



# Recent Updates on the Management of Adrenal Incidentalomas

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Adrenal incidentalomas represent an increasingly common clinical conundrum with significant implications for patients. The revised 2023 European Society of Endocrinology (ESE) guideline incorporates cutting-edge evidence for managing adrenal incidentalomas. This paper provides a concise review of the updated contents of the revised guideline. In the 2023 guideline, in patients without signs and symptoms of overt Cushing's syndrome, a post-dexamethasone cortisol level above 50 nmol/L (>1.8 µg/dL) should be considered as mild autonomous cortisol secretion. Regarding the criteria of benign adrenal adenomas, a homogeneous adrenal mass with ≤10 Hounsfield units on non-contrast computed tomography requires no further follow-up, irrespective of its size. The updated guideline also discusses steroid metabolomics using tandem mass spectrometry to discriminate malignancy. It underscores the importance of high-volume surgeons performing adrenalectomy and emphasizes the pivotal role of a multidisciplinary team approach in deciding the treatment plan for indeterminate adrenal masses. The guideline advocates for more proactive surgical treatment for indeterminate adrenal masses in young patients (<40 years) and pregnant women. This review of the 2023 ESE guideline underscores the ongoing evolution of the adrenal incidentaloma management landscape, emphasizing the need for further research and adaptation of diagnostic and therapeutic strategies.

**Keywords:** Adrenal cortex neoplasms; Cortisol; Adrenal cortex function tests; Steroids; Metabolomics

## INTRODUCTION

Adrenal incidentalomas, which are tumors of the adrenal gland discovered incidentally during radiologic examinations for other purposes, have emerged as an area of interest in the medical field. The incidence of adrenal incidentalomas has increased dramatically in recent years due to the widespread use of cross-sectional imaging scans [1]. Although the majority of these tumors are benign and nonfunctioning, certain types, including adrenal cortical carcinoma, pheochromocytoma, and function-

ing tumors, can significantly affect patients' health and necessitate therapeutic interventions.

Given the heterogeneous clinical landscape of adrenal incidentalomas, it is crucial to develop comprehensive, evidence-based guidelines to guide the appropriate diagnostic procedures, therapeutic management, and long-term monitoring of patients with adrenal incidentalomas. Since the National Institutes of Health issued the first guideline for managing adrenal incidentalomas, several other guidelines have been published by various organizations: the American Association of Clinical Endo-

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crinologists (AAACE) and American Association of Endocrine Surgeons (2009) [2], Canadian Urological Association (2011) [3], Italian Association of Clinical Endocrinologists (2011) [4], European Society of Endocrinology (ESE) (2016) [5], and Korean Endocrine Society (KES) (2017) [6]. Most of these guidelines concur on the initial hormonal and radiological assessment of adrenal incidentalomas. However, the management strategies for adrenal tumors with autonomous cortisol secretion and the follow-up protocols for non-operated tumors have evolved in light of emerging evidence.

The recently published 2023 ESE guideline has updated the previous 2016 version, specifically in terms of the assessment of malignancy risk, the definition and management of mild autonomous cortisol secretion (MACS), and the follow-up strategies for adrenal tumors [5,7]. Herein, we aim to concisely review current guidelines on adrenal incidentalomas, focusing on the recently published 2023 ESE guideline.

## ASSESSMENT OF HORMONE SECRETION

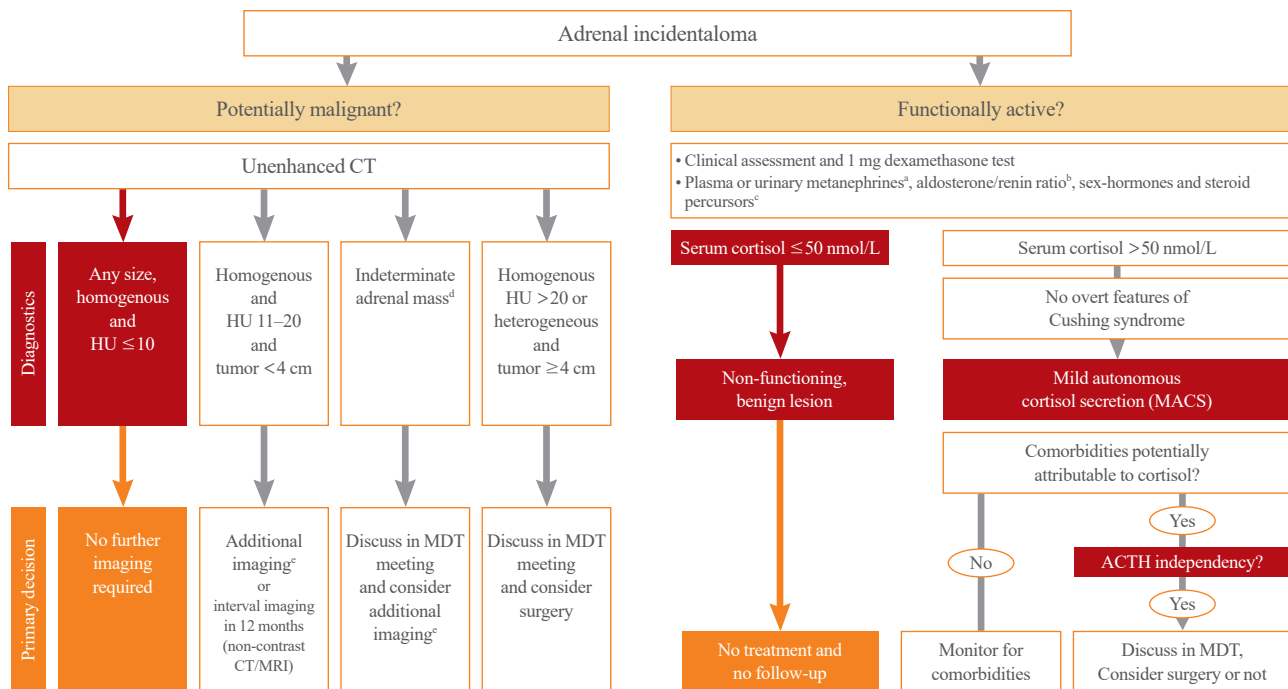
A comprehensive flow diagram detailing the management of

patients with adrenal incidentaloma is presented in Fig. 1. The key updates in the 2023 ESE guideline, as well as their differences with the 2016 ESE guideline and the 2017 KES guideline, are delineated in Table 1.

### Initially hormonal evaluation

All guidelines recommend a clinical assessment for symptoms and signs of adrenal hormone excess, as well as a 1-mg overnight dexamethasone suppression test (DST). A notable addition to the 2023 guideline is the statement that in frail patients with limited life expectancy, the DST may not be necessary. This is based on some evidence of increasing serum cortisol levels after a DST with age [8] and diminishing the clinical significance of MACS in patients over 65 years of age [9].

The 2016 ESE and 2017 KES guidelines recommend measuring plasma free or urinary fractionated metanephrines in all patients with adrenal incidentalomas to exclude pheochromocytoma. However, recent studies have demonstrated that an adrenal mass with  $\leq 10$  Hounsfield units (HU) on unenhanced computed tomography (CT) is unlikely to be pheochromocytoma [10,11]. Thus, the 2023 ESE guideline does not recommend



**Fig. 1.** Flow diagram on the management of patients with adrenal incidentaloma. Modified from Fassnacht et al. [7]. MDT, multidisciplinary team; ACTH, adrenocorticotropic hormone. <sup>a</sup>Only in adrenal tumors with > 10 Hounsfield units (HU) on unenhanced computed tomography (CT); <sup>b</sup>Only in patients with hypertension or hypokalemia; <sup>c</sup>Only in patients with findings suggestive of adrenocortical carcinoma; <sup>d</sup>Indeterminate adrenal mass: homogeneous with 11 to 20 HU and tumor  $\geq 4$  cm, homogeneous with > 20 HU and tumor < 4 cm, and heterogeneous tumors < 4 cm; <sup>e</sup>Fluorodeoxyglucose positron emission tomography/CT, adrenal magnetic resonance imaging (MRI) with chemical shift, or washout CT.

**Table 1.** Key Updates to the 2023 ESE Guideline

Remarks	2023 ESE guideline	2016 ESE guideline	2017 KES guideline
Category for serum cortisol after 1-mg DST	Recommend: MACS <sup>a</sup> : patients without features of overt Cushing's syndrome with serum cortisol after DST > 50 nmol/L (> 1.8 µg/dL) <sup>a</sup> Confirm ACTH-independency, repeat DST, consider conditions that alter the results Additional biochemical tests to assess the degree of cortisol secretion might be useful <sup>a</sup> .	Suggest: possible ACS <sup>a</sup> : serum cortisol after DST between 51 and 138 nmol/L (1.9–5.0 µg/dL) ACS <sup>a</sup> : serum cortisol after DST > 138 nmol/L (> 5.0 µg/dL) Additional biochemical tests might be required <sup>a</sup> .	Similar to the 2016 ESE guidelines
Treatment for patients with MACS	Recommend <sup>a</sup> : discussing surgery with the patient. Consider age, sex, general health, degree and persistence of non-suppressible cortisol after dexamethasone, severity of comorbidities, and patient's preference. The proposal to perform surgery should be established within an expert MDT <sup>a</sup>	Suggest <sup>a</sup> : an individualized approach for adrenal surgery. Consider age, degree of cortisol excess, general health, comorbidities, and patient's preference. In all patients considered for surgery, ACTH-independency of cortisol excess should be confirmed.	NA
Measurement of sex hormone and steroid precursors	Suggest: ideally, use multi-steroid profiling by tandem mass spectrometry <sup>a</sup> in patients in whom an adrenocortical carcinoma is suspected.	Suggest <sup>a</sup> : in patients with clinical or imaging features suggestive of adrenocortical carcinoma	Recommend <sup>a</sup> : all patients suspected of having adrenal cancer.
Benign criteria for no further imaging	Recommend <sup>a</sup> : homogeneous appearance and ≤ 10 HU on non-contrast CT	Suggest <sup>a</sup> : homogeneous appearance, smaller than 4 cm and ≤ 10 HU on non-contrast CT	Homogeneous appearance, smaller than 4 cm <sup>a</sup> and ≤ 10 HU on non-contrast CT+contrast washout in delayed images of contrast CT
Management of indeterminate adrenal nodules	(1) Adrenal mass with unenhanced HU between 11 and 20 and < 4 cm <sup>a</sup> Suggest: immediate additional imaging to avoid any follow-up imaging. Optional: interval imaging in 12 months by non-contrast CT (or MRI) (2) Adrenal mass ≥ 4 cm and unenhanced > 20 HU <sup>a</sup> Suggest: MDT, immediate surgery/staging Optional: follow-up imaging in 6–12 months (3) Adrenal mass ≥ 4 cm with unenhanced HU 11–20; or < 4 cm with unenhanced HU > 20; or tumor size < 4 cm with heterogeneous appearance Suggest: individualized approach in MDT	Three options <sup>a</sup> : (1) Immediate additional imaging with another modality (2) Interval imaging in 6 to 12 months (non-contrast CT or MRI) (3) Surgery without further delay.	Recommend: follow-up imaging in 3–6 months after the initial study and continuing for 1–2 years <sup>a</sup> Consider adrenalectomy <sup>a</sup> if the mass enlarges by 1 cm <sup>a</sup> or more and/or changes its appearance during observation
Surgical treatment	Recommend: surgery by an expert high-volume adrenal surgeon <sup>a</sup> in patients suspicious of malignancy Suggest: surgical resection if indeterminate adrenal mass on imaging in children, adolescents, pregnant women and adults < 40 years of age <sup>a</sup> .	NA	NA
Hormone follow-up of nonfunctioning tumors at initial evaluation	Recommend: against <sup>a</sup> repeated hormonal work-up unless new clinical signs of endocrine activity appear or comorbidities worsen	Suggest: against <sup>a</sup> repeated hormonal work-up unless new clinical signs of endocrine activity appear or comorbidities worsen	Recommend <sup>a</sup> : annual hormone tests for 4–5 years
Follow-up of patients with MACS	Recommend: only annual re-assessment of comorbidities potentially attributable to cortisol. If these comorbidities develop or worsen, referral to an endocrinologist.	Suggest: annual clinical re-assessment for comorbidities potentially related to cortisol excess. Based on the outcome of this evaluation the potential benefit of surgery should be considered.	Recommend: annual hormone tests for 4–5 years

(Continued to the next page)

Table 1. Continued

Remarks	2023 ESE guideline	2016 ESE guideline	2017 KES guideline
Approach to bilateral adrenal incidentaloma	Suggest following four-option schema <sup>a</sup> (1) bilateral (macronodular) hyperplasia, (2) bilateral adrenal adenomas, (3) two morphologically similar, but non-adenoma-like adrenal masses, (4) two morphologically different adrenal masses. Bilateral (macronodular) hyperplasia or bilateral adenomas: recommend assessment of comorbidities attributable to MACS <sup>a</sup> otherwise, similar to the 2016 ESE guideline	The same applies to the assessment of comorbidities that might be related to ACS. Bilateral hyperplasia without ACS: 17-hydroxyprogesterone Bilateral metastases, lymphoma, infiltrative inflammatory disease and hemorrhages: recommend assessment for adrenal insufficiency	Similar to the 2016 ESE guideline
Treatment for bilateral adrenal incidentaloma	(1) Bilateral hyperplasia <sup>a</sup> or bilateral adenomas with MACS: suggest individualized treatment options <sup>a</sup> (2) Suggest against bilateral adrenalectomy <sup>a</sup> in patients without clinical signs of overt Cushing's syndrome	Suggest <sup>a</sup> : the same recommendations for patients with unilateral adrenal incidentalomas Suggest that bilateral adrenalectomy is not performed <sup>a</sup> without clinical signs of overt Cushing's syndrome.	NA

Modified from Fassnacht et al. [7].

ESE, European Society of Endocrinology; KES, Korean Endocrine Society; DST, dexamethasone suppression test; MACS, mild autonomous cortisol secretion; ACTH, adrenocorticotropic hormone; ACS, autonomous cortisol secretion; MDT, multidisciplinary team; NA, not available; HU, Hounsfield unit; CT, computed tomography; MRI, magnetic resonance imaging.

<sup>a</sup>Relevant changes.

measuring plasma free or urinary fractionated metanephrines in patients with adrenal incidentaloma with  $\leq 10$  HU on unenhanced imaging. All guidelines recommend obtaining the plasma aldosterone/renin ratio in patients with hypertension or unexplained hypokalemia.

#### Terminology: mild autonomous cortisol secretion

In the 2016 ESE and the 2017 KES guidelines, the 1-mg overnight DST results are categorized as follows: cortisol levels of 1.8  $\mu\text{g}/\text{dL}$  or lower are considered normal, levels between 1.9 and 5.0  $\mu\text{g}/\text{dL}$  are classified as possible autonomous cortisol secretion, and levels exceeding 5.0  $\mu\text{g}/\text{dL}$  are labeled as autonomous cortisol secretion [5,6]. However, evidence indicates a pattern of relationship between increased serum cortisol levels after DST and the risk of comorbidities and mortality was not linear [8,9,12]. Therefore, the 2023 ESE guideline defines MACS as cases where serum cortisol levels after the 1-mg DST exceed 1.8  $\mu\text{g}/\text{dL}$  without any further stratification by degree of post-dexamethasone cortisol level. Moreover, the 2023 ESE guideline recommends testing adrenocorticotropic hormone (ACTH)-independency by demonstrating suppressed or low-normal morning plasma ACTH levels and a repeat DST to confirm MACS. Although the updated guideline emphasizes the confirmation of ACTH-independency, the diagnosis of MACS still relies on the 1-mg DST. Therefore, it is necessary to develop new diagnostic

markers for MACS.

In patients with MACS, a careful second clinical evaluation might be necessary to search for signs of overt Cushing's that may have been overlooked at first examination. Recent studies have shown that MACS is associated with an increased prevalence of cardiometabolic diseases such as diabetes mellitus and dyslipidemia, ranging from 15% to 40% [9,12-14]. Hence, all guidelines recommend clinical decision-making based on age, general conditions, the patient's preference, and the presence of comorbidities potentially attributable to hypercortisolism. However, debate continues regarding whether surgical treatment is necessary for MACS. As stated in the 2023 ESE guideline, there is currently a lack of randomized controlled trials for cardiovascular outcomes or mortality comparing conservative and surgical treatment, although some studies have demonstrated a decrease in comorbidities following surgical treatment [7,15,16]. The 2023 ESE guideline recommends a multidisciplinary team approach to determine the necessity of surgical intervention in MACS patients. Thus, there is a pressing need for randomized controlled trials to develop treatment strategies for MACS and to discern which MACS cases necessitate surgical intervention.

#### Follow-up hormonal evaluation: not recommended

The KES guideline recommends annual hormone tests in patients with initially nonfunctioning tumors for a minimum of 4

to 5 years, consistent with the 2009 AACE guideline [2,6]. This is based on the fact that approximately 28% of nonfunctioning tumors can develop MACS during a follow-up period of 2.9 years [17]. However, both ESE guidelines do not recommend additional functional tests for confirmed nonfunctioning adrenal tumors during the initial hormone work-up unless new clinical symptoms are identified. The 2023 ESE guideline states that MACS rarely develops into overt Cushing's syndrome (<1%) and that false-positive DST results are possible. Nevertheless, long-term studies with annual biochemical tests in patients with adrenal incidentalomas are needed to justify the single initial hormone evaluation.

## ASSESSMENT OF MALIGNANCY RISK

### Benign adrenal masses: homogeneous and $\leq 10$ HU on unenhanced CT, irrespective of size

The 2016 ESE guideline recommends against additional imaging follow-up for adrenal incidentalomas measuring <4 cm with  $\leq 10$  HU on unenhanced imaging [5]. The 2017 KES guideline recommends a comprehensive evaluation for malignancy risk, including size, HU on unenhanced imaging, washout characteristics, and homogeneity on CT [6]. However, it suggests no definite cutoff values for excluding malignancy.

In the 2023 ESE guideline, the size criterion (<4 cm) has been removed, and it is now advised not to perform additional imaging follow-up for homogeneous adrenal masses with  $\leq 10$  HU, irrespective of size [7]. Evidence indicates that values of  $\leq 10$  HU are only found in benign adrenal tumors. This change is intended to reduce the socio-economic costs associated with excessive follow-up examinations for benign adrenal masses [18, 19].

### Nonfunctioning adrenal tumors with 11 to 20 HU on unenhanced CT and a size <4 cm: immediate additional imaging

The KES guideline recommends follow-up examinations at intervals of 3 to 6 months for evaluation of malignancy, followed by annual examinations for the next 1 to 2 years, and does not specify the follow-up interval or duration based on the risk of malignancy [6].

One of the changes in the 2023 ESE guideline is the recommendation of immediate additional imaging for nonfunctioning adrenal tumors that are homogeneous, less than 4 cm in size, and have 11 to 20 HU [7]. If additional imaging confirms the adrenal tumor as benign, no further follow-up is recommended. Perform-

ing a follow-up non-contrast CT scan 12 months later could be an alternative approach. This is supported by data indicating that over 90% of homogeneous adrenal tumors, in the absence of extra-adrenal malignancy, are benign if the HU value is below 20 [17,20,21].

However, the optimal second-line imaging methods for determining malignancy have not been clarified. Thus, further studies are needed to identify additional imaging methods to be incorporated into the decision-making process.

### Indeterminate adrenal masses: an individualized approach in a multidisciplinary team meeting

The KES guideline recommends follow-up at 3 to 6 months after the initial imaging, continuing for 1 to 2 years regardless of imaging features. In the 2016 ESE guideline, three options were suggested for indeterminate lesions: immediate additional imaging, interval imaging at 6 to 12 months, and surgery without delay [5]. However, the 2023 guideline suggests an individualized approach involving a multidisciplinary team but explicitly states that an immediate imaging work-up is preferred over an interval imaging follow-up for indeterminate adrenal tumors that have not undergone surgical treatment [7]. This reflects an effort to perform more accurate initial assessments, thereby saving costs and time associated with unnecessary follow-up examinations.

If a patient chooses not to undergo adrenalectomy, one repeat non-contrast CT or magnetic resonance imaging after 6 to 12 months is suggested. Surgical treatment is considered if the mass grows significantly during this period. The KES guideline defines a significant increase in size as an increase of >1 cm in the maximum tumor diameter [6]. However, in the ESE guideline, growth suggestive of malignancy is indicated by an increase of >20% and  $\geq 5$  mm in the maximum tumor diameter [7]. If lesions grow below this threshold, additional imaging might be considered after 6 to 12 months.

However, there are still no recommendations on the follow-up duration. Hence, we need updates that consider individual risk groups and take into account factors such as HU values, size, and homogeneity of adrenal tumors.

### Role of steroid metabolomics

The 2017 KES guideline recommends measuring sex hormones and steroid precursors in all patients presenting with imaging findings suspicious of malignancy to ascertain potential hormonal overproduction and utilizing these parameters as tumor markers [6]. However, the 2017 KES guideline does not address the utility of urine or plasma steroid profiles using tandem mass

spectrometry.

With advances in mass spectrometry, numerous attempts have been made to analyze steroid profiles in order to discriminate malignant lesions or subtypes of adrenal tumors [20,22-27]. Urinary steroid profiles have demonstrated the potential to distinguish between benign and malignant adrenal tumors [23,27]. The integration of urinary steroid profiles with CT image findings led to even higher sensitivity and specificity for malignancy in a prospective study [20]. In addition to the 2016 ESE guideline, which highlighted the potential benefits of measuring sex steroids and steroid precursors, the updated guideline now further suggests that, ideally, steroid metabolomics could be conducted using tandem mass spectrometry for a more comprehensive and accurate diagnosis. However, steroid profiling is not widely available in routine practice.

## SURGICAL TREATMENT

All guidelines universally recommend that an experienced adrenal surgeon should perform adrenalectomy [5-7]. However, the 2023 ESE guideline further elaborates on this point by introducing the term “high-volume surgeon” and providing specific criteria for what constitutes a high-volume surgeon. The ESE panel defines a high-volume surgeon as one performing a minimum of 12 adrenalectomies per year and considers a surgeon managing over 20 cases as desirable [7].

Another distinctive feature of the 2023 ESE guideline is the emphasized recommendation for a minimally invasive approach to adrenalectomy. The 2023 ESE guideline recommends adopting a minimally invasive surgical approach for benign adrenal tumors requiring surgery due to hormone excess [7]. If the radiological findings are suspicious of malignancy and the size of the mass is  $\leq 6$  cm without local invasion, minimally invasive adrenalectomy is recommended [7]. Another notable update is the emphasis on a multidisciplinary team approach when considering surgical treatments.

The 2023 ESE guideline recommends that patients with MACS should receive perioperative stress-dose glucocorticoid treatment and should be followed up by an endocrinologist until the hypothalamic-pituitary-adrenal axis recovers.

## SPECIAL CIRCUMSTANCES

### Patients with bilateral adrenal incidentalomas

All guidelines recommend that bilateral adrenal incidentalomas should undergo the same clinical, radiological, and hormonal

evaluations as unilateral adrenal incidentalomas. This new approach to bilateral diseases is suggested in the 2023 ESE guideline in cases with the following radiological and hormonal results: (1) bilateral (macronodular) hyperplasia; (2) bilateral adrenal adenomas; (3) two morphologically similar but non-adenoma-like adrenal masses; (4) two morphologically different adrenal masses. In particular, the assessment of comorbidities attributable to cortisol excess is recommended in patients with bilateral macronodular hyperplasia.

### Adrenal incidentalomas in young or elderly patients

Similar to previous guidelines, the 2023 ESE guideline recommends the urgent assessment of adrenal incidentalomas in pregnant women and patients <40 years of age due to a higher risk of malignancy and hormone excess. However, a new recommendation has been made for surgical removal in cases of an indeterminate mass in children, adolescents, pregnant women, and adults under 40 years of age.

## CONCLUSIONS

The management of adrenal incidentalomas has significantly advanced over the years, with updated guidelines aiming to optimize diagnostic processes and therapeutic interventions. The 2023 ESE guideline, in particular, highlights the need for individualized approaches over standardized ones, introducing key modifications in hormonal evaluations, the assessment of malignancy risk, and surgical treatment. The definition and management of MACS have been refined, with the focus shifted toward an integrated understanding of ACTH-independency, patients' age, comorbidities attributable to cortisol excess, and preferences. This personalized approach is also seen in the appraisal of malignancy risk, focusing on HU values and tumor homogeneity, irrespective of size. The role of steroid metabolomics in diagnosis is increasingly acknowledged, although its use is yet to be mainstreamed. Importantly, the guideline recommends that surgical interventions should be performed by experienced surgeons using minimally invasive techniques when suitable. The guidelines also stress the importance of a multidisciplinary team approach in managing these cases.

Overall, these updated guidelines pave the way towards more accurate diagnosis and effective management of adrenal incidentalomas, potentially reducing unnecessary examinations and thereby easing the socio-economic burden incurred by these masses. Further research, including randomized controlled trials, is needed to strengthen these recommendations and to es-

establish more refined strategies for treating adrenal incidentalomas.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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