

Genetic testing in pituitary adenomas: a Pituitary Society International Consensus Statement

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Abstract

Genetic testing of patients with pituitary adenomas enables delivery of genotype-based precision care. Germline testing might identify variants predisposing to formation of pituitary adenomas and, potentially, other neoplasms. These include loss-of-function variants in *AIP*, *MEN1*, *CDKN1B*, *PRKAR1A*, *SDHA*, *SDHB*, *SDHC*, *SDHD* and *MAX*; *GPR101*-containing Xq26.3 microduplications; and postzygotic gain-of-function *GNAS* variants. Somatic testing might help identify and manage aggressive pituitary adenoma types and very rarely encountered pituitary carcinomas. This Pituitary Society Consensus Statement provides evidence-based guidance on the clinical application of these genetic tests, focusing on germline genetic testing, with recommendations regarding genes for inclusion in panel testing, test indications, pre-test counselling, test methodologies, and the interpretation and follow-up of results. As somatic genetic testing is gradually becoming available in clinical practice, recommendations are provided regarding clinical scenarios in which somatic testing might be considered and which genes to test. The consensus group concluded that genetic testing is an increasingly valuable adjunct in the assessment and management of people with pituitary adenomas. When indicated, genetic testing should ideally be undertaken within a multidisciplinary team comprising endocrine, genetic and laboratory expertise to ensure high-quality testing and safe and effective result interpretation and follow-up.

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Introduction

Pituitary adenomas arise from hormone-producing anterior pituitary cells and have traditionally been considered monoclonal neoplasms; however, emerging molecular studies suggest high levels of cellular and genomic complexity^{1,2}. These adenomas occur with an estimated prevalence of 10%, yet only around 1 in 1,000 people in the general population have clinically significant disease¹. Of those adenomas that become clinically relevant, <50% require surgery and <20% of resected adenomas are locally invasive; furthermore, malignancy of these lesions is extraordinarily rare, with a prevalence of ~1 per million population¹. As most pituitary adenomas are benign lesions with indolent behaviour, the Pituitary Society has retained the term ‘adenoma’ rather than the pathological designation of ‘PitNET’^{3,4}.

Most adult-onset pituitary adenomas are sporadic, sometimes driven by signalling disruptions and chromosomal instability, or by somatic variants that promote cell growth or hormone production^{5,6}. Nevertheless, approximately 5% of pituitary adenomas are associated with germline variants in well-characterized genes that confer inherited susceptibility⁷; this prevalence might change as broad next-generation sequencing (NGS) approaches are increasingly applied. Recognition of these genetic forms has important implications for diagnosis, management, surveillance and family counselling.

Germline pathogenic variants are enriched in paediatric and young adult (aged 18–30 years) patients, who typically present with early-onset somatotroph or lactotroph macroadenomas, some of which might be rapidly growing^{8–11}. The best-established germline causes of pituitary adenoma include variants in *AIP* (encoding aryl hydrocarbon receptor interacting protein) and *MEN1*, which produce familial isolated pituitary adenoma (FIPA) and multiple endocrine neoplasia type 1 (MEN1) syndrome, respectively, and account for most kindreds with familial pituitary adenomas^{12–14}. Other rare hereditary contributors include *CDKN1B* (MEN4 syndrome)¹⁵, *PRKARIA* (Carney complex)^{16,17}, the *SDHx* genes (phaeochromocytoma, paraganglioma and pituitary adenomas), *MAX* (MEN5 syndrome)^{18–20} and *GPR101* (X-linked acrogigantism (X-LAG))²¹.

Elucidation of somatic variants has further expanded the genomic landscape of sporadic pituitary adenomas. Activating *GNAS* variants, occurring either as postzygotic mosaic alterations causing McCune–Albright syndrome or as tumour-restricted somatic variants, lead to constitutive cAMP signalling in a subset of somatotroph adenomas²². *USP8* variants enhance epidermal growth factor receptor expression in some corticotroph adenomas^{23,24}. *SF3B1* variants have been linked to prolactinomas with aggressive features²⁵. Together with other, less frequent somatic variants, chromosomal instability and epigenetic deregulation, these alterations might influence the phenotype, endocrine activity and therapeutic responses^{1,5,6}.

Genetic testing is increasingly incorporated into the clinical evaluation of people with pituitary adenomas. Germline testing might identify inherited tumour predisposition syndromes and guide diagnosis, surveillance, family counselling and management. Somatic testing of adenoma tissue is emerging as an adjunctive assessment in selected clinical scenarios, particularly for aggressive or recurrent pituitary adenomas and carcinomas. Advances in NGS now allow efficient and accessible simultaneous detection of germline and somatic variants across multiple genes, enabling comprehensive genomic profiling during diagnostic workflows.

Such testing might lead to identification of hereditary syndromes, inform risk assessment and guide multidisciplinary management involving endocrinology, neurosurgery and clinical genetics. Yet, testing practices are inconsistent across health systems, in part reflecting

differences in cost, infrastructure availability and clinical expertise. This Pituitary Society Consensus Statement provides practical guidance for the diagnostic use of genetic testing across diverse clinical scenarios, emphasizing diagnostic application rather than long-term syndrome management. Complementing guidelines from the past few years on MEN1 syndrome¹⁴ and paediatric^{26,27} and aggressive²⁸ pituitary tumours, this Consensus Statement establishes an integrated, evidence-based framework that translates complex biological insights into clinical utility.

First, we recommend which germline pituitary adenoma predisposition genes should be tested (R1) and provide evidence supporting indications for germline genetic testing (R2–R5) and components of pre-test counselling (R6). Next, we recommend methodologies for genetic testing (R7–R10) and strategies for post-test follow-up (R11–R16). Finally, we recommend indications and strategies for somatic genetic testing of adenoma tissue when available (R17–R20). Definitions of key terms used in these recommendations are provided in Box 1.

Using an evidence-based, clinically oriented framework for germline and somatic genetic testing in pituitary adenomas, these recommendations aim to harmonize optimal clinical practice worldwide and ensure that the genomic advances underlying pituitary adenoma pathogenesis translate to maximal benefits for patients and their families.

Methods

The Pituitary Society International Pituitary Genetics (PitGen) Consensus Group was formed in December 2024. The Consensus Chair (S.M.C.D.), Basic Science Lead (C.L.A.), Clinical Lead (S.M.) and Steering Committee members (A.F.D., M.F., M.G., F.G., P.K., P.M., M.R., F.R.-Z., R.S., Y.T. and C.T.) were selected on the basis of their expertise as evidenced by publication records, active research in the field and clinical and/or laboratory experience.

The Consensus leaders (S.M.C.D., C.L.A., S.M.) identified topics to be addressed. Steering Committee members were assigned to develop evidence-based topic summaries through critical review of English-language, PubMed-indexed papers published before June 2025 using search terms including “pituitary adenoma” and “pituitary neuroendocrine tumour” with terms associated with the discussion topics, including “genes”, “genetics”, “genetic testing”, “next-generation sequencing”, “gene panel”, “Sanger sequencing”, “microarray”, “multiplex ligation-dependent probe amplification”, “variants of uncertain significance” and “somatic testing”. During the first virtual Steering Committee meeting in June 2025, proposed recommendations and fully referenced written summaries were presented and discussed. In the second virtual Steering Committee meeting in July 2025, recommendations were refined until complete consensus was achieved for each respective draft recommendation.

Pituitary Society Consensus Statements have historically used the GRADE framework of classifying recommendations as weak (based on very-low-quality or low-quality evidence) or strong (medium-quality or high-quality evidence)^{29–31}. However, in most centres, genetic testing of adults with pituitary adenomas has only entered clinical practice in the past 5 years, and most studies are only classifiable as low-quality or very-low-quality evidence. Therefore, in accordance with the Pituitary Society Consensus Statement on pituitary incidentalomas³², we distinguished between stronger ‘recommended’ and weaker ‘suggested’ recommendations based on the quality as well as consistency of evidence, the degree of concordance in expert opinion and the expected clinical effect. The term ‘recommended’ was used where there is objective and

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Box 1 | Definitions of key terms

Array comparative genomic hybridization: A microarray-based technique that compares patient and reference DNA to identify genomic copy-number gains and losses, without detecting sequence-level variants (Supplementary Table 1).

Benign variant: A genetic variant for which sufficient evidence exists to conclude that it is not disease-causing (American College of Medical Genetics and Genomics (ACMG) Class 1).

Cascade testing: Systematic genetic testing of at-risk relatives of an individual with a confirmed pathogenic or likely pathogenic variant to identify relatives heterozygous for the variant and guide clinical surveillance or management.

Chromosome microarray: A genome-wide assay that detects copy-number gains and losses across the genome at higher resolution than conventional karyotyping (Supplementary Table 1).

Copy-number variant: A structural genomic alteration involving deletion or duplication of a DNA segment, resulting in deviation from the normal diploid copy number and potentially affecting gene dosage.

Droplet digital PCR: A highly sensitive quantitative PCR method that partitions DNA into thousands of droplets, enabling precise detection and quantification of low-level variants, including mosaic variants (Supplementary Table 1).

Familial isolated pituitary adenoma: The occurrence of pituitary adenomas in two or more related individuals without evidence of a broader syndromic tumour predisposition condition. A causative genetic variant might or might not be identifiable.

Germline genetic testing: Analysis of DNA derived from germline cells (typically blood or saliva) to identify heritable genetic variants present in all cells of the body and transmissible to offspring.

Likely benign variant: A genetic variant for which available evidence supports a non-disease-causing role but it is insufficient for definitive benign classification (ACMG Class 2).

Likely pathogenic variant: A genetic variant with strong, but not definitive, evidence supporting a causal role in disease, with an estimated probability of pathogenicity greater than 90% (ACMG Class 4). Likely pathogenic variants are generally considered causative and used in patient and family management.

McCune–Albright syndrome: A rare genetic condition caused by postzygotic activating variants in *GNAS*, leading to somatic

mosaicism. It is classically defined by the triad of fibrous dysplasia of bone, café-au-lait skin pigmentation and endocrine hyperfunction, including growth hormone excess.

Multiplex ligation-dependent probe amplification: A targeted molecular technique used to detect copy-number changes in specific genomic regions by comparing relative probe amplification signals. In current practice, multiplex ligation-dependent probe amplification is commonly used as a complementary technique after sequencing-based testing to identify exon-level or whole-gene deletions and duplications (Supplementary Table 1).

Next-generation sequencing: High-throughput DNA sequencing technologies that enable parallel sequencing of millions of DNA fragments, allowing comprehensive analysis of multiple genes or entire genomes with high sensitivity (Supplementary Table 1).

Pathogenic variant: A genetic variant for which there is sufficient evidence to establish a causal role in disease, according to accepted variant classification frameworks (ACMG Class 5).

Single-nucleotide polymorphism array: A type of chromosome microarray that assesses genome-wide copy-number variation and allelic composition, enabling detection of deletions, duplications and regions of homozygosity (Supplementary Table 1).

Somatic genetic testing: Analysis of DNA from tumour tissue to identify acquired (non-inherited) genetic variants that have arisen in somatic cells and are present only in the tumour or a subset of tissues.

Somatic mosaicism: The presence of two or more genetically distinct cell populations within an individual arising from postzygotic variants, with the variant present in only a subset of cells or tissues.

Variant of uncertain significance: A genetic variant for which the available evidence is insufficient or conflicting, such that it cannot be reliably classified as either pathogenic or benign (ACMG Class 3). Variants of uncertain significance should not be used to guide clinical management but might be reclassified over time as additional evidence becomes available.

X-linked acrogigantism: A rare genetic condition caused by germline or somatic duplication of the *GPR101* gene on chromosome Xq26.3, characterized by early-onset growth hormone excess, typically presenting in infancy or early childhood with pituitary hyperplasia or adenoma.

consistent evidence that is concordant with expert opinion, whereas ‘suggested’ was used where there are conflicting results in the literature, or insufficient evidence for derived clinical benefit from the action. Limitations pertaining to ‘suggested’ recommendations are outlined in the rationale for each recommendation.

In October 2025, draft recommendations were disseminated to the full Consensus Group, comprising 24 experts from 14 countries, all members of the Pituitary Society and representing a broad range of healthcare systems and genetic testing accessibility. During the virtual Consensus Group meeting in November 2025, recommendations and

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supporting evidence were reviewed. Consensus Group members voted on each recommendation. Although only a majority vote ($\geq 12/24$) was required for consensus, all recommendations (either recommended or suggested) were approved with 100% consensus.

After the Consensus Group meeting, approved consensus recommendations and discussion viewpoints were collated. Relevant reports published after the initial cut-off date of June 2025 were identified in subsequent literature reviews. The final manuscript was compiled by the Consensus leaders in collaboration with the Steering Committee, with review and final approval by all Consensus Group members.

Germline pituitary adenoma predisposition genes

- **R1.** We recommend that germline gene testing, when clinically indicated, be undertaken as a gene panel test comprising *AIP*, *MEN1*, *CDKN1B* and *PRKARIA*. We suggest also including *SDHA*, *SDHB*, *SDHC*, *SDHD* and *MAX*, if available.

Germline variants in genes known to predispose to pituitary adenoma occur in a very small minority of patients³³. A growing list of candidate genes has been reported, including those associated with non-pituitary neuroendocrine tumours. Established predisposition genes commonly associated with other solid tumours have rarely been implicated in pituitary adenomas³³.

Germline panel testing of patients with pituitary adenomas should include only established pituitary adenoma predisposition genes to maximize clinical utility and minimize incidental or uncertain findings. Positive results obtained on such panel testing mostly reflect variants in *AIP* and *MEN1* (refs. 7,34). However, the possibility of variants in other established pituitary adenoma predisposition genes and the availability of concurrent gene testing through NGS panel testing support the use of a comprehensive gene list comprising *AIP*, *MEN1*, *CDKN1B* and *PRKARIA*. Ideally, *SDHA*, *SDHB*, *SDHC*, *SDHD* and *MAX* (which have been implicated as pituitary adenoma predisposition genes in the past 5–10 years) should also be included. This gene list reflects the most recent literature on gene–disease relationships for pituitary adenomas as outlined in the following sections, and is a notable difference from the recommendation restricted to *MEN1* and *AIP* testing reported in the 2023 Pituitary Society prolactinoma consensus statement²⁹. In addition to the advantage of involving a more recent review of the rapidly advancing genetics literature than in previous recommendations, the currently presented gene panel is intended for use in eligible patients regardless of pituitary adenoma subtype. Of note, *GPR101* and *GNAS* pertain to distinct syndromic phenotypes and are interrogated by non-panel-based testing addressed separately in recommendations R4 and R5, respectively.

Established pituitary adenoma predisposition genes

FIPA, representing about 2% of pituitary adenomas, is defined as kindreds in which at least two related members have pituitary adenomas³⁵. The most common cause of FIPA is germline variants in the *AIP* gene, which are present in ~15–25% of kindreds^{10,11,13,36}. *AIP* is a tumour suppressor gene that regulates cell proliferation, protein kinase A (PKA) activity and cAMP signalling, and is associated preferentially with somatotrophinomas, mixed growth hormone-secreting and prolactin-secreting adenomas, and prolactinomas^{11,13}. *AIP* pathogenic variants are most often associated with young-onset growth hormone-secreting macroadenomas (aged ≤ 30 years) and are the most frequent known genetic cause of pituitary gigantism, accounting for 30% of cases of pituitary gigantism^{9,10}.

Some MEN syndromes predispose to pituitary adenomas along with other neuroendocrine and non-endocrine tumours. For example, up

to 40% of patients with MEN1 syndrome develop pituitary adenomas¹⁴. *MEN1* encodes menin, a multifunctional tumour suppressor that regulates the cell cycle, genome stability and chromatin remodelling³⁷. Germline *CDKN1B* pathogenic variants are detected in 0.08–3.00% of patients with MEN1-like features but without alterations in *MEN1*; this combination defines MEN4 syndrome^{38,39}. *CDKN1B* encodes p27, a cyclin-dependent kinase inhibitor that regulates cell-cycle progression.

Pituitary adenomas and hyperplasia are a key feature in Carney complex, which is characterized by myxomas, spotty skin pigmentation and broad endocrine overactivity^{40,41}. Germline pathogenic variants in *PRKARIA* are identifiable in 40–80% of people with Carney complex and lead to inactivation of the regulatory subunit 1A of PKA, which results in its constitutive activation and increased cAMP signalling^{16,17,40}.

Pathogenic variants in the succinate dehydrogenase subunit (*SDHx*) genes are well-recognized causes of pheochromocytoma and paraganglioma⁴². Rarely, pituitary adenomas develop in individuals and kindreds with germline *SDHx* variants, often together with pheochromocytoma and paraganglioma as part of the ‘pheochromocytoma, paraganglioma and pituitary adenomas’ association^{20,43}. Current literature implicates *SDHA*, *SDHB*, *SDHC* and *SDHD* in pituitary tumorigenesis. By contrast, despite its established role in pheochromocytoma and paraganglioma, *SDHAF2* pathogenic variants have not been convincingly identified in patients with pituitary adenomas⁴⁴. Pituitary adenomas might also occur in patients with pheochromocytomas and other tumours due to pathogenic variants in the *MAX* gene, which is defined as MEN5 syndrome^{18,45}.

X-LAG is a form of gigantism with onset in early childhood that usually presents sporadically or, rarely, as FIPA^{21,46}. X-LAG is due to *GPR101* dysregulation caused by chromosome Xq26.3 duplications that disrupt an element of chromatin architecture termed a topologically associating domain; inclusion of the *VGLL1* region in the newly formed topologically associating domain seems to be essential to produce *GPR101* misexpression^{47,48}. X-LAG accounts for 10% of patients with pituitary gigantism, with median ages at onset and diagnosis of 18 months and 4 years, respectively^{49,50}. Penetrance is 100%⁴⁹.

McCune–Albright syndrome consists of polyostotic fibrous dysplasia, café-au-lait macules and endocrinopathies. Up to 20% of patients exhibit growth hormone and prolactin excess due to pituitary hyperplasia or adenomas^{51,52}. This syndrome is not inherited but is caused by postzygotic gain-of-function variants in the *GNAS* gene (at codons Arg201 and Gln227) that lead to somatic mosaicism and, ultimately, increased GTPase activity and cAMP signalling in affected tissues^{53,54}.

Emerging pituitary adenoma risk genes

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer, is an autosomal dominant condition caused by heterozygous germline pathogenic variants in mismatch repair genes, namely *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM*. These variants generally result in colorectal, gastrointestinal and uterine tumours, and pituitary adenomas have rarely been reported in patients with Lynch syndrome^{55–59}.

Heterozygous germline *CHEK2* pathogenic variants are fairly common in the general population and lead to a moderate predisposition to breast cancer, with weaker associations with other neoplasms. A report published in 2024 suggested enrichment of *CHEK2* pathogenic variants in people with pituitary adenomas compared with the general population, but the mechanistic basis for this association is unclear and larger datasets are required⁶⁰. Pituitary adenomas have been described in association with variants in other genes related to common solid neoplasia^{61–63}; their causative associations remain under investigation.

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PRKACB encodes a catalytic subunit of PKA; activating variants in this gene have been implicated in *PRKARIA*-negative Carney complex⁶⁴. For example, a *PRKACB*-containing germline 1p31.1 triplication has been implicated in *PRKARIA*-negative Carney complex with acromegaly⁶⁴.

Other genes with emerging evidence favouring germline association with pituitary adenoma predisposition include *CABLES1*, *PAM*, *PRLR*, *FGFR1*, *AHR*, *USP8* and *KDM1A*, as summarized elsewhere⁶⁵. Although such genes have been tested in the research setting, the variants detected are frequently benign or of uncertain significance and are therefore inappropriate for clinical testing⁶⁶.

Very rarely, pituitary adenomas are reported in association with genetic syndromes such as neurofibromatosis type 1, von Hippel–Lindau syndrome, tuberous sclerosis and MEN2 syndrome^{67,68}. The role of the corresponding syndrome genes (*NF1*, *VHL*, *TSC1*, *TSC2* and *RET*) in pituitary tumorigenesis remains unconfirmed.

Germline genetic testing indications

- **R2.** We recommend germline genetic testing in people with pituitary adenomas and any of the following criteria: somatotrophinoma or prolactinoma with onset at or before age 18 years; or history of pituitary adenoma in blood relatives; or personal history or a blood relative history of non-pituitary tumours associated with an established pituitary adenoma predisposition gene.
- **R3.** We suggest germline genetic testing in people with pituitary adenomas other than somatotrophinoma or prolactinoma and onset at or before age 18 years. We also suggest testing in people with somatotrophinoma or macroprolactinoma and onset between ages 19 and 30 years, inclusive, depending on the clinical context.

Traditionally, germline genetic testing for tumour predisposition syndromes is prompted when the probability of pathogenic variant detection is 10%⁶⁹; however, this figure might be different depending on the availability of reference datasets, the clinical actionability of finding a variant in a given gene and resource allowances. In patients with pituitary adenomas, positive gene panel results most frequently pertain to *AIP*, followed by *MEN1*, with variants only rarely encountered in other pituitary adenoma predisposition genes^{7,34}. Thus, apart from individuals and families with a specific multiple neoplasia phenotype who might benefit considerably from engagement in variant-guided tumour surveillance (Fig. 1), the indications for genetic testing in people with pituitary adenomas are focused on the probability of identifying variants in *AIP* or *MEN1*.

Regarding *AIP* testing, a cohort study of 1,405 patients with pituitary adenomas demonstrated a ≥10% probability of pathogenic or likely pathogenic *AIP* variant detection in the following proband groups: childhood-onset somatotrophinoma with positive family history of pituitary adenoma; childhood-onset non-somatotroph pituitary macroadenoma with positive family history; childhood-onset sporadic macroadenoma; somatotrophinoma with onset at 19–30 years and positive family history; and macrosomatotrophinoma with onset at ≥31 years and positive family history⁷⁰. In another study, *AIP* variants were detected in 12% of patients with sporadic macroprolactinomas diagnosed before 30 years⁷¹. *AIP* variants are rarely found outside of these settings^{70,71}. Regarding *MEN1*, pituitary adenomas are the first manifestation of MEN1 syndrome in up to 20% of people^{72,73}, and prolactinomas are the most common pituitary adenoma in people with *MEN1* pathogenic variants^{72,74}. Causative *MEN1* variants are found in 70–90% of individuals and families with typical features of MEN1 (ref. 75).

In people with a clinical diagnosis of Carney complex, *PRKARIA* variants are identified in 37% of patients with sporadic disease and in 60% of those with familial disease¹⁶.

Our recommended genetic testing indications align with but do not strictly follow these data for several reasons. We recommend genetic testing regardless of the size of the adenoma in childhood-onset disease. These adenomas, including microprolactinomas, are rare⁷⁶, and therefore genetic testing across this group should not be overly burdensome on resources. We note that this recommendation deviates from the 2023 Pituitary Society prolactinoma consensus statement²⁹, which recommends genetic testing in children with macroprolactinomas and excludes those with microprolactinomas. However, a subsequent meta-analysis demonstrated that *MEN1*-related and non-*MEN1*-related prolactinomas might behave similarly, and that *MEN1*-related prolactinomas might not necessarily progress to macroadenoma dimensions⁷⁷. Again, because of the rarity of childhood-onset pituitary adenomas, we suggest genetic testing in non-somatotrophinoma and non-prolactinoma subtypes despite the reduced probability of variant detection based on *AIP* datasets^{70,71}. Interestingly, there is an emerging association between *CDKN1B* variants and paediatric corticotrophinomas⁷⁸.

Furthermore, in patients with onset of disease in childhood or young adulthood (≤30 years), we do not mandate a positive family history given the incomplete penetrance of most pituitary adenoma predisposition genes and the possibility of a de novo rather than inherited variant⁶⁸. The likelihood of a pathogenic variant being de novo varies by gene, being rare in *AIP*⁸ versus approximately 30% in *PRKARIA*⁷⁹. In the young-adulthood-onset group, we suggest genetic testing in people with somatotrophinomas regardless of tumour diameter whereas we suggest testing only in macroprolactinomas because of the fairly high frequency of sporadic prolactinomas in this age group, particularly in women²⁹.

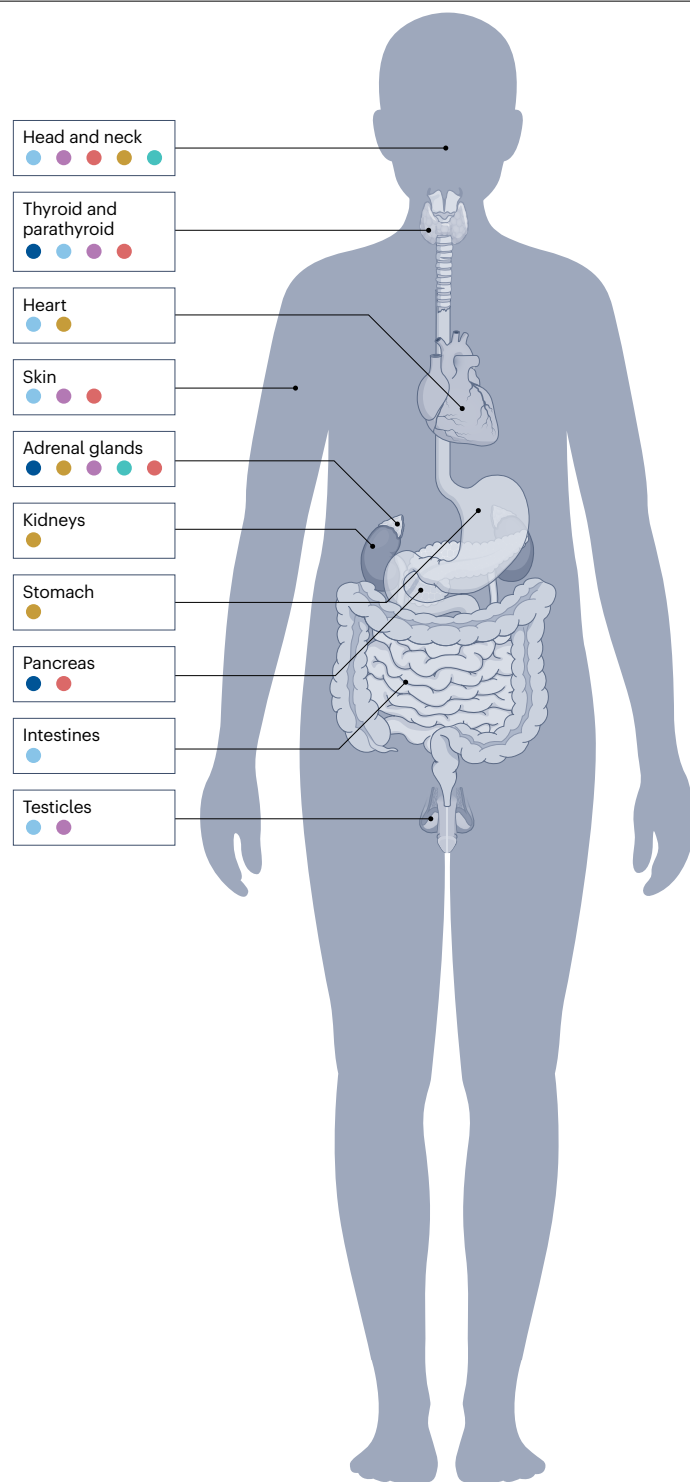
When considering family history indications, we do not specify the degree of relatedness of affected blood relatives because of the possibilities of incomplete penetrance and missed disease due to variable expressivity. We also do not specify which non-pituitary tumour types should be considered relevant given the various combinations of personal and family histories that might relate to the pituitary adenoma predisposition genes (see Fig. 1 for gene-specific manifestations).

Additional limitations in developing test indications based on published variant detection rates include the heterogeneity in gene lists studied, variant reporting and selection biases beyond stated inclusion criteria. With widespread gene panel testing and awareness of the range of established pituitary adenoma predisposition genes, future studies will hopefully elucidate precise variant detection rates across all established pituitary adenoma predisposition genes according to each consensus test indication.

- **R4.** We recommend Xq26.3 duplication testing for X-LAG in people with pituitary adenoma or hyperplasia with growth hormone excess and disease onset before age 5 years.

In the seminal study describing X-LAG, Xq26.3 duplications were observed in 13/43 (30%) of patients with gigantism (that is, childhood-onset growth hormone excess), all of whom had demonstrable rapid growth by age 1 year. By contrast, none of the patients with gigantism who tested negative for Xq26.3 duplications presented before age 5 years²¹. In subsequent reference laboratory testing, Xq26.3 duplications have been detected in approximately 80% of people with somatotrophinomas diagnosed by age 5 years (A.F.D., unpublished work).

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● **MEN1 (MEN1)**

- Non-pituitary manifestations:
 - Primary hyperparathyroidism
 - Neuroendocrine tumours^a
 - Angiofibroma
 - Collagenoma
 - Lipoma
 - Adrenal adenoma
 - Meningioma
- Surveillance: Brandi et al., 2025 (ref. ¹⁴)

● **CDKN1B (MEN4)**

- Non-pituitary manifestations:
 - Primary hyperparathyroidism
 - Adrenal lesions
 - Neuroendocrine tumours
- Surveillance: eviQ, 2025 (ref. ¹⁵⁶)

● **PRKAR1A (Carney complex)**

- Non-pituitary manifestations:
 - Spotty skin pigmentation and mucosal pigmentation
 - Myxoma
 - Schwannoma
 - Primary pigmented nodular adreno-cortical disease
 - Large-cell calcifying Sertoli cell tumours
 - Benign and malignant thyroid lesions
 - Other endocrine and non-endocrine neoplasms
- Surveillance: Stratakis, 2023 (ref. ¹⁵⁷)

● **SDHA, SDHB, SDHC and SDHD^b**

- Non-pituitary manifestations:
 - Paraganglioma
 - Pheochromocytoma
 - Renal cell carcinoma
 - Gastrointestinal stromal tumour
- Surveillance: Amar et al., 2021 (ref. ¹⁵⁵)

● **MAX**

- Non-pituitary manifestations:
 - Pheochromocytoma
 - Paraganglioma
- Surveillance: Casey et al., 2024 (ref. ¹⁵³)^c

● **GNAS (McCune–Albright syndrome)**

- Non-pituitary manifestations:
 - Polyostotic fibrous dysplasia
 - Café-au-lait skin macules
 - Peripheral precocious puberty
 - Leydig and/or Sertoli cell hyperplasia
 - Hyperthyroidism
 - Neonatal adrenal hypercortisolism
- Surveillance: Szymczuk et al., 2024 (ref. ¹¹⁸)

AIP (FIPA)

- Non-pituitary manifestations: none
- Surveillance: Korbonits et al., 2025 (ref. ⁸⁸)

GPR101 (X-LAG)

- Non-pituitary manifestations: none
- Surveillance: Daly et al., 2024 (ref. ⁴⁹)

Affected individuals show marked growth hormone excess, pituitary adenomas that are often a mixed somatotroph-lactotroph subtype and pituitary hyperplasia⁴⁹. Early genetic testing is recommended to enable clinical intervention prior to pubertal onset.

- **RS.** We suggest *GNAS* testing in people with pituitary adenoma or hyperplasia with growth hormone excess and clinical features

of McCune–Albright syndrome to confirm the diagnosis of McCune–Albright syndrome and distinguish the phenotype from other genetic syndromes.

In people with McCune–Albright syndrome, there is a variable rate of *GNAS* variant detection depending on the test approach used

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Fig. 1 | Non-pituitary manifestations associated with pituitary adenoma predisposition genes and resources to guide tumour surveillance. Schematic diagram depicting non-exhaustive lists and physical locations of key non-pituitary manifestations⁶⁸ in patients with pathogenic variants in *MEN1* (red), *CDKN1B* (dark blue), *PRKARIA* (light blue), *SDHx* (yellow), *MAX* (green) and *GNAS* (purple); there are no non-pituitary manifestations of *AIP* and *GPR101*. Surveillance recommendations pertaining to *MAX*⁴³, *SDHx*³⁵ and *MEN1* (ref. 14) are from international consensus groups; recommendations pertaining to *CDKN1B*¹⁵⁶, *GNAS*¹¹⁸, *PRKARIA*¹⁵⁷, *AIP*⁸⁸ and *GPR101* (ref. 49) are suggestions from individual experts. FIPA, familial isolated pituitary adenoma; MEN1, multiple

endocrine neoplasia type 1. ^aParticularly duodenopancreatic, thymic and bronchopulmonary neuroendocrine tumours¹⁴. ^bOnly applies to paternally inherited *SDHD* variants. Apart from isolated case reports of tumours associated with maternally inherited variants, *SDHD* penetrance is limited to paternally inherited variants. There is no consensus supporting tumour surveillance for maternally inherited *SDHD* variants. ^cOnly addresses pheochromocytoma and paraganglioma surveillance. There are currently no guidelines regarding pituitary adenoma surveillance in individuals with germline pathogenic *MAX* variants; we suggest pituitary adenoma surveillance concurrent with pheochromocytoma and paraganglioma surveillance.

(see ‘Genetic testing methodology’ section)⁸⁰. The typical pituitary manifestation of this multisystem condition is growth hormone excess, which occurs in approximately 20% of people with McCune–Albright syndrome⁵⁴. The mean age of diagnosis of growth hormone excess is 24 years⁸¹, and the diagnosis might be missed for several years; hence, an age threshold has not been applied to this test indication. Although McCune–Albright syndrome is usually recognized clinically, molecular confirmation might be valuable in select patients, such as when only limited features (such as somatotrophinoma and monostotic fibrous dysplasia) are present, or when the phenotypic presentation could be compatible with Carney complex, which can also manifest with growth hormone excess, thyroid nodules and café-au-lait pigmentation⁸². However, the detection of *GNAS* variants is technically challenging, and might not be available at all laboratories. Given the reduced utility and increased complexity of *GNAS* testing, this test indication is suggested rather than recommended.

Pre-test counselling

- **R6.** We recommend that pre-test counselling be conducted by clinicians with the expertise required to discuss the rationale of germline genetic testing, navigate test logistics, interpret results and discuss potential implications for the proband and family, including the possibility of unexpected or uncertain findings.

Appropriate pre-test counselling avoids unnecessary genetic testing and/or misinterpretation of test results that might lead to inappropriate management of patient care^{83,84}. Responsible clinicians should carefully consider the clinical relevance of genetic testing for both patients and their families, as well as the availability of accurate and cost-effective testing⁸⁵.

Clinicians involved in pre-test counselling should be proficient in the identification of clinical characteristics and personal and family history suggestive of a high likelihood of positive genetic test results^{83,86–88} (Fig. 2). They should also be able to discuss the clinical utility of testing, guide testing strategy in collaboration with an accredited testing laboratory and inform the patient about potential implications of test results⁸⁹.

Pre-test counselling might be undertaken by a clinician with combined endocrine and clinical genetics expertise, or it might involve a multidisciplinary team including an endocrinologist, clinical geneticist and/or genetic counsellor depending on the healthcare system and institution. The need for age-appropriate expertise should be considered in relation to the patient’s current age and age at onset, recognizing that some adults will have had childhood diagnoses^{83,86,90}. Where possible, patients should be treated in the setting of a multidisciplinary team or a pituitary tumour centre of excellence. In some regions, inadequate funding and/or infrastructure represent critical barriers

to genetic testing but the opportunity for genetic testing should be revisited in eligible patients as local access to testing and clinicians qualified to provide pre-test counselling might improve over time⁹¹.

Potential benefits and drawbacks of testing should be comprehensively discussed and patient concerns addressed before obtaining informed consent⁸⁹. It is also important to inform the patient about the option of not testing⁸³. The clinical use of testing for family members and any future offspring is often a major determinant in the decision-making process⁸⁹. Although patients typically agree to share information with family members, counselling might be helpful to facilitate discussion about testing with family members and to resolve conflicts if they arise⁹².

Noting that genetic assessment should be considered in all children with a pituitary adenoma (see R2–R4)²⁶, parental consent should be obtained for minors according to country-specific regulations. Conflicts might arise if parents refuse to provide consent, or if they have conflicting opinions⁸⁷; policy statements have been published addressing these issues⁹³.

Clinicians should also anticipate the possibility of finding variants of uncertain significance (VUS) and incidental findings unrelated to the target gene. With the widespread use of NGS techniques, the likelihood of finding VUS has dramatically increased. Patients should be advised of the possibility of finding VUS prior to testing given the interpretive challenges and anxiety these findings might subsequently cause⁹⁴. Patients should also be advised of the possibility of incidental findings that might arise due to contiguous gene deletions involving a pituitary adenoma predisposition gene in addition to other disease-associated genes. Incidental findings might also arise when genetic testing is being performed in a research setting, which often involves whole-exome sequencing or whole-genome sequencing. If research-based whole-exome sequencing or whole-genome sequencing testing is pursued, patients should ideally be provided with the option of not being informed of incidental findings⁹⁵.

Pre-test counselling should address the potential implications of the results on subsequent pituitary adenoma therapeutic guidance, surveillance for other tumours, cascade testing of at-risk family members and reproductive choices. The implications of genetic testing on therapeutic guidance and surveillance are gene-specific. For example, *AIP*-mutant somatotrophinomas might be less responsive than sporadic adenomas to treatment with somatostatin receptor ligands that are specific to somatostatin receptor 2 (ref. 8). In *MEN1* syndrome, probands and relatives with a pathogenic variant in *MEN1* should undergo *MEN1*-specific tumour surveillance to enable early detection and management of non-pituitary neoplasia¹⁴.

Cascade testing and family planning are generally addressed in the post-test setting. However, preliminary discussions with patients prior to testing can inform the importance of testing and guide the method

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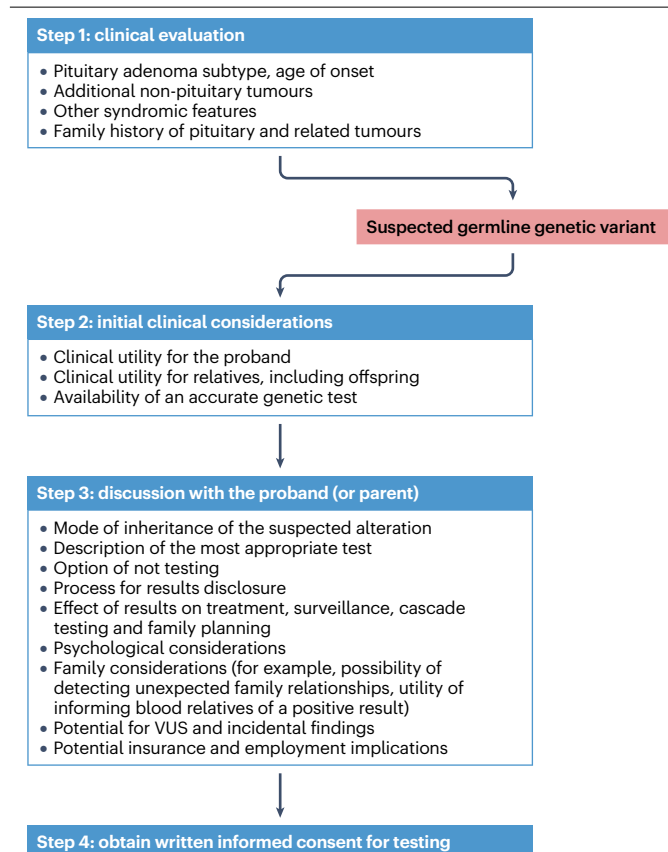


Fig. 2 | Elements of pre-test counselling. Schematic diagram describing the four steps of pre-test counselling and the recommended level of proficiency of the clinician in each step. Clinicians involved in pre-test counselling should be able to identify both the clinical characteristics and the personal and family history suggestive of a high likelihood of positive genetic test results^{83,86–88}. They should be able to discuss the clinical utility of the test, guide the testing strategy specific to the suspected condition, propose the most appropriate test methodology and inform the patient about potential result implications⁸⁹. VUS, variants of uncertain significance.

of results notification. The burden that test results can place on family relationships, and the possibility of revealing unexpected family relationships through genetic testing, should be carefully addressed. Informing patients about the reproductive implications of positive test results offers an opportunity to introduce the reproductive options available to families with heritable pathogenic variants.

Finally, pre-test counselling should address the potential for discrimination triggered by genetic test results. Many countries have legislation aimed at protecting individuals from discrimination^{96,97}. For instance, in the USA, the Genetic Information Nondiscrimination Act of 2008 protects most people against health insurance and employment discrimination based on genetic information⁸⁹.

Genetic testing methodology

- **R7.** We recommend performing germline genetic testing in an accredited laboratory and reviewing complex results with a multidisciplinary team with expertise in clinical genetics, genetic pathology and endocrinology.

Accreditation and quality requirements are crucial in genetic testing. Tests are often performed only once, with results providing lifelong guidance for the individual tested and their family members. Compliance with the International Organization for Standardization 15189 is accepted as the optimal approach to ensuring quality in genetic testing. Accredited laboratories should provide results accurately, efficiently and promptly⁹⁸, and there should be access to a multidisciplinary team with expertise in clinical genetics, molecular genetics and endocrinology to interpret complex results^{99,100}. The best available resources should be accessed, which might necessitate sending samples to external accredited laboratories.

- **R8.** We recommend classifying germline gene variants according to the five-category system of the American College of Medical Genetics and Genomics (ACMG): pathogenic variant (class 5), likely pathogenic variant (class 4), VUS (class 3), likely benign variant (class 2) or benign variant (class 1). Pathogenic and likely pathogenic variants should be regarded as positive results and diagnostic of the genetic condition. VUS do not establish or exclude the diagnosis.

The ACMG variant classification system⁹⁹ is a point-based system that ascribes the likelihood of pathogenicity for a given variant and has been widely adopted for hereditary endocrine tumour syndromes. Identification by an accredited laboratory of a heterozygous germline pathogenic or likely pathogenic variant in genes associated with pituitary adenomas establishes a heritable predisposition to pituitary adenomas, either occurring in isolation (for example, *AIP*) or as part of a multiple tumour syndrome (for example, *MEN1* or *SDHx*)^{87,100,101}. By contrast, VUS, particularly missense variants or in-frame deletions for which there is no well-established clinical association of pathogenicity or functional studies supporting a damaging effect on the protein, are more challenging to interpret^{102,103}. Databases describing genetic variations in the general population (such as gnomAD) and in disease (for example, ClinVar and OMIM), as well as computational tools used for in silico pathogenicity predictions (for example, REVEL and SpliceAI), can assist with variant classification^{104–106}. Pathogenicity points are also counted in the ACMG system for gene-specific phenotypes and compatible family history^{107,108}.

- **R9.** We recommend undertaking germline genetic testing for small nucleotide changes and copy-number variants using NGS multigene panels; however, a single-gene approach using Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) might be appropriate for specific phenotypes corresponding to a single gene or if NGS is not readily available.

Multiple genetic testing approaches might identify germline variants underlying pituitary adenomas (Supplementary Table 1). Historically, genetic testing consisted of single-nucleotide variant detection using Sanger sequencing. However, this approach requires gene prioritization based on phenotype and is inefficient if multiple genes require evaluation. Many laboratories have now transitioned to NGS panels given the improved cost–benefit value^{87,100,101}. Such NGS panels, with appropriate bioinformatic pipelines, can detect both single-nucleotide variants and copy-number variants^{7,109,110}.

Single-gene Sanger sequencing and MLPA might be appropriate for people with gene-specific phenotypes such as Carney complex (implicating *PRKARIA*) or isolated young-onset somatotrophinoma (most strongly associated with *AIP* variants). Targeted sequencing is also appropriate for cascade testing of family members in kindreds with

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an identified pathogenic or likely pathogenic variant, although NGS is increasingly used for cascade testing as well^{87,111}. In addition, Sanger sequencing can be used as a complementary test to NGS where the validity of the result is in question, such as with insufficient read-depth coverage at a given location, or to confirm *SDHA* variants that might be misidentified due to the presence of highly homologous *SDHA* pseudogenes¹¹². MLPA can be used as a complementary test to NGS panel testing where there is a high index of suspicion of a specific familial pituitary adenoma condition with normal NGS results. This approach might be particularly useful where copy-number variants are a recognized form of gene mutation such as the large deletions accounting for 4% of germline *MEN1* pathogenic variants¹¹³ and 20% of germline *PRKARIA* pathogenic variants⁷⁹.

- **R10.** We recommend using genetic testing methodologies tailored to the underlying genetic abnormalities in people with suspected X-LAG (specifically, germline chromosome microarray by single-nucleotide polymorphism array or array comparative genome hybridization to detect *GPR101*-containing Xq26.3 duplications) or McCune–Albright syndrome (specifically, droplet digital polymerase chain reaction or NGS of blood and/or affected tissues to detect postzygotic *GNAS* variants).

Testing for *GPR101* duplications in people with suspected X-LAG syndrome can be performed by single-nucleotide polymorphism array or array comparative genome hybridization. Droplet digital polymerase chain reaction might be useful in detecting low-level somatic mosaicism if chromosome microarray is negative^{49,111}. Typical scenarios of mosaicism include sporadic X-LAG in male individuals¹¹⁴ as well as McCune–Albright syndrome (a mosaic condition by definition)⁵³ and, rarely, *MEN1* syndrome¹¹⁵.

Identified Xq26.3 duplications should be confirmed to contain the *VGLL1* region essential for the X-LAG phenotype to manifest^{47,48}. This feature is usually apparent through mapping of the duplicated region against the reference genome. Emerging techniques that might be used in discrepant cases (for example, in people with Xq26.3 duplications without the X-LAG phenotype) include in silico modelling of chromatin structures or 4C/HiC-seq chromatin conformation capture techniques^{49,114}.

The likelihood of detecting *GNAS* variants in McCune–Albright syndrome varies according to the technique used, the tissue tested and the number of McCune–Albright syndrome features present in the person being tested⁸⁰. *GNAS* variant detection rates among people with one or more features of McCune–Albright syndrome are approximately 0–50% via variant-enriched Sanger sequencing of affected skin⁵⁴, 10–50% via variant-enriched Sanger sequencing of blood⁵⁴, 62% via droplet digital polymerase chain reaction of blood cell-free DNA¹¹⁶, 75% via variant-enriched NGS-based amplicon sequencing of blood¹¹⁷, 90% via variant-enriched Sanger sequencing of affected tissues other than skin⁵⁴ and 100% (limited published data) via variant-enriched NGS of affected tissues^{118,119}.

Post-test management

Recommendations 11–16 refer to the various steps involved in the management of patients after genetic testing. Noting the complexity of these steps, patients with positive genetic test results should ideally be referred to a general or endocrine-specific genetics service, regardless of whether the test was initially requested by a geneticist or non-geneticist. Referral to a genetics service might also be appropriate for patients with a negative genetic test result but with ongoing high

suspicion of a familial pituitary adenoma predisposition condition where tumour surveillance in family members and/or the use of broader genetic testing might be considered.

- **R11.** We recommend gene-specific tumour surveillance in people found to have a germline pituitary adenoma predisposition gene variant classified as pathogenic or likely pathogenic.

Germline pathogenic and likely pathogenic variants are considered positive genetic test results and should facilitate clinical care, genetic testing of blood relatives and reproductive counselling. Clinical care encompasses surveillance, if the gene is associated with tumours beyond the pituitary (see Fig. 1 for gene-specific guidance), and consideration of typical gene-specific pituitary adenoma features and management according to the gene in question. Recommended tumour surveillance protocols across the various genes typically begin in childhood. Protocols are governed by the usual or earliest reported age of clinical manifestation, noting that such age thresholds might be either lowered or raised as new information becomes available from prospective studies of gene-specific tumour surveillance.

Although aggressive pituitary adenomas occur in the setting of germline pituitary adenoma predisposition gene variants, aggressiveness is not a consistent finding and decisions on whether to intensify the treatment of a pituitary adenoma should consider all clinical factors⁵. For example, the biological behaviour of *MEN1*-related pituitary adenomas is generally similar to that of sporadic adenomas^{14,77,120,121}, except that plurihormonal excess and multifocality are more common in the former than in the latter¹²⁰. Thus, uniform consensus now exists across international guidelines, recommending that management of *MEN1*-associated pituitary adenomas be undertaken according to sporadic pituitary adenoma guidelines¹²⁰. By contrast, *AIP*-associated pituitary adenomas and X-LAG frequently exhibit treatment resistance, and a lower threshold for multimodal treatment might be used for these adenomas than for sporadic pituitary adenomas¹¹⁴.

- **R12.** We recommend offering cascade genetic testing to at-risk relatives of a person in whom a pathogenic or likely pathogenic pituitary adenoma predisposition gene variant has been identified.
- **R13.** We recommend that cascade testing in children be offered prior to the recommended starting age for tumour surveillance for the given gene.

Patients diagnosed with a germline pathogenic or likely pathogenic variant in a gene predisposing to pituitary adenomas should be encouraged to share their molecular diagnosis with blood relatives who might have inherited the variant. This enables at-risk relatives to pursue genetic testing and, if positive, to begin gene-specific surveillance. To minimize patient burden, the proband should be provided with a notification letter that they can pass on to relatives who can then pursue genetic testing in their local genetics service as they wish. Genetic counsellors in the genetic service responsible for the proband should be available to provide further support in contacting relatives, if required.

Cascade testing refers to testing of asymptomatic first-degree relatives and then moving out through the family tree according to who tests positive for the variant. In addition, blood relatives (whether adults or children) with features suggesting the genetic condition in question should undergo prompt testing for the known familial variant.

Implementation of cascade testing in practice remains variable and is influenced by educational status, beliefs, emotional responses of the proband (for example, guilt or anxiety), perception of relatives,

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and patterns of communication or conflicts within the family¹²². If a family member declines testing or is deceased, testing could be offered to more distant relatives.

In asymptomatic children, cascade testing should be performed prior to the recommended age for initiating tumour surveillance, which varies depending on the gene involved (Table 1). Age thresholds are best guided by international tumour surveillance consensus when available. In other cases, cascade testing might be considered prior to the earliest age of reported disease onset as a cautious approach, noting that this might not reflect the typical disease trajectory.

- **R14.** We recommend providing pre-conception reproductive counselling to people with pathogenic or likely pathogenic pituitary adenoma predisposition gene variants.

Genetic variations in established pituitary adenoma predisposing genes do not directly impair fertility. However, fertility might be affected in both male and female individuals with pituitary adenomas due to gonadotrophin deficiencies resulting from compression of the

pituitary gland by expanding adenoma masses and/or as a consequence of surgical or radiation treatment. Fertility might also be affected by hypersecretion of prolactin or adrenocorticotrophic hormone and cortisol, which also lead to hypogonadism¹²³.

Reproductive counselling should address both the likelihood of offspring inheriting the variant in question as well as the implications of penetrance. Inheritance patterns of pituitary adenoma predisposition gene variants are gene-specific, being autosomal dominant for variants in *AIP*, *MEN1*, *CDKN1B*, *PRKARIA*, *SDHA*, *SDHB* and *SDHC*⁸⁶; autosomal dominant but with a parent-of-origin effect (disease penetrance primarily associated with paternally transmitted variants) that is well established in *SDHD* and suspected in *MAX*¹²⁴; and X-linked dominant in *X-LAG*²¹. Disease penetrance is also variable. For instance, the penetrance of pituitary adenomas in people heterozygous for *AIP* variants is estimated to be approximately 20%^{10,11}, while *MEN1* variants demonstrate nearly 100% penetrance for parathyroid lesions and 40–60% penetrance for pituitary adenomas^{14,125}. Of note, McCune–Albright syndrome is a sporadic mosaic condition and is not familial. The causative *GNAS* variants are postzygotic mutations; they are not inherited or transmitted from parent to child as germline *GNAS* activation is considered incompatible with embryonic viability⁶⁸.

As for other genetic conditions, patients with transmissible pituitary adenoma predisposition gene variants should be informed of available reproductive options, including in vitro fertilization with pre-implantation genetic testing, which offers affected individuals the opportunity to have biological children without transmitting the genetic variant^{126,127}. This option might be particularly relevant for people carrying high-penetrance variants associated with severe phenotypes, such as *MEN1*, *PRKARIA*, and *SDHB* variants and Xq26.3 microduplications, and people already requiring in vitro fertilization (for example, because of infertility related to their pituitary adenoma). However, access to such specialized services might be limited in some countries.

- **R15.** We recommend that VUS be regarded as uninformative and not be used to guide management but they could be reclassified to a positive or negative result through careful variant assessment. Clinicians managing patients with VUS should consider requesting periodic variant reviews, particularly prior to pregnancy.

VUS should not be used for clinical decision-making, family screening or genetic counselling. However, appropriate follow-up of patients with these variants is necessary to enable potential reclassification as knowledge increases. For instance, in 2025, the International FIPA consortium reclassified the *AIP* missense variant p.(Arg304Gln) as likely benign after conflicting studies over several years questioned its pathogenicity¹²⁸. Similarly, the French TENGEn network proposed adjustments to the ACMG-AMP framework for the interpretation of *MEN1* missense variants, as 39 variants classified by TENGEn as pathogenic or likely pathogenic were classifiable only as VUS by ACMG-AMP¹⁰³. The US-based Clinical Genome Resource (ClinGen), which curates gene variants¹²⁹, and case review at national multidisciplinary team meetings, such as those held by the [EndoGen National Endocrine Genetics Network](#) in Australia and the TENGEn network, might aid clinicians in the VUS reclassification process.

- **R16.** We suggest further clinical-based or research-based genetic testing, as available, for people without an identifiable pathogenic or likely pathogenic variant but with clinical features strongly suggestive of a pituitary adenoma predisposition gene variant.

Table 1 | Recommended ages by which to offer cascade testing

Gene	Age ^a	Rationale
<i>AIP</i>	4 years	Youngest reported age of tumour onset (somatotrophinoma) ¹⁵²
<i>CDKN1B</i>	10 years	Youngest reported age of tumour onset (corticotrophinoma) ⁷⁸
<i>GNAS</i>	Not applicable; no germline inheritance	
<i>GPR101</i> (Xq26.3 microduplications) ^b	0–24 months	Tumour onset reported from infancy (pituitary adenoma or hyperplasia with marked growth hormone excess) ⁴⁹
<i>MAX</i>	10 years	Following international guidelines: clinical review from age 10 years, biochemical and radiological surveillance from age 15 years ¹⁵³
<i>MEN1</i>	5–10 years	Following international guidelines: clinical review from age 5 years, biochemical and radiological surveillance from age 10 years ¹⁴
<i>PRKARIA</i>	0–24 months	Tumour onset reported from infancy (cardiac and cutaneous myxomas, primary pigmented nodular adrenocortical disease, large cell calcifying Sertoli cell tumour) ^{41,154}
<i>SDHA</i> , <i>SDHC</i> and <i>SDHD</i> ^c	10–15 years	Following international guidelines: tumour surveillance starting between age 10 and 15 years ¹⁵⁵
<i>SDHB</i>	6–10 years	Following international guidelines: tumour surveillance starting between age 6 and 10 years ¹⁵⁵

^aExcept where indicated, age recommendations are based on limited data, not international guidelines. Consider the family situation and the latest literature when determining the age by which to offer cascade testing. ^bAs penetrance is complete, cascade testing is applicable to clinically affected relatives of probands, clinically unaffected infant siblings and offspring (as the condition might not yet be apparent), and parents of probands (both parents if the proband is female; mother only if the proband is male) irrespective of their clinical status if they plan to have more children (as a parent might theoretically be mosaic for the variant and hence unaffected). Notably, there have been no reports to date of father-to-daughter transmission of pathogenic Xq26.3 microduplications or of clinically unaffected individuals with a mosaic pathogenic Xq26.3 microduplication. ^cApplies only to paternally inherited *SDHD* variants.

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People with negative genetic testing results should generally be considered at low risk of having a familial tumour syndrome. However, some variants might escape detection because they fall outside the scope of standard testing methods (for example, deep intronic variants¹³⁰ or mosaicism¹¹⁵). In other patients, the causative variant might occur in a gene not yet associated with pituitary adenoma predisposition or in a gene currently untested in routine clinical practice.

If clinical features strongly suggest familial pituitary adenoma predisposition, referral for further clinical-based or research-based genetic testing¹³¹ might be appropriate. Such an approach might be particularly relevant if there is a strong family history, if unaffected relatives are already undergoing intensive tumour surveillance or if pre-implantation genetic testing would be considered¹²⁷.

Whole-exome sequencing or whole-genome sequencing might identify a missed variant but could reveal unexpected findings¹³². When used in clinical practice, the analysis should be limited to known pituitary adenoma predisposition genes. When used in a research setting, repeat testing using an accredited diagnostic test should be performed for confirmation of identified variants that would be considered to be causative.

Indications for somatic genetic testing

Somatic genetic testing of resected pituitary adenoma tissue in the research setting has revealed *GNAS* variants in somatotrophinomas and *USP8* variants in corticotrophinomas, widespread chromosomal disruption in functioning pituitary adenomas and aggressive non-functioning pituitary adenomas, and variants in *TP53*, *ATRX* and *SF3B1* in selected aggressive pituitary adenomas^{5,133}. In the clinical setting, somatic testing of pituitary adenomas requires expert multidisciplinary input with careful case and gene selection to maximize clinical utility as well as suitably stored surgical specimens according to laboratory requirements.

- **R17.** We recommend against *GNAS* and *USP8* somatic genetic testing in routine practice given the limited personalized management implications of finding a pathogenic variant in these genes.

Approximately 40% (range 4–50%) of somatotrophinomas are associated with somatic *GNAS* variants that lead to constitutive cAMP pathway activation^{134–136}. *USP8* variants, which are detected in 20–60% of corticotrophinomas^{23,136}, cluster in the 14-3-3 protein binding motif and enhance the proteolytic cleavage and catalytic activity of USP8, resulting in increased deubiquitination of the epidermal growth factor receptor, impairing its downregulation and sustaining epidermal growth factor signalling²³.

Somatotrophinomas with *GNAS* variants tend to be smaller and less invasive than those without *GNAS* variants, as well as more frequently of the densely granulated subtype that is often associated with improved somatostatin receptor ligand response¹³⁵; however, reports show no difference in therapeutic responsiveness¹³⁷. Corticotrophinomas with *USP8* variants are not consistently associated with adenoma size or invasiveness; although they are more likely to show remission after surgery compared with variant-negative corticotrophinomas, they are also more likely to recur^{133,138}. Thus, as the clinical relevance of *GNAS* and *USP8* status is unclear, the utility of somatic testing in practice remains unproven.

- **R18.** We suggest consideration of somatic genetic testing of surgically resected aggressive pituitary adenoma or pituitary carcinoma tissues, when available, to guide emerging targeted therapies when conventional therapies have been exhausted or are not suitable.

Guidelines from the European Society of Endocrinology suggest somatic testing in patients with aggressive pituitary adenomas and pituitary carcinomas with sustained progression after treatment with temozolomide²⁸. Outside of the pituitary setting, high tumour mutational burden¹³⁹ and mismatch repair deficiency (for example, due to mismatch repair gene variants)¹⁴⁰ predict response to immune-checkpoint inhibitor therapy, whereas the somatic *BRAF*^{V600E} variant predicts response to BRAF inhibitor therapy¹⁴¹. Importantly, as these genetic changes are uncommon in pituitary adenomas, there is scant and conflicting evidence regarding their predictive value^{68,142,143}. Nevertheless, somatic testing could be considered in people with aggressive pituitary adenomas or pituitary carcinomas if conventional therapies have been exhausted or are not suitable.

In a divergence from the European Society of Endocrinology guidelines²⁸, we note that temozolomide might not be suitable for all patients and that targeted therapies might be preferred instead. However, given the tentative evidence base for use of these therapies in pituitary adenomas, somatic testing to identify possible treatment targets should ideally be performed in a research setting. In particular, testing might provide an opportunity for patients to participate in 'basket trials', in which genetic testing of resected specimens guides the use of a targeted therapy irrespective of tumour type.

- **R19.** We suggest caution in using somatic genetic testing in people with aggressive pituitary adenomas or pituitary carcinomas purely for the purpose of prognostication as such lesions already exhibit aggressiveness.

It has been suggested that *TP53* and *SF3B1* somatic variants in dopamine agonist-resistant prolactinomas and *TP53* and *ATRX* somatic variants in corticotroph macroadenomas might predict aggressive adenoma behaviour²⁸. However, these adenomas already exhibit adverse prognoses because of their clinical features, and identification of these somatic variants does not add clinical value or lead to a specific or altered treatment strategy. Therefore, potential clinical benefit from somatic testing in these scenarios is not proven. If routine somatic testing of resected pituitary adenomas becomes feasible in the future, then identifying *TP53*, *ATRX* or *SF3B1* variants in pituitary adenomas that have not yet demonstrated treatment resistance or aggressive adenoma growth might be instructive early markers of future adenoma aggressiveness as variants in these genes seem to be enriched in aggressive pituitary adenomas and pituitary carcinomas^{25,144–146}.

- **R20.** We recommend assessing patients with somatic variants detected on pituitary adenoma testing to determine the utility of germline testing for the variant; that is, whether the variant is likely to be found in the germline and whether the result would guide management of the proband or their family.

Following clinical genetics principles, identification via somatic testing of a pathogenic or likely pathogenic variant that will probably be constitutional and actionable when present in the germline should prompt consideration of germline testing to distinguish between a purely somatic variant and a germline variant^{147,148}. Indicators of a somatic variant being constitutional include variant allele frequencies of 0.3–0.7 (lower and higher variant allele frequencies typically indicate purely somatic variants) and clinical markers (for example, young age of onset and a positive family history) of the corresponding heritable condition¹⁴⁹. Genes identified in international genetics guidelines as warranting germline testing when variants are found on somatic testing include *MEN1*, *MAX*, and the *SDHx* and mismatch repair genes,

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among other general cancer predisposition genes^{147,148}. The question of whether a variant identified on somatic testing is purely somatic or germline is ideally resolved with simultaneous paired tumour–germline testing; however, this approach is not usually feasible due to costs and logistical barriers¹⁴⁹. Instead, positive somatic test results should prompt careful multidisciplinary review of variant, gene and patient factors to determine the suitability of subsequent variant-specific germline testing.

Conclusions

With improved understanding of pituitary adenoma genetics, coupled with the increasing accessibility of genetic technologies, genetic testing has become a component of contemporary multidisciplinary care. Germline panel testing of pituitary adenoma predisposition genes and dedicated testing for X-LAG and McCune–Albright syndrome can guide management decisions for patients and their families. Comprehensive pre-test counselling, use of rigorous test methodologies in accredited laboratories and post-test follow-up are essential to maximizing the clinical benefits of genetic testing. Somatic genetic testing of surgically resected pituitary adenoma tissue is not routinely performed but might be considered in people with aggressive pituitary adenomas or pituitary carcinomas to guide the use of emerging targeted therapies. Where possible, genetic testing should be managed by a multidisciplinary team with appropriate expertise, either internally or via a reference laboratory or through referral to a pituitary tumour centre of excellence.

Future research priorities in the field include discovery and functional validation of emerging pituitary adenoma predisposition genes as well as elucidation of the mechanisms underlying the widespread somatic chromosomal disruption frequently observed in pituitary adenomas. In addition, emerging reports suggest that DNA methylation profiling and RNA transcriptome sequencing might refine diagnostic classification and prognostication in pituitary adenomas^{136,150,151}; however, clinical integration of such testing requires validation in prospective studies. Across these lines of enquiry, rigorously controlled pituitary adenoma tissue biobanking, collaborative patient registries and sequencing databases will be essential to build statistical power for metadata studies, and prospective trials are needed to establish gene-targeted medical therapies for pituitary adenomas.

The reduced costs of testing coupled with increased access to accredited test laboratories will enable improved understanding of the yield of germline testing across clinical scenarios. The potential prognostic benefit of somatic testing will prove critical for pituitary adenomas that have not yet exhibited biomarkers of aggressiveness. Results of these studies might justify expanded indications for germline and somatic testing, triggering a more positive and clinically actionable concordance between genetic testing results and genetic testing utility.

Published online: 25 August 2026

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Acknowledgements

The authors thank P. Dutta (Postgraduate Institute of Medical Education and Research, Chandigarh, India) for contributing to the discussion.

Author contributions

S.M.C.D., C.L.A., A.F.D., M.G., F.G., P.K., P.M., M.R., F.R.-Z., R.S., Y.T., C.T., M.F. and S.M. contributed to all aspects of the article. T.A., S.C., L.D., A.G.I., S.M.-G., D.A.N., A.M.P., I.S., J.W. and G.Z. contributed substantially to discussion of the content and reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41574-026-01291-4>.

Peer review information *Nature Reviews Endocrinology* thanks Marie-Lise Jaffrain-Rea, Laura Hernández Ramirez and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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Related links

EndoGen National Endocrine Genetics Network: <https://www.endocrinesociety.org.au/endogen.asp>

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Consensus statement

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