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Clinical Research Article

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Prospective Evaluation of Incidental Pituitary Imaging Findings in the Sella Turcica

Michael Kuo,[1] Marcel M. Maya,[2] Vivien Bonert,[1] and Shlomo Melmed[1]

[1]Pituitary Center, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA; and [2]Department of Imaging, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA

ORCiD numbers: 0000-0001-8236-7671 (M. M. Maya); 0000-0002-2355-3447 (S. Melmed).

Abbreviations: CT, computed tomography; ED, emergency department; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; MRI, magnetic resonance imaging; PTCOE, Pituitary Tumors Center of Excellence.

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Abstract

Purpose: Reported rates of incidentally discovered pituitary sellar lesions vary widely, at least in part because of the inadvertent inclusion of patients with a history suspicious for a pituitary disorder. We prospectively evaluated the incidence of truly incidental sellar findings detected on imaging at a large academic medical center.

Methods: Deidentified data were extracted from the electronic medical record of adults who underwent diagnostic computed tomography (CT) or magnetic resonance imaging (MRI) over a 1-year period for any cause unrelated to known or suspected pituitary disorder both in inpatient and outpatient settings. Patients with International Classification of Diseases, Ninth Revision, (ICD-9) and Tenth Revision (ICD-10) codes indicative of a sellar lesion and those with symptoms suggestive of sellar/parasellar mass effects were excluded.

Results: Of 9572 scans performed during the 1-year study period, 3840 met the inclusion criteria to comprise the study cohort; 13 were manually excluded because of findings or symptoms of sellar masses not otherwise captured. The overwhelming majority of evaluable images (n = 3782) showed no sellar lesions. Truly incidental sellar findings were detected in 45 (1.2%), most commonly among inpatients ($P < .001$). Partially empty sella and empty sella were the most frequent findings, and were twice as likely to be detected on MRI vs CT. All other incidentally discovered lesions, including one microadenoma and one macroadenoma, were detected only by MRI.

Conclusion: Frequency of incidental sellar lesions in patients with no known or suspected history of pituitary disorder is low. Given the small likelihood of aggressive behavior in these lesions, the clinical significance of truly incidentally discovered sellar lesions should not be overestimated.

Key Words: pituitary incidentaloma, pituitary adenoma, pituitary imaging, sellar lesion

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Patients with pituitary adenomas arising from differentiated hormone-expressing cells typically exhibit unique phenotypes depending on the specific hormonal secretory pattern [1, 2]. Clinically silent adenomas that do not hypersecrete hormones may be discovered incidentally while undergoing imaging evaluation for neurological disorders, including headache, head trauma, stroke, epilepsy, and vertigo [3]. In population studies, the estimated prevalence of pituitary adenomas is less than 1%, with 77 to 116 cases per 100 000, and 3 to 6 new cases are diagnosed per 100 000 per year [4-8]. Yet, autopsy studies show that approximately 10% of individuals harbor pituitary incidentalomas, and imaging studies show detection rates of 10% to 34% on magnetic resonance imaging (MRI) and 4% to 20% on computed tomography (CT) [3, 9-16]. These reports suggest that clinically inapparent lesions are common, but the widely varied definitions of "incidentaloma" in the literature, which may include asymptomatic lesions, nonfunctioning pituitary adenomas, and/or all incidentally detected pituitary or intrasellar findings, coupled with discordance among neuroradiologists in assessing focal areas of decreased intensity on MRI [17], challenges our understanding of their true frequency.

Importantly, these challenges may hinder accurate assessment and management of incidentally discovered sellar lesions. Evaluation of pituitary masses can be costly [18, 19], guideline recommendations for differential diagnosis and management of cystic lesions are lacking, and evidence-based risk stratification for follow-up surveillance based on anticipated tumor growth or complications remains difficult [20].

We prospectively studied the frequency of incidental sellar lesions identified at a tertiary referral academic medical center by diagnostic head CT and MRI scans performed over a 1-year period for any cause unrelated to known pituitary pathology or clinically suspected pituitary disorder. Using this rigorous definition of truly incidentally discovered sellar lesions, we aimed to understand the frequency of these findings, establish a platform for standardizing an approach to identify such lesions, and guide rational resource use by minimizing unnecessary evaluation of incidentally detected benign sellar lesions.

1. Materials and Methods

This prospective, single-center, investigator-initiated study evaluated the frequency of sellar lesions detected incidentally between January 1 and December 31, 2019, in diagnostic head CT or MRI for any cause unrelated to known or suspected pituitary pathology both in inpatients and outpatients at Cedars-Sinai Medical Center, a tertiary referral academic medical center with a level 1 trauma emergency department (ED). The study protocol was approved by the Cedars-Sinai Medical Center Institutional Review Board.

The study was prospectively designed to identify sellar lesions in a population with no known history of sellar or pituitary lesions or any clinical findings suggestive of pituitary hormonal dysfunction. Beginning January 1, 2019, the Cedars-Sinai Honest EIS Broker Committee extracted deidentified data weekly from the electronic medical record of all adult patients age 18 years or older who underwent head MRI with or without gadolinium or head CT with or without contrast, then excluded patients with a known history of sellar lesions based on International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) code criteria (Table 1). Patients with pituitary masses related to anterior pituitary hyperfunction or a history of abnormal pituitary hormone laboratory results were excluded, as were those with features of sellar/parasellar central mass effects such as visual field deficits, blurry vision, or vision loss suggestive of a pituitary mass. CT technique was based on helical imaging in the axial plane reformatted in sagittal and coronal planes. All series are reconstructed in 2.5-mm sections. Brain MRI was performed with 1.5 T and 3 T scanners, with 2-mm coronal and sagittal cuts.

Each patient in the resultant data set was deidentified and assigned a randomly generated patient identifier. For analysis, investigators had access only to deidentified patient demographics, hormone laboratory results obtained at our center during the 1-year study period either prior to imaging or recorded during intake, indication for imaging, and imaging diagnosis. Incidentally discovered masses were characterized for size, mass composition (solid vs cystic), and evidence of anterior pituitary dysfunction.

Clinical and imaging data were reviewed by an endocrinologist to ensure that patients with any evidence of abnormal pituitary findings were appropriately excluded per protocol. The radiologist reconfirmed imaging reports for patients included in the final cohort identified with incidental sellar findings.

Incidence of incidentally discovered lesions was calculated as the number of patients with positive CT and/or MRI imaging studies divided by the total number of patients imaged. Numerical variables were summarized by mean and SD. Categorical variables were summarized by frequency and percentage and compared between the groups. Differences in age were calculated using a 2-tailed *t* test; prior to *t*-testing, an *F* test was performed to evaluate equality of variance. Patients older than 85 years were classified as 85+ and were assumed to have an age of 85 for all calculations. The chi-square test was used for all other comparisons. Statistical significance was calculated

Table 1. International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) code criteria used to exclude patients with known history of sellar lesions

ICD-10	Diagnosis
D35.2	Benign neoplasm of pituitary gland
D35.7	Benign neoplasm of other specified endocrine glands
D35.9	Benign neoplasm of endocrine gland, unspecified
E22	Hyperfunction of pituitary gland
E22.8	Other hyperfunction of pituitary gland
E22.9	Hyperfunction of pituitary gland, unspecified
E22.0	Acromegaly and pituitary gigantism
E22.1	Hyperprolactinemia
E22.2	Syndrome of inappropriate secretion of antidiuretic hormone
E24	Cushing syndrome
E24.0	Pituitary-dependent Cushing disease
E24.8	Other Cushing syndrome
E24.9	Cushing syndrome, unspecified
E23	Hypofunction and other disorders of the pituitary gland
E23.0	Hypopituitarism
E23.3	Hypothalamic dysfunction, not elsewhere classified
E23.6	Other disorders of pituitary gland
E23.7	Disorder of pituitary gland, unspecified
E23.2	Diabetes insipidus
ICD9	**Diagnosis**
227.3	Benign neoplasm of pituitary gland and craniopharyngeal duct
227.9	Benign neoplasm of endocrine gland, site unspecified
194.3	Malignant neoplasm of pituitary gland and craniopharyngeal duct
198.89	Secondary malignant neoplasm of other specified sites
234.8	Carcinoma in situ of other specified sites
237.0	Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct
239.7	Neoplasm of unspecified nature of endocrine glands and other parts of nervous system
253.0	Acromegaly and gigantism
253.1	Other and unspecified anterior pituitary hyperfunction
253.2	Panhypopituitarism
253.3	Pituitary dwarfism
253.4	Other anterior pituitary disorders
253.5	Diabetes insipidus
253.6	Other disorders of neurohypophysis
253.7	Iatrogenic pituitary disorders
253.8	Other disorders of the pituitary and other syndromes of diencephalohypophyseal origin
253.9	Unspecified disorder of the pituitary gland and its hypothalamic control
259.8	Other specified endocrine disorders
259.9	Unspecified endocrine disorder

using an α level of .05 or less throughout. Microsoft Excel for Office 365 (Microsoft Corp) was used for statistical calculations.

2. Results

A total of 9572 patients underwent head CT or MRI during the study period, and 6820 (71%) met the inclusion criteria. Of these, 2980 (44%) were excluded because they underwent more than 1 head scan during the study period. The remaining 3840 (56%) patients comprised the study cohort (Fig. 1). Eight patients were subsequently excluded based on prior reports of sellar findings not captured on ICD-9 or ICD-10 coding, and 5 were excluded based on history of signs or symptoms consistent with a suspected pituitary disorder (Table 2).

Incidental sellar findings were reported in 45 (1.2%) patients, including 10 on CT and 35 on MRI. Partially empty sella and empty sella were the most frequent findings, and were twice as likely to be detected on MRI vs CT (Table 3). All incidentally discovered sellar lesions other than partially empty or empty sella, including one microadenoma and one macroadenoma, were detected only by MRI.

Incidental sellar findings were most often identified on evaluation for neurological conditions, including headache, stroke, vertigo/dizziness, and memory loss (Table 4).

Patient demographics in the overall cohort (N = 3840) and the subset with incidental sellar findings (n = 45) are shown in Table 5. The average age of those with a sellar lesion was higher compared with the overall study cohort (64 vs 59; $P = .032$), and there was also a higher percentage of women in this group (76% vs 57%; $P = .013$). Racial and ethnic distributions were similar.

In the overall cohort, 75% of head imaging studies were performed in outpatient settings, yet incidental sellar lesions were significantly more likely to be detected in an inpatient vs an outpatient setting compared with the overall study population ($P < .001$). No other comparisons between the overall cohort and the subset with incidental sellar lesions were statistically significant.

3. Discussion

This prospective study identified 45 patients with incidentally discovered sellar findings over a 1-year period, including 2 pituitary adenomas. These results represent less than 1.2% of the 3840 patients undergoing diagnostic head CT or MRI for any cause unrelated to suspected pituitary dysfunction.

We used the broadest definition of an "incidentaloma," and included any abnormal sellar finding detected on imaging, regardless of any known clinical significance and their eventual management. Importantly, we employed strict inclusion/exclusion criteria to narrow our focus to findings truly considered incidental. ICD-9 and ICD-10 codes were used to exclude patients with known pituitary pathologies, but these codes do not explicitly differentiate between

central/secondary and primary hormonal disturbances, or between pituitary vs medication-induced hormonal abnormalities. For example, patients with steroid-induced adrenal insufficiency and incidental sellar findings could have been inappropriately excluded, falsely lowering the prevalence of observed sellar findings. We therefore manually reviewed records for all patients with documented primary adrenal insufficiency, thyroid disorders, reproductive disorders, and other common endocrinological problems who were included in our overall cohort if their condition was unrelated to known pituitary dysfunction.

We excluded patients with signs and symptoms suspicious of pituitary pathology. In an earlier survey of 2598 patients undergoing pituitary MRI between 1999 and 2009 at our center, 282 sellar masses were identified as having been incidentally detected on prior head imaging and then referred for follow-up evaluation on pituitary MRI [21]. However, this group included patients presenting with visual loss or blurring, common features of patients with a mass effect from a pituitary adenoma [1]. Such patients were excluded from our present group. By contrast, although headache is a common symptom among patients presenting with pituitary macroadenoma [1], headache in the absence of other signs and symptoms suggestive of underlying pituitary pathology only very rarely indicates the presence of a pituitary tumor. Thus, our approach of broadly defining incidental sellar lesions while limiting findings to those most likely to be truly incidental leads to an inferred incidence for incidentally discovered sellar lesions that is much lower than previously reported for incidentalomas.

The estimated pituitary incidentaloma frequency rate of 10.7% based on autopsy studies comprising nearly 20 000 patients [9] may be an overestimation, and likely includes pituitary adenomas that were inappropriately classified as incidental [22]. In studies of patients with incidentally found "nonfunctioning" microadenomas, approximately 10% show hyperprolactinemia [15, 23] and 15% to 25% demonstrate one or more pituitary hormone deficits attributable to the lesion [14-16, 23]. In one series, one-fourth of those with hypogonadism confirmed symptoms of decreased libido only after the incidental lesion was detected [24]. Guidelines recommend obtaining a complete history, physical exam, and laboratory evaluations for pituitary dysfunction once an incidentaloma is detected [3]. The results shown here suggest exclusion of such lesions by comprehensive evaluation and/or careful assessment of patient records for suspicious signs and symptoms before imaging would yield a more accurately defined cohort with truly incidental findings. Such an analytical approach may explain the wide variances in reported frequencies among epidemiologic, imaging, and autopsy studies.

Using our narrow criteria to define truly incidentally discovered sellar lesions led to detection of findings that

Table 2. Manually excluded patients based on prior report of sellar findings not captured on International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10) coding or signs/symptoms suspicious of pituitary disorder

Prior reported sellar finding	n
Meningioma	1
Microadenoma	2
Partially empty sella	1
Pituitary tumor	1
Tuberculum sella	2
Enlarged sella	1
Features suspicious of pituitary disorder	**n**
Growth failure	1
Hypogonadism	2
Low prolactin	2

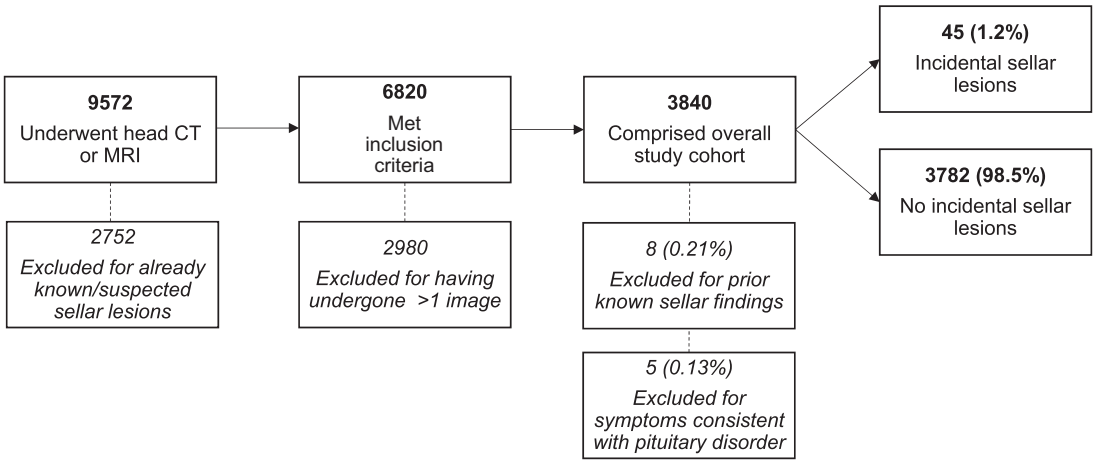

Figure 1. Identification of overall study cohort (N = 3840) and subset with incidental sellar imaging findings (n = 45).

Table 3. Incidental sellar findings detected on computed tomography (CT) and magnetic resonance imaging (MRI)

Diagnosis, n (%)	Detected on MRI (n = 35)	Detected on CT (n = 10)	Total
Partially empty sella	17 (49)	9 (90)	26 (58)
Pituitary enlargement	7 (20)	0 (0)	7 (16)
Empty sella	5 (14)	1 (10)	6 (13)
Tuberculum sella meningioma	3 (9)	0 (0)	3 (7)
Rathke cyst	1 (3)	0 (0)	1 (2)
Macroadenoma	1 (3)	0 (0)	1 (2)
Microadenoma	1 (3)	0 (0)	1 (2)
Total	35 (78)	10 (22)	45 (100)

Table 4. Indications for imaging study among patients with an incidental sellar finding

Indication	n (%)
Neurological	32 (71)
Headache	12 (27)
Stroke	5 (11)
Vertigo/dizziness	5 (11)
Memory loss	4 (9)
Paresthesia	2 (4)
Retinal disorder	2 (4)
Ataxia	1 (2)
Weakness	1 (2)
Mass	2 (4)
Multiple meningioma	1 (2)
Metastatic breast cancer	1 (2)
Systemic	2 (4)
Neurofibromatosis type 1	1 (2)
Connective tissue disorder	1 (2)
Miscellaneous	9 (20)
CSF leak	3 (7)
Trauma	2 (4)
Alcohol intoxication with motor vehicle accident	1 (2)
Carotid stenosis	1 (2)
Not available	2 (4)

Abbreviation: CSF, cerebrospinal fluid.

may not require further evaluation. Most of the incidental findings in our study were partially empty or empty sellas, in which the sellar space is filled with cerebrospinal fluid and the pituitary is flattened against the sellar rim [25]. A systematic review found that up to half of patients with primary empty sella show some degree of pituitary insufficiency [26]. Because patients with documented evidence of hypopituitarism were excluded from our cohort, we consider it more likely that our findings are secondary to increased intracranial pressure or changes in pituitary volume due to pregnancy or hypophysitis, or possibly secondary to spontaneous prior pituitary adenoma hemorrhage or infarction [25, 26]. Indeed, although only one incidental microadenoma was incidentally detected, the empty sella findings may represent evidence of previously undetected, clinically inapparent pituitary adenomas that spontaneously regressed.

Some patients diagnosed with empty sella may have had a hormone deficiency that was not documented or whose documentation was unknown to us. In the overall cohort, 75% of patients underwent imaging on referral from a clinic or the ED without subsequent hospital admission. Data were deidentified before analyses, and ED and outpatient medical records are less comprehensive than inpatient records. Thus, hormone testing reports were available for only 5 of 45 individuals with incidental findings, and biochemical results were normal in all cases. If we had inadvertently identified patients with incidental empty sella despite an underlying hypopituitarism, this would suggest that we may have *overestimated* the number of patients with no pituitary pathology who demonstrate incidental findings on imaging, and that the true prevalence rate is even lower than the 1.2% we observed.

Pituitary enlargement represented 16% of the lesions we found, which may include physiologic variations in pituitary size, including pituitary glands imaged in menstruating women [27]. An enlarged pituitary gland may also be seen with pituitary hyperplasia or hypophysitis. However, because the former may be secondary to sustained hypothyroidism [28, 29] and the latter is commonly associated with hormonal deficits [30], it is likely that patients with these disorders would have been excluded from our study. The clinical significance of idiopathic enlarged pituitary in the absence of endocrine findings is unknown, but our results suggest that follow-up of such patients would indicate a benign finding over the long term with therapeutic intervention likely not required [31].

We detected a single incidental 12-mm pituitary macroadenoma in a 52-year-old woman with neurofibromatosis type 1, known to be associated with silent corticotroph pituitary adenoma or acromegaly [32, 33]. A multidisciplinary team expert in neuroendocrine disease management such as at a Pituitary Tumors Center of Excellence (PTCOE) should manage such rarely presenting patients [34].

Table 5. Patient demographics in overall cohort and subset with incidental sellar imaging findings

	Overall cohort (N = 3840)	Incidental sellar findings (n = 45)	*P*
Age			
Mean, y (SD)	59 (20)	64 (16)	.032
≤ 85 y, n (%)	3515 (92)	41 (91)	.919
85 y +, n (%)	325 (8.5)	4 (8.9)	
Sex, n (%)			
Female	2197 (57)	34 (76)	.013
Male	1643 (43)	11 (24)	
Race			.054
White	2682 (70)	33 (73)	
Black or African American	394 (10)	6 (13)	
Asian	241 (6.3)	2 (4.4)	
Other	217 (5.7)	1 (2.2)	
Unknown	231 (6.0)	2 (4.4)	
American Indian or Alaska Native	5 (0.13)	1 (2.2)	
Native Hawaiian or other Pacific Islander	9 (0.23)	0 (0)	
Patient refused	17 (0.44)	0 (0)	
Missing data	44 (1.1)	0 (0)	
Ethnicity, n (%)	3840 (100)	45 (100)	.891
Non-Hispanic	3148 (82)	36 (80)	
Hispanic	370 (9.6)	5 (11)	
Unknown	261 (6.8)	4 (8.9)	
Patient refused	19 (0.49)	0 (0)	
Missing data	42 (1.1)	0 (0)	
CT scan, n (%)	1292 (34)	10 (100)	.605
CT brain wo contrast	1006 (78)	10 (100)	
CT brain wo/w contrast	149 (12)	0 (0)	
CT head brain wo contrast	75 (5.8)	0 (0)	
CT head brain wo/w contrast	54 (4.2)	0 (0)	
CT brain wo/w contrast fiducial markers	5 (0.39)	0 (0)	
CT brain wo contrast fiducial markers	3 (0.23)	0 (0)	
MRI, n (%)	2548 (66)	35 (78)	.452
MRI brain wo contrast	1024 (40)	18 (51)	
MRI brain wo/w contrast	1462 (57)	17 (49)	
MRI pituitary wo/w contrast	58 (2.3)	0 (0)	
MRI pituitary wo contrast	4 (0.16)	0 (0)	
Setting, n (%)			< .001
Inpatient	977 (25)	30 (67)	
Outpatient	2863 (75)	15 (33)	

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; w, with; wo, without.

Lesions were found more often using MRI than CT (78% vs 22%), consistent with the literature [10, 35], and all incidental findings except partially empty sella and empty sella were detected only on MRI. This, at least in part, may reflect advances in MRI technology that enables detection of smaller abnormalities compared to studies with CT conducted in the 1990s, affording MRI better resolution than CT for detecting microadenomas and for distinguishing soft-tissue parasellar involvement. Increased signal-to-noise ratio is a major advantage of 3 T MRI, which allows faster scanning times and image richness, resulting in improvements in overall image quality [36].

We detected a single microadenoma on MRI. Sensitivity for pituitary microadenoma detection increases 10% to 20% with the use of gadolinium contrast and may be higher with advanced techniques, such as dynamic and spoiled-gradient echo sequences [37, 38]. There are no rigorous studies examining the effect of gadolinium on the sensitivity of brain MRI in detecting pituitary microadenomas. Because use of pituitary MRI with contrast is not standard in the reported incidentaloma literature, our protocol appears consistent with methodology used for other studies of incidental findings.

Interestingly, sellar lesions were identified far more frequently among women vs men (76% vs 24%). We also found that the average age of the overall cohort was significantly lower than in the cohort with incidental lesions (59 vs 64; $P = .032$). There is no apparent clinical reason

for our observed older female predisposition in detecting incidental sellar lesions.

We recognize that using ICD-9 and ICD-10 codes to include or exclude patients with an underlying pituitary pathology may be subject to misclassification bias, stemming from incorrect diagnoses, incorrect coding of correct diagnoses, or even administrative errors derived from incorrect selection of diagnosis codes in the electronic medical record system. Although it is possible this may have influenced results, misclassification is a known, unavoidable limitation of studies relying on data obtained from medical records [39].

In conclusion, we report a very low frequency of incidental sellar findings in this prospective study of patients imaged at a large tertiary referral center with no known or suspected history of pituitary disease. Longitudinal studies suggest a low likelihood that incidentally discovered pituitary hyperplasia would become adenomatous or that adenomas would display aggressive, high-risk behavior [11, 13-15, 23, 31, 40]. Accordingly, although endocrinological evaluation of all abnormal findings is appropriate, and monitoring incidentally detected adenomas is certainly warranted [41-43], physicians should be cautious in not overestimating their potential clinical significance [44, 45]. This may be particularly important at smaller centers that lack experience in evaluating pituitary tumors, and underscores the importance of referring patients with known or suspected pituitary lesions to a PTCOE for further evaluation [34]. Our results provide a platform for implementing rational, cost-effective monitoring strategies for patients with truly incidental sellar findings.

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Additional Information

Correspondence: Shlomo Melmed, MB, ChB, Cedars-Sinai Medical Center, 8700 Beverly Blvd, NT2015, Los Angeles, CA 90048, USA. E-mail: Melmed@csmc.edu.

Disclosure Summary: The authors have nothing to disclose.

Data Availability: Restrictions apply to some or all the availability of data generated or analyzed during this study to preserve patient confidentiality. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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