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Consensus statement

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# Consensus on acromegaly therapeutic outcomes: an update

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## Abstract

The 15th Acromegaly Consensus Conference in September 2023 updated recommendations on therapeutic outcomes for acromegaly. Since the publication of medical management guidelines in 2018, new pharmacological agents and new treatment approaches have been developed. Fifty-two experts in the management of acromegaly reviewed the current literature and assessed changes in drug approvals, clinical practice standards and management. Current outcome goals were considered, with a focus on the effect of current and emerging somatostatin receptor ligands, the growth hormone receptor antagonist pegvisomant and the dopamine agonist cabergoline on biochemical control, clinical control, adenoma mass and surgical outcomes. Participants assessed factors that determine pharmacological choices, as well as the proposed use of each agent. Here, we present consensus recommendations highlighting how an evidence-based acromegaly management algorithm could be optimized in clinical practice.

## Sections



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## Introduction

Acromegaly, which is caused by excess levels of growth hormone (GH) and insulin-like growth factor 1 (IGF1), is usually the result of a pituitary somatotroph adenoma[1–3]. Comorbidities include acral and soft tissue overgrowth, osteoarticular complications, respiratory alterations and hypertension, as well as metabolic abnormalities, such as insulin resistance, diabetes mellitus, malignancy and cardiovascular-related morbidity and mortality[4–7]. Treatment is primarily aimed at preventing adenoma growth and normalizing GH and IGF1 levels to ameliorate signs and symptoms of the disease, manage the effects of comorbidities and ultimately reduce excess mortality[8–10].

Overall, biochemical control is achieved in about 50% of patients in referral centres following surgical adenoma resection, the preferred first-line therapeutic approach[11]. Approximately half of the patients requiring postoperative medical therapy achieve control of IGF1 levels[12]. Radiation therapy is an option for persistent active disease and clinically significant adenoma burden[8–10]. The approach to therapy is complex and requires comprehensive treatment by a multidisciplinary expert team to enable a personalized approach[8–10].

Since the publication of medical management guidelines in 2018, new pharmacological agents and new treatment approaches have been developed. Moreover, the understanding of optimal therapeutic goals and predictive outcome factors has also evolved. Therefore, currently an unmet need exists for updated and extended recommendations for acromegaly management to enable outcome prediction and choice of optimal tailored therapeutic approaches to be maximized to achieve disease control based on specific individual patient characteristics.

## Methods

In September 2023, the Acromegaly Consensus Group convened to update consensus guidelines (published in 2018) on medical management of acromegaly[8]. Since 2018, new pharmacological agents and approaches to treatment algorithms have been developed. Fifty-two worldwide recognized experts in acromegaly management reviewed the current literature for changes in drug use, practice standards and clinical recommendations since the 2018 consensus. The participants were selected on the basis of their recognized expertise in the field as reflected by their peer-reviewed publication record. Differences in geographical area were considered to account for national policies regulating the use of medical therapies. Updated consensus recommendations were graded using the Grading of Recommendations Assessment, Development and Evaluation system[13,14], and key recommendations are presented in Boxes 1 and 2. Changes from the 2018 consensus recommendations are presented in Tables 1 and 2. Updated changes between the 2018 and the current consensus recommendations also reflect updated guidelines and information not comprehensively addressed previously.

Meeting participants were assigned topics related to acromegaly treatment and outcomes by the Consensus Co-Chairs (S.M. and A.G.). Literature searches were conducted using PubMed for English-language papers published between October 2018 and August 2023. Search terms included 'acromegaly' and terms associated with each topic: 'biochemical outcomes', 'tumour volume', 'clinical symptoms', 'somatostatin receptor ligand', 'dopamine agonist', 'GH receptor antagonist', 'oestrogen', 'selective oestrogen receptor modulator', 'medical therapy', 'mortality', 'complications', 'surgical outcomes' and 'guidelines'. After a brief presentation on each topic to the group, subgroups discussed the topic and then reported to the entire group. Consensus recommendations were developed based on the presentations, discussions and reports. All participants voted orally on each recommendation. Divergences and differences between participant opinions were reconciled with an audience general vote, and the majority approved final statements included in the current manuscript after approval by all authors.

Studies presented and discussed during the Consensus were reported in the manuscript and included in the reference list. Evidence strength was graded as very low quality (VLQ), low quality (LQ), moderate quality (MQ) or high quality (HQ)[8], and consensus recommendations were classified as discretionary (DR) or strong (SR). Introductory sentences providing background evidence were graded with VLQ if based on expert opinion supported by one or a few small uncontrolled studies; with LQ if supported by a large series of small uncontrolled studies; with MQ if supported by one or a few large uncontrolled studies or meta-analyses; with HQ if supported by controlled studies or a large series of large uncontrolled studies with sufficiently long follow-up. Consensus statements and recommendations were classified as DR if based on VLQ or LQ evidence and as SR if based on MQ or HQ evidence. Statements were initially proposed by each work-subgroup after assigned topic discussion. Group outcomes were then presented to the entire group for further discussion and consensus finalization.

## Definition and prediction of treatment outcomes

Excess levels of GH and/or IGF1 lead to systemic complications, which, in turn, contribute to morbidity and excess mortality (HQ)[1–3,15–19]. Treatment is aimed to prevent adenoma growth and progression, achieve biochemical and clinical disease control, decrease the risk of acral and soft tissue overgrowth, decrease the risk of developing metabolic, cardiorespiratory, musculoskeletal and neoplastic complications and reduce mortality risk.

### Criteria for defining surgical control

Transsphenoidal surgery might lead to cure when undertaken by an experienced pituitary surgeon or when GH levels are judged to be too high to be controlled by medical therapy without pituitary mass debulking (HQ)[8,11,12]. As the term 'cure', defined as an absolute return to the premorbid condition, is seldom achieved, the term 'disease control' on medical treatment or 'remission' after surgery or radiotherapy is the preferred management goal[12].

**Biochemical criteria.** Consensus statements (Box 1):

- The Consensus group considers that suppressed GH after an oral glucose tolerance test (OGTT) predicts long-term remission but remission rates can be influenced by the assay cut-off and reproducibility, timing of measurement after surgery and the patient and phenotypic adenoma characteristics (SR).
- GH nadir levels <1 ng/ml during OGTT reflect postoperative long-term remission. However, when using modern ultrasensitive GH assays with OGTT, a GH cut-off of 0.4 ng/ml is recommended (DR).
- The Consensus group recommends measuring GH levels, both basal and during OGTT, and IGF1 levels 3 months after surgery (SR).
- An IGF1 level within the age-stratified normal range is indicative of biochemical control (SR).
- As residual tumour might persist after surgery, or, rarely, relapse even in the setting of postsurgical biochemical control, we recommend biochemical follow-up for at least 5 years and individualized monitoring strategies should be applied (SR).

## Box 1 | Key current consensus recommendations on definition and prediction of treatment outcomes

**Biochemical**

- The Consensus Group recommends measuring growth hormone (GH) levels, both basal and during an oral glucose tolerance test (OGTT), and insulin-like growth factor 1 (IGF1) levels 3 months after surgery (strong recommendation (SR)).
- Suppressed GH after OGTT predicts long-term remission. GH nadir levels <1 ng/ml during OGTT reflect postoperative long-term remission. However, when using modern ultrasensitive GH assays with OGTT, a GH cut-off of 0.4 ng/ml is recommended (discretionary recommendation (DR)).
- As residual adenoma tissue might persist after surgery, or, rarely, recur even in the setting of postsurgical biochemical control, we recommend biochemical follow-up for at least 5 years and individualized monitoring strategies should be applied (SR).
- An IGF1 level within the age-stratified normal range is indicative of biochemical control (SR).

**Imaging**

- Postoperative imaging assessment is not sufficient to define surgical remission even with complete visible adenoma removal (DR).
- The first follow-up MRI should be performed no sooner than 3 months after surgery to allow for involution of initial local damage, gel foam and adipose tissue packing (DR).
- Regular MRI follow-up is not indicated for all patients and should be determined on the basis of biochemical parameters and clinical features considering histopathological, molecular and radiological adenoma heterogeneity (SR).
- Radiological acquisition and interpretation should be overseen by neuroradiologists with specific pituitary expertise, ideally as part of an interdisciplinary team in alignment with criteria of a pituitary tumour centre of excellence, and following standardized imaging protocols (SR).
- Standardized criteria for adenoma progression (including changes in size, shape, location and growth rate) and imaging protocols should be established (SR).
- Rapid growth or largest diameter increase during medical therapy should be considered a sign of adenoma resistance requiring a change of therapeutic strategy (SR).
- MRI follow-up 6 months after initiation or switch to different medical therapies is recommended (SR).
- If MRI cannot identify residual tissue, PET imaging using [$^{11}$C]-methionine (Met-PET), although not widely available, might be useful in patients with persistent GH hypersecretion and active clinical disease (DR).

**Clinical**

- There are no specific criteria for clinical remission of acromegaly (DR).
- To improve long-term outcomes, a comprehensive approach to patient management is recommended to ensure optimal management of comorbidities regardless of biochemical control and disease activity (SR).
- In addition to biochemical parameters, information regarding persistent comorbidities, symptoms and treatment-related adverse events is often overlooked in patients not responding optimally to treatments, but they should be considered of importance (SR).
- Available clinical scores require further refinement and validation to enable their clinical application for evaluation of clinical outcomes (DR).
- Although disease control is mainly defined by evaluating biochemical parameters, assessments of clinical burden and management of complications still require long-term follow-up (SR).

**Molecular and histopathological**

- Assessment of whether the adenoma is densely or sparsely granulated is considered a minimum requirement to determine somatostatin receptor ligand (SRL) responsiveness (SR).
- When available, positive somatostatin receptor subtype 2 immunostaining intensity might predict postoperative SRL responsiveness (DR).
- Use of pathological and molecular predictors of SRL responsiveness should be complementary to clinical and imaging determinants (DR).
- Testing for genetic variants is only recommended in selected patients, including those with familial disorders, suspected multiple endocrine neoplasia type 1 or onset of acromegaly and/or gigantism at <18 years old (DR).
- The presence or absence of *GNAS* mutations should not be included in the outcome predictive algorithm as they do not predict SRL responsiveness (DR).
- Models integrating multiple biomarkers might be helpful in predicting SRL responsiveness (DR).

Currently, no unique single parameter with published age and sex population-specific thresholds that define long-term remission after surgery is available (VLQ). GH and IGF1 measurements have been considered predictive of long-term surgical remission or the probability of disease recurrence[8,12] (HQ). Measuring random GH or GH during OGTT early after surgery is a helpful determinant, unless patients have been pretreated with a somatostatin receptor ligand (SRL) (MQ). However, remission rates using these parameters are influenced by the assay cut-off and reproducibility, timing of measurement after surgery and patient and phenotypic adenoma characteristics (LQ).

In general, postoperative GH measurements are most accurate for predicting disease recurrence, in particular after OGTT[12] (LQ). Measuring GH 1 day after surgery in 94 patients showed that GH levels >1.55 ng/ml predicted lack of hormonal remission with a sensitivity of 75% and a specificity of 59% (ref. 20). Results from 17 patients in whom postoperative levels of GH during an OGTT were measured 1 week after surgery showed that GH levels <0.5 ng/ml were highly predictive of surgical remission[21]. When GH was measured in 81 patients postoperatively, GH nadir levels during OGTT stabilized by postoperative days 2–5 (ref. 22). By contrast, IGF1 levels might continue to decrease for up to 1–2 years

## Box 2 | Key current consensus recommendations on medical therapy outcomes

### General

- The optimal therapeutic approach should include individualized management based on clinical, imaging and pathological features, in a shared decision-making process from diagnosis to long-term patient and disease management (strong recommendation (SR)).
- The recommended biochemical treatment goal of medical therapy is normalization of insulin-like growth factor 1 (IGF1) levels within the age-related reference range specific for the assay used and also with a sex-specific reference range when assessing pubertal patients (SR).

### Somatostatin receptor ligands

- Accurate drug injection instructions are required (SR).
- Somatostatin receptor ligand (SRL)-induced biochemical outcomes should be evaluated with IGF1 measurements after the first 3 monthly injections, preferably immediately before the ensuing one, and further IGF1 measurements depend on the degree and rate of IGF1 reduction (SR).
- SRL doses should be titrated according to IGF1 values using dose escalation and adjustments to dose interval in selected patients (SR).
- As no additional adverse effects are encountered with high-dose SRLs, this approach could be recommended in selected patients (discretionary recommendation (DR)).
- When available, oral octreotide capsules should be considered equally effective, with similar adverse effects to injectable SRLs and should be recommended on the basis of patient preference (DR).
- In selected patients with large adenomas, therapeutic goals of SRL treatment should include adenoma mass shrinkage and prevention of persistent growth (DR).
- Biochemical results during SRL therapy might be useful to guide follow-up imaging frequency, and routine MRI surveillance is not suggested (DR).
- Imaging follow-up should be prompted specifically with the appearance of either visual or eye movement symptoms or withdrawal of treatment or in assessing radiation therapy outcomes (SR).
- Adenoma shrinkage induced by preoperative SRL treatment might not consistently result in improved surgical outcomes (DR).
- Although SRL-induced biochemical control is achieved in 40% of patients overall, this metric might not properly reflect clinical disease control (DR).
- Routine periodic abdominal ultrasound monitoring in patients receiving SRLs is not recommended (DR).
- Routine measurements of fasting levels of glucose and HbA1c should be undertaken in all patients receiving SRLs and particularly in those receiving pasireotide (SR).
- Electrocardiograms are not required before starting or during SRL therapy (DR).

### Pegvisomant

- Continuous yearly MRI monitoring during pegvisomant treatment is no longer necessary (SR).
- Symptoms (particularly fluid retention), quality of life and comorbidities often improve with pegvisomant treatment and should be monitored during treatment (SR).
- Injection sites should be rotated to prevent lipohypertrophy (SR).
- Liver function tests should be obtained before starting pegvisomant and monitored during dose titration and pegvisomant should be discontinued when transaminase levels exceed 5 times the upper limit of normal (SR).

### Combination treatments

- Combination therapy with SRLs and pegvisomant is a useful therapeutic approach in patients with acromegaly partially responsive to SRLs alone, or in those with an increase in adenoma size during pegvisomant monotherapy or in patients with diabetes mellitus (DR).
- Cabergoline might be used as an add-on therapy in patients with acromegaly not fully controlled by SRLs (DR).
- Liver enzymes should be monitored before and after starting combination SRL and pegvisomant treatment as it could be associated with an increased risk of increased liver enzyme levels compared with pegvisomant monotherapy (SR).
- Use of combination pasireotide plus pegvisomant treatment is suggested in patients with acromegaly who do not respond to first-line and second-line medical treatment, or in those in whom adenoma mass control is required. However, this approach should be considered with caution considering the high costs of these therapies and limited safety and efficacy results (DR).

### Medical treatment algorithm

- The effects of preoperative SRL treatment in improving surgical outcomes are as yet unclear, and more studies are needed to determine whether to widely recommend this approach (DR).
- SRLs represent the first-line option for medical therapy, and new therapeutic formulations have led to new opportunities for personalized approaches (SR).
- Cabergoline should only be considered as a first-line medical therapy in patients with IGF1 levels <2.0–2.5 times the upper limit of normal or in patients with mixed GH–prolactin-secreting adenomas (DR).
- Pegvisomant monotherapy is a valuable first-line medical option, particularly with severely impaired glucose metabolism and no adenoma mass concern with potential non-responsiveness to SRLs; that is, T2 MRI hyperintensity signal and very high IGF1 concentrations (SR).
- For patients with acromegaly inadequately controlled with first-line medical approaches, second-line treatment options should be considered (SR).
- Increasing the SRL dose and/or dose frequency to improve biochemical control in patients sensitive to SRLs but with acromegaly inadequately controlled on standard doses can be considered for off-label second-line treatment (DR).
- The addition of cabergoline to SRLs could be considered in patients responsive to SRLs and not reaching IGF1 normalization independently of serum levels of prolactin or adenoma prolactin immunostaining (DR).

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- Pegvisomant monotherapy might be the first choice as a second-line treatment in patients with pre-existing hyperglycaemia or diabetes mellitus (DR).
- Pegvisomant combined with SRLs could be considered as a second-line treatment in those with limited adherence to daily injections, when costs of therapy are a determinant and in patients with impaired glucose tolerance and/or with adenoma shrinkage during lanreotide and octreotide treatment (DR).
- When SRLs cannot be tolerated, pegvisomant combined with cabergoline might be considered (DR).
- Pasireotide long-acting release might be used in patients with acromegaly that is inadequately controlled, especially in patients with relevant or growing adenomas and a low risk of hyperglycaemia (SR).
- When monotherapy does not achieve biochemical control, pasireotide plus pegvisomant might be considered if control is not achieved with medical therapies (DR).
- Stereotactic radiosurgery or surgical intervention or reintervention should be considered, if control is not achieved with medical therapies (SR).
- Chemotherapies should be considered, limited to aggressive or malignant lesions (SR).

after surgery[22–25]. OGTT-suppressed GH and IGF1 measurements were concordant in 250 patients; 92% achieved postoperative GH normalization and had normalized IGF1 levels at 36 months[24]. In 97 patients with postoperative levels of IGF1 within the normal range, an abnormal postoperative GH suppression after surgery was predicted in most patients[26]. In patients treated with preoperative SRLs, biochemical assessment should be repeated at 3–6 months to confirm remission[12] (Box 2).

After surgery, residual adenoma tissue might persist or, rarely, recur (HQ). Therefore, even in the setting of biochemical control, postoperative biochemical follow-up is recommended for at least 5 years and individualized follow-up strategies are recommended[27], reflecting histopathological, molecular and radiological adenoma heterogeneity (MQ)[2,12]. Within the first year after surgery, IGF1 measurements every 3–6 months are appropriate to confirm remission, and then every 6–12 months to monitor for potential recurrence, and OGTT might be helpful in evaluating patients with borderline IGF1 levels[12].

**Imaging criteria.** Consensus statements (Box 1):

- Postoperative imaging assessment is not sufficient to define surgical remission even with complete visible adenoma removal (DR).
- The first follow-up MRI should be performed no sooner than 3 months after surgery to allow for involution of initial local damage, gel foam and adipose packing (DR).
- MRI should be performed at 3–6 months postoperatively as a baseline for subsequent assessment[12]. Regular MRI follow-up is not indicated for all patients and should be determined on the basis of biochemical parameters and clinical features considering histopathological, molecular and radiological adenoma heterogeneity[2] (SR).
- The recommendation is to continue evaluating maximal mass diameter reduction rather than overall adenoma volume, which is not standardized (DR).
- If MRI cannot identify residual tissue, PET imaging using [$^{11}$]C-methionine (Met-PET), although not widely available, might be useful in patients with persistent GH hypersecretion and active clinical disease (DR).

After the first follow-up MRI, which can be used as a baseline for further postoperative assessment, MRI should be performed upon signs of biochemical or clinical disease activity, or with changing a therapeutic modality, such as before second surgery or radiotherapy. Sometimes, MRI might not visualize small lesions or might misinterpret scar tissue as adenoma postoperatively (LQ). Repeated gadolinium administration could have adverse effects[28] and, furthermore, adenoma size rarely increases when biochemical parameters are controlled (LQ)[12]. Although not widely available, Met-PET might be useful for localization of residual adenoma when MRI cannot identify residual tissue with persistent GH hypersecretion[29,30] and when performed in conjunction with volumetric MRI (Met-PET/MRI) (Box 1).

**Clinical criteria.** Consensus statements (Box 1):

- There are no specific criteria for clinical remission of acromegaly (DR).
- To improve long-term outcomes, a comprehensive approach to patient management is recommended to ensure optimal management of comorbidities regardless of biochemical control and disease activity (SR).
- Available clinical scores require further refinement and validation to enable their clinical application for evaluation of clinical outcomes (DR).
- Although disease control is mainly defined by evaluating biochemical parameters, assessments of clinical burden and management of complications still require long-term follow-up (SR).

There is limited and controversial information regarding the course of symptoms, signs and comorbidities after surgical adenoma resection (LQ). Most studies evaluating outcomes focus on biochemical measures and rarely evaluate clinical improvement as an end point. Hypertension, diabetes mellitus, osteoarthrosis and sleep apnoea persist in a considerable proportion of patients even with biochemical control[7] (HQ).

Joint pain is reported in almost all patients and typically correlates with a radiological sign of osteoarthrosis in at least two joints in 90% of patients[3,7]. Although arthralgia and stiffness improve after biochemical control, hip, knee, ankle, shoulder and hand pain were still present in about 40–70% of patients despite biochemical control[31] (LQ). However, to date, available clinical scores are still not sufficiently validated and studies are needed to improve their application in patients after surgical resection[32].

The prevalence of diabetes mellitus in patients with active acromegaly ranges between 15% and 35%, and diabetes mellitus and impaired glucose tolerance statistically significantly improve with GH control[6,7]. Patients with associated diabetes mellitus have a 50% higher risk of cardiovascular disease and a twofold increased cardiovascular mortality than patients without associated diabetes mellitus[33]. However, another study showed that diabetes mellitus and hypertension

**Table 1 | Key changes from the 2018 to the current consensus recommendations on definition and prediction of treatment outcomes**

| Strategy | 2018 consensus recommendation[8] | Current consensus recommendation |
|---|---|---|
| Management approach | Multidisciplinary team approach at a pituitary tumour centre of excellence, where possible | Not modified |
| Defining and monitoring biochemical control | GH nadir <0.4 µg/l after OGTT using ultrasensitive assays | Not modified |
| | Wait at least 12 weeks after surgery to assess IGF1 levels (delayed decline versus persistent postoperative GH) | As adenoma recurrence could occur in patients with acromegaly under biochemical control, reflecting the heterogeneity of the disease, patients should be followed up for several years after operatively |
| | Do not measure GH in patients receiving pegvisomant (levels remain elevated) | |
| Defining and monitoring imaging and clinical control | Not addressed | Postoperative imaging is not sufficient to define surgical cure or remission |
| | | Pituitary MRI should be performed no sooner than 3 months after surgery |
| | | Continuous pituitary MRI follow-up is not indicated for all patients and should be determined on the basis of biochemical parameters and clinical features considering the heterogeneity of histopathological, molecular and radiological adenoma characteristics |
| | | Symptoms and comorbidities should be optimally managed |
| | | Available clinical scores should be refined for evaluation of therapy outcomes |
| | | Although disease control is mainly defined by evaluating biochemical parameters, the assessments of clinical burden and management of complications still remain a milestone of long-term follow-up of patients with acromegaly |
| Predictors of response to medical therapy | Not addressed | Imaging determinants: should be overseen by neuroradiologists expert in pituitary imaging; standardized imaging protocols should be followed, also given the importance for comparing medical treatments; MRI results should include measurement values for mass diameter and dimensions, degree of suprasellar and parasellar extension, absence or presence of cysts and T2 intensity |
| | | Pathological markers of SRL response: immunohistochemistry of SSTR2 expression is recommended to predict SRL responses; assessment of whether the adenoma is densely or sparsely granulated is considered a minimum requirement |
| | | Molecular markers: *AIP* mutations are extremely rare in adults and should be investigated only in selected patients |
| | | Biochemical parameters determining medical response: baseline GH and IGF1 values are the most important biochemical markers predicting medical response |
| Definition of medical treatment resistance | Not addressed | Biochemical response: recommended treatment goal is IGF1 normalization to the age-specific reference range and sex-reference range in puberty |
| | | Adenoma mass effects: rapid growth or increase of largest diameter requires a change of medical strategy; standardized criteria for progression including changes in size, shape, location and growth rate, and standardized imaging protocols should be established |
| | | Clinical features: comorbidities, symptoms and reduced QoL are often overlooked in patients with acromegaly who do not respond to treatment and should be considered important |
| Presurgical medical approach | Not addressed | Evidence favouring preoperative SRL effects in improving surgical outcomes is non-conclusive |
| First-line medical therapy in patients with persistent disease after surgery | SRL (octreotide LAR or lanreotide autogel)<br>Cabergoline if IGF1 <2.5 times ULN | First-line treatments should be determined by patient needs and comorbidities, disease characteristics and potential drug-related adverse events |
| | | SRL is recommended as first-line therapy |
| | | Development of an oral SRL has opened new opportunities for patients |
| | | Pegvisomant if glucose metabolism is impaired and no concerns on adenoma mass |
| | | Cabergoline if mild postoperative GH and/or IGF1 elevations |

AIP, aryl hydrocarbon receptor interacting protein; GH, growth hormone; IGF1, insulin-like growth factor 1; LAR, long-acting repeatable; OGTT, oral glucose tolerance test; QoL, quality of life; SRL, somatostatin receptor ligand; SSTR2, somatostatin receptor subtype 2; ULN, upper limit of normal.

**Table 2 | Key changes from the 2018 to the current consensus recommendations on medical therapy outcomes**

| Strategy | 2018 consensus recommendation[8] | Current consensus recommendation |
|---|---|---|
| SRL treatment outcomes | Not specifically detailed for specific treatment and not included in the table of 2018 recommendations | GH and IGF1 levels: IGF1 is the preferred marker to monitor SRL therapy; IGF1 should be measured after the first three injections, and further IGF1 measurements depend on the degree and rate of IGF1 reduction |
| | | Effect on adenoma shrinkage: biochemical results might be useful to guide follow-up imaging frequency; in SRL-responsive acromegaly, adenoma growth and progression are rare, and routine pituitary MRI surveillance is not recommended; imaging should be triggered particularly by visual or eye movement symptoms or withdrawal of treatment and initiation of radiation therapy |
| | | Clinical responses: increased focus on patient-reported outcome measures required; clinical parameters should be standardized, and accepted criteria for defining improvements in signs and symptoms are needed; symptoms and clinical evaluation, related to both acromegaly and medications, and monitoring comorbidities and potential adverse events; clinicians should be aware of discrepancies between clinical and biochemical outcomes; however, symptom burden should still be considered when deciding therapeutic approaches and the use of clinical tools and questionnaire remains crucial |
| | | Adverse effects: routine periodic abdominal ultrasound monitoring is not supported; routine monitoring of glucose levels with all SRLs and especially for pasireotide; caution when administered with other medications interfering with QT intervals |
| Pegvisomant treatment outcomes | Not specifically detailed for specific treatment and not included in the table of 2018 recommendations | IGF1 levels: IGF1 is the biomarker for pegvisomant therapy monitoring; maximal IGF1 lowering effect is achieved within 4–6 weeks with dose titration |
| | | Adenoma mass: yearly pituitary MRI monitoring is no longer considered necessary; after SRL withdrawal imaging might be performed within 6–12 months after starting pegvisomant |
| | | Clinical features: symptoms, QoL and comorbidities often improve and should be monitored; disease control is accompanied by improved sleep apnoea syndrome, hypertension, arthralgia and glucose homeostasis |
| | | Adverse effects: lipodystrophies can be minimized by rotation of injection sites; liver function tested before starting and monitored during dose titration; discontinue when transaminase levels exceed five times the ULN |
| Combination therapy | Not specifically detailed for specific treatment and not included in the table of 2018 recommendations | Cabergoline and pegvisomant: no firm evidence supporting this combination; might be considered, with potential to save costs, in patients with acromegaly resistant to SRLs, not controlled by pegvisomant alone and responsive to cabergoline |
| | | SRLs and pegvisomant: useful and safe therapeutic approach in patients with acromegaly partially responsive to SRLs alone, or those with adenoma size increase during pegvisomant monotherapy or diabetes mellitus; higher risk of increased levels of liver enzymes than pegvisomant alone |
| | | Pasireotide and pegvisomant: to consider in patients with acromegaly who do not respond to first-line and second-line medical treatment; high costs and no long-term efficacy information |
| Treatment outcome goals (2018) | Biochemical outcomes: measuring both GH and IGF1 levels; normalizing levels of IGF1 is a key goal; wait at least 12 weeks after surgery to assess IGF1 levels; using the same assay with accepted performance standards when monitoring IGF1 levels over time | Specifically detailed for specific treatments in the current consensus recommendations (see the previous rows in this table) |
| | Adenoma volume: reducing adenoma size and preventing persistent growth are relevant goals for patients with macroadenomas; reduction in diameter, rather than adenoma volume, is reproducible and sufficient to assess meaningful mass change | |
| | Clinical symptoms: assessing and managing hypertension and cardiac hypertrophy, diabetes mellitus and glucose intolerance, sleep apnoea and osteopathy is recommended; clinician-reported outcome instruments can be used to monitor indicators of disease activity | |

**Table 2 (continued) | Key changes from the 2018 to the current consensus recommendations on medical therapy outcomes**

| Strategy | 2018 consensus recommendation[8] | Current consensus recommendation |
|---|---|---|
| Second-line medical therapy if SRL is not successful in normalizing IGF1 | Partial response: increase SRL dose and/or increase frequency of lanreotide dosing; add cabergoline to SRL if IGF1 is moderately elevated | Increasing SRL dose and/or frequency even though off-label use |
| | Minimal or no response and mass concern: switch to pasireotide LAR | Pasireotide if relevant residual adenoma tissue in patients with acromegaly not adequately controlled on SRLs |
| | Minimal or no response and impaired glucose metabolism: switch to pegvisomant | Combination of SRLs with pegvisomant is effective in most patients |
| | Minimal or no response, mass concern and impaired glucose metabolism: add pegvisomant to SRL | Pegvisomant plus cabergoline might be considered when SRLs plus pegvisomant is not feasible due to SRL intolerance |
| Therapy if biochemical control is not achieved after second-line therapy | Stereotactic radiosurgery or surgical intervention (or reintervention). Temozolomide for unusually aggressive or proven malignant tumours (in close cooperation with a neuro-oncologist) | Limited but promising results of pasireotide with pegvisomant in patients with poorly responsive acromegaly |
| | | Combination of pegvisomant with cabergoline if patients resistant to SRLs, not controlled by pegvisomant |
| | | Temozolomide and other chemotherapies limited for particularly aggressive or malignant lesions undergoing radiation therapy with neuro-oncology supervision |
| Use of clinical outcome instruments | Objective tools (SAGIT and ACRODAT) can be used to assess and monitor indicators of disease activity. Patient QoL questionnaires (AcroQoL) are probably of limited value | Not modified |

GH, growth hormone; IGF1, insulin-like growth factor 1; LAR, long-acting repeatable; QoL, quality of life; SRL, somatostatin receptor ligand; ULN, upper limit of normal.

prevalence were similar at diagnosis and after a median postoperative follow-up of 7.4 years[34]. Artificial intelligence (AI) algorithms have identified acromegaly-specific facial features to predict the clinical diagnosis[35,36]. An AI model based on paired hand photographs taken at diagnosis and 3 months postoperatively predicts biochemical remission with 80% accuracy[37]. Although promising, these algorithms require further investigation to be implemented clinically (VLQ).

### Predictors of response to medical therapy

There have been advances in the elucidation of a predictive role for imaging, molecular and biochemical markers of medical therapy responsiveness (Box 1).

**Imaging determinants.** Consensus statements:

- Radiological acquisition and interpretation should be overseen by neuroradiologists with specific pituitary expertise, ideally as part of an interdisciplinary team in alignment with criteria of a pituitary tumour centre of excellence, and following standardized imaging protocols (SR).
- A standardized approach should be used in reporting MRI results (SR).

MRI has a key role in evaluating acromegaly, and the adoption of a standardized approach in imaging evaluation is important for subsequent comparison[38,39] (Box 1).

Both T1-weighted and T2-weighted spin echo MRI sequences are helpful (MQ). Coronal and sagittal (±axial) planes are required for analysis of mass size and extension and/or invasion; 1.5 T MRIs are a minimal requirement but ideally 3 T images, gadolinium-enhanced and 2–3 mm slice thickness (with no or minimal spacing) of the sellar region should be undertaken[40].

MRI reports should include mass diameters, suprasellar extension, degree of parasellar extension using the Knosp classification[41], absence or presence of cystic regions and T2 intensity compared with temporal lobe grey matter (or normal pituitary).

The role of imaging in supporting a decision for medical therapy is evolving (MQ). Associations between hormonal responses to SRL therapy and T2 MRI intensity have been proposed[42–46]. Hypointense adenomas were consistently associated with more favourable SRL responses, whereas hyperintense and isointense adenomas were identified as less responsive[42–46]. In contrast to previous observations with lanreotide or octreotide, increased T2 MRI adenoma intensity was associated with a more favourable biochemical response to pasireotide[47].

Machine learning with quantitative texture analysis, permitting detection of MRI-specific features not visually perceptible, has been proposed as being reliable for predicting SRL responsiveness (LQ). In 47 patients (24 responsive and 23 resistant), machine-learning-based MRI texture analysis correctly predicted SRL response in >80% of patients, with better performance than conventional qualitative and quantitative relative T2 signal intensity and immunohistochemical evaluations[48]. Similarly, radiomic features have predicted both densely and sparsely somatotroph granulation patterns, which might be extrapolated to predict SRL responsiveness[49].

Functional imaging with radiotracers targeting somatostatin (somatostatin receptor 2–5 (SSTR2–5)) and dopamine receptor expression predicted response to SRLs and dopamine agonist therapies, respectively[50] (LQ). However, uptake by remnant normal pituitary tissue confounds interpretations (LQ).

**Molecular markers of SRL response.** Consensus statements:

- Assessment of whether the adenoma is densely or sparsely granulated is considered a minimum requirement to determine SRL responsiveness (SR).
- When available, SSTR2 immunostaining intensity might predict postoperative SRL responses (DR).
- Testing for genetic variants is only recommended in selected patients, including those with familial disorders, suspected multiple endocrine neoplasia type 1 or with onset of acromegaly at <18 years old (DR).

- The presence or absence of *GNAS* mutations should not be included in the outcome predictive algorithm as they do not predict SRL responsiveness (DR).
- Models integrating multiple biomarkers might be helpful in predicting SRL responsiveness (DR).
- Use of pathological and molecular predictors of SRL responsiveness should be complementary (DR).

Pathological and molecular predictors of SRL responsiveness have shown different predictive roles and results. Although tumour histopathological granulation patterns and SSTR immunochemical expression were consistently demonstrated to be useful in predicting therapeutic response (MQ), genetic and molecular investigations have been less useful as accurate outcome determinants (LQ). For instance, a large multicentre study, including >150 patients, showed that patients with GH-secreting pituitary adenomas with low SSTR2 immunochemical expression exhibited lower biochemical control rates with SRLs than patients with high SSTR2 expression[51]. In another study, low SSTR2 expression showed an odds ratio of 4.17 for SRL resistance[52]. Patients with densely granulated adenomas were more likely to achieve biochemical control than those with sparsely granulated adenomas[53,54].

Germline *AIP* mutations, as well as other mutations associated with specific syndromes, are extremely rare in adults (MQ). Patients with *AIP* germline mutation and with X-linked acrogigantism have a suboptimal response to SRLs[55–57]. Furthermore, two large studies demonstrated that biochemical control rates were similar between patients with or without *GNAS* mutations[58,59].

Models combining multiple biomarkers[52,53,60–63] were tested in predicting SRL responsiveness. A model based on machine learning, including assessing SSTR2, SSTR5, cytokeratin granulation pattern, sex, age and pretreatment levels of GH and IGF1 levels, had an accuracy of 86% to predict SRL responsiveness[51].

**Biochemical parameters determining medical response.** Consensus statements:

- Measurements of circulating levels of GH and IGF1 are the most important biochemical markers to determine response to medical therapies (SR).
- Both random and nadir GH concentrations during OGTT are predictive of responses to medical therapies (DR).
- The acute octreotide test does not reliably predict the subsequent biochemical response to SRL therapy (DR).

Both GH and IGF1 assays exhibit methodological problems that are challenging to interpret (MQ). Low baseline IGF1 levels are associated with more favourable SRL biochemical responsiveness than high baseline levels[64–66] (MQ). Circulating levels of IGF1 are more likely to be suppressed with low initial IGF1 levels at diagnosis[64]. High IGF1 levels are also associated with more adverse responses to pegvisomant and pasireotide[61] (MQ).

High GH levels have been consistently associated with less favourable SRL responsiveness[53,61,67] (MQ). Patients with a paradoxical increase in GH levels during OGTT (≥20% GH increase versus baseline) exhibit a modestly favourable IGF1 reduction after SRL treatment, compared with the non-paradoxical responding group (VLQ).

GH reduction measured 2 h after a subcutaneous injection of 100 µg octreotide (short acute octreotide test) was investigated in predicting subsequent biochemical response[68], but the predictive usefulness of this test was precluded by overlap of biochemical outcome of extended SRL therapy in responders and non-responders to the acute test (LQ).

### Definition of medical treatment resistance

Compared with other patients, those with acromegaly that is resistant to treatment are more likely to have adenoma compressive mass effects, poor biochemical control, treatment-related burdens, related comorbidities and impaired quality of life (QoL)[6–9] (HQ) (Box 2).

**Biochemical response.** Consensus statements:

- IGF1 measurements, using modern, well-characterized assays, are the best indicators of biochemical disease activity during medical therapy (SR)[12,69,70].
- The recommended biochemical treatment goal of medical therapy is normalization of IGF1 levels within the age-related reference range specific for the assay used and also with a sex-specific reference range when assessing patients during puberty (SR)[8,12].
- In patients treated with a GH receptor antagonist, GH assessment is not informative (SR)[12].
- Random GH assessment is not likely to provide additional information in all patients but could be considered for symptomatic patients with IGF1 levels at the higher end of the upper limit of normal (ULN) (DR)[12].

**Adenoma mass effects.** Consensus statements:

- Standardized criteria for adenoma progression (including changes in size, shape, location and growth rate) and imaging protocols should be established (SR).
- Rapid growth or largest diameter increase during medical therapy should be considered a sign of adenoma resistance requiring a change of therapeutic strategy (SR).
- Whether the adenoma shrinks could not be considered a major component of the definition of 'resistance to medical therapy' (DR)[71].
- MRI follow-up 6 months after initiation or switch to different medical therapies is recommended (SR).
- Medical treatment should aim to achieve clinical and biochemical control in patients with visible postoperative residual adenoma tissue or microadenomas stable on serial imaging evaluations with MRI (DR).

In patients with large adenomas, mass reduction is particularly clinically relevant under the following conditions: when adenoma is contiguous with or in close proximity to the optic apparatus; when headaches or vision changes are caused by the mass; when pregnancy is desired; and when the adenoma presents histopathological markers of therapeutic resistance (MQ).

A 20% increase in largest diameter and/or an unusually rapid growth was suggested as a criterion of resistance and disease progression[72] (MQ). Minor changes in a high-risk location (for example, close to the optic chiasm) should also be considered clinically relevant (LQ). The same standards for imaging and results reporting should be used in follow-up as for diagnosis[12].

**Clinical features.** Consensus statements:

- Medical treatment should aim to achieve clinical and biochemical control in patients with visible postoperative residual adenoma tissue or microadenomas stable on serial imaging evaluations with MRI (DR).

- Age, germline mutations, histopathological characteristics, cytokeratin granulation, SSTR2 expression and proliferation markers are usually associated with enhanced risk of SRL resistance (DR).
- Besides biochemical parameters, information regarding persistent comorbidities, symptoms and treatment-related adverse events are often overlooked in patients not responding optimally to treatments, but they should be considered of importance (SR).

Poorly controlled acromegaly leads to increased morbidity and mortality caused by adenoma growth and long-term exposure to excess levels of GH and IGF1, as well as to persistent comorbidities, symptoms, multiple interventions and treatment-related adverse events (HQ). More information on comorbidities, treatment-related adverse events, patient-reported outcome measures and QoL in poorly responsive acromegaly is required (MQ). A description of treatment-related adverse events should include information on hypopituitarism and burden of treatments and medications, especially for those requiring multiple therapies.

The prevalence and severity of cardiovascular, metabolic, respiratory and musculoskeletal comorbidities might improve but might not revert to premorbid normalcy even with biochemical control[73,74] (MQ). Studies that characterize comorbidities specifically in patients with poorly controlled acromegaly are lacking (LQ). Psychopathology is linked to impaired physical functioning, poor body image, negative illness perception, mood disorders and treatment burden[73]. Impaired QoL might improve with biochemical control but does not necessarily normalize[75] (LQ). Overall, there is a paucity of data on patient-reported outcomes in treatment-resistant acromegaly[76]. Specific patient-related outcome measures for treatment-resistant acromegaly are needed to clarify the clinical burden, needs and treatment approaches.

## Medical therapy outcomes

Medical therapies (including SRLs and the dopamine agonist cabergoline) bind to somatostatin and dopamine receptors on the adenoma and suppress GH secretion (HQ). The GH receptor antagonist pegvisomant blocks peripheral GH actions, which leads to reduced IGF1 production (HQ). The synthetic SRLs lanreotide autogel, octreotide long-acting repeatable (LAR) injections or oral octreotide capsules (OOCs) mainly show affinity for SSTR2, whereas the multiligand SRL pasireotide has a broader affinity for four of the five SSTRs[12] (HQ). SRLs typically represent a first-line medical approach and are mostly used as adjuvant treatments for persistent active disease after surgery (HQ). SRLs could be prescribed as a primary therapy in selected patients when surgery is declined or contraindicated (for example, because of high anaesthesia or cardiovascular risk)[8] (LQ). The aims of medical therapy are to achieve comprehensive control of biochemical, clinical and tumoural features associated with the disease (Box 2).

### Somatostatin receptor ligands: treatment outcomes

Consensus statements:

- Adequate drug injection instructions are required (SR).
- SRL-induced biochemical outcomes should be evaluated with IGF1 measurements after the first three monthly injections, preferably immediately before the ensuing one, and further IGF1 measurements depend on the degree and rate of IGF1 reduction[77] (SR).
- SRL doses should be titrated according to IGF1 values using dose escalation and adjustments to dose interval in selected patients (SR).
- As no additional adverse effects are encountered with high-dose SRLs, this approach could be recommended in selected patients (DR).
- When available, OOCs should be considered equally effective with similar adverse effects to injectable SRLs and should be recommended on the basis of patient preference (DR).
- IGF1 levels are the most useful biomarker to assess disease control and should be measured after 2–4 weeks to determine optimal OOC dose titration (DR).
- Clinicians should be aware that over-treatment might lead to IGF1 over-suppression, especially in those treated with pasireotide, justifying decreasing the dose with time or after radiotherapy (DR)[78].

**GH and IGF1 levels.** A review that included 18 studies with octreotide LAR and 15 with lanreotide reported achievement of biochemical control ranging from 17% to 80% for octreotide LAR and from 27% to 78% for lanreotide[79,80]. Increasing maximal lanreotide injection doses to 180 mg every 28 days or shortening the interval of 120 mg to 21 days normalizes IGF1 concentrations in about one-third of patients with acromegaly, which is inadequately controlled by conventional SRL therapy with no additional adverse effects[81]. High-dose (60 mg every 28 days) or high-frequency (30 mg every 21 days) octreotide LAR reduced or normalized IGF1 levels in patients with acromegaly that was not controlled with conventional doses and dosing intervals; the high-dose scheme being superior to the high-frequency scheme[82].

OOCs at doses of 40–80 mg per day were effective in patients with acromegaly that was previously biochemically controlled on injectable SRLs (MQ). After 36 weeks, IGF1 concentrations remained in the reference range in 58.2% of patients and GH concentrations <2.5 ng/ml were seen in 77.7% of patients[83]. OOC was non-inferior to injectable SRLs, with a more favourable patient-reported symptom benefit[84]. A phase II, open-label, single-arm exploratory study showed that GH and IGF1 concentrations remained unchanged after switching injectable SRLs to paltusotine, an oral non-peptide small SSTR2 agonist[85].

After unsuccessful pituitary surgery or without prior treatment, pasireotide LAR at doses up to 60 mg every 28 days demonstrated superior efficacy over octreotide LAR at doses up to 30 mg every 28 days (31.3% versus 19.2% biochemical control at 12 months)[86]. In different studies, pasireotide LAR induced biochemical control in 11.4–20% of patients with acromegaly that was inadequately controlled with maximally approved doses of lanreotide or octreotide LAR[87–89].

**Effects on adenoma shrinkage.** Consensus statements:

- In patients with visual loss and optic chiasm compression, surgery is indicated (SR).
- In selected patients with large adenomas, therapeutic goals of SRL treatment should include adenoma mass shrinkage and prevention of persistent growth (DR).
- Reductions in maximal mass dimension of at least 20% are preferred, rather than overall volume, which has not been standardized (DR).
- Ideally, treatment should result in adenoma diameter reduction of 20–25%, which is considered clinically significant (DR).
- Critical local structures at risk should be considered (SR)[8].
- Adenoma diameter, rather than volume, is considered easier to measure and more accurately correlates to mass changes (DR)[90,91].
- Volume reduction can represent a better measure of favourable response and there is a need for methodologies to specifically

measure adenoma volume using novel imaging software and AI tools (DR).
- Biochemical results during SRL therapy might be useful to guide follow-up imaging frequency, and routine MRI surveillance is not suggested (DR).
- Imaging follow-up should be prompted specifically with the appearance of either visual or eye movement symptoms or withdrawal of treatment or in assessing radiation therapy outcomes (SR).
- Adenoma shrinkage induced by preoperative SRL treatment might not consistently result in improved surgical outcomes (DR).

Reported volume measurements are often inconsistent, particularly considering adenoma shape, scan details, interobserver differences and the methodology used (LQ). As such, reported volume measurements are not routinely performed.

T2 hypointensity at diagnosis is predictive of adenoma shrinkage with SRL treatment[8]. In this setting, 50% of patients exhibit adenoma shrinkage in the first month of both preoperative and postoperative SRL treatment, and there is a reasonable correlation with biochemical control[8]. Preoperative therapy with lanreotide 120 mg reduced adenoma size and visual symptoms in newly diagnosed patients with macroadenoma and optic chiasm compression[92]. Volume reduction (>25%) was observed in 61.9% of patients at the first month, and visual fields improved concomitantly with decreased GH and IGF1 levels.

Pasireotide might be associated with a greater effect on adenoma shrinkage than lanreotide and octreotide[44,88] (LQ). A systematic review and meta-analysis on the effectiveness of pasireotide that included six studies reported that 37.7% of patients achieved significant (25% of baseline volume) shrinkage[93]. Mutations in *AIP* or X-linked acrogigantism are typically associated with less favourable mass reduction than other forms of acromegaly[56].

In patients with SRL-induced hormone control, adenoma growth and progression are rarely reported, and routine MRI surveillance is not suggested, especially if initial MRI responses were favourable[94] (LQ).

**Clinical response.** Consensus statements:
- Although SRL-induced biochemical control is achieved in >40% of patients overall[95], this metric might not properly reflect clinical disease control (DR).
- Increased research focus on patient-reported outcome measures in acromegaly is required (DR).
- Clinical parameters and outcomes should be standardized, and criteria that have been validated for defining clinical improvements are needed (DR).
- Acromegaly and treatment-related symptoms, comorbidities and potential adverse effects of therapy should be monitored at each visit (DR).
- Clinicians should be aware of discrepancies between clinical and biochemical outcomes; however, symptom burden should still be considered when deciding on therapeutic approaches, and the use of clinical tools and questionnaires is helpful (DR).

Headache, arthralgias, soft tissue swelling, hyperhidrosis and QoL frequently improve with SRLs (LQ). In a prospective study using health-related QoL, with three validated questionnaires (RAND-36, Acromegaly Quality of Life (AcroQoL) and the Appearance Self-Esteem), patients reported improvement in all overall scores during the first 2.5 years of treatment[96].

Wide variability in patient-reported assessments and reporting is evident[27,97–100] (LQ). A systematic review and meta-analysis of patient-reported outcome measures reported that of 14 different patient-reported outcome measures used, only one (AcroQoL) was previously validated in this setting[101]. In general, reporting of patient-reported outcome measures was poor, and 34% of studies showed discrepancies between patient-reported outcome measures and biochemical outcomes, mostly revealing improvements in biochemical outcomes but not in patient-reported outcomes.

Discordance between biochemical parameters and symptoms is well recognized, and many patients report ongoing symptoms even when acromegaly is well controlled biochemically (LQ). In a study of patients on stable SRL doses, more than 80% experienced joint pain, swelling of soft tissue and fatigue and/or weakness. These symptoms occurred constantly and affected daily activities and were even present among those with biochemical control[102]. In a randomized phase III study including patients with biochemically controlled acromegaly receiving SRLs, about two-thirds still reported symptoms that interfered with daily life activities[103].

**Adverse effects.** Consensus statements:
- Routine periodic abdominal ultrasound monitoring in patients receiving SRLs is not recommended (DR).
- Geographical (or dietary) differences might determine a need for performing more frequent gallbladder ultrasounds as cholelithiasis requiring cholecystectomy has been reported[104] (DR).
- Routine fasting glucose and HbA1c measurements should be undertaken in all patients receiving SRLs and particularly in those receiving pasireotide (SR).
- Electrocardiograms are not required before starting or during SRL therapy (DR).
- The risks to benefits balance of SRLs should be evaluated and caution is required when they are administered concomitantly with other medications that effect QT intervals (DR).

As SSTRs are ubiquitously expressed, adverse effects of SRL treatment might manifest in multiple organs. In pooled analyses, up to 90–95% of patients experienced adverse effects with SRL treatment, which were mainly mild and transient[89,105] (HQ). However, in selected patients, down-titration might be required (VLQ). A drop-out of ~3–10% was reported for lanreotide and octreotide[66,102]. Effects of SRLs in the gastrointestinal tract lead to altered pancreatic exocrine enzyme secretion and reduced bowel motility[106].

More than half of patients receiving SRLs report gastrointestinal symptoms, including loperamide-responsive diarrhoea (10–55%), bloating (10–35%), nausea and vomiting (8–15%), steatorrhea (<10%) or general discomfort and/or pain, which usually resolve after 3–6 injections. Abnormalities in the biliary system owing to reduced bile flow and gallbladder motility might predispose patients to choledocholithiasis or cholecystolithiasis[106] (LQ). Although these latter events are fairly frequent (up to 35%), they are often asymptomatic in most study cohorts and gallbladder surgery is infrequently required[66,89,106].

Hyperglycaemia and diabetes mellitus are frequent complications of acromegaly (HQ). Nevertheless, SRLs might have detrimental effects on glucose metabolism[66,107] (MQ). Two meta-analyses confirm an overall marginal negative effect of octreotide and lanreotide on fasting glycaemia[108,109]. However, as SSTR5 is widely expressed on pancreatic β-cells and on enteroendocrine cells, pasireotide reduces secretion of insulin and glucagon-like peptide 1 (refs. 110–112) (MQ).

More than 50% of patients receiving pasireotide LAR experienced hyperglycaemia and diabetes mellitus, with an increased risk in those with pre-existing prediabetes[88,113]. For most patients, these symptoms are adequately managed with metformin and glucagon-like peptide 1 receptor agonists or dipeptidyl peptidase 4 inhibitors[114] (LQ).

In addition, cutaneous injection reactions occur in up to 20–25% of patients, ranging from mild local erythema to fibrous scars with lymphoid follicles[115] (LQ). Furthermore, SRLs have been associated with bradycardia and increased QT interval, possibly leading to decreased ventricular premature beats[116] (LQ).

### Pegvisomant treatment outcomes

Pegvisomant is a GH receptor antagonist that blocks GH actions, which leads to reduced IGF1 production[117,118] (HQ). Although pegvisomant acts peripherally, the drug has the limitation of not specifically targeting the primary adenoma source of excess GH secretion; however, it has the advantage of blocking GH actions irrespective of the hypersecreting adenoma properties (HQ).

Consensus statements:

- Continuous yearly MRI monitoring during pegvisomant treatment is no longer necessary (SR).
- In specific circumstances, such as SRL withdrawal, further imaging might be performed within 6–12 months after initiation of pegvisomant (DR).
- Imaging intervals should be scheduled on the basis of adenoma size and past growth characteristics independently of pegvisomant administration (DR).
- Diabetes mellitus (especially when managed with insulin) and obesity are factors that require increased pegvisomant doses to achieve biochemical control (DR)[119].
- Symptoms (particularly fluid retention), QoL and comorbidities often improve with pegvisomant treatment and should be monitored during treatment (SR).
- Disease control on pegvisomant treatment is accompanied by improved sleep apnoea syndrome, hypertension, arthralgias and glucose homeostasis (DR).
- Injection sites should be rotated to prevent lipohypertrophy (SR).
- Liver function tests should be obtained before starting pegvisomant and monitored during dose titration, and pegvisomant should be discontinued when transaminase levels exceed five times the ULN (SR).

**IGF1 levels.** More than 90% of patients receiving pegvisomant monotherapy in clinical trials achieved biochemical control; however, reported efficacy was 66% at 5 years and >70% at 10 years in most real-world safety surveillance studies[9]. In the ACROSTUDY cohort, which includes 2,221 patients treated with pegvisomant, monotherapy or in combination with SRLs[120]. The IGF1 normalization rate improved over time, increasing from 11.4% at initiation of pegvisomant to 75.4% at year 10 with the use of ≥30 mg pegvisomant per day. In a single-centre study including 45 patients treated for at least 5 years, 41 (91.1%) achieved normalized IGF1 levels[121]. Evaluation at 10 years (22 patients) showed that 91% of patients maintained full control. In the German ACROSTUDY subset, patients with diabetes mellitus had lower rates of IGF1 normalization (64% in the cohort with diabetes mellitus versus 75% in the cohort without diabetes mellitus)[122]. The maximal IGF1 lowering effect for a fixed pegvisomant dose is achieved within 4–6 weeks, and dose titration until normalization of IGF1 should occur at such time intervals[120].

**Adenoma mass.** In 2,090 patients treated with pegvisomant and imaged at least twice, locally reported MRIs showed that most patients (72.2%) had no change in adenoma size relative to prior imaging; 16.8% had a decrease, 6.8% an increase and 4.3% had both[123]. Changes in adenoma size were reported as adverse events for 90 patients (4.3%), of which 21 (1%) were related to treatment. Of those, eight patients (0.4%) had pegvisomant withdrawn[123]. In 2021, in an analysis of the ACROSTUDY database (2004–2017) of 2,221 patients, locally reported MRIs showed that 7.1% of patients had increased adenoma sizes[120]. However, for 264 of 519 patients, MRI results were re-assessed by central reading, which showed adenoma volume increased in 54 (3.0%) patients. A retrospective single-centre study derived from 10 years of pegvisomant treatment showed that maximal adenoma diameter was stable[121]. A meta-analysis showed an overall adenoma growth rate of 7.2% in patients receiving pegvisomant monotherapy[124]. These findings confirmed that in large observational studies using centralized MRI serial readings, an increase is adenoma size after pegvisomant is uncommon (~3%) and is similar to that observed in those not treated with medical therapy[8] (MQ).

**Clinical features.** An improved clinical outcome with pegvisomant is variable and dependent on the duration of disease and on associated comorbidities[125,126] (MQ). An extension study of ACROSTUDY evaluated changes in symptoms with the Patient-Assessed Acromegaly Symptom Questionnaire (PASQ) and QoL with AcroQoL[127]. Overall, patients treated with pegvisomant had small improvements in PASQ but there was no significant difference between groups with or without IGF1 control (LQ). In a 4-year longitudinal interim analysis of ACROSTUDY[113], patients with diabetes mellitus had a mean decrease in fasting blood levels of glucose of 20.2 mg/dl from baseline to year 4, whereas mean HbA1c remained unchanged[125]. In ACROSTUDY, the prevalence of comorbidities after pegvisomant versus before pegvisomant significantly decreased for hypertension from 51.3% to 10.5%, diabetes mellitus from 32.2% to 23.8%, sleep apnoea from 20.8% to 2.3% and symptomatic osteoarthritis from 21.3% to 7.6% (ref. 120). Data on glucose metabolism were in accordance with findings from other studies[125,128].

**Adverse effects.** In ACROSTUDY, 613 of 5,567 adverse effects considered treatment-related were reported in 16.5% of patients treated with pegvisomant. The most common adverse effects were increased transaminase levels (1.5%), lipohypertrophy (1.2%) and IGF1 levels below the lower limit of the reference range (1.1%)[120].

A multicentre retrospective study reported that lipodystrophy developed in 15% of patients[129]. According to a meta-analysis, lipohypertrophy was reported in 1.6% (ref. 124). In ACROSTUDY, adverse effects related to the administration site were reported in 3.5% of patients[120]. The most common treatment-related adverse effects linked to administration site that led to pegvisomant withdrawal were lipohypertrophy in 1.2% of patients and injection-site reaction adverse events in 0.8% (MQ).

A meta-analysis found evidence of elevated levels of transaminases in 3% of patients treated with pegvisomant[124]. In ACROSTUDY, 3.2% of patients had an alanine aminotransferase and/or aspartate transaminase value of more than three times the ULN at any time point during pegvisomant treatment[120]. Overall, hepatobiliary-related adverse effects were reported in 10.1% of patients, which led to pegvisomant withdrawal in 1.7% of patients. No liver failure was reported in the study. In a meta-analysis evaluating effects of the combination of SRLs with

pegvisomant[130], elevated transaminase levels were reported in 14% of patients[131–133].

### Combination treatments

Consensus statements:

- Monotherapy should be switched to another class of drug when disease control is not achieved at maximum tolerated doses and/or when treatment-related adverse events occur (SR).
- Combination therapy with SRLs and pegvisomant is a useful therapeutic approach in patients partially responsive to SRLs alone, or in those with an increase in adenoma size during pegvisomant monotherapy or in patients with diabetes mellitus (DR).
- Liver enzymes should be monitored before and after starting combination SRL and pegvisomant treatment as it could be associated with an increased risk of increased liver enzyme levels compared with pegvisomant monotherapy (SR).
- The addition of cabergoline with pegvisomant might be considered with the potential to lower costs in patients with acromegaly that does not respond to SRLs, which is not controlled by pegvisomant alone and is responsive to cabergoline; however, the evidence is insufficient to enable definitive conclusions regarding this combination (DR).
- Use of combination pasireotide plus pegvisomant is suggested in patients with acromegaly that does not respond to first-line and second-line medical treatment, or in those in whom adenoma mass control is required. However, this approach should be considered with caution considering the high costs of these therapies and limited safety and efficacy results (DR).

When management goals are not achieved with drug monotherapy, a combination of two drugs of different classes is suggested[8–10]. These combinations have been studied with sufficient detail to recommend their use in selected patients. However, use of combination therapies might be hampered by country-specific differences in cost re-imbursement[134] (VLQ).

**SRLs and pegvisomant.** In patients with acromegaly that is partially responsive to SRLs, the addition of pegvisomant enables normalization of IGF1 levels in most patients together with improved symptoms and glucose tolerance (HQ)[133,135,136]. Achievement of IGF1 levels within the normal range was observed in 55–96% of patients in a short-term prospective study that enrolled 52 patients[136]. Similarly, an efficacy of 91% was reported in a long-term prospective study[121]. Optimal disease control was maintained over time without requiring notable dose increases, as demonstrated when IGF1 levels were normalized in about 90% of patients treated with SRLs and pegvisomant for 10 years[121]. Adenoma volume remains unchanged or even decreases in most patients[122,137] after a decade of combination treatment[121]. The most frequent adverse events are injection-site reactions and transiently elevated levels of liver transaminases, which mainly occur within the first year of combination treatment[121,136] (MQ). Combination treatment is beneficial for systemic metabolic and cardiovascular comorbidities (MQ). SRLs might increase risks of impaired glucose metabolism, whereas the addition of pegvisomant might mitigate this effect of SRL, leading to an overall neutral metabolic effect that is sustained over time[121,128] (LQ). Combination treatment might also improve lipid profiles[121,128] (VLQ). Moreover, long-term addition of pegvisomant to SRLs improves cardiac structure and performance in patients with partial resistance to SRLs[121,138] (LQ).

Overall, this combination results in efficacious biochemical control, improved clinical outcomes, reduced risk of adenoma size increase, improved therapeutic adherence and reduced overall drug costs. These findings are supported by reported 10-year experience (HQ).

**Cabergoline and pegvisomant.** Cabergoline, a long-acting dopamine agonist, is orally administered and is less expensive than SRLs and pegvisomant (HQ). On the basis of observational studies, normalized IGF1 values with cabergoline monotherapy are attained in patients with mild disease (IGF1 levels less than two times ULN)[139] (MQ). To date, there is a paucity of studies investigating the results of combining cabergoline and pegvisomant[140–142] (VLQ).

A retrospective study reported that in 14 patients with resistance to SRLs and acromegaly that was not completely controlled after the switch to pegvisomant 10–30 mg per day, the addition of cabergoline at a final dose of 1.5 ± 0.7 mg per week normalized IGF1 levels in 4 (28%) patients[140]. In a single prospective study on the combination of pegvisomant and cabergoline in 24 patients[141], the addition of pegvisomant led to disease control in 13 patients.

Results on effects on adenoma size are limited and not conclusive for long-term clinical outcomes and potential adverse effects (VLQ).

**Pasireotide and pegvisomant.** The combination of pasireotide plus pegvisomant has shown promising results in real-life studies and a single clinical trial[137,143,144] (VLQ). A prospective, single-centre study included 61 patients considered to have biochemically controlled acromegaly who were treated with a dose-sparing strategy of pegvisomant in combination with SRLs[144]. After 12 months, biochemical control was achieved in 31 of 46 treated patients (67.4%)[144]. A subsequent extension study reported that control was sustained at 48 weeks[137].

In a real-life monocentre experience, six patients treated with the combination of pasireotide plus pegvisomant after failure of other multiple therapeutics achieved normal IGF1 levels[143,145]. The pasireotide dose was 60 mg monthly, and the mean pegvisomant dosage was 25 mg per day.

However, the incidence of diabetes mellitus increased from 33% at baseline to 69% at 24 weeks of treatment[144] and to 77% after 48 weeks of treatment[137]; these data include patients treated with pasireotide alone and in combination with pegvisomant. The combination of pasireotide plus pegvisomant was associated with a lower frequency of hyperglycaemia and HbA1c levels decreased compared with those treated with pasireotide alone[145].

### Medical treatment algorithm

Consensus statements:

- The optimal therapeutic approach should include individualized management based on clinical, imaging and pathological features, in a shared decision-making process from diagnosis to long-term patient and disease management (SR).

A proposed algorithm for medical treatment of acromegaly when acromegaly is inadequately controlled after pituitary surgery is depicted in Fig. 1.

**Presurgical approach.** Consensus statements:

- The effects of preoperative SRL treatment in improving surgical outcomes are as yet unclear, and more studies are needed to determine whether to widely recommend this approach (DR).

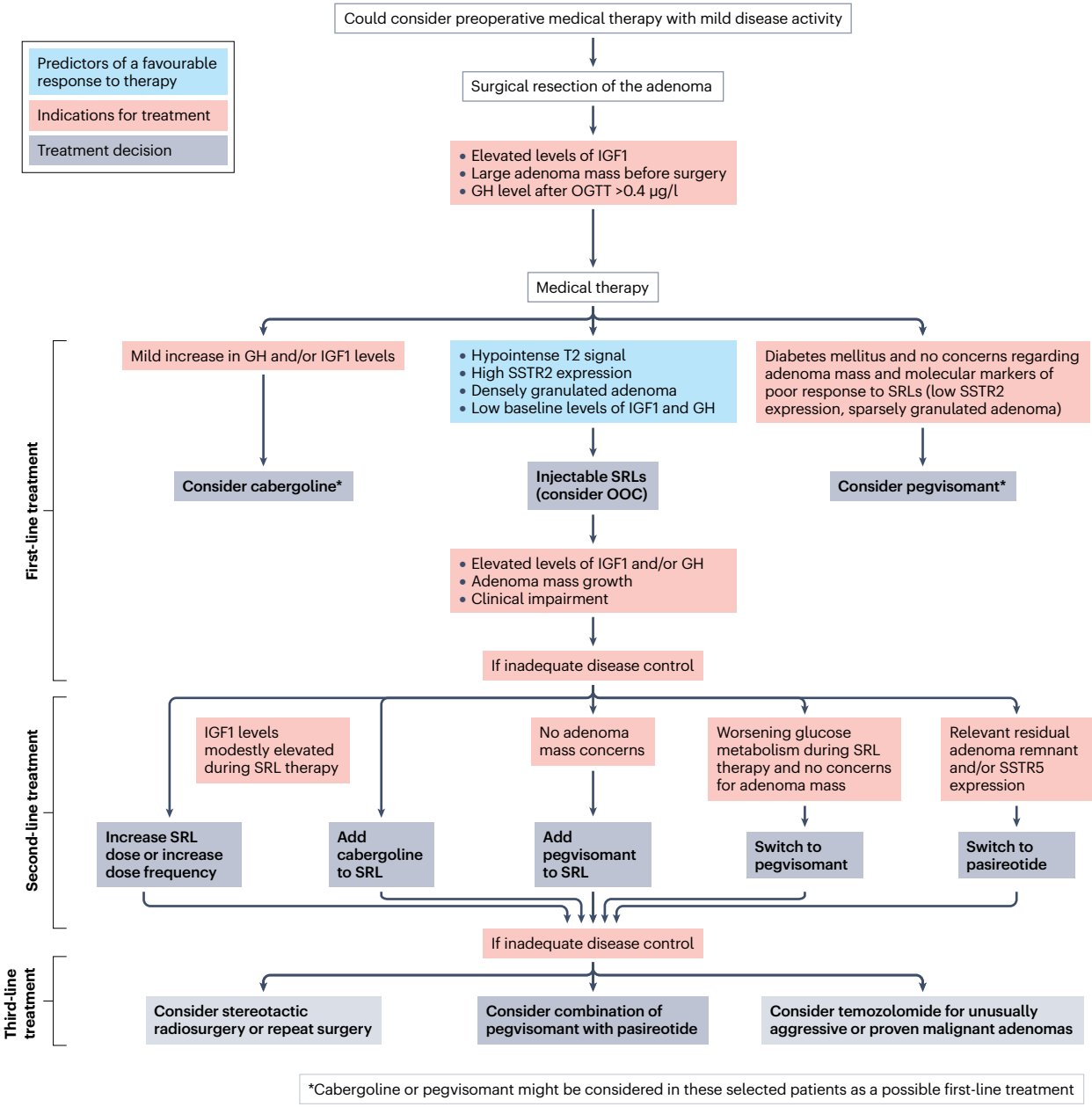


**Fig. 1 | A proposed updated algorithm for medical treatment in patients with acromegaly that is inadequately controlled after pituitary surgery.** The proposed algorithm depicts recommended therapeutic approaches to acromegaly. The cornerstone of the approach is based on initially anticipated surgical resection of the growth hormone (GH)-secreting adenoma. After surgery, first-line, second-line and third-line medical approaches are proposed as determined by the characteristics of the patient and the disease. Somatostatin receptor ligand (SRL; injectable or oral) can be followed by combination approaches, increasing SRL monotherapy dose or frequency and/or switching to pegvisomant or pasireotide monotherapy. First-line treatment with cabergoline and pegvisomant monotherapy might be considered in selected patients. In the absence of achieving disease control, combination of pasireotide with pegvisomant could be considered. After these decision-supported approaches for medical therapies, for a specific group of patients, stereotactic surgery, repeated surgery and/or use of chemotherapies (such as temozolomide) could be considered. IGF1, insulin-like growth factor 1; OGTT, oral glucose tolerance test; OOC, oral octreotide capsule; SSTR2, somatostatin receptor subtype 2; SSTR5, somatostatin receptor subtype 5.

Surgery is potentially curative but, even with modern techniques, might be associated with modest remission rates, especially in patients with macroadenomas (particularly with cavernous sinus invasiveness), potentially requiring lifelong postoperative medical treatments[146,147] (HQ). SRL efficacy in postoperative control has been hypothesized to also be useful in a preoperative setting[148] (LQ). In a meta-analysis, a significant benefit of preoperative medical treatment was observed when only prospective randomized controlled trials were

evaluated[149] (MQ). Meta-analyses and reviews based on prospective randomized controlled trials on resected GH-secreting macroadenomas showed improved short-term remission rates compared with no preoperative medical therapy[150,151] (LQ). However, previously published studies reported conflicting results on effects of preoperative medical treatment on surgical outcomes, achieving and sustaining normalization of IGF1 levels, with some studies reporting improved remission rates whereas others did not (VLQ). In a retrospective study including 110 consecutive newly diagnosed patients, long-term remission rates were higher in the cohort receiving presurgical SRL treatment than in those who did not receive this treatment[152].

**First-line medical treatment.** Consensus statements:

- SRLs represent the first-line option for medical therapy, and new therapeutic formulations have led to new opportunities for personalized approaches (SR).
- Cabergoline should only be considered as a first-line medical therapy in patients with IGF1 levels <2.0–2.5 times the ULN or in patients with mixed GH-prolactin-secreting adenomas (DR).
- Pegvisomant monotherapy is a valuable first-line medical option, particularly in patients with severely impaired glucose metabolism and no adenoma mass concern with potential non-responsiveness to SRLs; that is, T2 MRI hyperintensity signal and very high IGF1 concentrations (DR).

First-line medical treatment of acromegaly is used in patients in whom surgery is contraindicated or declined, as well as in patients not expected to be cured by surgical resection of the adenoma[8] (HQ). SRLs are still the mainstay treatment for biochemical control and adenoma size reduction, although with very variable efficacy rates among series[8] (HQ). However, despite overall improved disease outcomes and QoL, patients treated with SRLs often experience a considerable therapy-related burden[101–103] (LQ). New oral and subcutaneous-depot SRL formulations have been developed to avoid discomfort of parenteral administration and potentially improving both patients' QoL and therapeutic adherence[153]. These compounds show promising results in disease control with adequate safety profiles and non-inferiority compared with injectable formulations[154,155] (MQ). The development of new therapeutic formulations has opened new opportunities to increase personalized approaches, which might be considered of value in emergency situations, such as the COVID-19 pandemic, that limit patient access to care[156,157] (VLQ).

Cabergoline has the advantages of reduced costs and an oral route of administration (LQ). However, its positioning as a first-line medical approach is limited by modest efficacy and should be restricted to addressing mild postoperative increases in levels of IGF1 and/or GH[158,159] (VLQ).

It is recommended to monitor the potential risk of cardiac valvulopathy and development of impulse control disorders that might occur with long-term use of very high cabergoline doses[160–163].

**Second-line medical treatment.** Consensus statements:

- For patients with acromegaly inadequately controlled with first-line medical approaches, second-line treatment options should be considered (SR)[164,165].
- Increasing the SRL dose and/or dose frequency to improve biochemical control in patients sensitive to SRLs but with acromegaly inadequately controlled on standard doses can be considered for off-label second-line treatment (DR).
- The addition of cabergoline to SRLs could be considered in patients responsive to SRLs and not reaching IGF1 normalization independently of serum levels of prolactin or adenoma prolactin immunostaining (DR).
- Pegvisomant monotherapy might be the first choice as a second-line treatment in patients with pre-existing hyperglycaemia or diabetes mellitus (DR).
- Pegvisomant combined with SRLs could be considered as a second-line treatment in those with limited adherence to daily injections, when costs of therapy are a determinant and in patients with impaired glucose tolerance and/or with adenoma shrinkage during lanreotide and octreotide treatment (DR).
- When SRLs cannot be tolerated, pegvisomant combined with cabergoline might be considered (DR).
- Pasireotide LAR might be used in patients with acromegaly that is inadequately controlled, especially in patients with relevant or growing adenomas and with a low risk of hyperglycaemia (SR).

Increasing the SRL dose and/or frequency showed biochemical control in 18–36% of patients[81,82]. With adequate dose titration, the efficacy of pegvisomant monotherapy is favourable, and it might be the first choice as a second-line treatment in patients with pre-existing hyperglycaemia or diabetes mellitus[9,165] (Box 2). Pasireotide LAR might be used in patients with acromegaly inadequately controlled with octreotide[85] as the first choice for second-line treatment, especially in patients with relevant or growing adenomas, sparsely granulated histopathological characteristics, germline *AIP* mutations and with a low risk of hyperglycaemia[165] (Fig. 1). Combined treatment with SRL and pegvisomant achieved control in 80–96% (refs. 135,165) of patients, possibly enabling a reduction of doses or frequencies of pegvisomant administration (Box 2).

As there are limited reports on long-term efficacy and safety[139,140], combined pegvisomant and cabergoline treatment might be considered when therapy with SRLs and pegvisomant is not feasible owing to intolerance to SRLs (VLQ).

Oral oestrogens and selective oestrogen receptor modulators might reduce IGF1 levels. Therefore, when used for other indications alone or in combination with SRLs or cabergoline, they improve biochemical control in selected female patients (LQ)[166–169].

**Third-line medical treatment.** Consensus statements:

- When monotherapy does not achieve biochemical control, pasireotide plus pegvisomant might be considered (DR).
- Combination of cabergoline and pegvisomant cannot be recommended as no prospective results are available (DR).
- Stereotactic radiosurgery or surgical intervention or reintervention should be considered if control is not achieved with medical therapies (SR).
- Chemotherapies should be considered, limited to aggressive or malignant lesions (SR).

Interpretation of efficacy reports on third-line medical treatment and use of different combinations is hampered by the paucity of prospective data (VLQ). Limited but promising results on combining pasireotide with pegvisomant have been reported in the PAPE study and real-life cohort experiences, mostly with poorly responsive disease[136,142,143] (LQ). When monotherapy does not achieve biochemical control, pasireotide plus pegvisomant might be considered if no contraindications are present[136,142,143]. Although combining cabergoline

with pasireotide could have a similar additive effect, there are no published prospective studies on the efficacy of this approach.

If biochemical control is not achieved with medical therapies, stereotactic radiosurgery or surgical intervention or reintervention should be considered[7]. Temozolomide and other chemotherapies should be limited to aggressive or malignant lesions and be used under neuro-oncological supervision[8,9,170,171].

## Conclusions

Our recommendations for management of acromegaly have been updated and extended since the previous 2018 Consensus Statement[8]. Given the increased usage of combinations of drug classes, and with the promising results on novel oral formulations, patients now have more treatment options that are likely to achieve disease control specifically based on each patient's unique needs and characteristics. Increased knowledge on predictive factors and response outcomes to medical therapy has opened opportunities for enhanced personalization of treatments. A rigorous guide for clinicians to predict and to choose optimal tailored therapeutic approaches still requires further research. A comprehensive classification of pituitary adenoma outcomes incorporating molecular, pathological, imaging, biochemical and clinical information should prove helpful in this regard[172]. This approach would enable the evaluation of treatment responsiveness and outcomes using comprehensive phenotypes not based solely on biochemical parameters but also on clinical features and concomitant comorbidities.

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### References


1. Fleseriu, M., Langlois, F., Lim, D. S. T., Varlamov, E. V. & Melmed, S. Acromegaly: pathogenesis, diagnosis, and management. *Lancet Diabetes Endocrinol.* **10**, 804–826 (2022).
2. Melmed, S. et al. Clinical biology of the pituitary adenoma. *Endocr. Rev.* **43**, 1003–1037 (2022).
3. Colao, A. et al. Acromegaly. *Nat. Rev. Dis. Prim.* **5**, 20 (2019).
4. Bolfi, F., Neves, A. F., Boguszewski, C. L. & Nunes-Nogueira, V. S. Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis. *Eur. J. Endocrinol.* **179**, 59–71 (2018).
5. Esposito, D. et al. Decreasing mortality and changes in treatment patterns in patients with acromegaly from a nationwide study. *Eur. J. Endocrinol.* **178**, 459–469 (2018).
6. Melmed, S. et al. A consensus on the diagnosis and treatment of acromegaly complications. *Pituitary* **16**, 294–302 (2013).
7. Giustina, A. et al. A consensus on the diagnosis and treatment of acromegaly comorbidities: an update. *J. Clin. Endocrinol. Metab.* **105**, dgz096 (2020).
8. Melmed, S. et al. A consensus statement on acromegaly therapeutic outcomes. *Nat. Rev. Endocrinol.* **14**, 552–561 (2018).
9. Giustina, A. et al. Multidisciplinary management of acromegaly: a consensus. *Rev. Endocr. Metab. Disord.* **21**, 667–678 (2020).
10. Fleseriu, M. et al. A pituitary society update to acromegaly management guidelines. *Pituitary* **24**, 1–13 (2021).
11. Katznelson, L. et al. Acromegaly: an endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **99**, 3933–3951 (2014).
12. Giustina, A. et al. Consensus on criteria for acromegaly diagnosis and remission. *Pituitary* **27**, 7–22 (2024).
13. Guyatt, G. H. et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **336**, 924–926 (2008).
14. Swiglo, B. A. et al. 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 (2008).
15. Chiloiro, S. et al. Impact of the diagnostic delay of acromegaly on bone health: data from a real life and long term follow-up experience. *Pituitary* **25**, 831–841 (2022).
16. Cangiano, B. et al. Psychological complications in patients with acromegaly: relationships with sex, arthropathy, and quality of life. *Endocrine* **77**, 510–518 (2022).
17. Frara, S. et al. High prevalence of vertebral fractures associated with preoperative GH levels in patients with recent diagnosis of acromegaly. *J. Clin. Endocrinol. Metab.* **107**, e2843–e2850 (2022).
18. Giustina, A. Acromegaly and vertebral fractures: facts and questions. *Trends Endocrinol. Metab.* **31**, 274–275 (2020).
19. Giustina, A. Acromegaly and bone: an update. *Endocrinol. Metab.* **38**, 655–666 (2023).
20. Cardinal, T. et al. Postoperative GH and degree of reduction in IGF-1 predicts postoperative hormonal remission in acromegaly. *Front. Endocrinol.* **12**, 743052 (2021).
21. Feelders, R. A. et al. 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 (2005).
22. Wang, Y. Y. et al. 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 (2022).
23. Giustina, A., Mazziotti, G. & Fontanella, M. Commentary: postsurgical monitoring of acromegaly. *Neurosurgery* **73**, E746–E748 (2013).
24. Jung, I. H. et al. Revisiting the role of insulin-like growth factor-1 measurement after surgical treatment of acromegaly. *J. Clin. Endocrinol. Metab.* **106**, e2589–e2599 (2021).
25. Cunha, M. L. V. D., Borba, L. A. B. & Boguszewski, C. L. Random Gh and Igf-I levels after transsphenoidal surgery for acromegaly: relation with long-term remission. *Endocrine* **68**, 182–191 (2020).
26. Freda, P. U. et al. Prognostic value of nadir GH levels for long-term biochemical remission or recurrence in surgically treated acromegaly. *Pituitary* **24**, 170–183 (2021).
27. Giustina, A. et al. International multicenter validation study of the SAGIT® instrument in acromegaly. *J. Clin. Endocrinol. Metab.* **106**, 3555–3568 (2021).
28. Forghani, R. Adverse effects of gadolinium-based contrast agents: changes in practice patterns. *Top. Magn. Reson. Imaging* **25**, 163–169 (2016).
29. Koulouri, O. et al. Successful treatment of residual pituitary adenoma in persistent acromegaly following localisation by 11C-methionine PET co-registered with MRI. *Eur. J. Endocrinol.* **175**, 485–498 (2016).
30. Bashari, W. A. et al. PET-guided repeat transsphenoidal surgery for previously deemed unresectable lateral disease in acromegaly. *Neurosurg. Focus* **48**, E8 (2020).
31. Claessen, K. M., Mazziotti, G., Biermasz, N. R. & Giustina, A. Bone and joint disorders in acromegaly. *Neuroendocrinology* **103**, 86–95 (2016).
32. Martin, S. et al. Development and evaluation of the acromegaly symptom diary. *J. Patient Rep. Outcomes* **7**, 15 (2023).
33. Esposito, D. et al. Effect of diabetes on morbidity and mortality in patients with acromegaly. *J. Clin. Endocrinol. Metab.* **107**, 2483–2492 (2022).
34. Yen, Y. S. & Chen, H. S. Changes in cardiovascular risk factors in patients with acromegaly after trans-sphenoidal adenomectomy. *Endocr. J.* **67**, 1169–1177 (2020).
35. Kong, X., Gong, S., Su, L., Howard, N. & Kong, Y. Automatic detection of acromegaly from facial photographs using machine learning methods. *eBioMedicine* **27**, 94–102 (2018).
36. Meng, T. et al. Identifying facial features and predicting patients of acromegaly using three-dimensional imaging techniques and machine learning. *Front. Endocrinol.* **11**, 492 (2020).
37. Wang, M. et al. Using 2-dimensional hand photographs to predict postoperative biochemical remission in acromegaly patients: a transfer learning approach. *Quant. Imaging Med. Surg.* **13**, 3747–3759 (2023).
38. Casanueva, F. F. et al. Criteria for the definition of pituitary tumor centers of excellence (PTCOE): a pituitary society statement. *Pituitary* **20**, 489–498 (2017).
39. Giustina, A. et al. Pilot study to define criteria for pituitary tumors centers of excellence (PTCOE): results of an audit of leading international centers. *Pituitary* **26**, 583–596 (2023).
40. Gadelha, M. R. et al. Pituitary MRI standard and advanced sequences: role in the diagnosis and characterization of pituitary adenomas. *J. Clin. Endocrinol. Metab.* **107**, 1431–1440 (2022).
41. Micko, A. S., Wöhrer, A., Wolfsberger, S. & Knosp, E. Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. *J. Neurosurg.* **122**, 803–811 (2015).
42. Heck, A., Emblem, K. E., Casar-Borota, O., Bollerslev, J. & Ringstad, G. Quantitative analyses of T2-weighted MRI as a potential marker for response to somatostatin analogs in newly diagnosed acromegaly. *Endocrine* **52**, 333–343 (2016).
43. Potorac, I., Beckers, A. & Bonneville, J. F. 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 (2017).
44. Ruiz, S. et al. Magnetic resonance imaging as a predictor of therapeutic response to pasireotide in acromegaly. *Clin. Endocrinol.* **99**, 378–385 (2023).
45. Puig-Domingo, M. et al. Magnetic resonance imaging as a predictor of response to somatostatin analogs in acromegaly after surgical failure. *J. Clin. Endocrinol. Metab.* **95**, 4973–4978 (2010).
46. Bonneville, F. et al. MRI T2 signal intensity and tumor response in patients with GH-secreting pituitary macroadenoma: PRIMARYS post-hoc analysis. *Eur. J. Endocrinol.* **180**, 155–164 (2018).
47. Coopmans, E. C. et al. T2-signal intensity, SSTR expression, and somatostatin analogs efficacy predict response to pasireotide in acromegaly. *Eur. J. Endocrinol.* **182**, 595–605 (2020).
48. Kocak, B. et al. Predicting response to somatostatin analogues in acromegaly: machine learning-based high-dimensional quantitative texture analysis on T2-weighted MRI. *Eur. Radiol.* **29**, 2731–2739 (2019).
49. Park, Y. W. et al. Radiomics model predicts granulation pattern in growth hormone-secreting pituitary adenomas. *Pituitary* **23**, 691–700 (2020).
50. Bashari, W. A. et al. Using molecular imaging to enhance decision making in the management of pituitary adenomas. *J. Nucl. Med.* **62**, 57S–62S (2021).

51. Wildemberg, L. E. et al. Machine learning-based prediction model for treatment of acromegaly with first-generation somatostatin receptor ligands. *J. Clin. Endocrinol. Metab.* **106**, 2047–2056 (2021).
52. Hu, J. et al. Magnetic resonance spectroscopy may serve as a presurgical predictor of somatostatin analog therapy response in patients with growth hormone-secreting pituitary macroadenomas. *J. Endocrinol. Invest.* **42**, 443–451 (2019).
53. Berton, A. M. et al. Resistance to somatostatin analogs in Italian acromegaly patients: the MISS study. *J. Clin. Med.* **12**, 25 (2022).
54. Ilie, M. D. et al. Predictive factors of somatostatin receptor ligand response in acromegaly — a prospective study. *J. Clin. Endocrinol. Metab.* **107**, 2982–2991 (2022).
55. Oriola, J. et al. Germline mutations of AIP gene in somatotropinomas resistant to somatostatin analogues. *Eur. J. Endocrinol.* **168**, 9–13 (2012).
56. Daly, A. F. et al. Clinical characteristics and therapeutic responses in patients with germ-line AIP mutations and pituitary adenomas: an international collaborative study. *J. Clin. Endocrinol. Metab.* **95**, E373–E383 (2010).
57. Beckers, A. et al. X-linked acrogigantism syndrome: clinical profile and therapeutic responses. *Endocr. Relat. Cancer* **22**, 353–367 (2015).
58. Wildemberg, L. E. et al. *gsp* mutation is not a molecular biomarker of long-term response to first-generation somatostatin receptor ligands in acromegaly. *Cancers* **13**, 4857 (2021).
59. Puig-Domingo, M. et al. Molecular profiling for acromegaly treatment: a validation study. *Endocr. Relat. Cancer* **27**, 375–389 (2020).
60. Iacovazzo, D. et al. Factors predicting pasireotide responsiveness in somatotroph pituitary adenomas resistant to first-generation somatostatin analogues: an immunohistochemical study. *Eur. J. Endocrinol.* **174**, 241–250 (2016).
61. Chiloiro, S. et al. Pegvisomant and pasireotide LAR as second line therapy in acromegaly: clinical effectiveness and predictors of response. *Eur. J. Endocrinol.* **184**, 217–229 (2021).
62. Muhammad, A. et al. Pasireotide responsiveness in acromegaly is mainly driven by somatostatin receptor subtype 2 expression. *J. Clin. Endocrinol. Metab.* **104**, 915–924 (2019).
63. Cuevas-Ramos, D. et al. A structural and functional acromegaly classification. *J. Clin. Endocrinol. Metab.* **100**, 122–131 (2015).
64. Coopmans, E. C. et al. Multivariable prediction model for biochemical response to first-generation somatostatin receptor ligands in acromegaly. *J. Clin. Endocrinol. Metab.* **105**, dgaa387 (2020).
65. Sulu, C. et al. Machine learning as a clinical decision support tool for patients with acromegaly. *Pituitary* **25**, 486–495 (2022).
66. Caron, P. J. et al. Tumor shrinkage with lanreotide autogel 120 mg as primary therapy in acromegaly: results of a prospective multicenter clinical trial. *J. Clin. Endocrinol. Metab.* **99**, 1282–1290 (2014).
67. Biagetti, B. et al. Factors associated with therapeutic response in acromegaly diagnosed in the elderly in Spain. *Front. Endocrinol.* **13**, 984877 (2022).
68. Urai, S. et al. Newer parameters of the octreotide test in patients with acromegaly. *Pituitary* **27**, 33–43 (2024).
69. Bidlingmaier, M. et al. 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 (2014).
70. Chanson, P. et al. Reference values for IGF-I serum concentrations: comparison of six immunoassays. *J. Clin. Endocrinol. Metab.* **101**, 3450–3458 (2016).
71. Gola, M., Bonadonna, S., Mazziotti, G., Amato, G. & Giustina, A. Resistance to somatostatin analogs in acromegaly: an evolving concept? *J. Endocrinol. Invest.* **29**, 86–93 (2006).
72. Melmed, S. Acromegaly pathogenesis and treatment. *J. Clin. Invest.* **119**, 3189–3202 (2009).
73. Gadelha, M. R., Kasuki, L., Lim, D. S. T. & Fleseriu, M. Systemic complications of acromegaly and the impact of the current treatment landscape: an update. *Endocr. Rev.* **40**, 268–332 (2019).
74. Petrossians, P. et al. Acromegaly at diagnosis in 3173 patients from the Liège Acromegaly Survey (LAS) database. *Endocr. Relat. Cancer* **24**, 505–518 (2017).
75. Kyriakakis, N., Lynch, J., Gilbey, S. G., Webb, S. M. & Murray, R. D. Impaired quality of life in patients with treated acromegaly despite long-term biochemically stable disease: results from a 5-years prospective study. *Clin. Endocrinol.* **86**, 806–815 (2017).
76. van Trigt, V. R., Pelsma, I. C. M. & Biermasz, N. R. Patient-reported outcomes in refractory hormone-producing pituitary adenomas: an unmet need. *Pituitary* **26**, 307–317 (2023).
77. Maione, L. et al. IGF-I variability over repeated measures in patients with acromegaly under long-acting somatostatin receptor ligands. *J. Clin. Endocrinol. Metab.* **107**, e3644–e3653 (2022).
78. Marques, N. V., Wildemberg, L. E. A. & Gadelha, M. R. Long-term, real-world experience of pasireotide dose reduction in patients with acromegaly. *Endocr. Connect.* **12**, e230155 (2023).
79. Colao, A., Auriemma, R. S., Pivonello, R., Kasuki, L. & Gadelha, M. R. Interpreting biochemical control response rates with first-generation somatostatin analogues in acromegaly. *Pituitary* **19**, 235–247 (2016).
80. Carmichael, J. D., Bonert, V. S., Nuño, M., Ly, D. & Melmed, S. Acromegaly clinical trial methodology impact on reported biochemical efficacy rates of somatostatin receptor ligand treatments: a meta-analysis. *J. Clin. Endocrinol. Metab.* **99**, 1825–1833 (2014).
81. Giustina, A. et al. High-dose and high-frequency lanreotide autogel in acromegaly: a randomized, multicenter study. *J. Clin. Endocrinol. Metab.* **102**, 2454–2464 (2017).
82. Giustina, A. et al. High-dose intramuscular octreotide in patients with acromegaly inadequately controlled on conventional somatostatin analogue therapy: a randomised controlled trial. *Eur. J. Endocrinol.* **161**, 331–338 (2009).
83. Samson, S. L. et al. Maintenance of acromegaly control in patients switching from injectable somatostatin receptor ligands to oral octreotide. *J. Clin. Endocrinol. Metab.* **105**, e3785–e3797 (2020).
84. Fleseriu, M. et al. MPOWERED trial open-label extension: long-term efficacy and safety data for oral octreotide capsules in acromegaly. *J. Clin. Endocrinol. Metab.* **108**, 3214–3222 (2023).
85. Gadelha, M. R. et al. ACROBAT edge: safety and efficacy of switching injected SRLs to oral paltusotine in patients with acromegaly. *J. Clin. Endocrinol. Metab.* **108**, e148–e159 (2023).
86. Colao, A. et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. *J. Clin. Endocrinol. Metab.* **99**, 791–799 (2014).
87. Gadelha, M. et al. Evaluation of the efficacy and safety of switching to pasireotide in patients with acromegaly inadequately controlled with first-generation somatostatin analogs. *Front. Endocrinol.* **10**, 931 (2020).
88. Gadelha, M. R. et al. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. *Lancet Diabetes Endocrinol.* **2**, 875–884 (2014).
89. Colao, A. et al. Pasireotide for acromegaly: long-term outcomes from an extension to the phase III PAOLA study. *Eur. J. Endocrinol.* **182**, 583 (2020).
90. Colao, A., Auriemma, R. S. & Pivonello, R. The effects of somatostatin analogue therapy on pituitary tumor volume in patients with acromegaly. *Pituitary* **19**, 210–221 (2016).
91. Giustina, A. et al. Meta-analysis on the effects of octreotide on tumor mass in acromegaly. *PLoS ONE* **7**, e36411 (2012).
92. Benderradji, H. et al. Efficacy of lanreotide 120 mg primary therapy on tumour shrinkage and ophthalmologic symptoms in acromegaly after 1 month. *Clin. Endocrinol.* **97**, 52–63 (2022).
93. Mondin, A. et al. Pasireotide-induced shrinkage in GH and ACTH secreting pituitary adenoma: a systematic review and meta-analysis. *Front. Endocrinol.* **13**, 935759 (2022).
94. Grandgeorge, N., Barchetti, G., Grunenwald, S., Bonneville, F. & Caron, P. 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 (2020).
95. Gadelha, M. R., Wildemberg, L. E. & Kasuki, L. The future of somatostatin receptor ligands in acromegaly. *J. Clin. Endocrinol. Metab.* **107**, 297–308 (2022).
96. Wolters, T. L. C. et al. The effect of treatment on quality of life in patients with acromegaly: a prospective study. *Eur. J. Endocrinol.* **182**, 319–331 (2020).
97. Giustina, A. et al. Sagit®: a novel clinician-reported outcome for managing acromegaly in clinical practice. *Value Health* **17**, A355 (2014).
98. Giustina, A. et al. SAGIT®: clinician-reported outcome instrument for managing acromegaly in clinical practice — development and results from a pilot study. *Pituitary* **19**, 39–49 (2016).
99. Giustina, A. et al. Staging and managing patients with acromegaly in clinical practice: baseline data from the SAGIT® validation study. *Pituitary* **22**, 476–487 (2019).
100. Marazuela, M. et al. Acromegaly disease activity according to ACRODAT®, a cross-sectional study in Spain: ACROVAL study. *Endocrine* **75**, 525–536 (2022).
101. van der Meulen, M. et al. State of the art of patient-reported outcomes in acromegaly or GH deficiency: a systematic review and meta-analysis. *J. Clin. Endocrinol. Metab.* **107**, 1225–1238 (2022).
102. Geer, E. B. et al. Patient reported outcome data from acromegaly patients treated with injectable somatostatin receptor ligands (SRLs) in routine clinical practice. *BMC Endocr. Disord.* **20**, 117 (2020).
103. Fleseriu, M. et al. Disease and treatment-related burden in patients with acromegaly who are biochemically controlled on injectable somatostatin receptor ligands. *Front. Endocrinol.* **12**, 627711 (2021).
104. Prencipe, N. et al. Biliary adverse events in acromegaly during somatostatin receptor ligands: predictors of onset and response to ursodeoxycholic acid treatment. *Pituitary* **24**, 242–251 (2021).
105. Burness, C. B., Dhillon, S. & Keam, S. J. Lanreotide autogel(®): a review of its use in the treatment of patients with acromegaly. *Drugs* **74**, 1673–1691 (2014).
106. Bornschein, J., Drozdov, I. & Malfertheiner, P. Octreotide LAR: safety and tolerability issues. *Expert Opin. Drug Saf.* **8**, 755–768 (2009).
107. Frara, S., Maffezzoni, F., Mazziotti, G. & Giustina, A. Current and emerging aspects of diabetes mellitus in acromegaly. *Trends Endocrinol. Metab.* **27**, 470–483 (2016).
108. Mazziotti, G. et al. Effects of somatostatin analogs on glucose homeostasis: a metaanalysis of acromegaly studies. *J. Clin. Endocrinol. Metab.* **94**, 1500–1508 (2009).
109. Cozzolino, A. et al. Somatostatin analogs and glucose metabolism in acromegaly: a meta-analysis of prospective interventional studies. *J. Clin. Endocrinol. Metab.* **103**, 2089–2099 (2018).
110. Bolanowski, M., Kałużny, M., Witek, P. & Jawiarczyk-Przybyłowska, A. Pasireotide — a novel somatostatin receptor ligand after 20 years of use. *Rev. Endocr. Metab. Disord.* **23**, 601–620 (2022).
111. Barbot, M. et al. Is pasireotide-induced diabetes mellitus predictable? A pilot study on the effect of a single dose of pasireotide on glucose homeostasis. *Pituitary* **23**, 534–542 (2020).
112. Henry, R. R. et al. Hyperglycemia associated with pasireotide: results from a mechanistic study in healthy volunteers. *J. Clin. Endocrinol. Metab.* **98**, 3446–3453 (2013).
113. Gadelha, M. et al. Long-term efficacy and safety of pasireotide in patients with acromegaly: 14 years of single-center real-world experience. *J. Clin. Endocrinol. Metab.* **108**, e1571–e1579 (2023).

114. Samson, S. L. et al. Managing pasireotide-associated hyperglycemia: a randomized, open-label, phase IV study. *Pituitary* **24**, 887–903 (2021).
115. Caron, P., Cogne, M., Raingeard, I., Bex-Bachellerie, V. & Kuhn, J. M. Effectiveness and tolerability of 3-year lanreotide autogel treatment in patients with acromegaly. *Clin. Endocrinol.* **64**, 209–214 (2006).
116. Parolin, M., Dassie, F., Vettor, R., Steeds, R. P. & Maffei, P. Electrophysiological features in acromegaly: re-thinking the arrhythmic risk? *J. Endocrinol. Invest.* **44**, 209–221 (2021).
117. Giustina, A. et al. Pegvisomant in acromegaly: an update. *J. Endocrinol. Invest.* **40**, 577–589 (2017).
118. Trainer, P. J. et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. *N. Engl. J. Med.* **342**, 1171–1177 (2000).
119. Haberbosch, L. & Strasburger, C. J. Efficacy and safety of pegvisomant in the treatment of acromegaly. *Arch. Med. Res.* **54**, 102884 (2023).
120. Fleseriu, M. et al. More than a decade of real-world experience of pegvisomant for acromegaly: ACROSTUDY. *Eur. J. Endocrinol.* **185**, 525–538 (2021).
121. Pirchio, R. et al. Control of acromegaly in more than 90% of patients after 10 years of pegvisomant therapy: an European referral centre real-life experience. *J. Endocrinol. Invest.* **46**, 1027–1038 (2023).
122. Droste, M. et al. Therapy of acromegalic patients exacerbated by concomitant type 2 diabetes requires higher pegvisomant doses to normalise IGF1 levels. *Eur. J. Endocrinol.* **171**, 59–68 (2014).
123. Buchfelder, M. et al. Long-term treatment with pegvisomant: observations from 2090 acromegaly patients in ACROSTUDY. *Eur. J. Endocrinol.* **179**, 419–427 (2018).
124. Leonart, L. P., Tonin, F. S., Ferreira, V. L., Fernandez-Llimos, F. & Pontarolo, R. Effectiveness and safety of pegvisomant: a systematic review and meta-analysis of observational longitudinal studies. *Endocrine* **63**, 18–26 (2019).
125. Brue, T. et al. Diabetes in patients with acromegaly treated with pegvisomant: observations from acrostudy. *Endocrine* **63**, 563–572 (2019).
126. Chiloiro, S. et al. Effects of pegvisomant and pasireotide LAR on vertebral fractures in acromegaly resistant to first-generation SRLs. *J. Clin. Endocrinol. Metab.* **105**, dgz054 (2020).
127. Salvatori, R. et al. Patient-reported outcomes in patients with acromegaly treated with pegvisomant in the ACROSTUDY extension: a real-world experience. *Pituitary* **25**, 420–432 (2022).
128. Feola, T. et al. Pegvisomant improves glucose metabolism in acromegaly: a meta-analysis of prospective interventional studies. *J. Clin. Endocrinol. Metab.* **104**, 2892–2902 (2019).
129. Sesmilo, G. et al. Escape and lipodystrophy in acromegaly during pegvisomant therapy, a retrospective multicentre Spanish study. *Clin. Endocrinol.* **81**, 883–890 (2014).
130. Ma, L. et al. Combined therapy of somatostatin analogues with pegvisomant for the treatment of acromegaly: a meta-analysis of prospective studies. *BMC Endocr. Disord.* **20**, 126 (2020).
131. Neggers, S. J. et al. Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without pegvisomant. *J. Clin. Endocrinol. Metab.* **93**, 3853–3859 (2008).
132. Madsen, M., Poulsen, P. L., Orskov, H., Møller, N. & Jørgensen, J. O. Cotreatment with pegvisomant and a somatostatin analog (SA) in SA-responsive acromegalic patients. *J. Clin. Endocrinol. Metab.* **96**, 2405–2413 (2011).
133. van der Lely, A. J. et al. Coadministration of lanreotide autogel and pegvisomant normalizes IGF1 levels and is well tolerated in patients with acromegaly partially controlled by somatostatin analogs alone. *Eur. J. Endocrinol.* **164**, 325–333 (2011).
134. Giustina, A. et al. Standards of care for medical management of acromegaly in pituitary tumor centers of excellence (PTCOE). *Pituitary* **27**, 381–388 (2024).
135. Neggers, S. J. et al. Long-term efficacy and safety of pegvisomant in combination with long-acting somatostatin analogs in acromegaly. *J. Clin. Endocrinol. Metab.* **99**, 3644–3652 (2014).
136. Bonert, V. et al. Cost–effectiveness and efficacy of a novel combination regimen in acromegaly: a prospective, randomized trial. *J. Clin. Endocrinol. Metab.* **105**, dgaa444 (2020).
137. Muhammad, A. et al. Efficacy and safety of switching to pasireotide in acromegaly patients controlled with pegvisomant and somatostatin analogues: PAPE extension study. *Eur. J. Endocrinol.* **179**, 269–277 (2018).
138. Auriemma, R. S. et al. Effects of long-term combined treatment with somatostatin analogues and pegvisomant on cardiac structure and performance in acromegaly. *Endocrine* **55**, 872–884 (2017).
139. Sandret, L., Maison, P. & Chanson, P. Place of cabergoline in acromegaly: a meta-analysis. *J. Clin. Endocrinol. Metab.* **96**, 1327–1335 (2011).
140. Bernabeu, I. et al. Pegvisomant and cabergoline combination therapy in acromegaly. *Pituitary* **16**, 101–108 (2013).
141. Higham, C. E. et al. Effective combination treatment with cabergoline and low-dose pegvisomant in active acromegaly: a prospective clinical trial. *J. Clin. Endocrinol. Metab.* **97**, 1187–1193 (2012).
142. Strasburger, C. J. et al. Increasing frequency of combination medical therapy in the treatment of acromegaly with the GH receptor antagonist pegvisomant. *Eur. J. Endocrinol.* **178**, 321–329 (2018).
143. Chiloiro, S. et al. Pasireotide and pegvisomant combination treatment in acromegaly resistant to second-line therapies: a longitudinal study. *J. Clin. Endocrinol. Metab.* **104**, 5478–5482 (2019).
144. Muhammad, A. et al. Efficacy and safety of switching to pasireotide in patients with acromegaly controlled with pegvisomant and first-generation somatostatin analogues (PAPE Study). *J. Clin. Endocrinol. Metab.* **103**, 586–595 (2018).
145. Chiloiro, S. et al. Glucose metabolism outcomes in acromegaly patients on treatment with pasireotide-LAR or pasireotide-LAR plus pegvisomant. *Endocrine* **73**, 658–666 (2021).
146. Guo, X. et al. 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.* **137**, 618–628 (2022).
147. Mohyeldin, A. et al. Prospective intraoperative and histologic evaluation of cavernous sinus medial wall invasion by pituitary adenomas and its implications for acromegaly remission outcomes. *Sci. Rep.* **12**, 9919 (2022).
148. Albarel, F. et al. Preoperative medical treatment for patients with acromegaly: yes or no? *J. Endocr. Soc.* **6**, bvac114 (2022).
149. Pita-Gutierrez, F. et al. Place of preoperative treatment of acromegaly with somatostatin analog on surgical outcome: a systematic review and meta-analysis. *PLoS ONE* **8**, e61523 (2013).
150. Jacob, J. J. & Bevan, J. S. Should all patients with acromegaly receive somatostatin analogue therapy before surgery and, if so, for how long? *Clin. Endocrinol.* **81**, 812–817 (2014).
151. Nunes, V. S., Correa, J. M., Puga, M. E., Silva, E. M. & Boguszewski, C. L. Preoperative somatostatin analogues versus direct transsphenoidal surgery for newly-diagnosed acromegaly patients: a systematic review and meta-analysis using the GRADE system. *Pituitary* **18**, 500–508 (2015).
152. Albarel, F. et al. Pre-surgical medical treatment, a major prognostic factor for long-term remission in acromegaly. *Pituitary* **21**, 615–623 (2018).
153. Melmed, S. et al. Safety and efficacy of oral octreotide in acromegaly: results of a multicenter phase III trial. *J. Clin. Endocrinol. Metab.* **100**, 1699–1708 (2015).
154. Fleseriu, M. et al. 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 (2022).
155. Pavel, M. et al. Octreotide SC depot in patients with acromegaly and functioning neuroendocrine tumors: a phase 2, multicenter study. *Cancer Chemother. Pharmacol.* **83**, 375–385 (2019).
156. Giustina, A. et al. Results from ACROCOVID: an international survey on the care of acromegaly during the COVID-19 era. *Endocrine* **71**, 273–280 (2021).
157. Frara, S. et al. COVID-19 and the pituitary. *Pituitary* **24**, 465–481 (2021).
158. Melmed, S. Pituitary-tumor endocrinopathies. *N. Engl. J. Med.* **382**, 937–950 (2020).
159. Urwyler, S. A. et al. Efficacy of cabergoline in non-irradiated patients with acromegaly: a multi-centre cohort study. *Eur. J. Endocrinol.* **190**, 113–120 (2024).
160. Auriemma, R. S., Pivonello, R., Ferreri, L., Priscitelli, P. & Colao, A. Cabergoline use for pituitary tumors and valvular disorders. *Endocrinol. Metab. Clin. North Am.* **44**, 89–97 (2015).
161. Stiles, C. E., Tetteh-Wayoe, E. T., Bestwick, J., Steeds, R. P. & Drake, W. M. A meta-analysis of the prevalence of cardiac valvulopathy in hyperprolactinemic patients treated with cabergoline. *J. Clin. Endocrinol. Metab.* **104**, 523–538 (2019).
162. Hamidianjahromi, A. & Tritos, N. A. Impulse control disorders in hyperprolactinemic patients on dopamine agonist therapy. *Rev. Endocr. Metab. Disord.* **23**, 1089–1099 (2022).
163. Giustina, A., Boni, E., Romanelli, G., Grassi, V. & Giustina, G. Cardiopulmonary performance during exercise in acromegaly, and the effects of acute suppression of growth hormone hypersecretion with octreotide. *Am. J. Cardiol.* **75**, 1042–1047 (1995).
164. van der Lely, A. J. et al. Pegvisomant and not somatostatin receptor ligands (SRLs) is first-line medical therapy for acromegaly. *Eur. J. Endocrinol.* **182**, D17–D29 (2020).
165. Giustina, A., di Filippo, L., Uygur, M. M. & Frara, S. Modern approach to resistant acromegaly. *Endocrine* **80**, 303–307 (2023).
166. Coopmans, E. C., van der Lely, A. J. & Neggers, S. J. C. M. M. Approach to the patient with treatment-resistant acromegaly. *J. Clin. Endocrinol. Metab.* **107**, 1759–1766 (2022).
167. Stone, J. C., Clark, J., Cuneo, R., Russell, A. W. & Doi, S. A. Estrogen and selective estrogen receptor modulators (SERMs) for the treatment of acromegaly: a meta-analysis of published observational studies. *Pituitary* **17**, 284–295 (2014).
168. Duarte, F. H., Jallad, R. S. & Bronstein, M. D. Clomiphene citrate for treatment of acromegaly not controlled by conventional therapies. *J. Clin. Endocrinol. Metab.* **100**, 1863–1869 (2015).
169. Magalhães, J. et al. A prospective study on the efficacy of oral estrogen in female patients with acromegaly. *Pituitary* **25**, 433–443 (2022).
170. Ho, K. K. Y. et al. A tale of pituitary adenomas: to NET or not to NET: Pituitary Society position statement. *Pituitary* **22**, 569–573 (2019).
171. Whitelaw, B. C. How and when to use temozolomide to treat aggressive pituitary tumours. *Endocr. Relat. Cancer* **26**, R545–R552 (2019).
172. Ho, K. K. Y. et al. A proposed clinical classification for pituitary neoplasms to guide therapy and prognosis. *Lancet Diabetes Endocrinol.* **12**, 209–214 (2024).



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A.G. and S.M. contributed to all aspects of the article. L.d.F. wrote the article and reviewed and/or edited the manuscript before submission. M.F., M. Mercado, N.K., M.G., R.S., S.T., M.L., P. Maffei, A.M.P., E.B.G., L.K., A.J.v.d.L., J.B., D.E., S.M.W., E.V., S.N., P.C., K.K.Y.H., A.G.I., B.M.K.B., S.L.S., U.B.K., K.S., R.M.L., F.F.C., I.S., C.L.B., N.B., A.C., R.P., S.W.J.L., P.K., M.B., S.F., S.C., M.R.G., A.L., T.B., A.B., D.F., D.R.C., Y.G., M. Marazuela, P. Mortini and C.J.S. researched data for the article, contributed substantially to discussion of the content and reviewed and/or edited the manuscript before submission. M.P.-D. researched data for the article and reviewed and/or edited the manuscript before submission.

## Competing interests

S.M. received a research grant to their institution from Recordati Rare Diseases; is a consultant to Novo Nordisk and Crinetics. L.d.F. received a research grant to his institution from Abiogen Pharma S.p.A. M.F. received grants to their institution from Amryt, Crinetics, Ionis and Recordati Rare Diseases, received occasional consulting fees or has served as occasional advisory board member for Amryt, Crinetics, Camurus, Ipsen and Recordati Rare Diseases. N.K. has been a speaker for Pfizer, Ipsen and Recordati Rare Diseases, investigator for Pfizer and Ipsen and scientific advisory board for Pfizer, Ipsen and Recordati Rare Diseases. M.G. has received speakers honoraria from Ipsen and Pfizer. R.S. has been a consultant for Lundbeck, Amryt, Novo Nordisk, Camurus, Ascendis and Crinetics. S.T. has received honoraria, lecture and advisory fees and grants from Crinetics, Novartis, Strongbridge, HRA Pharma and Recordati Rare Diseases. P.M. has been a principal investigator in clinical trials of Ipsen, Pfizer and Camurus, received consultation fee and research support from Pfizer and Recordati Rare Diseases. E.B.G. is an investigator for research grants to MSKCC from Chiesi and Recordati Rare Diseases, consultant to Crinetics, Recordati and Chiesi. L.K. is on the advisory board for Novo Nordisk, Recordati Rare Diseases and Camurus and has received research support from Camarus. A.J.v.d.L. has received consulting and speaking fees from Amolyt Pharma and Pfizer. J.B. has received speakers fee from Novartis, Ipsen and Pfizer and unrestricted research grants from Novartis and Ipsen. D.E. has received lecture fees from Ipsen, Pfizer and Recordati Rare Diseases. S.M.W. is on scientific advisory boards for Novartis, Ipsen, Pfizer, Lilly, Strongbridge, Shire, Crinetics, Recordati Rare Diseases and HRA and has received speaker fees from Ipsen, HRA, Recordati Rare Diseases and Consilient Health, unrestricted research funds from Novartis, Ipsen, Pfizer and HRA and participated in clinical trials of Novartis, Recordati Rare Diseases and Cortendo. E.V. is on the advisory board for Recordati Rare Diseases and HRA Pharma, received speaker fees from Recordati Rare Diseases, HRA Pharma and Ipsen. S.N. has received consulting, research and speaking fees from Novo Nordisk, Crinetics, Recordati Rare Diseases and Pfizer. P.C. has received unrestricted research and educational grants from Ipsen, Recordati Rare Diseases, Advanz and Pfizer, is an investigator (principal or coordinator) for clinical trials funded by Chiasma, Recordati Rare Diseases, Pfizer, Crinetics and Debiopharm, is a member of advisory boards for Pfizer, Crinetics, Recordati Rare Diseases and Amolyt, lectures for Ipsen, Recordati Rare Diseases and Pfizer. A.G.I. occasionally consults for Crinetics, Camurus and Xeris, has received research grants to their institution from Recordati Rare Diseases, Xeris and Chiesi. B.M.K.B. is a principal investigator of an institutional grant from Crinetics and occasional consultant to Amolyt, Amryt, Camurus, Crinetics and Recordati Rare Diseases. S.L.S. is principal investigator for Chiasma (Chiesi) and Pasireotide (Novartis, now Recordati Rare Diseases). K.S. has received honoraria for consulting, speaking and scientific projects from the following companies: Pfizer, Recordati Rare Diseases, Camurus, Crinetics, Novo Nordisk and Ascendis. I.S. has received consulting and lecture fees from Pfizer, Medison Pharma, Novo Nordisk and OPKO Biologics and participated in clinical studies by Crinetics and Debiopharm. C.L.B. has received speaking fees from Ipsen, consulting fees from Ipsen, Recordati Rare Diseases and Novo Nordisk and is a principal investigator of clinical trials of Crinetics. A.C. is a principal investigator of research studies for Novartis, Ipsen and Pfizer, a consultant for Novartis, Ipsen and Pfizer, received honoraria from Novartis, Ipsen and Pfizer. P.K. participated in clinical trials of Carmus and Recordati Rare Diseases. 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## Additional information

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