THEMATIC REVIEW

The World Health Organization classifications of pituitary neuroendocrine tumours: a clinico-pathological appraisal

Chiara Villa1,2, Bertrand Baussart2,3, Guillaume Assié2,4, Gerald Raverot2,5,6,7 and Federico Roncaroli8

1Department of Neuropathology, Hôpital Universitaire Pitié-Salpêtrière, APHP, Sorbonne Université, Paris, France
2Inserm U1016, CNRS UMR 8104, Institut Cochin, Université Paris Descartes-Université de Paris, Paris, France
3Department of Neurosurgery, Hôpital Universitaire Pitié-Salpêtrière, APHP, Sorbonne Université, Paris, France
4Department of Endocrinology, Center for Rare Adrenal Diseases, Hôpital Cochin APHP, Paris, France
5Endocrinology Department, Reference Center for Rare Pituitary Diseases HYPO, “Groupement Hospitalier Est” Hospices Civils de Lyon, Bron, France
6Lyon 1 University, Villeurbanne, France
7Inserm U1052, CNRS UMR 5286, Cancer Research Center of Lyon, Lyon, France
8Geoffrey Jefferson Brain Research Centre, Division of Neuroscience, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom

Correspondence should be addressed to C Villa: chiara.villa@aphp.fr

This paper is part of a themed mini review collection addressing changes outlined in the 2022 WHO Endocrine Tumour Classification guideline.

Abstract

The classification of tumours of the pituitary gland has recently been revised in the 2021 5th edition World Health Organization (WHO) Classification of Central Nervous System Tumours (CNS5) and 2022 5th edition WHO Classification of Endocrine and Neuroendocrine Tumours (ENDO5). This brief review aims to appraise the most relevant changes and updates introduced in the two classifications. A new nomenclature has been introduced in CNS5 and ENDO5 to align adenohypophysial tumours with the classification framework of neuroendocrine neoplasia. The term pituitary neuroendocrine tumour (PitNET) with subtype information has therefore been adopted and preferred to adenoma. Pituitary carcinoma has been replaced by metastatic PitNET. The ICD-O coding has been changed from benign to malignant in line with NETs from other organs. Histological typing and subtyping based on immunohistochemistry for lineage-restricted pituitary transcription factors are regarded as the cornerstone for accurate classification. Such an approach does not fully reflect the complexity and dynamics of pituitary tumorigenesis and the variability of transcription factors expression. ENDO5 does not support a grading and/or staging system and argues that histological typing and subtyping are more robust than proliferation rate and invasiveness to stratify tumours with low or high risk of recurrence. However, the prognostic and predictive relevance of histotype is not fully validated. Recent studies suggest the existence of clinically relevant molecular subgroups and emphasize the need for a standardized, histo-molecular integrated approach to the diagnosis of PitNETs to further our understanding of their biology and overcome the unsolved issue of grading and/or staging system.

Key Words
- pituitary neuroendocrine tumour
- PitNET
- pituitary adenoma
- pituitary carcinoma
- metastatic PitNET
- WHO classification

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Introduction

The World Health Organization (WHO) regularly updates the classification of human tumours to reflect the progress in the understanding of their aetiology and pathogenesis, as well as the advances in diagnosis, molecular profiling, imaging modalities and treatment. New entities, changes in nomenclature, grading and staging, updated International Classification of Diseases (ICD), ICD Oncology (ICD-O) codes and new microscopic and molecular findings are introduced following scrutiny of evidence-based literature by designated authors of the chapters, which are then reviewed by a panel of experts. Although the WHO classifications are not intended to be guidelines, they are regarded as the benchmark for diagnosis, and therefore, the treatment of patients.

The WHO classification of tumours of the pituitary gland has been revised three times during the last 20 years as part of the Endocrine Tumour classification books (ENDO) published in 2004 (3rd edition, ENDO3) 2017 (4th edition, ENDO4) and 2022 (5th edition, ENDO5) (De Lellis et al. 2004, Lloyd et al. 2017). For the first time, the classification of primary tumours arising from adenohypophyseal cells has also been included in the 5th edition of the WHO classification of tumours of the Central Nervous System (CNS5) published in 2021, with the rationale that pituitary tumours are operated on by neurosurgeons and diagnosed by neuropathologists (Lopes et al. 2021).

Table 1 compares the changes of the last editions of WHO ENDO and CNS5.

Acknowledging the complexity and challenges of coordinating WHO books, this mini review aims to appraise the changes in the classification of adenohypophyseal tumours introduced in CNS5 and ENDO5. All updates on the other tumour entities occurring in the anterior and posterior pituitary and more broadly in the sellar and suprasellar region will not be discussed.

Changes in nomenclature and ICD-O coding

After the proposal of a change in the nomenclature of pituitary adenomas in 2016 (Asa et al. 2017) and the controversy that followed (Ho et al. 2019, 2020, 2021, 2022), the WHO and International Agency for Research on Cancer (IARC) opted for the combined definition of pituitary neuroendocrine tumour (PitNET)/pituitary adenoma (hereafter PitNET) to acknowledge the neuroendocrine phenotype of these neoplasms and their spectrum of clinical and biological behaviour. This change has been accompanied by a change in ICD-O coding from benign (/0) to malignant (/3) with the motivation of aligning PitNETs with NETs from other organs, and more specifically, with those that are most often cured by surgery and rarely metastasize such as well-differentiated appendiceal NETs. Notably, the ICD11 code has also been changed from 2F9A and XH9U0 in CNS5 that defines ‘neoplasms of unknown behaviour of endocrine glands & pituitary adenoma, NOS’ to code 2D12Y that classifies ‘other specified malignant neoplasms of other endocrine glands or related structures’. In most parts, ENDO5 used the 2017 WHO/IARC terminology for neuroendocrine neoplasms to achieve a consistent, reproducible classification of these tumours. It is worth emphasising that the morbidity caused by uncontrolled hormone secretion does not influence the code.

Given the predominant incidence of indolent lesions, the unpredictable behaviour of some PitNETs and the lack of agreement on their prognostic stratification, it remains unclear why the consensus panel of ENDO5 decided to adopt the code /3 rather than /1, which classifies uncertain malignant potential and reflects the ICD11 in CNS5. A code of malignancy attributed to PitNETs encompasses incidentalomas and aggressive tumours including metastatic lesions and reignites the controversy of equating the term ‘tumour’ to ‘malignancy’, which is largely incorrect and not the intended message of the International Pituitary Pathology Club proposal (Asa et al. 2017). It also raises concerns about the far-reaching consequences on tumour registration, epidemiology, treatment and surveillance.

Classification criteria: lineage-restricted pituitary transcription factors

ENDO5 recommends relying on the lineage-restricted pituitary transcription factors (TFs) TPIT, PIT1 and SF1 for the classification of PitNETs with the rationale that antibodies directed against TFs are more specific and reproducible than the immunostains for pituitary hormones. Although this approach has merits such as resolving the long-standing issue around null-cell PitNETs, it may be inadequate to define the full spectrum of adenohypophyseal tumours. An approach based on TFs does not fully account for the complex regulation of pituitary tumourigenesis, the variability in the expression of TFs, the existence of tumours with uncommitted cell lineage, and tumours displaying transdifferentiation (McDonald et al. 2017, 2021, Villa et al. 2019, Lenders et al. 2022). For instance, some PitNETs may lack staining for
the three lineage-restricted pituitary TFs (defined as triple negative), but they can still display distinct pituitary hormone and GATA3 expression (Turchini et al. 2020). SF1 may be weak to negative in gonadotroph tumours with oncocytic change, which still retain FSH and LH β-subunit expression (unpublished). Also, it is unclear if the expression of two TFs without immunostaining of corresponding hormones qualifies a PitNET as plurihormonal.

Furthermore, a TF-based classification has limitations such as the clinical classification of PIT1 lineage, which includes a broad spectrum of phenotypes with different hormone secretion (lactotroph vs somatotroph vs thyrotrroph PitNETs) and the limited acknowledgement of the recent insights into molecular profiling (Lopes et al. 2021).

Recent studies have demonstrated that the integration of immunohistochemical features and molecular profiling, such as genome-wide DNA methylation arrays, can resolve the diagnosis of those PitNETs with focal, and weak, or even lack of expression of TFs and/or pituitary hormones (Ricklefs et al. 2020, Dottermusch et al. 2022).

Table 1  A comparison of the major changes in the three WHO classifications of Endocrine Tumours and in the chapter on adenohypophyseal tumours in 5th edition of the Central Nervous System WHO Classification.

<table>
<thead>
<tr>
<th></th>
<th>ENDO3 WHO 2004</th>
<th>ENDO4 WHO 2017</th>
<th>CNS5 WHO 2021</th>
<th>ENDO5 WHO 2022</th>
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</thead>
<tbody>
<tr>
<td>Nomenclature</td>
<td>Typical adenoma</td>
<td>Adenoma (Subtype)</td>
<td>Pituitary adenoma / pituitary neuroendocrine tumour (PitNET) (Subtype)</td>
<td>Pituitary neuroendocrine tumour (PitNET) (Subtype)</td>
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<tr>
<td></td>
<td>Atypical adenoma Carcinoma</td>
<td>– Carcinoma</td>
<td>– Carcinoma</td>
<td>– Metastatic PitNET (Subtype)</td>
</tr>
<tr>
<td>ICD-O code⁴</td>
<td>8272/0 Typical adenoma</td>
<td>8272/0 Adenoma</td>
<td>8272/3 Pituitary adenoma / pituitary neuroendocrine tumour (PitNET)</td>
<td>8272/3 PitNET</td>
</tr>
<tr>
<td></td>
<td>8272/1 Atypical adenoma</td>
<td>–</td>
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<tr>
<td></td>
<td>8272/3 Carcinoma</td>
<td>8272/3 Carcinoma</td>
<td>8272/3 Carcinoma</td>
<td>8272/3 Metastatic PitNET</td>
</tr>
<tr>
<td>Terminology based on</td>
<td>Hormone secretion</td>
<td>Hormone secretion/pituitary cell lineage</td>
<td>Pituitary cell lineage</td>
<td>Pituitary cell lineage</td>
</tr>
<tr>
<td>Grading</td>
<td>No grading</td>
<td>No grading</td>
<td>No formal system</td>
<td>No grading; Ki67 and mitosis unproven</td>
</tr>
<tr>
<td>Staging</td>
<td>No staging</td>
<td>No staging</td>
<td>Dissemination in CSF and MRI/CT/PET</td>
<td>No staging; invasion unproven</td>
</tr>
<tr>
<td>Proliferation markers</td>
<td>Ki67: cut off 3%</td>
<td>Ki67 (hotspots count): no cut off</td>
<td>Ki67 (hotspots count): no cut off</td>
<td>Proliferative rate unproven</td>
</tr>
<tr>
<td></td>
<td>Mitosis: no cut off</td>
<td>Mitosis: no cut off (P53)</td>
<td>Mitosis: no cut off (P53)</td>
<td>–</td>
</tr>
<tr>
<td>High risk of recurrence tumours</td>
<td>Atypical adenoma</td>
<td>Invasive tumours, highly proliferative (Ki67 &amp; mitosis), rapid growth or Subtypes: – Crooke cell adenoma – Silent corticotroph – Lactotroph in men – Plurihormonal PIT1+ adenoma – Sparsely granulated somatotroph</td>
<td>Invasive tumours, highly proliferative (Ki67 &amp; mitosis), rapid growth or Subtypes: – Crooke cell adenoma – Silent corticotroph – Lactotroph in men – Plurihormonal PIT1+ adenoma – Sparsely granulated somatotroph</td>
<td>Only accurate histological subtyping</td>
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<td></td>
<td>Subtypes: – Crooke cell adenoma – Silent corticotroph – Acidophil stem cell tumours – Immature PIT1-lineage tumours – Sparsely granulated somatotroph – Null Cell</td>
</tr>
</tbody>
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⁴ICD-O code for tumour behaviour: /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma *in situ* and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site.
Multiomics and protein expression profiling identified tumours with intermediate lineage differentiation and suggested the need for less rigid typing and subtyping of PitNETs. Silent corticotroph tumours can show TPIT and GATA3 co-expression (Fig. 1). A subset of pure somatotroph tumours mainly GNAS-wildtype, that are regarded as plurihormonal in ENDO5, co-express PIT1 and SF1 but lack LH and FSH β-subunit expression (Cooper et al. 2010, Neou et al. 2020, Ricklets et al. 2020, Taniguchi-Ponciano et al. 2020a,b, Cui et al. 2021, Tebani et al. 2021, Silva-Ortega et al. 2021, Dottermusch et al. 2022).

The impact of molecular profiling in the classification of PitNETs

Considerable progress has been made in the molecular characterisation of PitNETs but unlike other tumour types, the use of molecular markers has not entered diagnostic practice. In this respect, the field of pituitary pathology is far from an integrated diagnosis recommended for CNS tumours (Lopes et al. 2021).

A classification relying on cell lineage and cell type has been validated by transcriptome, methylome, miRNAome,
chromosome profiling and exome sequencing studies. However, multi-omics studies have also highlighted the complexity of PitNETs and subgroups have emerged (Lopes et al. 2021). Three subtypes of corticotroph tumours have been identified when combining transcriptome and USP8 status (Reincke et al. 2015, Neou et al. 2020), and two subtypes of somatotroph tumours exist when combining transcriptome and GNAS status (Spada et al. 1990, Neou et al. 2020), which respectively show ubiquitous TPIT and PIT1 expression. Additional PitNET subsets including sparsely granulated somatotroph tumours clustered in the same transcriptomic group of thyrotroph and plurihormonal PIT1-lineage tumours (Neou et al. 2020, Ricklefs et al. 2020, Taniguchi-Ponciano et al. 2020a,b, Cui et al. 2021, Tebani et al. 2021, da Silva-Júnior et al. 2022); null-cell tumours clustered with gonadotroph PitNETs. Molecular studies shed some new insight into novel subtypes such as corticotroph tumours with a TRIM65-TPIT complex (Yao et al. 2022).

The clinical relevance of a combined histological and molecular classification is not yet established, but its impact is being investigated and validated. For instance, expression of SSTR5 receptors is high in almost all USP8-mutant corticotroph tumours, variable in the subgroup of USP8-wildtype cortisol-secreting tumours, and low in the subgroup of silent corticotrophs (Neou et al. 2020). Interestingly, unsupervised transcriptome classification has suggested that aggressive lesions are not characterized by a distinct molecular signature (Neou et al. 2020).

**The definition of aggressiveness of PitNETs**

It is widely accepted that PitNETs are usually indolent lesions with only a minority of them displaying aggressive behaviour. Benign-looking hormone-secreting lesions can cause severe morbidity and at times, cannot be cured by surgery, medical treatment, or radiotherapy. Metastatic spread is exceptional, occurring in about 0.13–0.4% of cases which often leads to poor patient outcomes. The survey of the ESE taskforce on Aggressive Pituitary Tumours/ Carcinomas showed that patients with aggressive PitNETs also have an unfavourable outcome due to unusually rapid growth rate, uncontrolled by repeat surgery, radiotherapy (RT) and/or demonstrating resistance to medical treatments (Dekkers et al. 2020, Raverot et al. 2021).

ENDO5 replaces the definition of ‘pituitary carcinoma’ with ‘metastatic PitNET’ further specified by the tumour type and subtype. This long-needed update is based on the idea that morphology of poorly differentiated neuroendocrine neoplasms such as small cell or large cell neuroendocrine carcinoma according to the WHO/IARC definition for pancreatic or digestive NETs is uncommonly observed in the pituitary gland. However, the chapter on metastatic PitNET does not comment on aggressive tumours, which remains a diagnostic challenge in pituitary pathology.

Despite previous studies (Trouillas et al. 2013, 2018, McCormack et al. 2018, Raverot et al. 2018, Burman et al. 2022) ENDO5 does not support any grading system or prognostic stratification proposal and only regards certain tumour types and subtypes including immature PIT1-lineage tumours, Crooke cell tumours, null cell tumours and biochemically non-functioning ‘silent’ corticotroph tumours as more aggressive. Such an approach makes the histotype the strongest prognostic and predictive indicators, but the evidence of a worse prognosis for these so-called ‘high risk of recurrence’ types and subtypes is limited and still unclear. For instance, PIT1-lineage and Crooke cell tumours are extremely rare; therefore, most of the conclusions are based on clinical cases or retrospective small series and, more importantly, are based on inconsistent definitions of aggressiveness. The terminology of ‘high-risk’ used in the 2017 classification has also been removed in ENDO5.

The authors of this mini review welcome the recommendation in CNS5 and ENDO5 to quantify mitotic activity and Ki-67 labelling index more accurately and to discourage a semi-quantitative approach that is too often subjective. Pathologists must indicate square millimetres rather than high-power fields and state the methodology of quantification in pathology reports. Inaccurate assessment of proliferation is in fact one of the causes of inconsistency in the PitNETs stratification, potentially leading to patient’s overtreatment. Nevertheless, no cut-off for mitotic activity and Ki-67 labelling index is provided, and no approach to quantification is suggested. Similar to the method proposed for gastro-entero-pancreatic neuroendocrine neoplasms (Klöppel & La Rosa 2018), the European Pituitary Pathology Group suggested the quantification in two hotspots regardless of staining intensity for a total of 500–1000 cells per hotspot and to report the labelling index as the percentage of positive nuclei out of the overall number of neoplastic cells (Villa et al. 2019).

As mentioned earlier, the term aggressive PitNET is still inconsistent across studies with many suggesting ill-defined terminologies such as refractory (Dai et al. 2016) or resistant tumour. Such a lack of consensus explains discordant results among publications (Fountas et al. 2018).
The European Society of Endocrinology (ESE) definition of aggressive pituitary tumours has also limitations, such as the requirement of lack of treatment response among the criteria. For this reason, the ESE definition is not applicable at the time of a patient's first operation (Raverot et al. 2018). The assessment of the growth rate can also be a challenge (Dekkers et al. 2020, Raverot et al. 2021).

A five-tiered prognostic classification was proposed in 2013 (Trouillas et al. 2013) and validated on 2565 patients by independent studies (Raverot et al. 2017, Lelotte et al. 2018, Asioli et al. 2019, Guaraldi et al. 2020, Sahakian et al. 2022). Tumours are stratified according to the invasion (1 or 2) and proliferative features (a or b) (Trouillas et al. 2013). If accurately defined, 2b tumours represent about 8% of all surgical series and showed a significant increased risk (4- to 8-fold) of recurrence and progression, irrespective of tumour type and subtype. Two recent surveys sponsored by the ESE (McCormack et al. 2018, Burman et al. 2022) showed that aggressive tumours and metastatic PitNETs are clinically and histologically similar. Moreover, the proportion of aggressive tumours and carcinomas with Ki-67 ≥3% (47% of tumours) and ≥10% (35% of tumours) compared with a cohort of unselected tumours (Raverot et al. 2017) were significantly different (24% and 3%, respectively). It was suggested that tumours with Ki-67 ≥10% (invasive and highly proliferative) are tumours with 'malignant potential' (Trouillas et al. 2020, Raverot et al. 2021).

The USP8 and USP48 mutational status seems a prognostically relevant molecular feature in corticotroph tumours. Such mutations are associated with a lower rate of tumour progression (Ma et al. 2015, Reincke et al. 2015, Treppiedi et al. 2021, 2022, Albani et al. 2022). Recently, molecular risk stratification for corticotroph tumours has been provided combining USP8 and TP53 mutational status (Perez-Rivas et al. 2022). Finally, the relevance and the clinical impact of studies on predictive biomarkers are not discussed in ENDO5.

**Definition of invasiveness: imaging and surgical evidence**

In the introductory chapter, ENDO5 reiterates the conceptual difference between staging and grading for PitNETs, which is often a source of confusion. It is worth reminding that stage defines the extent of a tumour whilst grade relates to light microscopic features. ENDO5 recognises the need for the multidisciplinary staging of PitNETs and of a prognostically relevant and predictive scoring system.

CNS5 emphasises that the involvement of parasellar structures affects the extent of surgical intervention and that the persistence of residual tumour after surgery impacts prognosis and guides post-operative treatment. Unlike CNS5, ENDO5 does not discuss the integration of tumour extension and pathological features in the diagnosis of PitNETs (Trouillas et al. 2013, Raverot et al. 2021).

Since the pioneering work by Hardy-Wilson and Knop (Knop et al. 1993), considerable progress has been made in the assessment of the invasiveness of PitNETs. Many publications have reported that invasion can be reliably identified pre-operatively using recent radiological criteria and intra-operatively by expert pituitary neurosurgeons (Micko et al. 2015, 2019, Rutkowski et al. 2020, Berkmann et al. 2021). The development of endoscopic approaches has greatly improved the surgeon’s vision during sellar exploration. Endoscopy is now widely used by expert surgical teams as it is more effective than microscopy in visualizing the medial wall of the cavernous sinus, which can be accurately explored in most patients (Dhandapani et al. 2016, Zoli et al. 2016). A strong correlation between cavernous sinus invasion assessed intra-operatively, and postoperative endocrine remission rate in secreting lesions has been reported (Micko et al. 2015, Zoli et al. 2016, Buchy et al. 2019). Thus, endoscopic exploration should currently be considered as a robust technique for the diagnosis of cavernous sinus invasion.

Imaging modalities also evolved to better analyse the cavernous sinus compartment and its potential invasion (Micko et al. 2020). The original MRI grading system proposed by Knop in 1993 has been implemented with the introduction of new grades related to parasellar extension (Micko et al. 2015). The site of parasellar invasion is relevant. The extent of resection and the rate of endocrine remission are significantly higher in tumours that involve the superior compartment of the cavernous sinus (classified as 3A) than those involving the inferior compartment (defined as 3B) (Micko et al. 2019). Many authors have since validated the revised classification in their surgical series (Buchy et al. 2019, Micko et al. 2019, Araujo-Castro et al. 2021, Fang et al. 2021). In view of this data, it should be concluded that MRI is a robust diagnostic tool to detect cavernous sinus invasion.

Finally, invasion of the cavernous sinus can be proven histologically. In a review published in 1996, Buchfelder et al. already concluded that histological examination of basal dura could confirm invasion, even if it was not suspected during surgery (Buchfelder et al. 1996). In our surgical experience, resection of the basal dura can be
performed in most patients. By adopting this strategy, the invasiveness of PitNETs can be confirmed overcoming the limitations related to surgical or radiological interpretation. Nevertheless, the implication of the outcome of microscopic invasion remains unclear. As recently reported (Ishida et al. 2022), direct histological confirmation of cavernous sinus invasion can also be obtained in rare cases where the medial wall could be removed.

**Conclusions**

This mini review has discussed and appraised the most salient changes introduced in CNS5 and ENDO5 in the classification of PitNETs.

In our experience, a classification solely based on cell lineage has the risk to be too simplistic and it does not fully reflect the complexity of PitNETs. Recent molecular studies have in fact identified clinically relevant molecular subgroups and a less rigid pituitary lineage with multiple expressions of TFs.

The assessment of mitotic activity and proliferation markers remains an area of uncertainty in both CNS5 and ENDO5 as no definitive cut-off or methodology for quantification is suggested. In the last decade, several independent studies have validated the clinicopathological stratification proposed in 2013, correlating the rate of proliferation with invasion. A discussion of these studies could have been beneficial.

It is our opinion that the prognostic and predictive relevance of tumour type and subtype is not fully validated and that the ICD-O coding of ‘malignant’ (/3) does not reflect the clinical behaviour of PitNETs. To avoid unintended consequences in patient care, prediction of aggressiveness for PitNETs will require a classification combining the integration of clinical (i.e. secretion status and invasion), pathological (i.e. type/subtype and proliferation) and molecular data as applied in the stratification of CNS tumours (Louis et al. 2021) overcoming the unsolved issue of grading and/or staging system.

We recommend the standardization of pathological, radiological, surgical and clinical reports to define the criteria that allow for the distinction of aggressive PitNETs from the more common indolent lesions. In this context, pituitary reference centres European Reference Network on Rare Endocrine Conditions, or Pituitary Tumour Centres of Excellence where trained pituitary physicians engage in a multidisciplinary approach is the most appropriate setting to standardization and establish a reproducible risk stratification (Casanueva et al. 2017, Pereira & Hiort 2021, Couselo et al. 2022, Iotova et al. 2022, Shishkov et al. 2022, Zamanipoor Najafabadi et al. 2023).

The authors hope this mini review will stimulate a constructive discussion to progress the fascinating field of pituitary pathology and further our understanding of the pathogenesis and behaviour of PitNETs.

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**Declaration of interest**

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**Author contribution statement**

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