf)* 97:686–688. <https://doi.org/10.1111/cen.14539>
 112. Grandgeorge N, Barchetti G, Grunenwald S, Bonneville F, Caron P (2020) Is MRI follow-up relevant in patients with GH-secreting pituitary adenomas primarily treated and responsive to long-acting somatostatin analogues (SMSa)? *Eur J Endocrinol* 182:123–130. <https://doi.org/10.1530/EJE-19-0681>
 113. Petrossians P, Daly AF, Natchev E, Maione L, Blijdorp K, Sahnoun-Fathallah M, Auriemma R, Diallo AM, Hulting AL, Ferone D, Hana V Jr, Filippini S, Sievers C, Nogueira C, Fajardo-Montanana C, Carvalho D, Hana V, Stalla GK, Jaffrain-Rea ML, Delemer B, Colao A, Brue T, Neggers S, Zachariewa S, Chanson P, Beckers A (2017) Acromegaly at diagnosis in 3173 patients from the liege acromegaly survey (LAS) database. *Endocr Relat Cancer* 24:505–518. <https://doi.org/10.1530/ERC-17-0253>
 114. Ritvonen E, Loytyniemi E, Jaatinen P, Ebeling T, Moilanen L, Nuutila P, Kauppinen-Makelin R, Schalin-Jantti C (2016) Mortality in acromegaly: a 20-year follow-up study. *Endocr Relat Cancer* 23:469–480. <https://doi.org/10.1530/ERC-16-0106>
 115. Gadelha MR, Kasuki L, Lim DST, Fleseriu M (2019) Systemic complications of acromegaly and the impact of the current treatment landscape: an update. *Endocr Rev* 40:268–332. <https://doi.org/10.1210/er.2018-00115>
 116. Colao A, Baldelli R, Marzullo P, Ferretti E, Ferone D, Gargiulo P, Petretta M, Tamburrano G, Lombardi G, Liuzzi A (2000) Systemic Hypertension and impaired glucose tolerance are independently correlated to the severity of the acromegalic cardiomyopathy. *J Clin Endocrinol Metab* 85:193–199. <https://doi.org/10.1210/jcem.85.1.6318>
 117. Esposito D, Olsson DS, Franzen S, Miftaraj M, Natman J, Gudbjornsdottir S, Johannsson G (2022) Effect of diabetes on morbidity and mortality in patients with acromegaly. *J Clin Endocrinol Metab* 107:2483–2492. <https://doi.org/10.1210/clinem/dgac400>
 118. Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, Samuels MH (2016) Hormonal replacement in hypopituitarism in adults: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 101:3888–3921. <https://doi.org/10.1210/jc.2016-2118>
 119. Esposito D, Ragnarsson O, Johannsson G, Olsson DS (2021) Incidence of Benign and malignant tumors in patients with acromegaly is increased: a Nationwide Population-based study. *J Clin Endocrinol Metab* 106:3487–3496. <https://doi.org/10.1210/clinem/dgab560>
 120. Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, Eaden JA, Rutter MD, Atkin WP, Saunders BP, Lucassen A, Jenkins P, Fairclough PD, Woodhouse CR (2010) British Society of, G., Association of Coloproctology for Great, B., Ireland: guidelines for Colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 59:666–689. <https://doi.org/10.1136/gut.2009.179804>
 121. Giustina A, Bronstein MD, Chanson P, Petersenn S, Casanueva FF, Sert C, Houchard A, Melmed S (2021) International multicenter validation study of the SAGIT(R) instrument in acromegaly. *J Clin Endocrinol Metab* 106:3555–3568. <https://doi.org/10.1210/clinem/dgab536>
 122. van der Lely AJ, Gomez R, Pleil A, Badia X, Brue T, Buchfelder M, Burman P, Clemmons D, Ghigo E, Jorgensen JOL, Luger A, van der Lans-Bussemaker J, Webb SM, Strasburger CJ (2017) Development of ACRODAT(R), a new software medical device to assess Disease activity in patients with acromegaly. *Pituitary* 20:692–701. <https://doi.org/10.1007/s11102-017-0835-5>
 123. Coopmans EC, Schneiders JJ, El-Sayed N, Erler NS, Hoffland LJ, van der Lely AJ, Petrossians P, Potorac J, Muhammad A, Neggers S (2020) T2-signal intensity, SSTR expression, and somatostatin analogs efficacy predict response to pasireotide in acromegaly. *Eur J Endocrinol* 182:595–605. <https://doi.org/10.1530/EJE-19-0840>
 124. Chiloiro S, Giampietro A, Mirra F, Donfrancesco F, Tartaglione T, Mattogno PP, Angelini F, Liverana L, Gessi M, Carmelo A, Rindi G, Giustina A, Fleseriu M, Pontecorvi A, De Marinis L, Bianchi A (2021) Pegvisomant and pasireotide LAR as second line therapy in acromegaly: clinical effectiveness and predictors of response. *Eur J Endocrinol* 184:217–229. <https://doi.org/10.1530/EJE-20-0767>
 125. Bonert V, Mirocha J, Carmichael J, Yuen KCJ, Araki T, Melmed S (2020) Cost-effectiveness and efficacy of a novel combination regimen in acromegaly: a prospective, randomized trial. *J Clin Endocrinol Metab*. <https://doi.org/10.1210/clinem/dgaa444>
 126. Feola T, Cozzolino A, Simonelli I, Sbardella E, Pozza C, Giannetta E, Gianfrilli D, Pasqualetti P, Lenzi A, Isidori AM (2019) Pegvisomant improves glucose metabolism in Acromegaly: a Meta-analysis of prospective interventional studies. *J Clin Endocrinol Metab* 104:2892–2902. <https://doi.org/10.1210/jc.2018-02281>
 127. Fleseriu M, Dreval A, Bondar I, Vagapova G, Macut D, Pokramovich YG, Molitch ME, Leonova N, Raverot G, Grineva E, Poteskhin YE, Gilgun-Sherki Y, Ludlam WH, Patou G, Haviv A, Gordon MB, Biermasz NR, Melmed S, Strasburger CJ (2022) Maintenance of response to oral octreotide compared with injectable somatostatin receptor ligands in patients with acromegaly: a phase 3, multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol* 10:102–111. [https://doi.org/10.1016/S2213-8587\(21\)00296-5](https://doi.org/10.1016/S2213-8587(21)00296-5)
 128. Fleseriu M, Molitch M, Dreval A, Pokramovich Y, Bondar I, Poteskhin Y, Macut D, Obermayer-Pietsch B, Gilgun-Sherki Y, Haviv A, Biermasz N, Strasburger CJ (2023) MPOWERED trial open-label extension: long-term efficacy and safety data for oral octreotide capsules in acromegaly. *J Clin Endocrinol Metab*. <https://doi.org/10.1210/clinem/dgad365>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.