



Acromegaly: A Critical Narrative Review of Pathogenesis, Tumour Classification, Systemic Manifestations and Evolving Therapeutic Paradigms

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This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Abstract

Acromegaly is a chronic disorder of growth hormone and insulin-like growth factor 1 excess, caused in almost all cases by a somatotroph pituitary neuroendocrine tumour. Three developments have changed the field within a single decade: the reclassification of pituitary neoplasms around transcription-factor lineage and tumour subtype, the accumulation of population-scale data on systemic morbidity and survival, and the arrival of orally administered and subcutaneously self-administered somatostatin receptor agonists alongside established injectable and receptor-antagonist therapies. These strands have largely been reviewed separately, and the practical question of whether tumour biology can be used to direct treatment selection remains unresolved. This critical narrative review synthesises evidence retrieved from scholarly databases and verified bibliographic sources, with searches completed on 21 July 2026, in order to examine how mechanistic understanding, histopathological and radiological classification, clinical phenotype and therapeutic choice relate to one another. Evidence indicates that somatic

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activating mutations of the stimulatory G protein alpha subunit, germline predisposition genes and chromatin-level dysregulation define partially distinct tumour subgroups, and that sparsely granulated morphology, low somatostatin receptor subtype 2 expression and hyperintense T2-weighted magnetic resonance signal converge on a phenotype that responds poorly to first-generation somatostatin receptor ligands. Support for acting on these markers rests largely on retrospective series and one prospective randomised protocol, so confidence in routine biomarker-directed prescribing remains moderate at best. Population studies show that mortality approaches that of the general population once biochemical control is achieved, yet arthropathy, vertebral fragility, sleep-disordered breathing and impaired quality of life frequently persist, indicating that current treatment targets are necessary but insufficient. Comparative efficacy estimates derived from network meta-analysis are internally inconsistent and sensitive to the evidence included. Priorities for research include prospective validation of predictive markers, trials powered for patient-reported and structural outcomes rather than hormone concentrations alone, and evidence generation in settings where access to surgical expertise and modern pharmacotherapy is constrained.

Keywords: *Acromegaly; growth hormone; insulin-like growth factor 1; pituitary neuroendocrine tumour; somatostatin receptor ligand; growth hormone receptor antagonist; tumour classification; precision medicine.*

1. Introduction

Acromegaly is a disorder of sustained growth hormone (GH) hypersecretion and consequent elevation of circulating insulin-like growth factor 1 (IGF-1), producing acral and facial change, soft-tissue overgrowth and a systemic burden that extends to the cardiovascular, metabolic, respiratory, skeletal and neoplastic domains (Colao *et al.*, 2019; Giustina & Colao, 2025). In more than nine of ten patients the source is a somatotroph pituitary neuroendocrine tumour (PitNET); extrapituitary disease driven by ectopic secretion of GH-releasing hormone (GHRH) accounts for a small minority (Fainstein-Day *et al.*, 2024; Stumpf *et al.*, 2025). The clinical syndrome was described long before its endocrine basis was understood, and its modern conceptualisation as a tumoural disease of a defined anterior pituitary lineage is comparatively recent.

Population-based data place the annual incidence at approximately 3.8 cases per million person-years and the prevalence at roughly 85 cases per million in a nationwide Danish cohort with complete registry linkage and chart validation (Dal *et al.*, 2016), with broadly comparable figures from a 59-year Icelandic series (Hoskuldottir *et al.*, 2015). These estimates are drawn from small, ethnically homogeneous Northern European populations with universal health coverage, and their transferability to health systems with different diagnostic capacity is uncertain. The insidious evolution of the phenotype produces substantial diagnostic latency: in a Swedish nationwide cohort of 603 patients the mean interval between the first registered acromegaly-associated comorbidity and the diagnosis itself was 5.5 years, a quarter of patients waited at least a decade, and excess mortality was confined to the group with the longest delay (Esposito *et al.*, 2020). An Italian series has since shown that delay interacts with age at diagnosis and hormonal burden in determining comorbidity load, complicating the assumption that delay acts as a simple linear exposure (Gasco *et al.*, 2025). A recent synthesis of epidemiological evidence similarly emphasises that observed incidence, prevalence and mortality patterns are influenced by case ascertainment, diagnostic timing and regional health-care context, reinforcing caution when extrapolating population-level estimates across settings (Esposito & Johannsson, 2026). Digital voice analysis has also been investigated as a machine-learning-assisted biomarker for acromegaly, illustrating continuing efforts to support earlier recognition while retaining the need for validation beyond selected cohorts (Vouzouneraki *et al.*, 2025).

Three largely independent literatures have developed rapidly and have not been brought into a single analytical frame. First, the molecular characterisation of somatotroph tumours has moved from the identification of activating mutations in the gene encoding the stimulatory G protein alpha subunit (*GNAS*) (Landis *et al.*, 1989) to transcriptomic, methylomic and chromatin-conformation studies that define reproducible tumour subgroups (Guo *et al.*, 2024; Kober *et al.*, 2024; J. Wang *et al.*, 2024), alongside a defined set of germline predisposition genes (Beckers *et al.*, 2013; Daly & Beckers, 2024; De Sousa & Daly, 2026). Second, the fifth edition of the World Health Organization (WHO) classification reframed pituitary adenomas as neuroendocrine tumours and organised them by adenohypophyseal cell lineage and transcription-factor expression rather than by hormone immunoreactivity alone (Asa *et al.*, 2022), a change whose prognostic and therapeutic consequences are still being negotiated (Ho *et al.*, 2023, 2024). Third, the therapeutic repertoire has widened from surgery, injectable somatostatin receptor ligands (SRLs), the GH receptor antagonist pegvisomant, dopamine agonists and radiotherapy to include oral octreotide capsules, the non-peptide selective somatostatin receptor subtype 2 agonist paltusotine and a self-administered subcutaneous octreotide depot (Biller *et al.*, 2026; Ferone *et al.*, 2025; Fleseriu *et al.*, 2022; Gadelha *et al.*, 2024). Recent precision-medicine frameworks have consequently focused on integrating clinical, imaging and tumour-related markers to individualise treatment selection, while recognising that biomarker-guided strategies require context-specific interpretation (Puig-Domingo *et al.*, 2026).

Existing reviews are informative but partial. Authoritative consensus statements address diagnostic and remission criteria (Giustina *et al.*, 2024), therapeutic outcomes (Melmed *et al.*, 2018, 2025) and complications (Giustina *et al.*, 2020, 2026), yet by design they codify expert agreement rather than interrogate the strength of the underlying evidence. Recent comprehensive reviews of medical therapy (Gadelha *et al.*, 2025) and of the disease as a whole (Giustina & Colao, 2025) provide excellent descriptive coverage but do not systematically confront the discrepancies between pathological prediction and clinical response, between biochemical control and patient-reported recovery, or between the conclusions of competing quantitative syntheses of drug efficacy. Two network meta-analyses published within months of each other reached materially different conclusions about which agents rank highest for biochemical control (Kaparounaki *et al.*, 2025; Salvatori *et al.*, 2026), a discordance that has not been examined critically. Evidence also remains geographically concentrated, with comparatively few analyses from low-resource and middle-income settings (Sharma *et al.*, 2025). Prospective longitudinal research on neoplastic outcomes has also evaluated cumulative IGF-1 exposure rather than

isolated measurements, further illustrating the importance of linking biochemical history with long-term systemic outcomes (Freda *et al.*, 2025).

1.1 Scope, Research Gap and Objectives

This review addresses adult and adolescent acromegaly caused by somatotroph neoplasia, together with the small ectopic GHRH-dependent subgroup, and covers pathogenesis, tumour classification, systemic clinical manifestations, diagnostic assessment and therapeutic strategy. Isolated pituitary gigantism is considered only where it illuminates mechanism or management of the adult disorder. Non-neoplastic causes of elevated growth hormone concentrations, animal models examined for their own sake, and health-economic modelling beyond its bearing on access to treatment lie outside the scope.

The specific gap addressed is the absence of an integrated critical appraisal linking the molecular and histopathological reclassification of somatotroph tumours to therapeutic decision-making and to outcomes that matter to patients. Pathological subtype, receptor expression and radiological signal are widely described as predictive, yet their prospective validation, reproducibility and incremental value over simple clinical variables are rarely assessed together. In parallel, the field continues to define success principally through hormone concentrations, although accumulating evidence indicates that skeletal, articular, respiratory and psychosocial impairment often persists after those targets are met.

The objectives are fivefold: to evaluate what current mechanistic evidence does and does not explain about somatotroph tumorigenesis and its clinical correlates; to assess whether contemporary tumour classification functions as a usable treatment-stratification instrument or principally as a descriptive taxonomy; to appraise critically the evidence on systemic morbidity, its reversibility and its relationship to biochemical status; to compare therapeutic modalities with explicit attention to the quality, consistency and limitations of the supporting evidence, including newly licensed oral agents; and to derive prioritised, defensible research directions. The intended contribution is an evidence-calibrated synthesis that distinguishes well-supported conclusions from provisional ones and states plainly where the literature does not currently permit a confident answer.

2. Methods for Literature Selection

2.1 Review Design and Rationale

A critical narrative design was selected because the review question spans molecular pathology, diagnostic assessment, systemic morbidity and comparative therapeutics, and because the constituent evidence bases differ fundamentally in design, outcome definition and measurement scale. A systematic review with a single pre-specified question would exclude most of the mechanistic and classificatory literature that is essential to the argument, while a meta-analysis is precluded by the heterogeneity of outcome definitions across the therapeutic trials, the small number of head-to-head comparisons and the near-absence of randomised evidence for surgery and radiotherapy. Two quantitative syntheses of medical therapy already exist and are appraised here rather than duplicated (Kaparounaki *et al.*, 2025; Salvatori *et al.*, 2026).

A narrative design does not licence selective citation. The review was conducted against the quality domains articulated in the Scale for the Assessment of Narrative Review Articles, namely explicit justification of importance, a stated aim, description of the literature search, referencing of statements, appropriate presentation of evidence and adequate presentation of data (Baethge *et al.*, 2019). Sources were appraised individually, conflicting findings were retained rather than reconciled, and the confidence attached to each conclusion is stated in the text.

2.2 Information Sources

Searches were run in PubMed, PubMed Central, Europe PMC, Crossref, the Directory of Open Access Journals and Google Scholar. These were supplemented by backward citation searching of retrieved reviews and consensus statements, forward citation searching for key trials and classification papers, related-article searching, and inspection of the reference lists of recent high-quality reviews. Consensus statements and clinical practice guidelines issued by professional bodies were retrieved directly and treated as expert-opinion sources rather than as primary evidence. Every reference retained was checked against at least two independent bibliographic records, and each digital object identifier was confirmed to resolve to the cited article before inclusion.

2.3 Search Strategy and Search Period

Search concepts were built around five axes: the disease and its tumoural substrate; pathogenic mechanism and molecular classification; clinical manifestations and comorbidity; diagnosis and disease-activity assessment; and therapeutic modality and outcome. Within each axis, controlled vocabulary and free-text synonyms were combined with the Boolean operator OR, and axes were combined with AND. Title and abstract fields were used for precision in high-yield concepts, with unrestricted fields applied to rarer terms such as those denoting germline predisposition syndromes and newly licensed agents.

The search period extended from 1 January 1989 to 21 July 2026. The starting year corresponds to the demonstration that guanosine triphosphatase-inhibiting mutations activate the stimulatory G protein alpha chain in human pituitary tumours, the finding that established acromegaly as a disorder with a defined somatic oncogenic driver and that anchors the modern mechanistic literature (Landis *et al.*, 1989). Foundational publications preceding this date were admitted where necessary to describe historical development, and no lower limit was applied to consensus documents that remain in current use.

2.4 Eligibility Criteria

Peer-reviewed original research, systematic reviews, meta-analyses, high-quality narrative reviews, consensus statements and professional guidelines were eligible when they addressed acromegaly, somatotroph neoplasia or directly relevant aspects of the GH-IGF-1 axis in humans. Randomised controlled trials, prospective and retrospective cohorts, cross-sectional and registry studies, and molecular and histopathological analyses of human tumour tissue were all admissible, with study design weighted during appraisal rather than used as a filter. Preclinical work was included only where it bore directly on a mechanistic claim that could not otherwise be supported, and was labelled as such in the text.

Publications were excluded when they were not peer-reviewed, when bibliographic identity or digital object identifier could not be confirmed, when the reported findings did not bear on the claim for which citation was contemplated, when they duplicated a larger or more recent analysis of the same population, or when they fell outside the search window. Case reports and small case series were not used to support general claims about efficacy, prevalence or prognosis. Non-English publications were not included, and no source was retained on the basis of an abstract alone where the full record could not be verified.

2.5 Screening, Duplicate Handling and Source Selection

Titles and abstracts were screened against the eligibility criteria, and records judged potentially relevant were assessed against the full bibliographic record and available full text. Duplicates arising from overlapping database coverage were identified by digital object identifier and, where that was absent, by matching author, title, journal and year. Where the same cohort was reported more than once, the most complete or most recent analysis was retained and the earlier report cited only where it contributed distinct information. Records that could not be verified bibliographically, or whose metadata were internally inconsistent across sources, were discarded irrespective of apparent relevance. No screening counts are reported, since the selection process was purposive and iterative rather than systematically enumerated.

Table 1. Search concept blocks, representative terms and Boolean strings applied across the scholarly sources searched

Concept block	Representative terms	Representative Boolean string	Analytical purpose	Supporting references
Disease and tumour substrate	acromegaly; gigantism; somatotroph tumour; somatotropinoma; GH-secreting adenoma; pituitary neuroendocrine tumour	("acromegaly"[ti] OR "somatotroph"[ti] OR "somatotropinoma"[ti]) AND ("pituitary"[tiab] OR "PitNET"[tiab])	Defines the population and lesion of interest	Asa <i>et al.</i> (2022); Colao <i>et al.</i> (2019)
Pathogenesis and molecular classification	<i>GNAS</i> ; gsp oncogene; <i>AIP</i> ; <i>GPR101</i> ; X-linked acrogigantism; <i>MEN1</i> ; transcriptome; DNA methylation; chromatin	("GNAS" OR "AIP" OR "GPR101" OR "MEN1") AND ("somatotroph" OR "acromegaly") AND ("mutation" OR "expression" OR "methylation")	Retrieves somatic and germline drivers and molecular subtyping	Beckers <i>et al.</i> (2013); Landis <i>et al.</i> (1989); Marrero-Rodríguez <i>et al.</i> (2024)
Histopathology and imaging phenotype	densely granulated; sparsely granulated; mammosomatotroph; PIT1 lineage; Ki-67; T2-weighted signal; radiomics	("granulation pattern" OR "sparsely granulated" OR "T2 signal") AND "acromegaly"	Captures subtype definitions and their radiological surrogates	Guaraldi <i>et al.</i> (2024); Potorac <i>et al.</i> (2016)
Clinical manifestations and comorbidity	cardiomyopathy; hypertension; diabetes; sleep apnoea; arthropathy; vertebral fracture; colorectal neoplasia; mortality; quality of life	"acromegaly" AND ("cardiovascular" OR "diabetes" OR "sleep apnoea" OR "arthropathy" OR "fracture" OR "cancer" OR "mortality" OR "quality of life")	Identifies organ-system morbidity and survival data	Gadelha <i>et al.</i> (2019); Giustina <i>et al.</i> (2026)
Diagnosis and disease-activity assessment	IGF-1 assay; oral glucose tolerance test; remission criteria; ACRODAT; SAGIT; magnetic resonance imaging	"acromegaly" AND ("IGF-1" OR "diagnosis" OR "remission criteria" OR "disease activity")	Retrieves biochemical, imaging and composite assessment tools	Giustina <i>et al.</i> (2024); Huang <i>et al.</i> (2024)
Therapy and outcome	transsphenoidal surgery; somatostatin receptor ligand; pasireotide; pegvisomant; cabergoline; oral octreotide; paltusotine; radiosurgery; resistance; combination therapy	"acromegaly" AND ("surgery" OR "somatostatin" OR "pegvisomant" OR "paltusotine" OR "radiosurgery") AND ("efficacy" OR "resistance" OR "outcome")	Retrieves comparative therapeutic evidence and treatment failure	Fleseriu <i>et al.</i> (2021); Melmed <i>et al.</i> (2025)

Note. GH = growth hormone; IGF-1 = insulin-like growth factor 1; PitNET = pituitary neuroendocrine tumour; ti = title field; tiab = title or abstract field. Gene symbols are italicised. Field tags shown follow PubMed syntax and were translated to the equivalent syntax of the other sources searched

2.6 Critical Appraisal and Evidence Synthesis

Each retained study was appraised for design appropriateness, sample size and representativeness, adequacy of comparison groups, validity of outcome measurement, transparency of analysis, handling of confounding, risk of selection and detection bias, funding source and external validity. No formal risk-of-bias instrument was applied, because the necessary information was not uniformly available and because a recognised tool was not administered in a reproducible manner across the heterogeneous evidence base.

Particular attention was given to whether biochemical surrogates or patient-relevant outcomes were reported, to whether comparator groups reflected contemporary standards of care, and to the proportion of evidence originating from single centres.

Synthesis proceeded thematically. Evidence was grouped around mechanisms, classificatory constructs, organ-system consequences and therapeutic decisions rather than by individual study. Within each theme, the strongest supporting evidence was identified, conflicting findings were set against it, plausible explanations for disagreement were examined, and the residual uncertainty was stated. Where trial evidence, registry evidence and mechanistic evidence pointed in different directions, the divergence was retained as an analytical finding.

Table 1 sets out the concept blocks and representative search strings used across sources. The table is included to make the search reproducible rather than to imply exhaustiveness; strings were adapted to the syntax of each source, and the terms listed are representative rather than complete. Its principal analytical value is to show that the search was constructed around the specific axes of this review, including terms for treatment resistance and patient-reported outcome, which are frequently omitted from searches oriented solely to biochemical efficacy.

3. Pathogenesis of Growth Hormone Excess

3.1 Regulation of the Somatotroph and the Transition to Autonomous Secretion

The somatotroph occupies a control point defined by two opposing hypothalamic inputs acting through G protein-coupled receptors: GHRH, which raises intracellular cyclic adenosine monophosphate and drives transcription, secretion and proliferation, and somatostatin, which acts principally through somatostatin receptor subtypes 2 and 5 to suppress this signal (Ben-Shlomo & Melmed, 2026). Hepatic IGF-1 generation provides negative feedback. Tumour formation disturbs this arrangement in a manner that is more nuanced than simple loss of inhibition, since most somatotroph tumours retain receptor expression and therefore remain partially responsive to pharmacological somatostatin receptor agonism. Structural work defining how octreotide and the non-peptide agonist paltusotine engage somatostatin receptor subtype 2 has clarified why selective and non-selective ligands differ in their functional profiles, and provides a mechanistic rationale for subtype-selective drug design (Zhao *et al.*, 2023). The pharmacological corollary is important for the argument developed later: because therapy is directed at a receptor whose expression varies between tumours, biological heterogeneity is expected to translate into heterogeneous drug response.

3.2 Somatic Drivers in Sporadic Somatotroph Tumours

Somatotroph tumours constitute roughly 15% to 20% of pituitary neuroendocrine tumours, and approximately 95% arise without an identifiable inherited cause (Marrero-Rodríguez *et al.*, 2024). The best-characterised somatic driver remains the activating mutation of *GNAS*, which impairs the intrinsic guanosine triphosphatase activity of the stimulatory G protein alpha subunit and produces constitutive adenylyl cyclase stimulation (Landis *et al.*, 1989). Aggregate estimates place somatic *GNAS* mutations in up to 40% of somatotroph tumours (Boguslawska & Korbonits, 2021), but reported prevalence varies considerably between series and populations; in a Korean surgical cohort of 126 patients, mutations were present in 59.5% of tumours, with a markedly different sex distribution between mutation-positive and mutation-negative groups, whereas age and cavernous sinus invasion grade did not differ (Jung *et al.*, 2021). The dispersion of prevalence estimates across studies is itself informative. It is unlikely to reflect true biological variation alone, and probably also reflects differences in sequencing depth, tissue sampling and the proportion of small, densely granulated tumours reaching surgery in each health system. Claims that mutation status predicts surgical or pharmacological outcome should therefore be treated as provisional; the association with response to first-generation SRLs is mechanistically coherent but has not been demonstrated consistently in prospective cohorts.

Beyond *GNAS*, the mutational landscape of sporadic somatotroph tumours is comparatively quiet, and explanatory weight has shifted towards lineage determination and epigenetic regulation. Differentiation along the somatotroph, lactotroph and thyrotroph axis is governed by the transcription factor encoded by *POU1F1*, and multi-omic profiling has identified transcriptomic patterns and regulatory microRNA changes associated with tumour progression (Marrero-Rodríguez *et al.*, 2024). Genome-wide methylation analysis of 48 somatotroph tumours showed that clustering on methylation data recapitulated previously defined transcriptomic subtypes, indicating that the molecular subgrouping is not an artefact of a single analytical platform (Kober *et al.*, 2024). Analysis of three-dimensional chromatin organisation has demonstrated that higher-order genome architecture contributes to the transcriptional programme of these tumours (Guo *et al.*, 2024), and integrated spatial transcriptomic and single-cell analysis has shown marked intratumoural heterogeneity, with regions of high and low copy-number variation differing in the expression of candidate pro-tumour genes (J. Wang *et al.*, 2024).

An independent transcriptomic classification of 46 prolactinomas and 58 somatotropinomas identified subtypes associated with differing sensitivity to dopamine agonists and somatostatin analogues, offering the most direct evidence to date that molecular subgrouping carries therapeutic information (Bioletto *et al.*, 2025). The finding is important but requires careful framing. The cohorts are modest, treatment response was assessed retrospectively against variable criteria, and the classification has not been tested prospectively or in an independent validation set with pre-specified thresholds. At present the evidence supports the existence of transcriptionally distinct subgroups with differing average treatment sensitivity; it does not support the use of transcriptomic class to select therapy for an individual patient.

Preclinical work has begun to identify targetable nodes downstream of these programmes. Inhibition of the tyrosine phosphatase SHP2 reduced somatotroph tumour growth in an experimental model (García Barberá *et al.*, 2025). This is a laboratory finding with no human efficacy data, and it is cited here as an indication of mechanistic direction rather than of therapeutic promise.

Table 2. Principal pathogenic drivers in acromegaly, associated tumour phenotype, therapeutic relevance and strength of supporting evidence

Driver or mechanism	Typical context	Associated tumour phenotype	Therapeutic relevance	Strength of evidence	Supporting references
Activating somatic <i>GNAS</i> mutation	Sporadic somatotroph tumour; reported prevalence varies widely between cohorts	Frequently smaller and densely granulated; sex distribution differs by mutation status in some cohorts	Mechanistically linked to somatostatin receptor signalling, but not validated as a treatment-selection marker	Established as a driver; inconsistent as a predictor	Landis <i>et al.</i> (1989); Jung <i>et al.</i> (2021); Ben-Shlomo and Melmed (2026)
Lineage transcription factor programme (<i>POU1F1</i>) and microRNA dysregulation	Sporadic tumours of the PIT1 lineage	Determines somatotroph, lactotroph and thyrotroph differentiation; altered microRNA expression with progression	Underpins lineage-based classification rather than drug selection	Moderate; multi-omic descriptive studies	Marrero-Rodríguez <i>et al.</i> (2024)
Transcriptomic and methylomic subtypes	Sporadic somatotroph tumours	Reproducible subgroups concordant across platforms; differing average drug sensitivity	Potential future stratification tool; not yet prospectively validated	Moderate; concordant but retrospective	Bioletto <i>et al.</i> (2025); Kober <i>et al.</i> (2024)
Higher-order chromatin organisation and intratumoural heterogeneity	Sporadic somatotroph tumours	Regionally variable copy-number state and gene expression within a single tumour	Suggests that single-fragment sampling may misclassify tumours	Emerging; single-cohort studies	Guo <i>et al.</i> (2024); J. Wang <i>et al.</i> (2024)
Germline <i>AIP</i> variants	Familial isolated pituitary adenoma; young-onset disease	Larger, more invasive tumours; relative resistance to first-generation ligands	Supports early genetic testing and family screening; may prompt earlier escalation	Moderate to strong for phenotype; incomplete penetrance limits prediction	Beckers <i>et al.</i> (2013); Hernández-Ramírez <i>et al.</i> (2015)
Xq26.3 microduplication affecting <i>GPR101</i>	X-linked acrogigantism; infancy or early childhood onset	Mixed GH- and prolactin-secreting macroadenoma or hyperplasia; extreme growth	Identifies a group requiring aggressive early intervention	Established mechanism; small patient numbers	Iacovazzo <i>et al.</i> (2016); Franke <i>et al.</i> (2022); Daly and Beckers (2024)
Other predisposition genes (<i>MEN1</i> , <i>CDKN1B</i> , <i>MAX</i> , <i>PRKARIA</i>); mosaic <i>GNAS</i>	Syndromic disease, including multiple endocrine neoplasia type 1 and McCune–Albright syndrome	Variable; often part of a wider endocrine phenotype	Determines syndromic surveillance rather than pituitary-directed drug choice	Established for principal genes; emerging for <i>NF1</i> , <i>PRKACB</i> , <i>PAM</i> , <i>CHEK2</i>	Brandi <i>et al.</i> (2025); De Sousa and Daly (2026)
Ectopic GHRH secretion by a neuroendocrine tumour	Rare; bronchial or pancreatic primary	Pituitary hyperplasia rather than adenoma in most cases	Resection of the primary tumour is the treatment of choice; pituitary surgery is usually inappropriate	Moderate; largest imaging series comprises 30 patients	Potorac <i>et al.</i> (2022); Fainstein-Day <i>et al.</i> (2024); Stumpf <i>et al.</i> (2025)
SHP2-dependent signalling	Experimental model only	Reduced tumour growth with pharmacological inhibition	No human data	Preclinical	García Barberá <i>et al.</i> (2025)

Note. GH = growth hormone; GHRH = growth hormone-releasing hormone; PIT1 = pituitary-specific positive transcription factor 1, encoded by *POU1F1*. Gene symbols are italicised. Strength of evidence reflects study design, replication and availability of prospective validation

3.3 Germline Predisposition and Syndromic Disease

A small but clinically distinctive fraction of disease is heritable. Germline variants are enriched in familial acromegaly kindreds and in patients whose GH excess began before epiphyseal closure, and the recognised predisposition genes include *AIP*, *MEN1*, *CDKN1B*, *MAX* and *PRKARIA*, together with Xq26.3 microduplication causing X-linked acrogigantism and postzygotic gain-of-function *GNAS* variants in McCune–Albright syndrome (De Sousa & Daly, 2026). Variants in *NF1*, *PRKACB*, *PAM* and *CHEK2* are regarded as emerging rather than established associations, a distinction that matters when counselling families and that is frequently blurred in secondary literature.

Mutations in *AIP* define the best-studied familial isolated pituitary adenoma phenotype, characterised by early onset, larger and more invasive tumours and relative resistance to first-generation SRLs (Beckers *et al.*, 2013). A seven-year international observational study of 216 familial isolated pituitary adenoma families and young patients, incorporating prospective clinical screening of apparently unaffected carriers, remains the principal source of evidence on penetrance and on the yield of family screening (Hernández-Ramírez *et al.*, 2015). Penetrance is incomplete, which has two consequences that are often understated: the clinical utility of cascade testing depends on the availability of an effective surveillance pathway, and estimates of genotype-associated severity derived from index cases are liable to ascertainment bias.

X-linked acrogigantism illustrates a distinct disease mechanism. Duplications at Xq26.3 disrupt the boundary of a topologically associating domain and place *GPR101* under the control of ectopic enhancers, producing an early-onset, often mixed GH- and prolactin-secreting lesion with hyperplastic features (Franke *et al.*, 2022). In a screening study of 153 patients with pituitary gigantism, 12 patients (7.8%) carried the duplication, with a female preponderance (Iacovazzo *et al.*, 2016). Approximately half of all pituitary gigantism has an identifiable genetic cause, and X-linked acrogigantism accounts for around a tenth of cases (Daly & Beckers, 2024). The conceptual significance of this entity extends beyond its rarity: it demonstrates that dysregulation of genome architecture, rather than alteration of a coding sequence, can be sufficient to produce a severe endocrine neoplastic phenotype. Management of gigantism remains challenging, and contemporary guidance for children and adolescents emphasises multidisciplinary care and early genetic evaluation (Andrews *et al.*, 2026; Korbonsits *et al.*, 2024). Acromegaly occurring within multiple endocrine neoplasia type 1 requires management that accounts for concurrent parathyroid and enteropancreatic disease, for which recent international recommendations provide a structured framework (Brandi *et al.*, 2025).

3.4 Ectopic Growth Hormone-Releasing Hormone Secretion

Acromegaly driven by ectopic GHRH production by neuroendocrine tumours, most often bronchial or pancreatic, is clinically and biochemically difficult to distinguish from the pituitary-dependent form (Fainstein-Day *et al.*, 2024; Stumpf *et al.*, 2025). Diagnostic clues include pituitary hyperplasia on magnetic resonance imaging (MRI), an elevated circulating GHRH concentration and identification of an extrapituitary lesion on whole-body imaging. A multicentre retrospective series of 30 patients characterised pituitary MRI appearances before and after treatment of the neuroendocrine tumour, providing the largest imaging dataset available for this entity (Potorac *et al.*, 2022). Resection of the neuroendocrine tumour is the preferred treatment where feasible, with somatostatin receptor agonists used for residual disease, and prolonged GHRH exposure may result in persistent hyperplasia or subsequent adenoma formation, so indefinite follow-up is warranted (Stumpf *et al.*, 2025). The clinical importance of this rare cause lies disproportionately in the consequence of missing it: transsphenoidal exploration of a hyperplastic gland is unlikely to be curative and exposes the patient to avoidable risk.

3.5 What Mechanistic Understanding Does and Does Not Explain

Three conclusions can be drawn with reasonable confidence. Constitutive activation of cyclic adenosine monophosphate signalling, whether through somatic *GNAS* mutation, germline lesions affecting related pathways or ectopic GHRH drive, is a recurrent route to somatotroph autonomy. Molecular subgrouping of sporadic tumours is reproducible across transcriptomic and methylomic platforms. Germline causes, although uncommon overall, are concentrated in young patients and in those with aggressive disease, which justifies age-directed genetic evaluation.

Several limitations qualify these conclusions. Almost all human molecular data derive from surgically resected tissue, which systematically over-represents larger and more invasive tumours and excludes patients treated medically from the outset. Cohorts are small, single-centre and cross-sectional, so temporal relationships between molecular state and clinical behaviour cannot be established. Genotype–phenotype associations are reported as group-level differences with substantial overlap, and none has been shown to discriminate reliably at the individual level. Independent replication is uncommon, and negative findings are probably under-reported. The absence of longitudinal molecular sampling means that the biology of acquired treatment resistance, arguably the most clinically consequential question in this domain, remains largely uncharacterised.

Table 2 summarises the principal drivers, their associated phenotypes and the strength of evidence supporting each. The table is intended to separate established from provisional associations, and its most instructive feature is the asymmetry between the depth of mechanistic description and the sparseness of prospective clinical validation: no entry in the therapeutic relevance column is currently supported by randomised evidence.

4. Tumour Classification and its Clinical Meaning

4.1 From Adenoma to Pituitary Neuroendocrine Tumour

The fifth edition of the WHO classification of endocrine and neuroendocrine tumours separated anterior from posterior lobe and hypothalamic neoplasms, reclassified well-differentiated adenohypophyseal tumours as PitNETs, and endorsed routine

immunohistochemistry for the pituitary transcription factors PIT1, TPIT, SF1, GATA3 and oestrogen receptor alpha as the primary basis for subtyping, with hormone immunoreactivity, granulation pattern and proliferation markers used as secondary descriptors (Asa *et al.*, 2022). Somatotroph tumours fall within the PIT1 lineage and may secrete GH alone or co-secrete prolactin, with several recognised morphological subtypes (Guaraldi *et al.*, 2024). The lineage-based architecture is a genuine conceptual advance: it explains why some clinically non-functioning tumours express somatotroph markers, and it provides a rational framework for assigning tumours of uncertain origin (Asa *et al.*, 2025).

The nomenclature change has been contested on clinical rather than morphological grounds. An interdisciplinary international workshop concluded that applying an oncological label to lesions that are overwhelmingly indolent risks misrepresenting prognosis to patients and to health systems, and argued that a comprehensive clinical classification is required alongside the histopathological one (Ho *et al.*, 2023). The same group subsequently proposed an integrated scoring system combining clinical, genetic, biochemical, radiological, pathological and molecular information, explicitly noting that the WHO system can be applied only to resected lesions, which represent a minority of clinically significant tumours (Ho *et al.*, 2024). This limitation deserves emphasis. A classification that requires tissue cannot inform the initial treatment decision in a patient managed medically from the outset, nor in the substantial group in whom surgery is declined or contraindicated. The proposed integrated score has not yet been prospectively validated, and until it is, its advantage over clinical judgement remains an expectation rather than a demonstrated result.

4.2 Subtype, Granulation and the Prediction of Behaviour

Within the somatotroph category, the distinction between densely and sparsely granulated tumours carries the greatest weight in clinical practice, and is supplemented by recognition of mammosomatotroph, mixed somatotroph–lactotroph, mature and immature PIT1-lineage plurihormonal and acidophil stem cell tumours (Guaraldi *et al.*, 2024). In a single-centre series of 94 patients with acromegaly, pure somatotroph, mammosomatotroph and mixed somatotroph–lactotroph tumours accounted for 53, 28 and 13 cases respectively, and mammosomatotroph tumours were smaller at presentation (Lv *et al.*, 2019). Single-centre surgical series of this size cannot establish subtype prevalence for the wider population, and referral patterns plausibly influence the distribution observed. Silent somatotroph tumours, which show GH immunoreactivity without clinical or biochemical acromegaly, represented 2% of tumours in a comparative study of 21 silent and 59 clinically functioning somatotroph tumours assessed for proliferation, differentiation and secretory activity (Chinezu *et al.*, 2017). Their existence complicates the assumption that hormone immunoreactivity, receptor expression and clinical syndrome are tightly coupled, and indicates that post-transcriptional or secretory defects can uncouple tumour phenotype from biochemical expression.

4.3 Invasion, Proliferation and Prognostic Grading

The clinicopathological grading scheme derived from a multicentre case-control study of 410 patients with eight-year postoperative follow-up classified tumours by size, type and grade, using MRI-defined cavernous or sphenoid sinus invasion together with Ki-67 labelling index, mitotic count and p53 immunoreactivity to define non-invasive, invasive and proliferative categories (Trouillas *et al.*, 2013). This remains the most influential attempt to link routinely available pathological and radiological variables to outcome. Its limitations are those of its design: retrospective case-control ascertainment, centre-specific thresholds for proliferation markers and an outcome definition that depends on local follow-up intensity. Reproducibility of Ki-67 assessment between laboratories is an acknowledged weakness that constrains the transferability of any threshold-based grade.

Approximately 40% of PitNETs overall are locally invasive and may not be surgically cured, and roughly 1% behave aggressively, with rare metastatic spread; the fifth edition classification emphasises that morphological features distinguish indolent from locally aggressive tumours, while noting that the proposed histological subtypes are not consistently predictive at the individual level (Casar-Borota *et al.*, 2025). That qualification is central to the argument of this review. Classification systems in this field describe populations well and individuals poorly, and the gap between the two is where clinical disappointment arises.

4.4 Radiological and Computational Surrogates for Tumour Subtype

Because subtype information is available only after surgery, considerable effort has been directed at non-invasive surrogates. In a multicentre study of 120 patients receiving primary somatostatin analogue monotherapy, tumours were hypointense, isointense or hyperintense on T2-weighted MRI in 84, 17 and 19 cases respectively, and signal intensity was related to hormonal and tumoral response (Potorac *et al.*, 2016). The signal is interpreted as reflecting granulation density, with hypointensity corresponding to densely granulated morphology and better ligand response. Methodological variation between centres in how T2 signal is defined and measured is substantial, and a dedicated analysis has argued explicitly for unification of quantitative and qualitative assessment before the marker can be relied upon (Godlewska-Nowak *et al.*, 2024). Quantitative texture analysis of T2-weighted images with machine learning has been proposed as a more reproducible alternative (Kocak *et al.*, 2019), and a multi-institutional radiomic model trained on 156 patients and externally validated in 45 reported discrimination of sparsely from densely granulated tumours from preoperative multiparametric MRI (J. Wang *et al.*, 2026). External validation in a modest independent cohort is a methodological strength relative to most of this literature, but the sample remains small, the models are not yet embedded in prospective treatment pathways, and calibration in populations with different scanner protocols is unknown.

4.5 Classification as a Stratification Instrument

Taken together, the evidence supports a measured conclusion. Contemporary classification has improved diagnostic precision, resolved the origin of ambiguous tumours and generated hypotheses about differential drug sensitivity. It has not yet been shown to improve outcomes when used prospectively to allocate treatment. The principal obstacles are the requirement for resected tissue,

inter-observer and inter-laboratory variability in the markers that carry the most prognostic weight, and the consistent finding that subtype-associated differences are statistical tendencies with wide overlap. Table 3 compares the principal somatotroph subtypes and their radiological correlates; its purpose is to make explicit which columns rest on replicated evidence and which remain provisional, and it should be read as a summary of central tendencies rather than as a decision rule.

Table 3. Somatotroph tumour subtypes, radiological correlates and reported associations with treatment response

Subtype or feature	Defining characteristics	Typical clinical presentation	Reported radiological correlate	Reported association with first-generation ligand response	Confidence	Supporting references
Densely granulated somatotroph tumour	PIT1 lineage; diffuse cytoplasmic GH; perinuclear keratin pattern	Often smaller; frequently older patients	T2-weighted hypointensity	Better biochemical and tumoral response reported	Moderate; replicated across centres but with overlapping distributions	Guaraldi <i>et al.</i> (2024); Potorac <i>et al.</i> (2016)
Sparsely granulated somatotroph tumour	PIT1 lineage; fibrous bodies on keratin staining	Often larger and more invasive; younger patients	T2-weighted hyperintensity	Poorer response reported	Moderate	Guaraldi <i>et al.</i> (2024); Potorac <i>et al.</i> (2016); J. Wang <i>et al.</i> (2026)
Mammosomatotroph and mixed somatotroph–lactotroph tumours	Co-expression or co-secretion of GH and prolactin	Mammosomatotroph tumours smaller in one surgical series	Not established	Not established	Low; single-centre data	Ly <i>et al.</i> (2019); Guaraldi <i>et al.</i> (2024)
Immature and mature PIT1-lineage plurihormonal tumours	PIT1 lineage with variable hormone expression	Variable; may be aggressive	Not established	Not established	Low	Asa <i>et al.</i> (2022); Guaraldi <i>et al.</i> (2024)
Silent somatotroph tumour	GH immunoreactivity without clinical or biochemical acromegaly	Presents as a non-functioning lesion	Not established	Not applicable	Low; 2% of tumours in the reference series	Chinezu <i>et al.</i> (2017)
Invasion and proliferation grade	MRI-defined cavernous or sphenoid sinus invasion with Ki-67, mitoses and p53	Higher grade associated with poorer eight-year status	Cavernous sinus invasion on MRI	Indirect; invasion reduces surgical remission	Moderate for prognosis; weak as a drug-selection tool	Trouillas <i>et al.</i> (2013); Casar-Borota <i>et al.</i> (2025)
Radiomic and machine learning surrogates	Quantitative texture features from preoperative MRI	Applicable before surgery	Model output rather than visual signal	Discriminates granulation subtype in external validation	Emerging; small external cohorts	Kocak <i>et al.</i> (2019); J. Wang <i>et al.</i> (2026)

Note. GH = growth hormone; MRI = magnetic resonance imaging; PIT1 = pituitary-specific positive transcription factor 1. Confidence reflects replication, study design and availability of external validation. Associations are population-level tendencies and are not sufficiently discriminatory for individual treatment allocation on current evidence

5. Systemic Clinical Manifestations and their Reversibility

5.1 Phenotype, Presentation and the Anatomy of Diagnostic Delay

The acromegalic phenotype develops over years, and its individual elements are individually unremarkable, which explains why patients are commonly managed within several specialties before the unifying diagnosis is made. Carpal tunnel syndrome illustrates the pattern with unusual clarity. In a Swedish nationwide cohort, patients with acromegaly had approximately a sixfold higher incidence of carpal tunnel surgery before the acromegaly diagnosis than the general population, 85% of those with both diagnoses underwent decompression first, at a mean interval of 2.2 years, and women were at higher risk than men (Vouzouneraki *et al.*, 2021). The inference is actionable: the diagnostic opportunity frequently arises in hand surgery, sleep medicine and rheumatology rather than in endocrinology. Female sex is associated with later diagnosis and different presenting features at diagnosis in pooled nationwide and meta-analytic data (Dal *et al.*, 2021), and diagnostic delay interacts with age and hormonal burden in determining the accumulated comorbidity load (Esposito *et al.*, 2020; Gasco *et al.*, 2025). Computational approaches to earlier detection, including automated recognition of facial features from photographs (Kong *et al.*, 2018), have demonstrated feasibility in case-control datasets but have not been evaluated prospectively in unselected populations, where the low prevalence of the disease would substantially reduce positive predictive value.

5.2 Cardiovascular Involvement

Cardiac disease in acromegaly encompasses biventricular enlargement, diastolic dysfunction, valvular disease, hypertension, arrhythmia and, less commonly, overt heart failure, and duration of hormone excess appears more closely related to the development of structural change than the absolute degree of hormone elevation (Sherin *et al.*, 2024). This distinction between

cumulative exposure and peak concentration is conceptually important, because it implies that early diagnosis may matter more for cardiac outcome than the depth of biochemical suppression subsequently achieved. The proposition is biologically plausible and consistent with observational data, but it has not been tested in a design capable of separating duration from severity, since the two are correlated in almost all cohorts. Contemporary reviews note that improved biochemical control and better management of conventional cardiovascular risk factors have reduced cardiovascular mortality to the point that neoplastic causes now account for the greatest share of deaths (Sherin *et al.*, 2024), an epidemiological transition also visible in mortality meta-analysis (Bolfi *et al.*, 2018).

5.3 Disordered Glucose Metabolism

Growth hormone excess induces insulin resistance and a characteristic body composition with reduced adipose mass, and diabetes mellitus in acromegaly carries clinically meaningful prognostic weight (Esposito *et al.*, 2024). In a Swedish matched-cohort analysis of 254 patients with acromegaly and concomitant type 2 diabetes compared with 532 without diabetes, the adjusted hazard ratio for overall mortality was 1.58 (95% confidence interval 1.12 to 2.23), with increased cardiovascular mortality (hazard ratio 2.11) and morbidity (hazard ratio 1.49) over a mean follow-up of 9.2 years (Esposito *et al.*, 2022). Whether hyperglycaemia resolves after successful treatment of GH excess is debated; the persistence of diabetes in a substantial proportion of patients after biochemical control indicates that irreversible beta-cell or vascular change may occur during the prolonged prediagnostic period (Samson, 2024). Management is complicated by the divergent metabolic effects of acromegaly therapies, and a treatment algorithm tailored to this specific setting has been proposed (Esposito *et al.*, 2024). Formal evidence remains thin: no randomised trial has compared glucose-lowering strategies specifically in acromegaly-associated diabetes, and recommendations are extrapolated from the general type 2 diabetes literature.

5.4 Sleep-Disordered Breathing

The relationship between disease activity and obstructive sleep apnoea (OSA) provides one of the clearest examples in this field of how study design determines the apparent answer. A meta-analysis of 24 studies comprising 734 patients found that OSA prevalence and the apnoea-hypopnoea index were similar in patients with active and inactive disease in cross-sectional comparisons, yet longitudinal comparison before and after treatment showed significant improvement, with a median follow-up of six months (Parolin *et al.*, 2020). The discrepancy is best explained by the cross-sectional design conflating patients whose disease was never severe with those whose severe disease had been treated, and by residual anatomical change persisting after hormonal normalisation. A subsequent prospective surgical study of 35 patients found OSA in 68.6% preoperatively, a median reduction in the respiratory event index of 9.5 events per hour after endoscopic transsphenoidal surgery, resolution in half of affected patients, and a relationship between change in respiratory event index and change in IGF-1 (Cho *et al.*, 2024). The sample is small and from a single centre, but the design supports a causal interpretation more strongly than the prevalence literature does.

5.5 Skeletal and Articular Disease

Acromegalic bone disease departs from the pattern familiar from other endocrine osteopathies. A meta-analysis of 41 studies including 1,935 patients found increased bone formation and resorption markers without a significant difference in lumbar spine bone mineral density, a tendency towards higher femoral neck density, and a markedly increased frequency of vertebral fracture, with an odds ratio of 8.26 (95% confidence interval 2.91 to 23.39) relative to controls, in close relationship with male sex, hypogonadism and active disease (Mazziotti *et al.*, 2015). Density measurement therefore misclassifies risk in this population, and the mechanistic explanation lies in altered microarchitecture rather than in reduced mass (Birtolo *et al.*, 2025; Mazziotti *et al.*, 2022). A systematic review of 24 studies reported vertebral fracture prevalence ranging from 6.5% to 87.1% and incidence from 5.6% to 42%, with fractures frequently multiple and disease activity and its duration acting as influencing factors, while hypogonadism did not appear to influence fracture frequency (Sorohan & Poiana, 2023). The extraordinary width of these ranges reflects genuine methodological divergence in fracture ascertainment rather than biological variability alone, and it argues strongly for standardised morphometric assessment. A cross-sectional study of 149 patients found vertebral fractures in 39.6%, associated with older age, longer disease duration, higher body mass index and higher IGF-1, and reported that volumetric density measured by quantitative computed tomography was lower in patients with fracture (Chen *et al.*, 2026), supporting the view that density assessed by a technique sensitive to trabecular compartment change is more informative than areal measurement.

Arthropathy is the complication most consistently reported by patients and least responsive to treatment. A multicentre cross-sectional questionnaire study of 411 patients across six United Kingdom endocrine centres, at a median of 13 years from diagnosis, found joint pain in 82.5%, with moderate or severe pain in 43.3% and 13.1% respectively; 26.5% had received at least one joint injection and 17.0% had at least one joint prosthesis, at a median age of 59 years (Kyriakakis *et al.*, 2026). Patients aged 50 years or younger reported less pain and required fewer procedures, but analgesic use was comparable, indicating that articular symptoms begin early. The cross-sectional design and reliance on self-report limit causal inference and invite recall bias, yet the scale of the reported burden is difficult to attribute to bias alone.

5.6 Neoplastic Risk

Cancer risk in acromegaly remains genuinely contested, and the disagreement is instructive about the influence of study design. A Danish nationwide cohort of 529 patients found an overall cancer standardised incidence ratio of 1.1 (95% confidence interval 0.9 to 1.4) after excluding the first year, with non-significant elevations for colorectal, breast and prostate cancer, while an accompanying meta-analysis of 23 studies gave a pooled standardised incidence ratio of 1.5 (95% confidence interval 1.2 to 1.8), with the highest ratios reported in single-centre studies and in studies with fewer than 10 cancer cases (Dal *et al.*, 2018). A more recent Danish

population-based study with up to 44 years of follow-up in 809 biochemically validated patients and 80,900 matched controls found no clear overall increase (incidence rate ratio 1.10, 95% confidence interval 0.93 to 1.30) but an increased risk of colorectal cancer (incidence rate ratio 1.78) and thyroid cancer (incidence rate ratio 3.68), with colorectal cancers more often localised at detection (Rosendal *et al.*, 2026). An Israeli health-maintenance cohort of 470 patients matched to 2,330 controls reported a higher prevalence of solid malignancy (21.3% versus 14.8%; odds ratio 1.6) driven principally by thyroid cancer (Duskin-Bitan *et al.*, 2025), and a Turkish tertiary-centre cohort of 393 patients reported a much higher overall standardised incidence ratio of 5.48, which remained elevated at 2.76 after excluding thyroid cancer and across multiple sensitivity analyses, with cumulative IGF-1 exposure independently predicting cancer (Ercan *et al.*, 2026). A Swedish nationwide analysis similarly found increased incidence of benign and malignant tumours (Esposito *et al.*, 2021).

Reconciling these findings requires attention to surveillance intensity rather than to biology alone. Tertiary referral cohorts subject patients to repeated imaging and colonoscopy, which detects indolent disease that would not otherwise be diagnosed; the localised stage distribution of colorectal cancers in the Danish cohort is consistent with such detection effects (Rosendal *et al.*, 2026). The Turkish authors addressed this directly through graded landmark analyses and reported stability of the non-thyroid estimate (Ercan *et al.*, 2026), which weakens but does not eliminate the surveillance explanation, since surveillance is not restricted to the early follow-up period. The defensible conclusion is that colorectal and thyroid risk are modestly and probably genuinely increased, that the magnitude is smaller in population-based than in referral-based designs, and that guidelines uniformly endorse colonoscopic screening while disagreeing on its optimal timing and interval (Kasuki *et al.*, 2022).

Table 4. Systemic manifestations of acromegaly, strength of association with disease activity and reported reversibility after treatment

Manifestation	Representative evidence	Association with disease activity	Reversibility with biochemical control	Confidence	Supporting references
Carpal tunnel syndrome and peripheral entrapment	Nationwide cohort; sixfold higher incidence of decompression before diagnosis	Strong; typically antedates diagnosis	Partial; often already operated	Moderate to strong	Vouzouneraki <i>et al.</i> (2021)
Cardiac structural and functional disease	Narrative synthesis of echocardiographic and outcome data	Duration of exposure more influential than peak hormone concentration	Partial; improves with control and risk-factor management	Moderate; confounded by correlated exposure duration and severity	Sherin <i>et al.</i> (2024); Gadelha <i>et al.</i> (2019)
Type 2 diabetes mellitus	Matched nationwide cohort (254 versus 532 patients)	Strong; diabetes raises overall and cardiovascular mortality	Incomplete; persists in a substantial proportion	Moderate to strong for prognosis; weak for management strategy	Esposito <i>et al.</i> (2022, 2024); Samson (2024); Esposito <i>et al.</i> (2024)
Obstructive sleep apnoea	Meta-analysis (24 studies, 734 patients); prospective surgical cohort (35 patients)	Not evident cross-sectionally; evident longitudinally	Substantial; resolution in half of affected patients after surgery in one cohort	Moderate; design-dependent findings	Parolin <i>et al.</i> (2020); Cho <i>et al.</i> (2024)
Vertebral fracture and altered bone microarchitecture	Meta-analysis (41 studies, 1,935 patients); systematic review (24 studies)	Strong; related to active disease, disease duration and male sex	Limited; fracture risk persists and is not tracked by areal density	Moderate; wide between-study variation in ascertainment	Mazziotti <i>et al.</i> (2015, 2022); Soroohan and Poiana (2023); Chen <i>et al.</i> (2026); Birtolo <i>et al.</i> (2025)
Arthropathy	Multicentre cross-sectional study (411 patients, six centres)	Present early and accumulates with disease duration	Poor; joint replacement required in 17.0%	Moderate; self-reported outcomes	Kyriakakis <i>et al.</i> (2026)
Colorectal and thyroid neoplasia	Nationwide cohorts and meta-analysis; referral cohorts	Modest increase; cumulative IGF-1 exposure predicts cancer in one cohort	Not applicable; screening recommended	Contested; estimates vary with study design and surveillance intensity	Dal <i>et al.</i> (2018); Kasuki <i>et al.</i> (2022); Duskin-Bitan <i>et al.</i> (2025); Ercan <i>et al.</i> (2026); Rosendal <i>et al.</i> (2026)
Impaired quality of life and fatigue	Two scoping reviews (21 and 20 studies)	Associated with disease burden, comorbidity and psychosocial factors	Incomplete; deficits persist after biochemical control	Low to moderate; heterogeneous instruments, few longitudinal data	Badia <i>et al.</i> (2004); Wang <i>et al.</i> (2024, 2025)
Frailty and functional decline in older patients	Multicentre case-control study (42 patients aged 65 years or more)	Musculoskeletal and bone disease more frequent than in controls	Not established	Low; small sample	Gagliardi <i>et al.</i> (2021); Quock <i>et al.</i> (2025)
Excess mortality	Meta-analysis of 26 studies	Confined to patients with active disease in both study periods	Normalised with biochemical control	Strong for the association; weak for attribution of the temporal trend	Bolfi <i>et al.</i> (2018)

Note. IGF-1 = insulin-like growth factor 1. Reversibility refers to change reported after achievement of biochemical targets by any modality. Confidence reflects study design, replication and consistency across cohorts

5.7 Quality of Life, Fatigue and Ageing

Patient-reported outcome is where the dissociation between biochemical success and clinical recovery is most visible. A scoping review of 21 studies identified ten categories of psychosocial factor associated with quality of life, with depression and anxiety most frequent, and found that the disease-specific Acromegaly Quality of Life Questionnaire (Badia *et al.*, 2004) was the most commonly used of seven validated instruments (W. Wang *et al.*, 2024). Only five of the included studies were interventional, and the authors noted the absence of longitudinal and qualitative research. A separate scoping review of 20 studies reported fatigue prevalence between 49% and 92%, influenced by sleep disturbance, comorbidity and disease-specific factors, with aerobic exercise, guided home rehabilitation and cognitive behavioural therapy among the interventions studied (W. Wang *et al.*, 2025). The breadth of these prevalence ranges reflects instrument heterogeneity and should not be read as an estimate. In older patients, a multicentre case-control study of 42 patients aged 65 years or more found more frequent musculoskeletal and bone disease than in matched controls, lower cognitive scores and poorer quality of life across physical, general health, vitality and social domains (Gagliardi *et al.*, 2021). Consistent with this, a Medicare analysis of 3,491 beneficiaries with acromegaly matched to controls found higher hospitalisation, emergency department, skilled nursing and home health use, and mean total all-cause costs of US\$45,830 compared with US\$18,922, with 69.6% of beneficiaries having no evidence of acromegaly-directed treatment during the observation period (Quock *et al.*, 2025). That last figure warrants scrutiny: it may indicate substantial undertreatment of older patients, or it may reflect the limitations of claims-based ascertainment in patients in long-term surgical remission.

5.8 Mortality

Mortality data provide the most encouraging finding in the modern literature and also the clearest evidence that biochemical control is not a complete treatment goal. A systematic review and meta-analysis of 26 studies found that mortality was increased in the 17 studies published before 2008 but not different from the general population in the nine published thereafter (standardised mortality ratio 1.35, 95% confidence interval 0.99 to 1.85); mortality was not increased where somatostatin analogues were used as adjuvant therapy (standardised mortality ratio 0.98, 95% confidence interval 0.83 to 1.15) but was more than doubled in series confined to surgery and radiotherapy (standardised mortality ratio 2.11, 95% confidence interval 1.54 to 2.91), and it was not increased in patients achieving biochemical control in either period (Bolfi *et al.*, 2018). Attributing the temporal improvement to medical therapy is tempting but not warranted by this design, because the same period saw changes in surgical technique, earlier diagnosis, better cardiovascular risk management and altered radiotherapy practice; confounding by calendar time cannot be separated from treatment effect in a meta-analysis of observational series.

Table 4 summarises the principal systemic manifestations, the strength of the evidence linking them to disease activity and the extent to which they reverse with treatment. The pattern that emerges from reading across the reversibility column is the central clinical observation of this review: the complications that respond best to hormonal normalisation are metabolic and respiratory, whereas articular and skeletal disease, and the psychosocial burden that accompanies them, frequently do not.

6. Diagnostic Assessment and the Definition of Disease Control

6.1 Biochemical Diagnosis and Assay Limitations

The 14th Acromegaly Consensus Conference, involving 56 experts from 16 countries, established that in a patient with typical clinical features an IGF-1 concentration exceeding 1.3 times the upper limit of normal for age confirms the diagnosis, that a random fasting GH measurement may inform prognosis but is not required for diagnosis, and that equivocal results should be resolved by repeat measurement using the same validated assay, with oral glucose tolerance testing reserved for persisting uncertainty (Giustina *et al.*, 2024). Serum IGF-1 is preferred for initial screening because of its stability and its integration of GH secretion over time (Yogi-Morren & Chanson, 2026).

The dependence of this framework on assay performance is its principal vulnerability. Interference by IGF-binding proteins prompted the development of mitigation techniques within immunoassays, and mass spectrometric methods were introduced in response to discordant immunoassay results (Huang *et al.*, 2024). A stable isotope dilution liquid chromatography–tandem mass spectrometry method applied to plasma from 25 consecutively diagnosed patients before and after 24 weeks of primary lanreotide therapy correlated well with a widely used commercial immunoassay across a broad concentration range, while avoiding immunocapture and its associated interference (Kay *et al.*, 2013). The practical implication is that a threshold expressed as a multiple of the upper limit of normal is only as reliable as the age-adjusted reference interval and the analytical platform on which it was derived, and that serial monitoring should not switch platforms. Consensus documents acknowledge this, but routine practice frequently does not.

6.2 Imaging and Pathological Contribution to Diagnosis

Pituitary MRI defines tumour size, cavernous sinus involvement and relation to the optic apparatus, and imaging characteristics contribute to prognosis as well as to anatomical description (Haberbosch *et al.*, 2026). In the ectopic GHRH-dependent form, pituitary hyperplasia rather than a discrete adenoma is the characteristic appearance, and recognition of this pattern prevents inappropriate transphenoidal exploration (Potorac *et al.*, 2022). Histopathological assessment contributes after surgery, with lineage and subtype determination as described in Section 4, and is not available to inform the initial treatment decision (Ho *et al.*, 2024).

6.3 Composite Assessment of Disease Activity

Biochemical targets capture only part of the clinical state, which motivated the development of composite instruments. A multicentre study of 162 patients across four centres in the Veneto region compared clinician judgement with the Acromegaly Disease Activity Tool and with the SAGIT instrument, which incorporates signs and symptoms, associated morbidity, GH, IGF-1 and tumour status (Dassie *et al.*, 2025). Such instruments address a real deficiency, since a patient with normalised IGF-1 and disabling arthropathy is not, in any clinically meaningful sense, in the same state as one with neither. Their limitations are equally real: both were developed with industry involvement, neither has been shown in a randomised comparison to improve management decisions or outcomes, and the reference standard against which they are validated is itself clinician judgement.

6.4 The Gap Between Criteria and Practice

Consensus criteria are not uniformly implemented. A Delphi process among 47 endocrinologists in five Nordic countries generated 37 statements on treatment and follow-up and reached consensus on only 41% of them, with agreement that pituitary surgery remains the primary therapy (Arlie-Søborg *et al.*, 2024). A comparable Delphi exercise across Gulf countries reported similar divergence in practice (Almalki *et al.*, 2025). Application of the current criteria in other settings shows the effect of criteria revision on apparent outcomes: an Indian single-centre series of 42 patients undergoing endoscopic transsphenoidal surgery reported remission defined by age-adjusted IGF-1 at three months in accordance with the 14th consensus criteria (Sharma *et al.*, 2025), and remission rates reported under different criteria are not directly comparable across eras. Contemporary commentary identifies several of these definitional questions as unresolved (Spencer-Segal & Nachtigall, 2026), and the practical consequence is that comparison of outcome data across cohorts requires explicit attention to the criteria in force at the time of measurement.

7. Evolving Therapeutic Paradigms

7.1 Surgery as First-Line Treatment and its Determinants

Transsphenoidal resection by an experienced pituitary surgeon remains the initial treatment for most patients in every major guideline and consensus document published over the past decade (Fleseriu *et al.*, 2021; Katznelson *et al.*, 2014; Melmed *et al.*, 2025), and the principal determinant of outcome is not surgical technique but tumour extension. A meta-analysis of 14 studies including 972 patients with biochemically confirmed GH-secreting tumours found pooled remission in 47.6% (95% confidence interval 40.8 to 54.4) of invasive macroadenomas, 76.4% (72.2 to 80.1) of non-invasive macroadenomas and 74.2% (66.3 to 80.7) of non-invasive microadenomas, with the difference attributable to cavernous sinus invasion rather than to tumour size among non-invasive lesions (Briceno *et al.*, 2017). This finding has a straightforward clinical consequence that is sometimes obscured by comparisons between surgical series: remission rates are not comparable between centres unless the distribution of cavernous sinus invasion is comparable.

Comparison of endoscopic and microsurgical approaches is confounded by case selection. A meta-analysis of 31 studies comprising 950 endoscopic and 2,137 microsurgical procedures found that patients undergoing endoscopy more often had macroadenomas and cavernous sinus invasion, yet achieved higher remission rates for non-invasive macroadenomas (83.8% versus 66.9%); sinusitis and intraoperative cerebrospinal fluid leak were more frequent after endoscopy and meningitis was more frequent after microsurgery (Phan *et al.*, 2017). Because allocation was not randomised and the baseline imbalance runs against the endoscopic group, the direction of any residual confounding is not predictable, and the appropriate conclusion is that the two approaches produce broadly similar biochemical results with differing complication profiles (Guinto *et al.*, 2024). Preoperative somatostatin analogue treatment has been examined as a means of improving surgical outcome; a meta-analysis of five randomised and seven non-randomised comparative studies concluded that it is safe and that any favourable effect is restricted to short-term cure rates in macroadenomas and invasive macroadenomas, with long-term benefit unproven (Yang *et al.*, 2019). Routine preoperative medical treatment therefore cannot be recommended on current evidence, although it retains a role in patients with severe systemic compromise.

7.2 First-Generation Somatostatin Receptor Ligands and the Prediction of Response

Octreotide and lanreotide remain the initial medical therapy in most treatment algorithms (Fleseriu *et al.*, 2021; Melmed *et al.*, 2025). Approximately half of patients do not achieve biochemical control, and identifying that group before treatment has become the central practical question in acromegaly pharmacotherapy (Marazuela *et al.*, 2024). Several markers converge on the same biological construct. Sparsely granulated morphology, low tumoural expression of somatostatin receptor subtype 2, reduced E-cadherin expression and T2-weighted hyperintensity all identify a poorly responsive phenotype (Gliga *et al.*, 2024; Potorac *et al.*, 2016). A prospective multicentre French cohort of naive patients examined receptor expression, granularity and T2 signal simultaneously, providing one of the few prospective datasets in this area (Ilie *et al.*, 2022). Digital image analysis of somatostatin receptor subtype 2 expression improved discrimination relative to conventional semiquantitative scoring, with the percentage of positive cells assessed digitally achieving an area under the curve of 0.917 in one series (Campana *et al.*, 2025), indicating that part of the inconsistency in the older literature is attributable to measurement technique rather than to biology.

Predictive models combining these variables have been developed. A multivariable model built on a large European registry found that baseline IGF-1 concentration was the strongest predictor of response, followed by body weight, with younger age at diagnosis associated with non-response (Coopmans *et al.*, 2020). A machine learning model incorporating receptor subtype 2 and 5 expression, granulation pattern, sex, age and pretreatment GH and IGF-1 achieved 86.3% accuracy with a positive predictive value of 83.3% and a negative predictive value of 87.5% (Wildenberg *et al.*, 2021), and a multibiomarker score incorporating immune microenvironment features has been proposed (Chiloiro *et al.*, 2024). These are encouraging results, but three cautions apply. The

models were developed and tested in the same cohorts or by internal resampling, without prospective external validation in an independent population; the outcome definitions differ between studies; and the marker requiring surgical tissue cannot inform primary medical therapy, which is precisely the situation in which prediction would be most valuable. The observation that simple clinical variables such as baseline IGF-1 carry substantial predictive weight (Coopmans *et al.*, 2020) raises the unresolved question of how much incremental information the pathological markers actually provide.

7.3 Second-Line Pharmacotherapy

Pasireotide, which binds somatostatin receptor subtype 5 with high affinity in addition to subtype 2, achieved biochemical control in significantly more patients than octreotide in a head-to-head randomised trial (31.3% versus 19.2% at 12 months), with normalisation of IGF-1 in 38.6% versus 23.6%, at the cost of hyperglycaemia-related adverse events in 57.3% versus 21.7% (Colao *et al.*, 2014). In patients inadequately controlled on octreotide or lanreotide, the randomised PAOLA trial found biochemical control at 24 weeks in 15% and 20% of patients receiving pasireotide 40 mg and 60 mg respectively, compared with none in the active control group (Gadelha *et al.*, 2014). Real-world data are more favourable than the trial estimates, with a meta-analysis of 12 studies comprising 409 patients reporting pooled IGF-1 control of 57.9% (95% confidence interval 48.4 to 66.8) and tumour shrinkage in 33.3% (Biagetti *et al.*, 2025). The discrepancy between trial and real-world estimates most likely reflects differences in control definitions, dose optimisation and patient selection rather than superior real-world efficacy, and it illustrates why the two evidence types should not be pooled. Counterintuitively, the response to pasireotide correlates principally with somatostatin receptor subtype 2 rather than subtype 5 expression (Muhammad *et al.*, 2019), a finding that complicates the simple receptor-affinity rationale for its use. Hyperglycaemia is the dominant safety consideration, and post hoc analyses have identified predictors and proposed management approaches (Feldt-Rasmussen *et al.*, 2024).

Pegvisomant blocks the GH receptor and therefore lowers IGF-1 without acting on the tumour. In the ACROSTUDY observational programme, the proportion of patients with normal IGF-1 rose from 53% at year 1 to 73% at year 10 as the mean daily dose increased from 12.8 mg to 18.9 mg; tumour size was unchanged in 72.2% of patients, and alanine or aspartate aminotransferase elevation exceeding three times the upper limit of normal occurred in 3% of those with normal baseline liver tests (Buchfelder *et al.*, 2018). Final data from the full monotherapy cohort confirmed this profile, with IGF-1 normalisation in 62.3% at last observation and no treatment-related deaths (Yuen *et al.*, 2026). The rising control rate over time is best interpreted as evidence of progressive dose optimisation and of selective attrition of non-responders rather than as increasing efficacy. Mortality analysis within the same programme found that IGF-1 within the normal range during pegvisomant therapy was associated with all-cause mortality indistinguishable from the general population, while higher on-treatment IGF-1 and longer disease duration before starting treatment were associated with higher mortality (Tritos *et al.*, 2020). This is observational evidence in which treatment response and prognosis are plausibly determined by shared factors, so it supports the value of achieving the target without establishing that the drug itself confers the survival benefit. Factors associated with failure to achieve control on pegvisomant have been characterised in the same dataset (Giampietro *et al.*, 2024). Combination of somatostatin analogues with pegvisomant normalised IGF-1 in most patients uncontrolled on high-dose analogue monotherapy in a meta-analysis of nine prospective studies, with neutral effects on glucose parameters, reduced fasting insulin and liver enzyme elevation in 14% (Ma *et al.*, 2020).

Cabergoline retains a place as an inexpensive oral option. A meta-analysis of individual data from 227 patients across 15 studies, none randomised or placebo-controlled, found that cabergoline monotherapy normalised IGF-1 in 34% of patients and that adding cabergoline after somatostatin analogue failure normalised IGF-1 in approximately half of cases, including in patients with normal prolactin concentrations (Sandret *et al.*, 2011). The absence of randomised evidence and the modest cohort size limit confidence, yet the real-world value of the drug, particularly where access to newer agents is constrained, is considerable (Shimon, 2024).

7.4 Oral and Self-Administered Somatostatin Receptor Agonists

The most substantial recent change in practice is the arrival of formulations that remove the requirement for clinic-administered injection. Oral octreotide capsules maintained biochemical control after switching from injectable ligands in a phase 3 programme extending to 13 months (Memed *et al.*, 2015), and the randomised MPOWERED trial demonstrated maintenance of response relative to injectable ligands in patients who had previously responded to both, using a non-inferiority margin of 20 percentage points (Fleseriu *et al.*, 2022), with durability confirmed in open-label extension (Fleseriu *et al.*, 2023). Comparison of the two pivotal trials showed consistent biochemical response and a consistent patient preference for oral treatment despite differing designs (Labadzhyan *et al.*, 2021). The 20-percentage-point non-inferiority margin is wide, and acceptance of it reflects a judgement that the convenience gain offsets a potentially meaningful efficacy loss, a trade-off that should be made explicit with patients rather than assumed.

Paltusotine, a non-peptide selective somatostatin receptor subtype 2 agonist, has generated the most convincing randomised data among the newer agents. In patients previously controlled on injected ligands, 83.3% (25 of 30) maintained IGF-1 at or below the upper limit of normal on paltusotine compared with 3.6% (1 of 28) on placebo, with superiority on all secondary endpoints including symptom score (Gadelha *et al.*, 2024). In medically untreated patients with biochemically uncontrolled disease, IGF-1 normalisation at 24 weeks occurred in 55.6% of paltusotine recipients compared with 5.3% of placebo recipients among 111 randomised patients (Biller *et al.*, 2026). Earlier phase 2 work had shown that IGF-1 and GH rose significantly within four weeks of paltusotine withdrawal, confirming a drug effect rather than spontaneous remission (Gadelha *et al.*, 2023; McLaren & Murray, 2023). Regulatory approval followed (Lee, 2026). Two limitations temper enthusiasm. The comparator in both pivotal trials was placebo rather than an active injectable ligand, so superiority over standard care has not been demonstrated; and the withdrawal-controlled design in previously controlled patients enriches for somatostatin-responsive tumours, which limits generalisability to ligand-resistant disease.

A subcutaneous octreotide depot permitting self-administration and room-temperature storage was superior to placebo in the ACROINNOVA 1 trial, with IGF-1 response in 72.2% versus 37.5% and combined IGF-1 and GH response in 70.0% versus 37.5% among 72 randomised patients, alongside improved quality of life and treatment satisfaction (Ferone *et al.*, 2025). The same design limitation applies. Antisense oligonucleotide targeting of the GH receptor was evaluated in a randomised open-label phase 2 study (Trainer *et al.*, 2018) and represents a mechanistically distinct approach that has not yet progressed to definitive trials.

7.5 Radiotherapy and Stereotactic Radiosurgery

Radiotherapy is now largely reserved for residual or recurrent disease not controlled by surgery and medical therapy. A meta-analysis of 20 studies including 1,533 patients estimated endocrine remission at 43.2% at five years and 56.9% at ten years, endocrine control at 55.0% and 69.7% respectively, ten-year local control of 92.8%, visual toxicity of 2.7% and hypopituitarism of 26.8%, with each 1 Gy increase in margin dose beyond 17 Gy associated with a 0.41% increase in visual toxicity risk (Singh *et al.*, 2020). An international multicentre cohort of 371 patients with a mean endocrine follow-up of 79 months reported actuarial initial and durable remission at 10 years of 69% and 59%, with a mean time to durable remission of 38 months, new endocrinopathy in 26% and new cranial neuropathy in 4%; cessation of IGF-1-lowering medication before radiosurgery was the only independent predictor of durable remission (Ding *et al.*, 2019). Primary radiosurgery in patients unsuitable for resection produced actuarial remission of 20% at two years and 42% at five years, with no significant difference from matched postoperative patients in tumour control, remission, recurrence or hypopituitarism (Mohammed *et al.*, 2020). Hypopituitarism accrues progressively, with actuarial rates of 7.8%, 22.4% and 31.3% at one, five and ten years in a multicentre analysis of pituitary adenomas including 251 patients with acromegaly (Cordeiro *et al.*, 2019).

Two features of this literature deserve emphasis. The long latency to remission means that medical therapy is required throughout the interval, and the observation that withholding IGF-1-lowering medication at the time of radiosurgery predicts durable remission (Ding *et al.*, 2019) is derived from non-randomised comparisons in which medication use is itself a marker of more active disease. Radiosurgery series are also subject to reporting from experienced centres within research consortia, so the complication estimates are likely to be favourable relative to general practice.

7.6 Aggressive, Refractory and Recurrent Disease and Management in Pregnancy

A minority of tumours behave aggressively despite multimodal treatment. Revised European guidance provides a practical algorithm for aggressive pituitary tumours and carcinomas, standardised reporting of imaging and histopathology, and consideration of molecular analysis (Raverot *et al.*, 2025), with temozolomide remaining the principal systemic option (McCormack, 2022). Management of recurrence after apparently successful surgery has been reviewed systematically, with repeat surgery, medical therapy and radiation all in use and no comparative evidence to rank them (Maroufi *et al.*, 2024). The evidence base here is necessarily weak, consisting of small series and registry reports, and guideline recommendations are appropriately framed as expert consensus.

Pregnancy represents a further situation in which evidence is limited and extrapolation is unavoidable. A systematic review and proportional meta-analysis of 19 observational studies encompassing 273 pregnancies in 211 women reported control of acromegaly during pregnancy in 62% and tumour growth in 9%, with no maternal or fetal deaths (Bandeira *et al.*, 2022). The absence of deaths in a pooled sample of this size is reassuring but cannot exclude uncommon adverse outcomes, and the included studies were observational, heterogeneous in their definitions of disease control and subject to publication bias favouring uneventful series. The practical implication is that most women can be counselled that pregnancy is usually well tolerated, while accepting that the evidence cannot support confident quantification of individual risk.

7.7 Comparative Efficacy and the Limits of Quantitative Synthesis

Two network meta-analyses published within a year illustrate how sensitive comparative conclusions are to inclusion criteria. A synthesis restricted to 18 randomised controlled trials reported comparable biochemical control among long-acting injectable ligands, pasireotide, pegvisomant, oral octreotide and paltusotine, with paltusotine showing significantly higher biochemical control than oral octreotide and than subcutaneous octreotide depot, pasireotide superior to octreotide long-acting release, and paltusotine ranking highest across endpoints (Salvatori *et al.*, 2026). A synthesis of 27 studies including both randomised and non-randomised designs, comprising 4,131 patients and 11 treatments, concluded instead that pegvisomant was the most effective treatment for IGF-1 normalisation, followed by pasireotide, with pasireotide best for tumour shrinkage (Kaparounaki *et al.*, 2025).

The divergence is explicable. The first analysis excluded non-randomised evidence and therefore excluded much of the observational data on pegvisomant dose escalation, in which control rates rise substantially over years (Buchfelder *et al.*, 2018; Yuen *et al.*, 2026); the second admitted non-randomised studies and thereby captured that effect while importing their susceptibility to selection bias. Both are also affected by the fact that placebo-controlled withdrawal trials of newer agents enrol populations already known to respond to somatostatin receptor agonism, which inflates apparent efficacy relative to unselected populations. Neither analysis should be read as establishing a treatment hierarchy. The defensible conclusion is that no agent has demonstrated superiority over another in an adequately powered head-to-head trial in an unselected population, with the partial exception of pasireotide over octreotide (Colao *et al.*, 2014), and that ranking probabilities derived from indirect comparison are not a sound basis for sequencing therapy in an individual patient.

Table 5. Therapeutic modalities in acromegaly: representative efficacy evidence, principal limitations and confidence

Modality	Representative efficacy evidence	Principal safety or tolerability concern	Principal limitation of the evidence	Confidence	Supporting references
Transsphenoidal surgery	Pooled remission 76.4% for non-invasive macroadenomas and 47.6% for invasive macroadenomas	Cerebrospinal fluid leak, sinusitis, hypopituitarism	No randomised comparisons; outcome dominated by cavernous sinus invasion and surgeon experience	Moderate to strong for effectiveness; weak for technique comparison	Briceno <i>et al.</i> (2017); Phan <i>et al.</i> (2017); Guinto <i>et al.</i> (2024)
Preoperative somatostatin analogue	Short-term cure improved in macroadenomas and invasive macroadenomas	As for somatostatin analogues	Benefit not shown for long-term outcome; heterogeneous comparators	Low to moderate	Yang <i>et al.</i> (2019)
First-generation somatostatin receptor ligands	Standard first-line medical therapy; approximately half of patients not controlled	Gastrointestinal effects, cholelithiasis	Response predictors not prospectively validated; tissue markers unavailable before surgery	Moderate	Fleseriu <i>et al.</i> (2021); Marazuela <i>et al.</i> (2024)
Pasireotide	31.3% versus 19.2% biochemical control against octreotide; 15% to 20% control after ligand failure; 57.9% in real-world meta-analysis	Hyperglycaemia in a majority of patients	Real-world and trial estimates diverge; response driven by receptor subtype 2 rather than subtype 5	Moderate to strong	Colao <i>et al.</i> (2014); Gadelha <i>et al.</i> (2014); Biagetti <i>et al.</i> (2025); Feldt-Rasmussen <i>et al.</i> (2024)
Pegvisomant	IGF-1 normalisation rising from 53% at year 1 to 73% at year 10; 62.3% at last observation in the full monotherapy cohort	Transaminase elevation; no tumoural effect	Observational programme; attrition and dose escalation confound temporal trends	Moderate	Buchfelder <i>et al.</i> (2018); Tritos <i>et al.</i> (2020); Yuen <i>et al.</i> (2026)
Somatostatin analogue plus pegvisomant	IGF-1 normalised in most patients uncontrolled on high-dose analogue monotherapy	Liver enzyme elevation in 14%	Prospective but non-randomised studies; small total sample	Moderate	Ma <i>et al.</i> (2020)
Cabergoline	IGF-1 normalised in 34% as monotherapy; approximately 50% when added after ligand failure	Generally well tolerated	No randomised or placebo-controlled trials; individual data from 227 patients	Low to moderate	Sandret <i>et al.</i> (2011); Shimon (2024)
Oral octreotide capsules	Maintenance of response versus injectable ligands in a randomised non-inferiority trial	Gastrointestinal effects	Wide non-inferiority margin; population pre-selected for response to both formulations	Moderate	Melmed <i>et al.</i> (2015); Fleseriu <i>et al.</i> (2022, 2023); Labadzhyan <i>et al.</i> (2021)
Paltusotine	83.3% versus 3.6% maintenance of control after switching; 55.6% versus 5.3% IGF-1 normalisation in untreated disease	Gastrointestinal effects typical of the class	Placebo rather than active comparator; withdrawal design enriches for responders	Moderate to strong within the studied populations	Gadelha <i>et al.</i> (2023, 2024); Biller <i>et al.</i> (2026); Lee (2026)
Octreotide subcutaneous depot	IGF-1 response 72.2% versus 37.5% against placebo	Consistent with standard of care	Placebo comparator; 72 patients; 24-week duration	Moderate	Ferone <i>et al.</i> (2025)
Stereotactic radiosurgery	Endocrine remission 43.2% at 5 years and 56.9% at 10 years; 10-year local control 92.8%	Hypopituitarism 26.8%; visual toxicity 2.7%	Retrospective consortium data; long latency requires interim medical therapy	Moderate	Singh <i>et al.</i> (2020); Ding <i>et al.</i> (2019); Mohammed <i>et al.</i> (2020); Cordeiro <i>et al.</i> (2019)
Temozolomide for aggressive tumours	Principal systemic option in guideline algorithms	Haematological and gastrointestinal toxicity	Small series; no randomised evidence	Low	McCormack (2022); Raverot <i>et al.</i> (2025)
Biomarker-guided treatment selection	Hormonal control 78% versus 53%; adjusted hazard ratio 2.53 for achieving control	Not applicable	Single network; 85 patients; requires resected tissue for one marker	Low to moderate; requires replication	Marques-Pamies <i>et al.</i> (2024, 2026)

Note. GH = growth hormone; IGF-1 = insulin-like growth factor 1. Efficacy figures are those reported in the cited sources and are not directly comparable across rows because outcome definitions, follow-up duration and patient selection differ. Confidence reflects study design, replication and representativeness of the population studied

7.8 Towards Biomarker-Directed and Personalised Treatment

The ACROFAST study represents the most direct test of biomarker-guided prescribing to date. Eighty-five patients were allocated to a personalised protocol, in which initial drug choice was informed by T2-weighted MRI signal and E-cadherin immunostaining, or to a control protocol beginning with first-generation ligands in all patients and escalating after demonstrated inadequate control. Hormonal control was achieved in 78% of the personalised group compared with 53% of the control group, with an adjusted hazard ratio for achieving control of 2.53 (95% confidence interval 1.30 to 4.80) and a shorter time to control (Marques-Pamies *et al.*, 2024). A post hoc economic analysis reported favourable cost-effectiveness for the personalised strategy (Marques-Pamies *et al.*, 2026).

This is an important result and should be interpreted carefully. The trial was modest in size, conducted in a single national network, and the control arm was constrained to a sequential escalation protocol that may be more rigid than ordinary clinical practice, so part of the observed benefit could reflect faster escalation rather than better initial selection. E-cadherin immunostaining requires resected tissue, restricting the strategy to postoperative patients. Replication in an independent setting, with a pragmatic comparator and patient-reported as well as biochemical endpoints, is required before biomarker-guided prescribing can be regarded as established. Care organisation may prove as influential as drug selection: standards of care for medical management within pituitary tumour centres of excellence have been articulated (Grottoli & Ghigo, 2024), although the evidence that centre designation improves outcomes remains observational.

Table 5 compares the principal therapeutic modalities. Reading across the limitations column makes the structural problem of this evidence base apparent: the newest agents have the most rigorous randomised evidence but the least representative trial populations, whereas the agents with the longest real-world experience have the weakest comparative evidence.

8. Integrated Critical Synthesis

Three tensions run through the evidence reviewed above, and each has practical consequences.

The first is the tension between biological description and clinical utility. Somatotroph tumours are now characterised in considerable depth at the genomic, epigenomic, transcriptomic and spatial level, and the resulting subgroups are reproducible across analytical platforms (Bioletto *et al.*, 2025; Kober *et al.*, 2024; J. Wang *et al.*, 2024). Almost none of this description has been converted into a prospectively validated decision rule. The one randomised test of biomarker-guided prescribing used two comparatively crude markers, T2-weighted signal and E-cadherin immunostaining, rather than any molecular classification (Marques-Pamies *et al.*, 2024). The gap is not principally one of biological insight; it is one of study design, since validating a predictive marker requires a prospective cohort with pre-specified thresholds and an outcome that is not also used to define the marker. The structural obstacle is that the most informative markers require resected tissue, so they cannot inform the decision that most influences the patient's trajectory, namely what to do first.

The second is the tension between biochemical control and clinical recovery. Mortality normalises when biochemical targets are met (Bolfi *et al.*, 2018; Tritos *et al.*, 2020), and sleep-disordered breathing improves substantially after effective treatment (Cho *et al.*, 2024; Parolin *et al.*, 2020). Arthropathy, vertebral fragility, fatigue and impaired quality of life frequently persist (Kyriakakis *et al.*, 2026; Sorohan & Poiana, 2023; W. Wang *et al.*, 2024, 2025), and in older patients functional and cognitive impairment is evident even in treated disease (Gagliardi *et al.*, 2021). A framework that defines success by hormone concentration alone therefore measures something necessary but incomplete. Composite disease-activity instruments attempt to address this (Dassie *et al.*, 2025), yet none has been shown to change management or outcome. The most defensible reading is that structural complications accrued during the prediagnostic interval are largely irreversible, which relocates the principal opportunity for improvement from therapeutic potency to earlier diagnosis. The carpal tunnel data support this directly: most patients pass through a surgical service years before the endocrine diagnosis is made (Vouzouneraki *et al.*, 2021).

The third is the tension between the quality of evidence and the pace of therapeutic change. The newest agents have been evaluated in well-conducted randomised trials, but against placebo and in populations selected for prior response to somatostatin receptor agonism (Biller *et al.*, 2026; Ferone *et al.*, 2025; Gadelha *et al.*, 2024). The older agents have decades of real-world experience but almost no comparative randomised evidence. Network meta-analysis cannot repair this asymmetry, and the contradictory rankings produced by two recent syntheses demonstrate as much (Kaparounaki *et al.*, 2025; Salvatori *et al.*, 2026). Clinicians are consequently asked to choose between agents on the basis of indirect comparisons whose conclusions change with the inclusion criteria. Convenience, tolerability, glycaemic effect, cost and the patient's own preference are legitimate and probably more reliable determinants of choice than ranking probabilities.

Cutting across all three is the geography of the evidence. Population-level estimates of incidence, comorbidity and mortality derive predominantly from Northern European registries with universal coverage and near-complete follow-up (Dal *et al.*, 2016, 2018; Esposito *et al.*, 2020; Rosendal *et al.*, 2026). Referral-based cohorts from other settings report materially different estimates, most strikingly for cancer risk (Ercan *et al.*, 2026). Delphi exercises in the Nordic countries and the Gulf states reached consensus on a minority of management statements (Almalki *et al.*, 2025; Arlien-Søborg *et al.*, 2024), indicating that practice varies considerably even among specialists. Where access to modern pharmacotherapy is limited, cabergoline and surgical expertise carry disproportionate weight (Sharma *et al.*, 2025; Shimon, 2024), and the evidence base offers little guidance on optimal strategy under resource constraint. The finding that most older beneficiaries in a large administrative dataset had no evidence of acromegaly-directed treatment (Quock *et al.*, 2025) suggests that undertreatment may be a larger source of avoidable morbidity in some settings than suboptimal drug selection.

9. Future Directions

The priorities set out below are ordered by the magnitude of the unresolved problem and by the feasibility of addressing it, and they distinguish work that could begin immediately from work that requires longer-term infrastructure.

The most immediate priority is prospective validation of predictive markers for medical therapy. The unresolved problem is that markers reported to predict response to first-generation somatostatin receptor ligands, principally granulation pattern, somatostatin receptor subtype 2 expression and T2-weighted signal, have been evaluated almost entirely in retrospective series with variable measurement technique and outcome definition (Ilie *et al.*, 2022; Marazuela *et al.*, 2024). Current evidence is inadequate because model development and testing have generally occurred in the same populations, and because the incremental value of tissue markers over routinely available clinical variables such as baseline IGF-1 has not been quantified (Coopmans *et al.*, 2020). The appropriate design is a multicentre prospective cohort with centrally read imaging, digitally quantified receptor immunohistochemistry (Campana *et al.*, 2025), pre-specified thresholds and blinded outcome assessment at a fixed interval, with formal assessment of incremental discrimination over a clinical baseline model. The relevant population is patients requiring medical therapy after surgery, and the primary outcome should combine biochemical control with symptom change. Such a study would establish whether biomarker-guided prescribing warrants the additional cost and complexity it imposes.

A closely related priority is replication of biomarker-guided treatment allocation in an independent setting. ACROFAST showed superiority of a personalised protocol over sequential escalation in 85 patients within a single national network (Marques-Pamies *et al.*, 2024). Replication should use a pragmatic comparator reflecting ordinary practice rather than a constrained escalation protocol, should be powered for time to control and for patient-reported outcome, and should include an explicit health-economic analysis in a second health system, since the existing economic evidence is post hoc (Marques-Pamies *et al.*, 2026).

The third priority concerns outcomes that patients actually experience. Trials in acromegaly are designed around hormone concentrations, and the persistence of arthropathy, skeletal fragility and fatigue after biochemical control indicates that these endpoints are not interchangeable (Kyriakakis *et al.*, 2026; W. Wang *et al.*, 2025). Randomised trials are required in which the primary outcome is joint pain, physical function or a validated quality-of-life instrument, with biochemical control as a secondary measure. Because articular disease is probably structural and largely irreversible, the most informative designs will test interventions directed at the joint itself, including exercise and rehabilitation programmes, rather than further intensification of hormone-lowering therapy. Trials should run for at least two years, given the slow evolution of musculoskeletal outcomes.

Fourth, the biology of acquired treatment resistance is essentially uncharacterised because molecular studies sample tumours once, at surgery (Guo *et al.*, 2024; J. Wang *et al.*, 2024). Paired sampling at initial surgery and at reoperation for recurrence, combined with prospective recording of treatment exposure, would allow the question to be addressed directly. Given the rarity of reoperation, this requires coordinated multicentre tissue banking within pituitary tumour centres of excellence (Grottoli & Ghigo, 2024), and is a medium-term rather than an immediate undertaking. The same infrastructure would permit assessment of whether intratumoural heterogeneity causes misclassification when a single tissue fragment is analysed.

Fifth, earlier diagnosis offers the largest potential gain in preventable morbidity and has received disproportionately little methodological attention. Diagnostic delay measured in years is consistently reported and is associated with comorbidity burden and mortality (Esposito *et al.*, 2020; Gasco *et al.*, 2025). Case-finding strategies based on comorbidity clustering, assisted where appropriate by computational methods (Kong *et al.*, 2018; Yogi-Morren & Chanson, 2026), require prospective evaluation in unselected populations attending hand surgery, sleep medicine and rheumatology services, with pre-specified thresholds and formal assessment of positive predictive value, cost per case detected and the harms of false-positive testing. Retrospective case-control accuracy estimates are not a sufficient basis for deployment.

Sixth, the evidence base requires geographical broadening. Incidence, comorbidity and survival estimates derive largely from small Northern European populations (Dal *et al.*, 2016; Hoskuldssdottir *et al.*, 2015), and cancer risk estimates diverge markedly between population-based and referral-based cohorts (Ercan *et al.*, 2026; Rosendal *et al.*, 2026). Registry development in middle-income settings, with standardised diagnostic criteria and validated case ascertainment, would allow assessment of whether the reported normalisation of mortality generalises to systems with different diagnostic and therapeutic capacity. Studies should also address explicitly what constitutes optimal management where second-line agents are unavailable, a question the current literature does not answer.

Finally, comparative effectiveness requires head-to-head randomised trials in unselected populations. The contradictory conclusions of recent indirect comparisons (Kaparounaki *et al.*, 2025; Salvatori *et al.*, 2026) will not be resolved by further network meta-analysis of the same underlying trials. Pragmatic randomised comparison of an oral selective receptor subtype 2 agonist against an injectable ligand, in patients not pre-selected for prior response and with co-primary biochemical and patient-reported endpoints, would answer the question that clinicians currently face. Such a trial would be feasible within existing international consortia and would be of considerably greater value than additional placebo-controlled withdrawal studies.

10. Conclusions

Acromegaly has been transformed from a disorder defined by its external phenotype into one understood as a neoplastic disease of a defined pituitary lineage with quantifiable systemic consequences, and the review objectives can be answered with differing degrees of confidence.

Mechanistic understanding is now substantial but explains less about individual clinical behaviour than its depth suggests. Constitutive activation of cyclic adenosine monophosphate signalling, whether through somatic mutation of the stimulatory G protein alpha subunit, germline predisposition or ectopic hypothalamic-hormone drive, is a recurrent route to somatotroph autonomy, and molecular subgroups of sporadic tumours are reproducible across independent analytical platforms. These are well-supported conclusions. The proposition that molecular class can be used to select therapy for a given patient is not; it remains a hypothesis supported by retrospective association and awaiting prospective test.

Contemporary tumour classification functions well as a taxonomy and poorly as a stratification instrument. Lineage-based subtyping has resolved diagnostic ambiguity and given a coherent account of tumours whose origin was previously uncertain. Its principal markers, however, require resected tissue, depend on assessments that vary between laboratories, and distinguish groups whose distributions overlap substantially. Radiological and computational surrogates partially circumvent the tissue requirement and have shown external validity in small cohorts, but they are not yet embedded in prospective treatment pathways.

The evidence on systemic morbidity supports a clear and clinically important asymmetry. Metabolic and respiratory complications improve appreciably when hormone concentrations are normalised, and excess mortality resolves in patients who achieve biochemical control. Articular, skeletal and psychosocial burden frequently persists, is poorly captured by biochemical targets, and appears to be determined substantially by the duration of undiagnosed disease. Excess cancer risk is modest, is concentrated in colorectal and thyroid sites, and is systematically larger in referral-based than in population-based designs, which indicates that surveillance intensity contributes to the reported association.

Therapeutically, surgery by experienced operators remains the foundation, with outcome governed chiefly by cavernous sinus invasion. Medical therapy has widened substantially, and oral and self-administered agents have demonstrated efficacy against placebo in well-conducted randomised trials. No agent has been shown superior to another in an adequately powered head-to-head comparison in an unselected population, with the partial exception of pasireotide over octreotide, and the discordant conclusions of recent indirect comparisons should discourage reliance on treatment rankings. Radiosurgery achieves progressive remission over years at the cost of accumulating hypopituitarism.

The broader significance of this synthesis is that the principal remaining opportunities in acromegaly lie less in additional pharmacological potency than in earlier recognition, in prospective validation of the predictive markers already described, in outcome measures that reflect what patients experience, and in extending reliable evidence to populations and health systems that the current literature scarcely represents.

11. Limitations

This work is a critical narrative review and carries the limitations intrinsic to that design. Source identification, selection and weighting involved judgement at every stage, and although the search concepts, information sources, eligibility criteria and appraisal approach are stated explicitly, selection bias and interpretive bias cannot be excluded. A different reviewer applying the same criteria could reasonably assemble a somewhat different evidence base and reach different emphases, particularly in domains where the literature is large and heterogeneous.

Access to subscription-only indexing services was not available, and the search was conducted using openly accessible scholarly databases, registry records and publisher pages. Grey literature, conference abstracts and unpublished data were not sought, and studies not published in English were not included, which may under-represent research from regions where acromegaly is reported in national-language journals. Sources whose bibliographic details could not be verified were excluded, a decision that protects accuracy but may have removed some genuine work with poor metadata.

The evidence base itself constrains what can be concluded. Study designs are highly heterogeneous, ranging from placebo-controlled randomised trials to single-centre retrospective series, and outcome definitions for biochemical control, remission and response have changed over the period covered, so figures reported in different eras are not strictly comparable. Quantitative synthesis was not undertaken, and the numerical estimates reproduced here are those of the original investigators, with their individual limitations. Much of the population-level evidence originates from a small number of Northern European countries with registry infrastructure and universal healthcare, so geographical representation is uneven and generalisability to other health systems is uncertain.

Several specific weaknesses recur across domains. Molecular and histopathological studies depend on surgically resected tissue and therefore systematically exclude medically managed patients. Observational treatment data are susceptible to confounding by indication, and long-term registry analyses are affected by differential attrition. Trials of newer agents have frequently enrolled patients pre-selected for response to somatostatin receptor agonism, which limits extrapolation to resistant disease. Evidence on long-term patient-reported and structural outcomes is scarce, and the field is developing quickly, so conclusions concerning the newest agents are necessarily provisional and may require revision as post-marketing experience accumulates.

Declaration of AI Use

This manuscript was prepared through the intellectual contributions of the author(s) to the study design, data analysis, interpretation of results, and scholarly content. Grammarly and ChatGPT were used solely to assist with grammatical refinement and reference formatting during manuscript revision. The author(s) accept full responsibility for the accuracy, integrity, and final content of the manuscript.

Competing Interests

Authors have declared that no competing interests exist.

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