*Journal of the Endocrine Society*, 2021, Vol. 5, No. 3, 1–9
doi:10.1210/jendso/bvaa205
Reports and Recommendations

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# Pituitary Neoplasm Nomenclature Workshop: Does Adenoma Stand the Test of Time?

**Ken Ho,[1] Maria Fleseriu,[2] Ursula Kaiser,[3] Roberto Salvatori,[4] Thierry Brue,[5] M. Beatriz Lopes,[6] Pamela Kunz,[7] Mark Molitch,[8] Sally A. Camper,[9] Mônica Gadelha,[10] Luis V. Syro,[11] Edward Laws,[3] Martin Reincke,[12] Hiroshi Nishioka,[13] Ashley Grossman,[14] Ariel Barkan,[9] Felipe Casanueva,[15] John Wass,[16] Adam Mamelak,[17] Laurence Katznelson,[18] Aart J. van der Lely,[19] Sally Radovick,[20] Martin Bidlingmaier,[12] Margaret Boguszewski,[21] Jens Bollerslev,[22] Andrew R. Hoffman,[18] Nelson Oyesiku,[23] Gerald Raverot,[24] Anat Ben-Shlomo,[17] Rob Fowkes,[25] Ilan Shimon,[26] Hidenori Fukuoka,[27] Alberto M. Pereira,[28] Yona Greenman,[29] Anthony P. Heaney,[30] Mark Gurnell,[31] Gudmundur Johannsson,[32] Robert Y. Osamura,[33] Michael Buchfelder,[34] Maria Chiara Zatelli,[35] Marta Korbonits,[36] Philippe Chanson,[37] Nienke Biermasz,[28] David R. Clemmons,[38] Niki Karavitaki,[39] Marcello D. Bronstein,[40] Peter Trainer,[41] and Shlomo Melmed[17]**

[1]The Garvan Institute of Medical Research, Sydney, Australia; [2]Oregon Health & Science University, Portland, OR, USA; [3]Brigham and Women's Hospital, Boston, MA, USA; [4]The Johns Hopkins University School of Medicine, Baltimore, MD, USA; [5]Aix-Marseille University, Marseille, France; [6]University of Virginia School of Medicine, Charlottesville, VA, USA; [7]Yale School of Medicine, New Haven, CT, USA; [8]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [9]University of Michigan Medical School, Ann Arbor, MI, USA; [10]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [11]Hospital Pablo Tobon Uribe and Clinica Medellin—Grupo Quirónsalud, Medellin, Colombia; [12]Klinikum der Universität, Ludwig-Maximilians-Universität, München, Germany; [13]Toranomon Hospital, Tokyo, Japan; [14]University of Oxford, Oxford, and Barts and the London School of Medicine, London, UK; [15]Santiago de Compostela University, Santiago de Compostela, Spain; [16]Churchill Hospital, Oxford, UK; [17]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [18]Stanford University School of Medicine, Stanford, CA, USA; [19]Erasmus University Medical Center, Rotterdam, The Netherlands; [20]Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, USA; [21]Federal University of Parana, Curitiba, Brazil; [22]University of Oslo, Oslo, Norway; [23]Emory University School of Medicine, Atlanta, GA, USA; [24]Hospices Civils de Lyon and Lyon 1 University, Lyon, France; [25]Royal Veterinary College, University of London, London, UK; [26]Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel; [27]Kobe University Hospital, Kobe, Japan; [28]Leiden University Medical Center, Leiden, The Netherlands; [29]Tel Aviv-Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel; [30]David Geffen School of Medicine University of California, Los Angeles, CA, USA; [31]University of Cambridge & Addenbrooke's Hospital, Cambridge, UK; [32]Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [33]Nippon Koukan Hospital Kawasaki & Keio University School of Medicine, Tokyo, Japan; [34]University Hospital Erlangen, Erlangen, Germany; [35]University of Ferrara, Ferrara, Italy; [36]Queen Mary University of London, UK; [37]University Paris-Saclay & Assistance Publique Hôpitaux de Paris, Hôpital Bicêtre, Le Kremlin-Bicêtre, France; [38]University of North Carolina

ISSN 2472-1972

School of Medicine, Chapel Hill, NC, USA; [39]University of Birmingham, Birmingham, UK; [40]University of São Paulo Medical School, São Paulo, Brazil; and [41]University of Manchester, Manchester, UK

**ORCiD numbers:** 0000-0002-2508-9588 (K. Ho); 0000-0002-8237-0704 (U. Kaiser); 0000-0001-6495-2244 (R. Salvatori); 0000-0001-8482-6691 (T. Brue); 0000-0001-8661-6727 (M. B. Lopes); 0000-0002-8492-3587 (M. Molitch); 0000-0001-8556-3379 (S. A. Camper); 0000-0002-9250-3558 (M. Gadelha); 0000-0002-9817-9875 (M. Reincke); 0000-0002-9279-5861 (H. Nishioka); 0000-0001-8115-5714 (L. Katznelson); 0000-0002-1059-0126 (A.J. van der Lely); 0000-0002-5306-0715 (M. Boguszewski); 0000-0002-0145-1917 (A. R. Hoffman); 0000-0002-9517-338X (G. Raverot); 0000-0002-2222-2056 (R. Fowkes); 0000-0001-9255-653X (H. Fukuoka); 0000-0003-4923-488X (Y. Greenman); 0000-0001-5745-6832 (M. Gurnell); 0000-0003-3484-8440 (G. Johannsson); 0000-0001-8408-7796 (M. C. Zatelli); 0000-0001-5096-5722 (P. Chanson); 0000-0001-5817-3594 (N. Biermasz); 0000-0002-4696-0643 (N. Karavitaki); 0000-0002-2355-3447 (S. Melmed).

**Abbreviations:** ACTH, adrenocorticotropin; GH, growth hormone; IARC, International Agency for Research on Cancer; MMP, metalloproteinase; NET, neuroendocrine tumor; PANOMEN, Pituitary Neoplasm Nomenclature; PitNET, pituitary neuroendocrine tumor; SMR, standardized mortality ratio; SST, somatostatin receptor.

Received: 18 November 2020; Editorial Decision: 30 December 2020; First Published Online: 9 February 2021; Corrected and Typeset: 10 February 2021.

## Abstract

The *WHO Classification of Endocrine Tumours* designates pituitary neoplasms as adenomas. A proposed nomenclature change to pituitary neuroendocrine tumors (PitNETs) has been met with concern by some stakeholder groups. The Pituitary Society coordinated the Pituitary Neoplasm Nomenclature (PANOMEN) workshop to address the topic. Experts in pituitary developmental biology, pathology, neurosurgery, endocrinology, and oncology, including representatives nominated by the Endocrine Society, European Society of Endocrinology, European Neuroendocrine Association, Growth Hormone Research Society, and International Society of Pituitary Surgeons. Clinical epidemiology, disease phenotype, management, and prognosis of pituitary adenomas differ from that of most NETs. The vast majority of pituitary adenomas are benign and do not adversely impact life expectancy. A nomenclature change to PitNET does not address the main challenge of prognostic prediction, assigns an uncertain malignancy designation to benign pituitary adenomas, and may adversely affect patients. Due to pandemic restrictions, the workshop was conducted virtually, with audiovisual lectures and written précis on each topic provided to all participants. Feedback was collated and summarized by Content Chairs and discussed during a virtual writing meeting moderated by Session Chairs, which yielded an evidence-based draft document sent to all participants for review and approval. There is not yet a case for adopting the PitNET nomenclature. The PANOMEN Workshop recommends that the term adenoma be retained and that the topic be revisited as new evidence on pituitary neoplasm biology emerges.

**Key Words:** Pituitary neoplasm, pituitary adenoma, tumor, neuroendocrine

Pituitary neoplasms are classified according to size, location, secretory function, cell type, and neoplastic behavior. Histologically, classification is defined by the *WHO Classification*, a series that is updated regularly based on advances in research that impact diagnostic pathology. The current 2017 *WHO Classification* designates pituitary neoplasms as "adenomas," recognizing that the vast majority of these lesions are benign and only a small subset exhibit aggressive and, exceptionally rarely, malignant characteristics [1].

In 2017, the International Pituitary Pathology Club proposed that pituitary adenomas be termed pituitary neuroendocrine tumors (PitNETs) because pituitary hormone-producing cells are neuroendocrine cells and invasive pituitary adenomas share some behavioral similarities with NETs [2]. The Pituitary Society highlighted significant concerns for the proposed change [3], which generated further discussion [4, 5].

To enable contributions from key stakeholders, the Pituitary Society convened an international multidisciplinary workshop, Pituitary Neoplasm Nomenclature (PANOMEN), designed to address whether categorizing pituitary adenomas as NETs is supported by scientific evidence, whether NET terminology is more appropriate and representative of pituitary neoplastic behavior compared with the term "adenoma," and whether changing to the NET nomenclature benefits patient care.

## Workshop Planning and Structure

Guiding principles that determined PANOMEN workshop planning were inclusiveness, stakeholder participation, transparency, editorial independence, and unbiased selection of speakers and discussants. Invitations were extended by the Pituitary Society to relevant professional societies including the Endocrine Society, European Society of Endocrinology, European Neuroendocrine Association, Growth Hormone Research Society, and International Society of Pituitary Surgeons, as well as to expert pituitary opinion leaders to ensure balanced multidisciplinary representation across developmental biology, pathology, neurosurgery, endocrinology, and oncology. An invitation was also extended to leaders of the International Agency for Research on Cancer (IARC), responsible for development of the WHO Classification series.

PANOMEN focused on clinical epidemiology, taxonomy, classification, and aggressive neoplasms; because of pandemic restrictions, it was conducted entirely virtually. Speakers delivered remote audiovisual lectures and disseminated written lecture précis for review by all participants. Content Chairs of each session, with complete editorial independence, integrated speaker précis and participants' comments into assigned topic summaries, which formed the backbone of a document developed for a virtual meeting moderated by respective Session Chairs.

From this virtual meeting, a Writing Group comprising Speakers, Content Chairs, Session Chairs, and Workshop Chairs developed a balanced and accurate evidence-based draft document, which was then circulated to all participants for further feedback. An edited draft was then recirculated for final review and acceptance. Workshop sponsors played no role in this process and did not review the draft before or after the virtual meeting.

## Epidemiology and Clinical Outcomes

### Pituitary Neoplasms

Pituitary tumors account for about 15% of all intracranial masses. The overwhelming majority of these are benign adenomas arising from adenohypophyseal cells [6, 7]. Population surveys show that pituitary adenomas affect health outcomes due to consequences of hormone excess or deficiency, or, less commonly, from a mass effect in about 1 in 1000 persons in the community [6]. However, pituitary neoplasms are much more common than clinically apparent. This is because autopsy and imaging studies of persons without a known history of pituitary disease show that 10% to 15% of the population harbor undiagnosed pituitary neoplasms, most of which are small [8-10]. Just over half of clinically significant pituitary adenomas undergo surgical resection; of these, about 15% are locally invasive [5, 7]. Thus, invasive behavior is uncommon even among neoplasms requiring surgery, and is very rarely encountered clinically because surgery is not indicated for the overwhelming majority of pituitary neoplasms. Pituitary carcinomas are exceptionally rare, accounting for <0.5% of invasive lesions [11].

Subclinical adenomas, which account for more than 99% of pituitary neoplasms, do not affect life expectancy. Among the 1% of pituitary clinically significant neoplasms, the order of prevalence is prolactin-secreting (50-60%), nonfunctioning (20-40%), growth hormone (GH)-secreting (10-15%), and adrenocorticotropin (ACTH)-secreting (5-8%) adenomas [6, 7, 12].

Prolactinomas are usually successfully treated with dopamine agonists, and surgery is required in <10% of patients [6, 7]. No standardized mortality ratio (SMR) has been reported for prolactinomas. Up to 25% of untreated nonsecreting adenomas enlarge under observation [6]; any growth is generally very slow, ranging from 0.4 mm to 1.0 mm/year. For symptomatic, surgically resected, nonsecreting adenomas, about one-third recur or progress over time [6]. The SMR for patients with invasive recurrent macroadenomas reported in studies from the United Kingdom, Denmark, and Sweden range from 1.1 to 3.6, with excess deaths due mainly to circulatory, respiratory, and infectious causes [13]. Acromegaly is usually treated first with surgery, and medical treatment is commonly required for those incompletely controlled. The SMR is 2.0 to 3.0 in untreated acromegaly but falls to that of the general population with effective hormonal control [14]. Over 90% of patients with Cushing disease have microadenomas and up to 80% of these can be controlled by surgery [6]. Disease control reduces hypercortisolemia-driven SMR from 3.7 to 1.2 [15, 16].

Reduced quality of life and morbidity are influenced by hormonal hypersecretion or hyposecretion and treatment effects, and rarely by adenoma mass effects [17].

### Neuroendocrine Tumors

NETs were first described in 1907 by Oberndorfer, who coined the term "Karzinoide," meaning cancer-like, to describe tumorlets found in the small intestine [18]. NETs, widely acknowledged as potentially cancerous, are epithelial neoplasms derived from neuroendocrine cells and most commonly originate in the gastrointestinal tract, followed by the lungs and other sites. Although of epithelial origin, pituitary adenomas are not classified as NETs [19]. Primary pituitary NETs (also referred to as carcinoids in the literature) are extremely rare (see "Aggressive Pituitary Neoplasms") and should be differentiated from metastatic NETs of other organs [20].

While NETs are rare, the age-adjusted incidence has risen over the past decades, and increased 6-fold to 6.98 per 100 000 in 2012 [21, 22]. A recent autopsy study reported a NET prevalence of about 0.5% [23]. Median survival is 9.3 years, with the highest rates seen in localized disease (>30 years), Grade 1 NETs (16.2 years), and NETs of the appendix (30 years) [21].

Treatment decisions for NETs are based on functional status, extent of disease, grade and differentiation, rate of growth, primary site, and somatostatin receptor (SST) expression status. NETs are extremely heterogeneous, and confusing nomenclature hampers accurate diagnosis, treatment selection, and epidemiologic studies.

## Taxonomy

### Human pituitary development and cellular differentiation

The anterior pituitary lobe is derived from embryonic oral ectoderm while the posterior lobe is derived from neural ectoderm [24, 25]. At 5 weeks' gestation, oral ectoderm invaginates to form Rathke's pouch, which then separates, and the pituitary stalk and posterior lobe form an evagination of neural ectoderm. By 13 weeks, the overall pituitary structure is established.

Signaling pathways important for early pituitary growth and development include those that regulate development of other organs from cranial placodes, as well as pathways common to pituitary and gastrointestinal neuroendocrine cells [25]. Transcription factors determine hormone-specific pituitary stem cell development. Immunohistochemistry (IHC) for pituitary hormones and cell-specific transcription factors enables classification of differentiated pituitary adenomas based on pituitary cell lineage (Table 1).

### Anterior pituitary cell type markers

Most functioning adenomas can be simply and reliably classified by IHC of pituitary hormones. The 2017 WHO classification is based on histological markers with pituitary hormones, low-molecular-weight cytokeratin (or CAM5.2), and transcription factors (Table 1). In adenomas that are either immunonegative or only faintly positive for pituitary hormones, transcription factor staining determines lineage classification [26]. Null cell adenomas are immunonegative for both pituitary hormones and specific transcription factors.

Transcription factor IHC also helps differentiate nonsecreting pituitary adenomas from nonadenomatous pituitary neoplasms, including craniopharyngiomas, meningiomas, and paragangliomas, as well as metastatic

**Table 1.** The 2017 WHO Pathological Classification of Pituitary Adenomas

| Adenoma type | Morphological variants | Pituitary hormones by immunohistochemistry | Transcription factors and other cofactors |
|---|---|---|---|
| Somatotroph | Densely granulated | GH, α-subunit | Pit-1 |
| | Sparsely granulated | GH | Pit-1 |
| | Mammosomatotroph | GH + PRL (in same cells) ± α-subunit | Pit-1, ERα |
| | Mixed somatotroph-lactotroph | GH + PRL (in different cells) ± α-subunit | Pit-1, ERα |
| Lactotroph | Sparsely granulated | PRL | Pit-1, ERα |
| | Densely granulated | PRL | Pit-1, ERα |
| | Acidophil stem cell | PRL, GH (focal and variable) | Pit-1, ERα |
| Thyrotroph | | β-TSH, α-subunit | Pit-1, GATA2 |
| Corticotroph | Densely granulated | ACTH | Tpit |
| | Sparsely granulated | ACTH | Tpit |
| | Silent[a] | ACTH | Tpit |
| | Crooke's cell | ACTH | Tpit |
| Gonadotroph | | β-FSH, β-LH, α-subunit (various combinations) | SF-1, GATA2, ERα |
| Null cell[a] | | None | None |
| Plurihormonal | Pit-1 positive[a] | GH, PRL, β-TSH ± α-subunit | Pit-1 |
| | Unusual immunohistochemical combinations | Various combinations | |

[a]Usually nonsecreting and clinically silent. Modified from Lopes MBS [1].

NETs that also express neuroendocrine markers such as synaptophysin, chromogranin A, and SSTs. These later markers are also positive in most pituitary tumors, although they are not used for diagnosis as they are not pituitary specific. Synaptophysin and SSTs, but not chromogranin A, are also expressed in follicular thyroid [27] and adrenal cortical adenomas [28], neither of which are classified as NETs. The question of whether pituitary adenomas are biologically distinct from extrapituitary neuroendocrine neoplasms [29] requires further rigorous comparative genomic and molecular single-cell analyses within and between tissue types.

## Classifications

### Surgical classifications

Cushing, in his 1912 monograph *The Pituitary Body and Its Disorders* [30], coined the term *pituitary adenomas* after analysis of 47 patients with pituitary disease.

Subsequently, Hardy's classification is based on the size and stage of pituitary adenomas, and describes "microadenomas" that are resectable with preservation of the normal pituitary gland [31]. Further subclassifications proposed by Kovacs and Horvath were based on adenoma electron microscopy ultrastructure [32]. Cavernous sinus invasion by pituitary adenomas forms the basis of the systematic imaging classification by Knosp [33].

The phenomenon of invasive pituitary adenomas remains poorly understood [34]. In a series of 354 surgically resected macroadenomas, histologic dural invasion was present in 45% of cases and increased in frequency with increasing adenoma size, but did not affect adenoma recurrence rates [35]. As invasiveness does not necessarily imply aggressiveness, there is a need for better understanding as to why some adenomas invade but are so rarely malignant. Indeed, malignancy, which is exceptionally rare among pituitary adenomas, is a strikingly differentiating characteristic from the natural history of most NETs.

### 2017 WHO classification of pituitary neoplasms

The 2017 WHO classification is based on immunoexpression of pituitary hormones, pituitary-specific transcription factors, and other cell differentiating co-factors [1]. Pituitary cell lineage-based classification has been validated by specific genomic, epigenetic, and methylation signatures [36].

The WHO solely classifies pituitary neoplasms as either *adenomas* or *carcinomas* and abandoned the 2004 category of *atypical adenoma* [19] due to a lack of clinical evidence that tumor behavior differed between typical and atypical adenomas [1]. Rather, the 2017 classification incorporated proliferation (mitotic count and Ki-67 labeling index) and tumor invasion in histological evaluation, both of which correlate with more aggressive tumor behavior. It also recognized histological variants of "high-risk" pituitary adenomas that behave more aggressively, represented mainly by sparsely granulated somatotroph adenomas, silent corticotroph adenomas, Crooke's cell adenomas, the newly termed plurihormonal PIT-1 positive adenomas, and lactotroph adenomas in men. However, it acknowledged a lack of histopathological prognosticators for these clinically aggressive pituitary adenomas.

#### What are the consequences of changing classification nomenclature?

Any suggestion to change a disease name should address biological relevance as well as practicality, acceptability, and nomenclature principles. When considering a change of pituitary neoplasm nomenclature from adenoma to NET, it is imperative to rigorously consider whether the distinction between endocrine and neuroendocrine neoplasm is conceptual or histological, and whether NETs and adenomas are morphologically distinct. Importantly, unlike NETs, the overwhelming majority of pituitary neoplasms do not require biopsy for histological definition, including those that are treated medically.

Rationales supporting a nomenclature change include recognizing that some pituitary tumors may not behave in a benign clinical manner. Thus, it has been argued that clinically aggressive tumors should not be termed "adenomas," a terminology implying a benign clinical behavior. However, a change to NET nomenclature does not provide additive guidance for distinguishing between tumors that remain benign and those that behave more aggressively. Furthermore, a proposed change to NET nomenclature also implies including relatively benign pituitary neoplasms in the very sizable category of neuroendocrine neoplasms arising in other organs/systems. This approach could potentially provide an integrated classification whereby benign pituitary adenomas are classified with the entire group of neuroendocrine neoplasms.

The WHO classification standardizes diagnosis for patient care and guides general pathologists, while also providing insights on best practice to centers that lack comprehensive resources for incorporating updated technology. It is not a tumor grading paradigm, likely because of the lack of rigorous histological and/or molecular markers that predict/correlate with tumor progression.

A classification that uses grading in a 5-tier scale combining pathological features (cell differentiation and proliferative markers) with radiological parameters (invasion), has been developed [37]. However, tumor staging is not synonymous with pathological classification, and although informative for tumor management [38, 39], may not predict tumor behavior, as invasiveness does not necessarily imply aggressive behavior.

Change in disease terminology also requires patient and physician education as well as consideration of adverse patient impact, including disease coding, epidemiologic data, and payor issues [40]. Although a formal nomenclature change would include pituitary-specific cell-type differentiation, recent manuscripts have begun to label adenohypophyseal tumors solely as "pituitary tumors" without further clarification as a way to avoid nomenclature ambiguity.

Selecting the right words to describe pituitary lesion pathology is particularly important for patients and caregivers. Because use of labels such as *cancer*, *nodule*, and *tumor* play a significant role in patient decision making [41], and because patients often associate the word *tumor* with a malignancy [42], nomenclature change to neuroendocrine tumor could lead to overtreatment, enhanced patient anxiety, and negative experiences. Inappropriate patient oncology designation may result in unforeseen subsequent medical record connotations. Appropriately communicating implications of a diagnosis, available treatments, and the natural history of low-risk lesions, including the vast majority of pituitary adenomas, remains paramount [41].

## Aggressive Pituitary Neoplasms

Pituitary adenomas account for more than 95% of the many tumor types that arise in the sella (eg, craniopharyngiomas, chordomas) [6, 7]. Of the adenomas, <0.1% of all clinically significant resected and nonresected lesions exhibit aggressive behavior [3]. In this context, the term *invasive* is inappropriately used as if synonymous with *aggressive*. Invasiveness may best be considered as an imaging diagnosis, sometimes found on pathological examination, and describes tumors that infiltrate adjacent structures, such as the cavernous sinuses, bone, and sphenoid sinus. Tumor invasion of the cavernous sinus based on imaging criteria is a strong predictor of recurrence after surgery [33, 37, 38]. A tumor is regarded as *aggressive* if there is unusually rapid growth rate, earlier and more frequent recurrences requiring repeated surgeries, and clinically relevant growth despite optimal standard therapies [43]. Thus, the terms invasive and non-invasive should refer only to imaging or morphological findings, and aggressive and non-aggressive pituitary adenomas to their clinical behavior [44].

The 2017 WHO classification recognizes pituitary tumors as having a low or high probability of recurrence [1]. Of pituitary tumors requiring surgical treatment, 15% are "aggressive" [37] but only 0.1% to 0.2% of these progress to become true carcinomas, as defined by evidence of cerebrospinal and/or systemic metastases [45-49]. Histopathological and molecular markers are unable to identify the very rare tumors that exhibit aggressive growth or very rarely malignancy. In a study of 166 aggressive pituitary tumors, including 40 pituitary carcinomas, a classical proliferation index, such as Ki-67, did not distinguish aggressive pituitary tumors from pituitary carcinomas, and there was no significant difference in clinical parameters [50]. No marker reliably seems to predict tumor behavior. Metalloproteinase 9 (MMP9) and PTTG correlate only with proliferative behavior [51].Whether tumor dedifferentiation represents an early pathogenic event or is a consequence of the carcinogenic process or intrapituitary signaling dysfunction is unknown [52, 53].

NETs (referred to as carcinoids in the literature) of the pituitary are exceedingly rare. Few cases of primary pituitary NETs have been reported [54-57], as have 8 cases of NET metastasis to the pituitary, most frequently of bronchopulmonary origin [20]. They can be distinguished from adenohypophyseal adenomas and other pituitary tumors by hormonal and transcription factor profiles.

## Summation and Conclusions

### Summary

#### Epidemiology

Pituitary adenomas are common, predominantly indolent neoplasms, more than 99% of which do not affect life expectancy. By contrast, NETs are uncommon, apart from small tumors in appendiceal and rectal locations, and are potentially cancerous and reduce life expectancy.

#### Taxonomy

The developmental biology and regulatory function of the pituitary gland is that of a neuroendocrine gland. Anterior pituitary cells and cell types are identified by immunohistochemistry of hormones, transcription factors, and cytokeratin markers. Neuroendocrine markers commonly found in pituitary tumors are also expressed in other endocrine neoplasms including thyroid follicular and adrenal cortical adenomas that are pathologically distinct and not classified as NETs.

#### Classification

Pituitary adenomas can be classified by size, radiological grade, function, ultrastructure, cell type, and lineage. The 2017 WHO classification is based on immune detection of pituitary hormones, pituitary-specific transcription factors, and other cell differentiating cofactors. Renaming adenomas to NETs does not change prognostic prediction of pituitary neoplasms. Terminology change carries connotations that may affect patient disease perception and management, assigns an uncertain malignancy designation to the vast majority of benign pituitary adenomas, and can adversely affect patient anxiety and overall disease management.

**Aggressive pituitary neoplasms**

Presently validated histological markers do not reliably predict high-risk behavior of pituitary neoplasms.

### Conclusions

There is not yet a convincing argument for adopting the PitNET nomenclature but the question requires ongoing study and further discussion as new evidence emerges.

**Epidemiology**

The clinical epidemiology, disease phenotype, management, and prognosis of pituitary neoplasms differ from most NETs.

**Taxonomy**

Referring to a pituitary adenoma as a NET may be accurate from a developmental perspective. Studies of the molecular and genomic landscape to distinguish tissue types are required. Specific histological markers are required to distinguish neuroendocrine from endocrine neoplasms.

**Classification**

Changes in classification should be justified by histological, pathological, and clinical evidence. A change to NET nomenclature does not guide identification of pituitary neoplasms that behave in a benign or aggressive manner. The proposed change disproportionately portrays mostly benign pituitary neoplasms as aggressive or malignant, which may adversely affect patient wellbeing.

**Aggressive pituitary neoplasms**

Further research is required to identify the very small number of indolent tumors that acquire aggressive and metastatic behavior.

## Recommendations

Following the PANOMEN workshop and review of the draft document, participants were asked: [1] whether the term tumor confers any advantage as a collective label for all pituitary neoplasms or to the subset of invasive pituitary adenomas; and [2] in the absence of rigorous pathological markers of high-risk behavior, whether imaging grades of invasiveness should be incorporated into a comprehensive pituitary classification and grading.

Seventy-nine percent (38/48) of authors recommend that the term "pituitary adenoma" not be replaced by "pituitary tumor," and 58% (28/48) do not favor using the term "tumor" to designate the very small subset of invasive adenomas.

Given the absence of rigorous pathological markers of high-risk behavior, 65% (31/48) recommend that imaging grades be incorporated into a classification of pituitary neoplasms. Integrating imaging grade with pathological classification would likely benefit prognostication for clinical management.

It is recommended that the outcome of the PANOMEN workshop be communicated to relevant stakeholder professional societies, including those represented at this workshop and to the IARC/WHO for consideration in future classifications of endocrine tumors. It is recommended that this topic be revisited and the question of NET nomenclature be discussed further as new evidence emerges. It is recommended that patient feedback be obtained before potential future nomenclature changes are considered.

## Open Questions

The workshop revealed controversy on issues which merit addressing in future workshops as new information emerges, including:

1. Do primary pituitary NETs occur as an entity? Some participants were skeptical as to the validity of published reports supporting a diagnosis of primary pituitary neuroendocrine tumor.
2. Is the difference between an endocrine and neuroendocrine cell conceptual or histological? Several participants questioned the specificity of traditional neuroendocrine markers (synaptophysin, chromogranin, neuron-specific enolase and somatostatin receptors) which are also expressed in follicular thyroid and adrenal cortical adenomas, neoplasms not regarded as of neuroendocrine origin.

## Acknowledgments

Drs. Chiara Villa, Olivera Casar-Borota, and Federico Roncaroli participated in the workshop and have declined authorship as they disagreed with the outcome. The Pituitary Neoplasm Nomenclature Workshop was supported by unrestricted educational grants to the Pituitary Society from Chiasma, Inc., Corcept Therapeutics, Ipsen Biopharmaceuticals, Novo Nordisk, Pfizer Inc., Strongbridge Biopharma, and Tiburio Therapeutics. Funding sources had no role in data collection, analysis, and interpretation, decision to publish, or preparation of the manuscript. The authors thank Bari Laner and the Pituitary Society for coordinating the workshop.

***Financial Support:*** Supported by unrestricted educational grants to the Pituitary Society from Chiasma, Inc., Corcept Therapeutics, Ipsen Biopharmaceuticals, Novo Nordisk, Pfizer Inc., Strongbridge Biopharma, and Tiburio Therapeutics. Funding sources had no role in data collection, analysis, and interpretation, decision to publish, or preparation of the manuscript.

***Author Contributions:*** K.H. and S.M. served as Workshop Chairs. M.M., P.K., S.C., H.N., M.B.L., E.L., L.V.S., T.B., A.G. served as Speakers; M.F., U.K., R.S., P.T. as Content Chairs; and M.G., J.W., F.C., A.B., M.R. as Session Chairs. All authors researched, reviewed, and commented on the data prior to and/or during the workshop. K.H. and S.M. prepared the manuscript drafts and all authors reviewed and approved the final manuscript.

## Additional Information

***Correspondence***: Ken Ho, MD, The Garvan Institute of Medical Research, 384 Victoria Street, Sydney, NSW 2010, Australia. Email: k.ho@garvan.org.au.

***Disclosures:*** The authors have declared that no conflict of interest exists.

***Data Availability:*** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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