A Consensus on Criteria for Cure of Acromegaly

A. Giustina, P. Chanson, M. D. Bronstein, A. Klibanski, S. Lamberts, F. F. Casanueva, P. Trainer, E. Ghigo, K. Ho, and S. Melmed

Department of Medical and Surgical Sciences (A.G.), University of Brescia, I-25018 Montichiari, Italy; Assistance Publique-Hôpitaux de Paris et Université Paris-Sud 11 (P.C.), Department of Endocrinology and Reproductive Diseases, F-94275 Le Kremlin-Bicêtre, France; Neuroendocrine Unit (M.D.B.), Division of Endocrinology and Metabolism, University of Sao Paulo Medical School, 05311-970 Sao Paulo, Brazil; Neuroendocrine Unit (A.K.), Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114; Department of Internal Medicine (S.L.), Division of Endocrinology, Erasmus Medical Center, 3000 CA Rotterdam, The Netherlands; Division of Endocrinology CHUS (F.F.C.), Department of Medicine, Santiago de Compostela University, 15782 Santiago de Compostela, Spain; Department of Endocrinology (P.T.), Christie Hospital, Manchester M20 4BX, United Kingdom; Division of Endocrinology (E.G.), University of Turin, 10129 Turin, Italy; Pituitary Research Unit (K.H.), Garvan Institute of Medical Research, Sydney, New South Wales 2010, Australia; and Department of Medicine (S.M.), Cedars-Sinai Medical Center, Los Angeles, California 90048

Objective: The Acromegaly Consensus Group met in April 2009 to revisit the guidelines on criteria for cure as defined in 2000.

Participants: Participants included 74 neurosurgeons and endocrinologists with extensive experience of treating acromegaly.

Evidence/Consensus Process: Relevant assays, biochemical measures, clinical outcomes, and definition of disease control were discussed, based on the available published evidence, and the strength of consensus statements was rated.

Conclusions: Criteria to define active acromegaly and disease control were agreed, and several significant changes were made to the 2000 guidelines. Appropriate methods of measuring and achieving disease control were summarized. **(*J Clin Endocrinol Metab* 95: 3141–3148, 2010)**

Guidelines published in 2009 summarized the latest consensus on the management of acromegaly (1). Several other consensus documents have been published on various aspects of acromegaly management since 2000 (2–6), and in 2000, the criteria for cure of acromegaly were defined (2). In April 2009, the Acromegaly Consensus Group that had produced these previous documents met to reevaluate and update the guidelines on criteria for cure. The meeting was sponsored by the Pituitary Society and the European Neuroendocrine Association and included endocrinologists and neurosurgeons skilled in the management of acromegaly.

Recommendations were graded, based on the GRADE system (7, 8), depending on the quality of evidence as very low quality (VLQ; expert opinion with one or a small number of small uncontrolled studies in support), low quality (LQ; large series of small uncontrolled studies), moderate quality (MQ; one or a small number of large uncontrolled studies or metaanalyses), or high quality (HQ; controlled studies or large series of large uncontrolled studies with sufficiently long follow-up). Recommendations were classed as discretionary recommendations (DR) if based on VLQ or LQ evidence and as strong recommendations (SR) if based in MQ and HQ evidence.

Assays

The most important assays used for the diagnosis, management, and monitoring of acromegaly are GH and IGF-I measurements. The lack of reliable assays, assay standard-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2009-2670 Received December 14, 2009. Accepted March 24, 2010.
First Published Online April 21, 2010

Abbreviations: DR, Discretionary recommendation; HQ, high quality; LQ, low quality; MQ, moderate quality; OGTT, oral glucose tolerance test; SR, strong recommendation; SRL, somatostatin receptor ligand; VLQ, very low quality.

ization, and adequate normative data are major issues in the interpretation of these biochemical measures (9–12). These factors can lead to major discrepancies in the values obtained in different laboratories.

The reasons for heterogeneity among GH immunoassay results include variable calibration, epitope specificity of the chosen antibody, and differences in the specificity of antibody recognition of different GH isoforms circulating in the serum (10). Furthermore, there is a lack of standardization between the use of mass units (micrograms per liter) and international units (milli-international units per liter), and several different conversion factors are used (for example, see Refs. 13–15). Problems with IGF-I assays include the variable quality of the assay performance (16), differences and deficiencies in reference ranges and age-stratified normative data, and the uncertain purity of the International Reference Reagent.

As a first step to improving the interpretation of GH assays, it is strongly recommended that the World Health Organization (WHO) international standard (WHO IS 98/574) be used and results be expressed in mass units (micrograms per liter) (SR) (17). Assays should also be standardized to measure the 22-kDa isoform of GH or, as a second-choice, standardized to multiple isoforms of GH (DR) (17). Additionally, there is a need to increase awareness of the potential problems with GH assays by engaging stakeholders, including academic and regulatory organizations, journal editors, diagnostic kit manufacturers, the International Federation of Clinical Chemistry (IFCC), and other professional endocrine societies (SR).

To improve IGF-I measurement, the highly purified recombinant IGF-I WHO first international standard (WHO IS 02/254) should be adopted (SR) (18). Other measures that will improve the quality of IGF-I measurement include the use of highly specific antibodies and the elimination of the confounding effects of binding proteins (DR) (19). Importantly, normative data must be drawn from a statistically valid control population (at least 1000 subjects) stratified by decade (20). An algorithm should be constructed to allow reporting in SD scores. The influence of gender and body mass index are modest and do not justify adjustment of normalized values.

The issues with GH and IGF-I measurements highlighted here reflect the inherent limitations of immunoassays. It is anticipated that the development of mass-spectroscopy-based technology may overcome these limitations.

The measurement of acid-labile subunit, other binding proteins (*e.g.* IGF-binding protein-3), or ghrelin offers no advantage over IGF-I measurement in the diagnosis and management of acromegaly (MQ) (19, 21–25).

GH and IGF-I Regulation

The measurement of GH and age-matched IGF-I concentrations are the most important biochemical variables for the diagnosis of acromegaly and for monitoring progression or treatment response (HQ) (11, 14, 21, 26).

The measurement of total IGF-I levels reflects GH secretory status in acromegaly (at baseline for diagnosis, after neurosurgery or radiotherapy, or during medical treatment) (HQ) (26–28). The measurement of free IGF-I and/or IGF-binding proteins does not provide additional clinical information (MQ) (19, 22, 26, 27).

In the investigation of suspected acromegaly, an elevated IGF-I level and a failure to suppress GH during an oral glucose tolerance test (OGTT) confirm the diagnosis (HQ) (29). In some cases, when the IGF-I and GH levels are clearly elevated, an OGTT may not be required (LQ) (21). During follow-up after neurosurgery or radiotherapy, controlled GH status can be defined as GH suppression during an OGTT (for patients not receiving medical therapy) and a normal IGF-I level (after 3–6 months for those that have undergone neurosurgery) (HQ) (29). When there is discrepancy between GH and IGF-I values, multiple GH sampling (three to five times over 2 h) is helpful (MQ) (14) (see below). For patients receiving medical treatment with a somatostatin receptor ligand (SRL) or dopamine agonist, IGF-I and random GH measurements are sufficient for assessment. In fact, an OGTT may not be helpful for monitoring response in patients receiving any medical treatment (MQ) (11, 29). In patients receiving a GH receptor antagonist, only IGF-I should be measured (HQ) (30).

Oral but not transdermal estrogens reduce IGF-I concentrations; results of IGF-I measurements in women receiving oral estrogens should therefore be interpreted with caution (MQ) (31–34).

Discrepant Biochemical Results

GH and IGF-I levels are closely correlated in patients with acromegaly and healthy individuals (HQ) (35, 36); however, discordance between GH and IGF-I levels has been noted in up to 30% of patients with acromegaly after treatment (MQ) (29, 32). Most discordance involves the measurement of normal GH levels and elevated IGF-I levels, but some cases exhibit elevated GH levels and normal IGF-I levels (MQ) (32, 34).

Apparent discrepant results may stem from inaccurate estimates of GH status, either from limited sampling (often a single or small number of GH measurements are obtained randomly or during dynamic testing, which may not accurately measure 24-h GH output) or from the lack

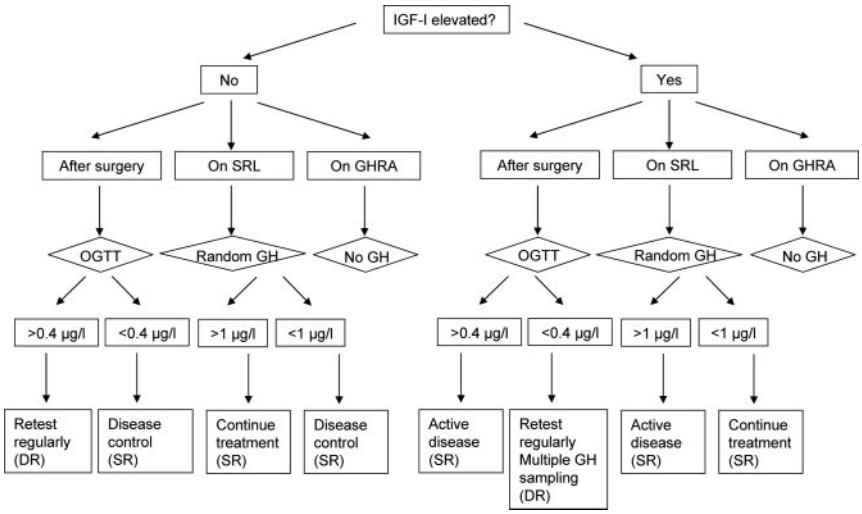

FIG. 1. Interpretation of GH and IGF-I levels in acromegaly. GHRA, GH receptor antagonist.

of assay standardization (MQ) (11). However, there are a number of other factors that can lead to discrepancies in GH/IGF-I levels, including hormone half-life, pulsatility, age, comorbidities, and genetic differences (LQ) (34, 37–42).

The combination of an elevated IGF-I level and a normal GH level is sometimes seen after radiation therapy because radiotherapy causes a flat GH secretory pattern (VLQ) (43). In contrast, a number of factors have been identified that can result in lower IGF-I levels relative to GH levels (either by reducing IGF-I levels or raising GH levels); these include nutritional or gastrointestinal disorders such as chronic inflammatory bowel disorder and anorexia nervosa (which can impair IGF-I production by the liver), hepatic or renal failure, oral estrogens, hypothyroidism, and poorly controlled type 1 diabetes (MQ) (11). In addition, patients with acromegaly in long-term remission may have discrete signs of mild GH excess (such as mild hypertension, relative glucose intolerance, and arthralgia) (LQ) (44, 45), and the chronicity of the acromegaly is an important factor when interpreting discordant results.

It should be noted that the timing of postoperative testing may affect apparent discrepancies. Because of the long IGF-I half-life and other factors regulating IGF-I, it can take several months after surgery for levels to be accurate (MQ) (46). If biochemical measurements 3–6 months after surgery show an elevated IGF-I level, further testing of GH with an OGTT, multiple GH sampling (three to five times over 2 h), or isolated GH measurement should be performed (SR) (14, 21, 35, 42, 43). If there is a significant discrepancy, further testing may be needed over time, and therapeutic decisions should be made according to the clinical context. Assessment of GH receptor polymorphisms may sometimes be helpful in this setting (DR) (47) (Fig.1).

Clinical Outcomes

Morbidity and mortality rates in uncontrolled acromegaly are increased due to the deleterious effect of raised GH and IGF-I, and sustained long-term treatment is needed to normalize these rates (HQ) (45, 48–51).

Comorbidities

The major comorbidities associated with acromegaly are cardiovascular disease, diabetes, hypertension, sleep apnea, arthritis, and metabolic bone disorders (osteoporosis). Effective biochemical control does not always result in effective control of comorbidities (MQ) (44, 52–58).

Optimal control of comorbidities should be achieved with the most effective treatments for both acromegaly and the specific comorbidities (SR) (45, 59–61). Cardiovascular disease, hypertension, diabetes, sleep apnea, and arthralgia are all improved, although only partial regression may occur, in patients with normalized GH levels (MQ) (59, 62). Cardiovascular risk factors should be actively identified and treated (SR) (52). Obstructive sleep apnea is a comorbidity that may occur in 25–60% of patients. Sleep quality and disturbances in patients with acromegaly require detailed assessment and appropriate referral for management (SR) (63). Patients with colonic polyps should be followed according to the international guidelines for colon cancer (SR) (64–67). When visual impairment is a symptom of acromegaly in the setting of chiasmal compression with macroadenomas, surgery is the primary treatment, but SRLs may decompress mass effects. Where surgery is not an option, SRLs could be used in specific cases under close ophthalmological monitoring (DR).

Tumor shrinkage with SRLs

Control of tumor mass is a major goal of acromegaly therapy, and surgery achieves this in many patients (HQ) (14, 68–72). The role of medical therapy in achieving tumor shrinkage is less well defined. In patients receiving SRL therapy, a detectable degree of shrinkage is seen in up to 80% of *de novo* patients in some treatment series (MQ) (73–82). The degree of tumor shrinkage after 3 months of SRL therapy may predict long-term (12 months) shrinkage (LQ) (81). Tumor shrinkage is not necessarily associated with biochemical remission (MQ) (83, 84).

The presurgical use of SRLs may improve surgical outcome, but this requires more data to confirm initial reports (SRL therapy has improved surgical outcome in some studies but not in others) (LQ) (85–90) and to define the

TABLE 1. Acromegaly treatment outcomes

Outcome	Criteria[a]	Management
Active disease	Random GH >1 μg/liter and nadir GH after OGTT ≥0.4 μg/liter	Periodic MRI
	Elevated IGF-I	Monitor and actively treat comorbidities
	Clinically active	Actively treat or change treatment
Controlled disease	Random GH <1 μg/liter or nadir GH after OGTT <0.4 μg/liter	Periodic but less frequent MRI[b]
	Age-sex normalized IGF-I	No change to current treatment; consider reducing SRL dose

MRI, Magnetic resonance imaging.

[a] Strong recommendations: assessment of GH during an OGTT and total IGF-I after surgery; random GH for patients on SRLs; if discrepant biochemical results, GH sampling three to five times over 2 h; always use reliable standardized assays and ultrasensitive assay for IGF-I and GH measurement.

[b] For example, every 2–3 yr.

patients that are most likely to benefit from pretreatment. There is no evidence that presurgical treatment with SRLs reduces the efficacy of surgery (MQ) (85, 87, 88).

Evidence is stronger for improvements in response to SRL therapy after surgical debulking (MQ) (91–94).

Mortality

Comorbidities and delays in diagnosis are the main factors influencing the prognosis of acromegaly (HQ) (49–51, 95). Both GH and IGF-I levels correlate with mortality, and mortality is close to levels expected in the general population when GH and serum IGF-I are controlled (MQ) (50).

In patients with discordant GH and IGF-I levels, the mortality risk does not appear to be elevated, but data are still insufficient (VLQ) (51).

Definition of Disease Control

Most of the case series (32, 34, 96) published in the last decade have suggested that use of the Cortina criteria (2) for defining disease control could have two main drawbacks: first, they were not sufficiently flexible to be applied to different treatment modalities; and second, cutoff limits for GH did not reflect the now widespread availability of ultrasensitive GH assays.

Therefore, optimal disease control (*i.e.* posttreatment remission of acromegaly) is now defined as IGF-I level (determined by a reliable standardized assay) in the age-adjusted normal range and a GH level less than 1.0 μg/liter from a random GH measurement (using an ultrasensitive assay) (MQ) (97). However, assays do not consistently report these values as reflective of biochemical control. Normalization of IGF-I is the only reliable marker of disease control under pegvisomant (HQ) (30).

In patients with acromegaly undergoing surgical management of GH-secreting tumors, OGTT can be used to assess the outcome (SR) (29, 42). There is substantial evidence to suggest that nadir GH levels less than 0.4 μg/liter (with ultrasensitive assays) may define control in these circumstances (MQ) (11, 34, 96, 98). In the case of discrepant biochemical results, multiple GH sampling may be useful (MQ) (14, 35, 43) (Table 1 and Fig. 1).

At present, there is no longer justification for staging the outcome of treatment in acromegaly, except to define active disease and controlled disease (SR) (2) (Table 1).

Summary

In the 10 yr since the criteria for cure of acromegaly were defined by the Acromegaly Consensus Group (2), significant progress has been made in the management of acromegaly. If managed appropriately by a multimodality team with specific experience of managing pituitary tumors, there is little justification for patients to have reduced life expectancy, frequent morbidity, or uncontrolled disease. Challenges related to criteria of cure include the need to standardize GH and IGF-I assays, how to interpret discrepant biochemical results, and how to refine treatment with SRLs to optimize tumor shrinkage.

Acknowledgments

We thank all participants in the Seventh Acromegaly Consensus Group meeting: John Ayuk (United Kingdom), Ariel Barkan (United States), Albert Beckers (Belgium), Paolo Beck-Peccoz (Italy), Bengt Åke Bengtsson (Sweden), Anat Ben-Shlomo (United States), Jerome Bertherat (France), John Bevan (United Kingdom), Beverly Biller (United States), Jens Bollerslev (Norway), Vivien Bonert (United States), Thierry Brue (France), Michael Buchfelder (Germany), Philippe Caron (France), Davide Carvalho (Portugal), Franco Cavagnini (Italy), Jens Christiansen (Denmark), David Clemmons (United States), Annamaria Colao (Italy), Renato Cozzi (Italy), Ettore Degli Uberti (Italy), Laura De

Marinis (Italy), Ernesto De Menis (Italy), Eva Marie Erfurth (Sweden), Rudolf Fahlbusch (Germany), Diego Ferone (Italy), Maria Fleseriu (United States), Pamela Freda (United States), Lawrence Frohman (United States), Monica Gadelha (Brazil), Rolf Gaillard (Switzerland), Yona Greenman (Israel), Feng Gu (China), Amir Hamrahian (United States), Ian Holdaway (New Zealand), Jens Jorgensen (Denmark), David Kleinberg (United States), Edward Laws (United States), Gaetano Lombardi (Italy), Marco Losa (Italy), Pietro Maffei (Italy), Josef Marek (Czech Republic), Gherardo Mazziotti (Italy), Moises Mercado (Mexico), Francesco Minuto (Italy), Mark Molitch (United States), Pietro Mortini (Italy), Robert Murray (United Kingdom), Stephan Petersenn (Germany), Ferdinand Roelfsema (The Netherlands), Roberto Salvatori (United States), Janet Schlechte (United States), Jochen Schopol (Germany), Omar Serri (Canada), Gunther Stalla (Germany), Brooke Swearingen (United States), Massimo Terzolo (Italy), George Tolis (Greece), Mary Lee Vance (United States), Aart Van der Lely (The Netherlands), John Wass (United Kingdom), Susan Webb (Spain), Margaret Wierman (United States), and Sema Yarman (Turkey). We acknowledge the editorial assistance provided by ESP Bioscience (supported by Ipsen) during the preparation of this manuscript.

Address all correspondence and requests for reprints to: Andrea Giustina, Department of Medical and Surgical Sciences, University of Brescia, Endocrine Service, Montichiari Hospital, Via Ciotti 154, 25018 Montichiari, Italy. E-mail: a.giustina@libero.it.

Disclosure Summary: A.K. and S.L. have nothing to declare. A.G. has consulted for Ipsen, Pfizer, and Italfarmaco and has received lecture fees from Novartis and Italfarmaco. P.C. is a consultant for and received lecture fees from Novartis, Ipsen, and Pfizer. The Service d'Endocrinologie et des Maladies de la Reproduction, Hôpital de Bicêtre, Le Kremlin-Bicêtre, received educational and research grants from Novartis, Ipsen, and Pfizer. M.D.B. is a consultant for Novartis and Pfizer and a speaker for Ipsen, Novartis, and Pfizer. F.F.C. has served as a consultant for and has received lecture fees from Novartis and Pfizer. P.T. has received lecture fees from Pfizer and Novartis and has served on advisory boards and received research grants from Pfizer, Novartis, and Ipsen. E.G. has received lecture fees from Novartis and Pfizer and received research grants from Novartis, Ipsen, Pfizer, Eli Lilly, and Novo Nordsik. K.H. has consulted and served on advisory boards. S.M. has consulted for Ipsen and received research grants from Ipsen and Novartis.

This work was supported by Sponsored by the Pituitary Society and the European Neuroendocrine Association, Supported by an unrestricted grant from Ipsen.

References

1. **Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, Clemmons D, Chanson P, Laws E, Schlechte J, Vance ML, Ho K, Giustina A** 2009 Guidelines for acromegaly management: an update. J Clin Endocrinol Metab 94:1509–1517
2. **Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K, Melmed S** 2000 Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 85:526–529
3. **Melmed S, Casanueva FF, Cavagnini F, Chanson P, Frohman L, Grossman A, Ho K, Kleinberg D, Lamberts S, Laws E, Lombardi G, Vance ML, Werder KV, Wass J, Giustina A** 2002 Guidelines for acromegaly management. J Clin Endocrinol Metab 87:4054–4058
4. **Melmed S, Casanueva F, Cavagnini F, Chanson P, Frohman LA, Gaillard R, Ghigo E, Ho K, Jaquet P, Kleinberg D, Lamberts S, Laws E, Lombardi G, Sheppard MC, Thorner M, Vance ML, Wass JA, Giustina A** 2005 Consensus statement: medical management of acromegaly. Eur J Endocrinol 153:737–740
5. **Giustina A, Casanueva FF, Cavagnini F, Chanson P, Clemmons D, Frohman LA, Gaillard R, Ho K, Jaquet P, Kleinberg DL, Lamberts SW, Lombardi G, Sheppard M, Strasburger CJ, Vance ML, Wass JA, Melmed S** 2003 Diagnosis and treatment of acromegaly complications. J Endocrinol Invest 26:1242–1247
6. **Giustina A, Barkan A, Chanson P, Grossman A, Hoffman A, Ghigo E, Casanueva F, Colao A, Lamberts S, Sheppard M, Melmed S** 2008 Guidelines for the treatment of growth hormone excess and growth hormone deficiency in adults. J Endocrinol Invest 31:820–838
7. **Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young Jr WF, Montori VM** 2008 Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 93:3266–3281
8. **Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ** 2008 GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336:924–926
9. **Pokrajac A, Wark G, Ellis AR, Wear J, Wieringa GE, Trainer PJ** 2007 Variation in GH and IGF-I assays limits the applicability of international consensus criteria to local practice. Clin Endocrinol (Oxf) 67:65–70
10. **Bidlingmaier M** 2008 Problems with GH assays and strategies toward standardization. Eur J Endocrinol 159(Suppl 1):S41–S44
11. **Arafat AM, Möhlig M, Weickert MO, Perschel FH, Purschwitz J, Spranger J, Strasburger CJ, Schöfl C, Pfeiffer AF** 2008 Growth hormone response during oral glucose tolerance test: the impact of assay method on the estimation of reference values in patients with acromegaly and in healthy controls, and the role of gender, age, and body mass index. J Clin Endocrinol Metab 93:1254–1262
12. **Melmed S** 2006 Medical progress: acromegaly. N Engl J Med 355:2558–2573
13. **Orme SM, McNally RJ, Cartwright RA, Belchetz PE** 1998 Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab 83:2730–2734
14. **Kaltsas GA, Isidori AM, Florakis D, Trainer PJ, Camacho-Hubner C, Afshar F, Sabin I, Jenkins JP, Chew SL, Monson JP, Besser GM, Grossman AB** 2001 Predictors of the outcome of surgical treatment in acromegaly and the value of the mean growth hormone day curve in assessing postoperative disease activity. J Clin Endocrinol Metab 86:1645–1652
15. **Baldelli R, Colao A, Razzore P, Jaffrain-Rea ML, Marzullo P, Ciccarelli E, Ferretti E, Ferone D, Gaia D, Camanni F, Lombardi G, Tamburrano G** 2000 Two-year follow-up of acromegalic patients treated with slow release lanreotide (30 mg). J Clin Endocrinol Metab 85:4099–4103
16. **Massart C, Poirier JY** 2006 Serum insulin-like growth factor-I measurement in the follow-up of treated acromegaly: comparison of four immunoassays Clin Chim Acta 373:176–179
17. **Trainer PJ, Barth J, Sturgeon C, Wieringaon G** 2006 Consensus statement on the standardisation of GH assays. Eur J Endocrinol 155:1–2
18. **Burns C, Rigsby P, Moore M, Rafferty B** 2009 The First International Standard For Insulin-like Growth Factor-1 (IGF-1) for immunoassay: preparation and calibration in an international collaborative study. Growth Horm IGF Res 19:457–462
19. **Sneppen SB, Lange M, Pedersen LM, Kristensen L LØ, Main KM, Juul A, Skakkebaek NE, Feldt-Rasmussen U** 2001 Total and free

insulin-like growth factor I, insulin-like growth factor binding protein 3 and acid-labile subunit reflect clinical activity in acromegaly. Growth Horm IGF Res 11:384–391

20. **Brabant G, von zur Mühlen A, Wüster C, Ranke MB, Kratzsch J, Kiess W, Ketelslegers JM, Wilhelmsen L, Hulthén L, Saller B, Mattsson A, Wilde J, Schemer R, Kann P** 2003 Serum insulin-like growth factor I reference values for an automated chemiluminescence immunoassay system: results from a multicenter study. Horm Res 60:53–60
21. **Minuto F, Resmini E, Boschetti M, Arvigo M, Sormani MP, Giusti M, Ferone D, Barreca A** 2004 Assessment of disease activity in acromegaly by means of a single blood sample: comparison of the 120th minute postglucose value with spontaneous GH secretion and with the IGF system. Clin Endocrinol (Oxf) 61:138–144
22. **Marzullo P, Di Somma C, Pratt KL, Khosravi J, Diamandis A, Lombardi G, Colao A, Rosenfeld RG** 2001 Usefulness of different biochemical markers of the insulin-like growth factor (IGF) family in diagnosing growth hormone excess and deficiency in adults. J Clin Endocrinol Metab 86:3001–3008
23. **Morrison KM, Bidlingmaier M, Stadler S, Wu Z, Skriver L, Strasburger CJ** 2007 Sample pre-treatment determines the clinical usefulness of acid-labile subunit immunoassays in the diagnosis of growth hormone deficiency and acromegaly. Eur J Endocrinol 156: 331–339
24. **Arosio M, Garrone S, Bruzzi P, Faglia G, Minuto F, Barreca A** 2001 Diagnostic value of the acid-labile subunit in acromegaly: evaluation in comparison with insulin-like growth factor (IGF) I, and IGF-binding protein-1, -2, and -3. J Clin Endocrinol Metab 86:1091–1098
25. **Barkan AL, Dimaraki EV, Jessup SK, Symons KV, Ermolenko M, Jaffe CA** 2003 Ghrelin secretion in humans is sexually dimorphic, suppressed by somatostatin, and not affected by the ambient growth hormone levels. J Clin Endocrinol Metab 88:2180–2184
26. **Clemmons DR** 2007 Value of insulin-like growth factor system markers in the assessment of growth hormone status. Endocrinol Metab Clin North Am 36:109–129
27. **Juul A** 2003 Serum levels of insulin-like growth factor I and its binding proteins in health and disease. Growth Horm IGF Res 13: 113–170
28. **Giustina A, Veldhuis JD** 1998 Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. Endocr Rev 19:717–797
29. **Carmichael JD, Bonert VS, Mirocha JM, Melmed S** 2009 The utility of oral glucose tolerance testing for diagnosis and assessment of treatment outcomes in 166 patients with acromegaly. J Clin Endocrinol Metab 94:523–527
30. **Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, Dimaraki EV, Stewart PM, Friend KE, Vance ML, Besser GM, Scarlett JA, Thorner MO, Parkinson C, Klibanski A, Powell JS, Barkan AL, Sheppard MC, Malsonado M, Rose DR, Clemmons DR, Johannsson G, Bengtsson BA, Stavrou S, Kleinberg DL, Cook DM, Phillips LS, Bidlingmaier M, Strasburger CJ, Hackett S, Zib K, Bennett WF, Davis RJ** 2000 Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med 342: 1171–1177
31. **Lau SL, McGrath S, Evain-Brion D, Smith R** 2008 Clinical and biochemical improvement in acromegaly during pregnancy. J Endocrinol Invest 31:255–261
32. **Alexopoulou O, Bex M, Abs R, T'Sjoen G, Velkeniers B, Maiter D** 2008 Divergence between growth hormone and insulin-like growth factor-1 concentrations in the follow-up of acromegaly. J Clin Endocrinol Metab 93:1324–1330
33. **Cozzi R, Barausse M, Lodrini S, Lasio G, Attanasio R** 2003 Estroprogestinic pill normalizes IGF-I levels in acromegalic women. J Endocrinol Invest 26:347–352
34. **Freda PU** 2009 Monitoring of acromegaly: what should be performed when GH and IGF-1 levels are discrepant? Clin Endocrinol (Oxf) 71:166–170
35. **Ho KY, Weissberger AJ** 1994 Characterization of 24-hour growth hormone secretion in acromegaly: implications for diagnosis and therapy. Clin Endocrinol (Oxf) 41:75–83
36. **Reutens AT, Veldhuis JD, Hoffman DM, Leung KC, Ho KK** 1996 A highly sensitive growth hormone (GH) enzyme-linked immunosorbent assay uncovers increased contribution of a tonic mode of GH secretion in adults with organic GH deficiency. J Clin Endocrinol Metab 81:1591–1597
37. **Colao A, Pivonello R, Cavallo LM, Gaccione M, Auriemma RS, Esposito F, Cappabianca P, Lombardi G** 2006 Age changes the diagnostic accuracy of mean profile and nadir growth hormone levels after oral glucose in postoperative patients with acromegaly. Clin Endocrinol (Oxf) 65:250–256
38. **Colao A, Pivonello R, Cappabianca P, Briganti F, Tortora F, Auriemma RS, De Martino MC, Marzullo P, Lombardi G** 2005 Effect of gender and gonadal status on the long-term response to somatostatin analogue treatment in acromegaly. Clin Endocrinol (Oxf) 63:342–349
39. **Meinhardt UJ, Ho KK** 2006 Modulation of growth hormone action by sex steroids. Clin Endocrinol (Oxf) 65:413–422
40. **Murray RD, Kim K, Ren SG, Chelly M, Umehara Y, Melmed S** 2004 Central and peripheral actions of somatostatin on the growth hormone-IGF-I axis. J Clin Invest 114:349–356
41. **Parkinson C, Renehan AG, Ryder WD, O'Dwyer ST, Shalet SM, Trainer PJ** 2002 Gender and age influence the relationship between serum GH and IGF-I in patients with acromegaly. Clin Endocrinol (Oxf) 57:59–64
42. **Vierhapper H, Heinze G, Gessl A, Exner M, Bieglmayr C** 2003 Use of the oral glucose tolerance test to define remission in acromegaly. Metabolism 52:181–185
43. **van der Klaauw AA, Pereira AM, van Thiel SW, Frolich M, Iranmanesh A, Veldhuis JD, Roelfsema F, Romijn JA** 2007 Attenuated pulse size, disorderly growth hormone and prolactin secretion with preserved nyctohemeral rhythm distinguish irradiated from surgically treated acromegaly patients. Clin Endocrinol (Oxf) 66:489–498
44. **Bex M, Abs R, T'Sjoen G, Mockel J, Velkeniers B, Muermans K, Maiter D** 2007 AcroBel the Belgian registry on acromegaly: a survey of the 'real-life' outcome in 418 acromegalic subjects. Eur J Endocrinol 157:399–409
45. **Puder JJ, Nilavar S, Post KD, Freda PU** 2005 Relationship between disease-related morbidity and biochemical markers of activity in patients with acromegaly. J Clin Endocrinol Metab 90:1972–1978
46. **Feelders RA, Bidlingmaier M, Strasburger CJ, Janssen JA, Uitterlinden P, Hofland LJ, Lamberts SW, van der Lely AJ, de Herder WW** 2005 Postoperative evaluation of patients with acromegaly: clinical significance and timing of oral glucose tolerance testing and measurement of (free) insulin-like growth factor I, acid-labile subunit, and growth hormone-binding protein levels. J Clin Endocrinol Metab 90:6480–6489
47. **Bianchi A, Giustina A, Cimino V, Pola R, Angelini F, Pontecorvi A, De Marinis L** 2009 Influence of growth hormone receptor d3 and full-length isoforms on biochemical treatment outcomes in acromegaly. J Clin Endocrinol Metab 94:2015–2022
48. **Ayuk J, Clayton RN, Holder G, Sheppard MC, Stewart PM, Bates AS** 2004 Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict excess mortality in patients with acromegaly. J Clin Endocrinol Metab 89: 1613–1617
49. **Dekkers OM, Biermasz NR, Pereira AM, Romijn JA, Vandenbroucke JP** 2008 Mortality in acromegaly: a metaanalysis. J Clin Endocrinol Metab 93:61–67
50. **Holdaway IM, Bolland MJ, Gamble GD** 2008 A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. Eur J Endocrinol 159:89–95
51. **Holdaway IM, Rajasoorya RC, Gamble GD** 2004 Factors influencing mortality in acromegaly. J Clin Endocrinol Metab 89:667–674
52. **Bogazzi F, Battolla L, Spinelli C, Rossi G, Gavioli S, Di Bello V, Cosci C, Sardella C, Volterrani D, Talini E, Pepe P, Falaschi F, Mariani G, Martino E** 2007 Risk factors for development of coro-

nary heart disease in patients with acromegaly: a five-year prospective study. J Clin Endocrinol Metab 92:4271–4277
53. **Bogazzi F, Cosci C, Sardella C, Costa A, Manetti L, Gasperi M, Rossi G, Bartalena L, Martino E** 2006 Identification of acromegalic patients at risk of developing colonic adenomas. J Clin Endocrinol Metab 91:1351–1356
54. **Bonadonna S, Mazziotti G, Nuzzo M, Bianchi A, Fusco A, De Marinis L, Giustina A** 2005 Increased prevalence of radiological spinal deformities in active acromegaly: a cross-sectional study in postmenopausal women. J Bone Miner Res 20:1837–1844
55. **Coculescu M, Niculescu D, Lichiardopol R, Purice M** 2007 Insulin resistance and insulin secretion in non-diabetic acromegalic patients. Exp Clin Endocrinol Diabetes 115:308–316
56. **Nemes A, Gavallér H, Csajbók E, Julesz J, Forster T, Csanády M** 2008 Aortic stiffness is increased in acromegaly: a transthoracic echocardiographic study. Int J Cardiol 124:121–123
57. **Pereira AM, van Thiel SW, Lindner JR, Roelfsema F, van der Wall EE, Morreau H, Smit JW, Romijn JA, Bax JJ** 2004 Increased prevalence of regurgitant valvular heart disease in acromegaly. J Clin Endocrinol Metab 89:71–75
58. **Mazziotti G, Bianchi A, Bonadonna S, Cimino V, Patelli I, Fusco A, Pontecorvi A, De Marinis L, Giustina A** 2008 Prevalence of vertebral fractures in men with acromegaly. J Clin Endocrinol Metab 93: 4649–4655
59. **Holdaway IM, Rajasoorya CR, Gamble GD, Stewart AW** 2003 Long-term treatment outcome in acromegaly. Growth Horm IGF Res 13:185–192
60. **Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK** 1994 Determinants of clinical outcome and survival in acromegaly. Clin Endocrinol (Oxf) 41:95–102
61. **Serri O, Beauregard C, Hardy J** 2004 Long-term biochemical status and disease-related morbidity in 53 postoperative patients with acromegaly. J Clin Endocrinol Metab 89:658–661
62. **Grunstein RR, Ho KK, Sullivan CE** 1994 Effect of octreotide, a somatostatin analog, on sleep apnea in patients with acromegaly. Ann Intern Med 121:478–483
63. **Davi MV, Dalle Carbonare L, Giustina A, Ferrari M, Frigo A, Lo Cascio V, Francia G** 2008 Sleep apnoea syndrome is highly prevalent in acromegaly and only partially reversible after biochemical control of the disease. Eur J Endocrinol 159:533–540
64. **Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, Dash C, Giardiello FM, Glick S, Johnson D, Johnson CD, Levin TR, Pickhardt PJ, Rex DK, Smith RA, Thorson A, Winawer SJ** 2008 Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 134:1570–1595
65. **Sung JJ, Lau JY, Young GP, Sano Y, Chiu HM, Byeon JS, Yeoh KG, Goh KL, Sollano J, Rerknimitr R, Matsuda T, Wu KC, Ng S, Leung SY, Makharia G, Chong VH, Ho KY, Brooks D, Lieberman DA, Chan FK** 2008 Asia Pacific consensus recommendations for colorectal cancer screening. Gut 57:1166–1176
66. **Van Cutsem EJ, Oliveira J** 2008 Colon cancer: ESMO clinical recommendations for diagnosis, adjuvant treatment and follow-up. Ann Oncol 19(Suppl 2):ii29–ii30
67. **Jenkins PJ, Fairclough PD** 2002 Screening guidelines for colorectal cancer and polyps in patients with acromegaly. Gut 51(Suppl 5): V13–V14
68. **Beauregard C, Truong U, Hardy J, Serri O** 2003 Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. Clin Endocrinol (Oxf) 58:86–91
69. **De P, Rees DA, Davies N, John R, Neal J, Mills RG, Vafidis J, Davies JS, Scanlon MF** 2003 Transsphenoidal surgery for acromegaly in Wales: results based on stringent criteria of remission. J Clin Endocrinol Metab 88:3567–3572
70. **Ludecke DK, Abe T** 2006 Transsphenoidal microsurgery for newly diagnosed acromegaly: a personal view after more than 1,000 operations. Neuroendocrinology 83:230–239
71. **Nomikos P, Buchfelder M, Fahlbusch R** 2005 The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure.' Eur J Endocrinol 152:379–387
72. **Shimon I, Cohen ZR, Ram Z, Hadani M** 2001 Transsphenoidal surgery for acromegaly: endocrinological follow-up of 98 patients. Neurosurgery 48:1239–1243; discussion 1244–1245
73. **Attanasio R, Lanzi R, Losa M, Valentini F, Grimaldi F, De Menis E, Davì MV, Battista C, Castello R, Cremonini N, Razzore P, Rosato F, Montini M, Cozzi R** 2008 Effects of lanreotide Autogel on growth hormone, insulin like growth factor 1, and tumor size in acromegaly: a 1-year prospective multicenter study. Endocr Pract 14:846–855
74. **Colao A, Pivonello R, Auriemma RS, Briganti F, Galdiero M, Tortora F, Caranci F, Cirillo S, Lombardi G** 2006 Predictors of tumor shrinkage after primary therapy with somatostatin analogs in acromegaly: a prospective study in 99 patients. J Clin Endocrinol Metab 91:2112–2118
75. **Cozzi R, Montini M, Attanasio R, Albizzi M, Lasio G, Lodrini S, Doneda P, Cortesi L, Pagani G** 2006 Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective study of its efficacy in the control of disease activity and tumor shrinkage. J Clin Endocrinol Metab 91:1397–1403
76. **Grottoli S, Celleno R, Gasco V, Pivonello R, Caramella D, Barreca A, Ragazzoni F, Pigliaru F, Alberti D, Ferrara R, Angeletti G** 2005 Efficacy and safety of 48 weeks of treatment with octreotide LAR in newly diagnosed acromegalic patients with macroadenomas: an open-label, multicenter, non-comparative study. J Endocrinol Invest 28:978–983
77. **Maiza JC, Vezzosi D, Matta M, Donadille F, Loubes-Lacroix F, Cournot M, Bennet A, Caron P** 2007 Long-term (up to 18 years) effects on GH/IGF-1 hypersecretion and tumour size of primary somatostatin analogue (SSTa) therapy in patients with GH-secreting pituitary adenoma responsive to SSTa. Clin Endocrinol (Oxf) 67: 282–289
78. **Melmed S, Sternberg R, Cook D, Klibanski A, Chanson P, Bonert V, Vance ML, Rhew D, Kleinberg D, Barkan A** 2005 A critical analysis of pituitary tumor shrinkage during primary medical therapy in acromegaly. J Clin Endocrinol Metab 90:4405–4410
79. **Mercado M, Borges F, Bouterfa H, Chang TC, Chervin A, Farrall AJ, Patocs A, Petersenn S, Podoba J, Safari M, Wardlaw J** 2007 A prospective, multicentre study to investigate the efficacy, safety and tolerability of octreotide LAR (long-acting repeatable octreotide) in the primary therapy of patients with acromegaly. Clin Endocrinol (Oxf) 66:859–868
80. **Newman CB, Melmed S, George A, Torigian D, Duhaney M, Snyder P, Young W, Klibanski A, Molitch ME, Gagel R, Sheeler L, Cook D, Malarkey W, Jackson I, Vance ML, Barkan A, Frohman L, Kleinberg DL** 1998 Octreotide as primary therapy for acromegaly. J Clin Endocrinol Metab 83:3034–3040
81. **Colao A, Pivonello R, Auriemma RS, Galdiero M, Savastano S, Grasso LF, Lombardi G** 2008 Growth hormone-secreting tumor shrinkage after 3 months of octreotide-long-acting release therapy predicts the response at 12 months. J Clin Endocrinol Metab 93: 3436–3442
82. **Colao A, Auriemma RS, Rebora A, Galdiero M, Resmini E, Minuto F, Lombardi G, Pivonello R, Ferone D** 2009 Significant tumour shrinkage after 12 months of lanreotide Autogel-120 mg treatment given first-line in acromegaly. Clin Endocrinol (Oxf) 71:237–245
83. **Amato G, Mazziotti G, Rotondi M, Iorio S, Doga M, Sorvillo F, Manganella G, Di Salle F, Giustina A, Carella C** 2002 Long-term effects of lanreotide SR and octreotide LAR on tumour shrinkage and GH hypersecretion in patients with previously untreated acromegaly. Clin Endocrinol (Oxf) 56:65–71
84. **Gola M, Bonadonna S, Mazziotti G, Amato G, Giustina A** 2006 Resistance to somatostatin analogs in acromegaly: an evolving concept? J Endocrinol Invest 29:86–93
85. **Abe T, Lüdecke DK** 2001 Effects of preoperative octreotide treat-

ment on different subtypes of 90 GH-secreting pituitary adenomas and outcome in one surgical centre. Eur J Endocrinol 145:137–145
86. **Ben-Shlomo A, Melmed S** 2003 Clinical review 154: the role of pharmacotherapy in perioperative management of patients with acromegaly. J Clin Endocrinol Metab 88:963–968
87. **Carlsen SM, Lund-Johansen M, Schreiner T, Aanderud S, Johannesen O, Svartberg J, Cooper JG, Hald JK, Fougner SL, Bollerslev J** 2008 Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized trial. J Clin Endocrinol Metab 93:2984–2990
88. **Colao A, Ferone D, Cappabianca P, del Basso De Caro ML, Marzullo P, Monticelli A, Alfieri A, Merola B, Calì A, de Divitiis E, Lombardi G** 1997 Effect of octreotide pretreatment on surgical outcome in acromegaly. J Clin Endocrinol Metab 82:3308–3314
89. **Losa M, Mortini P, Urbaz L, Ribotto P, Castrignanó T, Giovanelli M** 2006 Presurgical treatment with somatostatin analogs in patients with acromegaly: effects on the remission and complication rates. J Neurosurg 104:899–906
90. **Plockinger U, Quabbe HJ** 2005 Presurgical octreotide treatment in acromegaly: no improvement of final growth hormone (GH) concentration and pituitary function. A long-term case-control study. Acta Neurochir (Wien) 147:485–493; discussion 493
91. **Petrossians P, Borges-Martins L, Espinoza C, Daly A, Betea D, Valdes-Socin H, Stevenaert A, Chanson P, Beckers A** 2005 Gross total resection or debulking of pituitary adenomas improves hormonal control of acromegaly by somatostatin analogs. Eur J Endocrinol 152:61–66
92. **Colao A, Attanasio R, Pivonello R, Cappabianca P, Cavallo LM, Lasio G, Lodrini A, Lombardi G, Cozzi R** 2006 Partial surgical removal of growth hormone-secreting pituitary tumors enhances the response to somatostatin analogs in acromegaly. J Clin Endocrinol Metab 91:85–92
93. **Karavitaki N, Turner HE, Adams CB, Cudlip S, Byrne JV, Fazal-Sanderson V, Rowlers S, Trainer PJ, Wass JA** 2008 Surgical debulking of pituitary macroadenomas causing acromegaly improves control by lanreotide. Clin Endocrinol (Oxf) 68:970–975
94. **Jallad RS, Musolino NR, Kodaira S, Cescato VA, Bronstein MD** 2007 Does partial surgical tumour removal influence the response to octreotide-LAR in acromegalic patients previously resistant to the somatostatin analogue? Clin Endocrinol (Oxf) 67:310–315
95. **Biermasz NR, Dekker FW, Pereira AM, van Thiel SW, Schutte PJ, van Dulken H, Romijn JA, Roelfsema F** 2004 Determinants of survival in treated acromegaly in a single center: predictive value of serial insulin-like growth factor I measurements. J Clin Endocrinol Metab 89:2789–2796
96. **Dimaraki EV, Jaffe CA, DeMott-Friberg R, Chandler WF, Barkan AL** 2002 Acromegaly with apparently normal GH secretion: implications for diagnosis and follow-up. J Clin Endocrinol Metab 87: 3537–3542
97. **Freda PU, Post KD, Powell JS, Wardlaw SL** 1998 Evaluation of disease status with sensitive measures of growth hormone secretion in 60 postoperative patients with acromegaly. J Clin Endocrinol Metab 83:3808–3816
98. **Espinosa-de-Los-Monteros AL, Sosa E, Cheng S, Ochoa R, Sandoval C, Guinto G, Mendoza V, Hernandez I, Molina M, Mercado M** 2006 Biochemical evaluation of disease activity after pituitary surgery in acromegaly: a critical analysis of patients who spontaneously change disease status. Clin Endocrinol (Oxf) 64:245–249